Transcranial Direct Current Stimulation in Neuropsychiatric Disorders

Clinical Principles and Management

André R. Brunoni
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Second Edition

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Foreword to the Second Edition

After the successful first edition in 2016, Andre Brunoni, Michael Nitsche and Colleen Loo took the endeavour to edit a second edition with a new comprehensive structure covering all aspects of tDCS application to keep pace with the rapidly developing research field of non-invasive brain stimulation (NIBS). The book provides deep insights in tDCS research and application: Forward and reverse translation between computational modelling, animal models, human physiology and therapeutic applications as well as personalized, brain circuit or state focussed approaches represent exciting new avenues of tDCS research. At the same time, the clinical fields of tDCS use are growing in terms of disorders, applications from childhood to old age and settings, even reaching out to treatment at home.

As in its first edition, the chapters of this book again allow a deep reflection and discussion of research lines, their alternatives, limitations, chances and perspectives for informing young scientists new in the field, but also guiding experts in their future research as there are still many unexplored or unknown topics. Compared to other NIBS interventions, tDCS has been particularly fascinating for me in a threefold paradox: (1) How does tDCS with its probably most subtle mechanistic action among NIBS interventions induce pronounced neuromodulation of function and plasticity? Here, we need to remember that neurophysiological effects are rarely linear and minor changes matter, e.g. differences in rTMS protocols may lead to divergent effects (i.e. intermittent and continuous theta burst stimulation just differ in intervals, but neither in intensities, bursts shapes or frequencies). (2) How could we apply the least focal NIBS method – perhaps except high definition (HD) tDCS – based on individual fMRI data for personalized treatment within a precision medicine framework? Bipolar or multi-electrode montages meet functions not represented in a single cortex regions, and specificity may rather be achieved by combining specific tasks or interventions (i.e. motor or cognitive training) with tDCS than by targeting a specific cortex region. (3) Does an intermittent and acute treatment as tDCS (e.g. in contrast to deep brain stimulation) lead to post-stimulation effects maintained or even growing for weeks or months? Though this has not been proven to date, single studies seem to point to such a prolonged action after the acute treatment interval [1]. However, we know such effects from the fields of training and psychotherapy.

In many respects, tDCS may therefore challenge common but simplified views on brain function and topography, which may sneak in again through the backdoor, even if we feel that we have send them to the archive. I hope other readers will enjoy this book as much as I do.

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Reference

1. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, Veronezi BP, Nogueira BS, Aparicio LVM, Razza LB, Chamorro R, Tort LC, Fraguas R, Lotufo PA, Gattaz WF, Fregni F, Benseñor IM. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376:2523–33.

Foreword to the First Edition

Why writing a book on transcranial direct current stimulation (tDCS)? This question is especially relevant in the face of the rapidly increasing numbers of journals, open access publications, wikis and blogs. In parallel to the exponential spread of information sources, information and beliefs also tend to be found in shared virtual spaces, where they are amplified and reinforced. Critical reflection on concurrent and opposing opinions, or a synopsis of such opinions, is underrepresented in such "echo chambers". This is the case for the general public discourse and may also be true for the reception of scientific findings.

tDCS is a technically extremely simple method and easy to apply. Thus, people can be tempted to build the equipment themselves or try do-it-yourself (DIY) application without any expert guidance—numerous video clips for DIY tDCS on the web are just one form of public sharing of knowledge and convictions about this method that are echoed by other followers. People are also tempted to follow intuitive attitudes or convictions about tDCS, e.g. non-verified dose/parameter response assumptions, hypotheses on the functional anatomy of tDCS effects or a general idea of reinforcing brain functions with no side effects (cognitive enhancement). The 2016 paper "tDCS modulates neuronal activity and learning in pilot training" [1] is just one example where the title immediately and strongly suggests an application in real-world settings. Karl R. Popper's general rule, however, "that we are not to abandon the search for universal laws and for coherent theoretical system, nor ever give up our attempts to explain causally any kind of event we can describe" [2], which he proposed to be closely associated with the "principle of causality", should remind us to be careful about making assumptions. Admittedly, though, we often follow associative or correlative relations, particularly when applying insights from neuroscience to clinical situations.

Of course, a single book cannot counterbalance or overrule current trends in a scientific discussion. Moreover dispersed, "open access" pieces of data and information are also extremely valuable in a thorough discussion of scientific findings. Nevertheless, because this book combines a critical amount of data and hypotheses it allows the reader to appraise findings and theories on tDCS and its variants.

Andre Brunoni, Michael Nitsche, Colleen Loo and the other authors, all pioneers and leading experts in the field, have taken a brilliant approach to this endeavour and guide us through the state of the art in tDCS. The different chapters cover tDCS development, related technologies (e.g. transcranial alternating current stimulation, tACS, or transcranial random noise stimulation, tRNS), physiology and translational research from animal experiments to preclinical

studies in humans involving neurocognitive and neuropsychological approaches, electroencephalography and magnetic resonance imaging (MRI). Several chapters cover specific applications ranging from cerebellar and spinal tDCS to different applications in neuropsychiatric disorders. The final part of the book outlines and discusses safety-related, ethical and regulatory issues.

tDCS is part of the armamentarium of non-invasive brain stimulation (NIBS), which constitutes a growing array of techniques such as transcranial magnetic stimulation (TMS), paired associative stimulation (PAS) and transcutaneous vagal nerve stimulation.

Each NIBS technique, but also each variant of tDCS, is a neurophysiologically distinct method. The authors of this book are aware that tDCS is used as a non-focal approach on the most complex organ/system of the human body and that the differential action of tDCS on single neurons or neuronal circuits or glial cells is difficult to predict or target. Dose-response curves often show non-linear functions, which are currently not fully understood. Furthermore, dynamic effects of repeated tDCS administration, which are particularly important for therapeutic applications, still need to be elucidated. The combination of tDCS with psychotherapy and other interventions is currently being tested in pilot studies and is proving to be extremely challenging [3]. Such open methodological fields would provide a large experimental terrain for preclinical studies in cellular and animal models, but studies in this preclinical field are still underrepresented. Thus, the book may stimulate the transfer of research based on clinical or experimental data in humans to the preclinical field of cellular or animal research strategies (reverse translation).

This book is comprehensive and as such valuable. The task of preparing it motivated the editors and authors to move systematically through the field of research and to also cover topics which are not on the main track, e.g. the history of tDCS and ethical and regulatory issues. Consequently the content of chapters may overlap, as a reflection of different perspectives. This book allows the reader to jump between chapters to compare information, hypotheses and views. It is an excellent resource for senior and junior scientists, doctorate students and others to introduce them to this fascinating field of research.

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References

1. Choe J, Coffman BA, Bergstedt DT, Ziegler MD, Phillips ME. Transcranial direct current stimulation modulates neuronal activity and learning in pilot training. Front Hum Neurosci. 2016;10:34. https://doi.org/10.3389/fnhum.2016.00034.
2. Popper KR. The logic of scientific discovery. 11th impression rev. London: Hutchinson & Co. Publishers Ltd.; 1959. p. 61.
3. Bajbouj M, Padberg F. A perfect match: noninvasive brain stimulation and psychotherapy. Eur Arch Psychiatry Clin Neurosci. 2014;264 Suppl 1:S27–33.

Preface to the Second Edition

It is with pleasure that we, the editors, have organized the second edition of this book. While in its edition tDCS was presented by us as the youngest child of the family, we are proud that this member has just reached maturity. However, being an adult does not only bring new possibilities, but additional responsibilities as well. Considering this development, and the good reception that our first edition achieved in the community, this second edition was organized.

While the first edition was organized into 3 parts, the present edition now contains Introduction and Mechanism of Action, Research Methods, tDCS in the Life Cycle, Applications of tDCS in Neuropsychiatric Disorders, and The clinical use of tDCS. The first part updated chapters on tDCS mechanisms and animal studies of tDCS, aspects of the technique that have undergone immense research recently. The second part describes the methodology involved in tDCS research, with new chapters dedicated to the exciting combination of tDCS with neuroimaging modalities. In the third part, we describe the use of tDCS in special populations, such as child and adolescents, healthy adults, and the elderly. The fourth part was substantially expanded to describe either in more detail (or in more than one chapter) the use of tDCS in disorders such as depression and schizophrenia or to include the new controlled trials using tDCS in diverse neuropsychiatric disorders, such as ADHD, OCD, pain syndromes, and others. Finally, in the last part we cover aspects related to the daily practice of tDCS, such as regulatory aspects, combination of tDCS with pharmacotherapy and psychotherapy, home-use tDCS, and the safety and tolerability of the technique.

We are once again grateful for all the authors that dedicated their time and contributed to this book by providing their excellent chapters, especially in the difficult year that was 2020.

We hope that the second version of the book continues to be important to students and researchers as a reference in the field. Seasoned tDCS researchers will also find joy in reading this book, even if only to be mesmerized by the feeling that, after 20 years since its inception, and great care during the troubling years of childhood and adolescence, their collective sibling is a young adult. It took a village to raise this child, but she is now prepared to explore larger fields in the world of neuropsychiatry and neurosciences.

São Paulo, Brazil — André R. Brunoni
Dortmund, Germany — Michael A. Nitsche
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Preface to the First Edition

The clinical interest in non-invasive brain stimulation has grown exponentially over the past 25 years, with the development of non-pharmacological, neuromodulatory techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TDCS, the youngest sibling of the brain stimulation family, is in fact a "new old technique". With anecdotal reports of the use of the torpedo fish to treat pain and headache via its electrical discharges during the ancient history, electricity was indeed used in the nineteenth and twentieth centuries to treat several neurologic and psychiatric ailments, usually with sparse scientific foundations. Although more recently, in the 1960s and 1970s, the treatment of some psychiatric disorders was investigated using brain polarization (a technique similar to modern tDCS), the research did not endure—perhaps due to the stigma of electroconvulsive therapy or the concomitant development of pharmacotherapy in that period. TDCS reappraisal only took place in 1998–2000, when two independent European groups showed that the electric currents applied over the motor cortex induced changes in brain excitability. From then onwards, tDCS has been increasingly investigated and has attracted considerable attention in both basic and clinical research settings.

In the present book we aimed to present the main advancements regarding the use of tDCS in neuropsychiatric disorders. The book is divided into three parts. The first part discusses the mechanisms of action of tDCS under different perspectives, which encompass neurophysiological, neuroimaging and neuropsychological studies as well as animal studies and computer-based models. In the second part, state-or-the-art evidence of tDCS use in several neurological and psychiatric disorders is presented. The third and last part of the book discusses different possibilities of the clinical and research use of tDCS, including safety, ethical and regulatory aspects.

This book would not have been produced without the invaluable contribution of leading researchers and scientists of the field. We are grateful and thank these authors for their time and effort in writing informative, insightful and up-to-date chapters. We are also grateful to Springer for supporting our project, particularly Gabriel Natan Pires, the Springer associate editor who encouraged us to edit this book, and Susan Westendorf, the Springer project coordinator responsible for this book production.

We believe that this book will be useful to neurologists, psychiatrists and physicians interested in the potential clinical applications of tDCS. This book will also be of interest for neophytes, who are looking for a primer in

non-invasive brain stimulation. More experienced researchers will also enjoy reading this book as it contains top-quality work written by several tDCS experts. We, the editors, are convinced that Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management will be a captivating bedside book for many researchers in the field—us included.

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Part V The Clinical Use of tDCS

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Part I

Introduction and Mechanisms of Action

1 Historical Aspects of Transcranial Electric Stimulation

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1.1 The First Clinical-Therapeutic Electrical Applications: The Electric Fish

The roots, beginnings, and first attempts at using transcranial electrical stimulation, as a medical cure, can be found in the Greco-Roman period when electricity generated from fish organs was used to cure pain, headaches, gout, arthritis, and paralysis of various parts of the body [1–4]. However, the powers of *electric fish* had been probably known well before Roman times for being able to produce an electric discharge, as indicated by some Egyptian archeological findings on tombs that showed images of the electric fish in this period, and a therapeutic use cannot be excluded [1–5]. The ruins of Pompeii also contained frescoes of this fish [4].

The fish certain record of electrical therapeutic application was set out by Scribonius Largus (c.1–c.50 AD), one of the first physicians in ancient Rome during the periods of Tiberius (14–37 AD), Caligula (37–41 AD), and Claudius (41–54 AD) who, in his text on therapeutics *De Compositionibus Medicamentorum* (see Fig. 1.1), reported a collection of drug compounds or recipes in use by physicians at that time and mentioned the use of bioelectric phenomenon of certain fish (*Torpedo* and *Torpedo nobiliana*) for therapeutic ends [6–9].

These fish were known for being capable of producing an electric discharge, and their scientific name comes from the Latin *torpere* to be stiffened or paralyzed but also to be numb, insensitive [4, 5, 10].

In particular, Scribonius Largus suggested a remedy for headaches by placing recently caught black torpedo fish on the cranial surface of patients, making the fish emit its electrical discharge. He observed:

> Headache even if it is chronic and unbearable is taken away and remedied forever by a live torpedo placed on the spot which is in pain, until the pain ceases. As soon as the numbness has been felt the remedy should to be removed lest the ability to feel be taken from the part. Moreover, several torpedos of the same kind should to be prepared because the cure, that is, the torpor which is a sign of betterment, is sometimes effective only after two or three. [1]

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SCRIBONII LARGI
COMPOSITIONES
MEDICÆ.
IOANNES RHODIVS
recenſuit,
Notis illuſtrauit,
LEXICON SCRIBONIANVM
adiecit.

PATAVII, CIↃ IↃC LV.

Typis Pauli Frambotti Bibliopolæ.
SVPERIORVM PERMISSV.

Fig. 1.1 The *Compositiones medicamentorum* of Scribonius Largus, from 1655 Edition

Two fundamental points emerge from these statements. On the one hand, the paralyzing shock does not provoke convulsions but instead a temporary state of dullness and relief of painful symptoms, presumably stunning the peripheral skin receptors, or affecting spinal or brain structures inducing an immediate and residual transient period of pain relief. On the other hand, in certain situations, it was necessary to use more than one fish to obtain the desired narcotic effect. Scribonius Largus did not provide any source for the basis of his therapeutic approach, and it is probable that he would have developed such a method personally but perhaps with the suggestions of some fishermen [1, 9].

The electric fish continued to be used by physicians throughout the Greco-Roman period. For example, 30 years after the *Compositiones* of Scribonius Largus, the Greek physician Pedacio Dioscorides Anazarbeo (44–90 AD) in his book *De Materia Medica* suggested using the torpedo in the treatment of headaches [11, 12]. It seems that also Pliny the Younger (61–113) reported the use of the electric ray fish to reduce labor pains; however, the ancient Romans seem to have preferred using the dietary health properties of the fish rather than exploiting its electrical properties while alive [1, 3]. Galen of Pergamum (129–200 AD) criticized the dietary use of the torpedo denying its curative powers. He highlighted, instead, the efficacy of the paralyzing shock given off by the live fish due to thermic reaction and proposed it as a treatment for epilepsy and headache and maintained it to be the most effective form of cure [1]. He wrote:

> The whole torpedo, I mean the sea torpedo, is said by some to cure headache and prolapsus ani when applied. I indeed tried both, and the torpedo should be applied alive to the person who has the headache, and that it could be that this remedy is anodyne and should free the patient from pain as do other remedies which numb the senses: this I found to be so, and I think that he who tried this did so for the above mentioned reason. [12]

Many other physicians, Roman, Arabic, and Medieval, continued to mention the therapeutic capacity of the electric fish. Marcellus Empiricus (IV sec. d.C.), Aetius Amidenus (527–565), Alexander Trallianus (525–605), Paulus Aegineta (625–690), Avicenna (980–1037), Averroè (1126–1198), Ibn Sidah (1007–1066), and Dawud al Antaki (1543–1599) were among those who promoted the benefits of electric shocks emitted by the electric organs of certain fish in the treatment of headaches, depression, epilepsy, and arthritis [1, 12]. Electric fish were later used for the treatment of seizures, depression, and pain until the eighteenth century [1, 13].

1.2 Transcranial Electrical Stimulation: From Electrostatic Machines to Volta's Pile

In 1600, appears for the first time the term *electricus* in William Gilbert's *De Magnete* considering the attractant properties of substance like amber [14]. In the eighteenth century, sporadic attempts were made to treat mental diseases using *artificial electric energy* derived from electrostatic machines and stored in capacitors such as glass globes, cylinders, brass, and silk threads or huge Leyden jars. These were in use in the mid-1700s as portable electric devices and appear to have introduced a flourishing period in the medical use of electricity (see Fig. 1.2).

Kadosh and Elliott [15] underlined that from the 1740s onward, there was a widespread and commercial availability of transcranial electrical stimulation machines for personal and domestic use. During the Victorian and Edwardian period, electrical stimulation machines that dispensed static, frictional, faradic, or battery electrical current could be bought everywhere, and some physicians, therapists, and patients claimed that transcranial electrical stimulation could generate feelings of euphoria and even improve mental performance [16]. This produced some promising clinical results, but technology and methodology were incomplete.

The German Christian Kratzenstein (1723–1795), then a student at the University of Halle, accomplished what was considered the first electrotherapy cure in 1744, healing a young woman of a contracted finger. He predicted that

Fig. 1.2 (**a**–**c**) Simple machines that harnessed electricity in 1700s and an example of central galvanization technique

electricity would be useful not only in physical, but also mental patients, whose health worries and anxieties prevented them from sleeping, and could become a remedy for hypochondriasis and women with hysterical conditions. Kratzenstein published two clinical cases in *Abhandlung von dem nutzen der electricität in der arzneywissenschaft* (translated in Priestley's 1767 *History and Present State of Electricity*, p. 472) [14, 17].

The French physician Charles-Georges Le Roy (1723–1789) (see Fig. 1.3) in 1755 reported in detail his cure of what today may be called a case of hysterical or psychogenic blindness [18]. He placed conducting wires around the patient's head and led one wire to his leg. The wires were connected to an array of Leyden jars and three shocks were administered in the hope that sight would be restored.

After the patient received his first electric stimulation, he reacted with convulsions of the eyes, and he saw rays of light for the first time. When he received the third stimulation, somewhat stronger than the others, he screamed and fainted; as a result of this treatment, he began to regain his eyesight. In another case with blindness along with the pain of the stimulation, the patient did perceive vivid flashes of light (phosphenes) and underwent the treatment several times in the following days. Nonetheless, he

Fig. 1.3 Charles-Georges Le Roy

remained blind. Figure 1.4 reports the therapeutical use of electricity adopted by Le Roy.

The British lay preacher in Worcester Cathedral Richard Lovett (1692–1780), in 1755, demonstrated to have successfully treated some mental afflictions with an electrostatic machine [19, 20]. In 1756, he published the book *The Subtil Medium Prov'd*, considered to be the first English manual for electro-medical applications. In 1774, Lovett published his text *The Electrical Philosopher, Containing a New System of Physics Founded on the Principle of a Universal Plenum of Elementary Fire*. His work impressed John Wesley (1703–1791), one of the founders of the reformist movement in the eighteenth century, who in 1759 wrote:

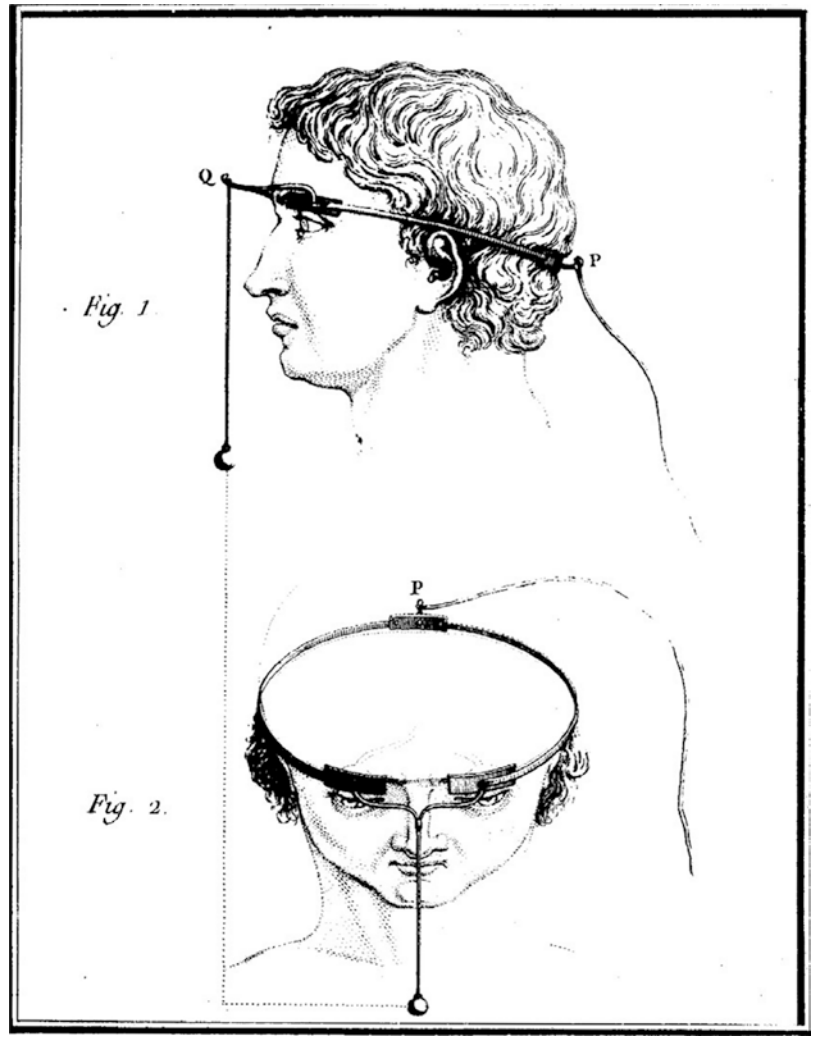

Fig. 1.4 The apparatus used by Dr Charles Le Roy in his attempt to cure blindness with electrical stimulation

> I doubt not but more nervous disorders would be cured in one year by this single remedy than the whole of the English Materia Medica will cure by the end of the century. [21]

In Lovett and Wesley's time, nerves were considered to be fine tubes through which mysterious fluid flowed; Wesley hypothesized that: …*what if the electric ether is the only fluid in the universe fine enough to flow through them?* Regarding this physical and metaphysical mechanism and the general enthusiasm of that time, Wesley admitted to some limitation to electrical treatments because he had little results with longstanding paralysis, and he also noted a characteristic inconsistency in the response to treatment, considered now as a typical placebo response [14].

In 1777, the Italian physicist Tiberio Cavallo (1749–1809) published *A Complete Treatise on Electricity in Theory and Practice, with Original Experiments* in which he reported cures for epilepsy, paralysis, chorea, deafness, and blindness [22]. In 1780, Cavallo, published *An Essay on the Theory and Practice of Medical Electricity* [23], which, apart from some personal clinical observations, contained the interesting description of a patient affected by St Vitus' dance and cured with electricity by the English physician John Fothergill (1712–1780). Fothergill, renowned for his support of Benjamin Franklin's publications on electricity, contributed a preface for them.

Physicians of the period recommended that currents of no more than 5–10 mA should be applied to the head because higher currents could have risks of burning and shock. Some side effects were reported, including headaches, flashes of light, dizziness, and nausea, especially when connections were imperfect or broken. The consequences could be more serious. In 1783, the Dutch physician Jan Ingenhousz (1730–1799) knocked himself unconscious and amnestic when he carried out electrical experiments, and Benjamin Franklin (1706–1790) suffered retrograde amnesia after accidentally administering an electric shock to his head [24]. Including Franklin's experiments (1757), other physicians applied electricity treatment on functional symptoms, for example, the Scots Robert Whytt and Andrew Duncan, respectively, in 1765 and 1784 [14].

At the end of the eighteenth and the beginning of the nineteenth century, we had a flurry of technological development with Leyden jars and rudimentary batteries developed by Luigi Galvani (1737–1798) and Alessandro Volta (1745–1827) between 1791 and 1800. In 1831, Faraday discovered the induction current, which provided the first continuous electrical current and quickly led to the production of practical machines for channeling mechanical energy into electrical. Many hospitals developed departments with electrical induction machines, and this new technology was very quickly put into action [14].

Undoubtedly, with the invention of the electric battery in 1799 by Volta, experience on the effects of the electric current on humans became more systematic. The studies that led him to develop this revolutionary device began in 1792, after Volta read the work of Galvani on the existence of an intrinsic electricity in living organisms [25–29]. Volta himself, Galvani, and especially his nephew Giovanni Aldini (1762–1834) (see Fig. 1.5) started to use electric stimulation using the voltaic pile on patients with

Fig. 1.5 Giovanni Aldini

depression, epilepsy, amaurosis, and other diseases. Galvani interpreted epileptic disorders as electrical phenomena and used electro-medical applications, like Volta, who carried out short electrotherapeutic applications at the *Conservatorio delle Zitelle Povere* of Como with encouraging results [30, 31].

The most relevant contribution can be seen in Aldini's publication, in 1804, *Essai Theorique et Experimental sur le Galvanisms*, in which after spreading and defending the work of his famous uncle, he recommended galvanism as "electric therapy" to aid mental ailments and even to revive the dead [32, 33].

The core idea was that if nervous energy was by its nature electrical, then mental diseases could be interpreted as alterations of an electrical nature. The galvanic stimulation of nervous regions could help to correct such defects. Aldini applied galvanic currents to the crown of patients affected by depression after having experimented with the effect of the treatment on himself with electrodes in both ears, or in one ear and his mouth, or on the forehead and nose [34]. He experienced an unpleasant sensation due to the immediate shock on opening the circuit followed by a prolonged insomnia and by hyperactivity, which lasted several days [33, 34]. Passing the current between the ears produced violent convulsions and pain, but he claimed good results in patients suffering from melancholia. The most rigorous account of these applications involved Luigi Lanzarini, a 27-year-old farm worker, who was affected by a serious form of depression and who arrived at the *Ospedale Sant'Orsola* of Bologna, on May 17, 1801. Aldini began treatment using the voltaic pile, containing 15 metal discs, increasing them in number so as to increase the intensity of stimulation during the treatment. The optimal effects were achieved when the patient held his hand at the base of the pile, while the arc emerging from the upper part of the apparatus was touching the appropriately shaven and lubricated superior parietal bone. Figure 1.6 shows the therapeutic procedure carried out on Lanzarini.

The depressive state of the patient progressively improved in the following days, and after a brief observation period at Aldini's home, he was permitted to go back to his family in his hometown. Aldini applied his electrotherapeutic experiences also at the *Salpêtriere* in Paris where he met the renowned psychiatrist Philippe Pinel (1745–1826) who had heard word of Aldini's electrotherapeutic applications and was very curious to personally see the effects on his mentally ill patients. The results, however, were quite poor due to patients being often in a state of agitation and being quite frightened when faced with Aldini's strange apparatus. Aldini attempted to avoid this situation by putting each electric arc on the ears and even on the earrings of female patients. When Aldini left Paris, Pinel attempted several times to use Galvanism on some patients, but no accounts in writing of these experiments were found [33]. Successively, Aldini became a sort of traveling showman, demonstrating the effect of application of current to cadavers in many European cities with particularly theatrical demonstrations. His experiments on the heads of executed criminals in London are well known [33].

In his therapies, Aldini lacked instruments to indicate the intensity of the current used and took into account only the number of copper and zinc discs in the voltaic pile that were indicative of a

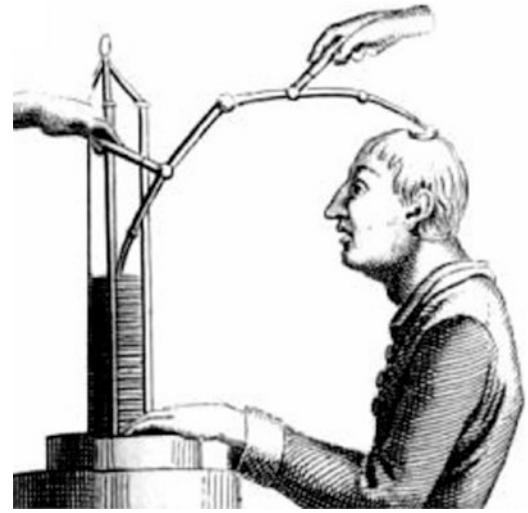

Fig. 1.6 Aldini's patient Luigi Lanzarini suffers from melancholia to whom galvanism is being applied in the head

coarse gradation of stimulation delivered. Moreover, in the absence of a nonrational principle on the therapeutic effect of electric currents, Aldini merely pointed out that after the delivery a general rearrangement of brain function occurred, similar to what happened in violent trauma brain injury. This finding is more reminiscent of the practice of electroshock than that of a lasting modulation of the brain using transcranial direct stimulation at low voltage (tDCS or polarization). However, Aldini in this application used low current voltage for extended periods of time provoking a fleeting daze but neither seizures nor generalized symptoms such as apnea, cyanosis, and amnesia [2, 32].

In the same period as Aldini, other European clinical researchers made use of galvanic current to treat mental disorders [3, 35]. In 1801 in Germany, Friedrich Ludwig Augustin (1776–1854) recounted a case of treatment using Galvanic current for a catalectic crisis with paralysis to one arm and leg with intermittent fever. After 3 weeks of treatment, the paralysis disappeared and the patient appeared more alive with their humor much improved [36]. In the same year, again in Germany, Christian Heinrich Ernst Bischoff (1781–1861) pointed out that he treated depression, hysterical paralysis, and stupor with remarkable results using Volta's pile [37]. Figure 1.7 shows the depiction of the instruments used by Bischoff in his clinical practice.

The German Karl Johann Christian Grapengiesser (1773–1813) reported the treatment of a young female with a 4-year history of hysterical aphonia using galvanic current applied to blisters on the throat over a period of 5 days [38].

In Italy, in 1804, the psychiatrist Gian Pietro Tonelli described some clinical cases of transcranial galvanic stimulation in two patients who:

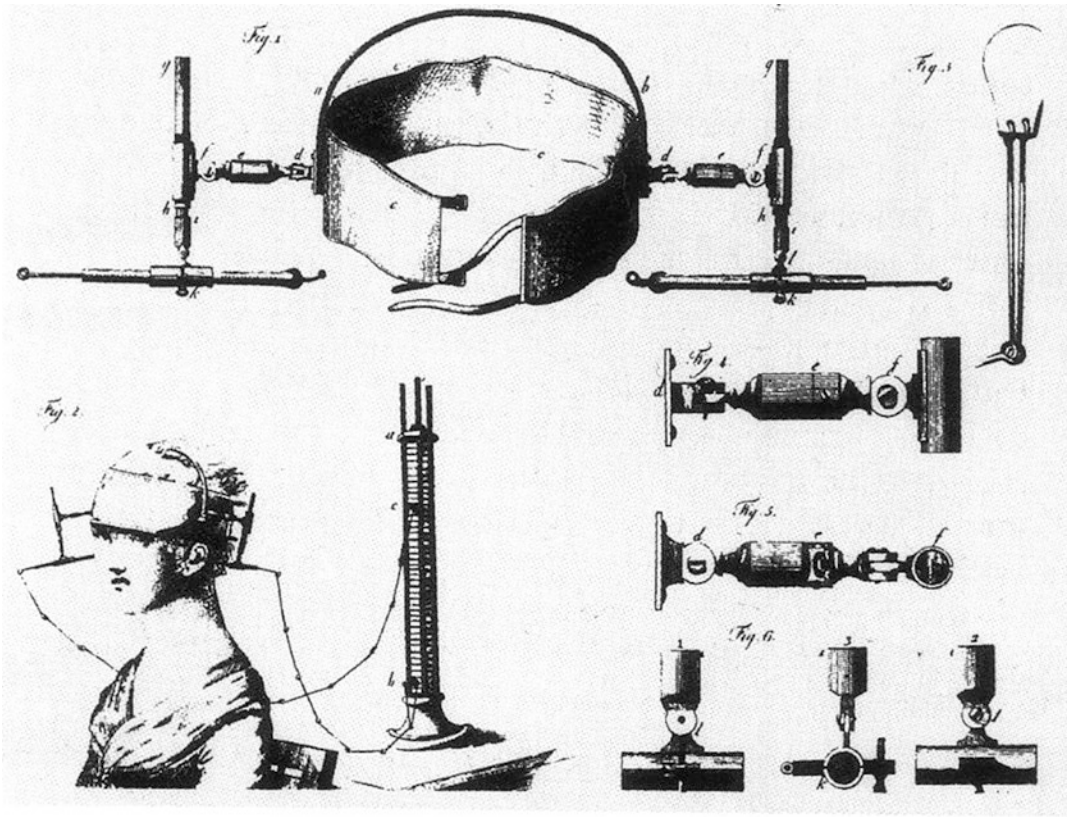

Fig. 1.7 Instruments used by Bischoff in his clinical practice of electric stimulation

> … due to strong hemorrhage, terror, and other causes they were rendered cognitively impaired so that their faculties languished exceedingly, and the sense organs, especially vision, had lost much of their energy. [31]

After application of the galvanic current, patients claimed to feel much better:… *because it seemed to them they were internally washed by a life-giving fluid, which awakened the power of their spirit, and made the sensory organs pristine again*. Tonelli remarked that these effects also corresponded to: "… *a certain liveliness, and a more cheerful and relaxed attitudes which showed in the face and they testified to recognizing stronger images and greater mobility in the eye*" [31].

During the 1850s, electrotherapy came into use again as a therapeutic agent for neurological and psychiatric diseases in European, and North American asylums, in a form other than the indiscriminate use it had over the previous century [16]. There was a differentiation between galvanic and faradic electric currents, their various strengths, long- or short-term application, etc. [39, 40].

Some illustrious neuroscientists, in the second half of the nineteenth and beginning of the twentieth centuries, embraced transcranial electrical stimulation for the treatment of psychiatric and neurological diseases. For example, in France, Francois Magendie (1783–1855), Jean-Martin Charcot (1825–1893), and Joseph Babinski (1857–1932) verified the effect of electricity respectively in patients with epilepsy, melancholia, and hysterical conditions [41, 42]. In Germany, Jan Evangelista Purkinje (1787–1869) considered the application of electricity to cure neurological diseases, and in Italy, Carlo Matteucci (1811–1862) reported in the treatment of neurological diseases such as chorea, neuralgias, and paralysis [43]. A name that is not famous but of particular interest is the Norwegian Christian Engelskjön who maintained that it was not the direction of the current which influenced the electrotherapeutic result but rather the differentiation between galvanic (continuous) and faradic (interrupted) current. Therefore, depression and paralysis should be treated with an ascending galvanic flux caused by the cathode, while mania and other excited states should be treated with descending galvanic current caused by the anodal effect. Engelskjön used the two types of current in treating two kinds of migraine: one linked to vasoconstrictive damage and the other vasodilation: the faradic current was used as an anti-vasoconstrictor, while the galvanic current was used to limit the pain due to vasodilation [44, 45]. Also in this period, other physicians treated migraine with electrotherapy [46].

In the same period, numerous medical practitioners, in Europe and North America, began applying electrical methods to their patients, warning in some cases against the then unwarranted application of electric stimulation to almost all the mentally ill [47–66].

Among the illnesses treated were neurasthenia, melancholia, mania, hysteria, but also hallucinations, migraine, and dementia. Patients with depressive symptoms or hysterical reactions were said to benefit most from this form of therapy [20]. The preferred technique was the application of one electrode to either the scalp or the rear of the neck, round about the second or third cervical vertebra, and another to a distant region of the body such as the hand or foot. Electricity was usually applied in daily or alternate daily sessions, lasting from 10 to 20 min [20]. Intensity was reported by investigators according to the number of battery cells used, between 20 and 35, and treatment varied in length, from seconds to minutes [35]. Several clinicians observed that electrical treatments, and more specifically galvanic therapy, were capable of inducing epileptic convulsions if too strong a current was used [67].

The most important contributor to this entire development seems to be the German psychiatrist Rudolf Gottfried Arndt (1835–1900) (see Fig. 1.8) who, in a fascinating 130-page review, did the most to unveil the psychological and organic background of the role and influence of electricity with regard to neuro- and psychopathology [48–50, 68]. Of particular interest in this period for originality is the paper of [69] entitled 'Electricity in aphasia' where he described electrotherapy application in two cases of fluent aphasia.

Arndt carried out studies on electric stimulating treatment in severe psychoses with depressive symptoms or even catatonia, hypochondriac

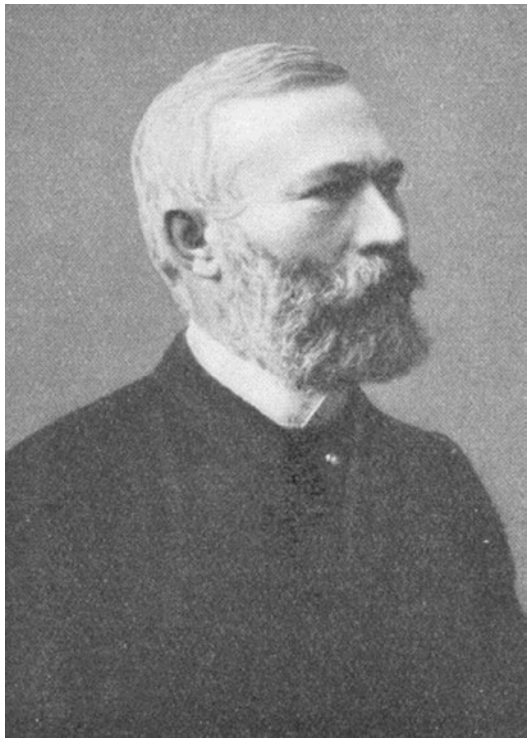

Fig. 1.8 Rudolf Gottfried Arndt

delusion, and melancholia, suggesting the use of faradic current (alternate current) as a stimulant against passivity, stupor, weakness, and manic-depressive disorder. On the other hand, direct current was to be applied in other forms of affective disorders, psychoses, and psychotic symptoms. He reported that vertical, horizontal, and diagonal galvanization on the head, with both electrodes attached to the cranial bone, sometimes supported by simultaneous galvanization of the sympathetic system (vagus nerve stimulation) and the cervical spinal cord was especially successful in fresh, recently developed psychoses and anxieties. He also recommended galvanization of the head and the auditory center against acoustic hallucination. Arndt [70] also highlighted the difficulties connected with electrical stimulation in the treatment of mental disorders when he wrote:

> The electric current is a two edged sword … it may aggravate some forms of mental derangement and even make them incurable … great care, patience and confidence are required, qualities only found in man convinced of the final effect of his treatment. Mere attendants, nurses or assistants, who simply do what they are told, and because it is their duty, will never have the success of a medical man convinced of the efficiency of electricity. [70]

In contrast to his colleagues, who described individual cases, another German psychiatrist Wilhelm Tigges (1830–1914) published studies on differential individual groups of patients with similar sickness or symptoms. His conclusions were that electric brain stimulation was effective with patients suffering from depression and hence should be used in those for whom conventional therapy could no longer help. He found that for patients whom we would now consider schizophrenic rich in positive symptoms, electrotherapy showed little or no effect [68, 71–73].

A repeated observation in these studies was that different polarities (cathodal or anodal) had different effects (sedative, stimulative, etc.) depending also on differences among individual patients and the type of electric current used. A sedative effect resulted when a negative pole was applied to the scalp. A sleep-inducing effect was also reported by the French physician Stéphane Leduc (1853–1939). He experimented with low-intensity electrical stimulation periodically interrupted (100/200 times per second with 8–16 V and 2 mA) passed transcranially in animals. The result he obtained was the appearance of a state of astonished immobility progressively culminating in a state of inhibition comparable to chloroform narcosis [74]. Leduc called this condition electric sleep (and by later authors electronarcosis) and was obtained by applying electrodes in an axial direction on the forehead and to the rear of the head which, after a short period of excitement, was accompanied by vegetative phenomena [74–77]. He recommended transcranial electric stimulation in cases of cerebral neurasthenia.

It should be noted that there were in this phase plenty of excesses and exaggerations, typically found in the early stages of the application of a new therapeutic technique, which sometimes led to an excess of zeal. In addition to the reports of the successful use of electricity

to treat mental illness, some clinicians raised doubts about the efficacy of electricity in treating mental illness [67]. Electricity was also applied in an extreme way during the First World War (but also in the Second World War) submitting traumatized soldiers to electric stimulation in order to discipline and return them to the front [78].

In the following years, incongruent results, or none at all, led to the gradual abandonment of electric therapy until the 1930s when electroconvulsive therapy was introduced. Electroconvulsive therapy (ECT) could be considered the first modern example of the therapeutic application of brain stimulation for the treatment of psychopathologies. The Italian psychiatrist Ugo Cerletti (1877–1963) relied on a young colleague Lucio Bini (1908–1964) for the development of an instrument able to ensure maximum safety in the application of electrical current. These original scientists used ordinary alternating current propagated in sine waves and in measured intensity as a means of producing convulsive seizures. However, they received harsh criticism about the project, which was presented by Bini at the *Congress of Neuropsychiatry of Munseigen* in 1937 on the treatment of schizophrenia. In March 1938, the method was introduced at the *Academy of Medicine* in Rome, and in April 1938, the first real application of ECT was performed by Cerletti and Bini on a patient affected by an apathetic and abulic condition with diagnosed schizophrenia [79]. Figure 1.9 shows the apparatus used by Cerletti and Bini in their first ECT experience.

ECT fundamentally altered the management of mental illness and gave birth to the development of numerous electrostimulation instruments in Europe and the USA [80, 81]. The popularity of ECT greatly decreased in the 1960s and 1970s, due to the use of more effective neuroleptics and as a result of a strong anti-ECT movement [82]. However, ECT has recently come back into use for the treatment of serious cases of patients with depression present with psychological and somatic symptoms [83].

It should be noted that in the 1950s in Italy, electroconvulsive therapy coexisted with prolonged transcranial low-intensity electrical stimulation as an alternative method deriving from the electroshock therapy of Cerletti and Bini [84, 85]. For example, Corradini (1950) reported the analysis of the prolonged transcranial electrical stimulation at a low tension on 52 patients affected by psychosis or depression.

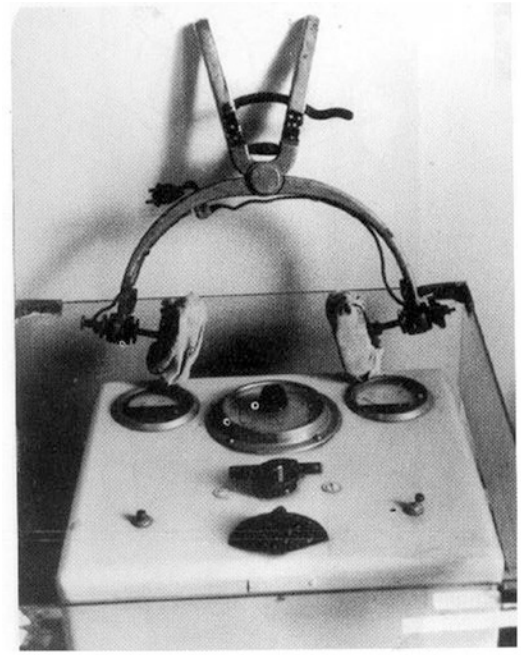

Fig. 1.9 Apparatus used by Cerletti and Bini in their first electroconvulsive experience

Clearly, transcranial direct current stimulation (i.e., tDCS) differs fundamentally from electroconvulsive therapy (ECT). While ECT consists of inducing convulsive activity with alternating current, tDCS induces modulation of the brain function with continuous current to produce physiological changes and spontaneously influence neuronal activity without seizures [86]. The current used in tDCS (typically 0.25–2 mA) is also of a much lower intensity than that used in modern ECT (800–900 mA). Although tDCS can barely excite silent cells, it is very effective in changing spontaneous cell firing [86]. Evidence suggests that unlike ECT, tDCS does not cause memory disturbances or loss of consciousness, nor does the patient need to be sedated or given muscle relaxants [87].

1.3 The Reappraisal of Transcranial Direct Current Stimulation (tDCS) from 1960 Onward

In the 1960s, some studies on animals confirmed that anodal tDCS increases the spontaneous firing rate and excitability of cortical neurons by depolarizing the membrane, whereas cathodal tDCS leads to hyperpolarization of neuronal membranes and thus invokes decrease of the neuronal firing rate and excitability [88–90].

For example, Bindman et al. [89] showed that currents as low as 0.25 μA/mm^2 applied to the exposed pia via surface electrodes (3 μA from 12 mm^2 saline cup on exposed pia surface) could influence spontaneous activity and the evoked response of neurons for hours following just minutes of stimulation in rat preparations (see Fig. 1.10).

Purpura and McMurtry [90] showed similar effects in cat preparations for currents as low as 20 μA/mm^2 from cortical surface wick electrodes ranging in area from 10 to 20 mm^2. These scientists showed that currents, at magnitudes much lower than those necessary for the initiation of an action potential, could still lead to alterations in the level of neural excitability.

In the 1960s, more systematic studies in normal and clinical subjects with tDCS were performed. For example, Lippold and Readfearn [91], using very slow scalp tDCS up to 50–500 μA in 32 normal subjects, showed that scalp anodal currents stimulation induced an increase in alertness, mood, and motor activity, whereas cathodal currents produced quietness and apathy. In a second study, with depressed patients, Redfearn, Lippold, and Costain (1964) [92] demonstrated that direct anodal scalp current improved mood in more than half of their 26 patients. Herjanic and Moss-Herjanic [93] reported short but encouraging results in the use of tDCS on schizophrenic patients. These results were confirmed in further double-blind studies (e.g., [94–96]), but other studies failed to report significant effects in psychiatric patients [97–99].

On the whole, these studies showed a clinical variability due probably to inaccurate and heterogeneous diagnostic criteria in recruiting psychiatric patients and in specifying the position of the electrodes. The latter is important as the earlier experiments were carried out using either one electrode over the scalp and another elsewhere on the body (often the knee), rather than both electrodes positioned on the scalp. This change in technique characterized the application of the method in neuropsychiatric disorders [100]. These incongruent results and the subsequent progress made in treating psychiatric disorders with drugs led to the abandonment of the tDCS [87].

However, by the end of the 1990s, more precise and systematic observations were made about the efficacy of polarization on humans [101]. Priori and colleagues tested in normal subjects the functional effects of very weak DC (0.5 mA, duration <7 s) on the motor areas of the cerebral cortex, examining the modification in motor evoked potentials (MEPs) elicited in the small hand muscle of subjects by TMS. Four

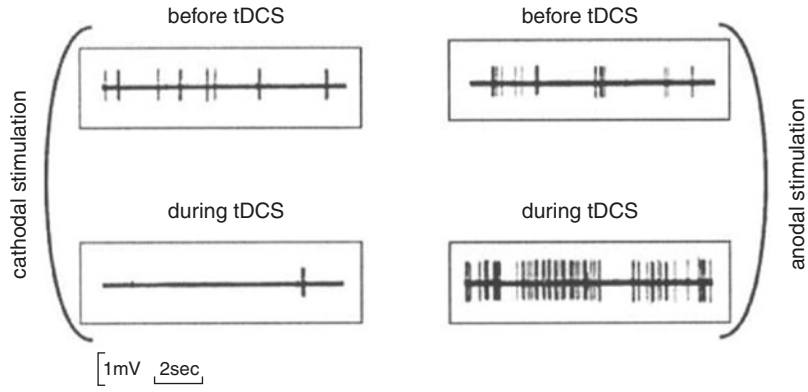

Fig. 1.10 The physiological mechanisms of anodal and cathodal tDCS on spike activity in rat preparation. (Modified by Bindman et al. [89])

experiments were performed polarizing the cortex by using two electrodes placed on the scalp, one over the left motor cortex (7 cm lateral to vertex) and the other under the chin. These findings provided direct evidence that a very low electric field crosses the skull and may influence brain excitability (see Fig. 1.11).

The mechanism could be explained in two ways: one is that scalp anodal tDCS hyperpolarizes superficial excitatory interneurons in cortical motor areas. Another explanation is that anodal scalp tDCS depolarizes superficial inhibitory interneurons (facilitating activity) in the cortex.

Shortly after, Nitsche and Paulus established that prolonged (minutes) tDCS could produce lasting and polarity-specific changes in cortical excitability [102]. Cathodic polarization applied to the motor cortex can induce a considerable reduction in cortical excitability, while anodic polarization increases excitability [102]. There was a full re-evaluation of the use of electrical current stimulation of the brain with neurophysiological and therapeutic objectives.

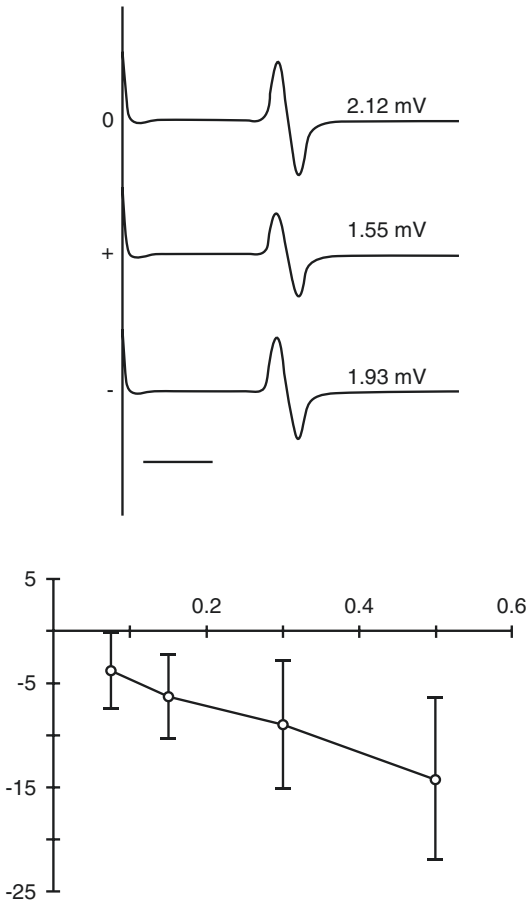

Fig. 1.11 The effect of weak scalp tDCS (0.3 mA, 7 s) on the motor potential evoked by transcranial magnetic brain stimulation in a subject in the study of Priori et al. [101]. In the upper panel: 0, control condition; +, anodal condition polarization; −, cathodal conditioning polarization

Within the last decades, tDCS has seen a wide range of potential applications and can be used to explore basic aspects of neurosciences [103–107].

In 2000s, pilot clinical studies were performed for indications spanning depression [108], pain [109], epilepsy [110], spinal and cerebellar stimulation [111], and a broad range of neuropsychiatric [112] and neuropsychological disorders [113–115]. tDCS has also been explored for rehabilitation including after stroke [116]. Moreover, due to the perceived safety of tDCS, it was initially validated for neurophysiological changes in healthy subjects and continues to be investigated in healthy individuals for changes in behavior and cognitive performance [117, 118].

1.4 Concluding Remarks

The first clinical experience with electric fish, and a four-century-long history of electrotherapeutic applications, has led to the modern use of tDCS. This history includes various degrees of success and the therapeutic value of electricity in the treatment of mental disorders followed by a cyclical course throughout the centuries. Clinicians approached transcranial electric stimulation with great enthusiasm in the eighteenth century, only to abandon it at the end of the nineteenth century, when they failed to produce consistent results, raising doubts about the efficacy of electrotherapy [67, 119]. In the twentieth century, several experimental studies clearly demonstrated using motor evoked potentials that tDCS resulted in changes in motor-cortical excitability. Recently, with the adoption of more adequate protocols of experimentation, the ability of tDCS to treat a number of clinical conditions such as affective disorders, chronic pain

conditions, and post-lesional cognitive disorders has been demonstrated.

As pointed out by Bikson et al. [120], controlled investigation involving tDCS for treating psychiatric or cognitive disorders should not be compared with improvised devices or practices that apply uncontrolled electricity to the brain without reference to established protocols.

Today, tDCS is recognized as an effective technique in the application of direct current to the scalp, usually delivered by a small battery-driven stimulator, by attaching electrodes of different polarities to the skin and emitting a constant current. tDCS is an easy, noninvasive technique which causes minimal disturbance to the subject and is able to produce prolonged variations of cerebral excitability while influencing neuronal plasticity. The simplicity and economics of the technique, the minor nature of adverse effects, and the long-lasting results render tDCS a promising rehabilitative procedure.

References

1. Kellaway P. The part played by electric fish in the early history of bioelectricity and electrotherapy. Bull Hist Med. 1946;20:112–37.
2. Brazier MAB. The emergence of electrophysiology as an aid to neurology. In: Aminoff MJL, editor. Electrodiagnosis in clinical neurology. 1st ed. London: Churchill Livingstone Inc.; 1980.
3. Finger S. Origins of neurosciences. A history of explorations into brain function. 1st ed. New York: Oxford University Press; 1994.
4. Finger S, Piccolino M. The shocking history of electric fishes: from ancient epochs to the birth of modern neurophysiology. New York: Oxford University Press; 2011.
5. Debru A. The power of torpedo fish as a pathological model to the understanding of nervous transmission in Antiquity. C R Biol. 2006;329:298–302.
6. Scribonii Largi. Compositiones medicae. Ioannes Rhodius recensuit, notis illustravit, lexicon Scribonianum adjecit. Patavii: Typis Pauli Frambotti Bibliopolae; 1655.
7. Benedetti E. Scribonio Largo e l'elettroshock. Minerva Med. 1948;39:426–39.
8. Rocchietta S. Un formulario dell'antica Roma: il "De compositione medicamentorum" di Scribonio Largo. Minerva Med. 1974;65:735–7.
9. Maggioni F, Mainardi F, Dainese F, Campagnaro A, Zanchin G. Terapie per la cefalea in Scribonio Largo. Neurol Sci. 2005;26:S431–3.
10. Moller P. Electric fishes: history and behavior. London: Chapman and Hall; 1995.
11. Pedacii Dioscoridis Anazarbei, De materia medica libri sex. Lugduni: Apud [et per] Balthazarem Arnolletum; 1553.
12. Stillings D. A survey of the history of electrical stimulation for pain to 1900. Med Instrum. 1975;9:255–9.
13. Schwalb JM, Hamani C. The history and future of deep brain stimulation. Neurotherapeutics. 2008;5:3–13.
14. McWhirter L, Carson A, Stone J. The body electric: a long view of electrical therapy for functional neurological disorders. Brain. 2015;138:1113–20.
15. Kadosh RC, Elliott P. Neuroscience: brain stimulation has a long history. Nature. 2013;500:529.
16. Elliott P. Electricity and the brain: an historical evaluation. In: Kadosh RC, editor. The stimulated brain: cognitive enhancement using non-invasive brain stimulation. London: Academic Press; 2014.
17. Licht S. History of electrotherapy. 3rd ed. Baltimore: Williams & Wilkins; 1983.
18. Le Roy C. Ou l'on rend compte de quelques tentatives que l'on a faites pour guerir plusieurs maladies par l'electricite. Memoires de Mathematique et de Physique tires des registres de cette Academie Histoire de l'Academie Royale des Sci avec les. 1755;60:87–95.
19. Lovett R. The subtil medium prov'd: or, that wonderful power of nature, so long ago conjectur'd by the most ancient and remarkable philosophers, which they call'd sometimes æther, but oftener elementary fire, verify'd. shewing, that all the distinguishing and essential qualities ascrib'd to æther by them, and the most eminent modern philosophers, are to be found in electrical fire, and that too in the utmost degree of perfection. giving an account not only of the progress and several gradations of electricity …. J. Hinton, in Newgate-Street, W. Sandby, in Fleet-Street, and R. Lovett, at Worcester. 1756.
20. Stainbrook E. The use of electricity in psychiatry treatment during the nineteenth century. Bull Hist Med. 1948;22:156–77.
21. Wesley J. The desideratum; or, electricity made plain and useful – by a lover of mankind, and of common sense. London: Balliére, Tindall & Cox; 1759.
22. Cavallo T. A complete treatise of electricity in theory and practice: with original experiments. London: Printed for Edward and Charles Dilly; 1777.
23. Cavallo T. An essay on the theory and practice of medical electricity. London: Printed for the Author; 1780.
24. Finger S, Zaromb F. Benjamin Franklin and shock-induced amnesia. Am Psychol. 2006;61:240–8.
25. Galvani L. De viribus electricitatis in motu musculari Commentarius cum Joannis Aldini dissertatione et notis. Accesserunt epistolae ad animalis electricitatis theoriam pertinentes. Mutinae, apund Societatem typographicam. 1792.

26. Volta A. On the electricity excited by the mere contact of conducting substances of different species. Philos Trans R Soc Lond. 1800;90:403–31.
27. Goldensohn ES. Animal electricity from Bologna to Boston. Electroencephalogr Clin Neurophysiol. 1998;106:94–100.
28. Piccolino M. The bicentennial of the Voltaic battery (1800–2000): the artificial electric organic. Trends Neurosci. 2000;23:147–51.
29. Piccolino M. Luigi Galvani and animal electricity: two centuries after the foundation of electrophysiology. Trends Neurosci. 1997;20:443–8.
30. Benassi E. Spunti di elettropatologia e di elettroterapia nell'opera di Luigi Galvani. Atti Mem Accad Stor. 1942;8:116–25.
31. Benassi E. Qualche documento sulla pratica delle cure elettriche agli albori della galvanoterapia. Atti Mem Accad Stor. 1950;16:92–101.
32. Bourguignon A. La de'couverte par Aldini (1804) des effets the'rapeutiquesde l'e'lectrochoc sur la me'lancolie. Paris: Masson; 1964.
33. Parent A. Giovanni Aldini: from animal electricity to human brain stimulation. Can J Neurol Sci. 2004;31:576–84.
34. Aldini G. Essai théorique et expérimental sur le Galvanisme. de Fournier Fils Paris. 1804.
35. Lolas F. Brain polarization: behavioural and therapeutic effects. Biol Psychiatry. 1977;12:37–47.
36. Augustin FL. Vom Galvanism. Berlin. 1801.
37. Bischoff C. Commentatio de Usu galvanismi. Jena. 1801.
38. Grappengiesser C. Observations and experiments, made with the view of employing galvanism for the cure of certain diseases. Lond Med Phys J. 1802;41:250–9.
39. Harms E. The origin and early history of electrotheraphy and electroshock. Am J Psychiatry. 1954–1955;111:932–3.
40. Fodstad H, Hariz M. Electricity in the treatment of nervous system disease. Acta Neurochir Suppl. 2007;97:11–9.
41. Charcot JM. Phénomènes produits par l'application sur la voûte du crane du courant galvanique, pendant la période léthargique de l'hypnotisme chez les hystériques. Prog Med. 1882;10(20–21):63–4.
42. Babinski J. Sur un cas de mélanconie guéri à la suite immédiate d'un accès provoqué de vertige voltaique. Soc Neurol. 1903;7:mai.
43. Matteucci C. Note sur un phénomène très curieux produit sur un malade affecté de paralysie, par un courant électrique très faible. Ann Méd Psychol. 1843;2:128.
44. Engelskjön C. Die ungleichartige therapeutische Wirkungsweise der beiden elektrischen Stromesarten und die elektrodiagnostische Gesichtsfelduntersuchung. (Eine schematische Uebersicht). Arch Psychiatr Nervenkr. 1884;15:136–9.
45. Engelskjön C. Die ungleichartige therapeutische Wirkungsweise der beiden elektrischen Stromesarten und die elektrodiagnostische Gesichtsfelduntersuchung. Arch Psychiatr Nervenkr. 1884;15:305–58.
46. Koehler PJ, Boes CJ. A history of non-drug treatment in headache, particularly migrane. Brain. 2010;133:2489–500.
47. Althaus J. On the therapeutical use of electricity by induction. Lancet. 1857;2(162–164):187–90.
48. Arndt R. Die electricität in der psychiatrie. Arch Psichiatr Nervenkr. 1870;2:259–337.
49. Arndt R. Zur galvanischen Behandlung der Psychosen. Z Allz Psychiatr. 1872;28:425–65.
50. Arndt R. Zur Electrotherapie der psychischen Krankheiten. Z Allz Psychiatr. 1878;34:483–574.
51. Beard G. The treatment of insanity by electricity. J Ment Sci. 1873–1874;19:355–60.
52. Berlie MA. Du traitement de l'alienation mentale dans les asiles d'Angleterre. Ann Méd Psychol. 1849;5:224–9.
53. Berkwitz N. Faradic shock treatment of the "functional" psychoses. Lancet. 1939;59:351–5.
54. Eulenberg A. Lehrbuch der functionellen Nervenkrankheiten auf physiologischen. Berlin: Verlag Von August Hirschwald; 1871.
55. Frommhold K. Die Migraine und ihre Heilung durch Elektricitat. Pesth: Heckenast; 1868.
56. Gruenberg K. High frequency electric current in the treatment of alcoholic hallucinosis. Am Rev Sov Med. 1944;1:544–7.
57. Newth AH. The galvanic current applied in the treatment of insanity. J Ment Sci. 1873–1874;19:79–86.
58. Newth AH. The electro-neural pathology of insanity. J Ment Sci. 1878;24:76–82.
59. Newth AH. The value of electricity in the treatment of insanity. J Ment Sci. 1884;30:354–9.
60. Robertson A. Case of insanity of seven years' duration: treatment by electricity. J Ment Sci. 1884;30:54–7.
61. Rorie J. On the treatment of hallucinations by electrization. J Ment Sci. 1862;8:363–5.
62. Schivardi P. Delirio melancolico guarito coll'elettricità, coadiuvata dalla idroterapia. Arch Ital Mal Nerv. 1868;3:325–7.
63. Severi D. Contribuzione alla cura dell'emicrania coll'elettricità. Il Galvani. 1874;2:398–402.
64. Swolfs O. Du Traitement Électrothérapeutique en Neuropathologie. J Neurol Hypnol. 1897;20:422.
65. Teilleux I. De l'application de l'électricité au traitment de l'aliénation mentale. Ann Méd-Psychol. 1859;15:353.
66. Wiglesworth J. On the use of galvanism in the treatment of certain forms of insanity. J Ment Sci. 1887;33:385–95.
67. Beveridge AW, Renvoize EB. Electricity: a history of its use in the treatment of mental ilness in Britain during the second half of the 19th century. Br J Psychiatry. 1988;153:157–62.
68. Steinberg H. A pioneer work on electric brain stimulation in psychotic patients. Rudolf Gottfried Arndt and his 1870s studies. Brain Stimul. 2013;6:477–81.

69. Ottoni G. L'elettricità nell'afasia. Il Galvani. 1873;1:249–67.
70. Ardnt R. Electricity. In: Tuke DH, editor. Dictionary of psychological medicine. London: J & A Churchill; 1892.
71. Steinberg H. Transcranial direct current stimulation (tDCS) has a history reaching back to the 19th century. Psychol Med. 2013;43:669–71.
72. Tigges W. Behandlung der Psychosen mit Electricität. I. *Allgeimeines*. Allg Z Psychiatr. 1883;39:697–738.
73. Tigges W. Behandlung der Psychosen mit Electricität. II. Specielles. *Allgeimeines*. Allg Z Psychiatr. 1885;41:477–525.
74. Leduc S. Production de sommeil et anesthésie generale et locale par courant intermittent de bas voltage. Arch Electron Med. 1902;10:617–21.
75. Leduc S, Rouxeau A. L'inhibition respiratoire par les courants intermittents de basse tension. C R Séan Biol Paris. 1903;55:897–9.
76. Dallongeville M. L'appareil original de Stéphane Leduc et les appareils électroniques modernes produisant des courants rectangulaires. J Radiol Arch Electron Med. 1956;37:627–8.
77. Appell CP. Effect of electrosleep: review of research. Goteborg Psychol Rep. 1972;2:1–24.
78. Tatu L, Bogousslavsky J, Moulin T, Chopard JL. The "torpillage" neurologists of World War I: electric therapy to send hysterics back to the front. Neurology. 2010;75:279–83.
79. Cerletti U, Bini L. L'Elettroschok. Arch Gen Neurol Psichiatr Psicoanal. 1938;19:226.
80. Delmas-Marsalet P. Èlectro-choc et thérapeutiques nouvelles en neuro-psychiatrie. Paris Èditeurs: J.-B. Baillière et Fils. Hauefeuille; 1946.
81. Pulver SE. The first electroconvulsive treatment given in the United States. Am J Psychiatry. 1961;117:845–6.
82. Passione R. Italian psychiatry in an international context: Ugo Cerletti and the case of electroshock. Hist Psychiatry. 2004;15:83–104.
83. Gilman SL. Electrotherapy and mental illness: then and now. Hist Psychiatry. 2008;19:339–57.
84. Riboli B. Elettroterapia transcerebrale a bassa intensità. Rass Studi Psichiatr. 1950;34:742–9.
85. Corradini E. L'elettroshock a bassa intensità. Rass Studi Psichiatr. 1950;18:22–39.
86. Terzuolo CA, Bullock TH. Measurement of imposed voltage gradient adequate to modulate neuronal firing. Proc Natl Acad Sci U S A. 1956;42:687–94.
87. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol. 2003;114:589–95.
88. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal aactivity. Exp Neurol. 1962;5:436–52.
89. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
90. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
91. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct current through the human brain. Br J Psychiatry. 1964;110:768–72.
92. Redfearn JW, Lippold OC, Costain R. A preliminary account of the clinical effects of polarizing the brain in certain paychiatric disorders. Br J Psychiatry. 1964;110:773–85.
93. Herjanic M, Moss-Herjanic B. Clinical report on a new therapeutic technique: polarization. Can Psychiatr Assoc J. 1967;12:423–4.
94. Costain R, Redfearn JW, Lippold OC. A controlled trial of the therapeutic effects of polarization of the brain in depressive ilness. Br J Psychiatry. 1964;110:786–99.
95. Ramsay JC, Schlagenhauf G. Treatment of depression with low voltage direct currents. South Med J. 1966;59:932–6.
96. Carney MW, Cashman MD, Sheffield BF. Polarization in depression. Br J Psychiatry. 1970;117:474–5.
97. Dawson J, Montagu JD. Small direct currents and the human brain. Br J Psychiatry. 1965;111:368.
98. Lifshitz K, Harper P. A trial of transcranial polarization in chronic schizophrenics. Br J Psychiatry. 1968;114:635–7.
99. Arfai E, Theano G, Montagu JD, Robin A. A controlled study of polarization in depression. Br J Psychiatry. 1970;116:433–4.
100. Guleyupoglu B, Schestatsky P, Edwards D, Fregni F, Bikson M. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J Neurosci Methods. 2013;15:297–311.
101. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9:2257–60.
102. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527:633–9.
103. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. NeuroImage. 2014;15:895–908.
104. Brunoni AR, Fregni F, Pagano RL. Translational research in transcranial direct current stimulation (tDCS): a systematic review of studies in animals. Rev Neurosci. 2011;22:471–81.
105. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Marabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175–95.
106. Pelletier SJ, Cicchetti F. Cellular and molecular mechanisms of action of transcranial direct

current stimulation: evidence from in vitro and in vivo models. Int J Neuropsychopharmacol. 2015;18(2):pyu047. https://doi.org/10.1093/ijnp/pyu047.
107. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev. 2013;37:1702–12.
108. Meron D, Hedger N, Garner M, Baldwin DS. Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. Neurosci Biobehav Rev. 2015;57:46–62.
109. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev. 2014;4:CD003208.
110. San-Juan D, Morales-Quezada L, Orozco Garduño AJ, Alonso-Vanegas M, González-Aragón MF, Espinoza López DA, et al. Transcranial direct current stimulation in epilepsy. Brain Stimul. 2015;8:455–64.
111. Priori A, Ciocca M, Parazzini M, Vergari M, Ferrucci R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists. J Physiol. 2014;15:3345–69.
112. Tortella G, Casati R, Aparicio LV, Mantovani A, Senço N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry. 2015;5:88–102.
113. Shin YI, Foerster Á, Nitsche MA. Transcranial direct current stimulation (tDCS) – application in neuropsychology. Neuropsychologia. 2015;69:154–75.
114. Summers JJ, Kang N, Cauraugh JH. Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis. Ageing Res Rev. 2016;25:42–54.
115. Utz KS, Dimova V, Oppenländer K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology – a review of current data and future implications. Neuropsychologia. 2010;48:2789–810.
116. Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematicreview and meta-analysis. J Neurol Neurosurg Psychiatry. 2016;87:345–55. https://doi.org/10.1136/jnnp-2015-311242.
117. Tremblay S, Lepage JF, Latulipe-Loiselle A, Fregni F, Pascual-Leone A, Théoret H. The uncertain outcome of prefrontal tDCS. Brain Stimul. 2014;7:773–83.
118. Filmer HL, Dux PE, Mattingley JB. Applications of transcranial direct current stimulation for understanding brain function. Trends Neurosci. 2014;37:742–53.
119. Colwell H. An essay on the history of electrotherapy and diagnosis. London: Heinemann; 1922.
120. Bikson M, Bestmann S, Edwards D. Neuroscience: transcranial devices are not playthings. Nature. 2013;501:167. https://doi.org/10.1038/50ss67b.

2 Basic Mechanisms of Transcranial Alternating Current and Random Noise Stimulation

Andrea Antal, Nir Grossman, and Walter Paulus

2.1 Introduction

Transcranial alternating current stimulation (tACS) non-invasively induces oscillating electric fields in the brain by applying currents that periodically reverse direction via scalp electrodes. The currents are typically generated with current-guided (rather than voltage-controlled) electronic circuits to ensure a constant current flow independently of individual skin and skull resistances. A constant electric current flow is ensured by adapting the voltage to the resistance, according to Ohm's law. The narrow definition of tACS typically encompasses sinusoidally oscillating current without DC offset at a single frequency [10, 13]. Variations may include DC offset [51], multiple frequencies such as theta gamma coupling [3] or multiple electrodes [4, 5], offering distinct spatiotemporal patterns of cerebral electric fields. When averaged over time, the mean membrane potential is not affected by tACS without DC offset (but see the Gildemeister effect at higher frequencies in the kilohertz range; [29]). On short time scales, the depolarizing or hyperpolarizing effects are assumed to be strong enough to modify neuronal activity and to induce immediate effects [27].

tACS is typically applied in an open-loop fashion without feedback. A closed-loop control of the stimulation parameters may offer neuromodulatory benefits, for example, on memory performance with sleep spindles as input signal [50]. The electric fields are strongest beneath the electrodes; depending on the location of the second electrode, deeper brain structures can be targeted [38].

The modern use of sinusoidal tACS without DC offset started with Antal and colleagues [10], being followed by many other studies (e.g. [14, 27, 30, 42, 44, 45, 49]). Most of these investigations used tACS frequencies in the physiologic EEG-detectable range (0.5–70 Hz), especially when the intended outcome is to interact or influence oscillations in the EEG range [34, 35, 40, 52, 64].

Magnitude of the Electric Fields That Are Generated in the Brain via tACS Using tACS the current density is small, with a few milliampere current via a few square centimetre electrodes [55]; they result in weak sub-threshold cerebral electric fields of ~1 mV/mm and thereby modulate spontaneous firing rates [48], but cannot directly evoke action potentials such as in electroconvulsive therapy (ECT). The latter with intensities of several hundred milliampere is only used under anaesthesia [11].

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Finite element method (FEM) modelling of the electric fields has shown a significant shunting of up ~90% through the scalp depending on electrode distance, due to the high conductivity of the skin and low conductivity of the skull [37]. Recent studies have measured the intracranial electric fields in primates [58], human cadaver [73], and in epilepsy patients with intracranial electrodes [39, 58]. Collectively, these studies have shown that the cerebral electric field induced by tACS with typical current amplitude and electrode size ranges between 0.2 and 1 mV/mm.

Classical surface EEG recordings document oscillations up to 100 Hz; higher frequencies such as high ripple oscillations in epilepsy patients need to be recorded with invasive electrodes. Here, it is frequently erroneously assumed that bone impedance increases with increasing frequency. Although it is frequently discussed, it seems that bone impedance does not change substantially in these frequency ranges [12, 70]. Accordingly, tACS in the kilohertz frequency range can modulate cortical excitability [19].

2.2 Neurophysiological Effects

Several animal studies have investigated the neurophysiological effect of tACS on single cell activity (e.g. [23, 26, 28, 47, 59, 62, 63]). Collectively, these studies have shown that tACS can induce alternating electric fields of 0.5–1 mV/mm that result in a small periodic sub-threshold membrane depolarization in Purkinje cells as it was observed in 1988 [21]. Ozen and colleagues applied tACS via stainless steel wires to the skull of anesthetized rats and simultaneously recorded intracranial activity [59]. They found that tACS at a frequency similar to the endogenous cortical slow oscillations (i.e. 0.8–1.7 Hz) efficiently entrains the neural activity across the cortex with a threshold of approximately 1 mV/mm. Reato and colleagues tested tACS in rat slices [63]. They applied electrical stimulation to hippocampal slices and also simulated the effect on the neural network, finding entrainment with a threshold of 0.2 mV/mm. Fröhlich and McCormick used tACS in cortical slices of ferrets [26] finding an entrainment threshold of 0.5 mV/mm.

The amplitude of the membrane polarization drops at high tACS frequencies due to the capacitive low-pass filtering property of the membrane. For example, Deans and colleagues [23] found a coupling constant of only 0.05 mV per mV/mm when tACS was applied at 100 Hz. In this case, a cerebral field of 1 mV/mm will polarize a neuron by only 0.05 mV, which is potentially below the noise level. The depolarization of a single cell induced by the weak electric fields may be amplified by the synaptic connectivity across the cells [26, 63].

2.3 Evidence in Humans

What Is the Neurophysiological Evidence of tACS in Humans? In humans, neural activity can be measured non-invasively using electroencephalography (EEG) or magnetoencephalography (MEG). For example, in the first tACS-EEG study, an enhancement of the EEG alpha band amplitude was seen at the posterior part of the brain after 10 Hz tACS [34] with after-effects for 30 min after 10 min of stimulation [56]. In addition, Voss and colleagues [74] showed that 25 and 40 Hz tACS during sleep can increase oscillation power at that frequency range and lead to lucid dreaming. Nevertheless, the strong artefact that is induced by the tACS, renders EEG and MEG recording during stimulation difficult to interpret. Some studies suggested that the stimulation artefact can be mitigated using spatial filtering [44] away from the stimulation sites [57].

More often the effect of tACS is measured after the end of the stimulation. The after-effect of the stimulation was suggested to be mechanistically linked to the 'Ca^{2+} increase-hypothesis', with a small increase of intracellular Ca^{2+} inducing long-term depression (LTD) and a large increase to long-term potentiation (LTP) [33]. A support of the role of LTP/LTD was presented by Moliadze and colleagues who showed that 140 Hz tACS at 0.4 mA induced LTD but at 1 mA induced LTP [55, 77].

The change in neural activity during tACS can be measured indirectly using blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI). It was shown that

tACS applied at the individual alpha frequency reduced the amplitude of the BOLD response to visual stimuli [76], but 10 Hz tACS (i.e. not at the individual alpha frequency) showed an effect on BOLD after the end of the stimulation but not during the simulation [2]. Cabral-Calderin and colleagues indicated that the effect of tACS on BOLD signal depends on the tACS frequency. The effect on BOLD due to 10 Hz tACS (decreased BOLD) was opposite to the one due to 40 Hz tACS [17].

The magnitude of the neural entrainment depends on the tACS frequency and the frequency of the endogenous neural activity. In principle, stimulation at frequencies similar to the endogenous ones is expected to induce a stronger neural entrainment or required less current to achieve a given entrainment level, a mechanism explained by the Arnold tongue [67]. Nevertheless, tACS can induce effects on frequency bands that are different from the applied frequency due to the neural cross-frequency coupling property [3, 18, 41], and this effect can occur at remote locations due to neural connectivity.

2.4 Distinct tACS Variants

tACS with Multiple Electrodes/Sites The currents in tACS are typically applied via a bipolar electrode configuration; however, multi-site electrode configuration arranged in, for example, centre-surround geometry [22] can help to focus the generated fields and reduce extraneous induction of phosphenes due to current flowing via the retina [60, 69].

The currents in tACS can be also applied to two or more sites at a different phase (e.g. in-phase vs. anti-phase) via a tripolar (or quadrupolar) electrode configuration. Polanía and colleagues used this approach to show that in-phase tACS of the frontal and parietal sites at the theta frequency could improve working memory-matching reaction compared to sham while anti-phase tACS deteriorates the performance in that task [61]. In general, brain areas that are stimulated in-phase are expected to facilitate their communications with each other; for example, changing the inter-hemispheric phase-coherence in the gamma range via 40 Hz tACS has led to increased number of spontaneous perceptual reversals of ambiguous motion stimuli [16].

Random Noise Stimulation The application of random noise (or white noise), that is, a flat power density distribution across a broad band of frequencies, called transcranial random noise stimulation (or tRNS) was first proposed by Terney and colleagues to desynchronize pathological cortical rhythms [71]. Typical applications use a frequency range between 0.1 and 640 Hz (full spectrum) or 101 and 640 Hz (high-frequency stimulation). The lower boundary at 0.1 Hz was chosen to avoid DC effects, and the higher boundary was chosen according to the I-wave frequency or fast thalamic somatosensory evoked potential frequencies. The probability function of the stimulation follows a Gaussian or bell-shaped curve with zero mean and a variance, where 99% of all generated current levels are within the target amplitude. It was shown that tRNS with frequencies between 100 and 640 Hz can increase the excitability in the motor cortex [71].

It is still unclear if tRNS entrains resonance frequencies or works via stochastic mechanisms, via specific modulation of the excitatory-inhibitory balance in the brain or by an increase in synchronization by amplifying sub-threshold activity [9, 25, 71]. It was also suggested that tRNS might result in repetitive opening of Na^+ channels, as is observed in rat hippocampal slices during the application of pulsed AC stimulation [68]. In humans, in a pilot study, the Na^+ channel blocker carbamazepine showed a tendency towards decreasing the size of MEP amplitude after the motor cortex stimulation [20].

tACS with DC Offset The tACS currents are typically alternated in a symmetrical biphasic fashion, but it can be applied as well with a DC offset [13, 24, 31, 51]. Of course, as with any other technique, stimulation can be delivered intermittently (e.g. [24]; 5 intervals with 1 min gap).

tACS with 3D Focality Interferential non-invasive strategies for ACS (e.g. temporal interference – tACS: TI-tACS) and intersectional strategies for transcranial pulsed stimulation (ISPS) were recently introduced with the aim to enhance the spatiotemporal precision and penetrability of electrical stimulation and reach deeper brain areas [32, 73].

Transcranial application of two electrically isolated currents at kilohertz frequencies can temporally interfere (TI) deep in the brain to create an envelope amplitude that changes periodically at a slow difference frequency, for example 10 Hz [32]. In the mouse, TI-tACS can recruit neural activity selectively in deeper brain structure, that is, the hippocampus, without recruiting neurons of the overlying cortex. In addition, the stimulation locus of TI-tACS can be steered by simply changing the current ratio without physically moving the electrodes, mapping different regions of the motor cortex.

Time-shifted multiple short pulses of currents via different pairs of electrodes intersect in the brain. This intersectional short pulse stimulation (ISPS) can be performed with pulses of 2.5 or 10 μs duration with 5 or 50 μs inter-pulse interval [73]. By spatiotemporally rotating stimulation, deeper areas in rodents were reached. Application of ISPS in healthy human subjects modulated the amplitude of alpha activity in the visual cortex, as shown by simultaneously recorded EEG.

2.5 Clinical Applications

tACS has the potential to normalize abnormal oscillatory activity in the human brain; nevertheless, the number of clinical studies applying this kind of neuromodulatory approach is so far limited as compared to tDCS. The most frequently treated conditions are tinnitus (five tACS/tRNS studies), depression and schizophrenia (four studies).

Tinnitus has been attributed to reduced activity in the alpha range in the auditory cortex. For the reduction of the symptoms of tinnitus, it has been shown that low-frequency tRNS (0.1–100 Hz) was more effective than either tDCS or, interestingly, tACS using the individual alpha frequency [72]. Another study reported a significantly more pronounced reduction in loudness and distress in pure tone tinnitus compared to narrow band noise tinnitus when high-frequency tRNS was applied [43]. Based on these results, tRNS over the auditory cortex is a promising treatment option for different types of tinnitus; nevertheless, a clear mechanistic explanation for the different results obtained with different types of tRNS does still not exist [53].

Similarly, tACS was able to modify network oscillations in schizophrenia [1] and in patients with depression [6]. In a recent randomized double-blind, sham-controlled clinical trial [1], schizophrenia patients with auditory hallucinations received twice-daily 10 Hz-tACS for 5 days. After treatment, clinical improvement of auditory hallucinations correlated with enhancement of alpha oscillations. In another study [6], a significant reduction in alpha power over the left frontal regions was also found after the completion of for weeks 10 Hz-tACS in depression patients. However, concerning the clinical improvement, there was no difference between treatment conditions (10 Hz-tACS, 40 Hz-tACS, sham). The exact underlying mechanism of this effect has not yet been determined. Although the immediate after-effect of tACS may be enhancement in alpha power, repeated application of tACS may lead to a resetting of oscillators, potentially through homeostatic mechanisms that can result in a decrease in alpha power.

tACS might be a treatment option for patients suffering from tremor in Parkinson's disease (PD). Oscillatory activity, originating from the globus pallidus internus, is increased in these patients. Brittain and coworkers [15] applied tACS over the motor cortex in patients diagnosed with tremor-dominant PD. tACS was most effective at the individual tremor frequency for inducing cortical phase cancellation, presumably due to suppression of the resting tremor amplitude. This study used a closed-loop stimulation setup in which the tremor frequency was measured online and motor cortex stimulation parameters

were adjusted according to the measured activity. It was proposed that closed-loop individually adjusted stimulation can considerably surpass the efficacy as compared to open-loop approaches. Krause and colleagues [46] studied the effects of 10 and 20 Hz (without closed-loop) as well as sham tACS in PD patients and healthy controls. The application of 20 Hz tACS reduced the cortico-muscular coherence amplitude in the beta band upon isometric contraction during fast finger tapping in PD patients, but not in healthy control subjects. These results suggest that tACS could probably entrain cortical oscillations in PD patients.

Repetitive transorbital alternating current stimulation (rtACS) as a tool for visual rehabilitation also demonstrated promising results (for a recent review, see [66]). During this intervention, electrodes are positioned near the eye aiming to inject current to the eyeball and thereby stimulating the retina (max 1.5 mA). rtACS has been proposed to induce vision restoration by activating residual visual functions in patients with damage to the retina, optic nerve or visual system [28].

With regard to tRNS, it was recently demonstrated that visual training coupled with brain stimulation can dramatically reduce the training period from months to weeks and lead to improvements in healthy subjects and chronic cortically blind patients, indicating the potential of this procedure to help restore damaged visual abilities [36].

tACS applied to the left prefrontal cortex (PFC) and left temporal cortex at a theta-band frequency was shown to improve performance in working-memory tasks of elderly people [65]. These results support the feasibility of utilizing tACS to prevent cognitive decline in this population.

2.6 Conclusion

The field of tACS-is still in its infancy. Since the first tACS study published 12 years ago [10], the method has been advanced in many ways; nevertheless, there are still concerns about several issues. To study the efficacy (e.g. causal role in cognition) of tACS of the human brain is particularly challenging, because a natural consequence of entrainment is that several parameters of the oscillation are manipulated at once. Furthermore, even when similar study designs are used, there are many possible sources for varying outcomes of experiments, based on the individual differences in the responsiveness to tACS.

The so-far insufficient duration of the aftereffects (except 140 Hz tACS) [54, 55] might be increased using longer stimulation duration or repetitive stimulation during days or weeks, or with optimized stimulation protocols, such as an intermittent short stimulation paradigm (8 s stimulation and 8 s pause) [75]. Many studies suggest that tACS can entrain cortical oscillations and can also induce short-term plasticity [48, 77].

Compared to tDCS, tACS and tRNS have a better blinding potential with less itching, tingling or burning sensations [7, 8]. Furthermore, the absence of a polarity effect (anode-cathode) as compared to tDCS provides an additional degree of freedom concerning the control of current flow directions. Retinal phosphene perception during tACS in a wide frequency range (6–70 Hz) is a side effect of specifically tACS.

Multi-electrode arrays together with electric field modelling allows for targeting more complex neuronal assemblies, such as the *coherence* between two or more brain regions. Control stimulation frequencies should be chosen outside of harmonics.

tACS has the potential to causally probe and treat oscillatory activity in the human brain. Development of hypothesis-driven approaches based on brain oscillations and behaviour is expected to provide another perspective that can bring major progress in the near future [5].

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References

1. Ahn S, Mellin JM, Alagapan S, Alexander ML, Gilmore JH, Jarskog LF, Fröhlich F. Targeting reduced neural oscillations in patients with schizo-

phrenia by transcranial alternating current stimulation. Neuroimage. 2019;186:126–36.
2. Alekseichuk I, Diers K, Paulus W, Antal A. Transcranial electrical stimulation of the occipital cortex during visual perception modifies the magnitude of BOLD activity: a combined tES-fMRI approach. Neuroimage. 2016;140:110–7.
3. Alekseichuk I, Turi Z, Amador de Lara G, Antal A, Paulus W. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr Biol. 2016;26:1513–21.
4. Alekseichuk I, Falchier AY, Linn G, Xu T, Milham MP, Schroeder CE, Opitz A. Electric field dynamics in the brain during multi-electrode transcranial electric stimulation. Nat Commun. 2019;10:2573.
5. Alekseichuk I, Turi Z, Veit S, Paulus W. Model-driven neuromodulation of the right posterior region promotes encoding of long-term memories. Brain Stimul. 2020;13:474–83.
6. Alexander ML, Alagapan S, Lugo CE, Mellin JM, Lustenberger C, Rubinow DR, Fröhlich F. Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). Transl Psychiatry. 2019;9:106–10.
7. Ambrus GG, Zimmer M, Kincses TZ, Harza I, Kovacs G, Paulus W, Antal A. The enhancement of cortical excitability over the DLPFC before and during training impairs categorization in the prototype distortion task. Neuropsychologia. 2011;49:1974–80.
8. Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol. 2011;122:803–7.
9. Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast. 2016;2016:3616807.
10. Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 2008;1:97–105.
11. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, CD MC, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, Ugawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128:1774–809.
12. Antonakakis M, Schrader S, Wollbrink A, Oostenveld R, Rampp S, Haueisen J, Wolters CH. The effect of stimulation type, head modeling, and combined EEG and MEG on the source reconstruction of the somatosensory P20/N20 component. Hum Brain Mapp. 2019;40:5011–28.
13. Bikson M, Ghodratitoostani I, Grabner RH, Hartwigsen G, Hirata A, Kirton A, Knotkova H, Krupitsky E, Marangolo P, Hanlon CA, Woods AJ, Gillick BT, Charvet L, Lamm C, Madeo G, Holczer A, Almeida J, Antal A, Ay MR, Baeken C, Blumberger DM, Campanella S, Camprodon JA, Christiansen L, Colleen L, Crinion J, Fitzgerald P, Gallimberti L, Ghobadi-Azbari P, Nakamura-Palacios EM, Potok W, Praharaj SK, Ruff CC, Schlaug G, Siebner HR, Stagg CJ, Thielscher A, Wenderoth N, Yuan TF, Zhang X, Ekhtiari H. Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. Brain Stimul. 2020;13(4):1124–49.
14. Bland NS, Sale MV. Current challenges: the ups and downs of tACS. Exp Brain Res. 2019;237:3071–88.
15. Brittain JS, Probert-Smith P, Aziz T, Brown P. Tremor suppression by rhythmic transcranial current stimulation. Curr Biol. 2013;23:436–40.
16. Cabral-Calderin Y, Schmidt-Samoa C, Wilke M. Rhythmic gamma stimulation affects bistable perception. J Cogn Neurosci. 2015;27:1298–307.
17. Cabral-Calderin Y, Anne Weinrich C, Schmidt-Samoa C, Poland E, Dechent P, Bähr M, Wilke M. Transcranial alternating current stimulation affects the BOLD signal in a frequency and task-dependent manner. Hum Brain Mapp. 2016;37:94–121.
18. Canolty R, Edwards E, Dalal S, Soltani M, Nagarajan S, Kirsch H, Berger MS, Barbaro RT, Knight R. High gamma power is phase-locked to theta oscillations in human neocortex. Sci Rep. 2006;313:1626–8.
19. Chaieb L, Antal A, Paulus W. Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor Neurol Neurosci. 2011;29:167–75.
20. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci. 2015;9:1–9.
21. Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. J Physiol. 1988;402:751–71.
22. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri -precise head model of transcranial DC stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2:201–7.
23. Deans JK, Powell AD, Jefferys JGR. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J Physiol. 2007;583:555–65.
24. Eggert T, Dorn H, Sauter C, Nitsche MA, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul. 2013;6:938–45.
25. Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist. 2017;23:109–23.

26. Fröhlich F, McCormick D. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67:129–43.
27. Fröhlich F, Sellers KK, Cordle AL. Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. Expert Rev Neurother. 2015;15:145–67.
28. Gall C, Schmidt S, Schittkowski MP, Antal A, Ambrus GG, Paulus W, Dannhauer M, Michalik R, Mante A, Bola M, Lux A, Kropf S, Brandt SA, Sabel BA. Alternating current stimulation for vision restoration after optic nerve damage: a randomized clinical trial. PLoS One. 2016;11:e0156134.
29. Gildemeister M, Koch H, Schindler B. Eine Vorrichtung zur Erzeugung sinusreiner Wechselströme für physiologische Zwecke. Pflügers Arch. 1944;247:360–5.
30. Grabner RH, Krenn J, Fink A, Arendasy M, Benedek M. Effects of alpha and gamma transcranial alternating current stimulation (tACS) on verbal creativity and intelligence test performance. Neuropsychologia. 2018;118:91–8.
31. Groppa S, Bergmann TO, Siems C, Mölle M, Marshall L, Siebner HR. Slow-oscillatory transcranial direct current stimulation can induce bidirectional shifts in motor cortical excitability in awake humans. Neuroscience. 2010;166:1219–25.
32. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, Cassara AM, Neufeld E, Kuster N, Tsai LH, Pascual-Leone A, Boyden ES. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169:1029–41.e1016.
33. Grundey J, Barlay J, Batsikadze G, Kuo MF, Paulus W, Nitsche M. Nicotine modulates human brain plasticity via calcium-dependent mechanisms. J Physiol. 2018;596:5429–41.
34. Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol. 2014;24:333–9.
35. Helfrich RF, Knepper H, Nolte G, Strüber D, Rach S, Herrmann CS, Schneider TR, Engel AK. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. 2014;12:e1002031.
36. Herpich F, Melnick MD, Agosta S, Huxlin KR, Tadin D, Battelli L. Boosting learning efficacy with noninvasive brain stimulation in intact and brain-damaged humans. J Neurosci. 2019;39:5551–61.
37. Holdefer RN, Sadleir R, Russell MJ. Predicted current densities in the brain during transcranial electrical stimulation. Clin Neurophysiol. 2006;117:1388–97.
38. Huang Y, Parra LC. Can transcranial electric stimulation with multiple electrodes reach deep targets? Brain Stimul. 2019;12:30–40.
39. Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, Bikson M, Doyle WK, Devinsky O, Parra LC. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. Elife. 2017;6:e18834.
40. Jaušovec N, Jaušovec K. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). Biol Psychol. 2014;96:42–7.
41. Jensen O, Colgin L. Cross-frequency coupling between neuronal oscillations. Trends Cogn Sci. 2007;11:267–9.
42. Jones KT, Arciniega H, Berryhill ME. Replacing tDCS with theta tACS provides selective, but not general WM benefits. Brain Res. 2019;1720:146324.
43. Joos K, De Ridder D, Vanneste S. The differential effect of low- versus high-frequency random noise stimulation in the treatment of tinnitus. Exp Brain Res. 2015;233:1433–40.
44. Kasten FH, Herrmann CS. Recovering brain dynamics during concurrent tACS-M/EEG: an overview of analysis approaches and their methodological and interpretational pitfalls. Brain Topogr. 2019;32(6):1013–19.
45. Ketz N, Jones AP, Bryant NB, Clark VP, Pilly PK. Closed-loop slow-wave tACS improves sleep-dependent long-term memory generalization by modulating endogenous oscillations. J Neurosci. 2018;38:7314–26.
46. Krause V, Wach C, Südmeyer M, Ferrea S, Schnitzler A, Pollok B. Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease. Front Hum Neurosci. 2013;7:928.
47. Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci U S A. 2019;116:5747–55.
48. Liu A, Voroslakos M, Kronberg G, Henin S, Krause MR, Huang Y, Opitz A, Mehta A, Pack CC, Krekelberg B, Berenyi A, Parra LC, Melloni L, Devinsky O, Buzsaki G. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9:5092.
49. Lorenz R, Simmons LE, Monti RP, Arthur JL, Limal S, Laakso I, Leech R, Violante IR. Efficiently searching through large tACS parameter spaces using closed-loop Bayesian optimization. Brain Stimul. 2019;12:1484–9.
50. Lustenberger C, Boyle MR, Alagapan S, Mellin JM, Vaughn BV, Fröhlich F. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr Biol. 2016;26:2127–36.
51. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444:610–3.
52. Mehta AR, Brittain JS, Brown P. The selective influence of rhythmic cortical versus cerebellar transcranial stimulation on human physiological tremor. J Neurosci. 2014;34:7501–8.
53. Mohsen S, Mahmoudian S, Talebian S, Pourbakht A. Multisite transcranial random noise stimulation (tRNS) modulates the distress network activity and oscillatory powers in subjects with chronic tinnitus. J Clin Neurosci. 2019;67:178–84.

54. Moliadze V, Antal A, Paulus W. Boosting brain excitability by transcranial high frequency stimulation in the ripple range. J Physiol. 2010;588:4891–904.
55. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul. 2012;5:505–11.
56. Neuling T, Rach S, Herrmann C. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci. 2013;7:161.
57. Neuling T, Ruhnau P, Fuscà M, Demarchi G, Herrmann CS, Weisz N. Neuroimage. Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. 2015;118:406–13.
58. Opitz A, Falchier A, Yan CG, Yeagle EM, Linn GS, Megevand P, Thielscher A, Deborah AR, Milham MP, Mehta AD, Schroeder CE. Spatiotemporal structure of intracranial electric fields induced by transcranial electric stimulation in humans and nonhuman primates. Sci Rep. 2016;6:31236.
59. Ozen S, Sirota A, Belluscio M, Anastassiou C, Stark E, Koch C. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30:11476–85.
60. Paulus W. On the difficulties of separating retinal from cortical origins of phosphenes when using transcranial alternating current stimulation (tACS). Clin Neurophysiol. 2010;121:987–91.
61. Polania R, Nitsche M, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012;22:1314–8.
62. Radman T, Su Y, An JH, Parra LC, Bikson M. Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. J Neurosci. 2007;27:3030–6.
63. Reato D, Rahman A, Biksn M, Parra L. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30:15067–79.
64. Reato D, Rahman A, Bikson M, Parra L. Effects of weak transcranial alternating current stimulation on brain activity – a review of known mechanisms from animal studies. Front Hum Neurosci. 2013;7:1–8.
65. Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci. 2019;22:820–7.
66. Sabel BA, Thut G, Haueisen J, Henrich-Noack P, Herrmann CS, Hunold A, Kammer T, Matteo B, Sergeeva EG, Waleszczyk W, Antal A. Vision modulation, plasticity and restoration using non-invasive brain stimulation – an IFCN sponsered review. Clin Neurophysiol. 2020;131:887–91.
67. Salchow C, Strohmeier D, Klee S, Jannek D, Schiecke K, Witte H, Nehorai A, Haueisen J. Rod driven frequency entrainment and resonance phenomena. Front Hum Neurosci. 2016;10:413–5.
68. Schoen I, Fromherz P. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak capacitive currents on a silicon chip. J Neurophysiol. 2008;100:346–57.
69. Schutter DJ, Hortensius R. Retinal origin of phosphenes to transcranial alternating current stimulation. Clin Neurophysiol. 2010;121:1080–4.
70. Tang C, Yo F, Cheng G, Gao D, Fu F, Yang G, Dong X. Correlation between structure and resistivity variations of the live human skull. IEEE Trans Biomed Eng. 2008;55:2286–92.
71. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28:14147–55.
72. Vanneste S, Fregni F, De Ridder D. Head-to-head comparison of transcranial random noise stimulation, transcranial AC stimulation, and transcranial DC stimulation for tinnitus. Front Psych. 2013;4:31–3.
73. Voroslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernandez-Ruiz A, Kozak G, Kincses ZT, Ivanyi B, Buzsaki G, Berenyi A. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9:483–90.
74. Voss U, Holzmann R, Hobson A, Paulus W, Koppehele-Gossel J, Klimke A, Nitsche MA. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci. 2014;17:810–2.
75. Vossen A, Gross J, Thut G. Alpha Power Increase After Transcranial Alternating Current Stimulation at Alpha Frequency (alpha-tACS) Reflects Plastic Changes Rather Than Entrainment. Brain Stimul. 2015;8(3):499–508
76. Vosskuhl J, Huster RJ, Herrmann CS. BOLD signal effects of transcranial alternating current stimulation (tACS) in the alpha range: a concurrent tACS-fMRI study. Neuroimage. 2016;140:118–25.
77. Wischnewski M, Engelhardt M, Salehinejad MA, Schutter DJLG, Kuo MF, Nitsche MA. NMDA receptor-mediated motor cortex plasticity after 20 Hz transcranial alternating current stimulation. Cereb Cortex. 2019;29:2924–31.

3 Physiology of Transcranial Direct and Alternating Current Stimulation

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3.1 Introduction

Brain stimulation techniques have generated renewed interest in recent decades as promising tools to explore human cerebral functions and to treat neurological and psychiatric diseases [1]. Apart from invasive stimulation paradigms such as deep brain and vagal nerve stimulation, non-invasive tools like transcranial magnetic or electrical stimulation (tES), including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are attractive for use in humans, because they permit painless modulation of cortical activity and excitability through the intact skull [2]. This chapter gives an overview of the physiological effects of tES. Their application and impact on brain functions and cognitive processes are also discussed.

3.2 tDCS

Tonic application of direct currents to the brain, although a relatively old method in strict terms, has regained increasing interest as a potentially valuable tool for the induction and modulation of central nervous system neuroplasticity. About 55 years ago, it was demonstrated that in anaesthetised rats, direct currents, delivered by intracerebral or epidural electrodes, induce stimulation polarity-dependent activity and excitability alterations of the sensorimotor cortex, which can be stable for hours after the end of stimulation [3]. A few years later, it was verified that also transcranial application of direct currents can induce an intracerebral current flow sufficiently large to achieve physiological and functional effects [4, 5]. The number of studies in humans in these early days was however limited. In one of the few neurophysiological studies, it was found that this kind of stimulation alters EEG patterns and evoked potentials at the cortical level in humans [6]. With regard to cognitive and behavioural effects, early clinical studies describe a mixed impact on depression and other psychiatric diseases [7–9] and improved performance in a choice reaction time task in healthy subjects [10]. In the fol-

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lowing years, electrical stimulation of the human brain via transcranial application of direct currents as a tool to influence brain function was nearly forgotten, most probably due to mixed results of initial studies and limited options to explore physiological effects in humans. Nevertheless, in the last decades, it has been re-evaluated following the development of methods that allow probing its neurophysiological effects (e.g. transcranial magnetic stimulation – TMS, functional magnetic resonance imaging – fMRI and positron emission tomography – PET). tDCS developed into a technique that reliably induces and modulates neuroplasticity in the human cerebral cortex non-invasively and painlessly in order to elicit prolonged – but yet reversible – shifts of cortical excitability [2, 11–13]. This section offers an overview of tDCS protocols and their physiological effects.

3.2.1 tDCS Protocols and Effects

For tDCS, the direct current is usually applied via conductive rubber or metal electrodes embedded in a sponge soaked with saline, or covered with cream or gel or by gel-filled cap electrodes [14]. The electrodes are connected to a stimulator delivering constant current which is essential for stable current strength to ensure reliable tDCS effects. Usually applied stimulation parameters range from 1 to 2 mA current intensity, from 3.5 to 100 cm^2 electrode size and up to 20 min stimulation duration in most studies, although longer stimulation duration and higher stimulation intensity have been probed. These parameters are considered safe, as shown by behavioural measures, electroencephalography (EEG), serum neurone-specific enolase concentration, diffusion-weighted and contrast-enhanced MRI measures and missing severe side effects in healthy and diseased humans, as well as in animal experiments [2, 12, 13, 15–19]. Electrode positions above cranial foraminae and fissures should be evaluated with caution or avoided because these could increase effective current density relevantly and thus have damaging effects. Although tDCS is usually well tolerated, at the beginning of stimulation most subjects will perceive a slight itching sensation, which normally fades with time [20, 21]. To avoid retinal phosphenes due to the tenfold higher sensitivity of the retina compared to the brain to electrical stimulation [22], as well as stimulation make-and-break effects, ramping up and down of current intensity for 8–30 s at both, the start and end of stimulation is suggested [23]. Blinding can furthermore be improved by application of topical anaesthesia to reduce somatosensory perception [24], especially with higher stimulation intensities, and application of ketoprofen to reduce erythema under the electrodes [25]. For an extensive methodological overview, please refer to Woods et al. [14].

Physiological tDCS effects, including efficacy, direction and focality of neuronal excitability changes, are determined by *stimulation polarity, current density, stimulation duration, electrode size, configuration and position*. These parameters are discussed in the following sections.

Electrode Position/Configuration/ Current Direction

Stimulation polarity determines the direction of cortical excitability changes elicited by tDCS at the macroscopic level within specific limits of stimulation intensity and duration. In most studies, both in humans and animals, anodal DC stimulation enhances cortical excitability and activity, whereas cathodal stimulation results in reversed effects [11, 12, 26]. However, deviating results have also been reported for subgroups of neurons [26, 27], hippocampal slice preparations [28] and specific return electrode positions [29]. One explanation for these heterogeneous effects is the fact that not so much the polarity of the electrode over the stimulated area per se is the decisive factor for the net effects of tDCS on excitability, but rather the direction of current flow relative to neuronal orientation: the respective current has to flow along the longitudinal axis of a given neuron to induce relevant effects on membrane polarity [30]. Polarisation of the soma and axon might determine the direction of the effects more than dendritic polarisation, because of higher receptor and ion channel density at the soma and axon level. Consequently, the position of the return electrode is critical for achieving the intended

excitability shifts, because together with the stimulation electrode it determines the electric field orientation in relation to neuronal orientation. In accordance, the position of the return electrode had been shown to determine the direction of the effects and efficacy of tDCS to induce cortical excitability alterations for motor and visual cortex stimulation [11, 29, 31, 32], and identical electrode arrangements result in opposite effects on cortical excitability in case of antagonistically oriented neurons [28]. Moreover, for motor cortex stimulation, it was demonstrated that positioning of the return electrode at the shoulder or arm results in diminished efficacy, as compared to the "classical" bipolar electrode configuration with the return electrode positioned over the contralateral orbit [33]. On the other hand, too low inter-electrode distance results in massive shunting of current flow between electrodes via the skin. Thus, also distance between electrodes is relevant for the efficacy of tDCS.

The "classical" tDCS protocols to induce neuroplastic excitability alterations involve stimulation with two relatively large electrodes (usual size between 25 and 35 cm^2) positioned on the head. These electrodes induce relatively non-focal effects of the underlying cortex, but also at remote areas, as shown experimentally for stimulation of the primary motor cortex [34, 35], and via modelling approaches [36]. Low focality is not necessarily a problem for each application of tDCS. In clinical syndromes, modulation of pathologically altered excitability of larger regions might be preferable, and in some cases, where the intended effects are thought to originate from an interaction of task- and stimulation-generated activity alterations, functional focality might result from this interaction. However, focality is crucial for basic studies aiming to explore the contribution of a specific area to brain function. Thus, new tDCS protocols suited to increase focality of stimulation have been developed. At least two factors contribute to the low focality of tDCS, the size of the relatively large electrode positioned over the target area and the physiological effects of the return electrode, if positioned at the scalp. Focality of tDCS over the target area can be enhanced by reducing electrode size and keeping current density constant. By this modification of the stimulation protocol, it has been shown for the motor cortex that a more selective alteration of excitability of specific hand muscle representations is accomplished [35]. Following the same rationale, increasing the size of the return electrode at constant current strength of 1 mA from 35 to 100 cm^2 makes this electrode functionally inefficient with respect to the area under that electrode, most probably due to reduced current density, and thus results in an at least functionally monopolar stimulation [35]. Alternatively, the return electrode can be positioned at another location than the scalp, for example, the neck, shoulder, arm or knee [7, 29, 37]. However, this remote position of the return electrode might diminish the efficacy of stimulation [33], and it is unclear if other sets of neurons would be affected by these approaches due to different electrical field orientation.

Based on modelling of electrical field strength, alternative electrode configurations have been developed to optimise stimulation focality and tDCS with one central electrode over the target region, and four electrodes arranged in its vicinity (4 × 1, or HD-tDCS) is one of these approaches. Here relatively small electrodes are used, and a central stimulation electrode is surrounded by four return electrodes placed nearby the central electrode [36]. Since the distance between the respective electrodes is relatively short, and thus shunting is enhanced relative to the more conventional electrode arrangements, current density has to be relatively high to obtain similar effects as with the large electrodes. Taking this into account, the cortical excitability alterations induced by this protocol seem to be similar to those elicited by conventional tDCS [38]. However, information about the physiological focality of these excitability alterations is not available so far. The functional efficacy of this electrode configuration has been demonstrated in some pilot studies, including pain perception [39]. Another optimising future strategy might be multi-electrode approaches. These can be based on functional networks [40], or arranged to tackle a specific target region based on modelling approaches [41, 42].

Current Intensity/Density

In most of the studies, in which conventional tDCS with relatively large electrodes (see above) is applied, current intensity is set at 1–2 mA, which results in about 0.03–0.06 mA/cm^2 current density at the level of the skin. Resulting electrical fields and current densities at the level of the brain depend on the tissue properties between the electrode and the brain and might differ accordingly, as suggested by the results of modelling studies [43]. These stimulation intensities are sufficient to induce relevant excitability shifts in the human primary motor cortex (M1) and alter physiological, perceptual and cognitive processes in prefrontal, parietal, temporal and occipital cortices [2, 11, 13, 44, 45]. Increasing current density within certain limits might increase efficacy of stimulation due to a larger membrane polarisation shift [11]. It might also affect additional neuronal populations because of a greater efficacy of the electrical field in deeper cortical layers and different sensitivities of specific neuronal populations to DC stimulation [26]. Moreover, because of physiologically-based non-linearity of tDCS effects (see also below), more intensive stimulation can convert the directionality of effects [46, 47], and different participant populations might display altered sensitivity to tDCS [48].

Stimulation Duration/Interval

Stimulation duration determines the occurrence and duration of after-effects of DC stimulation in animals and humans. In humans, a typical protocol to induce acute effects of tDCS on cortical excitability without generating after-effects is applied with a stimulation duration of 4 s [11]. This stimulation protocol induces the respective excitability alterations only during stimulation. tDCS for more than 3 min seems necessary to induce cortical excitability and activity alterations, which outlast stimulation [11]. Hereby, at least within certain limits, extended stimulation protocols induce prolongation of the resulting after-effects. tDCS from 3 to 7 min results in polarity-specific excitability alterations for some minutes after the end of stimulation, whereas anodal tDCS for 13 min and cathodal tDCS for 9 min results in after-effects lasting for about 1 h in the human motor cortex [12, 16]. This specific duration dependency of effects does gradually differ for other cortical regions, including the visual cortex [32]. Moreover, this relation between stimulation duration, and duration of after-effects, is not linear under all conditions: recently it was shown that anodal tDCS for 26 min results in excitability-diminishing and not -enhancing after-effects, most probably caused by intraneuronal calcium overflow [49]. Thus, for the induction of after-effects lasting relevantly longer than 1 h after tDCS, which are desirable especially to achieve therapeutic effects in clinical studies, simply prolonging stimulation duration might not be the optimal strategy. One alternative might be the repetition of stimulation sessions. Indeed, repeating cathodal or anodal tDCS within a time window of 30 min increases and prolongs the after-effects of both anodal and cathodal tDCS relevantly, for anodal tDCS, for more than 24 h after stimulation [49, 50]. On the other hand, tDCS intervals of 3 and 24 h diminished the after-effects of the second protocol in both studies conducted in healthy participants. Thus, specific timing is important for prolongation of tDCS effects on cortical excitability. Moreover, the results of these studies suggest that consecutive tDCS protocols might interact even when the overt impact on cortical excitability has vanished. Therefore, a sufficient interval between experimental sessions is recommended, when it is not intended to induce cumulative after-effects.

Taken together, for tDCS various protocols are available, which differ with respect to stimulation polarity, current density, stimulation duration, as well as electrode size and placement. Dependent on these parameters, stimulation protocols can be customised at least to a certain extent to achieve the desired direction, strength, focality and duration of effects on cortical activity and excitability. However, systematic studies about optimised physiological and functional effects are rare so far. For functional effects, the development of optimised protocols might

have to take into account not only the impact of tDCS on cortical processes, but also the interaction between stimulation and task-related cortical activity alterations, which might not be trivial in each case. Another future challenge is the development of individually adapted stimulation protocols, which take inter-individual differences of anatomy and physiology into account. It should also be noted that, given the large number of tDCS studies investigating the effects of different parameters, a one-to-one transferability of effects obtained by stimulation of one target region to another cannot be taken for granted due to state dependency, anatomical differences and other factors [16, 51–53]. Therefore, titration of stimulation parameters is recommended if no reference is available for a particular tDCS protocol [13, 52, 53].

3.2.2 tDCS Physiology

A multitude of studies has been conducted to explore the physiological effects of tDCS in the last years. The primary motor hand area (M1) has been widely used as a model system in these studies in order to explore the modulation of cortical excitability by tDCS, mostly for practical reasons, because it is situated at the convexity of the precentral gyrus with a minimal distance to the scalp surface, and therefore can easily be reached by TMS, which is usually applied to monitor cortical excitability, including specific stimulation protocols to monitor different types of intracortical neurons as well as cortical output neurons [54]. Therefore, most of the existing knowledge about basic physiology of tDCS originates from studies in the human motor cortex. However, physiological effects of tDCS on other cortical areas have also been explored, and beyond TMS, evoked potential measures, EEG, and functional imaging have contributed to our understanding of the physiological background of tDCS. Whereas regional effects of tDCS were in the focus of investigations during the first years, the impact of tDCS on cortical network activity became a new topic of research recently.

Regional Effects of tDCS

Acute Alteration of Cortical Excitability

The primary mechanism of DC stimulation on the cerebral cortex is a subthreshold modulation of neuronal resting membrane potentials. Current has to enter and leave a given neuron to exert any physiological effects due to physical reasons, thus in any case, DC stimulation – independent from the polarity of the electrode over a target area – will have de- and hyperpolarising effects on a given neuron. For the direction of the effects on cortical excitability and activity, it is relevant to acknowledge that the soma and initial axon segment of a neuron are more sensitive for the alteration of membrane potentials via weak electrical fields. Thus, the physiological effects of DC stimulation might primarily depend on alteration of these membrane segments [55]. In animal experiments, anodal stimulation (i.e. stimulation with the anode positioned over the respective target region) results in an enhancement of cortical excitability, and activity, while cathodal stimulation has antagonistic effects [26, 27]. However, this polarity-dependent effect has to be qualified. As mentioned above, orientation of electrical field relative to neuronal orientation determines the direction of the effects. Accordingly, antagonistic effects of DC stimulation were described not only for subgroups of neurons, but also for specific preparations, such as hippocampal slice experiments [27, 28]. In humans, similar stimulation polarity-dependent effects have been shown for short stimulation durations of few seconds, which do not induce after-effects. Anodal tDCS enhances cortical excitability, while cathodal stimulation diminishes it in the human motor cortex, as demonstrated by TMS at the macroscale level. These effects are largely restricted to global parameters of corticospinal excitability, which are determined by ion channel conductivity, such as single-pulse MEP amplitudes induced by medium TMS intensity and recruitment curves. They do not involve major alterations of intracortical facilitation and inhibition, as monitored by TMS double-pulse stimulation protocols [11, 56]. Accordingly, blocking voltage-gated sodium

and calcium channels abolishes the excitability enhancement accomplished by anodal tDCS, but blocking glutamatergic NMDA receptors or enhancement of GABAergic inhibition does not affect the acute effects of tDCS [57, 58]. Thus, taken together, the primary effects of tDCS seem to involve polarity-specific membrane potential alterations, but no synaptic effects. It is important to realise that these effects are observable at the macroscale level. TMS affects large groups of neurons, and thus it cannot be excluded, but due to the physiological effects of stimulation described above, it is probable that specific groups of neurons react differently to tDCS.

Sustained Change of Cortical Excitability and Activity

In experiments in anaesthetised rats, Bindman and colleagues described prolonged enhancements of cortical activity and excitability lasting for hours after anodal stimulation, while cathodal DC stimulation had antagonistic effects, if stimulation was conducted for 5 min or longer [3]. Identically directed after-effects of tDCS are accomplished when stimulation duration exceeds 3 min in humans. tDCS over the motor cortex for up to 7 min results in after-effects of about 5–10 min duration, while longer stimulation durations for up to 13 min induce excitability alterations stable for about 60–90 min [11, 12, 16] (Fig. 3.1). However, the duration of the after-effects might differ between cortical regions, with somewhat shorter lasting effects induced by tDCS over the visual cortex with identical stimulation durations [32, 59].

At the cortico-spinal level, tDCS elicits similar after-effects as those accomplished during short stimulation. The slope of the recruitment curve is

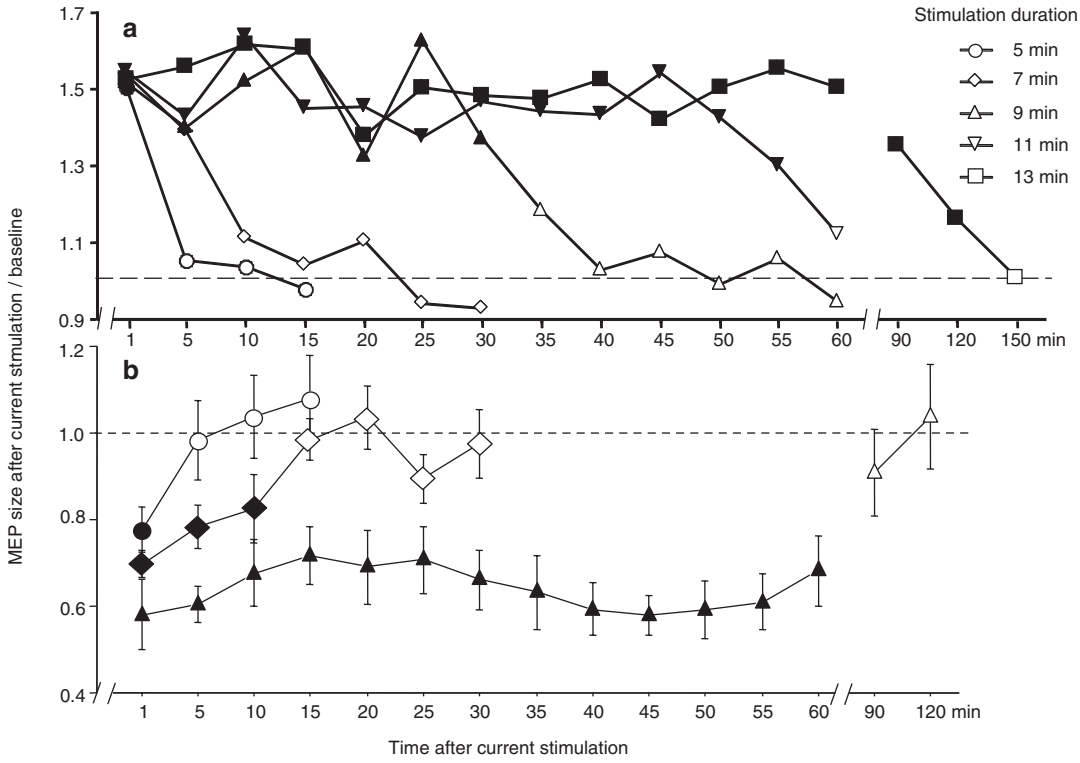

Fig. 3.1 After-effects of transcranial direct current stimulation (tDCS) on motor cortical excitability. tDCS of the human motor cortex modulates TMS-elicited MEP amplitudes after stimulation for up to an hour, depending on stimulation duration. Anodal stimulation (**a**) enhances, while cathodal (**b**) diminishes cortical excitability. Note that 5–7 min stimulation results in short-lasting after-effects, while prolonged tDCS increases the duration of the after-effects over-proportionally. (Nitsche et al. [12, 16], with permission of *Neurology* and *Clin Neurophysiol*)

reduced after cathodal tDCS, but enhanced after anodal stimulation [56]. For intracortical effects, anodal tDCS enhances intracortical facilitation and reduces intracortical inhibition, whereas cathodal tDCS induces antagonistic effects [56]. Most probably, these effects are accomplished by combined modulation of motor cortical afferents and motor cortex output neurons with conventional large electrodes, since selective premotor stimulation induces only the above-mentioned intracortical effects in M1, while focal stimulation over M1 with a small electrode only resulted in the above-mentioned cortico-spinal effects [60]. Because block of glutamatergic NMDA receptors abolishes the after-effects of tDCS, and the NMDA receptor agonist d-cycloserine prolonged the after-effects of anodal stimulation [57, 61]; it can be assumed that tDCS induces plasticity of the glutamatergic system, which is calcium-dependent. Calcium dependence of tDCS-induced plasticity has been demonstrated in another study [57]. These results are in accordance with animal experiments, in which it was shown that anodal tDCS enhances neuronal calcium content [62]. Beyond modulation of the glutamatergic system, it has recently been shown that both – anodal and cathodal tDCS– reduce free GABA in the cortical areas under the electrodes [63]. This result fits with an enhancing effect of both anodal and cathodal tDCS on TMS-induced I-wave facilitation, which is controlled by the GABAergic system [56]. GABA reduction has been shown to enhance glutamatergic plasticity in animal slice experiments and could have a facilitating effect on tDCS-induced plasticity in humans as well. It is worth to be mentioned that the induction of plasticity by tDCS seems to require spontaneous neuronal activity, as shown by Fritsch et al. [64]. This makes sense, because neuronal activity in the presence of subthreshold membrane depolarisation will enhance calcium influx relative to pure subthreshold depolarisation, or spontaneous activity alone, which in isolation might not suffice to open NMDA receptor channels.

Beyond the "classic" tDCS protocols, which induce after-effects of about 1 h duration, and thus early-phase plasticity, late-phase plasticity, which lasts for more than 24 h after intervention, can be induced by repeated tDCS within a critical time window of 30 min [49] similar to animal experiments [65]. Interestingly, continuous anodal tDCS with doubled stimulation protocol duration resulted in excitability-diminishing plasticity, and increasing the interval to 3 or 24 h duration diminished the efficacy of the stimulation protocol in the same study. The late-phase LTP-like effects of repeated anodal tDCS depend on the glutamatergic system. The excitability diminution induced by 26 min continuous stimulation might result from intracellular calcium overflow, since calcium channel block abolished this effect [49].

In summary, it can thus be concluded that the after-effects of tDCS depend on glutamatergic mechanisms, and that tDCS-induced reduction of GABA might serve as a "gating" mechanism.

Recently, stimulation intensity and duration have been extended beyond these classic protocols. Here it is shown that for anodal tDCS, prolongation of stimulation duration for up to 30 min, with a stimulation intensity of up to 3 mA, did result in fairly homogeneous excitability enhancement, with slightly better effects of stronger stimulation intensities [66, 67]. This effect was not only observable for TMS parameters, but also for MRI-derived measures of blood flow [68]. For cathodal tDCS, however, respective systematic titration of current intensity and stimulation duration resulted in an inverted U-shaped effect, with 1 and 3 mA resulting in an excitability diminution, while 2 mA current strength enhanced excitability [47]. This nonlinear effect might be caused by the known calcium dynamics of neuroplasticity [69], with low calcium influx inducing LTD, higher calcium influx inducing LTP and even higher calcium influx antagonised by opening of hyperpolarising potassium channels [70]. Alternative explanations, such as effects of tDCS on deeper cortical layers with larger stimulation intensity, can however not be ruled out at present.

Pharmacology of tDCS

Neuromodulators have a relevant impact on glutamatergic plasticity in animal models and humans

[71] (Fig. 3.2). In accordance, monoamines and acetylcholine have a prominent impact also on tDCS-induced plasticity. For dopamine, physiological receptor activity is critical for the induction of after-effects, because these are abolished by D2 receptor block [72]. Interestingly, increasing dopamine receptor activation by the non-selective precursor l-dopa has dosage-dependent non-linear effects on tDCS-generated plasticity. Whereas low- and high-dosage l-dopa abolish excitability-enhancing and -diminishing plasticity, medium dosage prolonged the excitability-diminishing after-effects of cathodal tDCS and converted anodal tDCS-induced facilitation into inhibition [73, 74]. Similar effects were accomplished with the D2 agonist bromocriptine [75]. In contrast, D1 receptor activation under D2 receptor block re-established tDCS-induced plasticity of both stimulation polarities dosage-dependently [76, 77]. Taken together, dopamine has prominent non-linear effects on tDCS-induced plasticity, which depend on dosage and receptor subtype activity. For the cholinergic system, enhancement of global cholinergic activation resulted in a similar effect as medium-dosage l-dopa on tDCS-generated plasticity, that is,

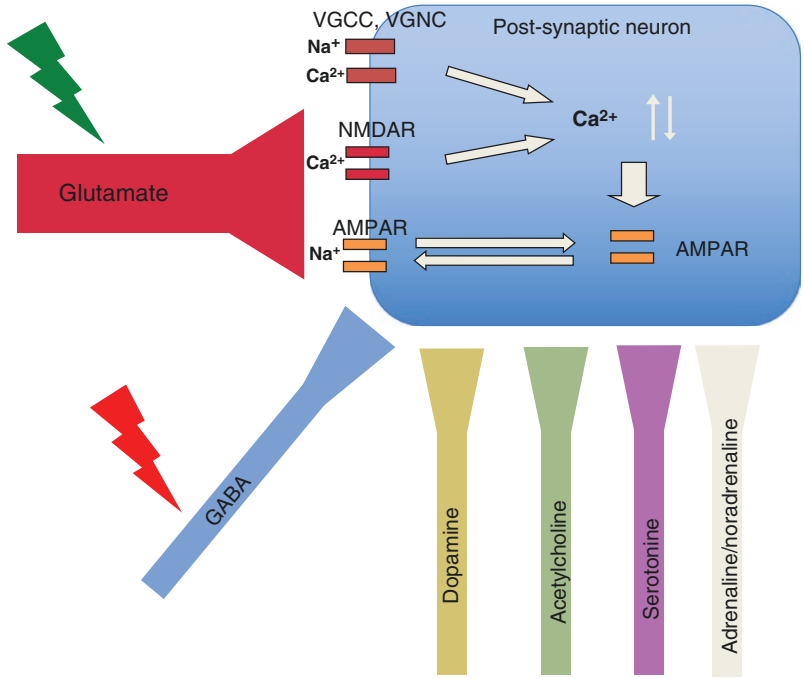

Fig. 3.2 Mechanisms and modulatory effects of tDCS-generated glutamatergic plasticity. In this figure, the main plasticity mechanism of glutamatergic synapses and the modulatory impact of other neurotransmitters and ion channels are displayed. As far as explored, tDCS has an enhancing effect on glutamatergic neurons (green arrow) [55, 121], while several studies showed that they reduce GABA activity (red arrow) [61, 122]. The release of glutamate activates NMDA receptors, which have calcium (Ca^{2+}) channel properties, if it is sufficiently strong. Depending on the amount of the consecutive intraneuronal calcium increase, enzyme cascades are activated which result in post-synaptic insertion or removal of glutamatergic AMPA receptors. The amount of post-synaptic AMPA receptors determines if a given activation of a pre-synaptic neuron results in supra-threshold post-synaptic activation. Thus, a modification of AMPA receptor density is the main basis for LTP and LTD. The activity of voltage-dependent calcium channels contributes to intracellular calcium alterations and the activation of sodium (Na^+) channels to the resting membrane potential, which affect the probability that NMDA receptors are activated and presynaptic activity results in a post-synaptic action potential. Various neurotransmitters such as GABA, dopamine, acetylcholine, serotonin, adrenaline and noradrenaline influence these principal mechanisms of action in a complex, sometimes non-linear way via their specific receptors, and they also have an impact on glutamatergic receptors and ion channels

a slight prolongation of cathodal tDCS-induced excitability diminution and a conversion of anodal tDCS-induced after-effects from facilitation into excitability reduction [78]. At least for anodal tDCS, these effects depend on activation of nicotinic receptors, since nicotine and the nicotinic α4β2 agonist varenicline had a similar effect on tDCS-induced plasticity [79, 80]. Recently it could furthermore be shown that this modulation depends on glutamate and calcium influx [81].

For serotonin, activation by a selective serotonin reuptake inhibitor (SSRI) facilitated and prolonged the after-effects of anodal tDCS and converted plasticity induced by cathodal stimulation into facilitation [82]. This effect was further enhanced after long-term application of SSRI [83]. Similar effects are obtained by enhancing of noradrenergic tone via the noradrenaline reuptake inhibitor reboxetine [84].

These studies show a prominent and complex impact of neuromodulators on tDCS-induced plasticity, which might, for example, be relevant for treatment of patients suffering from neurological and psychiatric diseases, where neuromodulator activity is often pathologically altered and counteracted upon by pharmacological intervention.

tDCS Effect on Cortical Regions Other than M1

Most of the above-mentioned studies were performed in the human primary motor cortex, but the effects of tDCS are not restricted to this region. In the last years, numerous studies have been conducted, which show a similar functional or physiological impact of tDCS on a multitude of cortical regions. Neurophysiological effects have been demonstrated for the visual cortex, where anodal and cathodal tDCS have similar effects on cortical excitability as motor cortex stimulation; however, antagonistic effects were also observed when the return electrode was positioned at the neck [29]. tDCS over the visual cortex results in shorter duration of the after-effects, as compared to stimulation over M1 with identical stimulation protocols. For tDCS of the somato-sensory cortex, anodal tDCS increased respective SEP amplitudes for at least 60 min after stimulation in one study [85], and cathodal tDCS reduced those in another one [86]. For auditory cortex stimulation, anodal tDCS over the temporal and cathodal tDCS over the temporo-parietal cortex enhanced the respective evoked potentials [87]. The recent development of concurrent TMS-EEG recordings allows the investigation of physiological mechanisms of tDCS via direct monitoring of cortical excitability. Anodal tDCS increased mean field power of TMS-evoked cortical potentials both during and following tDCS over the posterior parietal cortex, and also the dorsolateral prefrontal cortex [88, 89], although results are somewhat heterogeneous at present [90]. Such methodological advance will further contribute to the understanding of tDCS physiology into larger detail. Finally, it has been demonstrated that tDCS can also affect the spinal cord and the cerebellum [91]. For the latter, its complex folding seems to result in antagonistic effects dependent on the depth of penetration, which makes sense, given the relationship of tDCS effects from the relation of electrical field and neuronal orientation [92].

Inter-Regional Effects of tDCS

Apart from the regional effects of tDCS under the stimulation electrodes, remote effects on topographically distant cortical and subcortical areas were described relatively early [34]. However, it was unclear whether those effects are caused by physiological spreading of cortical activity or by physical current spread. Simulation studies, although not physiologically validated so far, are in favour for at least a partial contribution of spread of current flow [36]. In addition, physiological effects of tDCS on remote areas have been described. Premotor anodal tDCS enhances intracortical facilitation of M1, most probably due to the activation of premotor-primary motor cortex afferents [60], and combined dorsal premotor and supplementary motor area (SMA) stimulation alters motor and somatosensory evoked potentials [93]. For parietal cortex stimulation, anodal tDCS enhanced, but cathodal tDCS reduced MEP amplitudes. Moreover, anodal tDCS over the posterior parietal cortex increased both ipsilateral M1 intracortical inhibition and facilitation, as well as parietal-motor cortical connectivity [94].

Furthermore, anodal tDCS over the posterior parietal cortex increased cortico-cortical potentials elicited by TMS in both local and surrounding and contralateral regions [89].

Recently, functional connectivity approaches have been applied to explore cortical network alterations induced by tDCS. For motor cortex stimulation under resting conditions, an fMRI study revealed that nodal minimum path length increased after anodal tDCS over M1, which means that functional connectivity of this area with topographically distant regions of the whole brain significantly decreased. In contrast to this generally reduced whole brain connectivity of M1, functional connectivity was enhanced between the primary motor cortex on the one hand and premotor and superior parietal areas on the other hand [95]. In another study, cathodal tDCS of the primary motor cortex increased functional connectivity between the stimulated M1 and the contralateral M1 and premotor cortices [63]. A similar effect of tDCS was described for anodal stimulation combined with motor practice in an EEG study, where functional connectivity was enhanced between primary motor, premotor and sensorimotor areas in the high gamma band [96]. Moreover, anodal tDCS of the primary motor cortex alters cortico-subcortical connectivity of the motor cortex at rest. Specifically, it was shown to enhance connectivity with the ipsilateral caudate nucleus and thalamus [97]. Alterations of intrinsic motor cortex connectivity by tDCS have also been demonstrated: cathodal stimulation increased local connectivity, most likely due to cortical noise reduction accomplished by the respective excitability and activity diminution, while anodal tDCS enhanced long-distance connectivity within this area [97]. Therefore, it can be concluded by the results of these studies that motor cortex tDCS alters the connectivity of large parts of the motor network.

Beyond tDCS of the motor cortex, stimulation of the dorsolateral prefrontal cortex has been demonstrated to induce widespread alterations of functional connectivity, including the default mode network and attention-related networks in healthy subjects [98, 99]. A study conducted by Mainzer and co-workers showed that respective connectivity alterations are brain state-dependent. Whereas anodal tDCS over the left inferior frontal gyrus under resting conditions enhanced functional connectivity of a network associated with language processing, respective stimulation reduced respective connectivity in a language task and improved performance, thus suggesting that tDCS conducted during task performance enhanced the efficacy of processing [100].

To summarise, in addition to its regional effects under the stimulation electrodes, tDCS has prominent effects on functional networks at both cortical and subcortical levels. The relevance of these network alterations for cognition and behaviour needs to be explored in more detail in future studies.

3.3 tACS

It is well established that sensory and association areas of the brain are organised in a distributed manner. This segregation requires efficient communication mechanisms allowing the brain to integrate information both within and across different areas to guide behaviour. The question is, how can the human brain achieve this relatively fast and efficient integration of information? A prominent hypothesis suggests that neural oscillations play a fundamental role in cognitive functions supporting both neural communication and plasticity. Despite the large amount of empirical data, so far the majority of these studies have provided only correlative evidence for the impact of neural oscillations on cognitive performance, whereas its causal role is still to be determined. In order to probe the causal neurophysiology underlying function and behaviour of neural oscillations, tACS has emerged as a promising technique to achieve this goal.

tACS is a variant of tES, which modulates oscillatory brain activity via application of alternating currents with sinusoidal waveforms. Growing evidence from human research suggests that, during stimulation, oscillatory brain activity, as measured with electro-encephalography (EEG) and more recently with magneto-encephalography (MEG), phase-locks to

rhythmic trains of stimulation [101, 102]. tACS is presumed to affect neuronal membrane potentials by subthreshold (i.e. no action potential generation) oscillatory electrical stimulation with specific frequencies and to interact with ongoing rhythmic cortical activities. Interestingly, the observed entrainment effects are more prominent when the frequency of stimulation matches the dominant frequency of the stimulated structure [103]. However, for specific stimulation frequencies, also neuroplastic excitability modifications have been described [104–107]. By its modulating effect on task-related oscillatory brain activity, tACS appears to be a useful tool to investigate the causality of physiological phenomena for cognition and behaviour. In this section, we discuss the possible physiological effects of tACS as well as examples of its effects on cognition and behaviour.

3.3.1 tACS Protocols and Effects

The application of tACS employs a similar set-up as conventional tDCS, except for the polarity of stimulation. While anodal or cathodal stimulation in case of tDCS describes the constant polarity of an electrode during the whole intervention and determines the direction of effects, the polarity of the two electrodes in tACS alternates every half cycle. The efficacy of tACS is mainly determined by the intensity, frequency and phase of the stimulation protocol, which result in modulation of cortical excitability and/or oscillations.

Physiological Effects of tACS

Similar to tDCS, tACS is assumed to not induce cortical activity, but to modulate spontaneous activity via sub-threshold membrane polarisation. One potentially relevant effect is modulation of spontaneous oscillatory activity. In accordance, computational modelling suggests that external electric stimulation with a relatively low amplitude, as applied in tACS, is indeed sufficient for synchronising oscillatory activity of neural networks [108]. Animal studies demonstrated synchronisation of neuronal spike activity corresponding to the externally applied frequency of oscillations within different frequency bands [109], a phenomenon termed entrainment. While the results of that initial investigation were promising, tACS was applied in rodents at current intensities that would be prohibited in humans. Thus, the question remains as to whether conventional current intensities applied in humans have the capability of inducing entrainment in vivo and during wake states. A recent study presented data from non-human primates, a highly realistic model of the human brain, demonstrating that tACS reliably entrains the spiking activity of single neurons in awake monkey. Crucially, this entrainment was shown to be limited to the frequency of stimulation and the vicinity of the targeted brain region [110]. With increasing electric field strength, more neurons were entrained to the stimulation frequency. Importantly, concurrent electric field recordings demonstrated that these spike timing changes occur in a field regime that are practicable in humans (i.e. electric fields <0.5 mV/mm, which are achievable in humans for tACS intensities between 1 and 2 mA). Together, these results provide compelling evidence that tACS applied at conventional intensities in humans have the capability of genuinely inducing entrainment of neural oscillations.

Regarding studies in humans, when tACS is applied within the individual alpha frequency for 10 min over the occipital lobe, the corresponding spectral power was facilitated, and this effect outlasted the intervention [111, 112]. Likewise, it was shown that by prefrontal stimulation in the gamma frequency range, but not at other frequencies, during REM sleep, where gamma band activity is presumed to have important functional relevance, brain activity in these frequencies was enhanced [113]. Similar effects were obtained for beta frequency stimulation of the motor cortex, where it was also shown that the oscillatory aftereffects depended on glutamatergic mechanisms, because block of NMDA receptors abolished these [114]. Thus, taken together, these studies deliver evidence for a modulatory effect of tACS on spontaneous cortical oscillatory activity.

Beyond its impact on oscillatory brain activity, tACS can also affect cortical excitability. These effects seem critically to depend on stimu-

lation frequency and intensity and differ between online and after-effects. For the primary motor cortex, online effects on cortical excitability were selectively obtained by 20 Hz stimulation, but not by tACS within other physiological frequency bands. Since 20 Hz is the predominant frequency in the resting motor cortex, this result fits nicely with the modulatory impact of tACS on oscillatory brain activity [115]. For after-effects, even longer tACS durations (2–10 min) within similar frequency ranges showed no effect on MEPs with a peak-to-peak stimulation amplitude of 1 mA [104, 116]. Enhancing, however, stimulation intensity to 2 mA and stimulation duration to 15 min resulted in neuroplastic excitability enhancement lasting for at least 60 min after the end of stimulation and respective after-effects dependent on the activity of NMDA receptors [114]. For other frequency bands, already lower stimulation intensities and durations induce neuroplasticity. tACS over M1 with 140 Hz and 0.63 A/m^2 for 10 min significantly enhanced cortical excitability during and after stimulation [106]. In the same study, lower stimulation intensity with 0.25 A/m^2 resulted in a decrease of excitability. Interestingly, hippocampal plasticity is closely related to respective oscillations, which might explain the relatively high propensity of this frequency band for plasticity induction. With even higher frequency stimulation outside the physiological range of brain oscillations, including stimulation frequencies between 2 and 5 kHz, tACS (0.2 A/m^2 for 10 min) induces MEP enhancements lasting for more than 1 h [117]. The respective mechanisms of these stimulation frequencies are not well explored. To summarise, tACS may non-linearly alter cortical excitability during and after intervention. The presence and direction of this effect depends on stimulation frequency, intensity and duration.

tACS Effects on Cognition and Behaviour

The modulatory impact of tACS on oscillatory cortical activities has an impact on cognition and behaviour. Numerous studies were conducted for uni-regional tACS to explore the relevance of oscillatory activity of a specific area for performance. A couple of studies were performed in the visual domain. For visual perception, stimulation with beta or alpha frequency significantly reduced phosphene thresholds in illuminated or dark conditions, respectively [118]. Since beta frequencies are predominant in illuminated surroundings, whereas alpha frequencies dominate under light deprivation, this study suggests that tACS can modulate visual perception via its impact on naturally occurring cortical oscillations. In another study with tACS over V1, contrast perception was enhanced under high gamma (60 Hz) frequency stimulation, while spatial attention remained unchanged [119], underscoring the region-specific effect of tACS. Beyond visual areas, other cortical modalities have also been shown to be affected by tACS. Somatosensory tactile perception was enhanced specifically with tACS over the sensory cortex in the alpha (10–14 Hz) and high gamma (52–70 Hz) range [115]. For the motor system, 20 Hz tACS slowed down voluntary movement, but 70 Hz stimulation enhanced motor performance [120, 121]. Interestingly, a more recent study combined tACS and fMRI to reveal the neural mechanisms underlying these tACS-driven motor performance improvements [122]. This study showed that a remote area relative to the location of the target electrode – the dorsomedial prefrontal cortex (dmPFC) which is known to be engaged in cognitive and motor control – regulates the tACS-induced behavioural changes. More specifically, this study revealed that these changes not only result from activity modulations underneath the stimulation electrode but also reflect compensatory modulation within connected and functionally related brain networks. Another study showed increased behavioural variability following 10 Hz tACS [123] and also facilitated motor sequence learning, but only when applied at alpha frequency, which is associated with the inhibition of irrelevant stimuli during cognitive tasks [121, 124]. In addition to relative elementary cognitive processes, tACS was employed to alter more complex functions. Working memory performance was altered by tACS in the theta frequency range (6.5 Hz) over the left DLPFC

[125], and sleep-dependent consciousness levels were affected by tACS in the gamma frequency range [113] (Fig. 3.3). Similarly, rhythmic stimulation with gamma frequency over the left middle frontal gyrus enhanced fluid intelligence in another study [126].

In the above-mentioned studies, tACS was applied with standard frequencies across subjects. However, individual alignment of stimulation parameters to physiological oscillations might be also a promising approach. Cecere and co-workers (2015) explored the relevance of adjustment of tACS over V1 to individual oscillatory activity in a cross-modal sound-induced visual illusion task. tACS was applied with the individual alpha frequency or ±2 Hz. As compared to stimulation with individual alpha frequency, the deviating stimulation protocols enlarged or shrunken the illusion perception time window, demonstrating a critical impact of specific alpha frequency on this perceptual process.

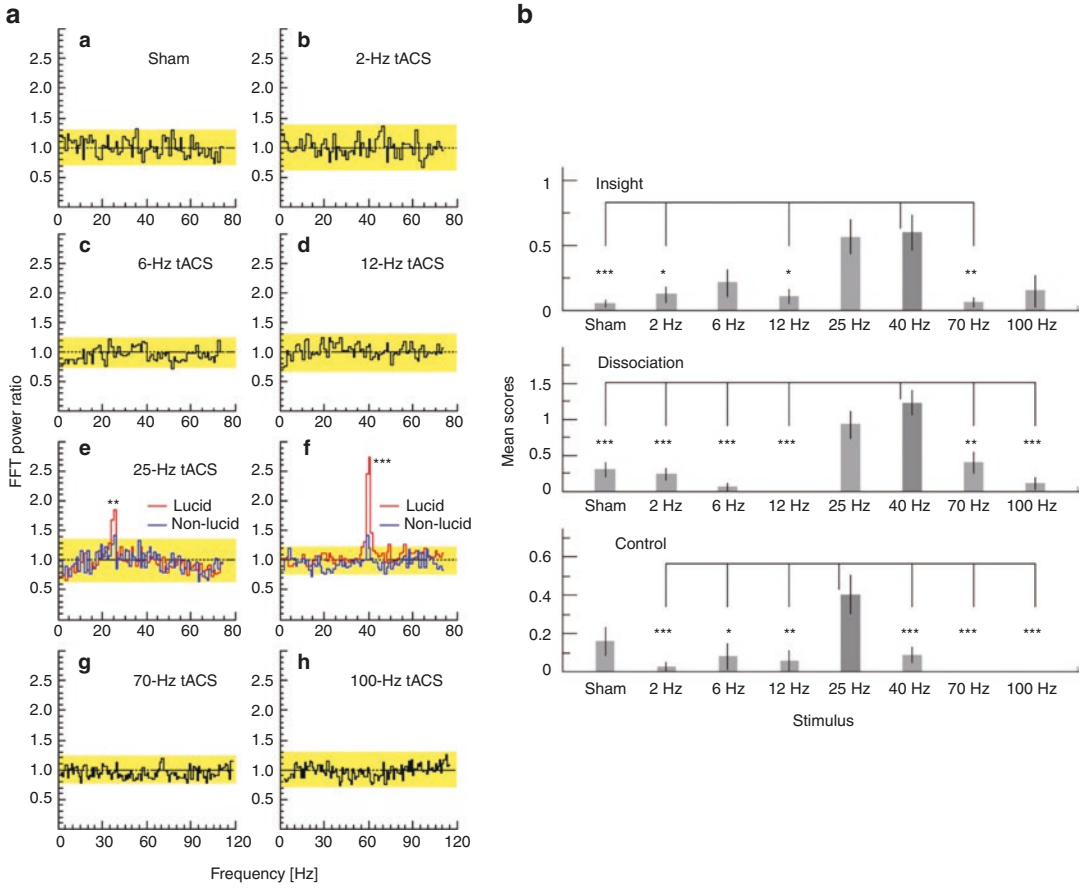

Fig. 3.3 Enhancing self-awareness during dreaming with high gamma tACS. (**a**) Grand average FFT power ratios of activity during (phase II) versus activity before stimulation (phase I) for the different stimulation conditions: sham, 2, 6, 12, 25, 40, 70 and 100 Hz (**a**–**h**). Yellow shading represents mean values ±2 s.e. Any excursions outside of this range are considered to be significant at least at the $P < 0.05$ level. Note that, with 40-Hz and 25-Hz stimulation, lucid dreams (red line) were accompanied by a significantly larger increase in the respective frequency band than non-lucid dreams (blue line). (**b**) Selected contrasts of mean scores (s.e.) for the LuCiD factors' insight, dissociation and control. The contrasts for insight and dissociation were strongest during stimulation with 40 Hz (40-Hz reference condition is shaded, top and middle frame). Control was increased most during stimulation with 25 Hz (25-Hz reference condition is shaded, bottom frame). $^{***}P < 0.001$, $^{**}P \leq 0.01$, $^{*}P \leq 0.05$. (Voss et al. [113], with permission of *Nature Neuroscience*)

Furthermore, individually adjusted tACS offers the potential to modulate peripheral and periodic motor movements such as tremor with individually adjusted frequency alignment [127]. In that study, stimulation was not only adjusted to individual frequency, but also phase-locked to oscillatory activity. tACS in phase with oscillatory activity enhanced, whereas antagonistic stimulation reduced tremor considerably, presumably via phase cancellation effects. Taken together, these studies show that tACS adjusted to physiological oscillations is able to modulate cognitive processes of different complexity in different domains, and that sophisticated approaches like individual adjustment of tACS frequency and phase-locked stimulation are promising approaches to improve insight about the relevance of regional oscillations for performance.

Beyond exploration of regional effects, tACS is suited to explore the relevance of oscillatory brain activity for task-relevant interactions between cortical areas. Specifically, tACS offers the opportunity to explore the causal relevance of functional oscillatory connectivity for task performance via combined stimulation of distant, but functionally connected cortical areas. A couple of studies demonstrated this effect for perceptual tasks. Anti-phasic tACS over parietal and occipital areas in the alpha frequency range (6–10 Hz), which increases a presumed inhibitory alpha effect, reduced the performance of a visual detection task [128]. Moreover, a phase-specific tACS effect was observed by anti-phasic (180-degree difference) 40 Hz stimulation bilaterally over the parieto-occipital junction. Here, motion perception was altered possibly via modulation of interhemispheric functional coupling in the gamma range [101, 129]. In the latter study, 4 × 1 tACS, with the same electrode montage as used in 4 × 1-tDCS, was applied in order to separately adjust different phase angles of the electrodes placed over the two hemispheres [101]. Beyond these elementary processes, also modification of more complex cognitive tasks was explored. For working memory performance, it was shown that parietal and frontal areas connect during task performance in the theta frequency range. In accordance with the hypothesis that synchronisation between both areas is causally relevant for task performance, synchronised stimulation with 6 Hz frequency improved reaction time, whereas antagonistic tACS diminished performance [130]. Likewise, interhemispheric anti-phase tACS over F3/F4 with slow-wave frequencies (0.75 Hz, current density 5.17 A/m^2) during a nap reduced activity in delta-frequency bands, which was correlated with impaired memory recall [131]. In a recent study, researchers aimed to identify a causal link between reduced frontotemporal brain oscillatory dynamics and working memory deficits in the elderly [132]. The investigators first conducted an EEG study where they found that phase–amplitude coupling in temporal regions correlated with working memory performance in the younger group but not in the older group. Moreover, theta-phase synchronisation between frontal and temporal regions – which is thought to reflect the influence of the frontal cortex on content processing and storage in temporal areas – was absent in the elderly group but not in the young group. These results suggested the possibility of a causal relationship between these neural signatures and working memory performance, which the authors explored in a subsequent tACS study. They applied tACS to strengthen frontotemporal theta-phase synchronisation [130] in the older adult group while they were performing the working memory task. tACS led to an improvement of working memory that resembled performance levels seen in younger subjects. These positive behavioural effects started about 10 min after the onset of stimulation and outlasted the stimulation period by about 1 h. Thus, these results provide novel evidence that non-pharmacological interventions based on tACS protocols could improve cognitive decline in healthy ageing.

Turning to examples at even higher cognitive processes, in an initial EEG study, it was demonstrated that gamma phase-coupling between the medial fronto-polar and superior parietal cortex correlated with the accuracy of making decisions based on subjective preferences [133]. This correlative evidence was causally confirmed with multi-site tACS, where it was shown that

transcranially inducing decoupling between the frontopolar and parietal regions identified in the EEG study indeed impaired the ability of human participants to correctly choose between alternatives containing primary rewards [134].

Taken together, tACS is able to modulate cognitive functions, and beyond regional modulation of oscillatory activity, also specific network alterations are suited to modify functional connectivity and performance.

3.4 General Remarks

Since tDCS and tACS have been re-introduced as tools to induce acute and neuroplastic alterations of cortical excitability and activity and to modulate cognitive processes, an increasing number of studies have been conducted to develop protocols enhancing the efficacy of stimulation and to explore the physiological basics of the effects. For tDCS, the determinants of efficacy, such as stimulation intensity, duration and repetition intervals, have been identified, and protocols which allow a relatively focal stimulation have been developed. It has been shown that the dependence of tDCS efficacy on these stimulation parameters is not linear in each case. Future work should focus on further optimising stimulation protocols, which will be important especially for clinical applications, where stable alterations of cortical excitability and activity are needed. Moreover, given the partial non-linearity of the effects, exploring optimal combinations of stimulation with performance would be an important, but not trivial, topic of future research. Since most of the studies reported in this review were conducted in the primary motor cortex, the transferability of the respective results to other cortical areas has yet to be explored. With regard to the mechanisms of action, pharmacological, TMS, EEG and functional imaging studies have revealed the main physiological mechanisms of tDCS, that is, the primary effect of membrane polarisation, the dependence of the after-effects from alterations of glutamatergic synapses and the complex alteration of tDCS-induced plasticity by neuromodulators. Furthermore, it became increasingly clear recently that the effects of tDCS are not only restricted to the area under the electrodes. The stimulation also induces alterations of connectivity within cortical and cortico-subcortical networks. As for tACS, experiments in both animals and humans, as well as results from computational simulation, increased insights into the basic physiology. However, the development of tACS protocols is still in a relatively early state as compared to tDCS. Further investigations including the combination of neurophysiological recordings and neuroimaging techniques will be desirable to improve mechanistic understanding. Although knowledge about the physiological basis of tDCS and tACS is incomplete, respective studies provide a basis, which might also be important for evaluating new fields of application in future.

References

1. Ziemann U, et al. Consensus: motor cortex plasticity protocols. Brain Stimul. 2008;1:164–82.
2. Nitsche MA, Paulus W. Transcranial direct current stimulation--update 2011. Restor Neurol Neurosci. 2011;29:463–92.
3. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
4. Rush S, Driscoll DA. Current distribution in the brain from surface electrodes. Anesth Analg. 1968;47:717–23.
5. Dymond AM, Coger RW, Serafetinides EA. Intracerebral current levels in man during electrosleep therapy. Biol Psychiatry. 1975;10:101–4.
6. Pfurtscheller G. Spectrum analysis of EEG: before, during and after extracranial stimulation in man. Elektromed Biomed Tech. 1970;15:225–30.
7. Costain R, Redfearn JW, Lippold OC. A controlled trial of the therapeutic effect of polarization of the brain in depressive illness. Br J Psychiatry. 1964;110:786–99.
8. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry. 1964;110:768–72.
9. Lolas F. Brain polarization: behavioral and therapeutic effects. Biol Psychiatry. 1977;12:37–47.
10. Elbert T, Lutzenberger W, Rockstroh B, Birbaumer N. The influence of low-level transcortical DC-currents on response speed in humans. Int J Neurosci. 1981;14:101–14.

11. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
12. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57:1899–901.
13. Nitsche MA, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1:206–23.
14. Woods AJ, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127:1031–48.
15. Bikson M, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9:641–61.
16. Nitsche MA, et al. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114:600–4.
17. Nitsche MA, et al. MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin Neurophysiol. 2004;115:2419–23.
18. Iyer MB, et al. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology. 2005;64:872–5.
19. Liebetanz D, et al. Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol. 2009;120:1161–7.
20. Ambrus GG, et al. The fade-in--short stimulation--fade out approach to sham tDCS--reliable at 1 mA for naïve and experienced subjects, but not investigators. Brain Stimul. 2012;5:499–504.
21. Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol. 2011;122:803–7.
22. Paulus W. On the difficulties of separating retinal from cortical origins of phosphenes when using transcranial alternating current stimulation (tACS). Clin Neurophysiol. 2010;121:987–91.
23. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 2006;117:845–50.
24. Guleyupoglu B, Febles N, Minhas P, Hahn C, Bikson M. Reduced discomfort during high-definition transcutaneous stimulation using 6% benzocaine. Front Neuroeng. 2014;7:28.
25. Guarienti F, et al. Reducing transcranial direct current stimulation-induced erythema with skin pretreatment: considerations for sham-controlled clinical trials. Neuromodulation. 2015;18:261–5.
26. Purpura DP, Mcmurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
27. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
28. Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. J Neurophysiol. 2012;107:1881–9.
29. Accornero N, Li Voti P, La Riccia M, Gregori B. Visual evoked potentials modulation during direct current cortical polarization. Exp Brain Res. 2007;178:261–6.
30. Roth BJ. Mechanisms for electrical stimulation of excitable tissue. Crit Rev Biomed Eng. 1994;22:253–305.
31. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9:2257–60.
32. Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci. 2004;45:702–7.
33. Moliadze V, Antal A, Paulus W. Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. Clin Neurophysiol. 2010;121:2165–71.
34. Lang N, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain. Eur J Neurosci. 2005;22:495–504.
35. Nitsche MA, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol. 2007;97:3109–17.
36. Datta A, et al. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2:201–7, 207.e1.
37. Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A. Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci. 2007;26:242–9.
38. Kuo HI, et al. Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimul. 2013;6:644–8.
39. Borckardt JJ, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain. 2012;13:112–20.
40. Fischer DB, et al. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. Neuroimage. 2017;157:34–44.
41. Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng. 2011;8:046011.
42. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. Neuroimage. 2014;89:216–25.

43. Puonti O, Saturnino GB, Madsen KH, Thielscher A. Value and limitations of intracranial recordings for validating electric field modeling for transcranial brain stimulation. Neuroimage. 2020;208:116431.
44. Kuo MF, Nitsche MA. Effects of transcranial electrical stimulation on cognition. Clin EEG Neurosci. 2012;43:192–9.
45. Shin YI, Foerster Á, Nitsche MA. Transcranial direct current stimulation (tDCS) – application in neuropsychology. Neuropsychologia. 2015;69:154–75.
46. Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol. 2013;591:1987–2000.
47. Mosayebi Samani M, Agboada D, Jamil A, Kuo MF, Nitsche MA. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. Cortex. 2019;119:350–61.
48. Moliadze V, et al. Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. Clin Neurophysiol. 2015;126:1392–9.
49. Monte-Silva K, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul. 2013;6:424–32.
50. Monte-Silva K, Kuo MF, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol. 2010;103:1735–40.
51. Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:859–62.
52. Boggio PS, et al. Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett. 2006;404:232–6.
53. Cuypers K, et al. Is motor learning mediated by tDCS intensity. PLoS One. 2013;8:e67344.
54. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55:187–99.
55. Rahman A, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol. 2013;591:2563–78.
56. Nitsche MA, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005;568:291–303.
57. Nitsche MA, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301.
58. Nitsche MA, et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci. 2004;19:2720–6.
59. Antal A, Paulus W. Investigating neuroplastic changes in the human brain induced by transcranial direct (tDCS) and alternating current (tACS) stimulation methods. Clin EEG Neurosci. 2012;43:175.
60. Boros K, Poreisz C, Münchau A, Paulus W, Nitsche MA. Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. Eur J Neurosci. 2008;27:1292–300.
61. Nitsche MA, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology. 2004;29:1573–8.
62. Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 1995;684:206–8.
63. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29:5202–6.
64. Fritsch B, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66:198–204.
65. Reymann KG, Frey JU. The late maintenance of hippocampal LTP: requirements, phases, "synaptic tagging", "late-associativity" and implications. Neuropharmacology. 2007;52:24–40.
66. Agboada D, Mosayebi Samani M, Jamil A, Kuo MF, Nitsche MA. Expanding the parameter space of anodal transcranial direct current stimulation of the primary motor cortex. Sci Rep. 2019;9:18185.
67. Jamil A, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol. 2017;595:1273–88.
68. Jamil A, et al. Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: an fMRI study. Hum Brain Mapp. 2020;41:1644–66.
69. Lisman J, Three E. Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. J Physiol. 2001;532:285.
70. Misonou H, et al. Regulation of ion channel localization and phosphorylation by neuronal activity. Nat Neurosci. 2004;7:711–8.
71. Nitsche MA, Müller-Dahlhaus F, Paulus W, Ziemann U. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. J Physiol. 2012;590:4641–62.
72. Nitsche MA, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur J Neurosci. 2006;23:1651–7.
73. Kuo MF, Paulus W, Nitsche MA. Boosting focally-induced brain plasticity by dopamine. Cereb Cortex. 2008;18:648–51.
74. Monte-Silva K, Liebetanz D, Grundey J, Paulus W, Nitsche MA. Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. J Physiol. 2010;588:3415–24.
75. Fresnoza S, et al. Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:10701–9.

76. Nitsche MA, et al. D1-receptor impact on neuroplasticity in humans. J Neurosci. 2009;29:2648–53.
77. Fresnoza S, Paulus W, Nitsche MA, Kuo MF. Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:2744–53.
78. Kuo MF, Grosch J, Fregni F, Paulus W, Nitsche MA. Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. J Neurosci. 2007;27:14442–7.
79. Batsikadze G, Paulus W, Grundey J, Kuo MF, Nitsche MA. Effect of the nicotinic α4β2-receptor partial agonist varenicline on non-invasive brain stimulation-induced neuroplasticity in the human motor cortex. Cereb Cortex. 2015;25:3249–59.
80. Thirugnanasambandam N, et al. Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. Neuropsychopharmacology. 2011;36:879–86.
81. Lugon MD, et al. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. Cereb Cortex. 2017;27:544–53.
82. Nitsche MA, et al. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatry. 2009;66:503–8.
83. Kuo HI, et al. Chronic enhancement of serotonin facilitates excitatory transcranial direct current stimulation-induced neuroplasticity. Neuropsychopharmacology. 2016;41:1223–30.
84. Kuo HI, et al. Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation-induced neuroplasticity in humans. J Physiol. 2017;595:1305–14.
85. Matsunaga K, Nitsche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol. 2004;115:456–60.
86. Dieckhöfer A, et al. Transcranial direct current stimulation applied over the somatosensory cortex – differential effect on low and high frequency SEPs. Clin Neurophysiol. 2006;117:2221–7.
87. Zaehle T, Beretta M, Jäncke L, Herrmann CS, Sandmann P. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. Exp Brain Res. 2011;215:135–40.
88. Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. Neuroimage. 2017;152:142–57.
89. Romero Lauro LJ, et al. TDCS increases cortical excitability: direct evidence from TMS-EEG. Cortex. 2014;58:99–111.
90. Gordon PC, et al. Modulation of cortical responses by transcranial direct current stimulation of dorsolateral prefrontal cortex: a resting-state EEG and TMS-EEG study. Brain Stimul. 2018;11:1024–32.
91. Priori A, Ciocca M, Parazzini M, Vergari M, Ferrucci R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists. J Physiol. 2014;592:3345–69.
92. Batsikadze G, et al. Effects of cerebellar transcranial direct current stimulation on cerebellar-brain inhibition in humans: a systematic evaluation. Brain Stimul. 2019;12:1177–86.
93. Kirimoto H, et al. Transcranial direct current stimulation over the motor association cortex induces plastic changes in ipsilateral primary motor and somatosensory cortices. Clin Neurophysiol. 2011;122:777–83.
94. Rivera-Urbina GN, et al. Parietal transcranial direct current stimulation modulates primary motor cortex excitability. Eur J Neurosci. 2015;41:845–55.
95. Polanía R, Paulus W, Antal A, Nitsche MA. Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. Neuroimage. 2011;54:2287–96.
96. Polanía R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp. 2011;32:1236–49.
97. Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp. 2012;33:2499–508.
98. Keeser D, et al. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31:15284–93.
99. Peña-Gómez C, et al. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul. 2012;5:252–63.
100. Meinzer M, et al. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci. 2012;32:1859–66.
101. Helfrich RF, et al. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol. 2014;24:333–9.
102. Witkowski M, et al. Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS). Neuroimage. 2016;140:89–98.
103. Reato D, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci. 2013;7:687.
104. Antal A, et al. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 2008;1:97–105.
105. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28:14147–55.

106. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul. 2012;5:505–11.
107. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. Brain Stimul. 2015;8:499–508.
108. Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67(1):129–43. https://doi.org/10.1016/j.neuron.2010.06.005.
109. Ozen S, Sirota A, Belluscio MA, Anastassiou CA, Stark E, Koch C, Buzsáki G. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30(34):11476–85. https://doi.org/10.1523/JNEUROSCI.5252-09.2010.
110. Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci U S A. 2019;116:5747–55.
111. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One. 2010;5:e13766.
112. Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci. 2013;7:161.
113. Voss U, et al. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci. 2014;17:810–2.
114. Wischnewski M, et al. NMDA receptor-mediated motor cortex plasticity after 20 Hz transcranial alternating current stimulation. Cereb Cortex. 2019;29(7):2924–31.
115. Feurra M, et al. Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. J Neurosci. 2011;31:12165–70.
116. Schutter DJ, Hortensius R. Brain oscillations and frequency-dependent modulation of cortical excitability. Brain Stimul. 2011;4:97–103.
117. Chaieb L, Antal A, Paulus W. Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor Neurol Neurosci. 2011;29:167–75.
118. Kanai R, Chaieb L, Antal A, Walsh V, Paulus W. Frequency-dependent electrical stimulation of the visual cortex. Curr Biol. 2008;18:1839–43.
119. Laczó B, Antal A, Niebergall R, Treue S, Paulus W. Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. Brain Stimul. 2012;5:484–91.
120. Pogosyan A, Gaynor LD, Eusebio A, Brown P. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol. 2009;19:1637–41.
121. Joundi RA, Jenkinson N, Brittain JS, Aziz TZ, Brown P. Driving oscillatory activity in the human cortex enhances motor performance. Curr Biol. 2012;22:403–7.
122. Moisa M, Polania R, Grueschow M, Ruff CC. Brain network mechanisms underlying motor enhancement by transcranial entrainment of gamma oscillations. J Neurosci. 2016;36:12053–65.
123. Wach C, et al. Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. Behav Brain Res. 2013;241:1–6.
124. Jensen O, Colgin LL. Cross-frequency coupling between neuronal oscillations. Trends Cogn Sci. 2007;11:267–9.
125. Sela T, Kilim A, Lavidor M. Transcranial alternating current stimulation increases risk-taking behavior in the balloon analog risk task. Front Neurosci. 2012;6:22.
126. Santarnecchi E, et al. Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. Curr Biol. 2013;23:1449–53.
127. Brittain JS, Probert-Smith P, Aziz TZ, Brown P. Tremor suppression by rhythmic transcranial current stimulation. Curr Biol. 2013;23:436–40.
128. Brignani D, Ruzzoli M, Mauri P, Miniussi C. Is transcranial alternating current stimulation effective in modulating brain oscillations. PLoS One. 2013;8:e56589.
129. Strüber D, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. Brain Topogr. 2014;27:158–71.
130. Polanía R, Paulus W, Nitsche MA. Noninvasively decoding the contents of visual working memory in the human prefrontal cortex within high-gamma oscillatory patterns. J Cogn Neurosci. 2012;24:304–14.
131. Garside P, Arizpe J, Lau CI, Goh C, Walsh V. Cross-hemispheric alternating current stimulation during a nap disrupts slow wave activity and associated memory consolidation. Brain Stimul. 2015;8:520–7.
132. Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci. 2019;22:820–7.
133. Polanía R, Krajbich I, Grueschow M, Ruff CC. Neural oscillations and synchronization differentially support evidence accumulation in perceptual and value-based decision making. Neuron. 2014;82:709–20.
134. Polanía R, Moisa M, Opitz A, Grueschow M, Ruff CC. The precision of value-based choices depends causally on fronto-parietal phase coupling. Nat Commun. 2015;6:8090.

4 Animal Models of tES: Methods, Techniques, and Safety

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4.1 Methods

Why Use Animal Models?

The efficacy and specificity of tES benefits from an enhanced understanding of the underlying mechanisms of action. A detailed investigation and isolated demonstration of independent mechanisms is not fully tractable using just human subjects. Animal models allow for isolation and characterization of specific tES cellular pathways. Evidently, there are differences between animals and humans. Like any model, animal experiments with direct current stimulation (DCS), alternating current stimulation (ACS), and other forms of electric stimulation are intended to reproduce relevant features of human applications, so as to have translational relevance. Therefore, the "why" and "how" of tDCS and tACS animal models depend on translational relevance—which is the focus of this chapter. Translational outcomes from animal experiments can then (1) retrospectively provide mechanistic explanations for findings in humans and (2) prospectively progress rational optimization of tES protocols. The benefits of using animal models include, but are not limited to, the following:

1. The tES parameter space is large, spanning dose selection (electrode montage, current intensity, duration, frequency for AC), the potential use of biomarkers to titrate and customize dose, subject selection, and pairing of tES with cognitive/motor/rehabilitation training. Comprehensively, testing this wide parameter space in humans is impractical, thereby necessitating the use of animal models to optimize tES development [1–5].
2. Animal models allow for the rapid screening of stimulation parameters and analysis of neurophysiological/molecular changes in ways not possible in humans. They also facilitate quantitative and qualitative assessment of the tES-related safety parameters, the underlying mechanisms, acute and aftereffects, and their application to psychiatric pathologies [6–10].
3. Animal models allow for modulation of synaptic efficacy to be characterized quantitatively with pathway specificity [11]. Given the interest to evaluate synaptic plasticity from electric stimulation (ES), the mechanisms of plasticity can be analyzed using specific pharmacology and detailed cellular and molecular analysis not possible in human experiments [12, 13]. Brain slices allow for a precise control of drug concentration, the background level and nature of the ongoing activity, and the electric field orientation relative to slice—the latter especially relevant for tDCS [14, 15].

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4. The role of specific neuronal cell types [16] and compartments (soma, dendrite, axon) within neurons [11, 17–19], as well as non-neuronal cells including glia [20–22] and endothelial cells [23, 24] in mediating tDCS/tACS responses, can be studied.
5. Animal models support dissociations of mechanisms that are readily explained by actions on single cells versus mechanisms that inherently depend on coupled neuronal networks [25–29]. In the latter case, the response of a connected and active system is unique from the response of single neurons in isolation.
6. A simplistic "sliding scale" explanation of anodal and cathodal tDCS, increasing and decreasing "excitability," respectively, seems unlikely to capture the nuance of brain function. Animal models can help advance a more thorough understanding of tDCS effects, including consideration for state-dependent changes as well as changes in information processing that are not simply explained by "less" or "more" activity [30]. Thus, while animal models helped underpin the notion of polarity specific excitability changes [31, 32], ongoing animal experiments have demonstrated complex dose-response [11, 15, 33–36].

To have meaningful relevance to human tES, animal studies must be designed with consideration for (1) correctly emulating the delivery of the current stimulation to the brain, and (2) measuring responses that can be used to draw translationally relevant inferences such that outcomes from animal models should relate to targeted brain processes in humans (Fig. 4.1a).

Classification of Animal Studies and Relevance to Clinical Protocols

In this chapter and the next one, we will cover the effects of tES on neurophysiology, behavior, and molecular response of the brain in animal studies. We will focus on macro-electrodes rather than microelectrodes and on sustained rather than pulsed waveforms lasting seconds to minutes rather than milliseconds. For the purpose of this chapter, studies referring to any type of electrical current applied directly to the brain (i.e., not through the skull) will be referred to as ES or DCS (for DC waveforms) or ACS (for sinusoidal waveforms). The term tES/tDCS/tACS will be reserved specifically for noninvasive stimulation in humans and animals. Animal studies can be broadly classified by the location of the stimulation electrodes. These classes are briefly described as follows:

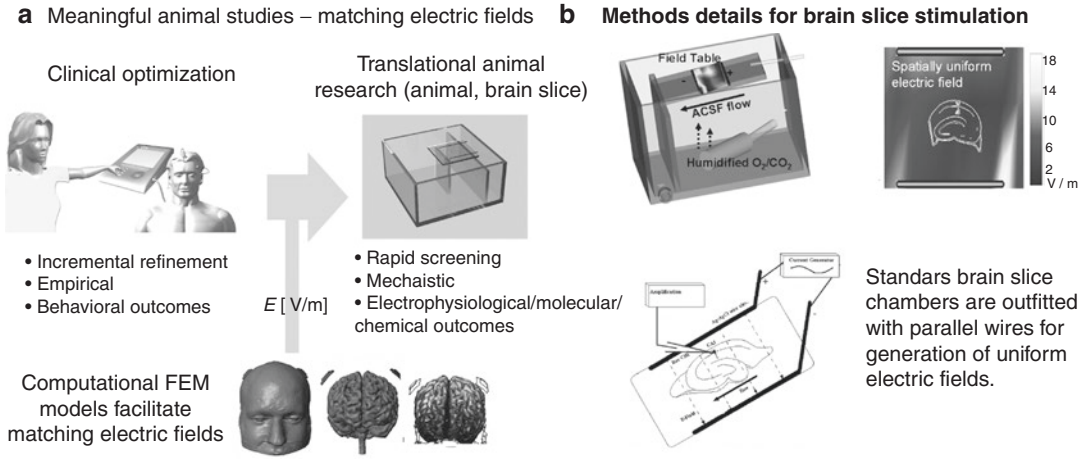


Fig. 4.1 Relevance of animal models to study tES mechanisms. (**a**) Meaningful translational research in animals requires replication of electric fields generated clinically in animal brain/tissue. (**b**) For in vitro brain slice studies, the generation of a uniform electric field with the use of two long parallel wires placed across a shallow bath allows for the replication of electrical fields. The uniform electric field in the chamber can be calibrated using a field-recording electrode. (Adapted from [9])

1. *Transcranial stimulation*: Recent animal studies with tES used transcranial stimulation with a skull screw as the electrode, or skull-mounted electrolyte-filled cup and electrode [12, 37–39]. Surface electrodes are in principle less invasive than other methods, although even for surface electrodes there are different levels of invasiveness. Electrodes that leave the scalp intact typically use adhesives and require conductive solutions to interface the electrode with the skin. Subcutaneous electrodes are typically fixed with skull screws, but if the electrode penetrates completely through the skull, the stimulation method is no longer considered transcranial.

   One advantage of transcranial stimulation is to prevent electrochemical products from reaching the brain. Recent experiments mostly use rodents [7, 12, 24, 31, 37, 38, 40], but cats [41] and other animal models have been tested as well. In rodent models, an "active" electrode is placed on the head and a "passive" return electrode is mounted on the body [10]. This setup is typically used for "unipolar" stimulation in the sense the polarity of the "active" electrode determines if stimulation is "anodal" or "cathodal." However, as with human tDCS, both electrodes are active and "anodal"/"cathodal" reflects the hypothesis that outcomes are determined by stimulation of the brain region under a given electrode. In a study using anesthetized rabbits, four silver ball electrodes formed a single virtual electrode to stimulate the targeted brain region [42]. Alternatively, two cranial electrodes produced bipolar stimulation [40].

   Since the cranium is not penetrated, the effects of ES are quantified through behavioral tests [4, 43–46], noninvasive recordings with electroencephalograms [4, 5, 47], transcranial imaging techniques that require methods to increase skull transparency [20, 21, 24], intracranial electrophysiology while accounting for skull defects from recording electrode penetration [3, 48–50], noninvasive electrical interrogation with external stimulations such as transcranial electrical stimulation [38], or histology after sacrifice [51–55]. In principle, animal experiments with transcranial stimulation have special relevance from a translational point of view, as they can link neurophysiologic mechanisms with behavior [42]. However, there are relatively few such studies at present [1, 12, 56–58] and the relevance of animal behavior to clinical disorders remains debated. Transcranial studies are quite important from the perspective of clinical safety as they come closest to the clinical use of tES [6–8, 51, 59].
2. *Intracranial stimulation*: In older DCS animal studies, typically done on cats, monkeys, and rats, an electrode was placed directly on the cortical surface [31, 32]. When an electrode is placed inside the skull, then one cannot rule out potential confounds from electrochemical changes at the electrode interface which can diffuse into the brain. This is less of a concern with ACS, which is typically charge-balanced and avoids buildup of electrochemical byproducts. For DCS, these byproducts are polarity specific and can produce changes that reverse with polarity [60]. Electrochemical byproducts can be reduced with suitable electrodes (e.g., Ag/AgCl) or wrapping the electrodes in cotton [61]. Prolonged DCS through a poorly selected electrode material (e.g., steel) produces significant accumulation of electrochemical products on the metal [60]. For cortical electrodes, it is generally assumed that current flow through the nearby cortex will be unidirectional. Passage of direct current through invasive electrodes is known to produce electrochemical lesions of the local tissue [9]. Thus, in terms of clinical safety of tES, these studies are less relevant. Nevertheless, this form of stimulation has revealed some fundamental aspects of ES. Two important findings from this early work are polarity-specific cortical excitability changes and lasting aftereffects when stimulation is sustained [31, 62].
3. *In vitro stimulation*: The use of brain slices to study the effects of weak DCS dates back to work done in the 1980s [63–67], with comparable approaches adapted for ACS [26, 68]. Brain slice models, usually rodents, allow for

detailed probing of specific brain regions using a range of quantitative electrophysiological, pharmacological, molecular, and imaging techniques [1, 14, 15, 34, 46, 69–71]. For in vitro studies, the stimulation electrodes are typically placed in the bath distanced from the tissue to shield from electrochemical products at the electrodes and to produce a controlled uniform field across the tissue (Fig. 4.1b). In isolated tissue, the direction of current flow can also be precisely controlled. Techniques have also been developed for stimulating in vitro monolayer cultures [72] including in transwell (membrane used for cell cultures) monolayer models [73]. In a seminal series of papers, Chan and Nicholson used isolated turtle cerebellum to study ACS modulations of spiking patterns [74, 75]. Slice studies have provided the most quantitative and sophisticated insights into tES principles—leading to the development of hypotheses regarding mechanisms of actions such as cell polarization [11, 16, 18, 35], plasticity induction [14, 15, 34], and oscillation effects [26–28, 76, 77].

4.2 Modes of Noninvasive Electrical Brain Stimulation

In this section, we will briefly introduce different modes of electric field stimulation which have been used in animal studies of noninvasive electrical brain stimulation.

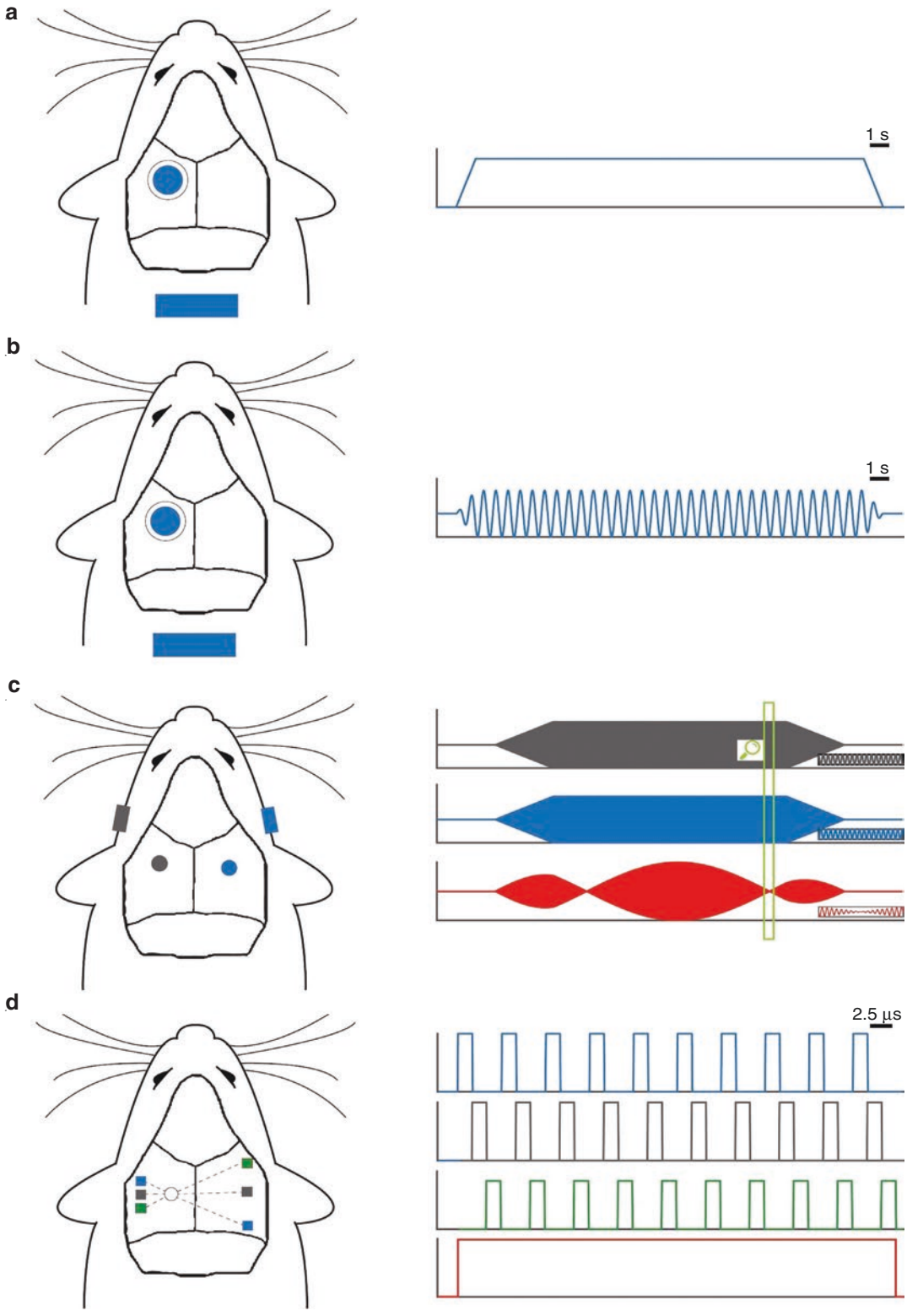
Direct Current Stimulation (DCS) and Alternating Current Stimulation (ACS)

Direct current stimulation (DCS) and alternating current stimulation (ACS) are two conventional waveforms used in animal studies. In DCS, a constant and unidirectional direct current is used to generate the static electric field between anode and cathode electrodes (Fig. 4.2a). In ACS, an alternating current flows between the pair of electrodes (Fig. 4.2b). Applied ACS generally refers to sinusoidal waveforms. When different pulses such as monophasic, charge-balanced biphasic, or charge-imbalanced biphasic are used, this is typically not called ACS (tACS) in the literature. While most research conducted on animals predominantly studied the effects of DCS, there is also a considerable number of studies on the effects of ACS.

High-Definition Stimulation (HD)

Datta et al. first proposed to use multiple small electrodes to achieve more focal stimulation as compared to conventional stimulation with large sponge electrodes [78]. These small electrodes are now often referred to as "high-definition" electrodes. Dmochowski et al. suggested an optimization method for where to best place these multiple small electrodes to obtain more focal stimulation in a specific brain area of interest [79]. The approach can also be used to maximize the intensity of stimulation on a target in the brain, with fixed constraints on the scalp currents. This method can also be used to increase the total intensity of stimulation by distributing currents across multiple electrodes [80]. Since any waveform can be applied using HD electrodes (HD-tDCS, HD-tACS, pulsed), this mode of stimulation should be thought of as an electrode configuration method [81].

Fig. 4.2 Schematic of different tES techniques applied to in vivo animal models [50, 82]. (**a**, **b**) The active electrode is placed over the area of interest and the returning electrode is usually attached on the neck or the chest to deliver (**a**) conventional tDCS waveform or (**b**) conventional tACS with an alternating waveform as examples. (**c**) TIS in which two pairs of electrodes are used to apply two high-frequency sinusoidal current waveforms (black and blue waveform). An amplitude-modulated signal will be generated in deep brain structures (red waveform). (**d**) IPS. Multiplexing between different pairs of electrodes. Each waveform depicts one of these short pulses. Note, in conventional tDCS and tACS, the resulting brain electric field waveform directly tracked the applied current (same trace) with a weight dependent on the brain region location, while in TIS and IPS the resulting brain electric field is a weighted sum (for each region) of the applied currents


a
1 s
b
1 s
c
d
2.5 µs

Temporal Interference Stimulation (TIS)
Temporal interference stimulation (TIS) consists of at least two pairs of electrodes delivering high-frequency sinusoidal AC stimulation on the scalp. The stimulation frequency of electrodes differs from each other slightly, such as 2 and 2.01 kHz, causing interference that can result in amplitude-modulated electric fields in deep structures of the brain (Fig 4.2c). The amplitude of fields is modulated at the difference frequency, 10 Hz in the example. Grossman et al. have argued the unmodulated kHz frequency component has little or no effect on neurons with a slow membrane response of ~30 ms [82]. On the other hand, amplitude-modulated (AM) electric fields can modulate neural firing rates. However, recent in vitro experiments suggest that field magnitudes required for this response to amplitude-modulated fields need to be significantly larger than the ones used in other tES approaches [77]. This study aims to understand the mechanisms governing both sensitivity and selectivity to TIS. Computational modeling of field distribution in the brain suggests that one may in fact achieve focal amplitude modulation in deep brain areas [83, 84]. However, the intensity of modulation is smaller than with conventional HD stimulation, and the unmodulated high-frequency fields are much stronger on the cortical surface [77, 84].

Intersectional Short Pulse (ISP)
Vöröslakos et al. suggested a new tES protocol to distribute current spatially similar to conventional HD-tES [50]. In this technique, which is called "intersectional short pulse" stimulation, current pulses are delivered in temporal succession across a sequence of scalp electrode pairs. While each pair is active for only ~60 μs, the polarization of the neuronal membrane sums up the effect of the electric fields of all pulses due to a slow membrane time constant (Fig. 4.2d). One suggested advantage of ISP is the ability to deliver higher current intensities while limiting the average current delivered through each electrode. The net effect is similar to the HD stimulation whereby scalp currents are distributed in space by virtue of controlling the maximum current through each electrode, while with ISP the current is distributed in time [80]. For both ISP and TIS, the argument is made that the high-frequency currents at the scalp surface minimize peripheral sensation. However, a recent study on skin sensations with various waveforms challenges this claim (under preparation).

4.3 Stimulation Artifact in Recording

Electric stimulation generates voltages in the tissue that are several orders of magnitude larger than electrophysiological signals: several volts of artifact caused by stimulation versus millivolts of neural activity for intracranial recordings, and microvolts for scalp recordings. Therefore, a frequent problem when attempting to record neural signals during stimulation is the distortion or saturation of the recording amplifier. To avoid this, (1) the amplifiers need to have a sufficiently large dynamic range and intensity resolution to resolve the smaller neural signals; (2) appropriate analog filters can be implemented; and/or (3) additional steps to minimize or correct for stimulation artifacts can be implemented. Overall, any approaches to manage stimulation artifacts should consider the features of interest in the neural signals. For example, if the DC component of the recording is not important for the objective of the study, a high-pass filter can remove the voltage artifact caused by DCS. Measuring the slope of fEPSP is an example of such a recording [35]. Moreover, aspects of the recording apparatus itself, such as drift in electrode conditions and field uniformity, may result in artifacts even under DCS.

A standard approach to reduce stimulation artifacts in neural recordings is to place a second recording electrode as a reference close to the electrode of interest. For example, when recording the transmembrane potential, one can subtract the adjacent extracellular electrode signal from the intracellular electrode since both electrodes have identical artifacts due to proximity. Another possible approach is to place the second electrode on the isopotential line with the

first one, where the iso-potential electrode location is selected as a region with comparable artifact as the recording electrode but not comparable electrophysiological signal of interest. The above approach has proven effective for extracellular potential recording and current-clamp recording under diverse conditions [11, 16]. Voltage-clamp recording under conditions of ongoing extracellular stimulation should only be conducted with caution over the possibility the amplifier will "correct" for the artifact producing a "signal" that reflects the artifact.

An additional source of distortions for relatively high-frequency stimulation is capacitive coupling at the electrode. This occurs for kilohertz-frequency stimulation as well as any kind of rectangular or pulsed waveform which contains broad-band components that are difficult to remove. Examples of such capacitive effects are capacitive-walled glass recording electrodes [85]. This distortion is magnified in patch-clamp and even sharp intracellular recording electrodes since they have higher resistance and capacitance [85]. In addition, amplifiers can be another source of distortion such as patch-clamp amplifiers [86].

For in vivo recordings, one should also note that nonstationarity of the current flow pattern due to movement, including cardioballistic, can cause large irregular voltage fluctuations even under DCS, that is the simplest of all waveforms [87, 88]. An example of that is the pulsing of the blood that causes large voltage fluctuations during DCS, which are particularly pronounced in scalp recordings [89]. A recent study using intracranial recordings and sinusoidal AC stimulation found it difficult to remove the AC artifacts due to nonstationarity, for example, subject movements [90]. AC stimulation with sinusoidal waveforms is narrowband and can in theory be removed. However, in practice, even small nonlinear distortions can lead to harmonics that contaminate the signal across the frequency spectrum. One of the few neural features that can be measured with little risk for stimulation artifacts is neuronal firing with microelectrodes. The distinct unitary spiking events are distinguishable enough from stimulation artifacts so that they can readily be identified [11, 27, 40, 50, 68]. Otherwise, local field potentials or EEG activity in concurrent stimulation should always be evaluated with great care. The only way to really rule out confounds from stimulation artifacts is to measure effects on the neural activity before and after stimulation.

4.4 Safety

4.4.1 Dose-Response and Safety

Any attempt to develop safety standards for any tES protocol requires assumptions to be made about dose-response. One approach to the dose-response curve is to use the lowest documented current intensity that produces a measurable destructive brain tissue response in an animal model at any stimulation duration. Animal studies have so far presented a wide range of thresholds that may be considered "safe." It is difficult to establish a single lowest threshold for tissue damage because of differences in methods across animal studies. Studies differ in stimulation setups, the number of animals used, the state of the animals undergoing tES, the time at which an animal is euthanized post stimulation, etc. [6–8, 51]. Animal studies are also limited in time points for measurement of tissue damage since the collection of tissue for analysis often requires terminal procedures. Therefore, there is a general lack of long-term follow-up. But perhaps the strongest limitation is the difficulty in equating invasive animal studies with noninvasive tES in humans. It is not clear if the relevant translational measure is current density, field magnitude, total current, total charge, or total charge per volume or per area of tissue [10].

In addition, the relative sensitivity of animal versus human tissue to tES injury is unclear. While developing safety guidelines could be challenging, rodent studies focusing on brain injury are summarized here. It is prudent not to approach injury thresholds derived from rodent studies when developing human safety guidelines. Given the electrode montage and interindividual differences, and scaling consolidated

animal tES safety data to humans, computational models have indicated that conventional tES protocols are orders of magnitude below the threshold for damage [91]. Since most in vivo animal studies investigated the safety limits of tDCS, we will focus most of the next section on the available findings of tDCS safety limits.

4.4.2 Safety Limits for Tissue Injury

Animal studies have been used to identify the intensity and duration of tDCS at which brain damage first manifests. Data establishing the safety limits solely focus on current intensity or charge density [6, 92]. Results from the three main studies investigating the safety thresholds for epicranial tDCS, measured in terms of brain lesions, are summarized in Table 4.1 [6–8]. All studies applied tDCS using an electrode on the surface of the rat skull. This epicranial electrode contact area was smaller relative to the return electrode positioned on the body. Given the variation in stimulation parameters summarized in Table 4.1, the lowest tDCS current intensity at which histological damage was recorded for each study was: (1) Liebetanz: 500 μA applied through 2.1 mm diameter circular electrode (3.5 mm^2 surface area) for 10 min; (2) Fritsch: 600 μA applied through 4 mm diameter circular electrode (12.5 mm^2 surface area) for 20 min; and (3) Jackson: 500 μA applied through 5 × 5 mm square electrode (25 mm^2 surface area) for 60 min. The discrepancies between the results of the three studies might arise from the variability of electrode montage, that is, size and location of the return electrode.

One might argue that the presence of lesions indicates that the brain has already undergone damage. Are there more sensitive safety measures than brain lesions? The inflammatory response is one of the sub-lesion predictors of brain injury, which has been evaluated in a few studies [7, 8, 51]. However, these three studies

Table 4.1 In vivo animal studies deriving the safety limit for tDCS-mediated tissue injury

Author	Liebetanz et al. [6]	Jackson et al. [7]	Fritsch et al. [8]
Species	Rat	Rat	Rat
Stimulation method	Epicranial	Epicranial	Epicranial
Stimulation polarity	Cathodal	Anodal	Anodal
Area of stimulation	Frontal cortex	−2.5 mm Bregma	Motor cortex
Return electrode	Rubber plate on chest (with jacket)	On the neck	Implanted platinum plate on the chest
Stimulation duration	10, 30, 90 or 270 min	60 min	20 min
Electrode surface area	3.5 mm^2	5.3, 10.6 and 25 mm^2	12.56 mm^2
Current intensity	1,10, 50, 100, 500, and 1000 μA	150, 300, 500, 100 and 2500 μA	600
Damage detection	H&E staining	H&E, Iba1	Fluoro-Jade C stain
Brain state	Anesthetized	Anesthetized	Anesthetized and alert
Threshold for neurodegeneration (electrode current density)	143 A/m^2 (10 min of stimulation)	20 A/m^2	47.8 A/m^2
Threshold for neurodegeneration (electrode charge density)	52,400 C/m^2	72,000 C/m^2	57,325 C/m^2
Threshold for neurodegeneration (electrode current intensity and surface area, duration)	500 μA 3.5 mm^2 10 min	500 μA 25 mm^2 60 min	600 μA 12.5 mm^2 20 min
Scaling factor	240	134	288
Estimated current intensity threshold for humans	120 mA	67 mA	173 mA

Scaling factor and resulting human thresholds are adapted from [9]

had a different timeline for euthanasia after tDCS for pre-lesion analysis which may affect the result. Nonetheless, an increase in immune and inflammatory biomarkers such as microglia is observed at the current intensities higher than the ones used in behavioral studies. It is worth noting that these intensities are also close to the lesion thresholds. Fritsch et al. reported the activation of microglia 24 h after tDCS at the electrode current density of 31.8 A/m^2. They found this value to be lesser than the electrode current density threshold needed for neurodegeneration, that is, 47.8 A/m^2 [8]. They also suggested that the current density threshold ranging between microglial activation and neurodegeneration can evoke a pre-lesional inflammatory response. An earlier rodent study reported an increase in the density of microglia after both anodal and cathodal tDCS within the stimulated brain region [51]. This increased density would suggest microglia shift toward their active state during tDCS. Another study on microglial activation also used both anodal and cathodal tDCS on mice at the current intensity of 0.1 mA and found that the microglial processes were shorter, indicating their activation, when observed immediately after tDCS but normal when observed 3 h post tDCS [20]. Both studies indicated that tDCS shifts microglia to their more active state in two different ways. One possible way is that morphological changes in microglial cells occur as the primary results of tDCS or as the result of tDCS-induced neurodegeneration.

High-resolution computational modeling has been helpful to scale the results from animal studies to approximate the safety thresholds in tDCS applications on humans. However, these estimated safety thresholds have to be considered with caution due to some limitations including what we outline here. It is possible that the susceptibility of humans and tissue to damage from tDCS is different. In addition, there are experimental limits for detecting various modes of damage, including dose-response assumptions. Moreover, anatomical differences can complicate scaling rodent results from rat to human predictions. Finally, variations in the method of stimulation, that is, transdermal versus epicranial, can lead to different safety limits [93]. In spite of the limitations of basing human safety standards on rat histology, including lack of long-term data and associated behavioral changes, this data represent an outer safety limit that cannot be approached during clinical tDCS.

The computational rat model by Jackson et al. predicts the current produced in the brain for the three studies summarized in Table 4.1 [9]. They derived a scaling factor by comparing the resulting peak electric field in the brain per mA at the electrode in rats to the peak electric field produced in the brain per mA at the electrode in humans. This scaling factor allows for the prediction of current magnitude that needs to be applied in the human using a common montage (M1-SO) to approximate the electric field produced in the brain of a rat for a given current. Applying this scaling factor to the damage threshold observed in each of these rodent studies allows us to predict a current intensity damage threshold in humans. The estimated scaling factors are within the range of 134–288 for the three studies in Table 4.1 [7]. Utilizing the reported current intensity thresholds for damage in animal models and the aforementioned scaling factors, Jackson et al. reported the range of 67–120 mA as the predicted human damage threshold. While there is considerable variability in these thresholds, they are still approximately two orders of magnitude above maximum currents intensities used during tDCS on humans.

Prior studies determined the tDCS safety thresholds by changing current intensity, electrode surface area, and stimulation duration (Table 4.1). It is worth noting that a similar current intensity threshold, with similar parameters and tDCS method, leads to considerable neuronal damage in awake animals as compared to the anesthetized ones [8]. This will have bearing on scaling the rodent data to direct human tDCS safety measures as human experiments are conducted on subjects in an awake state.

What could be the exact mechanism for the tDCS induced lesions? Even though excitotoxicity and heat generated by stimulation are among the suggested mechanisms [6, 94], there is insufficient experimental evidence to support the claim.

There is a scarcity of animal models explicitly considering the safety limits of tACS. It is not clear that injury mechanisms for DCS and ACS are comparable and so how much studies of tDCS safety informs tACS. There are hundreds of studies that did not explicitly address safety but did not report any damaging, lasting aftereffects following application of clinically relevant intensities [26–29, 40]. Among these are many studies that applied intensities much higher than used in humans [26, 28]. For both tDCS, tACS, and other forms of noninvasive electrical brain stimulation, one can rationally consider these studies as providing indirect evidence for safety. However, it should be noted that many human studies did report lasting aftereffects following application of clinically relevant intensities [95–98].

Our knowledge of the only safety data on transcranial TIS (tTIS) comes from a study in awake mice [9]. In this study, tTIS was applied with a current intensity of 250 μA for 20 min distributed over two electrode pairs. This did not cause measurable tissue damage as assessed with neuronal density, number of apoptotic cells, or DNA damage. In their functional evaluation, however, currents were three times stronger, which would have generated fields in the order of 400 V/m [11].

Another safety concern is with regard to the effect of tES on preexisting neurological conditions. A few studies have investigated the effects of tES on animal stroke models. Kim et al. assessed whether DCS increased preexisting infarct volume in a rat stroke model [99]. Their results showed no increase at the doses tested at 100 μA for 20 min and 0.785 cm^2 surface area of the epicranial electrode. But they found a potential neuroprotective effect in the form of reduced neuronal axon deterioration. Another group also reported protective effects of intracranial cathodal stimulation, that is, DC, 2 and 10 Hz at 100 μA, in ischemic stroke rats while they did not observe any significant effect at 50 Hz stimulation [100]. However, results from a study in a mouse model presented different effects of DCS on postischemic lesion volume [101]. According to Peruzzotti-Jametti et al., anodal DCS at 250 μA for 40 min with 4.52 mm^2 surface area of the epicranial electrode worsened the lesion volume and exacerbated the dysregulation of postischemic blood-brain barrier, whereas the cathodal DCS had a neuroprotective effect. This discrepancy between the results obtained from rat versus mouse study could be associated with the smaller size of a mouse's brain compared to that of a rat [91].

4.5 The Quasi-Uniform Assumption

Replication of tES human experiments in animal studies cannot merely be done by using the same stimulation parameters or by scaling down the stimulation parameters by some (arbitrary) factor (e.g., mice are X smaller than humans, so tDCS is applied to mice with X less current and X less electrode size). These clinical parameters include stimulation waveforms (tDCS, tACS), electrode montage, that is, shape and location, and the specifics of the waveform, such as duration, intensity in mA applied, and ramp. It is noteworthy that the electric field varies across different brain regions as the current flow has a complex spatial pattern across the brain. This results in a dose-specific electric field (current density) that varies significantly across the brain regions. The electric field distribution across the brain represents and determines the electrical actions of tDCS.

The electric field across the brain is not a simple function of any dose parameter. For example, the electrode current density does not map simply to the peak electric field in the brain [102]. Datta et al. estimated the electric fields generated in the brain using computational modeling [78]. They introduced computational models using realistic anatomy, and their estimation of peak electric field generated during tDCS has converged to between 0.2 and 0.5 V/m (0.05–0.14 A/m^2 current density) for a 1 mA intensity. Electric field scales linearly with a current intensity such that 2 mA would produce a range of 0.4–1 V/m (0.1–0.28 A/m^2 current density). These peaks represent local electric field maximum, and weaker electric fields are generated across much of the brain using conventional tDCS montages.

In addition, due to subject-specific idiosyncratic cortical folding, the electric field is clustered [78], with many local maxima (Fig. 4.3a). There is thus no single uniform electric field generated in the brain during tDCS but rather a range of electric field magnitudes varying across the brain. Therefore, the question is: Given this complexity of electric field distribution across brain structures, what can and should be mimicked in animal models?

One solution is to calculate the electric field in the brain region of interest, and then to replicate the selected electric field in the animal model (Fig. 4.3b, c). This approach replicates the electric field which is approximately uniform at the length scale of individual neurons [103] (Fig. 4.3a). This approach is supported by evidence suggesting electric fields generated during tDCS are largely uniform across any specific cortical column (neuronal dendritic tree) of interest (Fig. 4.3b); hence, one can speak of a single electric field in reference to a region of interest.

However, it is important to realize the limitations of the quasi-uniform assumption. Considering the peak of the electric field either across the whole brain or in a subregion can result in a discrepancy between expected and actual electric field. One reason for this mismatch is that field amplitude can change by orders of magnitudes in different brain regions and even across local gyri [30, 40]. The average and/or median value of the electric field can be up to ten times smaller than the peak amplitudes depending on local geometry and conductivity properties. Another consideration is that the coupling constant might vary across species. For example, given the same electric field stimulation to both a human and a rat cortical neuron, the amount of

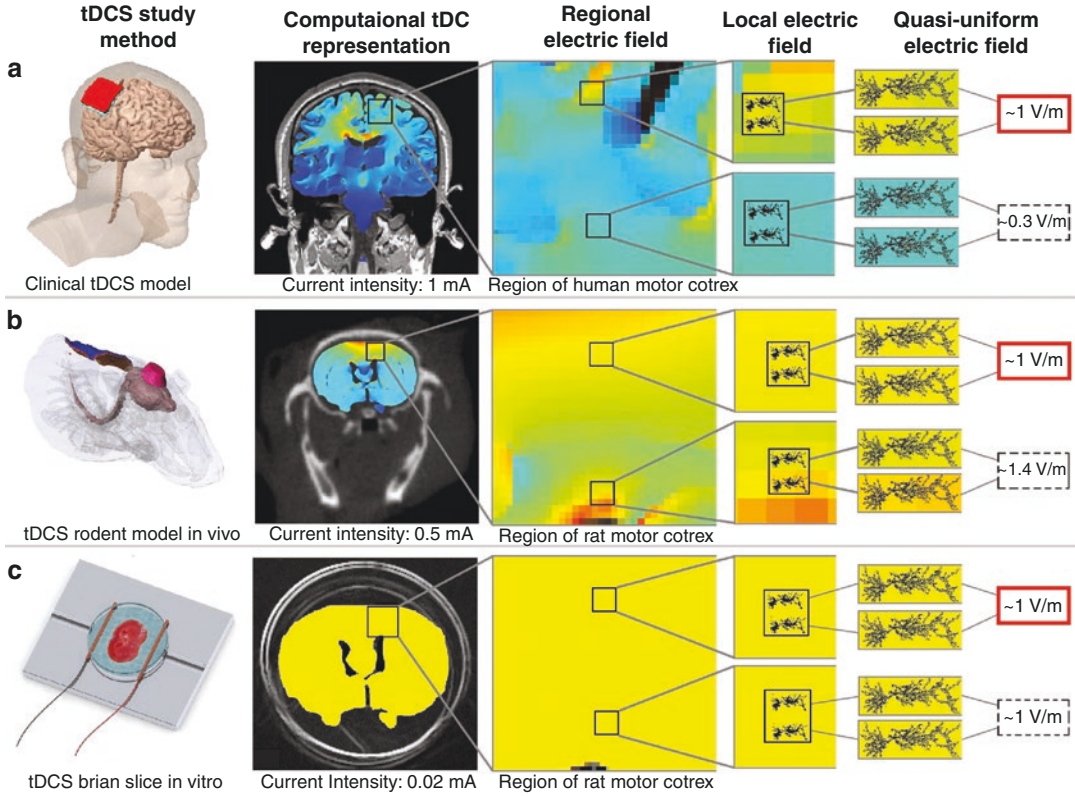


Fig. 4.3 The quasi-uniform assumption in modeling and animal studies. A high-resolution finite-element method (FEM) computational model of predicted current distribution during tDCS in a slice of the whole brain, a cortical column, and a neuron in (**a**) human, (**b**) rat in vivo, and (**c**) rat brain slice in vitro

neuronal polarization can be different. This species-dependent discrepancy is due to different size and geometry of neurons as will be explained more in detail in Chap. 6.

In the following, we address the limitations and approaches to estimating field magnitudes for each category of animal research:

1. *Transcranial stimulation*: Similar to the procedures in human tES, the computational approaches can be used to model the electric field across the brain and guide the stimulation design [104–106]. For example, the position of the return/reference electrode affects the current flow even under the active electrode [107, 108]. The recent development of anatomically precise animal models can be helpful for the design of future studies [83, 109–111]. An alternative method is to incorporate concentric sphere models scaled to size to determine the electric field intensity generated in the animal brain [42]. In cases where the electrode is placed directly on the skull, one can, to a first approximation, assume a maximum potential current density in the brain is equal to the average electrode current density [92]. However, it is important to address the direction of current flow as the direction of the electric field may vary across the brain. This can be more complicated in deep structures of the brain or animals with a more gyrated cortex. To measure the electric field directly, intracerebral electrodes must be placed in a region of interest [40, 50]. It is important to realize that the electric field is not uniform throughout the animal brain, and the insertion and presence of electrodes may itself distort current flow.
2. *Intracranial stimulation*: Here similar considerations apply as above. One could assume that current density under the electrode in the brain is equal to the average current density at the electrode. However, depending on the electrode design, the current density may be orders of magnitude higher at electrode edges [112–114]. This is an issue that is aggravated for small electrodes where the electric field near a monopolar source can be very high leading to further complications [31]. As with scalp electrodes in tES, when a sponge of cotton wrapper is used, its contact areas should be used in calculations [9].
3. *In vitro studies*: Experimental design is more straightforward in this category. In these experiments, long parallel wires or plates are placed in a bath across the entire tissue (Fig. 4.3c). If it is done carefully, this method generates a uniform electric field across the entire tissue and can be readily calibrated to match tES levels [11, 65, 115]. The uniformity of the electric field across brain slices has been verified [11], though exceptions have been reported [36]. The presence of conductive fluid around the brain slices may dull any laminar inhomogeneity effects to resistivity. Due to electrochemical reactions at the interface of electrodes and the fluid, the electrodes should be placed away from the tissue of interest in the bath.

4.6 Dose Translation and Meaningful Animal Studies

One of the most fundamental sources of ambiguity in interpreting and designing meaningful animal tES experiments relates to dose. Many proposed mechanisms of action are based on animal studies in which the electric field intensities or durations are higher than those of clinical trials. It is not clear that these high-intensity experiments scale proportionally to lower dose human experiments. Animal experiments often intentionally select high intensities for stimulation so as to more reliably detect small effects, for example, [11, 15, 19, 82, 116]. Though early animal studies remain informative about tES mechanisms, their techniques were invasive and intensities of electric field stimulation were higher than during tES on the human scalp [117]. Recent in vivo animal studies have often used higher current densities compared to human experiments while adopting a noninvasive method of tES [8, 118].

The assumption of a monotonic relationship between intensity and outcome can be problem-

atic due to the nonlinear nature of nervous systems. One possible issue is the asymmetry in the strength of the electric stimulation effects with changing polarity [15, 19]. According to these results, effects achieved under one electric polarity cannot be simply reversed by changing the polarity. Some have argued that high-stimulation intensities can produce opposite effects [119]. As discussed later, DC electric fields can increase excitability and elevate evoked responses (e.g., synaptic efficacy) in a polarity specific manner. But if the DC intensity is increased significantly, neuronal excitability may increase to a point where the neuron generates high-frequency discharges, and the responsiveness of a very active neuron to a stimulus may then decrease. This phenomenon has been shown in brain slices [11] and may explain in vivo results using high DC current intensities [120]. One example of this type of nonlinearity has been reported in the application of tDCS to the motor cortex to modulate motor evoked response (MEP) in human experiments [121]. Based on their results, cathodal tDCS at two different current intensities had the opposite effect on MEP, that is, switching from excitability diminution to enhancement. Overall, the nonlinearity and state dependence of dose-response may be pertinent to the understanding of mechanisms and rational optimization of tES techniques.

However, in vitro studies that explored field strength-response curves did indicate a surprisingly linear response curve over low intensities in their results [11, 15, 28]. In particular, membrane polarization appears to be linear with electric field strength, which is quantified by the neuronal coupling constant [11, 16, 28]. In vitro studies that have explicitly explored the lower electric field limit of sensitivity to fields reported statistically significant responses at <0.2 V/m, which is within human tDCS range [28, 115, 122].

Regardless, we urge caution when transferring conclusions from animal studies with high field magnitudes (>5 V/m) to clinical tES with lower intensities (<1 V/m). While these experiments are valuable for suggesting tES mechanisms, just as with drugs, increasing the dose beyond clinical levels by orders of magnitude can induce physiological changes that are not clinically relevant. For example, some animal studies have shown DC application can control the orientation of neuronal processes and their growth direction [123, 124], but both the duration and intensity of electric fields were often orders of magnitude greater than tDCS used in clinical settings. Additionally, mechanisms such as electroporation and joule heating can be produced by some forms of electric stimulation, but the waveforms required to produce these effects are not relevant to tES [6, 92, 125]. Thus, some mechanisms which require waveforms incompatible with tES, and their associated animal studies, are not considered further here.

The issues surrounding dose-response are important yet are often overlooked when translating from animal to human tES. Dose translation is inherently linked with mechanism, affecting experimental design. Deciding which stimulation parameters are considered relevant for scaling, and the insights from animal models can shape clinical practice, including dose optimization.

References

1. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66:198–204.
2. Yu X, Li Y, Wen H, Zhang Y, Tian X. Intensity-dependent effects of repetitive anodal transcranial direct current stimulation on learning and memory in a rat model of Alzheimer's disease. Neurobiol Learn Mem. 2015;123:168–78.
3. Krause MR, Zanos TP, Csorba BA, Pilly PK, Choe J, Phillips ME, et al. Transcranial direct current stimulation facilitates associative learning and alters functional connectivity in the primate brain. Curr Biol. 2017;27:3086–3096.e3.
4. Binder S, Rawohl J, Born J, Marshall L. Transcranial slow oscillation stimulation during NREM sleep enhances acquisition of the radial maze task and modulates cortical network activity in rats. Front Behav Neurosci. 2014;7:220. Available from: http://journal.frontiersin.org/article/10.3389/fnbeh.2013.00220/abstract.
5. Binder S, Berg K, Gasca F, Lafon B, Parra LC, Born J, et al. Transcranial slow oscillation stimulation during sleep enhances memory consolidation in rats. Brain Stimul. 2014;7:508–15.

6. Liebetanz D, Koch R, Mayenfels S, König F, Paulus W, Nitsche MA. Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol. 2009;120:1161–7.
7. Jackson MP, Truong D, Brownlow ML, Wagner JA, McKinley RA, Bikson M, et al. Safety parameter considerations of anodal transcranial direct current stimulation in rats. Brain Behav Immun. 2017;64:152–61.
8. Fritsch B, Gellner A-K, Reis J. Transcranial electrical brain stimulation in alert rodents. J Vis Exp. 2017;(129):56242.
9. Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of transcranial direct current stimulation: methods and mechanisms. Clin Neurophysiol. 2016;127:3425–54.
10. Jackson MP, Bikson M, Liebetanz D, Nitsche M. How to consider animal data in tDCS safety standards. Brain Stimul. 2017;10:1141–2.
11. Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices *in vitro*: modulation of neuronal function by electric fields. J Physiol. 2004;557:175–90.
12. Yoon KJ, Oh B-M, Kim D-Y. Functional improvement and neuroplastic effects of anodal transcranial direct current stimulation (tDCS) delivered 1 day vs. 1 week after cerebral ischemia in rats. Brain Res. 2012;1452:61–72.
13. Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 1995;684:206–8.
14. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul. 2017;10:51–8.
15. Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts hebbian plasticity in vitro. Brain Stimul. 2020;13:287–301.
16. Radman T, Ramos RL, Brumberg JC, Bikson M. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul. 2009;2:215–228. e3.
17. Maeda K, Maruyama R, Nagae T, Inoue M, Aonishi T, Miyakawa H. Weak sinusoidal electric fields entrain spontaneous Ca transients in the dendritic tufts of CA1 pyramidal cells in rat hippocampal slice preparations. PLoS One. 2015;10:e0122263.
18. Chakraborty D, Truong DQ, Bikson M, Kaphzan H. Neuromodulation of axon terminals. Cereb Cortex. 2018;28:2786–94.
19. Lafon B, Rahman A, Bikson M, Parra LC. Direct current stimulation alters neuronal input/output function. Brain Stimul. 2017;10:36–45.
20. Monai H, Ohkura M, Tanaka M, Oe Y, Konno A, Hirai H, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun. 2016;7:11100.
21. Mishima T, Nagai T, Yahagi K, Akther S, Oe Y, Monai H, et al. Transcranial direct current stimulation (tDCS) induces adrenergic receptor-dependent microglial morphological changes in mice. eNeuro. 2019;6(5):ENEURO.0204-19.2019.
22. Monai H, Hirase H. Astrocytes as a target of transcranial direct current stimulation (tDCS) to treat depression. Neurosci Res. 2018;126:15–21.
23. Cancel LM, Arias K, Bikson M, Tarbell JM. Direct current stimulation of endothelial monolayers induces a transient and reversible increase in transport due to the electroosmotic effect. Sci Rep. 2018;8:9265.
24. Shin DW, Fan J, Luu E, Khalid W, Xia Y, Khadka N, et al. In vivo modulation of the blood-brain barrier permeability by transcranial direct current stimulation (tDCS). Ann Biomed Eng. 2020;48:1256–70.
25. Parra LC, Bikson M. Model of the effect of extracellular fields on spike time coherence. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2004;2004:4584–7.
26. Deans JK, Powell AD, Jefferys JGR. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields: AC electric fields. J Physiol. 2007;583:555–65.
27. Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67:129–43.
28. Reato D, Rahman A, Bikson M, Parra LC. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30:15067–79.
29. Reato D, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci. 2013;7:687.
30. Esmaeilpour Z, Marangolo P, Hampstead BM, Bestmann S, Galletta E, Knotkova H, et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. Brain Stimul. 2018;11:310–21.
31. Bindman LJ, Lippold OCJ, Redfearn JWT. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
32. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
33. Faraji J, Gomez-Palacio-Schjetnan A, Luczak A, Metz GA. Beyond the silence: bilateral somatosensory stimulation enhances skilled movement quality and neural density in intact behaving rats. Behav Brain Res. 2013;253:78–89.
34. Rahman A, Lafon B, Parra LC, Bikson M. Direct current stimulation boosts synaptic gain and cooperativity in vitro. J Physiol. 2017;595:3535–47.

35. Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects: somatic and terminal origin of DCS effects. J Physiol. 2013;591:2563–78.
36. Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. J Neurophysiol. 2012;107:1881–9.
37. Bolzoni F, Bączyk M, Jankowska E. Subcortical effects of transcranial direct current stimulation in the rat. J Physiol. 2013;591:4027–42.
38. Cambiaghi M, Velikova S, Gonzalez-Rosa JJ, Cursi M, Comi G, Leocani L. Brain transcranial direct current stimulation modulates motor excitability in mice. Eur J Neurosci. 2010;31:704–9.
39. Liebetanz D, Klinker F, Hering D, Koch R, Nitsche MA, Potschka H, et al. Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. Epilepsia. 2006;47:1216–24.
40. Ozen S, Sirota A, Belluscio MA, Anastassiou CA, Stark E, Koch C, et al. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30:11476–85.
41. Bolzoni F, Pettersson L-G, Jankowska E. Evidence for long-lasting subcortical facilitation by transcranial direct current stimulation in the cat. J Physiol. 2013;591:3381–99.
42. Marquez-Ruiz J, Leal-Campanario R, Sanchez-Campusano R, Molaee-Ardekani B, Wendling F, Miranda PC, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. Proc Natl Acad Sci. 2012;109:6710–5.
43. Schweid L, Rushmore RJ, Valero-Cabré A. Cathodal transcranial direct current stimulation on posterior parietal cortex disrupts visuo-spatial processing in the contralateral visual field. Exp Brain Res. 2008;186:409–17.
44. Li Y, Tian X, Qian L, Yu X, Jiang W. Anodal transcranial direct current stimulation relieves the unilateral bias of a rat model of Parkinson's disease. In: 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Boston: IEEE; 2011. p. 765–8. Available from: http://ieeexplore.ieee.org/document/6090175/.
45. Zobeiri M, van Luijtelaar G. Noninvasive transcranial direct current stimulation in a genetic absence model. Epilepsy Behav. 2013;26:42–50.
46. Barbati SA, Cocco S, Longo V, Spinelli M, Gironi K, Mattera A, et al. Enhancing plasticity mechanisms in the mouse motor cortex by anodal transcranial direct-current stimulation: the contribution of nitric oxide signaling. Cereb Cortex. 2020;30:2972–85.
47. Dhamne SC, Ekstein D, Zhuo Z, Gersner R, Zurakowski D, Loddenkemper T, et al. Acute seizure suppression by transcranial direct current stimulation in rats. Ann Clin Transl Neurol. 2015;2:843–56.
48. Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci. 2019;116:5747–55.
49. Kar K, Duijnhouwer J, Krekelberg B. Transcranial alternating current stimulation attenuates neuronal adaptation. J Neurosci. 2017;37:2325–35.
50. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9:483.
51. Rueger MA, Keuters MH, Walberer M, Braun R, Klein R, Sparing R, et al. Multi-session transcranial direct current stimulation (tDCS) elicits inflammatory and regenerative processes in the rat brain. PLoS One. 2012;7:e43776.
52. Wachter D, Wrede A, Schulz-Schaeffer W, Taghizadeh-Waghefi A, Nitsche MA, Kutschenko A, et al. Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat. Exp Neurol. 2011;227:322–7.
53. Winkler C, Reis J, Hoffmann N, Gellner A-K, Münkel C, Curado MR, et al. Anodal transcranial direct current stimulation enhances survival and integration of dopaminergic cell transplants in a rat Parkinson model. eNeuro. 2017;4:ENEURO.0063-17.2017.
54. Paciello F, Podda MV, Rolesi R, Cocco S, Petrosini L, Troiani D, et al. Anodal transcranial direct current stimulation affects auditory cortex plasticity in normal-hearing and noise-exposed rats. Brain Stimul. 2018;11:1008–23.
55. Gellner A-K, Reis J, Holtick C, Schubert C, Fritsch B. Direct current stimulation-induced synaptic plasticity in the sensorimotor cortex: structure follows function. Brain Stimul. 2020;13:80–8.
56. Yang W-J, Wen H-Z, Zhou L-X, Luo Y-P, Hou W-S, Wang X, et al. After-effects of repetitive anodal transcranial direct current stimulation on learning and memory in a rat model of Alzheimer's disease. Neurobiol Learn Mem. 2019;161:37–45.
57. Pedron S, Beverley J, Haffen E, Andrieu P, Steiner H, Van Waes V. Transcranial direct current stimulation produces long-lasting attenuation of cocaine-induced behavioral responses and gene regulation in corticostriatal circuits. Addict Biol. 2017;22:1267–78.
58. Guo T, Fang J, Tong ZY, He S, Luo Y. Transcranial direct current stimulation ameliorates cognitive impairment via modulating oxidative stress, inflammation, and autophagy in a rat model of vascular dementia. Front Neurosci. 2020;14:28.
59. de Oliveira C, de Freitas JS, Macedo IC, Scarabelot VL, Ströher R, Santos DS, et al. Transcranial direct current stimulation (tDCS) modulates biometric and inflammatory parameters and anxiety-like behavior in obese rats. Neuropeptides. 2019;73:1–10.
60. Merrill DR, Bikson M, Jefferys JGR. Electrical stimulation of excitable tissue: design of effica-

cious and safe protocols. J Neurosci Methods. 2005;141:171–98.
61. Redfearn JW, Lippold OC, Costain R. A preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders. Br J Psychiatry. 1964;110:773–85.
62. Bindman LJ, Lippold OCJ, Redfearn JWT. Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. Nature. 1962;196:584–5.
63. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol. 2005;568:653–63.
64. Durand DM, Bikson M. Suppression and control of epileptiform activity by electrical stimulation: a review. Proc IEEE. 2001;89:1065–82.
65. Gluckman BJ, Neel EJ, Netoff TI, Ditto WL, Spano ML, Schiff SJ. Electric field suppression of epileptiform activity in hippocampal slices. J Neurophysiol. 1996;76:4202–5.
66. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
67. Jefferys JG. Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. J Physiol. 1981;319:143–52.
68. Radman T, Su Y, An JH, Parra LC, Bikson M. Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. J Neurosci. 2007;27:3030–6.
69. Sun Y, Lipton JO, Boyle LM, Madsen JR, Goldenberg MC, Pascual-Leone A, et al. Direct current stimulation induces mGluR5-dependent neocortical plasticity. Ann Neurol. 2016;80:233–46.
70. Sun Y, Dhamne SC, Carretero-Guillén A, Salvador R, Goldenberg MC, Godlewski BR, et al. Drug-responsive inhomogeneous cortical modulation by direct current stimulation. Ann Neurol. 2020;88(3):489–502.
71. Yu T-H, Wu Y-J, Chien M-E, Hsu K-S. Transcranial direct current stimulation induces hippocampal metaplasticity mediated by brain-derived neurotrophic factor. Neuropharmacology. 2019;144:358–67.
72. Huang R, Peng L, Hertz L. Effects of a low-voltage static electric field on energy metabolism in astrocytes. Bioelectromagnetics. 1997;18:77–80.
73. Lopez-Quintero SV, Datta A, Amaya R, Elwassif M, Bikson M, Tarbell JM. DBS-relevant electric fields increase hydraulic conductivity of in vitro endothelial monolayers. J Neural Eng. 2010;7:16005.
74. Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. J Physiol. 1988;402:751–71.
75. Chan CY, Nicholson C. Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum. J Physiol. 1986;371:89–114.
76. Reato D, Bikson M, Parra LC. Lasting modulation of in vitro oscillatory activity with weak direct current stimulation. J Neurophysiol. 2015;113:1334–41.
77. Esmaeilpour Z, Kronberg G, Reato D, Parra LC, Bikson M. Temporal interference stimulation targets deep brain regions by modulating neural oscillations [Internet]. Neuroscience. 2019:1–33. Cold Spring Harbor Laboratory. Available from: http://biorxiv.org/lookup/doi/10.1101/2019.12.25.888412.
78. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2:201–207.e1.
79. Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng. 2011;8:046011.
80. Huang Y, Parra LC. Can transcranial electric stimulation with multiple electrodes reach deep targets? Brain Stimul. 2019;12:30–40.
81. Bikson M, Esmaeilpour Z, Adair D, Kronberg G, Tyler WJ, Antal A, et al. Transcranial electrical stimulation nomenclature. Brain Stimul. 2019;12:1349–66.
82. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169:1029–1041.e16.
83. Rampersad S, Roig-Solvas B, Yarossi M, Kulkarni PP, Santarnecchi E, Dorval AD, et al. Prospects for transcranial temporal interference stimulation in humans: a computational study. NeuroImage. 2019;202:116124.
84. Huang Y, Datta A, Parra LC. Optimization of interferential stimulation of the human brain with electrode arrays. J Neural Eng. 2020;17(3):036023. Available from: http://iopscience.iop.org/10.1088/1741-2552/ab92b3.
85. FallahRad M, Zannou AL, Khadka N, Prescott SA, Ratté S, Zhang T, et al. Electrophysiology equipment for reliable study of kHz electrical stimulation. J Physiol. 2019;597:2131–7.
86. Lesperance LS, Lankarany M, Zhang TC, Esteller R, Ratté S, Prescott SA. Artifactual hyperpolarization during extracellular electrical stimulation: proposed mechanism of high-rate neuromodulation disproved. Brain Stimul. 2018;11:582–91.
87. Noury N, Hipp JF, Siegel M. Physiological processes non-linearly affect electrophysiological recordings during transcranial electric stimulation. NeuroImage. 2016;140:99–109.
88. Noury N, Siegel M. Phase properties of transcranial electrical stimulation artifacts in electrophysiological recordings. NeuroImage. 2017;158:406–16.
89. Gebodh N, Esmaeilpour Z, Adair D, Chelette K, Dmochowski J, Woods AJ, et al. Inherent physiological artifacts in EEG during tDCS. NeuroImage. 2019;185:408–24.

90. Lafon B, Henin S, Huang Y, Friedman D, Melloni L, Thesen T, et al. Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. Nat Commun. 2017;8:1199.
91. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9:641–61.
92. Bikson M, Datta A, Elwassif M. Establishing safety limits for transcranial direct current stimulation. Clin Neurophysiol. 2009;120:1033–4.
93. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175–95.
94. McCreery DB, Agnew WF. Changes in extracellular potassium and calcium concentration and neural activity during prolonged electrical stimulation of the cat cerebral cortex at defined charge densities. Exp Neurol. 1983;79:371–96.
95. Angelakis E, Liouta E, Andreadis N, Leonardos A, Ktonas P, Stavrinou LC, et al. Transcranial alternating current stimulation reduces symptoms in intractable idiopathic cervical dystonia: a case study. Neurosci Lett. 2013;533:39–43.
96. Chaieb L, Antal A, Paulus W. Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor Neurol Neurosci. 2011;29:167–75.
97. Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci. 2013;7:161.
98. Kasten FH, Dowsett J, Herrmann CS. Sustained aftereffect of α-tACS lasts up to 70 min after stimulation. Front Hum Neurosci. 2016;10:245.
99. Kim SJ, Kim BK, Ko YJ, Bang MS, Kim MH, Han TR. Functional and histologic changes after repeated transcranial direct current stimulation in rat stroke model. J Korean Med Sci. 2010;25:1499.
100. Baba T, Kameda M, Yasuhara T, Morimoto T, Kondo A, Shingo T, et al. Electrical stimulation of the cerebral cortex exerts antiapoptotic, angiogenic, and anti-inflammatory effects in ischemic stroke rats through phosphoinositide 3-kinase/Akt signaling pathway. Stroke. 2009;40(11):e598–605. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.109.563627.
101. Peruzzotti-Jametti L, Cambiaghi M, Bacigaluppi M, Gallizioli M, Gaude E, Mari S, et al. Safety and efficacy of transcranial direct current stimulation in acute experimental ischemic stroke. Stroke. 2013;44:3166–74.
102. Miranda PC, Correia L, Salvador R, Basser PJ. The role of tissue heterogeneity in neural stimulation by applied electric fields. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2007;2007:1715–8.
103. Bikson M, Dmochowski J, Rahman A. The "quasi-uniform" assumption in animal and computational models of non-invasive electrical stimulation. Brain Stimul. 2013;6:704–5.
104. Gasca F, Richter L, Schweikard A. Simulation of a conductive shield plate for the focalization of transcranial magnetic stimulation in the rat. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2010;2010:1593–6.
105. Bernabei JM, Lee WH, Peterchev AV. Modeling transcranial electric stimulation in mouse: a high resolution finite element study. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2014;2014:406–9.
106. Lee WH, Lisanby SH, Laine AF, Peterchev AV. Electric field model of transcranial electric stimulation in nonhuman primates: correspondence to individual motor threshold. IEEE Trans Biomed Eng. 2015;62:2095–105.
107. Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. Clin Neurophysiol. 2010;121:1976–8.
108. Brunoni AR, Fregni F, Pagano RL. Translational research in transcranial direct current stimulation (tDCS): a systematic review of studies in animals. Rev Neurosci. 2011;22:471–81.
109. Hadar R, Winter R, Edemann-Callesen H, Wieske F, Habelt B, Khadka N, et al. Prevention of schizophrenia deficits via non-invasive adolescent frontal cortex stimulation in rats. Mol Psychiatry. 2020;25:896–905.
110. Negahbani E, Stitt IM, Davey M, Doan TT, Dannhauer M, Hoover AC, et al. Transcranial alternating current stimulation (tACS) entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform [Internet]. Neuroscience. 2019:1–44. Available from: http://biorxiv.org/lookup/doi/10.1101/563163.
111. Sandrini M, Xu B, Volochayev R, Awosika O, Wang W-T, Butman JA, et al. Transcranial direct current stimulation facilitates response inhibition through dynamic modulation of the fronto-basal ganglia network. Brain Stimul. 2020;13:96–104.
112. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol. 2006;117:1623–9.
113. Minhas P, Datta A, Bikson M. Cutaneous perception during tDCS: role of electrode shape and sponge salinity. Clin Neurophysiol. 2011;122:637–8.
114. Kronberg G, Bikson M. Electrode assembly design for transcranial direct current stimulation: a FEM modeling study. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2012;2012:891–5.
115. Francis JT, Gluckman BJ, Schiff SJ. Sensitivity of neurons to weak electric fields. J Neurosci. 2003;23:7255–61.
116. Andreasen M, Nedergaard S. Dendritic electrogenesis in rat hippocampal CA1 pyramidal neurons: functional aspects of Na+ and Ca2+ currents in apical dendrites. Hippocampus. 1996;6:79–95.

117. Esmaeilpour Z, Schestatsky P, Bikson M, Brunoni AR, Pellegrinelli A, Piovesan FX, et al. Notes on human trials of transcranial direct current stimulation between 1960 and 1998. Front Hum Neurosci. 2017;11:71. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00071/full.
118. Fregni F, Liebetanz D, Monte-Silva KK, Oliveira MB, Santos AA, Nitsche MA, et al. Effects of transcranial direct current stimulation coupled with repetitive electrical stimulation on cortical spreading depression. Exp Neurol. 2007;204:462–6.
119. Mosayebi Samani M, Agboada D, Jamil A, Kuo M-F, Nitsche MA. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. Cortex. 2019;119:350–61.
120. Purpura DP, Mcmurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
121. Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans: effect of tDCS on cortical excitability. J Physiol. 2013;591:1987–2000.
122. Jefferys JGR, Deans J, Bikson M, Fox J. Effects of weak electric fields on the activity of neurons and neuronal networks. Radiat Prot Dosim. 2003;106:321–3.
123. Alexander JK, Fuss B, Colello RJ. Electric field-induced astrocyte alignment directs neurite outgrowth. Neuron Glia Biol. 2006;2:93–103.
124. Li L, El-Hayek YH, Liu B, Chen Y, Gomez E, Wu X, et al. Direct-current electrical field guides neuronal stem/progenitor cell migration. Stem Cells. 2008;26:2193–200.
125. Datta A, Elwassif M, Bikson M. Bio-heat transfer model of transcranial DC stimulation: comparison of conventional pad versus ring electrode. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc. 2009;2009:670–3.

5 Animal Studies on the Mechanisms of Low-Intensity Transcranial Electric Stimulation

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5.1 Neuronal Polarization and Need for Amplification

In this section, we discuss the acute effects of weak electric fields at the level of a single neuron. While electric fields produced in the brain during low-intensity transcranial stimulation in humans (e.g., tDCS, tACS) are generally below 1 V/m, we consider here fields of up to 20 V/m as "weak" as they are not expected to activate individual neurons in isolation.

First, we describe the dominant view of the "somatic doctrine" that considers how electric fields affect neurons by incrementally polarizing the soma. Second, we review the somatic doctrine's origin in classical animal studies. Third, we describe the recent advancement in our understanding of the important role played by polarization of dendrites and axons by electric fields. Next, we summarize recent efforts to quantify neuronal polarization. We then outline possible amplification mechanisms of the electric field stimulation, which are generally single-neuron level.

5.1.1 The Somatic Doctrine

Electric stimulation causes current to flow across the brain, which is reflected in voltage differences across the brain [1]. As it flows across the brain, any current that passes through a neuron will cause neuronal membrane polarization. Importantly, electric stimulation does not result in a pure depolarization or hyperpolarization across a neuron. Rather, inward current, which flows from outside to the inside of the neuron, hyperpolarizes the membrane and outward current, which flows from inside to the outside of the neuron, depolarizes the membrane [2, 3]. Since current that enters a neuron must also exit, the polarization of every neuron should be considered in terms of neuronal compartments, in which each compartment (e.g., the soma, a given dendrite branch) experiences its own direction and magnitude of polarization [3].

It is often the case that the compartments at one end of a neuron are hyperpolarized while the compartments at the other end are depolarized, so that the profile of membrane polarization appears as a gradient from one end of the neuron to the other [3]. The relative direction between the neuron morphology and the electric field determines the sign of polarization across compartments. As it has been demonstrated in single-neuron recording, DCS in the "anodal" direction results in depolarization of soma and basal dendrites but hyperpolarization of the apical dendrites in an L5

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pyramidal neuron, with polarization maximal when the electric field direction is parallel to the somatodendritic axis [4]. Reversing the direction of current flow to the "cathodal" direction inverts this polarization profile (Fig. 5.1). For ACS, opposite ends of a neuron remain polarized in opposite directions, with the polarities alternating with each ACS phase [6–8]—as the direction of current flow switches between the anodal and cathodal directions.

Polarization of soma can shape the excitability of a neuron as it plays an important role in action potential generation. The "somatic doctrine" tries to explain the effects of the electric field based on somatic polarization alone. As summarized below, early studies in animal models supported

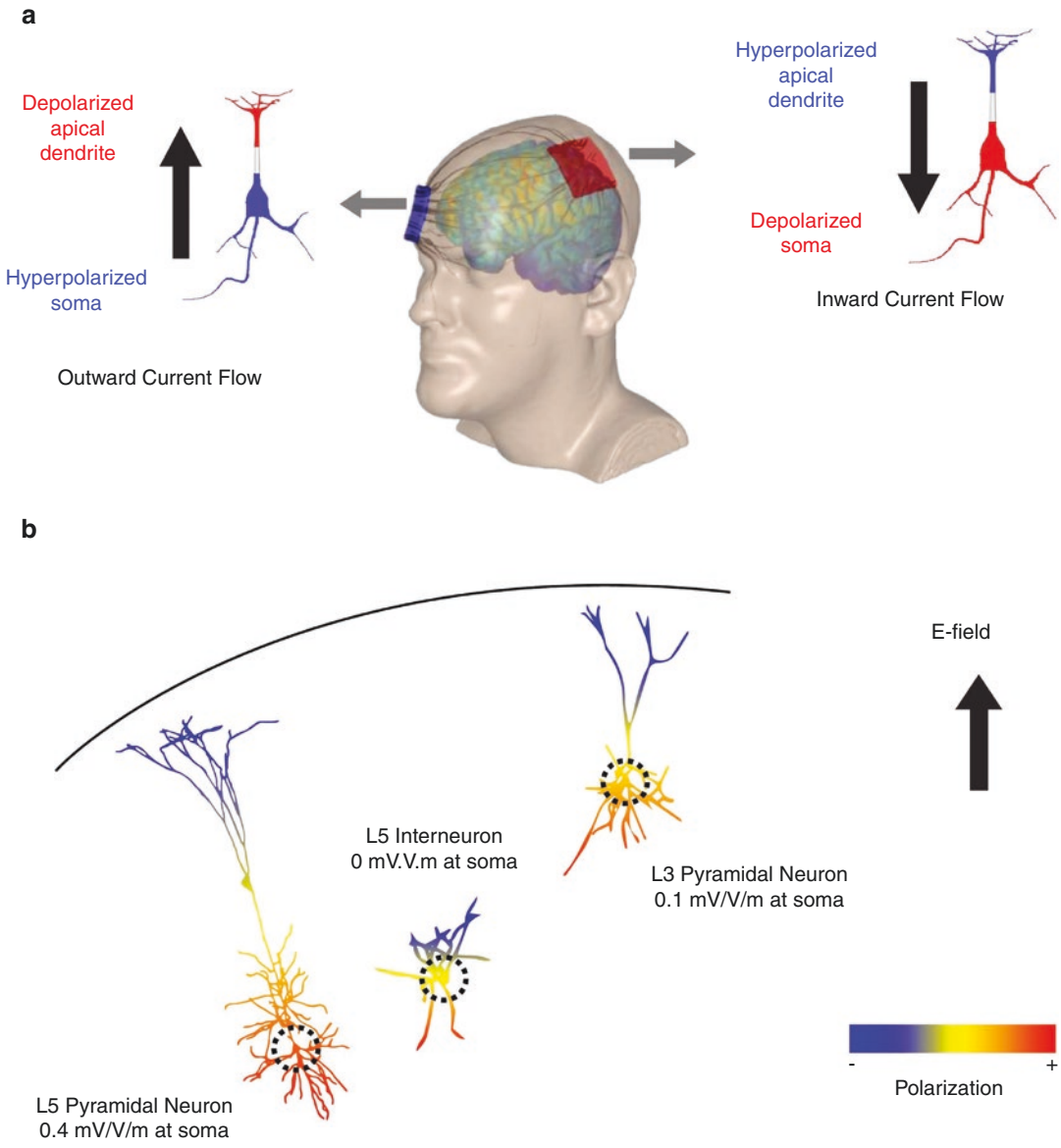

Fig. 5.1 The principle of somatic doctrine and polarization (Adapted from Ref. [5]). (**a**) Schematic of how a neuron will be polarized under different electric field polarities. (**b**) Quantification of somatic polarization in cortical neurons of rats during DCS

soma-centered explanation for changes in firing rate, and ongoing studies expanded on such effects. At the same time, polarization by electric fields of other neuronal compartments such as dendrites, axon hillock, and axon has been shown to affect the excitability of neurons. Human studies are predominantly designed and interpreted in light of somatic polarization. Indeed, the canonical human neurophysiology tDCS that heralded our contemporary area of low-intensity tES studies reported polarity-specific effects consistent with the somatic doctrine [9]. However, ongoing human studies show nuanced dose and polarity response [10]. Thus, for all its limitations, the somatic doctrine remains an important basis to start understanding weak stimulation mechanisms.

We emphasize that the current has a complex spatial flow in the brain during electric stimulation. In a lissencephalic brain, brain regions under the anode electrode and cathode electrode are exposed to radially-inward (anodal) and radially-outward (cathodal) direct current flow; however, intermediate brain regions are stimulated with tangentially-direct current flow [11]. For folded cortex, current crossing across gyri can create a highly mixed pattern of directionality even directly under electrodes, though overall there is more inward/outward radial current near the anode/cathode [12]. The application of the somatic doctrine, as used in explaining tDCS clinical studies, assumes a consistently directed radial current flow in a region of interest and assigns no somatic polarization in regions with tangential current flow. Tangential currents cannot simply be overlooked as animal studies have demonstrated that tangential current flow affected synaptic efficacy acutely during DCS in hippocampal and cortical slices [3, 12, 13]. Cortical folding is thus a complication concerning the directionality of the current flow and resulting polarity-specific somatic polarization. Electrode montage influences the nonuniformity of the electric field across cortical patches. Consequently, the somatic doctrine is dependent on electrode montage, and this can complicate the interpretation of clinical results [14].

5.1.2 Early Evidence on Modulation of Excitability, Polarity-Specific Effects

While a historical review of electric stimulation is beyond the scope of this chapter, it is helpful to review a few early studies, which motivated the somatic doctrine. In 1870, a report on the effects of electric stimulation on the brain by Fritsch and Hitzig demonstrated that a negative current can suppress cortical excitability while a positive current can enhance it [15]. (Positive and negative here means inward and outward flow of positive charges, respectively. In clinical studies, they are referred to as anodal and cathodal stimulation.) This early finding suggested that the brain is electrically excitable. Later, it was revealed that electric stimulation is capable of modulating ongoing firing patterns whereby a positive current stimulation increased neuronal firing rate and a negative current stimulation had an inhibitory effect on neural discharges [16, 17]. To explain their observation, Creutzfeldt claimed that changes in neural excitability are epiphenomenal results of electric stimulation [17]. Terzuolo and Bullock assigned a physiological role to electric field stimulation [16]. The recent work on the effects of electric field stimulation is mostly in agreement with the latter hypothesis suggesting a direct effect of electric field on excitability [18–21]. The polarity of these effects is consistent with the polarization of the soma, namely, positive currents will depolarize the soma and therefore facilitate firing [13]. However, there has been recently an ongoing debate on whether peripheral nerve stimulation can have a causal role in the reported effect with regard to tACS [22, 23].

The polarity-specific effects on neural firing were confirmed by further animal studies in the early 1960s [24, 25]. Additionally, the change in excitability due to the electric field seems to accumulate over time and can outlast the period of stimulation. These results alongside other findings such as modulation of epileptic discharges [26] and lasting effects through protein synthesis [27] supported the importance of the somatic doctrine in explaining the effectiveness of the electric field.

5.1.3 Polarization of Nonsomatic Components

One might wonder whether the somatic doctrine can explain the range of effects that have been reported due to electric field stimulation. To answer this question, we need to emphasize that other compartments, such as dendrites, axon, and terminals, also undergo membrane polarization during electric field stimulation, and they are overlooked in the somatic doctrine (Fig. 5.1). There is a risk that this simplification is misleading when interpreting results or designing a new experimental setup.

Dendritic trees are also electrically excitable membranes, and electric stimulation can influence them to evoke subthreshold or suprathreshold activities [28]. In a pyramidal neuron, membrane polarization of basal dendrites has the same sign as the soma, while the apical dendrites are polarized in the opposite direction [2, 3]. Subthreshold stimulation can influence the synaptic input since electric fields can change the strength of dendritic input in the postsynaptic neurons [29]. This can be a key factor in the modulation of synaptic plasticity, and it is discussed in more detail in Sect. 5.6.2. Dendrites are also capable of exhibiting activities such as spiking during a suprathreshold stimulation [2, 30–32]. It is worth noting that star-shaped neurons such as basal ganglia neurons and thalamocortical cells can be polarized in the same way with different electric field directions [14].

Axons are also sensitive to electric fields. The magnitude and sign of axonal polarization depend on their morphology [33–35]. While the initial segment of the axon is most likely polarized with the same sign as soma [30], this assumption does not necessarily hold up for the rest of the axon. Acute brain slice studies indicate that electric field stimulation can modulate the excitability of axons by measuring changes in presynaptic (antidromic) volley [3, 13, 36]. An interesting finding in a recent intracellular study in mouse cortical slices demonstrated that the axonal terminals are four times more sensitive to electric field stimulation compared to the soma [37]. They also showed that modulating membrane potential of axonal terminals can shape action potential dynamics and synaptic input.

5.1.4 Membrane Polarization and Coupling Constants

Quantifying polarization of various compartments is a key step toward developing a predictive understanding of the effects of electric stimulation. Using electrophysiological recording from the turtle cerebellum, Chan et al. measured the amount of polarization during stimulation with a very low-frequency sinusoidal current [30, 38]. They reported that morphology details of a neuron are key factors determining the sensitivity of a neuron to electric stimulation. Using the rat brain slice, this work has been extended to hippocampal and cortical neurons with the approach of intracellular recording of polarization during weak DCS [3, 12, 39, 40]. The basic observation is that membrane polarization increases linearly with field magnitude [3], provided the fields are small enough, that is, <30 V/m [4], to not engage nonlinear channel properties. In other words, stimulation intensities are not strong enough to significantly activate voltage-gated channels, and thus the passive properties of membrane determine the amount of polarization.

The amount of polarization that is induced by an applied electric field in this linear regime can be quantified by the coupling constant, also referred to as the "coupling strength" or "polarization length" [4]. Under a uniform electric field, the membrane polarization, V_{tm} (in Volts), can be expressed as: $V_{tm} = G^*E$, where G is the coupling constant (in V per V/m, or simply: m) and E is the electric field (in V/m) along the somatodendritic axis. Based on experimental results, the somatic coupling constant, G, was reported to be in the range of 0.1–0.3 mm for hippocampal and cortical pyramidal neurons in rats [3, 4, 6]. Additionally, the measured coupling constant of ferret cortical neurons is approximately 0.25 mm [18].

The orientation of a neuron with regard to the electric field affects both sign and magnitude of coupling strength. In other words, the maximum

magnitude of polarization across the somatodendritic axis occurs when the electric field is parallel to this axis [3, 30]. This corresponds to an electric field radial to the cortical surface. Additionally, the magnitude of somatic polarization depends on the length of the neuron and the dendritic asymmetry around the soma in accordance with both experimental [4, 41] and computational studies [42]. Polarization is strongest at the distal ends of a neuron, whereas there is no polarization of the middle compartments of the neuronal structure. Therefore, interneurons with a soma in the center of the cell will not experience somatic polarization, whereas pyramidal neurons that have a soma located at the basal end of the cell will experience relatively stronger somatic polarization [4].

So far, we have discussed findings on the amount of polarization during DCS. To address the same issue during ACS, Deans et al. demonstrated an approximate inverse relationship between the amount of polarization and frequency of stimulation [6]. According to their results, the effects of ACS at 10 Hz were similar to those of DCS, while the effectiveness of the electric field decreased with frequency due to the capacitive properties of the neuronal membrane. This inverse relationship suggests that high-frequency stimulation should be less effective.

The coupling constant has thus far only been measured in animal models, and we have no direct measures of human cortical neurons. Biophysically realistic models of cortical L5 neurons suggest that somatic membrane polarization does not vary considerably between rats and humans [42]. Nonetheless, generally longer human neurons may polarize more strongly, and it would be important to make direct empirical measures of this important variable.

Measurement of the electric field in the human brain revealed that the peak of the electric field in the brain is about 0.3 V/m for 1 mA current intensities [43]. Considering this electric field intensity, the maximum somatic polarization for the most sensitive neurons is about 0.1 mV. With 2 mA tES which is fairly prevalent in clinical trials, somatic polarization will be less than 0.2 mV. Compared with the endogenous background activity in the brain, this amount of polarization is relatively small. Alongside the results from animal studies and the minimum electric field needed to observe a meaningful effect of electric stimulation, one might ask how this small amount of electric stimulation can alter behavioral outcomes in humans. In what follows, we try to explore the possible answers to this question on the level of a single neuron or a network of neurons.

5.1.5 Amplification Through Both Timing and Rate

At the level of a single neuron, a weak electric field can modulate the occurrence of action potentials. An action potential is an all-or-none response that occurs when the somatic membrane potential is sufficiently depolarized. Once this threshold is reached, the neuron is said to "fire" or "spike." The threshold of depolarization needed to generate a spike in action potential varies with the type of neurons but, in general, is about 20 mV above the resting potential. Since weak tES is unable to polarize a neuron to this extent, the effect of polarization can only modulate ongoing activity by facilitating or suppressing neuronal firing. One frequent argument is that neurons are close to the threshold of firing due to ongoing activity. Consequently, a small amount of polarization can make a significant change in spiking behavior. Animal experiments have demonstrated modulation of both the firing rate and the specific timing of action potentials [6, 7, 16, 18, 19, 21, 44].

In 1965, Terzuolo and Bullock used a preparation of the nonadapting stretch receptor of the crayfish abdomen and also of the cardiac ganglion of the lobster to study the effect of electric fields on neural firing [16]. They were able to show that neural firing in an active state was remarkably influenced by DCS as low as 1 V/m in a single neuron. In addition, current intensities of more than 20 times of this amount were needed to elicit a spike when a neuron is at rest state. Reato et al. demonstrated an effect of weak electric stimulation on gamma activity in vitro with field magni-

tudes as low as 0.2 V/m [19]. Computational modeling suggested that this modulation was significantly affected by network interactions. Recently, Vöröslakos et al. reported that fields of 1 V/m can achieve a significant effect on spiking activity in deep layers of the rat visual cortex [44]. However, this intensity was not strong enough to modulate network oscillations.

As we mentioned earlier, weak electric fields can also modulate spike timing when a neuron is in an active state. Using intracellular depolarizing current injection into CA1 pyramidal neurons (Fig. 5.2a), Radman et al. found that DCS can modulate the latency of spiking depending on its polarity [7]. Positive DCS can shorten this latency while negative DCS can increase it compared to the control condition. Moreover, they also reported that changes in spike latency can be quantified by multiplying electric field-induced membrane polarization by the inverse of the current ramp slope (Fig. 5.2b, c). Therefore, the slope of the current ramp is the gain for the amplification, and DCS can be more effective in spike latency modulation when this slope is smaller. Another interesting finding in their work is how ACS can modulate oscillatory responses generated by current injection in a neuron. They found that an alternating electric field as low as 1 V/m is able to induce coherent spiking in neurons oscillating at 30 Hz, that is, gamma oscillation. Later, a more detailed quantification was introduced to describe the relationship between the spike timing phase and the coupling constant for biophysically realistic CA1 pyramidal neurons [45]. It is essential to note that the reported effect can only be due to amplification at a single neuron level. Research on entrainment in neural networks during ACS has indicated that electric fields as low as 0.2 V/m can be significantly effective [19]. By comparing these values, one might suggest that amplification can be enhanced more at the network level.

It is not clear how these in vitro results in rodent slices translate to clinical studies. Krause et al. performed single- and multiunit activity recording from the prefrontal cortex of macaque [46]. Their gyrencephalic cortex and skull thickness, which is close to that of humans, make macaque an ideal animal model. Their study revealed that the spike timing could only be modulated by tDCS with intensities similar to those used in clinical trials while the firing rate is not affected. In addition, intracellular recording from neurons in deep brain structures demonstrated that tACS with intensities within the range of human experiments affected spike timing but not spiking rate in alert nonhuman primate [47]. Overall, these results suggest that low-intensity electric fields are capable of shaping neural activity in the human brain.

What can explain these aforementioned sensitivities to weak electric stimulation in an active state? One frequent argument is that neurons are close to the threshold of firing due to ongoing activity. Consequently, a small amount of polarization can make a significant change in spiking behavior. It is important to emphasize that the level of amplification can depend on neuron types since the coupling constant is not the same for all types of neurons.

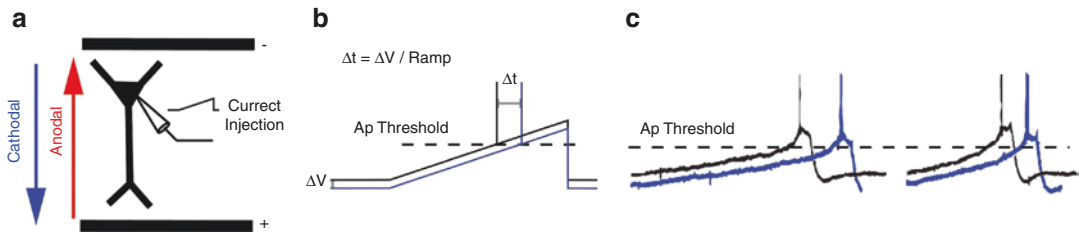

Fig. 5.2 (**a**) Schematic of the experimental setup in which a depolarizing current ramp is injected into a pyramidal neuron during DCS or control condition. (**b**) Schematic of timing amplification. (**c**) Intracellular response to depolarizing current ramp with 0.4 nA/s (left) and 0.7 nA/s (right) in control (black) and cathodal DCS (blue) conditions (Adapted from Ref. [7])

While low-intensity tES has subthreshold effects on neurons, simultaneous electric field stimulation with ongoing neural activity can result in suprathreshold responses and long-lasting changes in neurons. However, it is still an ongoing debate on whether to apply the electric field before or during a behavioral or cognitive task [48].

5.1.6 Seizure Threshold and Modulation

Since somatic polarization is a key factor in triggering seizures during stimulation, considering the coupling constant can be insightful with regard to field intensities capable of modulating seizure activity. Conventional tDCS in humans can generate <1 V/m electric field in the brain resulting in subthreshold membrane polarization. In contrast, TMS or deep brain stimulation is able to produce fields of 100 V/m which generates suprathreshold activation of neurons. In vitro animal studies showed DCS over 20 V/m, which corresponds to >60 mA tDCS, can generate spikes in neurons with the most sensitivity to electric fields [7]. Additionally, it is reported that electric fields about 100 V/m, which corresponds to >500 mA tDCS, are capable of triggering epileptiform activity in acute hippocampal slices [3]. It is noteworthy that these values were recorded in quiescent brain slices and they may vary in an active network. In line with somatic doctrine, experimental results suggest that electric fields as low as 1 mV can affect ongoing epileptiform activity [49–53]. In particular, negative DCS can suppress ongoing epileptiform activity due to hyperpolarizing soma, and positive DCS can enhance this activity because of further somatic depolarization.

5.2 Synaptic Processing and Plasticity

Many of the effects discussed above are acute, that is, they are observed during the period of stimulation and disappear when stimulation stops. However, clinically we are interested in changes that outlast the period of stimulation. It is often argued that the lasting effects of stimulation of tDCS may be mediated by synaptic plasticity [40, 54–57]. Synaptic plasticity is known to be one of the underlying mechanisms of learning and memory formation [58]. This section addresses the contribution of animal studies to understanding plasticity generated by weak DC electric fields only. We do not have enough data on AC electric fields.

Animal studies in the 1960s established that weak DCS could produce lasting physiological changes in neural activity. These sustained changes could not be explained as persistent "reverberating circuit" of activation [27, 59]. Especially notable are the animal studies by Bindman and colleagues that showed that prolonged DCS can produce polarity-specific and lasting changes in cortical excitability [24]. This motivated their early work treating depressive patients with tDCS [60, 61]. Persistent changes in excitability were observed in a study using stimulation protocols lasting up to 13 min in humans [9, 62]. These multi-minute protocols are frequently adopted in tDCS research. Lasting changes with ACS have recently been demonstrated in animals when endogenous neural oscillations were present [21]. Long-lasting changes beyond the transient effects of DCS- and ACS-induced polarization would require synaptic changes or changes in neuronal excitability [40, 54, 63, 64]. In a recent study, the impairment of LTP of cerebellar purkinje cells resulted in the elimination of the effect of anodal DCS on vestibulo-ocular reflex habituation [65]. This study depicts the dependency of DCS-induced positive effect on underlying plasticity during a cerebellar task. Moreover, both in humans and animal studies, changes in synaptically mediated evoked responses are considered reliable hallmarks of long-term plastic changes that could support lasting clinical effects [40, 46, 64, 66–68].

5.2.1 Paradigms for Modulation of Synaptic Plasticity by Electric Stimulation

Animal studies of tES allow us to formulate and test distinct theories on how stimulation can lead

to lasting changes in function. Electric fields generated by tES are subthreshold. They are too weak to trigger an action potential in quiescent neurons, resulting in only transient polarizations. These acute effects can lead to lasting changes in synaptic efficacy mediated through different paradigms such as the following:

1. Modulation of membrane polarization due to the electric field may induce changes in synaptic efficacy regardless of any past, ongoing, or future synaptic activity or state of the neuron. However, weak polarization was not sufficient to induce plastic changes in synaptic efficacy in cortical brain slice models, when there is no background activity [40].
2. Changes in action potential rate or timing, secondary to neuronal polarization, may affect synaptic efficacy since they are important factors in determining synaptic plasticity. Classic animal studies indicated that weak DCS is sufficient to induce short- and long-term plastic changes [25, 27]. However, these studies do not directly provide a causal link between altered neuronal activity during stimulation and prolonged after-effects.
3. Incremental polarization of the membrane in combination with ongoing synaptic activity may induce synaptic plasticity. The theory is that the induction of plasticity requires synaptic coactivation during ES. It has been shown that in vitro synaptic potentiation under anodal stimulation only occurs with concurrent synaptic stimulation at specific frequencies [40]. In a rabbit study, DCS was combined with repeated somatosensory stimulation leading to polarity-specific lasting changes with cathodal stimulation [64]. If one assumes that tES exerts a postsynaptic priming effect, that is, polarization of soma, then coactivation of afferent synaptic input could be conceived as Hebbian reinforcement. This learning mechanism has been shown in cortical slice models as well as in vivo [69, 70]. Clinically, this plasticity paradigm is broadly analogous to combining tES with a cognitive task or specific behavior that coactivates a targeted network or combining tES with TMS [71–74].
4. Incremental polarization of the membrane may boost ongoing endogenous synaptic plasticity similar to a model of associative learning [64] and has been shown to follow the rules of Hebbian plasticity—specificity and associativity in hippocampal slices [54]. Clinically, this paradigm is analogous to combining tES with training [75]. Synaptic plasticity experiments typically distinguish between a long-term potentiation (LTP) of synaptic efficacy and long-term depression (LTD). It has been shown in rat visual cortex slices that the same tetanic stimulation induced LTD or LTP depending on the level of polarization of the postsynaptic neuron [76]. Hence, incremental polarization of the membrane may modulate LTP/LTD.
5. Meta-plasticity is defined as sustained polarization before or after the generation of endogenous plasticity that "primes" the brain to respond differently to potentiation [77]. Evidence from brain slices shows that priming with DCS modulates subsequent tetanus-induced synaptic plasticity in a polarity-specific manner [78].
6. Oscillatory network dynamics that induce LTP, which when modulated, can result in lasting effects of electric fields [21, 79]. Such modulation may reflect interference with the finely tuned excitatory-inhibitory synaptic balance during oscillations [19].
7. Synaptic tagging and capture hypothesis could offer another explanation for the observed effect of ES [80, 81]. In this case, ES might be guiding the process of formation of molecular tags for some plasticity proteins whose synthesis is induced by successive strong synaptic stimulation, either tetanic or theta-burst. There might be different origins for the formation of these molecular tags ranging from ES exposure-induced modification of existing proteins to changes in spontaneous neuronal spiking and/or miniature synaptic potentials, or even the expression of new proteins by early gene induction. DCS is indeed shown to modulate the response to a successive protocol of synaptic potentiation in a polarity-specific manner [78].

The influence of DCS on cortical plasticity has also been demonstrated in humans [82, 83].

Aside from these possible synaptic plasticity effects, there may be nonsynaptic origins of lasting plastic changes following ES. Though the synapse is typically considered the locus of plastic changes, "nonsynaptic" changes have been noted after DCS in peripheral axons [63]. In brain slice models, where background synaptic activity is absent, orthodromic synaptic and antidromic nonsynaptic axonal inputs can be precisely isolated. This allows more precise isolation of synaptic and nonsynaptic mechanisms. However, functional outcomes of nonsynaptic changes in the CNS would still be expected to affect synaptic processing [84].

5.2.2 Effects of Direct Current Stimulation on LTP and LTD In Vitro

A wide array of animal studies using tetanic stimulation to induce LTP/LTD have demonstrated multiple forms of plasticity involving distinct pre- and postsynaptic mechanisms on distinct time scales. DCS-induced lasting changes in excitability were reported [24] a decade before the well-lauded discovery of LTP by Bliss and Lomo [85]. However, the research on tetanic LTP outpaced the investigation of the DCS-induced plasticity changes.

LTP/LTD induced by either tetanic stimulation or DC may, unsurprisingly, share some common molecular substrates [27, 78, 86]. NMDA receptor-mediated LTP/LTD are the most common forms [87] and have been implicated in lasting tDCS effects in both humans [88] and rodents in in vivo [89] and in vitro DCS-induced plasticity [40, 55].

DCS with the anode closer to CA1 apical dendrites is referred to as anodal stimulation as this corresponds to a positive inward current for cortical pyramidal neurons. Conversely, DCS with the cathode closer to CA1 apical dendrites is referred to as cathodal stimulation. So anodal DCS would depolarize soma and basal dendrites and hyperpolarize apical dendrites. Conversely, cathodal DCS would hyperpolarize soma and basal dendrites and depolarize apical dendrites. A study done by the Grassi group in hippocampal CA3-CA1 synapses exhibited an increase and decrease in LTP with anodal and cathodal DCS, respectively [78]. Subsequent studies highlighted the fact that DCS modulation effects are not as binary and simple [54, 55]. These studies identified DCS as a modulator of synaptic activity, not its inducer. They also brought attention to the dependency of the DCS-modulation effects on spatial and temporal patterns of endogenous synaptic activity. When DCS at 20 V/m was coupled with tetanic plasticity induction, anodal stimulation enhanced LTP in basal dendrites while cathodal stimulation enhanced LTP in apical dendrites. Interestingly, both anodal and cathodal stimulation modulated LTD in the same direction [55]. This asymmetry of DCS effects might arise from ceiling effects of one/multiple cellular processes that design the endogenous state in a way that its modulation is allowed only in one direction.

Afferent axonal polarization is shown to drive the changes in synaptic activity during DCS [39]. The observed changes are probably due to the orientation of pre- and postsynaptic neurons relative to the electric field. Paired pulse analysis in both rabbit and rodent models also pointed to the presynaptic origin of these tDCS-induced effects [64, 89], while the other studies did not find tDCS affecting the presynaptic component [55]. There is a unified emphasis on the DCS-induced change in the postsynaptic membrane potential during the endogenous synaptic activity that drives its effects on ongoing synaptic activity [39, 54, 55, 78]. In any event of DCS, there is simultaneous depolarization and hyperpolarization of different compartments within the same neuron, that is, the polarity of soma and the basal dendrites is opposed to that of apical dendrites and that leads to varying effects as discussed below.

Contrary to the DCS-induced effects on tetanic-LTP, the modulation of TBS-LTP is not as complex as depicted by the studies done in CA1 Schaffer Collateral synapses (Fig. 5.3). Irrespective of the dendritic location of the elec-

trodes, anodal stimulation augments the existing LTP, whereas cathodal DCS seemed to not affect LTP in either of the compartments [54]. Why is this discrepancy in the observation of DCS effects in the two scenarios? This could be explained by the general principle proposed by Kronberg et al. [54]. In an event of endogenous plasticity being primarily driven by the somatic sources of depolarization, for example, spikes, as is the case with TBS-LTP, DCS-induced polarization at the soma determines the effects on plasticity. In this case, no matter the dendritic location, anodal stimulation will depolarize the soma that will result in an enhanced LTP. Direct evidence from intracellular recording studies has demonstrated that DCS increased postsynaptic somatic spiking. This resulted in enhancement of TBS-LTP [90]. When dendritic sources of depolarization, for example, subthreshold depolarization of dendritic spikes, primarily drive the endogenous plasticity, such as in most of the tetanic-LTP forms, DCS-induced polarization at the dendrite determines the effects on plasticity. Since different dendritic segments do not share the same sign of polarity, the observed modulation of synaptic plasticity varies depending on the type of stimulation and the location of electrodes. It is, therefore, the interaction between the induced electric field, neuron morphology, and the endogenous brain dynamics that determines the DCS-mediated synaptic function output [54].

In the same study, ACS (5 Hz) when coupled with TBS bursts that were timed to either the peak or the trough of the sinusoidal AC resulted in the modulation of TBS-LTP as described (Fig. 5.3c). The applied electric field at the peak of the AC was identical to anodal constant current, whereas the one at the trough of the AC was identical to cathodal constant current. The effects of AC were similar to those of the analogous constant current paradigm, indicating that plasticity modulation is consistent with the instantaneous incremental membrane polarization on a millisecond timescale [54].

Another emerging aspect is the compliance of Hebbian rules by DCS modulation. The modulation effects of DCS are not only input specific but also exhibit associative properties [54]. These

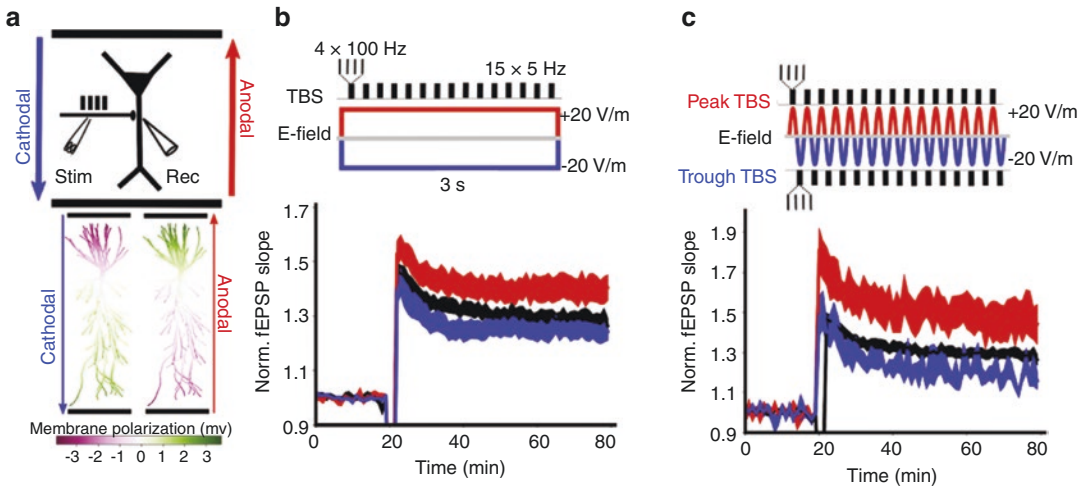

Fig. 5.3 Effect of electric fields on TBS-induced LTP in the hippocampal Schaffer Collateral pathway. (**a**) Top: Schematic of the experimental setup, showing the orientation of electric fields generated by parallel wires (black). Location of stimulation (Stim) with TBS and recording (Rec) of fEPSP are indicated relative to a CA1 pyramidal neuron soma (black triangle). Bottom: Membrane polarization throughout a model pyramidal neuron in response to 20 V/m anodal (red) or cathodal (blue) DCS. Green compartments are depolarized due to DCS, while magenta compartments are hyperpolarized by DCS. (**b**) Constant current stimulation applied during TBS modulates the resulting LTP. (**c**) ACS (5 Hz) was applied and TBS bursts were timed to either the peak (red) or the trough (blue) of the sinusoidal AC. LTP was induced at the 20 min mark. (Adapted from Ref. [54])

results align with the tDCS-induced facilitation of associative learning in the primate brain [46].

Since electric stimulation has a distinct modulatory effect on various compartments of the neuron (see Sect. 5.6.1), the interaction between the multiple compartments makes it difficult to predict the outcome on synaptic plasticity. Prolonged tDCS will trigger effects operating on both shorter time scales, for example, membrane polarization and plasticity induction, as well as longer time scale, for example, cell motility and immune responses. Different mechanisms will then interact with each other to produce the results.

5.2.3 Molecular Mechanisms of tES-Induced Effects on Synaptic Plasticity

Since the tES-induced effects are primarily driven by the influence on the underlying synaptic plasticity, it is no surprise that the molecular underpinnings of these observed effects are similar to what forms the basis of induction and maintenance of synaptic plasticity. For example, the BDNF/TrKB pathway, which is a potent modulator of these common forms of LTP/LTD [91], has also been implicated in lasting tDCS effects in both humans and in vitro animal studies [40, 78]. BDNF/ TrkB was also shown to mediate the metaplastic effect of anodal DCS on the induction of hippocampal CA1 LTP [92]. In addition, BDNF val66met polymorphism, which partially affects activity-dependent BDNF secretion, impaired motor skill acquisition in both humans and mice [24]. The enhancement of anodal tDCS-induced motor learning was subjective to the secretion of activity-dependent BDNF.

Toward the end of the twentieth century, stimulated brain slices were probed for different possible molecular targets. DCS was found to affect cyclic adenosine monophosphate "cAMP," the protein kinase C family "PKC," and calcium, each of which play a role in LTP/LTD [86, 93]. Recent in vivo animal work has shown the dependency of lasting tDCS effects on the adenosine A1 receptor [64] and NMDA receptor activation [89]. In vitro current stimulation of brain slices led to an immediate increase in the c-*fos* and *zif268*, two of the immediate early genes known to regulate downstream target genes [78]. These genes play an important role in the maintenance of long-term neuronal changes and memory formation [94–98].

It is highly probable that multiple other signaling events, including but not limited to phosphorylation, recruitment, or shuffling of various synaptic proteins, mediate tDCS effects. The manner of interaction between the primary, polarizing effect of tDCS and the molecular mechanism still eludes us. We are yet to fully leverage the wealth of techniques and tools developed by tetanic stimulation LTP as well as TBS-LTP research to deconstruct the mechanistic pathway of tDCS-induced modulation of synaptic plasticity.

5.3 Morphological Changes

A plethora of in vivo and in vitro studies have highlighted the influence of high-intensity electric fields of more than 50 V/m on nervous development and regeneration [99, 100]. While not necessarily "weak" (as focused on in other sections of this chapter), and in some cases directed to peripheral nerves with microelectrodes, these results suggest a novel mechanism that may impact tDCS/tACS outcomes. Electric fields are known to govern the directed migration of neuronal cells, also referred to as electrotaxis. This is further linked to development, membrane protein redistribution, cell proliferation, and recovery from injury [100–102]. A study in the medullary explants from chick embryos exposed to an electric field of ~60 V/m featured the preferential growth of neural processes toward the cathode and their stunted development toward the anode [103]. Electric fields also affected the growth rate of the neurites, as they could grow about three times faster toward the cathode at 70 V/m [104].

Electrotaxis has been extensively characterized in vivo. Application of 1 μA of current for 3 weeks to a sprouting rat nerve resulted in an

increase in responsiveness with cathodal stimulation, when cathode was placed in the direction of growth of the sprouting nerve, in the hind paw sensitivity assessment [105]. Physiological correlates have also been measured in association with the functional recovery of the neurons exposed to low-intensity extracellular fields. Administration of 30-min currents generating fields of approximately 10 V/m for 20 days, after the cut-suture intervention of the sciatic nerve, resulted in nerve regeneration and electromyographic (EMG) activity in 67% of the animals receiving stimulation. Here too, growth was directed toward the cathode, as compared to only 17% growth toward the reversed polarity [106]. Subsequent studies further supported an increase in neurofilament growth toward the cathode in damaged sciatic nerves [107], morphological regeneration after nerve transection [108], and complete recovery of associated function [109].

Two plausible mechanisms underlie the axonal growth and guidance. First, the number of cytoplasmic projections that guide axonal growth, also referred to as filopodia, toward the cathode is double that of the ones growing toward the anode [110]. This might be serving as an augmentation mechanism, not a necessary one, since galvanotropic behavior is seen without filopodia. The second mechanism is electric field-induced receptor migration [110]. Acetylcholine (Ach) receptors were shown to cluster towards both the anode and the cathode during DC stimulation of Xenopus muscle cells at 400 V/m for 20–40 min, followed by continued accumulation toward the cathode [111, 112]. These receptors can increase intracellular calcium concentration via second messenger pathways. This localized shift of intracellular calcium might then promote the growth of neural processes.

In addition to affecting the axonal growth and guidance, electric fields are known to affect the dendritic spines as well. In an ischemia rat model, daily 10 Hz, 0.1 mA tDCS over a period of 2 weeks increased spine density and improved motor function [113]. Anodal tDCS at 2.2 mA/m^2, when combined with electrical forepaw stimulation, increased spine density and enlarged head sizes of new spines in the sensorimotor (M1/S1) cortex [114]. This tDCS-induced regrowth of dendrites and axons was further supported by the upregulation of MAP-2, a critical protein in dendritic outgrowth and remodeling, and GAP-43, a protein found in axonal growth cones [115]. DCS at 25 V/m and 50 V/m applied to differentiated neurons in vitro increased GAP-43 expression as well [102].

5.4 Network Effects

How electric field stimulation can modulate a neural network has been an active area of research. The activity of neurons in an active network is different than those of neurons in a quiescent state. Similarly, electric field stimulation can produce responses in an active network not expected from single neurons. These responses are specific to the network's architecture and level of activity. A key aspect of network activity is rhythmic firing which results in oscillatory brain signals. Both clinical trials and animal experiments reported that electric stimulation modulates oscillations in the brain [79, 116]. It is essential to emphasize that the underlying mechanisms are not the same for different endogenous oscillations in the brain, for example, slow-wave, alpha, or gamma oscillations have entirely different physiological origins. Consequently, the effects of electric field stimulation on active networks are likely to depend on network dynamics leading to each type of oscillation. In this section, we summarize animal studies on how electric stimulation can affect activities within neural networks with different techniques of stimulation and outline the suggested explanatory mechanisms to this date.

Slow-wave oscillations that are common during sleep consist of a succession of high firing activity (Up state) and almost no spiking state (Down state) [117]. Frölich et al. showed that anodal DCS (soma-depolarizing) can significantly reduce the duration of the Down state, while the Up state was unchanged by weak electric fields. Based on their hypothesis, this resulted in a reduction of the oscillation period. In rat hippocampal slices, amplitude of gamma

oscillations can be modulated with DCS, and the modulation is strongest when applied fields are oscillating at theta frequencies [19]. Later, the same group showed that prolonged DCS caused lasting effects on gamma oscillations and multi-unit activity [21]. Recordings in nonhuman primates showed that tDCS with 2 mA had a significant effect on local field potentials in a broad range of frequencies [46], although there are some concerns that this may be the result of physiological artifacts also observed in human EEG [118].

tACS has been used as an intervention to target specific oscillatory patterns in the brain [119, 120] (Fig. 5.4a). Studies on mechanisms of action include both in vivo and in vitro experiments. One such mechanism is resonance whereby ACS modulates endogenous activity at the same frequency of the stimulation [18, 19, 121]. For instance, fields as weak as 0.2 V/m are able to enhance the firing activity during gamma oscillation in hippocampal CA3 if the frequency of oscillation matches that of the endogenous rhythm [19]. ACS within the frequency range of cortical slow oscillations can also entrain endogenous activity in anesthetized rats [122]. Stronger fields managed to entrain a larger number of neurons, consistent with findings from in vitro experiments [6]. A study in awake head-fixed ferrets [123] suggests that low-intensity electric fields (<0.5 V/m) can selectively entrain alpha oscillations (11–17 Hz).

What are the mechanisms underlying the aforementioned effects of ACS? The proposed explanations are often tied to the specific mechanism underlying a given endogenous oscillation. The temporal biasing of spikes is one possible mechanism for the ACS-induced effects. Small amounts of polarization generated by an exogenous electric field can shift spike occurrence or spike timing when a neuron is close to the threshold of action potential generation. Network entrainment is another way ACS can influence oscillatory behaviors, particularly in a network with coherent oscillation. When the frequency of weak ACS is matched with the endogenous oscillation, time shifts can accumulate over several cycles. This results in a temporal alignment of spiking activity in a network whereby there will be a constant phase difference between applied ACS and native rhythm. In the case of a network with less regular oscillation, ACS can exert its effects through enforcing a firing pattern. In this manner, the exogenous electric field counteracts with the endogenous oscillation. Imposing a firing pattern requires the external electric field to be strong enough to overpower native rhythm.

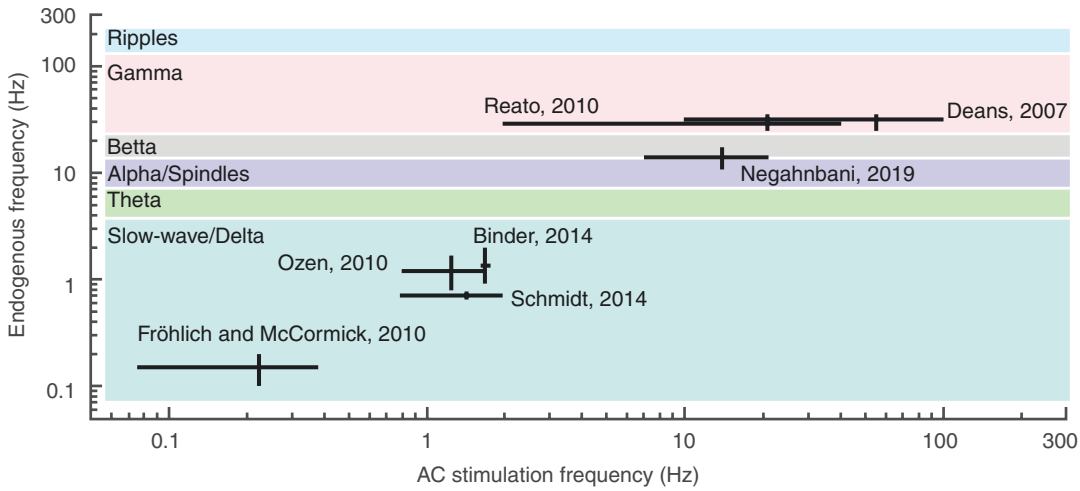

Fig. 5.4 Effects of ACS on a network of neurons (Adapted and modified from Ref. [79]). Schematics of the in vitro and in vivo animal models applying AC (sinusoidal) stimulation on oscillatory rhythms. Colors indicate frequency bands

These endogenous oscillations can be the result of balanced interactions between excitatory and inhibitory neurons. In such networks, excitatory inputs drive inhibitory neurons to control the timing of the network. ACS, when applied, can enhance the temporal alignment of firing patterns of excitatory neurons. This ACS-induced elevated level of synchrony is followed by stronger activation of inhibitory neurons, resulting in increased suppression of excitatory neurons. This suppression can cause the network to "skip a beat" resulting in half as many cycles, that is, half harmonic [6, 19]. For example, the strong ACS-induced modulation of gamma oscillations is a result of an overshoot of the dynamic balance between excitatory and inhibitory interactions. A similar effect was observed with amplitude-modulated ACS [124]. The high-frequency carrier (2 kHz) had only minimal effects, but once modulated in amplitude at lower frequencies (10 Hz), there was a strong modulation of the endogenous gamma rhythm. In temporal interferential stimulation (TIS), a similar amplitude-modulated high-frequency oscillation is generated. Grossman et al. have argued that the spatial selectivity observed in TIS is the result of this specificity of AM-modulated fields [125]. It is not yet clear how the high-frequency stimulation of the carrier becomes more effective when it is modulated in amplitude at lower frequencies. One modeling study suggests an interaction of axonal activation with the high frequency and network adaptation effects as lower frequencies [125].

Networks with slow-wave oscillations (0.5–4 Hz) were also reported to be sensitive to applied ACS [18, 121]. Slow-wave oscillations are identified by synchronized neural activities alternating between Up and Down states. The high level of neural activities during Up state are governed by excitatory interactions. This heightened level of activity is followed by depletion of the available cellular resources and the collapse of the excitatory activities. This leads the network to transition to Down state, where the neurons become quiescent and there is simultaneous recovery of the resources. Consequently, a small amount of depolarization can shift the network to the active states again.

Another proposed mechanism of tACS is the attenuation of neural adaptation. In a nonhuman primate study, Kar et al. applied tACS with 2 mA peak-to-peak at 10 Hz to surface electrodes over the vertex and lateral to the middle temporal area (MT) on the scalp [126]. While they did not observe neural entrainment, they reported tACS-induced attenuation in spiking adaptation to the visual input. Sodium- and calcium-gated potassium channels have been implicated in this adaptation mechanism; therefore, Kar et al. suggest that the 10 Hz field oscillation may affect these channels.

5.5 Interneurons and Nonneuronal Effects

5.5.1 Interneurons

Many interneurons have a relatively symmetric morphology compared with pyramidal neurons. This will result in weaker somatic polarization as reported in both experimental results in cortical slices [4] and biophysically realistic computational models [42]. However, we cannot ignore the effects of polarization of other compartments such as dendrites and axon during stimulation. Additionally, interneurons have a great variety of morphology which includes neurons with asymmetric dendritic trees [127]. The study of interneurons is particularly important because they play a pivotal role in plasticity and brain oscillations [128]. Recent studies have explored the effects of weak electric stimulation on interneurons. For example, DCS modulated paired-pulse facilitation in hippocampal slices suggest an effect of DCS on interneurons [13]. Similarly, computational modelling suggests that ACS could modulate the activity of fast-spiking interneurons through indirect network effects [123]. Further studies are needed to fully characterize the effects of DCS and ACS on the functional and morphological attributes of interneurons.

5.5.2 Glia

Glial cells represent about half of cells in the human brain while the precise glia-neuron ratio varies in different brain regions [129]. Astrocytes, microglia, and oligodendrocytes are three different glial cell types in the CNS. It is increasingly recognized and understood that glial cells do not act only passively as a supportive role for neurons, but rather are actively involved in information processing [130]. There are few studies that have investigated the primary effects of electric stimulation on glia. Any activation of neurons or synaptic function will trigger a secondary glial response—in this sense any tDCS effects on neurons include glial-neuronal interactions. This section however focuses on evidence for primary glial response to electrical stimulation.

Several studies reported that DCS can cause protrusion elongation in both astrocytes and microglia in culture preparations. In addition, cell alignment is possible at higher intensities of stimulation [102]. In such a case, the orientation of microglia is parallel and the orientation of astrocytes is perpendicular to the electric field direction [131]. These studies offered evidence for the responsiveness of glial cells to electric field stimulation as direct effects [131]. Since most in vivo studies focusing on how electric field stimulation affects glial cells have investigated the inflammatory response, we will review them in the next section. Here, we point out other possible mechanisms for modulation of glial cell activities due to electric stimulation.

A computational model suggested that applied electric fields can produce polarization in astrocytes which are within the range of their ongoing endogenous polarization [132]. This polarization is further influenced by the presence of voltage-sensitive channels across the membrane of astrocytes. Astrocytes play a role in the regulation and reuptake of excess extracellular potassium and sodium changes produced by neuronal activity, including processes such as potassium spatial buffering that is driven by glial membrane polarization [133]. The application of direct current in vivo can activate these ionic clearance processes [134]. While it has been reported that extracellular potassium concentration does not change during DCS in vitro [135], it should be noted that the brain slice preparation interferes with extracellular concentration mechanisms [136].

Calcium signaling is a means of communication between astrocytes and neurons [137]. Electrical activation of one astrocyte can cause activation of others in a local astrocytic network and thereby affect the neuronal processing [138]. In addition, learning can be impaired in the absence of astrocytic calcium signaling, highlighting the importance of astrocytes in learning [139]. Interestingly, the application of anodal tDCS with a current density of 50 A/m^2 for 10 min induced a high-level of astrocytic Ca^{+2} surge across cortical areas of awake mice. As the authors did not observe a significant change in local field potential, they concluded that this is a direct effect of tDCS on astrocytes leading to metaplasticity mediated by noradrenergic transmission [140].

Microglial cells function as immune cells and phagocytes in CNS; however, there is a growing body of evidence showing their active role in synaptic plasticity [141]. A recent study showed that in vivo anodal tDCS caused morphological changes of microglia such as enlargement of soma and decreased their motility in mice. These results were obtained 3 h after tDCS, and they were absent if the animals were under anesthesia during tDCS. The authors speculated that tDCS could slow down the surveillance of microglia, and this might help the initiation of synaptic changes.

Myelination and metabolic support are the main functions of oligodendrocytes in CNS. An in vivo ACS study in adult rats showed that stimulation of corticospinal axons can promote the proliferation and differentiation of oligodendrocyte-specific progenitors after multiple sessions of stimulation [142]. In addition, it has been reported that cathodal tDCS over the ischemic region recruited oligodendrocyte precursors toward the lesion in adult rats, while tDCS promoted neurogenesis regardless of its polarity [143].

5.5.3 Inflammation, Angiogenesis, and Apoptosis

In addition to the above-stated effects, tES is known to modulate other vital physiological processes of inflammation, angiogenesis, and apoptosis. In vitro studies demonstrated the high-intensity DCS-induced accelerated and polarized migration of different peripheral immune cells, including neutrophils [144], lymphocytes [145], macrophages [146], and polymorphonuclear cells [147, 148]. Stimulation of cultured primary astrocytes as well as astrocytic cell lines resulted in increased energy metabolism [149] and perpendicular alignment to the electric field [150, 151]. Depending on the intensity and direction, tDCS effects could be pro-inflammatory or anti-inflammatory in nature. Both cathodal and anodal stimulation at 500 μA, 15 min for 10 sessions resulted in increased proliferation of activated microglia in the ipsilateral side of motor cortex [152]. In another study, anodal tDCS at current strength of 200 μA, 30 min for 10 days in the rat model of vascular dementia reduced the number of activated microglia and astroglia. There was a reduced expression of pro-inflammatory factors such as IL-1β, IL-6, and TNF-α, indicating the attenuated inflammatory response in the hippocampus [153]. Cathodal tDCS at 500 μA for 15 min for 5 consecutive days attenuated the activation of astrocyte and microglia, reduced the expression of pro-inflammatory IL-1β, IL-6, and TNF-α, and upregulated the anti-inflammatory IL-10 in rat model of middle cerebral artery occlusion [154]. Bicephalic tDCS at the current density of 33.4 A/m^2 also reduced the levels of IL-1β and TNF-α in the cerebral cortices of obese rats [155]. It is to be noted that most of these studies used higher-intensity electric fields than expected in human tDCS.

Large electric fields (50–400 V/m) applied for long periods of time are known to direct the migration, reorientation, cell-division, and elongation of endothelial cells in culture [156–162]. In vitro DCS also stimulated the secretion of vascular endothelial growth factor (VEGF) [156, 159, 161], nitric oxide, and interleukin-8 [160, 163]. All three are critical players in angiogenesis. Furthermore, DCS-induced increase in capillary density in a rabbit model of myocardial infarction [164] and a rat model of hindlimb ischemia [156] suggests a positive modulatory effect on angiogenesis. Electric fields may induce significant angiogenesis through the increased expression of VEGF [156, 165], activation of VEGF receptor 2 (VEGFR2), and downstream activation of phosphoinositide 3-kinase (PI3K)/Akt, extracellular regulated kinase 1,2 (Erk1/2), as well as the c-Jun NH2-terminal kinase (JNK) signaling pathways [158, 159, 161, 163]. DCS induced the upregulation and increased activation of chemokine receptors CXCR4 and CXCR2 in an in vitro study [162]. Both chemokine receptors are necessary for endothelial cell chemotaxis [166, 167]. Endothelial cells form the blood–brain barrier (BBB) that tightly regulates transport between the brain extracellular space and blood. As such, any action of DCS on endothelial cells would significantly affect the brain function. tDCS with a current density of 8.0 mA/cm^2 increased the permeability of BBB, and this modulation was dependent on nitric oxide [168].

Electric stimulation has been shown to affect apoptotic processes. In ischemic mice, cathodal tDCS significantly decreased the number of cortical and striatal caspase-3 positive cells, but anodal stimulation had an opposite effect [169]. ACS (100 μA, 2 Hz) decreased the number of apoptotic cells in the cortex, but not in the striatum of ischemic rats, and these antiapoptotic effects were exerted through Akt phosphorylation [165]. An in vitro study with fibroblasts exposed to a 100 V/m stimulation demonstrated the upregulation of antiapoptotic proteins, namely apoptosis inhibitor 5, caspase 8, and Fas-associated death domain-like apoptosis regulator and the protein kinase C epsilon [170], which further highlights the ES-induced attenuation of apoptosis. DCS at 100 V/m, when applied to injured rat dorsal root ganglion (DRG) cells for an hour, decreased the apoptotic rate of DRG cells [171]. In an in vitro study with biofilms, low-frequency low-voltage AC accelerated the apoptotic process in bioelectrical reactor biofilms [172].

5.6 Applications to Clinical Pathologies

The noninvasiveness and low cost of tES methods have made it versatile and widely studied as a potential treatment for various diseases [173, 174]. tES is especially favorable as a treatment tool for psychiatric disorders because of low-cost, portability, and ease of use. tES effects can be directly assessed with behavioral and cognitive tests, which are more direct and informative in humans than animals [46, 153, 175–180]. It is easy to interpret human behavior and assess psychological processes as compared to animals. For these reasons, a majority of published findings are of tDCS effects in humans and relatively few are in animal models. Among the animal studies, most involved highly invasive methodologies (e.g., tissue damage, brain slice, and protein-synthesis experiments). Nonetheless, some studies treating animal models of neuropsychiatric disorders with tDCS are briefly outlined below.

5.6.1 Stroke

Since the application of tES and more specifically tDCS has shown promising results as a therapeutic intervention in stroke patients, several groups have attempted to use animal models of stroke to study the effectiveness of electric field stimulation and the underlying functional and cellular mechanisms explaining these effects. One important factor to consider is when tES should be applied after a stroke. While there are clinical studies that have delineated beneficial effects of tACS in patients during recovery after chronic stroke [181], animal studies have not attempted to investigate the efficacy of this technique of stimulation in stroke models yet. We can categorize studies based on the time of intervention into acute, that is, less than<24 h after stroke, and subacute, 1–7 days after stroke groups [182].

Different reports outlined the potential benefit of ipsilateral cathodal tDCS within a few hours following the stroke induction, namely reduction in various stroke-related outcome measures such as infarct growth, edema, inflammation, and the number of apoptotic cells [169, 183]. Additionally, DCS can be used for the purpose of rehabilitation to regain cognitive and motor performances when it is applied in the subacute phase. While there is a debate on the effectiveness of DCS with regard to the polarity of the electric field, there is accumulating evidence suggesting an improvement in the recovery and neural growth such as elevated levels of microtubule and growth-associated protein due to DCS application [115]. Overall, these results suggest a rehabilitative benefit of tDCS for stroke patients.

5.6.2 Addiction

A handful of studies using tDCS as a treatment for addiction in animals have been conducted. Anodal tDCS at 0.2 mA, when applied to the frontal cortex for 20 min twice a day for 5 consecutive days, was sufficient to reduce anxiety- and depression-like behavior in nicotine-addicted mice [184]. Repeated anodal tDCS impaired cocaine-induced place preference conditioning and locomotor activation [185]. In this study, repeated anodal tDCS also reduced cocaine-induced expression of Zif268 in specific cortico-striatal circuits for 3 weeks in female mice. tDCS-mediated modulation of cortical excitability is shown to have a beneficial impact on food addiction as well, and the underlying biochemical response involves lipid-, protein-, and metal-/nonmetal ion-driven mechanisms [186].

5.6.3 Alzheimer's Disease

The main methods of noninvasive brain stimulation for Alzheimer's disease are TMS and anodal tDCS, and preliminary findings suggest that both techniques reduced cognitive deficits in Alzheimer's patients [121–123]. To replicate the cognitive symptoms of Alzheimer's, intraperitoneal injections of scopolamine were given to rats that subsequently received 0.1 mA of anodal tDCS for 20 min twice a day, five times a week [187]. After 2 weeks of treatment, rats treated with tDCS had slightly increased cognitive function in com-

parison to the rats just treated with tacrine. After the 4 weeks of treatment, rats that received tDCS therapy had motor behavior improvements and increased acetylcholine activity. Improved cognitive function and memory performance effects of repetitive anodal tDCS lasted for 2 months in a rat model of Alzheimer's [188]. In another study, tDCS when delivered for 20 min/day, 5 days/week over 3 weeks at 50 μA to triple transgenic (3X Tg) Alzheimer's mice failed to improve memory performance and alter the expression of neuropathological hallmarks of Alzheimer's [189]. Anodal tDCS when delivered for 30 min/day over 5 days at 200 μA alleviated the cognitive impairment, assessed by Morris Water Maze task, in a rat model of vascular dementia [153].

5.6.4 Chronic Stress and Depression

Though numerous tDCS studies have shown a therapeutic effect in humans and in animal models, the limits to tDCS effects were only recently tested [190]. In this study, tDCS efficacy was measured in chronic stress mice models. After subjecting rats to chronic restraint-induced stress (CRS) for 11 weeks, rats were given 20 min anodal tDCS treatment sessions for 8 days. Behavioral tests were performed after the 11 weeks of CRS, immediately and 24 h after tDCS treatment. Control rats were not subject to CRS but were randomly given either sham or tDCS treatment. tDCS treatment reversed the stress-induced allodynia and increased the pain threshold in unstressed animals. tDCS was only able to decrease BDNF release in the spinal cord and brainstem of unstressed rats. Interestingly, CRS rats treated with tDCS had a weak reduction in pain sensitivity even though no change of BDNF levels was detected indicating that a different mechanism may be involved in the attenuation of pain sensitivity. The results from this study highlight that tDCS treatments alone may not be sufficient to produce long-term effects when chronic stress is present. Chronic stress-induced pain threshold in rats was evaluated using a hot plate and tail flick latency (TFL) tests. In another study, active bicephalic tDCS increased the pain threshold and thereby reduced stress-induced hyperalgesia [191].

Anodal tDCS, when delivered at 200 μA for ten sessions, attenuated depression-like behavior induced by chronic corticosterone exposure in mice, and these effects were long-lasting [192]. tDCS at 0.1 mA for 10 min was also shown to alleviate depression-like behavior induced by chronic restrained stress in mice [140].

5.7 Prospects for Animal Research in tDCS/tACS Informing Ongoing Human Trials

A central challenge for tDCS/tACS studies is translating data collected from animal models of tDCS/tACS to inform the interpretation and design of human protocols. Historically, tDCS/tACS animal studies have informed human testing. Notably, the demonstration that prolonged DCS/ACS protocols, lasting for minutes, in animals can lead to short- and long-term plasticity encouraged the use of such protocols in humans [193]. The polarity dependence of DCS was first demonstrated in animal models [16, 25, 30]. Animal models demonstrated that low-intensity DCS/ACS can modulate ongoing neuronal activity, which provides a possible physiological substrate for the effects observed in human clinical trials [3]—countering the argument that weak fields, such as those applied in tDCS/tACS, are physiologically inert. In some cases, animal studies of DCS/ACS were conducted contemporaneously with human testing providing confirmatory evidence, for example, that AC can entrain oscillations [177, 194] or that tDCS plasticity is NMDA dependent [195]. On the other hand, there are scarce examples of modern animal tES studies influencing how human trials are conducted and analyzed. This reflects how tES protocols have remained largely unchanged with the majority of protocols applying 1–2 mA over 10–30 min using two large pad electrodes without any customization based on an individual's biomarkers.

Developments in tES protocols were driven by clinical neurophysiology [196] rather than extrapolated from animal models. Often animal studies confirm findings in humans rather than suggesting novel improvements to the current protocols; a notable example being the identification of the role of BDNF polymorphism [40]. We believe development in animal tES studies combined with an increased emphasis on designing these experiments for clinical relevance would accelerate the development and application of tES in humans. This includes an increased emphasis of the plastic, rather than acute effects of stimulation [40, 197]. Simultaneously, results from human trials also point to a need to critically address issues such as nonlinear dose–response, state dependency, and inter-subject variability.

Animal experiments provide a degree of cellular resolution, state control, and rapid screening not available in human subjects to help detangle complex interactions [3]. We propose that meaningful translation to human applications would be accelerated by the exploration of data that appears, at first glance, to be conflicting between animals and humans. For example, the acute effects of DCS in animals are monotonic across a very wide intensity and brain-state range, for example, anodal/cathodal almost always results in excitatory/inhibitory effects after accounting for orientation of neurons relative to the field [16, 78]. This is in direct contrast with clinical neurophysiology studies showing that many pharmacological, dose-dependent, and brain-state perpetrators can qualitatively change the direction of neuromodulation [19, 196]. As another example, ACS in animals can influence ongoing oscillations in a myriad of ways and is dependent on the nature of endogenous activity and stimulation frequency [21, 116, 194], while human testing with tACS and EEG are typically limited to testing one or a few frequencies [198]. Rather than speculating which protocols are effective, it would be useful to consider cellular effects from animals in comparison to network effects observed in human studies. The most impactful translational animal studies will be those that explain results from humans in previously unexpected ways and that can suggest nontrivial methods to optimize tES outcome in human trials.

References

1. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2:201–7.e1.
2. Andreasen M, Nedergaard S. Dendritic electrogenesis in rat hippocampal CA1 pyramidal neurons: functional aspects of Na+ and Ca2+ currents in apical dendrites. Hippocampus. 1996;6:79–95.
3. Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices *in vitro*: modulation of neuronal function by electric fields. J Physiol. 2004;557:175–90.
4. Radman T, Ramos RL, Brumberg JC, Bikson M. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul. 2009;2:215–28. e3.
5. Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of transcranial direct current stimulation: methods and mechanisms. Clin Neurophysiol. 2016;127:3425–54.
6. Deans JK, Powell AD, Jefferys JGR. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields: AC electric fields. J Physiol. 2007;583:555–65.
7. Radman T, Su Y, An JH, Parra LC, Bikson M. Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. J Neurosci. 2007;27:3030–6.
8. Maeda K, Maruyama R, Nagae T, Inoue M, Aonishi T, Miyakawa H. Weak sinusoidal electric fields entrain spontaneous Ca transients in the dendritic tufts of CA1 pyramidal cells in rat hippocampal slice preparations. PLoS One. 2015;10:e0122263.
9. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
10. Esmaeilpour Z, Marangolo P, Hampstead BM, Bestmann S, Galletta E, Knotkova H, et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. Brain Stimul. 2018;11:310–21.
11. Datta A, Elwassif M, Battaglia F, Bikson M. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. J Neural Eng. 2008;5:163–74.
12. Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal

effects: somatic and terminal origin of DCS effects. J Physiol. 2013;591:2563–78.
13. Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. J Neurophysiol. 2012;107:1881–9.
14. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9:5092.
15. Carlson C, Devinsky O. The excitable cerebral cortex. Epilepsy Behav. 2009;15:131–2.
16. Terzuolo CA, Bullock TH. Measurement of imposed voltage gradient adequate to modulate neuronal firing. Proc Natl Acad Sci. 1956;42:687–94.
17. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
18. Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67:129–43.
19. Reato D, Rahman A, Bikson M, Parra LC. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30:15067–79.
20. Ali MM, Sellers KK, Frohlich F. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. J Neurosci. 2013;33:11262–75.
21. Reato D, Bikson M, Parra LC. Lasting modulation of in vitro oscillatory activity with weak direct current stimulation. J Neurophysiol. 2015;113:1334–41.
22. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat Commun. 2019;10:266.
23. Vieira PG, Krause MR, Pack CC. tACS entrains neural activity while somatosensory input is blocked [Internet]. Neuroscience. 2019. Available from: http://biorxiv.org/lookup/doi/10.1101/691022.
24. Bindman LJ, Lippold OCJ, Redfearn JWT. Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents. Nature. 1962;196:584–5.
25. Bindman LJ, Lippold OCJ, Redfearn JWT. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
26. Purpura DP, Mcmurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
27. Gartside IB. Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. Nature. 1968;220:383–4.
28. Kandel ER, editor. Principles of neural science. 5th ed. New York: McGraw-Hill; 2013.
29. Lafon B, Rahman A, Bikson M, Parra LC. Direct current stimulation alters neuronal input/output function. Brain Stimul Basic Transl Clin Res Neuromodulation. Elsevier. 2017;10:36–45.
30. Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. J Physiol. 1988;402:751–71.
31. Wong RK, Stewart M. Different firing patterns generated in dendrites and somata of CA1 pyramidal neurones in guinea-pig hippocampus. J Physiol. 1992;457:675–87.
32. Delgado-Lezama R, Perrier J-F, Hounsgaard J. Local facilitation of plateau potentials in dendrites of turtle motoneurones by synaptic activation of metabotropic receptors. J Physiol. 1999;515:203–7.
33. Bullock TH, Hagiwara S. Intracellular recording from the giant synapse of the squid. J Gen Physiol. 1957;40:565–77.
34. Takeuchi A, Takeuchi N. Electrical changes in pre- and postsynaptic axons of the giant synapse of Loligo. J Gen Physiol. 1962;45:1181–93.
35. Salvador R, Mekonnen A, Ruffini G, Miranda PC. Modeling the electric field induced in a high resolution realistic head model during transcranial current stimulation. 2010 Annu Int Conf IEEE Eng Med Biol [Internet]. Buenos Aires: IEEE; 2010 [cited 2020 Jun 5]. p. 2073–6. Available from: http://ieeexplore.ieee.org/document/5626315/.
36. Jefferys JG. Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. J Physiol. 1981;319:143–52.
37. Chakraborty D, Truong DQ, Bikson M, Kaphzan H. Neuromodulation of axon terminals. Cereb Cortex. 2018;28:2786–94.
38. Chan CY, Nicholson C. Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum. J Physiol. 1986;371:89–114.
39. Rahman A, Lafon B, Parra LC, Bikson M. Direct current stimulation boosts synaptic gain and cooperativity in vitro. J Physiol. 2017;595:3535–47.
40. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66:198–204.
41. Svirskis G, Gutman A, Hounsgaard J. Detection of a membrane shunt by DC field polarization during intracellular and whole cell recording. J Neurophysiol. 1997;77:579–86.
42. Aberra AS, Peterchev AV, Grill WM. Biophysically realistic neuron models for simulation of cortical stimulation. J Neural Eng. 2018;15:066023.
43. Huang Y, Liu AA, Lafon B, Friedman D, Dayan M, Wang X, et al. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. elife. 2017;6:e18834.

44. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9:483.
45. Anastassiou CA, Montgomery SM, Barahona M, Buzsaki G, Koch C. The effect of spatially inhomogeneous extracellular electric fields on neurons. J Neurosci. 2010;30:1925–36.
46. Krause MR, Zanos TP, Csorba BA, Pilly PK, Choe J, Phillips ME, et al. Transcranial direct current stimulation facilitates associative learning and alters functional connectivity in the primate brain. Curr Biol. 2017;27:3086–96.e3.
47. Krause MR, Vieira PG, Csorba BA, Pilly PK, Pack CC. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci. 2019;116:5747–55.
48. Cabral ME, Baltar A, Borba R, Galvão S, Santos L, Fregni F, et al. Transcranial direct current stimulation: before, during, or after motor training? Neuroreport. 2015;26:618–22.
49. Gluckman BJ, Neel EJ, Netoff TI, Ditto WL, Spano ML, Schiff SJ. Electric field suppression of epileptiform activity in hippocampal slices. J Neurophysiol. 1996;76:4202–5.
50. Ghai RS, Bikson M, Durand DM. Effects of applied electric fields on low-calcium epileptiform activity in the CA1 region of rat hippocampal slices. J Neurophysiol. 2000;84:274–80.
51. Durand DM, Bikson M. Suppression and control of epileptiform activity by electrical stimulation: a review. Proc IEEE. 2001;89:1065–82.
52. Su Y, Radman T, Vaynshteyn J, Parra LC, Bikson M. Effects of high-frequency stimulation on epileptiform activity in vitro: ON/OFF control paradigm. Epilepsia. 2008;49:1586–93.
53. Sunderam S, Gluckman B, Reato D, Bikson M. Toward rational design of electrical stimulation strategies for epilepsy control. Epilepsy Behav. 2010;17:6–22.
54. Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts hebbian plasticity in vitro. Brain Stimul. 2020;13:287–301.
55. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul. 2017;10:51–8.
56. Nitsche MA, Müller-Dahlhaus F, Paulus W, Ziemann U. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. J Physiol. 2012;590:4641–62.
57. Mosayebi Samani M, Agboada D, Jamil A, Kuo M-F, Nitsche MA. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. Cortex. 2019;119:350–61.
58. Lisman JE, McIntyre CC. Synaptic plasticity: a molecular memory switch. Curr Biol: CB. 2001;11:R788–91.
59. Gartside IB. Mechanisms of sustained increases of firing rate of neurons in the rat cerebral cortex after polarization: reverberating circuits or modification of synaptic conductance? Nature. 1968;220:382–3.
60. Redfearn JW, Lippold OC, Costain R. A preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders. Br J Psychiatry J Ment Sci. 1964;110:773–85.
61. Costain R, Redfearn JW, Lippold OC. A controlled trial of the therapeutic effect of polarization of the brain in depressive illness. Br J Psychiatry J Ment Sci. 1964;110:786–99.
62. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol. 2003;114:2220–2; author reply 2222–2223.
63. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol. 2005;568:653–63.
64. Marquez-Ruiz J, Leal-Campanario R, Sanchez-Campusano R, Molaee-Ardekani B, Wendling F, Miranda PC, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. Proc Natl Acad Sci. 2012;109:6710–5.
65. Das S, Spoor M, Sibindi TM, Holland P, Schonewille M, De Zeeuw CI, et al. Impairment of long-term plasticity of cerebellar Purkinje cells eliminates the effect of anodal direct current stimulation on vestibulo-ocular reflex habituation. Front Neurosci. 2017;11:444.
66. Boroda E, Sponheim SR, Fiecas M, Lim KO. Transcranial direct current stimulation (tDCS) elicits stimulus-specific enhancement of cortical plasticity. NeuroImage. 2020;211:116598.
67. Sun Y, Lipton JO, Boyle LM, Madsen JR, Goldenberg MC, Pascual-Leone A, et al. Direct current stimulation induces mGluR5-dependent neocortical plasticity. Ann Neurol. 2016;80:233–46.
68. Paciello F, Podda MV, Rolesi R, Cocco S, Petrosini L, Troiani D, et al. Anodal transcranial direct current stimulation affects auditory cortex plasticity in normal-hearing and noise-exposed rats. Brain Stimul. 2018;11:1008–23.
69. Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP. Strengthening of horizontal cortical connections following skill learning. Nat Neurosci. 1998;1:230–4.
70. Hess G, Donoghue JP. Facilitation of long-term potentiation in layer II/III horizontal connections of rat motor cortex following layer I stimulation: route of effect and cholinergic contributions. Exp Brain Res. 1999;127:279–90.
71. Bae EB, Lee JH, Song J-J. Single-session of combined tDCS-TMS may increase therapeutic effects in subjects with tinnitus. Front Neurol. 2020;11:160.
72. Milot M-H, Palimeris S, Corriveau H, Tremblay F, Boudrias M-H. Effects of a tailored strength train-

ing program of the upper limb combined with transcranial direct current stimulation (tDCS) in chronic stroke patients: study protocol for a randomised, double-blind, controlled trial. BMC Sports Sci Med Rehabil. 2019;11:8.
73. Han T, Xu Z, Liu C, Li S, Song P, Huang Q, et al. Simultaneously applying cathodal tDCS with low frequency rTMS at the motor cortex boosts inhibitory aftereffects. J Neurosci Methods. 2019;324:108308.
74. Nemanich ST, Rich TL, Chen C-Y, Menk J, Rudser K, Chen M, et al. Influence of combined transcranial direct current stimulation and motor training on corticospinal excitability in children with unilateral cerebral palsy. Front Hum Neurosci. 2019;13:137.
75. Bolognini N, Fregni F, Casati C, Olgiati E, Vallar G. Brain polarization of parietal cortex augments training-induced improvement of visual exploratory and attentional skills. Brain Res. 2010;1349:76–89.
76. Artola A, Bröcher S, Singer W. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature. 1990;347:69–72.
77. Abraham WC. Metaplasticity: tuning synapses and networks for plasticity. Nat Rev Neurosci. 2008;9:387.
78. Ranieri F, Podda MV, Riccardi E, Frisullo G, Dileone M, Profice P, et al. Modulation of LTP at rat hippocampal CA3-CA1 synapses by direct current stimulation. J Neurophysiol. 2012;107:1868–80.
79. Reato D, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Front Hum Neurosci [Internet]. 2013 [cited 2020 Jun 5];7. Available from: http://journal.frontiersin.org/article/10.3389/fnhum.2013.00687/abstract.
80. Frey U, Morris RG. Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. Trends Neurosci. 1998;21:181–8.
81. Barco A, Lopez de Armentia M, Alarcon JM. Synapse-specific stabilization of plasticity processes: the synaptic tagging and capture hypothesis revisited 10 years later. Neurosci Biobehav Rev. 2008;32:831–51.
82. Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. J Neurosci. 2004;24:3379–85.
83. Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res. 2004;156:439–43.
84. Mozzachiodi R, Byrne JH. More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory. Trends Neurosci. 2010;33:17–26.
85. Bliss TV, Gardner-Medwin AR. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. J Physiol. 1973;232:357–74.
86. Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 1995;684:206–8.
87. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron. 2004;44:5–21.
88. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301.
89. Rohan JG, Carhuatanta KA, McInturf SM, Miklasevich MK, Jankord R. Modulating hippocampal plasticity with in vivo brain stimulation. J Neurosci. 2015;35:12824–32.
90. Farahani F, Kronberg G, FallahRad M, Oviedo HV, Parra LC. Effects of direct current stimulation on synaptic plasticity in a single neuron. Brain Stimul. 2021;14:588–97.
91. Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem Cold Spring Harb N. 2003;10:86–98.
92. Yu T-H, Wu Y-J, Chien M-E, Hsu K-S. Transcranial direct current stimulation induces hippocampal metaplasticity mediated by brain-derived neurotrophic factor. Neuropharmacology. 2019;144:358–67.
93. Islam N, Aftabuddin M, Moriwaki A, Hori Y. Induction of N-methyl-D-asparate receptor mediated c-fos protein in the rat brain by incomplete ischaemia. Indian J Med Res. 1994;100:281–8.
94. Pérez-Cadahía B, Drobic B, Davie JR. Activation and function of immediate-early genes in the nervous system. Biochem Cell Biol Biochim Biol Cell. 2011;89:61–73.
95. Abraham WC, Dragunow M, Tate WP. The role of immediate early genes in the stabilization of long-term potentiation. Mol Neurobiol. 1991;5:297–314.
96. Abraham WC, Christie BR, Logan B, Lawlor P, Dragunow M. Immediate early gene expression associated with the persistence of heterosynaptic long-term depression in the hippocampus. Proc Natl Acad Sci U S A. 1994;91:10049–53.
97. Cole AJ, Saffen DW, Baraban JM, Worley PF. Rapid increase of an immediate early gene messenger RNA in hippocampal neurons by synaptic NMDA receptor activation. Nature. 1989;340:474–6.
98. Jones MW, Errington ML, French PJ, Fine A, Bliss TV, Garel S, et al. A requirement for the immediate early gene Zif268 in the expression of late LTP and long-term memories. Nat Neurosci. 2001;4:289–96.
99. McCaig CD, Rajnicek AM. Electrical fields, nerve growth and nerve regeneration. Exp Physiol. 1991;76:473–94.
100. McCaig CD, Rajnicek AM, Song B, Zhao M. Controlling cell behavior electrically: cur-

rent views and future potential. Physiol Rev. 2005;85:943–78.
101. Zhao M. Electrical fields in wound healing-An overriding signal that directs cell migration. Semin Cell Dev Biol. 2009;20:674–82.
102. Pelletier SJ, Lagacé M, St-Amour I, Arsenault D, Cisbani G, Chabrat A, et al. The morphological and molecular changes of brain cells exposed to direct current electric field stimulation. Int J Neuropsychopharmacol. 2014;18:pyu090.
103. Marsh G, Beams HW. In vitro control of growing chick nerve fibers by applied electric currents. J Cell Comp Physiol. 1946;27:139–57.
104. Jaffe LF, Poo MM. Neurites grow faster towards the cathode than the anode in a steady field. J Exp Zool. 1979;209:115–28.
105. Pomeranz B, Mullen M, Markus H. Effect of applied electrical fields on sprouting of intact saphenous nerve in adult rat. Brain Res. 1984;303:331–6.
106. McDevitt L, Fortner P, Pomeranz B. Application of weak electric field to the hindpaw enhances sciatic motor nerve regeneration in the adult rat. Brain Res. 1987;416:308–14.
107. Politis MJ, Zanakis MF, Albala BJ. Facilitated regeneration in the rat peripheral nervous system using applied electric fields. J Trauma. 1988;28:1375–81.
108. Román GC, Strahlendorf HK, Coates PW, Rowley BA. Stimulation of sciatic nerve regeneration in the adult rat by low-intensity electric current. Exp Neurol. 1987;98:222–32.
109. Beveridge JA, Politis MJ. Use of exogenous electric current in the treatment of delayed lesions in peripheral nerves. Plast Reconstr Surg. 1988;82:573–9.
110. McCaig CD. Dynamic aspects of amphibian neurite growth and the effects of an applied electric field. J Physiol. 1986;375:55–69.
111. Stollberg J, Fraser SE. Acetylcholine receptors and concanavalin A-binding sites on cultured Xenopus muscle cells: electrophoresis, diffusion, and aggregation. J Cell Biol. 1988;107:1397–408.
112. Stollberg J, Fraser SE. Local accumulation of acetylcholine receptors is neither necessary nor sufficient to induce cluster formation. J Neurosci. 1990;10:247–55.
113. Jiang T, Xu RX, Zhang AW, Di W, Xiao ZJ, Miao JY, et al. Effects of transcranial direct current stimulation on hemichannel pannexin-1 and neural plasticity in rat model of cerebral infarction. Neuroscience. 2012;226:421–6.
114. Gellner A-K, Reis J, Holtick C, Schubert C, Fritsch B. Direct current stimulation-induced synaptic plasticity in the sensorimotor cortex: structure follows function. Brain Stimul. 2020;13:80–8.
115. Yoon KJ, Oh B-M, Kim D-Y. Functional improvement and neuroplastic effects of anodal transcranial direct current stimulation (tDCS) delivered 1day vs. 1week after cerebral ischemia in rats. Brain Res. 2012;1452:61–72.
116. Fröhlich F. Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. Prog Brain Res [Internet]. Elsevier; 2015 [cited 2020 Jun 7]. p. 41–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0079612315001314.
117. Sejnowski TJ, Destexhe A. Why do we sleep?11 Published on the World Wide Web on 7 November 2000. Brain Res. 2000;886:208–23.
118. Gebodh N, Esmaeilpour Z, Adair D, Chelette K, Dmochowski J, Woods AJ, et al. Inherent physiological artifacts in EEG during tDCS. NeuroImage. 2019;185:408–24.
119. Antal A, Varga ET, Kincses TZ, Nitsche MA, Paulus W. Oscillatory brain activity and transcranial direct current stimulation in humans. Neuroreport. 2004;15:1307–10.
120. Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci. 2013;7:279.
121. Schmidt SL, Iyengar AK, Foulser AA, Boyle MR, Fröhlich F. Endogenous cortical oscillations constrain neuromodulation by weak electric fields. Brain Stimul. 2014;7:878–89.
122. Ozen S, Sirota A, Belluscio MA, Anastassiou CA, Stark E, Koch C, et al. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30:11476–85.
123. Negahbani E, Stitt IM, Davey M, Doan TT, Dannhauer M, Hoover AC, et al. Transcranial alternating current stimulation (tACS) entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform [Internet]. Neuroscience. 2019. Available from: http://biorxiv.org/lookup/doi/10.1101/563163.
124. Esmaeilpour Z, Kronberg G, Reato D, Parra LC, Bikson M. Temporal interference stimulation targets deep brain regions by modulating neural oscillations [Internet]. Neuroscience. 2019. Available from: http://biorxiv.org/lookup/doi/10.1101/2019.12.25.888412.
125. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169:1029–41.e16.
126. Kar K, Duijnhouwer J, Krekelberg B. Transcranial alternating current stimulation attenuates neuronal adaptation. J Neurosci. 2017;37:2325–35.
127. Freund TF, Buzsáki G. Interneurons of the hippocampus. Hippocampus. 1996;6:347–470.
128. Kepecs A, Fishell G. Interneuron cell types are fit to function. Nature. 2014;505:318–26.
129. von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting: quantifying neurons and glia in human brain. J Comp Neurol. 2016;524:3865–95.
130. Di Castro MA, Chuquet J, Liaudet N, Bhaukaurally K, Santello M, Bouvier D, et al. Local Ca2+ detection and modulation of synaptic release by astrocytes. Nat Neurosci. 2011;14:1276–84.

131. Gellner A-K, Reis J, Fritsch B. Glia: a neglected player in non-invasive direct current brain stimulation. Front Cell Neurosci [Internet]. 2016 [cited 2020 Jun 5];10. Available from: http://journal.frontiersin.org/Article/10.3389/fncel.2016.00188/abstract.
132. Ruohonen J, Karhu J. tDCS possibly stimulates glial cells. Clin Neurophysiol. 2012;123:2006–9.
133. Dallérac G, Chever O, Rouach N. How do astrocytes shape synaptic transmission? Insights from electrophysiology. Front Cell Neurosci [Internet]. 2013 [cited 2020 Jun 4];7. Available from: http://journal.frontiersin.org/article/10.3389/fncel.2013.00159/abstract.
134. Gardner-Medwin AR, Nicholson C. Changes of extracellular potassium activity induced by electric current through brain tissue in the rat. J Physiol. 1983;335:375–92.
135. Lian J, Bikson M, Sciortino C, Stacey WC, Durand DM. Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro. J Physiol. 2003;547:427–34.
136. An JH, Su Y, Radman T, Bikson M. Effects of glucose and glutamine concentration in the formulation of the artificial cerebrospinal fluid (ACSF). Brain Res. 2008;1218:77–86.
137. Pasti L, Volterra A, Pozzan T, Carmignoto G. Intracellular calcium oscillations in astrocytes: a highly plastic, bidirectional form of communication between neurons and astrocytes in situ. J Neurosci. 1997;17:7817–30.
138. Poskanzer KE, Yuste R. Astrocytic regulation of cortical UP states. Proc Natl Acad Sci. 2011;108:18453–8.
139. Padmashri R, Suresh A, Boska MD, Dunaevsky A. Motor-skill learning is dependent on astrocytic activity. Neural Plast. 2015;2015:938023.
140. Monai H, Ohkura M, Tanaka M, Oe Y, Konno A, Hirai H, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun. 2016;7:11100.
141. Schafer DP, Lehrman EK, Stevens B. The "quadpartite" synapse: microglia-synapse interactions in the developing and mature CNS. Glia. 2013;61:24–36.
142. Li Q, Brus-Ramer M, Martin JH, McDonald JW. Electrical stimulation of the medullary pyramid promotes proliferation and differentiation of oligodendrocyte progenitor cells in the corticospinal tract of the adult rat. Neurosci Lett. 2010;479:128–33.
143. Braun R, Klein R, Walter HL, Ohren M, Freudenmacher L, Getachew K, et al. Transcranial direct current stimulation accelerates recovery of function, induces neurogenesis and recruits oligodendrocyte precursors in a rat model of stroke. Exp Neurol. 2016;279:127–36.
144. Zhao M, Song B, Pu J, Wada T, Reid B, Tai G, et al. Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN. Nature. 2006;442:457–60.
145. Li J, Nandagopal S, Wu D, Romanuik SF, Paul K, Thomson DJ, et al. Activated T lymphocytes migrate toward the cathode of DC electric fields in microfluidic devices. Lab Chip. 2011;11:1298–304.
146. Orida N, Feldman JD. Directional protrusive pseudopodial activity and motility in macrophages induced by extracellular electric fields. Cell Motil. 1982;2:243–55.
147. Franke K, Gruler H. Galvanotaxis of human granulocytes: electric field jump studies. Eur Biophys J: EBJ. 1990;18:335–46.
148. Pelletier SJ, Cicchetti F. Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. Int J Neuropsychopharmacol. 2015;18:pyu047.
149. Huang R, Peng L, Hertz L. Effects of a low-voltage static electric field on energy metabolism in astrocytes. Bioelectromagnetics. 1997;18:77–80.
150. Borgens RB, Shi R, Mohr TJ, Jaeger CB. Mammalian cortical astrocytes align themselves in a physiological voltage gradient. Exp Neurol. 1994;128:41–9.
151. Alexander JK, Fuss B, Colello RJ. Electric field-induced astrocyte alignment directs neurite outgrowth. Neuron Glia Biol. 2006;2:93–103.
152. Rueger MA, Keuters MH, Walberer M, Braun R, Klein R, Sparing R, et al. Multi-session transcranial direct current stimulation (tDCS) elicits inflammatory and regenerative processes in the rat brain. PLoS One. 2012;7:e43776.
153. Guo T, Fang J, Tong ZY, He S, Luo Y. Transcranial direct current stimulation ameliorates cognitive impairment via modulating oxidative stress, inflammation, and autophagy in a rat model of vascular dementia. Front Neurosci. 2020;14:28.
154. Zhang K, Guo L, Zhang J, Rui G, An G, Zhou Y, et al. tDCS accelerates the rehabilitation of MCAO-induced motor function deficits via neurogenesis modulated by the Notch1 signaling pathway. Neurorehabil Neural Repair. 2020;34:640–51.
155. de Oliveira C, de Freitas JS, Macedo IC, Scarabelot VL, Ströher R, Santos DS, et al. Transcranial direct current stimulation (tDCS) modulates biometric and inflammatory parameters and anxiety-like behavior in obese rats. Neuropeptides. 2019;73:1–10.
156. Kanno S, Oda N, Abe M, Saito S, Hori K, Handa Y, et al. Establishment of a simple and practical procedure applicable to therapeutic angiogenesis. Circulation. 1999;99:2682–7.
157. Bai H, McCaig CD, Forrester JV, Zhao M. DC electric fields induce distinct preangiogenic responses in microvascular and macrovascular cells. Arterioscler Thromb Vasc Biol. 2004;24:1234–9.
158. Zhao M, Bai H, Wang E, Forrester JV, McCaig CD. Electrical stimulation directly induces preangiogenic responses in vascular endothelial cells by signaling through VEGF receptors. J Cell Sci. 2004;117:397–405.
159. Zhao Z, Qin L, Reid B, Pu J, Hara T, Zhao M. Directing migration of endothelial progenitor

cells with applied DC electric fields. Stem Cell Res. 2012;8:38–48.
160. Long H, Yang G, Wang Z. Galvanotactic migration of EA.Hy926 endothelial cells in a novel designed electric field bioreactor. Cell Biochem Biophys. 2011;61:481–91.
161. Chen Y, Ye L, Guan L, Fan P, Liu R, Liu H, et al. Physiological electric field works via the VEGF receptor to stimulate neovessel formation of vascular endothelial cells in a 3D environment. Biol Open. 2018;7:bio035204.
162. Cunha F, Rajnicek AM, McCaig CD. Electrical stimulation directs migration, enhances and orients cell division and upregulates the chemokine receptors CXCR4 and CXCR2 in endothelial cells. J Vasc Res. 2019;56:39–53.
163. Bai H, Forrester JV, Zhao M. DC electric stimulation upregulates angiogenic factors in endothelial cells through activation of VEGF receptors. Cytokine. 2011;55:110–5.
164. Zhang P, Liu Z-T, He G-X, Liu J-P, Feng J. Low-voltage direct-current stimulation is safe and promotes angiogenesis in rabbits with myocardial infarction. Cell Biochem Biophys. 2011;59:19–27.
165. Baba T, Kameda M, Yasuhara T, Morimoto T, Kondo A, Shingo T, et al. Electrical stimulation of the cerebral cortex exerts antiapoptotic, angiogenic, and anti-inflammatory effects in ischemic stroke rats through phosphoinositide 3-kinase/Akt signaling pathway. Stroke. 2009;40:e598–605.
166. Ganju RK, Brubaker SA, Meyer J, Dutt P, Yang Y, Qin S, et al. The alpha-chemokine, stromal cell-derived factor-1alpha, binds to the transmembrane G-protein-coupled CXCR-4 receptor and activates multiple signal transduction pathways. J Biol Chem. 1998;273:23169–75.
167. Sai J, Fan G-H, Wang D, Richmond A. The C-terminal domain LLKIL motif of CXCR2 is required for ligand-mediated polarization of early signals during chemotaxis. J Cell Sci. 2004;117:5489–96.
168. Shin DW, Fan J, Luu E, Khalid W, Xia Y, Khadka N, et al. In vivo modulation of the blood-brain barrier permeability by transcranial direct current stimulation (tDCS). Ann Biomed Eng. 2020;48:1256–70.
169. Peruzzotti-Jametti L, Cambiaghi M, Bacigaluppi M, Gallizioli M, Gaude E, Mari S, et al. Safety and efficacy of transcranial direct current stimulation in acute experimental ischemic stroke. Stroke. 2013;44:3166–74.
170. Jennings J, Chen D, Feldman D. Transcriptional response of dermal fibroblasts in direct current electric fields. Bioelectromagnetics. 2008;29:394–405.
171. Hu M, Hong L, He S, Huang G, Cheng Y, Chen Q. Effects of electrical stimulation on cell activity, cell cycle, cell apoptosis and β-catenin pathway in the injured dorsal root ganglion cell. Mol Med Rep. 2020;21:2385–94.
172. Hoseinzadeh E, Wei C, Farzadkia M, Rezaee A. Effects of low frequency-low voltage alternating electric current on apoptosis progression in bio-electrical reactor biofilm. Front Bioeng Biotechnol. 2020;8:2.
173. Mondino M, Bennabi D, Poulet E, Galvao F, Brunelin J, Haffen E. Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders? World J Biol Psychiatry. 2014;15:261–75.
174. Tortella G, Casati R, Aparicio LVM, Mantovani A, Senço N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry. 2015;5:88–102.
175. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 2016;9:501–17.
176. Harris DM, Rantalainen T, Muthalib M, Johnson L, Duckham RL, Smith ST, et al. Concurrent exergaming and transcranial direct current stimulation to improve balance in people with Parkinson's disease: study protocol for a randomised controlled trial. Trials. 2018;19:387.
177. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. Aleman A, editor. PLoS One. 2010;5:e13766.
178. Esse Wilson J, Trumbo MC, Wilson JK, Tesche CD. Transcranial direct current stimulation (tDCS) over right temporoparietal junction (rTPJ) for social cognition and social skills in adults with autism spectrum disorder (ASD). J Neural Transm Vienna Austria 1996. 2018;125:1857–66.
179. Leffa DT, Bellaver B, Salvi AA, de Oliveira C, Caumo W, Grevet EH, et al. Transcranial direct current stimulation improves long-term memory deficits in an animal model of attention-deficit/hyperactivity disorder and modulates oxidative and inflammatory parameters. Brain Stimul. 2018;11:743–51.
180. Valero-Cabré A, Sanches C, Godard J, Fracchia O, Dubois B, Levy R, et al. Language boosting by transcranial stimulation in progressive supranuclear palsy. Neurology. 2019;93:e537–47.
181. Fedorov A, Chibisova Y, Szymaszek A, Alexandrov M, Gall C, Sabel BA. Non-invasive alternating current stimulation induces recovery from stroke. Restor Neurol Neurosci. 2010;28:825–33.
182. Boonzaier J, van Tilborg GAF, Neggers SFW, Dijkhuizen RM. Noninvasive brain stimulation to enhance functional recovery after stroke: studies in animal models. Neurorehabil Neural Repair. 2018;32:927–40.
183. Notturno F, Marzetti L, Pizzella V, Uncini A, Zappasodi F. Local and remote effects of transcranial direct current stimulation on the electrical activity of the motor cortical network: tDCS effects on motor network EEG activity. Hum Brain Mapp. 2014;35:2220–32.

184. Pedron S, Monnin J, Haffen E, Sechter D, Van Waes V. Repeated transcranial direct current stimulation prevents abnormal behaviors associated with abstinence from chronic nicotine consumption. Neuropsychopharmacology. 2014;39:981–8.
185. Pedron S, Beverley J, Haffen E, Andrieu P, Steiner H, Van Waes V. Transcranial direct current stimulation produces long-lasting attenuation of cocaine-induced behavioral responses and gene regulation in corticostriatal circuits. Addict Biol. 2017;22:1267–78.
186. Surowka AD, Ziomber A, Czyzycki M, Migliori A, Kasper K, Szczerbowska-Boruchowska M. Molecular and elemental effects underlying the biochemical action of transcranial direct current stimulation (tDCS) in appetite control. Spectrochim Acta A Mol Biomol Spectrosc. 2018;195:199–209.
187. Yu SH, Park SD, Sim KC. The effect of tDCS on cognition and neurologic recovery of rats with Alzheimer's disease. J Phys Ther Sci. 2014;26:247–9.
188. Yang W-J, Wen H-Z, Zhou L-X, Luo Y-P, Hou W-S, Wang X, et al. After-effects of repetitive anodal transcranial direct current stimulation on learning and memory in a rat model of Alzheimer's disease. Neurobiol Learn Mem. 2019;161:37–45.
189. Gondard E, Soto-Montenegro ML, Cassol A, Lozano AM, Hamani C. Transcranial direct current stimulation does not improve memory deficits or alter pathological hallmarks in a rodent model of Alzheimer's disease. J Psychiatr Res. 2019;114:93–8.
190. Spezia Adachi LN, Quevedo AS, de Souza A, Scarabelot VL, Rozisky JR, de Oliveira C, et al. Exogenously induced brain activation regulates neuronal activity by top-down modulation: conceptualized model for electrical brain stimulation. Exp Brain Res. 2015;233:1377–89.
191. Fregni F, Macedo IC, Spezia-Adachi LN, Scarabelot VL, Laste G, Souza A, et al. Transcranial direct current stimulation (tDCS) prevents chronic stress-induced hyperalgesia in rats. Brain Stimul. 2018;11:299–301.
192. Peanlikhit T, Van Waes V, Pedron S, Risold P-Y, Haffen E, Etiévant A, et al. The antidepressant-like effect of tDCS in mice: a behavioral and neurobiological characterization. Brain Stimul. 2017;10:748–56.
193. Dhamne SC, Ekstein D, Zhuo Z, Gersner R, Zurakowski D, Loddenkemper T, et al. Acute seizure suppression by transcranial direct current stimulation in rats. Ann Clin Transl Neurol. 2015;2:843–56.
194. Abd Hamid AI, Gall C, Speck O, Antal A, Sabel BA. Effects of alternating current stimulation on the healthy and diseased brain. Front Neurosci. 2015;9:391.
195. Rroji O, van Kuyck K, Nuttin B, Wenderoth N. Anodal tDCS over the primary motor cortex facilitates long-term memory formation reflecting use-dependent plasticity. PLoS One. 2015;10:e0127270.
196. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175–95.
197. Jefferys JGR, Deans J, Bikson M, Fox J. Effects of weak electric fields on the activity of neurons and neuronal networks. Radiat Prot Dosim. 2003;106:321–3.
198. Müller NG, Vellage A-K, Heinze H-J, Zaehle T. Entrainment of human alpha oscillations selectively enhances visual conjunction search. PLoS One. 2015;10:e0143533.

Part II

Research Methods

TMS-Evoked EEG Response in Neuropsychiatric Disorders

6

Pedro C. Gordon and Ulf Ziemann

6.1 Introduction

Transcranial magnetic stimulation (TMS) allows direct probing of the human brain in a safe and noninvasive fashion, which ensues several potential applications in the study and treatment of neuropsychiatric disorders. Previous neurophysiological studies using TMS focused largely on stimulation of the motor cortex, quantifying the response by accessing the motor evoked potential (MEP) with electromyography (TMS-EMG). Through these studies, several measurement paradigms were designed to aid the elucidation of neurophysiological underpinnings of neuropsychiatric disorders, as well as the description of cortical responses to different neuroplasticity interventions [64]. However, by requiring motor cortex stimulation and motor evoked responses as a read-out, this technique entails limitations. First, there is an intrinsic restriction regarding the cortical regions that are amenable to be investigated, since the method depends on targeting the motor cortex. Second, MEPs are a rather indirect measure of cortical responses, and as such imply the risk of confounding factors, which may come from spinal cord, peripheral nerves, and muscle. These are significant limitations if one aims to study neuropsychiatric disorders and related brain functions, which may involve predominantly brain regions other than the motor cortex.

To circumvent these limitations, an alternative method should be able to probe any cortical region and obtain read-out signals directly from the cortex. This was made possible by combining TMS with electroencephalography (EEG): Measuring EEG activity concomitant to the application of TMS allows the investigation of the local cortical responses to a stimulus applied to any cortical area (provided that such area can be effectively stimulated by TMS) [28, 70]. This development implies that a read-out can be directly extracted from the cortex, by means of EEG signals, unlike TMS-EMG which relies on an indirect measure of cortical responsivity such as motor evoked responses. Moreover, TMS-EEG provides multidimensional information: By recording the continuous EEG response over several electrodes atop the scalp, it is possible to observe the evolution of the cortical responses in time and space across distributed networks. Here, we will describe the technical steps that are necessary to perform a TMS-EEG measurement, as well as the nature of the obtained data and its caveats (Sect. 6.2). We will also describe current results regarding the neurophysiological basis of results obtained through TMS-EEG measurement (Sect. 6.3); and finally, how TMS-EEG can be and has been applied to neuropsychiatric disorders (Sect. 6.4).

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6.2 Technical Aspects

6.2.1 General Issues

In simple terms, TMS-EEG involves recording EEG activity in response to a focal cortical stimulation, which is provided by the TMS pulse. Therefore, any TMS-EEG experiment naturally requires the placement of electrodes on the surface of the scalp, which detect voltage differences produced by postsynaptic potentials in a large number of neurons underneath the electrodes. As with any EEG measurement, the signal obtained is the spatial and temporal summation of excitatory and inhibitory postsynaptic potentials originating from the activity of a large population of cortical pyramidal neurons and interneurons [35]. By analyzing the EEG signal that immediately follows a cortical stimulus (the TMS pulse), one can observe how this cortical region reacts and how the response evolves over time and propagates to other cortical areas. Also, by comparing the nature of these responses between different populations, or in the same population at different time points (e.g., different states such as wakefulness vs. sleep, or before and after an intervention), one can draw conclusions regarding the underlying cortical mechanisms, which may explain the differences. Despite this seemingly straightforward rationale, it is imperative to keep in mind the several measures that should be taken into account to enable the feasibility of this method, as well as appropriate interpretation of its results. Below we will briefly describe the methods necessary for performing TMS-EEG studies and some specific issues that should be considered.

The first TMS-evoked EEG recordings were performed by Cracco et al. [12], and since then the technique has been significantly refined. Unlike simple EEG, which passively records cortical potentials, TMS-EEG involves perturbation of cortical activity, by means of the induction of a brief but strong electromagnetic field in the cortex. As would be expected, this electromagnetic field inevitably interacts with the EEG electrodes, placed between the TMS coil and the subject's scalp, and thus always produces undesirable artifacts and potential risks. Standard EEG disk electrodes are inappropriate for TMS-EEG, as the eddy currents induced by the magnetic field significantly increase the electrodes' temperature, interfering with conductivity proprieties and posing a safety hazard [65]. In order to minimize this effect, EEG electrodes for TMS-EEG should be small Ag/AgCl pellet or slit ring ("c-shape" ring) electrodes [28, 65, 73]. Ideally, special care should be taken when preparing the electrodes' placement, aiming for impedances below 5 kΩ. At the same time, one should avoid the creation of "bridges" between electrodes, by limiting the amount of conductive gel applied [28]. The TMS coil should be positioned atop the subject's head, but avoiding direct touch with the electrodes, which may cause disruption of the EEG signal and the smearing of conductive gel, which would create the aforementioned "bridges." This may be done by placing a plastic spacer between the coil and the subject's head [66], at the cost of higher stimulation intensity needed to effectively stimulate the brain.

Regarding coil placement, it is important to consider the use of neuronavigation for target selection and maintenance of coil placement, based on individual structural magnetic resonance imaging (MRI). TMS applied to nonmotor areas lack a clear read-out, as is the case with MEPs from motor cortex stimulation, which could be used for proper coil placement with respect to the target. Neuronavigation allows identification of specific cortical targets with respect to the individual's brain anatomy, also accounting for anatomical variations and monitoring proper coil directionality, for example, perpendicular to the targeted sulcus [21]. Finally, real-time monitoring during an experiment is desirable in order to correct possible coil displacement during a session, minding that seemingly small deviations of the coil's location, orientation, and angulation can significantly alter evoked responses [37]. Therefore, neuronavigation should guide proper coil placement, and its use is generally recommended in TMS-EEG studies, in particular those involving nonmotor cortex targets [70].

6.2.2 EEG Artifacts

Another issue of TMS-EEG is that the high current discharge involved in TMS pulses generates a massive electrical artifact in the EEG signal, of amplitude several orders of magnitude higher than the average EEG signals from cortical activity. This saturates standard EEG amplifiers, hindering the signal acquisition for hundreds of milliseconds after the pulse and precluding any meaningful interpretation of the signal following cortical stimulation. First solutions to this issue were the development of an amplifier with a sample-and-hold circuit, in which the incoming signal is decoupled from the amplifier within a few milliseconds around the TMS pulse, preventing its saturation [29, 73]. Currently, other solutions have been developed and TMS-compatible EEG amplifiers can limit the information loss to a couple of milliseconds around the TMS pulse, thus allowing proper analysis and interpretation of the signal within approximately 10 ms following the TMS [28].

There are other sources of artifacts beyond the TMS artifact that should be taken into consideration. TMS-EEG responses are of small amplitude compared to other sources of noise, and therefore are sensitive to being obscured by such sources, which also includes ongoing brain activity nonrelated to TMS response. In order to guarantee proper signal-to-noise ratio of these responses, it is recommended to record and then average approximately 100 trials [2, 42, 61]. This averages out signals not correlated to the direct cortical stimulation (non-time-locked to TMS), while the specific TMS-evoked activity remains in the averaged signal. Nevertheless, some sources of interference still significantly disturb EEG recordings despite the averaging, either due to very high signal amplitude in comparison to cortical activity, or because they are also evoked by the TMS pulse, such as eye blinks and scalp muscle activity. Dealing with these sources may involve extensive data postprocessing, for example, the manual exclusion of the trials and channels severely contaminated by noise. Furthermore, signal components related to eye blinks and muscle activity can be removed using independent component analysis (ICA) [62]. MATLAB toolboxes have been developed to aid this TMS-EEG data postprocessing, which helps making this rather complex data analysis more user-friendly and standardized [2, 61]. Application of ICA is not trivial, as the TMS-evoked brain responses and to be removed artifacts such as eye blinks and muscle responses are not independent. Therefore, more advanced techniques have been developed to separate the signals, such as signal-space projection (SSP) [44, 71] and the SOUND algorithm [47].

Yet another source of confounding signals in TMS-EEG data is the presence of sensory evoked potentials (SEP). In addition to direct cortical stimulation, the electromagnetic field induced by the TMS pulse inevitably depolarizes somatosensory nerve terminals in the scalp and cranial muscles at or near the stimulation site, provoking somatosensory perception. Also, TMS produces a loud high-pitched click when it discharges, leading to auditory perception. Both percepts lead to a cortical response that can be observed in the EEG, namely the SEPs [49, 53]. Dealing with this confounding factor is very challenging, as TMS invariably provokes sensorial perceptions, which generate signals that are not possible to reliably remove via standard data postprocessing such as ICA, since by nature these responses have a cortical source and are also time-locked to the TMS pulse. The use of masking noise (noise containing the same frequency distribution as the TMS coil click delivered to the subject through earphones) has been advocated to suppress the auditory SEP, with good results [46, 68]. However, this does not prevent the bone-conducted component of auditory stimulation. This can be addressed by using a spacer between coil and head. Moreover, this does not entirely prevent SEPs from somatosensory inputs. Although this issue is still a matter of discussion, it is currently recommended to use a “sham” procedure in TMS-EEG experiments. A sham procedure would simulate all the sensorial stimuli of a TMS pulse (coil click, activation of somatosensory scalp receptors and muscles) but would not generate an electromagnetic field in the cortex. Sham procedures usually involve a

second TMS coil placed distant from the scalp, which reproduces the auditory stimulus, and short electrical pulses delivered by scalp electrodes placed between the EEG electrodes, which reproduce the somatosensory stimulus [11, 23]. The removal of the signal corresponding to the "realistic sham" condition from the "real" TMS-EEG trials would then reveal the true TMS-evoked activity, thus allowing the results to be attributed specifically to direct activation by the TMS pulse, rather than the unwanted indirect activation by peripherally evoked potentials.

6.2.3 Outcome Measures

As mentioned above, TMS-EEG data is extracted from several (typically at least 100) trials, representing instances in which a TMS pulse is applied while EEG is recorded. The averaging of the signal time-locked to the pulse allows the visualization of TMS-evoked potentials (TEP), a series of deflections that peak at specific time points [42]. An example of this measure is shown in Fig. 6.1a. The location of these peaks in space (scalp distribution) and time (latency after TMS pulse) depend on the stimulated cortical site, and the amplitude of each peak is considered to represent different physiological properties of the cortex, modulated by brain state, as discussed in the next session [26, 38]. Results regarding the amplitude of these peaks can be compared in a few ways. A region of interest might be selected a priori and the signal from the respective electrodes averaged to provide a single signal, with its amplitude representing the measure of interest [28]. Alternatively, instead of selecting regions of interest, it is possible to integrate the signal from all the channels by means of the global mean field potential, which provides the evolution in time of an averaged cortical response over the entire scalp [70]. Concerning the statistical comparison between two data sets (e.g., patients vs. healthy controls, or within a population prior to and after intervention), an alternative to selecting regions and times of interest is the application of cluster-based permutation tests. Briefly, this method allows for a given statistical test to be carried out in several signal clusters in time and space. This procedure provides as a result a set of adjacent electrodes at a certain time window after the TMS pulse where the compared signals are statistically different. This allows the analysis of all data without resorting to dimensionality reduction, at low risk of false positive results [45, 52].

In addition, the signal can be analyzed in the frequency domain. Spectral analysis of EEG signals has been widely studied in the form of oscillations, which are believed to represent the underpinning of a broad variety of different neurophysiological processes and behaviors [5]. Differently from the resting-state EEG, which shows the overall activity of the cortex at rest, spectral analysis of TMS-EEG allows the probing into the oscillatory response of the targeted cortical area, and its evolution as the neural activation propagates to other cortical areas. These results are exemplified in Fig. 6.1b. Focal cortical stimulation elicits different patterns of oscillatory activity, depending on the state and nature of the stimulated cortex [63]. In short, time-frequency analysis of TMS-EEG signal can be obtained by estimating the change in spectral distribution across time after the TMS pulse in each trial, and averaging the results across trials [54].

A further development of TMS-EEG data analysis is the estimation of neural response transmission between cortical regions following the TMS pulse. For example, the signal propagation from the stimulated left prefrontal cortex to the contralateral hemisphere can be quantified as a function of the concomitant activation of both hemispheres following the TMS pulse, estimated using TEP amplitude from these regions [74]. Frequency-based connectivity analyses have also been proposed as a measure of signal propagation from the stimulated motor cortex to other regions [55]. Another example of a complementary TMS-EEG metrics is the perturbation complexity index (PCI), which uses the signal to estimate the complexity of the evoked brain activity in response to a direct stimulus, yielding

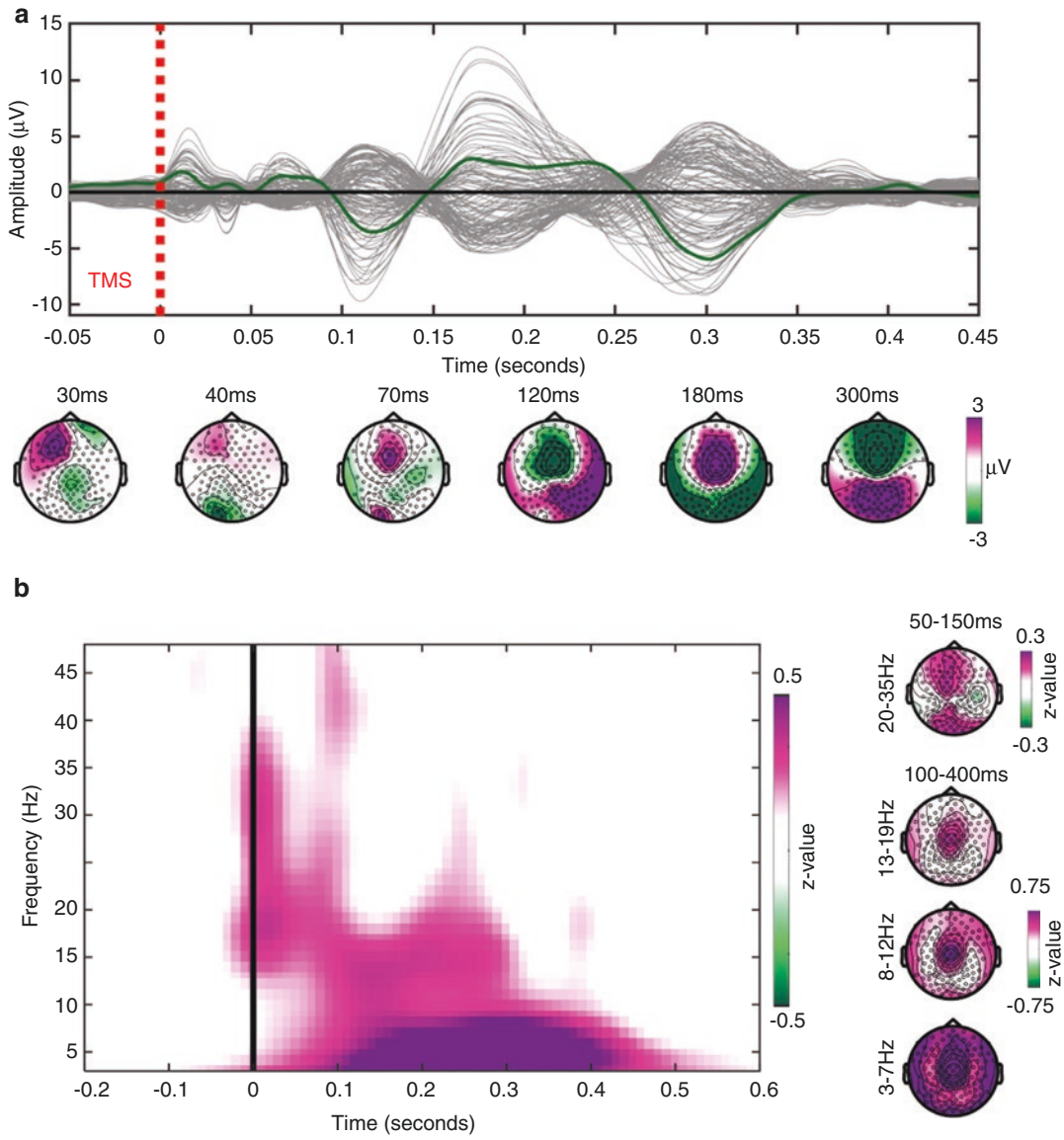

Fig. 6.1 TMS-evoked and TMS-induced responses from a single subject, average of 160 trials of TMS applied to the dorsomedial prefrontal cortex at the time 0 seconds. (**a**) Time course of the TMS-evoked response amplitudes recorded by 126 electrodes, referenced to the average of all electrodes (in the butterfly plot, dark green refers to the Fz electrode, close to the site of stimulation). Topographical plots below show the distribution of the amplitudes on the scalp surface at different time points after the TMS pulse. (**b**) Time-frequency plot of the TMS response, averaged across all 126 electrodes. Color coded results refer to the change of the standardized value of the spectral power (z-value) with respect to the baseline (time before TMS pulse). Topographical plots to the right show the distribution of the power on the scalp surface in different frequency bands and time windows after the TMS pulse

a single value as outcome between 0 and 1 measure [8]. This estimate was developed to assess the severity of patients with disorders of consciousness, assuming that more severe cases would account for a less complex cortical response to TMS due to the severity of brain damage and its inability to process inputs, thus yielding a comparatively lower index [9].

6.3 Physiology

TMS-EEG can be seen as a development from TMS-EMG, allowing the probing and signal acquisition from multiple cortical areas other than motor cortex. The resulting signals can provide relevant information on the cortical functioning and lead to a broader understanding of the neurophysiology and its alterations in clinical conditions. However, for that to be possible, the physiological significance of each measure first needs to be clarified.

The TEP components were proposed to represent each a particular process in the cortical response to the TMS pulse. Given that there exists a large body of neurophysiological studies of TMS-EMG responses, early TMS-EEG experiments first targeted the motor cortex, aiming to relate TMS-EEG to TMS-EMG outcomes. It was observed that the amplitude of early TEPs (peaks from 15 to 80 ms after the TMS pulse) are correlated with the MEP amplitude, and both are correlated to TMS intensity [19, 39]. This suggests that the amplitude of early TEPs represent the current local motor cortical excitability. The use of pharmacological agents has also helped to elucidate this phenomenon. The administration of positive allosteric modulators at the GABA-A receptor (diazepam, alprazolam and zolpidem) increased the N45 potential (the amplitude of the negative peak observed 45 ms after the TMS pulse) elicited by TMS of motor cortex [57]. Similarly, the NMDA receptor antagonist dextromethorphan increased the N45 amplitude [40]. Indeed, local cortical excitability involves the interplay between GABAergic and glutamatergic interneurons, with the relative activity of these two neuronal systems determining the neuronal population's excitability/inhibition balance and downstream signaling [27].

Later TEPs, on the other hand, were related to other neurophysiological processes, namely long-distance connections and GABA-B receptor-mediated activity. By delivering a conditioning pulse around 100 ms before the test stimulus, the cortex is placed into a low responsivity state, a paradigm named "long-interval intracortical inhibition" (LICI) [72], which was found to be mediated by GABA-B activity [77]. Applying this paired-pulse TMS technique in TMS-EEG experiments demonstrated that the N100 (negative peak observed 100 ms after the TMS pulse) can be suppressed both in the motor cortex [58] and the dorsolateral prefrontal cortex (DLPFC) [15, 17, 18]. Moreover, administration of a GABA-B receptor agonist (baclofen) increased the amplitude of the N100 at the site of stimulation [57, 58].

TMS-induced oscillatory cortical responses add additional information of relevant physiological significance. Rosanova et al. [63] reasoned that regions of the sensory cortex respond to incoming sensorial activation by oscillations in specific frequency bands, depending on the region (auditory, visual, somatosensory), proposing that this reveals the "natural frequency" of that region; and in their experiment TMS pulses were used to provide direct activation of cortical areas other than sensory regions [63]. Results revealed that TMS of frontal cortex led to oscillatory response in the high beta/gamma range (around 30 Hz), TMS of motor cortex in the high alpha/low beta range (around 18 Hz) and TMS of parietal cortex in the theta/low alpha range (around 8 Hz). Later studies found that changes caused by intervention in focal cortical responses were specifically found in their respective natural frequency. For instance, a pharmacological study of TMS to the motor cortex found that GABA-A (diazepam, alprazolam, zolpidem) and a GABA-B receptor agonist (baclofen) alter specifically TMS-induced oscillations in the alpha and beta band [56]. Furthermore, TMS to the occipital cortex elicits oscillatory response in the alpha band (around 10 Hz), a response that could be modulated by visual attention, further suggesting the physiological function of induced oscillations as a natural oscillatory pattern specific for the cortical area of interest [25, 69].

6.4 Neuropsychiatry

The advantage of TMS-EEG in enabling readouts from cortical regions beyond the motor cortex offers particular benefits for the study of

neuropsychiatric conditions. This method has the potential to reveal diagnostic biomarkers of disordered cortical network function by comparing TMS-EEG measures between a clinical population and healthy controls, thus potentially revealing pathophysiological mechanisms of the studied disorder. TMS-EEG measures can also be used to investigate the response to treatment in a clinical population, possibly delimiting the neurophysiological processes associated with better prognosis and clinical response to treatment. These uses of TMS-EEG measures in neuropsychiatric disorders will be exemplified below.

6.4.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

Bruckmann et al. [4] proposed the use of the N100 amplitude as a disease marker for ADHD, observing that affected individuals had a reduced N100 amplitude evoked by TMS of the motor cortex compared to healthy controls, a result consistent across different age strata [4]. This led the authors to suggest that the reduced N100 amplitude points to a deficient top-down control of motor inhibition, as proposed by disease models, and consistent with the later observed pharmaco-TMS-EEG findings summarized above, which showed increased N100 amplitudes in higher inhibitory states. Also, a decreased N100 amplitude inhibition in no-go trials during the execution of a motor task (cued go/no-go task), corroborated the deficient motor control inhibition as a mechanism behind ADHD symptoms [13].

6.4.2 Schizophrenia

TMS-EMG studies have suggested a GABA-B cortical deficiency in subjects with schizophrenia [59], which is in line with results from genetic and neuroimaging studies pointing to a cortical inhibitory deficit in this population [67]. In agreement with the hypothesis of GABA-B deficiency in the prefrontal cortex, N100 amplitude was found to be reduced in subjects with schizophrenia when targeting TMS to the DLPFC, but not motor cortex [51]. The capability of TMS-EEG in probing different cortical targets made this investigation possible, providing evidence on how the disease distinctly impacts different brain regions.

Combining the analysis of LICI (a TMS paired-pulse protocol that elicits GABA-B-dependent inhibitory cortical responses) and TMS-induced oscillatory responses revealed that in subjects with schizophrenia, paired-pulse TMS did not properly inhibit the oscillatory response in the gamma frequency band, which corresponds to the prefrontal cortex natural oscillatory response [17, 18, 60]. The authors suggested that the deficient prefrontal GABAergic activity in schizophrenia may be not only a disease marker, but also the cause of excessive gamma oscillations, which leads to aberrant plasticity, and ultimately translating into learning disarray, inflexible thinking and consequently schizophrenia symptoms [60]. Indeed, subjects with schizophrenia showed persistent oscillations in the gamma frequency range in response to TMS, a measure that was positively correlated with the severity of positive symptoms [22]. Future studies should investigate possible treatments that can return the cortical inhibition to normal levels in the prefrontal cortex, and whether this translates into clinical improvement, as has been done in the motor cortex with TMS-EMG [24, 34].

6.4.3 Mood Disorders

A study comparing healthy subjects to subjects with major depressive disorder (MDD) and bipolar disorder has demonstrated that TMS of the premotor cortex induced less than normal oscillations in the high-beta (21–30 Hz) and gamma (>30 Hz) frequency bands in the clinical populations, these corresponding to the natural frequencies of this cortical area [7, 63]. Concomitantly, subjects with MDD showed significantly lower amplitudes of early TEPs in response to DLPFC stimulation, with N45 amplitude reduction showing significant diagnostic value, with 76%

accuracy in correctly identifying subjects with MDD [75]. These two findings are intimately correlated: As mentioned before, early TMS responses relate to local cortical excitability, particularly the state of the glutamate/GABA-A dynamics, with enhancement of N45 amplitude after pharmacological challenge by positive allosteric modulators at the GABA-A receptor [57] and NMDA receptor inhibition [40]. A dysfunction of this dynamics observed in MDD, with reduced N45, can therefore explain the failure of the DLPFC in recruiting the local natural frequency in the gamma band. This phenomenon might have central importance in the pathophysiology of depressive disorders and might explain the efficacy of repetitive TMS protocols that induce prefrontal cortex facilitation in the treatment of refractory MDD [41].

Aiming to use this phenomenon as a treatment response marker, one study investigated TMS-EEG oscillatory responses in subjects with bipolar disorder prior and following treatment. Although findings confirmed a deficit of the TMS-induced response of prefrontal cortex in the high-beta/gamma frequency band in the clinical population compared to healthy controls, no change in the oscillatory response was seen following treatment, irrespective of clinical improvement, leading the authors to suggest this alteration as a static disease marker in people diagnosed with bipolar disorder [6].

6.4.4 Substance Abuse Disorders

Acute alcohol consumption was consistently shown to decrease N100 amplitude when targeting both the motor cortex and in DLPFC [32, 33, 43], opposite to the N100 amplitude increase following administration of the GABA-B agonist baclofen [57]. This suggests that the neurophysiological disinhibiting effect of alcohol involves disruption of GABA-B receptor-mediated cortical activity. A pilot paired-pulse TMS study also pointed to deficient LICI when testing the DLPFC in subjects with alcohol abuse disorder under treatment, suggesting that the inhibitory deficiency is not limited to alcohol consumption, but may be a disease marker [48]. Unfortunately, there is as of yet a lack of TMS-EEG studies involving clinical populations of patients with substance-related disorders.

6.4.5 Alzheimer's Disease (AD)

Initial TMS-EEG studies with AD subjects pointed to a significant reduction of the P30 amplitude to TMS of motor cortex, an abnormality that was also found in cortical areas distant from the stimulated motor cortex, such as the ipsi- and contralateral temporoparietal regions [30, 31]. As early TEPs are believed to reflect local cortical excitability at the site of stimulation, it was suggested that cortical atrophy and loss of connectivity between cortical areas seen in AD might be responsible for the observed P30 decrease. In line with this result, Casarotto et al. [10] found that early TEP amplitudes are decreased in subjects with AD, independent of age or cortical atrophy (the use of MRI-informed online estimation of the TMS-induced electric field guaranteed proper cortical stimulation despite cortical atrophy in AD) [10]. On the other hand, Ferreri and colleagues [20] found an increase in P30 in subjects with AD who were naïve to medication, suggesting cortical hyperexcitability as a marker of AD, and that previous results were confounded by the use of medication.

TMS-EEG was also used to test the effects of an intervention, namely repetitive TMS to the precuneus, as a therapeutic measure to improve cognitive dysfunction. TMS-EEG showed increased cortical responsivity, with increased amplitude of evoked responses, only when the target was the precuneus, not a control region (posterior parietal cortex), pointing to the specificity of TMS-EEG in detecting change in a focal cortical area [36]. Moreover, the EEG response to the stimulus was observed both locally and also in a region corresponding to the medial prefrontal cortex, suggesting that the rTMS protocol had an effect over the frontal-parietal working memory network, which is centrally involved in the physiopathology of AD [16].

6.5 Future Directions

In addition to advancing the development of pathophysiological models and disease markers, the combination of TMS and EEG can have further applications. Of particular interest is the use of EEG signals to guide the application of TMS pulses. TMS responses, and neurophysiological processes in general, are greatly influenced by the current neuronal state, which modulates the likelihood of neuronal firing, downstream signaling, and neuroplasticity [46, 50]. Therefore, it is expected that the application of repetitive TMS might lead to differential immediate and neuroplastic effects when applied in different brain states. This was tested in the motor cortex, as TMS pulses applied to different phases of a relevant local oscillation (the sensorimotor μ-rhythm in the alpha frequency band) evoked MEPs of different amplitudes and led to different degrees of neuroplasticity [79]. Using this rationale, paradigms of EEG-informed repetitive TMS are potentially highly interesting as a treatment tool, possibly enhancing efficacy of therapeutic noninvasive brain stimulation for neuropsychiatric conditions [78].

Regarding its use in neurophysiological research, we have seen that TMS-EEG showed several relevant results in the study of neuropsychiatric disorders. Nevertheless, there are fundamentally important issues that need to be addressed in advancing the field, such as uniform standards of data collection and data processing, so that results from TMS-EEG studies become reliable and valid across different centers around the world. This would need necessarily include the use of proper methods to remove spurious cortical responses, such as SEPs, to reveal the true nature of the brain response to TMS [3].

The physiological meaning of the TMS-EEG measures also deserves further attention. One of the advantages of TMS-EEG measures is the plurality of information it can provide, from the amplitudes of evoked potentials to changes in oscillatory pattern and cortical-cortical connectivity, probed in many different cortical areas. Nevertheless, most of our assumptions regarding the physiological nature of these measures are translated from other fields, such as the study of the motor cortex. However, there is already substantial evidence that TMS-EEG effects in areas other than motor cortex are different from those obtained with motor cortex stimulation. A solid understanding of the physiological meaning of TMS-EEG measures in different cortical areas is of significant importance for their proper interpretation in healthy subjects and neuropsychiatric disorders. With this aim, pharmaco-TMS-EEG studies using drugs with known and specific mode of action in the central nervous system can be of particular interest, revealing the relevance of different neurochemical pathways and the pharmaco-physiological mechanisms of TMS-evoked and -induced EEG responses [14].

Finally, studies in neuropsychiatry should consider going beyond the description of focal changes in cortical functioning, and instead explore the network effects of disease and interventions. Ultimately, neuropsychiatric disorders are characterized by complex dysfunctions of brain networks, which are responsible for specific classes of neuronal functions and whose disturbance generates the clinical symptoms observed. TMS-EEG has the potential to probe the pathophysiology of these networks, helping to bridge the gap between neurophysiological findings and clinical practice and thus providing a more accurate description of the mechanisms behind these disorders, explaining their symptoms and proposing personalized treatment pathways [1, 76].

In conclusion, despite the currently already available studies of TMS-EEG in neuropsychiatric disorders, TMS-EEG is still an emergent technology, and there is much untapped potential for the application of TMS-EEG in the field, which will continue to provide insight into the neurobiological underpinnings of neuropsychiatric disorders and facilitate treatment options.

References

1. Anderson RJ, Hoy KE, et al. Repetitive transcranial magnetic stimulation for treatment resistant depression: re-establishing connections. Clin Neurophysiol. 2016;127(11):3394–405.
2. Atluri S, Frehlich M, et al. TMSEEG: a MATLAB-based graphical user Interface for processing

electrophysiological signals during transcranial magnetic stimulation. Front Neural Circuits. 2016;10:78.
3. Belardinelli P, Biabani M, et al. Reproducibility in TMS-EEG studies: a call for data sharing, standard procedures and effective experimental control. Brain Stimul. 2019;12(3):787–90.
4. Bruckmann S, Hauk D, et al. Cortical inhibition in attention deficit hyperactivity disorder: new insights from the electroencephalographic response to transcranial magnetic stimulation. Brain. 2012;135(Pt 7):2215–30.
5. Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. Science. 2004;304(5679):1926–9.
6. Canali P, Casarotto S, et al. Abnormal brain oscillations persist after recovery from bipolar depression. Eur Psychiatry. 2017;41:10–5.
7. Canali P, Sarasso S, et al. Shared reduction of oscillatory natural frequencies in bipolar disorder, major depressive disorder and schizophrenia. J Affect Disord. 2015;184:111–5.
8. Casali AG, Gosseries O, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med. 2013;5(198):198ra105.
9. Casarotto S, Comanducci A, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol. 2016;80(5):718–29.
10. Casarotto S, Maatta S, et al. Transcranial magnetic stimulation-evoked EEG/cortical potentials in physiological and pathological aging. Neuroreport. 2011;22(12):592–7.
11. Conde V, Tomasevic L, Akopian I, Stanek K, Saturnino GB, Thielscher A, Bergmann TO, Siebner HR. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. Neuroimage. 2019;185:300–12.
12. Cracco RQ, Amassian VE, et al. Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr Clin Neurophysiol. 1989;74(6):417–24.
13. D'Agati E, Hoegl T, et al. Motor cortical inhibition in ADHD: modulation of the transcranial magnetic stimulation-evoked N100 in a response control task. J Neural Transm (Vienna). 2014;121(3):315–25.
14. Darmani G, Ziemann U. Pharmacophysiology of TMS-evoked EEG potentials: a mini-review. Brain Stimul. 2019;12(3):829–31.
15. Daskalakis ZJ, Farzan F, et al. Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. Neuropsychopharmacology. 2008;33(12):2860–9.
16. Drzezga A, Becker JA, et al. Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden. Brain. 2011;134(Pt 6):1635–46.
17. Farzan F, Barr MS, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. Brain. 2010a;133(Pt 5):1505–14.
18. Farzan F, Barr MS, et al. Reliability of long-interval cortical inhibition in healthy human subjects: a TMS-EEG study. J Neurophysiol. 2010b;104(3):1339–46.
19. Ferreri F, Pasqualetti P, et al. Human brain connectivity during single and paired pulse transcranial magnetic stimulation. NeuroImage. 2011;54(1):90–102.
20. Ferreri F, Vecchio F, et al. Sensorimotor cortex excitability and connectivity in Alzheimer's disease: a TMS-EEG co-registration study. Hum Brain Mapp. 2016;37(6):2083–96.
21. Fox PT, Narayana S, et al. Column-based model of electric field excitation of cerebral cortex. Hum Brain Mapp. 2004;22(1):1–14.
22. Frantseva M, Cui J, et al. Disrupted cortical conductivity in schizophrenia: TMS-EEG study. Cereb Cortex. 2014;24(1):211–21.
23. Gordon PC, Desideri D, et al. Comparison of cortical EEG responses to realistic sham versus real TMS of human motor cortex. Brain Stimul. 2018;11(6):1322–30.
24. Gordon PC, Valiengo L, et al. Changes in motor cortical excitability in schizophrenia following transcranial direct current stimulation. Prog Neuro-Psychopharmacol Biol Psychiatry. 2019;90:43–8.
25. Herring JD, Thut G, et al. Attention modulates TMS-locked alpha oscillations in the visual cortex. J Neurosci. 2015;35(43):14435–47.
26. Hill AT, Rogasch NC, et al. TMS-EEG: a window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. Neurosci Biobehav Rev. 2016;64:175–84.
27. Hu H, Gan J, et al. Interneurons. Fast-spiking, parvalbumin(+) GABAergic interneurons: from cellular design to microcircuit function. Science. 2014;345(6196):1255263.
28. Ilmoniemi RJ, Kicic D. Methodology for combined TMS and EEG. Brain Topogr. 2010;22(4):233–48.
29. Ilmoniemi RJ, Virtanen J, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport. 1997;8(16):3537–40.
30. Julkunen P, Jauhiainen AM, et al. Combining transcranial magnetic stimulation and electroencephalography may contribute to assess the severity of Alzheimer's disease. Int J Alzheimers Dis. 2011;2011:654794.
31. Julkunen P, Jauhiainen AM, et al. Navigated TMS combined with EEG in mild cognitive impairment and Alzheimer's disease: a pilot study. J Neurosci Methods. 2008;172(2):270–6.
32. Kahkonen S, Wilenius J. Effects of alcohol on TMS-evoked N100 responses. J Neurosci Methods. 2007;166(1):104–8.
33. Kahkonen S, Wilenius J, et al. Alcohol reduces prefrontal cortical excitability in humans: a combined TMS and EEG study. Neuropsychopharmacology. 2003;28(4):747–54.
34. Kaster TS, de Jesus D, et al. Clozapine potentiation of GABA mediated cortical inhibition in treatment resistant schizophrenia. Schizophr Res. 2015;165(2–3):157–62.

35. Kirschstein T, Kohling R. What is the source of the EEG? Clin EEG Neurosci. 2009;40(3):146–9.
36. Koch G, Bonni S, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. NeuroImage. 2018;169:302–11.
37. Komssi S, Aronen HJ, et al. Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin Neurophysiol. 2002;113(2):175–84.
38. Komssi S, Kahkonen S. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev. 2006;52(1):183–92.
39. Komssi S, Kahkonen S, et al. The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp. 2004;21(3):154–64.
40. König, F., P. Belardinelli, et al. TMS-EEG signatures of glutamatergic neurotransmission in human cortex. bioRxiv. 2019.
41. Lefaucheur JP, Aleman A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol. 2020;131(2):474–528.
42. Lioumis P, Kicic D, et al. Reproducibility of TMS-evoked EEG responses. Hum Brain Mapp. 2009;30(4):1387–96.
43. Loheswaran G, Barr MS, et al. Alcohol impairs N100 response to dorsolateral prefrontal cortex stimulation. Sci Rep. 2018;8(1):3428.
44. Maki H, Ilmoniemi RJ. EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations. Clin Neurophysiol. 2010;121(4):492–501.
45. Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods. 2007;164(1):177–90.
46. Massimini M, Ferrarelli F, et al. Breakdown of cortical effective connectivity during sleep. Science. 2005;309(5744):2228–32.
47. Mutanen TP, Metsomaa J, et al. Automatic and robust noise suppression in EEG and MEG: the SOUND algorithm. NeuroImage. 2018;166:135–51.
48. Naim-Feil J, Bradshaw JL, et al. Cortical inhibition within motor and frontal regions in alcohol dependence post-detoxification: a pilot TMS-EEG study. World J Biol Psychiatry. 2016;17(7):547–56.
49. Nikouline V, Ruohonen J, et al. The role of the coil click in TMS assessed with simultaneous EEG. Clin Neurophysiol. 1999;110(8):1325–8.
50. Nikulin VV, Kicic D, et al. Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur J Neurosci. 2003;18(5):1206–12.
51. Noda Y, Barr MS, et al. Reduced short-latency afferent inhibition in prefrontal but not motor cortex and its association with executive function in schizophrenia: a combined TMS-EEG study. Schizophr Bull. 2018;44(1):193–202.
52. Oostenveld R, Fries P, et al. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci. 2011;2011:156869.
53. Paus T, Sipila PK, et al. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J Neurophysiol. 2001;86(4):1983–90.
54. Pellicciari MC, Veniero D, et al. Characterizing the cortical oscillatory response to TMS pulse. Front Cell Neurosci. 2017;11:38.
55. Petrichella S, Johnson N, et al. The influence of corticospinal activity on TMS-evoked activity and connectivity in healthy subjects: a TMS-EEG study. PLoS One. 2017;12(4):e0174879.
56. Premoli I, Bergmann TO, et al. The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex. NeuroImage. 2017;163:1–12.
57. Premoli I, Castellanos N, et al. TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci. 2014a;34(16):5603–12.
58. Premoli I, Rivolta D, et al. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. NeuroImage. 2014b;103:152–62.
59. Radhu N, de Jesus DR, et al. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clin Neurophysiol. 2013;124(7):1309–20.
60. Radhu N, Garcia Dominguez L, et al. Evidence for inhibitory deficits in the prefrontal cortex in schizophrenia. Brain. 2015;138(Pt 2):483–97.
61. Rogasch NC, Sullivan C, et al. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: a review and introduction to the open-source TESA software. NeuroImage. 2017;147:934–51.
62. Rogasch NC, Thomson RH, et al. Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. NeuroImage. 2014;101:425–39.
63. Rosanova M, Casali A, et al. Natural frequencies of human corticothalamic circuits. J Neurosci. 2009;29(24):7679–85.
64. Rossini PM, Rossi S. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology. 2007;68(7):484–8.
65. Roth BJ, Pascual-Leone A, et al. The heating of metal electrodes during rapid-rate magnetic stimulation: a possible safety hazard. Electroencephalogr Clin Neurophysiol. 1992;85(2):116–23.
66. Ruddy KL, Woolley DG, et al. Improving the quality of combined EEG-TMS neural recordings: introducing the coil spacer. J Neurosci Methods. 2018;294:34–9.

67. Schmidt MJ, Mirnics K. Neurodevelopment, GABA system dysfunction, and schizophrenia. Neuropsychopharmacology. 2015;40(1):190–206.
68. ter Braack EM, de Vos CC, et al. Masking the auditory evoked potential in TMS-EEG: a comparison of various methods. Brain Topogr. 2015;28(3):520–8.
69. Thut G, Miniussi C. New insights into rhythmic brain activity from TMS-EEG studies. Trends Cogn Sci. 2009;13(4):182–9.
70. Tremblay S, Rogasch NC, et al. Clinical utility and prospective of TMS-EEG. Clin Neurophysiol. 2019;130(5):802–44.
71. Uusitalo MA, Ilmoniemi RJ. Signal-space projection method for separating MEG or EEG into components. Med Biol Eng Comput. 1997;35(2):135–40.
72. Valls-Sole J, Pascual-Leone A, et al. Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol. 1992;85(6):355–64.
73. Virtanen J, Ruohonen J, et al. Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. Med Biol Eng Comput. 1999;37(3):322–6.
74. Voineskos AN, Farzan F, et al. The role of the corpus callosum in transcranial magnetic stimulation induced interhemispheric signal propagation. Biol Psychiatry. 2010;68(9):825–31.
75. Voineskos D, Blumberger DM, et al. Altered transcranial magnetic stimulation-electroencephalographic markers of inhibition and excitation in the dorsolateral prefrontal cortex in major depressive disorder. Biol Psychiatry. 2019;85(6):477–86.
76. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3(5):472–80.
77. Ziemann U, Reis J, et al. TMS and drugs revisited 2014. Clin Neurophysiol. 2015;126(10):1847–68.
78. Zrenner B, Zrenner C, et al. Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS. Brain Stimul. 2020;13(1):197–205.
79. Zrenner C, Desideri D, et al. Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. Brain Stimul. 2018;11(2):374–89.

Multimodal Association of tDCS with Electroencephalography

7

Nadia Bolognini and Lorenzo Diana

7.1 Introduction: A Brief Picture of the Present State of Research

In recent years, there has been an exponential rise in the number of studies that employ non-invasive brain stimulation to gain understanding of the neural substrates underlying normal and pathological behaviour (see Parts III–IV of this book), as well as an adjuvant tool for treating brain dysfunction associated with neuropsychiatric disorders (see Part V of this book). As clearly explained in the previous chapters of this book, non-invasive brain stimulation includes several methods that can be divided into two main categories: transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). The latter includes different modalities, namely, transcranial direct current (tDCS), alternating current (tACS) and random noise (tRNS) stimulation. All of these methods involve the application of weak electrical currents to the scalp using at least two electrodes [1]. These currents induce changes in the electrical activity of neurons, thus modifying the neurons' synaptic efficiency. Although these changes are insufficient to induce action potentials, they introduce variation in the response thresholds of the stimulated neurons [2]. Typically, through this variation, anodal tDCS and tRNS increase neuronal excitability and cathodal tDCS decreases excitability, whereas tACS modifies neuronal excitability through the entrainment of the desired neuronal firing frequency [3]. Thanks to the important developments that have been made in recent years, many technical difficulties that were originally faced during the development of tES in human research have been solved, the methodological foundations have been laid [1] and we are now clarifying the mechanisms of action of tES better and better. On these solid bases, we are now expanding and refining the experimental and clinical use of tES: fostering an integrated use of this technique with neuroimaging is one of these future goals. This chapter aims to introduce the reader to some basic principles of the multimodal approach. We begin with a brief definition of "multimodal association" and then move on to a description of the advantages of such an approach. Afterwards, we provide a more specific description of how we can combine tES with electroencephalography (EEG). In this respect, we list the basic technical elements that allow the best

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integration of tES, and in particular tDCS, with EEG. Finally, we show how this approach can be used for diagnostic or prognostic purposes in neuropsychiatry.

7.2 Principles of Multimodal Association

Over the last decade, we have observed an increase in the popularity of approaches that combine more than one method to establish, in vivo, the consequences of a given experimental manipulation, due to the increased accuracy of multiple imaging techniques [4]. The possibility of altering brain functions with tES, while simultaneously assessing those functions with neuroimaging, is essential to understand whether and how tES affects sensory motor, cognitive and affective functions. In general, every method used to track changes in brain activity has its pros and cons. For example, EEG has an excellent temporal resolution but has limitations in the spatial component; functional magnetic resonance imaging (fMRI) has the opposite features: good spatial resolution and low temporal resolution. Moreover, electrophysiological and haemodynamic/metabolic signals reflect distinct aspects of the underlying neural activity. From a methodological perspective, the combination of complementary approaches within the same experimental setting should boost the amount of information that we can obtain beyond what is achievable with each method independently. Therefore, the ideal situation is to combine non-invasive brain stimulation with the collection of both behavioural indexes of changes and more than one measure of brain activity (e.g. EEG, fMRI or magnetic resonance spectroscopy) to overcome the intrinsic limits in spatial and temporal resolution of each recording technique. Such an approach will offer a more complete framework for understanding the effects of tES in vivo [5–7] by tracking changes at different levels of analysis (behavioural and neural). Moreover, electrophysiological correlates of tES effects can be employed to optimise important parameters, common to many neuromodulatory approaches, such as electrodes montage, current intensity and duration of stimulation, thus improving the efficacy of such techniques both in experimental and clinical settings [6].

The main challenge of the multimodal association approach is a technical one, given that the limits of combining different devices are mostly due to technical problems. This challenge implies clear understanding of the functional principles of the combined methods and of the distinct (due to the different measures), but linked, neural effects that are being measured (e.g. electrophysiological vs. haemodynamic). Moreover, we must be aware of, if and how, the recorded signal that is being altered by such combinations. For example, tES involves the use of currents that not only change the function of neurons but also the capability of the EEG amplifier and electrodes to record the signal. Similarly, tES current flow produces a magnetic field, and MRI recording is sensitive to local magnetic fields [8]. It follows that we need to identify a reliable method to record data during concurrent stimulation and registration without affecting signal quality to obtain a biological signal that accurately reflects the measured process, rather than a technical artefact.

7.3 Advantages of Combining tES with Other Methods

We are at the beginning of the development of these multimodal approaches, but we have at our disposal several methods that can be combined with tES to study brain functions. The simplest and best-known one is the use of TMS to track cortical excitability shifts induced by tES, as traditionally conducted in studies in the tES literature, such as in the seminal studies by Priori and colleagues [9] and by Nitsche and Paulus [10] at the turn of this century. Another approach involves the recording of the metabolic changes brought about by tES by means of fMRI, positron emission tomography (PET) and, more recently, functional near-infrared spectroscopy (fNIRS). PET and fMRI, in particular, offer a clear picture of the whole brain's activity with uniform sensitivity and high spatial resolution (see Chap. 12).

One supplemental method that can be used to obtain images of human brain functioning is EEG. EEG allows measuring the electrical activity of populations of neurons while a subject is in a given state (e.g. at rest with open or closed eyes, or performing a perceptual or behavioural task). Neural activity generates electrical currents that pass through the skull and give rise to small potential fluctuations/differences, which can be recorded by means of electrodes fixed to the scalp. EEG has a relatively poor spatial sensitivity; nonetheless, it offers some important advantages if combined with tES, given that both are based on the same electrophysiological basis. EEG is based on the theory of volume conduction, which describes the flow of ionic currents that are generated by nerves and cells in the extracellular space. tES uses the same principles to change neuronal states, although the current is applied to the scalp to reach the neurons. In other words, the advantage of recording the EEG during tES lies in the fact that the measured signal is directly coupled to neuronal electrical activity and therefore reflects the electrical state of neurons (Fig. 7.1). Currents recorded with EEG result from transmembrane currents in neurons, which are the currents that can be specifically modified by tES. In brief, tES can change membrane permeability and, consequently, ionic current flows [11–13], while EEG measures the

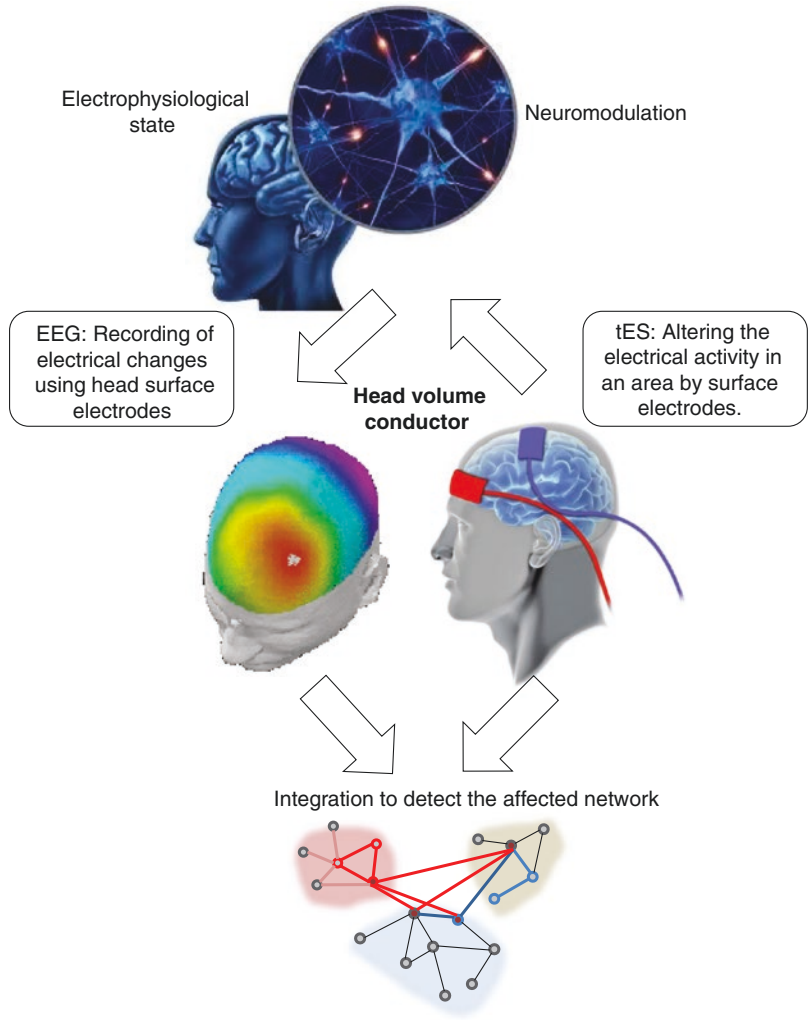

Fig. 7.1 The currents that are recorded by electroencephalography (EEG) result from transmembrane currents in neurons; these currents can be specifically modified by transcranial electrical stimulation (tES). Stimulating a cortical area is likely to affect the underlying region in addition to other areas of the system, and this pattern of activation may be responsible for the final tES-induced behavioural effect. By combining tES and EEG, it becomes possible to acquire simultaneous measurements of the activity of the entire brain, providing a broad picture of cortical responses and a focal picture of which network has been affected

voltage fluctuations that result from ionic current flows [14]. Consequently, the recording of EEG during tES provides an assessment of the effects of tES on neural processing in the stimulated brain region. Crucially, the local activation caused by tES spreads trans-synaptically to distal connected areas. Such activity propagation can be reliably traced by simultaneous EEG recording, which therefore reflects rapid causal interactions among multiple groups of neurons or, at least, areas. Hence, EEG offers the potential to simultaneously identify local and distal neural responses to tES, enabling elucidation of the stages of processing over time and across circuits [15, 16]. This property is relevant because although tES modifies neuronal activity in a circumscribed area under the stimulating electrode [17, 18], changes in cortical excitability do not remain confined to the stimulated area but spread to interconnected regions [19]. In tES research, one of the main goals of multimodal neuroimaging is the evaluation of such network changes. Indeed, according to the process of emergence, the behavioural output of a complex system, such as our brain, arises via specific interactions between minor entities; consequently, the final tES effect cannot be merely ascribed to the response of simpler subunits that compose the stimulated area. Therefore, evaluating the effects at the level of network activity is fundamental for interpreting and predicting the final behavioural outcome of tES; in this sense, the EEG system is a valuable tool.

The objective of the next section is to describe the essential technical steps to create an optimal combination of tES with EEG recording.

7.4 Technical Aspects for the Combined Use of tES and EEG

There are two main methodological approaches to combining tES and EEG that depend on the temporal relationship between tES delivery and EEG recording: the "offline" method, which evaluates the short- and long-term after-effects that follow tES delivery; and the "online method," which evaluates the immediate changes occurring during tES [20]. Only the online method can be defined as a true multimodal approach (e.g. [7, 21–39]), although the offline method can also provide important information. When designing an experiment, it is crucial to specify whether an online or an offline method is going to be adopted because these two approaches require completely different technical procedures and provide different information about the mechanisms of action of tES. Pragmatically, the first technical problem to face is how to position the tES electrodes without interfering with the EEG electrodes. The ideal situation is to have dedicated pre-cabled caps in which the stimulating electrodes are mixed with the recording electrodes (e.g. [7, 26, 29, 40–42]). Nonetheless, when dedicated systems are not available, the simplest solution is to locate the so-called "active" (or target) rubber electrode under the cap, making sure that EEG electrodes are not over or too close to it. Here, a net-shaped elastic mesh tissue bandage can be used to fix the tES electrode; this will avoid interference with the EEG electrodes. However, this arrangement is not ideal because it does not provide easy access to the tES electrode if any problem occurs, and electrodes can drift from their original location. An additional issue is the production of bridging between electrodes. Therefore, some researchers have placed plastic foil on the top of tES electrodes with the aim of preventing unwanted bridging or contact with the EEG cap [21, 43]. An alternative solution is to deactivate/remove the EEG electrodes that are positioned over the active tES electrode [35, 38, 44], or to make a selection of electrodes based on the research question [32–34]. A final option is to create a dedicated tES-EEG cap by making some specific gaps (cuts) on the cap between EEG electrodes. This approach would enable direct access to the active tES electrode [23]. In addition, tES electrodes can be shaped in a more rounded form so that they can be fitted between EEG electrodes [45] or even as rings so that the EEG electrode can be located in the centre of the tES electrodes [46], as shown in Fig. 7.2. It should be noted that reducing the electrode's surface area increases current density; accordingly,

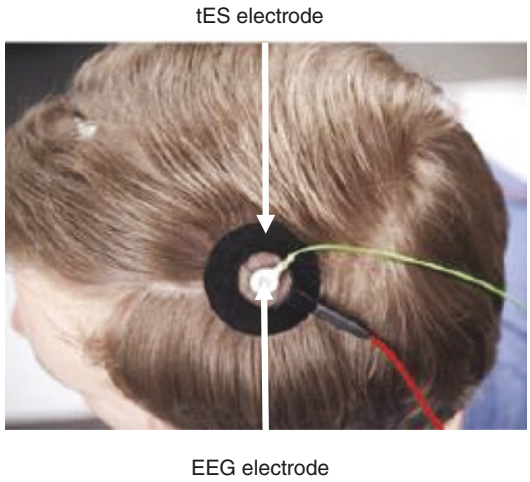

Fig. 7.2 Depiction of an experimental setup that utilises two concentric electrodes: a central electrode to record the EEG signal and a ring electrode to deliver tES. (From Sehm et al. [46])

the current intensity should be adapted. With respect to the return (reference) electrode, it can be located outside the recording space (e.g. shoulder, cheek, part of the forehead, but it should be considered that locations like supraorbital or similar can affect the prefrontal cortex; see for instance [2] and other chapters). If it is necessary to locate it on the head, one of the procedures described above for the active electrode should be adopted. While in sequential recording (offline method), we face only the challenge of positioning the tES and EEG electrodes over the scalp to avoid reciprocal interference, the co-registering of the online method involves additional problems. As stated before, EEG is used to record electrical activity over the scalp, whereas tES involves the application of electrical current over the same scalp, but at a different order of magnitude (i.e. bigger). Therefore, the co-registering can be technically challenging because the tES-induced charges in the electrodes, amplifiers and skin can saturate the recording amplifier for few seconds before recovery of the EEG signal. In general, the new generation of amplifiers offers a large operational range for the registration of electrophysiological signals; this range is obtained by adjusting the amplifier sensitivity, which allows the co-registration without many problems, apart from a few seconds of saturation (~2 s) when the tES current is switched on and off or when an intensity variation is introduced. In some cases, the artefact appears only in the EEG channels close to the tES electrodes [22, 34]. In this respect, although we can use, with some precautions, the "standard" tES electrodes placed in saline-soaked sponges during EEG recording, tES could also be delivered through sintered AgCl electrodes [41, 47], that is, the same electrodes used to record EEG. The advantage of AgCl sintered ring electrodes, for recording EEG, is that they are less sensible to polarisation effects and therefore have optimum long-term stability and low-frequency noise [48]. Generally speaking, in the standard approach, a physiological saline solution is applied to wet the sponge, taking care that the solution does not soak too much the hair (causing dripping) while ensuring that the sponges remain consistently wet. If caution is not used, the physiological solution can leak from the sponges; if this is the case, the features of the contact area will be modified, and they might even cause bridging between the tES and EEG electrodes or between EEG electrodes. To improve scalp contact and avoid unwanted bridging between electrodes, it is possible to apply an electro-conductive gel under the surface of the electrode (without a sponge) to make the contact area, and therefore the current distribution, uniform (see [49] for suggestions on electrode setting and to avoid unwanted skin sensations). In some cases, there is also the possibility to use conductive EEG "adhesive" and a relatively dry paste (i.e. Ten20®; Weaver and Company, Colorado, USA), which holds the electrodes in place and prevents bridging due to leaking of the gel [25, 27, 35]. In the attempt to overcome the previously mentioned disadvantages, Wunder and colleagues [39] devised an integrated cap which features dry EEG electrodes (i.e. small polyurethane baseplates with Ag/AgCl-coated multiple pins) and silicon-isolated textile pockets suitable for the conventional tES electrodes in saline-soaked sponges. In the last years, some integrated solutions have been made available on the market, but the presence of tES-related artefacts in the EEG signal still represents

a challenging problem for an optimal online co-registration [29, 36].

We will now address some important issues related to the noise introduced by the tES during EEG recording. Firstly, the stimulating device is composed of an electronic circuit that can be the source of unwanted external noise; this noise should be minimised by using a stimulator with adequate isolation. It is possible to test and quantify these problems by performing experiments with a phantom head (e.g. a cantaloupe melon), as recently done [30, 50]. In this way, one can easily identify an unwanted artefact, such as instrumental frequency injection. "Phantom" data can be used to define the spectral characteristics and the spatial distribution of tES-related, non-physiological artefacts; eventually the tES data retrieved from the phantom can be compared with the sham data. Complementary approaches to detect and remove tES-induced artefacts may include independent component analysis [41, 51] and filtering the data with a 0.5–70-Hz band pass filter [22].

When recording electrical brain activity, we have to take into account different sources of noise, like the electrical activity generated by eye, head or jaw movements. In some cases, these physiological artefacts can be minimised by instructing the subjects and by recording this activity (e.g. electro-oculography for eye movements and blinks) for post hoc removal. However, it has to be noted that physiological artefacts, such as ocular and cardiac activity, can interact with tES-induced voltage changes during tES-EEG co-registration; hence, they should be carefully monitored (see [52] for a comprehensive discussion and possible solutions for tDCS-EEG setups).

While all the above-mentioned considerations are equally relevant for all tES modalities, tACS or tRNS involve an important additional challenge because they act by inducing an oscillation that contaminates the entire recorded signal. In this case, it has been suggested that it might be possible to clean the signal from tACS-induced artefacts with dedicated algorithms for data analysis [53, 54]. However, further developments in this direction are still needed.

In the next section, we will focus on the tDCS-EEG combination because the bulk of work regarding the multimodal association approach involves tDCS. A description of the combination of other tES techniques with EEG, with online and offline designs, can be found in the following works: tACS [55–64], pulsed/oscillatory stimulation [65–68] and tRNS [44, 69].

7.5 tDCS–EEG in Studying Cortical Excitability, Connectivity and Plasticity

As discussed above, the basic mechanisms underlying the direct neuromodulatory effects of tES are well established due to several studies of animal models [70, 71] and in human subjects [72]. However, a number of works have also highlighted the complexity of the technique and the non-linearity of the induced effects [73–75], as well as the large inter-subject variability [76–78]. Overall, our understanding of tES-induced online and offline effects on neural activity remains fragmented. Given these premises, the importance of electrophysiological studies aimed at clarifying the consequences of neuromodulation by tDCS becomes evident. EEG-based investigations are even more important if we consider that tDCS-induced effects are sensitive to the specific state of the stimulated area [79–82].

Another issue is related to the spatial and temporal resolution of tDCS, which are considered to be very low; however, recently, this picture has been shown to not always be true. Many lines of evidence, including those that combine tDCS and EEG, indicate that the final effect, on both behavioural and neural activity, can be very focal [83]. The specificity of the effects of tDCS effects results from the fact that this form of brain stimulation principally affects neurons that are close to the discharge threshold, which means that the final effect emerges from a change in the activity of a specific, circumscribed neural network, which is related to the subject's state or to a given cognitive process [84, 85].

Since the beginning of this century, EEG has been used to track the products of cortical excit-

ability shifts brought about by tES (e.g. [86]) and to predict the spatio-temporal dynamics of functional connectivity (e.g. [19]). The online and offline methods described above, as well as the issue of how the combined tDCS-EEG approach can be utilised in interactive and rhythmic (i.e. using repetitive TMS; [87]) manners, have been extensively discussed elsewhere [20, 88]. In the following section, after reporting a gross description of the main studies in this field (both online and offline approaches), we will briefly describe only some recent advances (for an overview of the seminal works, see the review paper by Miniussi and co-workers [20]).

The majority of the studies have recorded EEG activity in the resting state, such as by analysing neural oscillations associated with tDCS by frequency changes [22, 24, 26, 28, 41, 43, 89–94] or by recording the effects of tDCS on functional connectivity [19, 30, 31]. In some instances, TMS was also incorporated to probe changes in excitability or connectivity before and after tDCS [25, 69, 91, 95–97] and even during tDCS stimulation [35]. Several studies have recorded EEG activity to evaluate how tDCS modulates the activity of different sensory areas, including visual [21, 39, 86, 98], auditory [38, 99] and somatosensory [46, 100–103] areas. Others studies have analysed event-related potentials (ERPs) or changes in signal frequency in an active state, that is, during the execution of a task, in different contexts, including: decision-making [34], social cognition [104] mismatch negativity [82], inhibitory control [23, 105–107], working memory [36, 108–112], motor imagery [33, 113], motor performance (e.g. finger tapping [114]), language [115–118] and attention [37, 119, 120].

It is very difficult to compare and reconcile the results from all of these studies given their heterogeneity with respect to the stimulation parameters (e.g. density and duration), electrode montage (i.e. bipolar vs. unipolar), studied population, targeted areas and the task performed by the subjects. Collectively, the main message offered is that the tDCS-EEG combination can be used to effectively evaluate changes in cortical excitability, connectivity and plasticity. Such changes depend on several factors, a finding that stresses the existence of a "non-linear" brain response to tDCS, which reflects the variability of behavioural outcomes [69, 77, 78]. In particular, investigations of cortical rhythms have shown that tDCS directly modulates rhythmic cortical synchronisation during and after its delivery. The majority of these studies found an increase in almost all bands (delta, theta, alpha and beta), which appeared to be more prevalent and reliable after anodal tDCS. Nonetheless, Donaldson and colleagues [94], stimulating the right temporoparietal junction, found long-range, delta and theta power changes in the frontal region after cathodal stimulation, further highlighting the complexity of brain responses to electrical perturbations. Indeed, we have to keep in mind that neuronal networks are very sensitive to electric field modulation [121], and the efficacy of tDCS might depend on the intrinsic network structure [122]. In this regard, it has also been suggested that network effects may be related to the concepts of noise and stochastic resonance [85], where a weak stimulation (such as the neuromodulation itself) that is added to the system's fluctuations enhances (or reduces) the biological signal, in turn potentiating the response of the stimulated network.

An interesting result regarding the interaction between brain activity and stimulation was reported by Accornero et al. [22]. The authors evaluated changes in EEG frequency as a marker of excitability changes induced by different electrode montages, bipolar and unipolar, that targeted the prefrontal cortex. The bipolar montage involved positioning both electrodes over prefrontal areas (cathodal right and anodal left, or vice versa), whereas in the unipolar montage, one electrode was positioned over the prefrontal cortex, while the other was positioned on the opposite wrist. The first finding was that anodal tDCS induced changes in the mean frequency of the EEG; these changes occurred very rapidly (after 1 min of stimulation) and remained substantial and consistent throughout the whole stimulation period (15 min). The second, and most interesting, finding was related to the interaction between the electrode montage and the stimulated cortex, as indexed by changes in the EEG mean fre-

quency that were constrained to the cortical area that was stimulated. As illustrated in Fig. 7.3, anodal tDCS to the left prefrontal area, cathodal tDCS to the right prefrontal area or both together (bipolar stimulation) increased the EEG mean frequency; in contrast, when the montage was "reversed", meaning cathodal tDCS to the left prefrontal area or anodal tDCS to the right prefrontal area, but not both together, the EEG mean frequency was decreased. The changes induced by unipolar anodal and cathodal tDCS were similar in terms of absolute size (anodal tDCS increased cortical excitability, whereas cathodal tDCS decreased it) but were specific for the stimulated site. In other words, the primary aspect that determined the decrease or increase in the mean frequency was related to the circuitry of the frontal cortex that was stimulated [22]. This evidence shows how prefrontal areas act "as a whole" to modulate the brain activity recorded by EEG, highlighting that the main factor that determines whether the mean frequency will decrease or increase is not only the stimulation, but the combination of stimulation type with the stimulated network. This type of result is relevant when we want to test the efficacy of a montage for

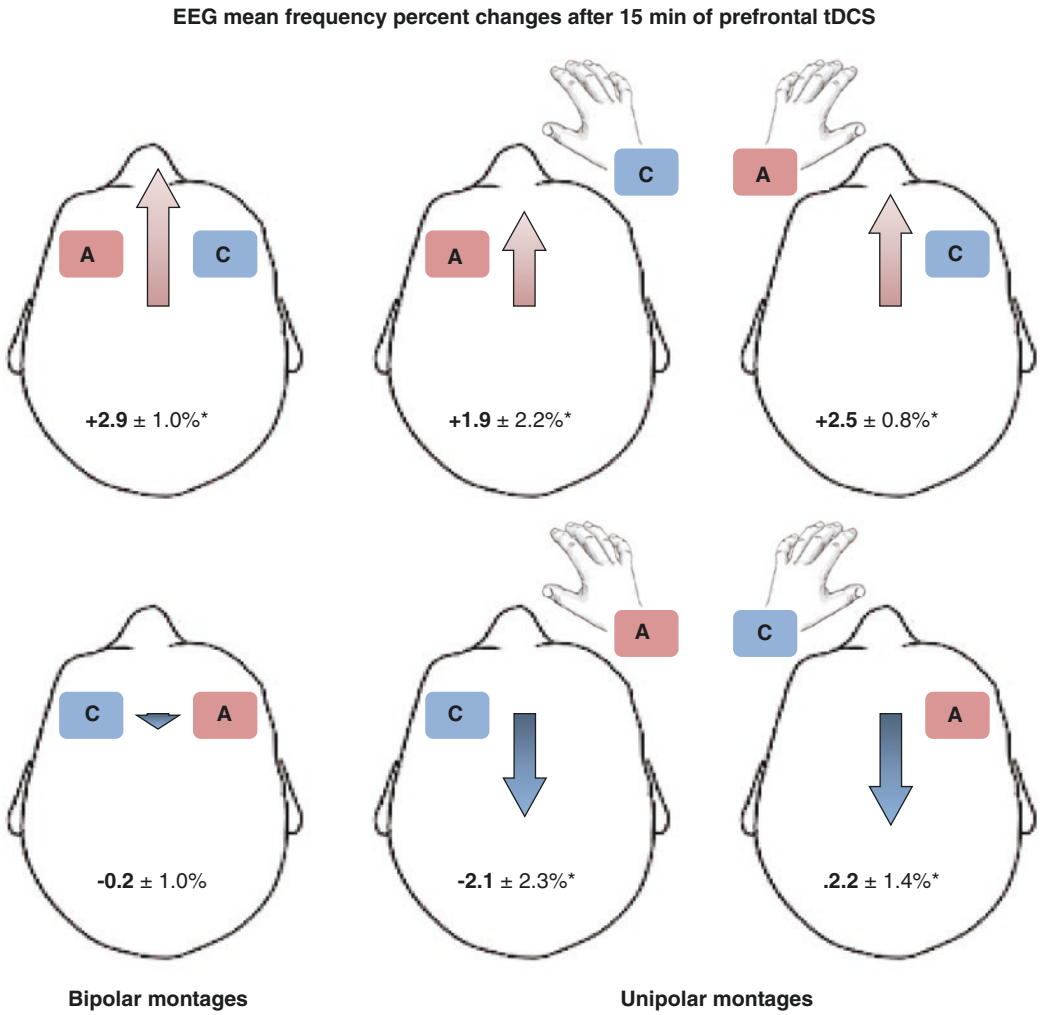

Fig. 7.3 Percentage change in the EEG mean frequency recorded after 15 min of stimulation compared with that recorded at baseline (5 min before tES). Values represent the mean ± standard deviation. The *vertical arrow* height indicates the magnitude of the intensity of the effect. A anodal, C cathodal. (Adapted from Accornero et al. [22])

pathologies such as depression, because an imbalance in the activity of the prefrontal cortices is considered to be of key importance in this type of application [123, 124]. This evidence may also be important as a potential explanation for the frequent finding, in both cognitive and perceptual studies, of the failure of some electrode montages (e.g. cathodal) to effectively modify (e.g. inhibit) prefrontal activity. Therefore, considering that EEG frequency correlates with many psychological features also relevant for clinical symptoms, such as mental arousal level [125] and mood and performance in various tasks [126, 127], it becomes obvious that a priori knowledge of which tDCS montage and methodology is most effective in inducing changes in EEG frequency could guide the optimal therapeutic use of tDCS.

Additionally, several other works have shown that tDCS modulates the amplitude and latency of some ERP components in a very specific way (see Reinhart and Woodman [83] for a commentary), although not to the same extent in every condition (e.g. [82]), nor in every single individual (e.g. [110]). Overall, the key point from these studies is that the final tDCS effect depends on the state of the neural system at the time of the stimulation. Impey and Knott [82] found that tDCS induces a modulation of the mismatch negativity elicited by an auditory sensory discrimination task, and the observed effect was condition-specific and not spatially constrained to the stimulated area. They found tDCS-induced changes in the mismatch negativity component, which originates from the prefrontal cortex, although the stimulating electrode was located over the temporal cortex. Of interest, the modulation was present only when the deviant changes were difficult to detect, whereas it was absent in easy conditions. This last result suggests that the effects of tDCS are sensitive to task difficulty (e.g. [15, 79]). Along the same line, a study by Tseng and colleagues [110] showed that the outcome of tDCS is not always uniform; rather, it depends on individual differences in performance level. In a visual short-term memory task, anodal tDCS over the posterior parietal cortex was able to improve performance and the related EEG components in low performers, but not in high performers. Indeed, after tDCS, low performers showed an increased amplitude in the EEG components related to attentional deployment and memory access (i.e. the N2pc and contralateral delay activity or sustained parietal contralateral negativity), whereas high performers showed equally large waveforms in the above-mentioned EEG components, both before and after tDCS, along with the absence of tDCS effects on behaviour.

The take-home message from these few examples is that tDCS can change cortical excitability and that such changes can be reliably detected with EEG. Importantly, the effects of tDCS are not mapped as a unidirectional, linear change solely on the stimulation features, such as polarity, intensity and electrode montage; likewise, behavioural changes by tDCS are not always linear and systematic in every experimental condition. All these changes depend on the stimulation parameters, as well as the brain state during the tDCS delivery [128–130].

As discussed in the previous sections, applying an electrical field to a non-linear dynamic system, such as the brain, seems to have many non-trivial effects that preclude a simple extrapolation to behaviour. For this reason, the use of the combination of EEG and tDCS offers additional insight into the level of action of tDCS, as EEG can contribute to the identification and understanding of the physiological conditions associated with non-linear tES-induced effects which may be, in some instances, even unforeseeable. For example, investigating the impact of different current intensities in healthy subjects, Hoy and co-workers [108] found that anodal tDCS at 1 mA was able to induce a greater cognitive enhancement than when it was delivered at an intensity of 2 mA. Accordingly, increased theta event-related synchronisation and alpha event-related desynchronisation were detected with the EEG co-registration mainly following the stimulation at 1 mA, as compared to sham tDCS [108]. More recently, Nikolin et al. [36] compared the effects of different tDCS intensities (1 and 2 mA, and three sham conditions) on working memory both at behavioural level (i.e. response times and accuracy in a 3-back task) and electrophysiologi-

cal level (i.e. P3, an ERP component thought to originate in the dorsolateral prefrontal cortex). Although the behavioural performance was not affected by either stimulation intensity, the P3 amplitude was significantly modulated by tDCS, with the largest effects after tDCS at 1 mA. Importantly, the electrophysiological effects (i.e. P3 modulation) were found even after one sham stimulation with a current intensity of 0.034 mA, which was not expected to alter brain activity.

To conclude, the concurrent adoption of EEG will enable more reliable, clearer predictions of what we should expect after the application of tDCS in a given task and on specific neural mechanisms. This knowledge becomes even more important if tES is used with therapeutic purposes because of the inherent difficulty in predicting clinical outcomes and determining the individual patient's response to tES. In the following section, an overview of the clinical feasibility of simultaneous tDCS and EEG recording in neurological and psychiatric diseases is provided.

7.6 Multimodal Imaging as a Diagnostic/Prognostic Tool in Neuropsychiatric Disorders

Behavioural studies have revealed many potential therapeutic applications of tDCS, in particular as a rehabilitation tool for a wide variety of diseases that involve changes in cortical excitability (e.g. [2, 131–135]; see also Part IV of this book).

Deepening our understanding of the neuroplastic effects of tDCS is essential to improve clinical outcomes of rehabilitation. From this perspective, the combined use of tES and EEG in clinical practice should allow the identification of prognostic factors as well as predictors of the clinical response to stimulation. This knowledge should increase the success rate of tES-based rehabilitation programmes by making them individually tailored. This is still a clinical challenge of the combination of tES and EEG, since, to date, too few clinical studies have been conducted following these lines, even though multiple opportunities can be foreseen.

Beginning with the simplest application, tDCS neuromodulatory features can be exploited to modulate the altered balance between excitatory and inhibitory patterns typical of human epilepsy, as well as other diseases with similar pathophysiology [136, 137]. Abnormal increases in the excitability of the cerebral cortex are fundamental characteristics of epilepsy, and interictal activity on EEG reflects this indirectly. Therefore, EEG recording can be used to track online and offline whether cathodal tDCS can potentially reduce ictal events, allowing continuous monitoring of interictal epileptiform activity, as biomarker, both during and after the stimulation. For example, Faria et al. [41] polarised, with tDCS, the brain of two patients with refractory epilepsy while recording online EEG to observe changes in epileptogenic activity. Repeated sessions of tDCS, with the cathode positioned over the area of epileptogenic activity, induced a significant reduction in interictal epileptiform EEG discharges both during and after the stimulations. More recently, in the study by Lin and colleagues [138], nine patients with partial refractory epilepsy received multiple applications of cathodal tDCS. The authors reported a cumulative effect of tDCS leading to a general reduction of seizure frequency. However, no reduction of epileptiform discharges was observed. These few examples suggest that further steps have to be taken to detect reliable EEG markers of tDCS efficacy, which need to take into account the inter-individual variability of patients. In this direction, a recent work [139] indicates that functional connectivity between the epileptic focus and other areas may contribute to explain the effects of cathodal tDCS.

Roizenblatt et al. [140] used EEG to evaluate whether tDCS-induced pain changes in fibromyalgia are associated with changes in sleep structure by comparing changes in EEG sleep parameters induced by anodal tDCS over the primary motor cortex (M1) or over the dorsolateral prefrontal cortex (DLPFC); in both cases, the return electrode was placed over the contralateral supraorbital area. Anodal tDCS was shown to

affect sleep depending on the site of stimulation: whereas M1 stimulation increased sleep efficiency, decreased arousal and increased delta activity in non-REM sleep, DLPFC stimulation decreased sleep efficiency, increased REM and sleep latency, increased alpha activity and decreased delta activity in non-REM sleep. Importantly, the decrease in REM latency and the increase in sleep efficiency by tDCS over M1 were associated with an improvement in fibromyalgia. These findings are relevant to understand the possible mechanisms at the basis of tDCS-induced pain relief in fibromyalgia and suggest that the effects likely depend on sleep modulation that is specific to the modulation of M1 activity [140].

EEG can also be used to predict clinical responses to tDCS, as done by Vanneste and coworkers [141] who explored whether the functional state of the brain at baseline could be used to discriminate between responders and non-responders to a bi-frontal tDCS-based treatment of tinnitus. Prior to tDCS application, the baseline EEG activity of the responders showed increased functional connectivity in the gamma band, which was not detected in non-responders [141]. The relevance of EEG functional interactions to elucidate tES effects in tinnitus was also showed by a recent tRNS study [142].

Another important aspect, as suggested by the study of Notturno et al. [114], is that tDCS can change the strength of synaptic connections between motor areas [19], which may favour motor recovery. Indeed, the induction of local modulation of membrane polarisation as well as long-lasting synaptic modifications by tDCS over M1 could result in changes in both local band power and in the functional architecture of the motor network. Therefore, the optimal use of tDCS in post-stroke motor rehabilitation may be based on the direct evaluation of EEG-derived functional connectivity changes during and after tDCS [16], or by analysing if baseline (before tDCS) functional connectivity can predict the clinical outcomes of brain stimulation [143, 144]. For instance, Hordacre and colleagues [143] assessed in chronic stroke patients whether measures of resting state functional connectivity could predict changes in corticospinal excitability after anodal tDCS of the lesioned motor cortex. Stronger functional connectivity in the alpha band between the lesioned M1 and two clusters of electrodes (i.e. ipsilesional parietal and contralesional fronto-parietal) was associated with an increase of corticospinal excitability after anodal tDCS. The message conveyed by this study is that EEG biomarkers may be used to improve the clinical use of tDCS for stroke as well as for other neurological diseases associated with alterations of oscillatory brain activity, for example, by taking specific connectivity thresholds to identify patients who would more likely benefit from a neuromodulation therapy [144].

Another interesting development is the use of tDCS in combination with EEG-based brain–computer (or machine) interface systems (BCIs or BMIs). BCIs are used to record, decode, and translate measurable neurophysiological signals that are associated with the user's intention or state to drive external devices. EEG-based BCIs make use of specific EEG frequencies or event-related brain potentials [145]. Soekadar and colleagues [27] evaluated, in healthy subjects, the feasibility of combining EEG-based BCIs with tDCS by investigating the influence of simultaneous tDCS on EEG recordings across different frequency bands. Participants were instructed to self-regulate EEG-recorded motor-related oscillations (i.e. desynchronisation of mu rhythms associated with motor imagery), which were translated into online cursor movements on a computer screen. During the BCI session, sham or active tDCS was delivered: the active tDCS electrode was placed immediately anterior (1 cm) to the EEG electrode used for online BCI control (C4), and the reference electrode was placed over the left supraorbital region. The application of tDCS was associated with a significant signal increase across the lower frequency bands (delta and theta) in the proximity of the stimulation electrode as well as at larger distances (>8 cm). Similarly, an offline method was used to evaluate the increase of mu rhythm in stroke patients [146]. Mu rhythm of the affected hemisphere increased after anodal tDCS over the primary motor cortex, whereas it did not change after

sham tDCS [146]. This evidence provides the first demonstration that the delivery of tDCS in close proximity to an EEG channel for learned self-regulation of brain oscillatory activity is feasible and safe. Furthermore, EEG changes can be used to characterise the mechanisms of motor recovery following tDCS-BCI treatments. A recent study by Mane et al. [147] investigated in chronic stroke patients the effects of a BCI treatment, alone or combined with tDCS, on EEG spectral power and related motor improvements. Interestingly, the authors found that different EEG features were associated to BCI treatment (i.e. changes in theta power and interactions between theta, alpha and beta power) and tDCS-BCI treatment (i.e. power-based asymmetry index), suggesting the involvement of distinct neural mechanisms of recovery associated to different treatments. The potential to modulate, with tDCS, the activity of brain areas that are functionally related to BMI control is important for improving the therapeutic applicability of BMI, and it opens up new opportunities to investigate the association between learned self-regulation of brain activity, including oscillatory activity, and tDCS-induced behavioural changes.

More recently, tDCS has attracted considerable interest as a therapeutic option for disorders of consciousness (DoC; see Chap. 36), such as vegetative state/unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS). In patients with altered consciousness, where overt, behavioural responses may be at times absent or fluctuant, EEG can be useful to monitor the clinical course, to detect changes of cerebral activity after tDCS and to identify biomarkers of response to brain stimulation (e.g. [148–151]). For example, Cavinato and colleagues [150], in a sham-controlled study, applied anodal tDCS to the left DLPFC of patients in UWS and patients in an MCS. The analysis of EEG spectral power and functional connectivity (i.e. coherence analysis) after repeated sessions of tDCS revealed different patterns for the two groups of patients: whereas MCS patients showed some clinical improvements accompanied by increased power and coherence (mostly at alpha and beta frequency of fronto-parietal channels), UWS showed no clinical modifications and only small local changes on the site of stimulation. Notably, spared connectivity is quintessential for the brain to produce complex patterns of activity that are at the same time integrated and differentiated; indeed, such a complexity can discriminate between different states of consciousness (see, e.g. [152]). The centrality of functional connectivity was also highlighted by Thibaut et al. [149] who identified the preservation of theta band connectivity as a biomarker of response to tDCS, and, more recently, by Hermann and colleagues [151] who found increased long-range cortico-cortical functional connectivity in the theta-alpha band in responders, compared to non-responders (see Fig. 7.4).

Finally, a number of recent studies looked at EEG frequencies and ERPs as indexes of tDCS-induced clinical improvements in psychiatric disorders, such as schizophrenia (e.g. [153–155]) and depression (e.g. [156, 157]; see also [158] for a review). For example, in a study with schizophrenic patients, Kim and collaborators [154] considered amplitude, latency and variability of the auditory P300, an ERP generated by the detection of a deviant tone within a set of same tones, which was found to correlate with symptom severity of schizophrenia [159]. After repeated sessions of anodal stimulation of the left DLPFC, P300 latency and inter-trial variability were associated with an improvement of negative symptoms (e.g. blunted affects and apathy), whereas reduced P300, inter-trial variability and inter-trial coherence at theta frequency featured decreased positive symptoms, such as hallucinations and delusions. In the field of psychiatric disorders, tDCS has been increasingly used to treat depression, although it is well known that not all patients respond to this intervention [133]. EEG may be particularly useful to address whether and how tDCS might be clinically helpful in depression. For instance, Al-Kaysi and colleagues [156] investigated whether baseline EEG spectral power (i.e. measured before the beginning of the treatment) could identify responders and non-responders to a tDCS treatment for major depressive disorder. Despite the small number of participants, the authors found that

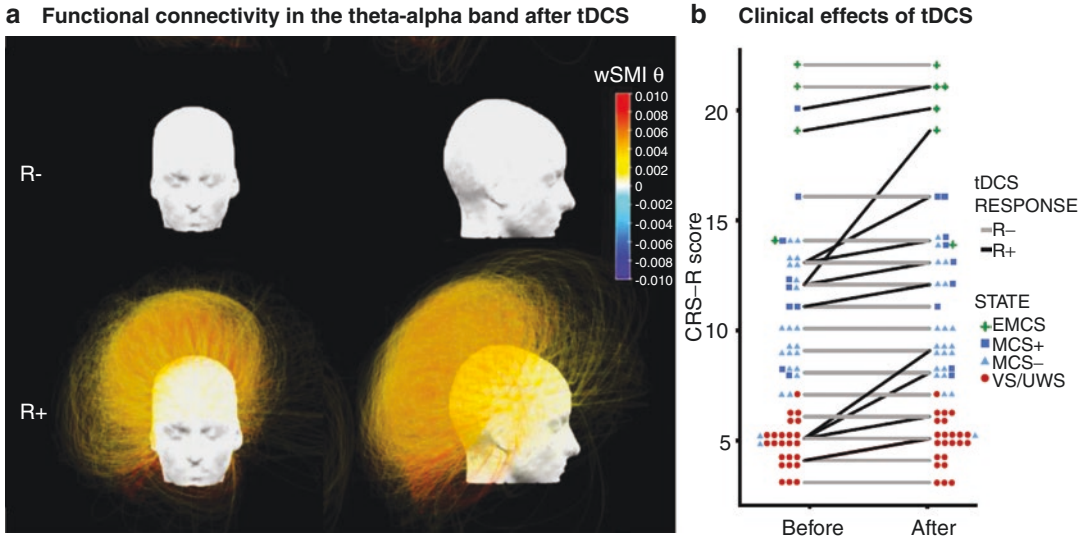

Fig. 7.4 (**a**) 3D representation of functional connectivity in the theta-alpha band in disorders of consciousness following anodal tDCS applied over the DLPC. Connectivity changes in the theta-alpha band were assessed by the weighted symbolic mutual information (wSMI θ), a measure of global information sharing across brain areas that evaluates the extent to which two EEG channels present non-random joint fluctuations, suggesting that they share common sources. A cluster of 5918 pairs of electrodes, located over a centro-parietal hub encompassing parietal and occipital cortices, showed increased functional connectivity in responders (R+) after tDCS as compared to before the stimulation, while no change emerged in non-responders (R−). (**b**) Clinical effects of tDCS as assessed with the Coma Recovery Scale-Revised (CRS-R). The graph shows individual CRS-R scores before and after tDCS, which are represented for R+ (black lines) and R− (grey lines), along with the patients' state: VS/UWS vegetative state/unresponsive wakefulness syndrome, EMCS exit minimally conscious state, MCS minimally conscious state. (Adapted from Hermann et al. [151], licensed under CC BY 4.0. https://creativecommons.org/licenses/by/4.0/)

baseline brain activity in two frontal channels (i.e. FC4-AF8) could predict post-treatment mood improvements in eight out of ten of patients. Notably, altered activity of the right prefrontal cortex was previously found in depressed patients compared to healthy subjects [160]. Moreover, the activity of two parietal channels (i.e. CPz-CP2) showed very good predictive value with respect to cognitive improvements, at least in terms of processing speed, a main cognitive marker of depression.

In brief, these examples illustrate how the combination of EEG and tES can be used in clinical settings to identify patients who could potentially respond to a rehabilitation protocol based on neuromodulation and which tES protocol would be suited for a given patient (predictive role); on the other hand, combining EEG and tES may allow the evaluation of cortical activity changes that form the basis of a clinical improvement (assessment role), enriching our understanding of the mechanisms of action of neuromodulation in neuropsychiatric diseases.

7.7 Conclusions and Final Remarks

Research must certainly move ahead to improve the development of multimodal association approaches. There is still much work to do to determine the optimal implementation of tES with simultaneous EEG recoding. First of all, it is necessary to develop and share theoretical models and standardised procedures of application and analysis; the present knowledge provides inspiration for important progresses in this field. As reported in this overview, at least in healthy subjects, many behavioural effects brought about by tES have been substantiated by electrophysiological data, and we are learning that changes in some tES parameters are fundamental for improving the

efficacy of the stimulation and for modelling behavioural effects. All of these aspects need to be further explored, in patients with psychiatric or neurological diseases as well, because we cannot take for granted that a protocol that has been found to be effective in healthy subjects could be simply and directly transferred to a clinical setting. In particular, given that the effects of tES are strongly dependent on the system state, application of the parameters that have been developed in healthy populations might not induce the same response in a system that has a completely different homeostasis due to pathological alterations of brain functioning.

References

1. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127(2):1031–48.
2. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5:175–95.
3. Paulus W. Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods. Neuropsychol Rehabil. 2011;21:602–17.
4. He B, Liu Z. Multimodal functional neuroimaging: integrating functional MRI and EEG/MEG. IEEE Rev Biomed Eng. 2008;1:23–40.
5. Hunter MA, Coffman BA, Trumbo MC, Clark VP. Tracking the neuroplastic changes associated with transcranial direct current stimulation: a push for multimodal imaging. Front Hum Neurosci. 2013;7:495.
6. Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. NeuroImage. 2016;140:4–19.
7. Giovannella M, Ibañez D, Gregori-Pla C, Kacprzak M, Mitjà G, Ruffini G, et al. Concurrent measurement of cerebral hemodynamics and electroencephalography during transcranial direct current stimulation. Neurophotonics. 2018;5(1):015001.
8. Antal A, Bikson M, Datta A, Lafon B, Dechent P, Parra LC, et al. Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain. NeuroImage. 2012;85(Pt 3):1040–7.
9. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9:2257–60.
10. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
11. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125:2238–47.
12. Medeiros LF, de Souza IC, Vidor LP, de Souza A, Deitos A, Volz MS, et al. Neurobiological effects of transcranial direct current stimulation: a review. Front Psych. 2012;3:110.
13. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301.
14. Rugg MD, Coles MGH. Electrophysiology of mind: event-related brain potentials and cognition. New York: Oxford University Press; 1995.
15. Bortoletto M, Veniero D, Thut G, Miniussi C. The contribution of TMS-EEG coregistration in the exploration of the human cortical connectome. Neurosci Biobehav Rev. 2015;49:114–24.
16. Luft CD, Pereda E, Banissy MJ, Bhattacharya J. Best of both worlds: promise of combining brain stimulation and brain connectome. Front Syst Neurosci. 2014;8:132.
17. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol. 2006;117:1623–9.
18. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. NeuroImage. 2007;35:1113–24.
19. Polania R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp. 2011;32:1236–49.
20. Miniussi C, Brignani D, Pellicciari MC. Combining transcranial electrical stimulation with electroencephalography: a multimodal approach. Clin EEG Neurosci. 2012;43:184–91.
21. Accornero N, Li Voti P, La Riccia M, Gregori B. Visual evoked potentials modulation during direct current cortical polarization. Exp Brain Res. 2007;178:261–6.
22. Accornero N, Capozza M, Pieroni L, Pro S, Davi L, Mecarelli O. EEG mean frequency changes in healthy subjects during prefrontal transcranial direct current stimulation. J Neurophysiol. 2014;112:1367–75.
23. Cunillera T, Brignani D, Cucurell D, Fuentemilla L, Miniussi C. The right inferior frontal cortex in response inhibition: a tDCS-ERP co-registration study. NeuroImage. 2016; https://doi.org/10.1016/j.neuroimage.2015.11.044.
24. Mangia AL, Pirini M, Cappello A. Transcranial direct current stimulation and power spectral param-

eters: a tDCS/EEG co-registration study. Front Hum Neurosci. 2014;8:601.
25. Romero Lauro LJ, Rosanova M, Mattavelli G, Convento S, Pisoni A, Opitz A, et al. TDCS increases cortical excitability: direct evidence from TMS-EEG. Cortex. 2014;58:99–111.
26. Roy A, Baxter B, He B. High-definition transcranial direct current stimulation induces both acute and persistent changes in broadband cortical synchronization: a simultaneous tDCS-EEG study. IEEE Trans Biomed Eng. 2014;61:1967–78.
27. Soekadar SR, Witkowski M, Cossio EG, Birbaumer N, Cohen LG. Learned EEG-based brain selfregulation of motor-related oscillations during application of transcranial electric brain stimulation: feasibility and limitations. Front Behav Neurosci. 2014;8:93.
28. Song M, Shin Y, Yun K. Beta-frequency EEG activity increased during transcranial direct current stimulation. Neuroreport. 2014;25:1433–6.
29. Boonstra TW, Nikolin S, Meisener AC, Martin DM, Loo CK. Change in mean frequency of resting-state electroencephalography after transcranial direct current stimulation. Front Hum Neurosci. 2016;10:270.
30. Mancini M, Brignani D, Conforto S, Mauri P, Miniussi C, Pellicciari MC. Assessing cortical synchronization during transcranial direct current stimulation: a graph-theoretical analysis. NeuroImage. 2016;140:57–65.
31. Vecchio F, Pellicciari MC, Miraglia F, Brignani D, Miniussi C, Rossini PM. Effects of transcranial direct current stimulation on the functional coupling of the sensorimotor cortical network. NeuroImage. 2016;140:50–6.
32. Fiene M, Rufener KS, Kuehne M, Matzke M, Heinze HJ, Zaehle T. Electrophysiological and behavioral effects of frontal transcranial direct current stimulation on cognitive fatigue in multiple sclerosis. J Neurol. 2018;265(3):607–17.
33. Mondini V, Mangia AL, Cappello A. Single-session tDCS over the dominant hemisphere affects contralateral spectral EEG power, but does not enhance neurofeedback-guided event-related desynchronization of the non-dominant hemisphere's sensorimotor rhythm. PLoS One. 2018;13(3):e0193004.
34. Wischnewski M, Bekkering H, Schutter DJLG. Frontal cortex electrophysiology in reward- and punishment-related feedback processing during advice-guided decision making: an interleaved EEG-DC stimulation study. Cogn Affect Behav Neurosci. 2018;18(2):249–62.
35. Varoli E, Pisoni A, Mattavelli GC, Vergallito A, Gallucci A, Mauro LD, et al. Tracking the effect of cathodal transcranial direct current stimulation on cortical excitability and connectivity by means of TMS-EEG. Front Neurosci. 2018;12:319.
36. Nikolin S, Martin D, Loo CK, Boonstra TW. Effects of TDCS dosage on working memory in healthy participants. Brain Stimul. 2018;11(3):518–27.
37. Brosnan MB, Arvaneh M, Harty S, Maguire T, O'Connell R, Robertson IH, et al. Prefrontal modulation of visual processing and sustained attention in aging, a tDCS-EEG coregistration approach. J Cogn Neurosci. 2018;30(11):1630–45.
38. Kunzelmann K, Meier L, Grieder M, Morishima Y, Dierks T. No effect of transcranial direct current stimulation of the auditory cortex on auditory-evoked potentials. Front Neurosci. 2018;12:880.
39. Wunder S, Hunold A, Fiedler P, Schlegelmilch F, Schellhorn K, Haueisen J. Novel bifunctional cap for simultaneous electroencephalography and transcranial electrical stimulation. Sci Rep. 2018;8(1):1–11.
40. Faria P, Leal A, Miranda PC. Comparing different electrode configurations using the 10-10 international system in tDCS: a finite element model analysis. Conf Proc IEEE Eng Med Biol Soc. 2009;2009:1596–9.
41. Faria P, Fregni F, Sebastiao F, Dias AI, Leal A. Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy. Epilepsy Behav. 2012;25:417–25.
42. Schestatsky P, Morales-Quezada L, Fregni F. Simultaneous EEG monitoring during transcranial direct current stimulation. J Vis Exp. 2013;76:e50426.
43. Miller J, Berger B, Sauseng P. Anodal transcranial direct current stimulation (tDCS) increases frontal midline theta activity in the human EEG: a preliminary investigation of non-invasive stimulation. Neurosci Lett. 2015;588:114–9.
44. Van Doren J, Langguth B, Schecklmann M. Electroencephalographic effects of transcranial random noise stimulation in the auditory cortex. Brain Stimul. 2014;7:807–12.
45. Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol. 2011;122:803–7.
46. Sehm B, Hoff M, Gundlach C, Taubert M, Conde V, Villringer A, et al. A novel ring electrode setup for the recording of somatosensory evoked potentials during transcranial direct current stimulation (tDCS). J Neurosci Methods. 2013;212:234–6.
47. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2:201–7.
48. Tallgren P, Vanhatalo S, Kaila K, Voipio J. Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. Clin Neurophysiol. 2005;116:799–806.
49. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol. 2015;126:2181–8.
50. Veniero D, Bortoletto M, Miniussi C. TMS-EEG coregistration: on TMS-induced artifact. Clin Neurophysiol. 2009;120:1392–9.

51. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. NeuroImage. 2014;85(Pt 3):895–908.
52. Gebodh N, Esmaeilpour Z, Adair D, Chelette K, Dmochowski J, Woods AJ, et al. Inherent physiological artifacts in EEG during tDCS. Neuroimage. 2019;185:408–24.
53. Helfrich RF, Knepper H, Nolte G, Struber D, Rach S, Herrmann CS, et al. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. 2014;12:e1002031.
54. Kohli S, Casson AJ. Removal of gross artifacts of transcranial alternating current stimulation in simultaneous EEG monitoring. Sensors (Basel). 2019;19(1):E190.
55. Cecere R, Rees G, Romei V. Individual differences in alpha frequency drive crossmodal illusory perception. Curr Biol. 2014;25:231–5.
56. Herrmann CS, Strüber D, Helfrich RF, Engel AK. EEG oscillations: from correlation to causality. Int J Psychophysiol. 2016;103:12–21.
57. Neuling T, Wagner S, Wolters CH, Zaehle T, Herrmann CS. Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. Front Psych. 2012;3:83.
58. Neuling T, Ruhnau P, Fusca M, Demarchi G, Herrmann CS, Weisz N. Friends, not foes: magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. NeuroImage. 2015;118:406–13.
59. Polania R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012;22:1314–8.
60. Schmidt S, Mante A, Ronnefarth M, Fleischmann R, Gall C, Brandt SA. Progressive enhancement of alpha activity and visual function in patients with optic neuropathy: a two-week repeated session alternating current stimulation study. Brain Stimul. 2013;6:87–93.
61. Schroeder MJ, Barr RE. Quantitative analysis of the electroencephalogram during cranial electrotherapy stimulation. Clin Neurophysiol. 2001;112:2075–83.
62. Voss U, Holzmann R, Hobson A, Paulus W, Koppehele-Gossel J, Klimke A, et al. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. Nat Neurosci. 2014;17:810–2.
63. Lustenberger C, Boyle MR, Alagapan S, Mellin JM, Vaughn BV, Fröhlich F. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr Biol. 2016;26(16):2127–36.
64. Ahn S, Mellin JM, Alagapan S, Alexander ML, Gilmore JH, Jarskog LF, et al. Targeting reduced neural oscillations in patients with schizophrenia by transcranial alternating current stimulation. Neuroimage. 2019;186:126–36.
65. Eggert T, Dorn H, Sauter C, Nitsche MA, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul. 2013;6:938–45.
66. Kirov R, Weiss C, Siebner HR, Born J, Marshall L. Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. Proc Natl Acad Sci U S A. 2009;106:15460–5.
67. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444:610–3.
68. Bueno-Lopez A, Eggert T, Dorn H, Danker-Hopfe H. Slow oscillatory transcranial direct current stimulation (so-tDCS) during slow wave sleep has no effects on declarative memory in healthy young subjects. Brain Stimul. 2019;12(4):948–58.
69. Fertonani A, Pirulli C, Bollini A, Miniussi C, Bortoletto M. Age-related changes in cortical connectivity influence the neuromodulatory effects of transcranial electrical stimulation. Neurobiol Aging. 2019;82:77–87.
70. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
71. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
72. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist. 2011;17:37–53.
73. Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity- dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol. 2013;591:1987–2000.
74. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul. 2012;5:505–11.
75. Pirulli C, Fertonani A, Miniussi C. Is neural hyperpolarization by cathodal stimulation always detrimental at the behavioral level? Front Behav Neurosci. 2014;8:226.
76. Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front Syst Neurosci. 2014;8:25.
77. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci. 2015;9:181.
78. Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimul. 2014;7:468–75.

79. Bortoletto M, Pellicciari MC, Rodella C, Miniussi C. The interaction with task-induced activity is more important than polarization: a tDCS study. Brain Stimul. 2015;8:269–76.
80. Furuya S, Klaus M, Nitsche MA, Paulus W, Altenmuller E. Ceiling effects prevent further improvement of transcranial stimulation in skilled musicians. J Neurosci. 2014;34:13834–9.
81. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul. 2015;8:253–9.
82. Impey D, Knott V. Effect of transcranial direct current stimulation (tDCS) on MMN-indexed auditory discrimination: a pilot study. J Neural Transm (Vienna). 2015;122:1175–85.
83. Reinhart RM, Woodman GF. The surprising temporal specificity of direct-current stimulation. Trends Neurosci. 2015;38:459–61.
84. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat Neurosci. 2013;16:838–44.
85. Miniussi C, Harris JA, Ruzzoli M. Modelling noninvasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev. 2013;37:1702–12.
86. Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci. 2004;45:702–7.
87. Thut G, Miniussi C. New insights into rhythmic brain activity from TMS-EEG studies. Trends Cogn Sci. 2009;13:182–9.
88. Miniussi C, Thut G. Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain Topogr. 2010;22:249–56.
89. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol. 2005;568:653–63.
90. Moliadze V, Andreas S, Lyzhko E, Schmanke T, Gurashvili T, Freitag CM, et al. Ten minutes of 1mA transcranial direct current stimulation was well tolerated by children and adolescents: self-reports and resting state EEG analysis. Brain Res Bull. 2015;119:25–33.
91. Pellicciari MC, Brignani D, Miniussi C. Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. NeuroImage. 2013;83:569–80.
92. Spitoni GF, Cimmino RL, Bozzacchi C, Pizzamiglio L, Di Russo F. Modulation of spontaneous alpha brain rhythms using low-intensity transcranial direct current stimulation. Front Hum Neurosci. 2013;7:529.
93. Tadini L, El-Nazer R, Brunoni AR, Williams J, Carvas M, Boggio P, et al. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. J ECT. 2011;27:134–40.
94. Donaldson PH, Kirkovski M, Yang JS, Bekkali S, Enticott PG. High-definition tDCS to the right temporoparietal junction modulates slow-wave resting state power and coherence in healthy adults. J Neurophysiol. 2019;122(4):1735–44.
95. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. Cereb Cortex. 2018;28(4):1132–40.
96. Gordon PC, Zrenner C, Desideri D, Belardinelli P, Zrenner B, Brunoni AR, et al. Modulation of cortical responses by transcranial direct current stimulation of dorsolateral prefrontal cortex: a resting-state EEG and TMS-EEG study. Brain Stimul. 2018;11(5):1024–32.
97. Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Impact of concurrent task performance on transcranial direct current stimulation (tDCS)-Induced changes in cortical physiology and working memory. Cortex. 2019;113:37–57.
98. Strigaro G, Mayer I, Chen JC, Cantello R, Rothwell JC. Transcranial direct current stimulation effects on single and paired flash visual evoked potentials. Clin EEG Neurosci. 2014;46:208–13.
99. Zaehle T, Beretta M, Jancke L, Herrmann CS, Sandmann P. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. Exp Brain Res. 2011;215:135–40.
100. Antal A, Brepohl N, Poreisz C, Boros K, Csifcsak G, Paulus W. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain. 2008;24:56–63.
101. Csifcsak G, Antal A, Hillers F, Levold M, Bachmann CG, Happe S, et al. Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. Pain Med. 2009;10:122–32.
102. Dieckhofer A, Waberski TD, Nitsche M, Paulus W, Buchner H, Gobbele R. Transcranial direct current stimulation applied over the somatosensory cortex - differential effect on low and high frequency SEPs. Clin Neurophysiol. 2006;117:2221–7.
103. Matsunaga K, Nitsche MA, Tsuji S, Rothwell JC. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol. 2004;115:456–60.
104. Donaldson PH, Kirkovski M, Rinehart NJ, Enticott PG. A double-blind HD-tDCS/EEG study examining right temporoparietal junction involvement in facial emotion processing. Soc Neurosci. 2019;14(6):681–96.
105. Jacobson L, Ezra A, Berger U, Lavidor M. Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation. Clin Neurophysiol. 2012;123:979–84.

106. Dubreuil-Vall L, Chau P, Ruffini G, Widge AS, Camprodon JA. tDCS to the left DLPFC modulates cognitive and physiological correlates of executive function in a state-dependent manner. Brain Stimul. 2019;12(6):1456–63.
107. Boudewyn M, Roberts BM, Mizrak E, Ranganath C, Carter CS. Prefrontal transcranial direct current stimulation (tDCS) enhances behavioral and EEG markers of proactive control. Cogn Neurosci. 2019;10(2):57–65.
108. Hoy KE, Emonson MR, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia. 2013;51:1777–84.
109. Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, et al. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. NeuroImage. 2011;55:644–57.
110. Tseng P, Hsu TY, Chang CF, Tzeng OJ, Hung DL, Muggleton NG, et al. Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. J Neurosci. 2012;32:10554–61.
111. Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci. 2011;12:2.
112. Jones KT, Johnson EL, Berryhill ME. Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. NeuroImage. 2020;211:116615.
113. Matsumoto J, Fujiwara T, Takahashi O, Liu M, Kimura A, Ushiba J. Modulation of mu rhythm desynchronization during motor imagery by transcranial direct current stimulation. J Neuroeng Rehabil. 2010;7:27.
114. Notturno F, Marzetti L, Pizzella V, Uncini A, Zappasodi F. Local and remote effects of transcranial direct current stimulation on the electrical activity of the motor cortical network. Hum Brain Mapp. 2014;35:2220–32.
115. Wirth M, Rahman RA, Kuenecke J, Koenig T, Horn H, Sommer W, et al. Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia. 2011;49:3989–98.
116. Wu D, Wang J, Yuan Y. Effects of transcranial direct current stimulation on naming and cortical excitability in stroke patients with aphasia. Neurosci Lett. 2015;589:115–20.
117. Radman N, Britz J, Buetler K, Weekes BS, Spierer L, Annoni JM. Dorsolateral prefrontal transcranial direct current stimulation modulates language processing but does not facilitate overt second language word production. Front Neurosci. 2018;12:490.
118. Baptista NI, Manfredi M, Boggio PS. Medial prefrontal cortex stimulation modulates irony processing as indexed by the N400. Soc Neurosci. 2018;13(4):495–510.
119. Luna FG, Román-Caballero R, Barttfeld P, Lupiáñez J, Martín-Arévalo E. A high-definition tDCS and EEG study on attention and vigilance: brain stimulation mitigates the executive but not the arousal vigilance decrement. Neuropsychologia. 2020; https://doi.org/10.1016/j.neuropsychologia.2020.107447.
120. Zink N, Kang K, Li SC, Beste C. Anodal transcranial direct current stimulation (atDCS) enhances the efficiency of functional brain network communication during auditory attentional control. J Neurophysiol. 2020; https://doi.org/10.1152/jn.00074.2020.
121. Francis JT, Gluckman BJ, Schiff SJ. Sensitivity of neurons to weak electric fields. J Neurosci. 2003;23:7255–61.
122. Kutchko KM, Frohlich F. Emergence of metastable state dynamics in interconnected cortical networks with propagation delays. PLoS Comput Biol. 2013;9:e1003304.
123. Ho KA, Bai S, Martin D, Alonzo A, Dokos S, Puras P, et al. A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression. J Affect Disord. 2014;167:251–8.
124. Loo CK, Martin DM. Could transcranial direct current stimulation have unexpected additional benefits in the treatment of depressed patients? Expert Rev Neurother. 2012;12:751–3.
125. Makeig S, Jung TP. Changes in alertness are a principal component of variance in the EEG spectrum. Neuroreport. 1995;7:213–6.
126. Gruzelier J. A theory of alpha/theta neurofeedback, creative performance enhancement, long distance functional connectivity and psychological integration. Cogn Process. 2009;10(Suppl 1):S101–9.
127. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev. 1999;29:169–95.
128. Benwell CS, Learmonth G, Miniussi C, Harvey M, Thut G. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: evidence from biparietal tDCS influence on lateralized attention bias. Cortex. 2015;69:152–65.
129. Learmonth G, Thut G, Benwell CS, Harvey M. The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. Neuropsychologia. 2015;74:108–19.
130. Sarkar A, Dowker A, Cohen KR. Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. J Neurosci. 2014;34:16605–10.
131. Bolognini N, Pascual-Leone A, Fregni F. Using noninvasive brain stimulation to augment motor

training- induced plasticity. J Neuroeng Rehabil. 2009;6:8.
132. Bolognini N, Convento S, Banco E, Mattioli F, Tesio L, Vallar G. Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex. Brain. 2015;138:428–39.
133. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31.
134. Fregni F, Nitsche MA, Loo CK, Brunoni AR, Marangolo P, Leite J, et al. Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. Clin Res Regul Aff. 2015;32:22–35.
135. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. NeuroImage. 2014;85:948–60.
136. Okun M, Lampl I. Instantaneous correlation of excitation and inhibition during ongoing and sensory evoked activities. Nat Neurosci. 2008;11(5):535–7.
137. Krause B, Márquez-Ruiz J, Cohen KR. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Front Hum Neurosci. 2013;7:602.
138. Lin LC, Ouyang CS, Chiang CT, Yang RC, Wu RC, Wu HC. Cumulative effect of transcranial direct current stimulation in patients with partial refractory epilepsy and its association with phase lag index-A preliminary study. Epilepsy Behav. 2018;84:142–7.
139. Tecchio F, Cottone C, Porcaro C, Cancelli A, Di Lazzaro V, Assenza G. Brain functional connectivity changes after transcranial direct current stimulation in epileptic patients. Front Neural Circuits. 2018;12:44.
140. Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufi KS, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract. 2007;7:297–306.
141. Vanneste S, Focquaert F, Van de Heyning P, De Ridder D. Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. Exp Brain Res. 2011;210:217–27.
142. Mohsen S, Mahmoudian S, Talebian S, Pourbakht A. Multisite transcranial random noise stimulation (tRNS) modulates the distress network activity and oscillatory powers in subjects with chronic tinnitus. J Clin Neurosci. 2019;67:178–84.
143. Hordacre B, Moezzi B, Ridding MC. Neuroplasticity and network connectivity of the motor cortex following stroke: A transcranial direct current stimulation study. Hum Brain Mapp. 2018;39(8):3326–39.
144. Hordacre B, Moezzi B, Ridding MC. Towards targeted brain stimulation in stroke: connectivity as a biomarker of response. J Exp Neurosci. 2018;12:1179069518809060.
145. Daly JJ, Wolpaw JR. Brain-computer interfaces in neurological rehabilitation. Lancet Neurol. 2008;7:1032–43.
146. Kasashima Y, Fujiwara T, Matsushika Y, Tsuji T, Hase K, Ushiyama J, et al. Modulation of event-related desynchronization during motor imagery with transcranial direct current stimulation (tDCS) in patients with chronic hemiparetic stroke. Exp Brain Res. 2012;221:263–8.
147. Mane R, Chew E, Phua KS, Ang KK, Vinod AP, Guan C. Quantitative EEG as biomarkers for the monitoring of post-stroke motor recovery in BCI and tDCS rehabilitation. Conf Proc IEEE Eng Med Biol Soc. 2018;2018(07):3610–3.
148. Bai Y, Xia X, Wang Y, Guo Y, Yang Y, He J, et al. Fronto-parietal coherence response to tDCS modulation in patients with disorders of consciousness. Int J Neurosci. 2018;128(7):587–94.
149. Thibaut A, Chennu S, Chatelle C, Martens G, Annen J, Cassol H, et al. Theta network centrality correlates with tDCS response in disorders of consciousness. Brain Stimul. 2018;11(6):1407–9.
150. Cavinato M, Genna C, Formaggio E, Gregorio C, Storti SF, Manganotti P, et al. Behavioural and electrophysiological effects of tDCS to prefrontal cortex in patients with disorders of consciousness. Clin Neurophysiol. 2019;130(2):231–8.
151. Hermann B, Raimondo F, Hirsch L, Huang Y, Denis-Valente M, Pérez P, et al. Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. Sci Rep. 2020;10(1):4323.
152. Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol. 2016;80(5):718–29.
153. Kim M, Yoon YB, Lee TH, Lee TY, Kwon JS. The effect of tDCS on auditory hallucination and P50 sensory gating in patients with schizophrenia: a pilot study. Schizophr Res. 2018;192:469–70.
154. Kim M, Lee TH, Hwang WJ, Lee TY, Kwon JS. Auditory P300 as a neurophysiological correlate of symptomatic improvement by transcranial direct current stimulation in patients with schizophrenia: a pilot study. Clin EEG Neurosci. 2018; https://doi.org/10.1177/1550059418815228.
155. Rassovsky Y, Dunn W, Wynn JK, Wu AD, Iacoboni M, Hellemann G, et al. Single transcranial direct current stimulation in schizophrenia: randomized, cross-over study of neurocognition, social cognition, ERPs, and side effects. PLoS One. 2018;13(5):e0197023.
156. Al-Kaysi AM, Al-Ani A, Loo CK, Powell TY, Martin DM, Breakspear M, et al. Predicting tDCS treatment outcomes of patients with major depressive disorder using automated EEG classification. J Affect Disord. 2017;208:597–603.

157. Nikolin S, Martin D, Loo CK, Iacoviello BM, Boonstra TW. Assessing neurophysiological changes associated with combined transcranial direct current stimulation and cognitive-emotional training for treatment-resistant depression. Eur J Neurosci. 2020;51(10):2119–33.
158. Kim M, Kwak YB, Lee TY, Kwon JS. Modulation of electrophysiology by transcranial direct current stimulation in psychiatric disorders: a systematic review. Psychiatry Investig. 2018;15(5):434–44.
159. Higashima M, Nagasawa T, Kawasaki Y, Oka T, Sakai N, Tsukada T, et al. Auditory P300 amplitude as a state marker for positive symptoms in schizophrenia: cross-sectional and retrospective longitudinal studies. Schizophr Res. 2003;59(2–3):147–57.
160. Saletu B, Anderer P, Saletu-Zyhlarz GM. EEG topography and tomography (LORETA) in diagnosis and pharmacotherapy of depression. Clin EEG Neurosci. 2010;41(4):203–10.

8 tDCS and Magnetic Resonance Imaging

Ainslie Johnstone, Emily Hinson, and Charlotte J. Stagg

8.1 Introduction

Transcranial direct current stimulation (tDCS) is a promising tool for neuroscience applications and a potential adjunct therapy for a range of neurological and psychiatric disorders. However, before we can fully utilize the potential of tDCS, more needs to be understood about the neural mechanisms underpinning stimulation. In the past, the effects of tDCS have been studied primarily through experiments utilizing transcranial magnetic stimulation (TMS), sometimes in combination with pharmacological agents (see Chap. 38 in this volume and [1]) which have added greatly to our understanding of the local physiological effects of tDCS.

In recent years, however, there has been an increasing interest in using advanced neuroimaging techniques to study the effects of tDCS, both in healthy controls and clinical populations. Once the technical difficulties are overcome (see below), the combination of tDCS with magnetic resonance (MR) is a powerful tool that allows to study not only of the brain regions directly stimulated by tDCS, but unlike most TMS approaches, we can also understand how tDCS modulates activity in the rest of the brain.

It is worth noting, particularly in a book highlighting the use of tDCS in psychiatric disorders, that the effects of tDCS are dependent on the site of stimulation, the duration of stimulation and the electrode configuration used, to a greater or lesser extent. The vast majority of studies investigating the mechanistic underpinnings of tDCS have studied the 'conventional' electrode placement as first described by Nitsche and Paulus [2] (Fig. 8.1a), with one electrode over the primary

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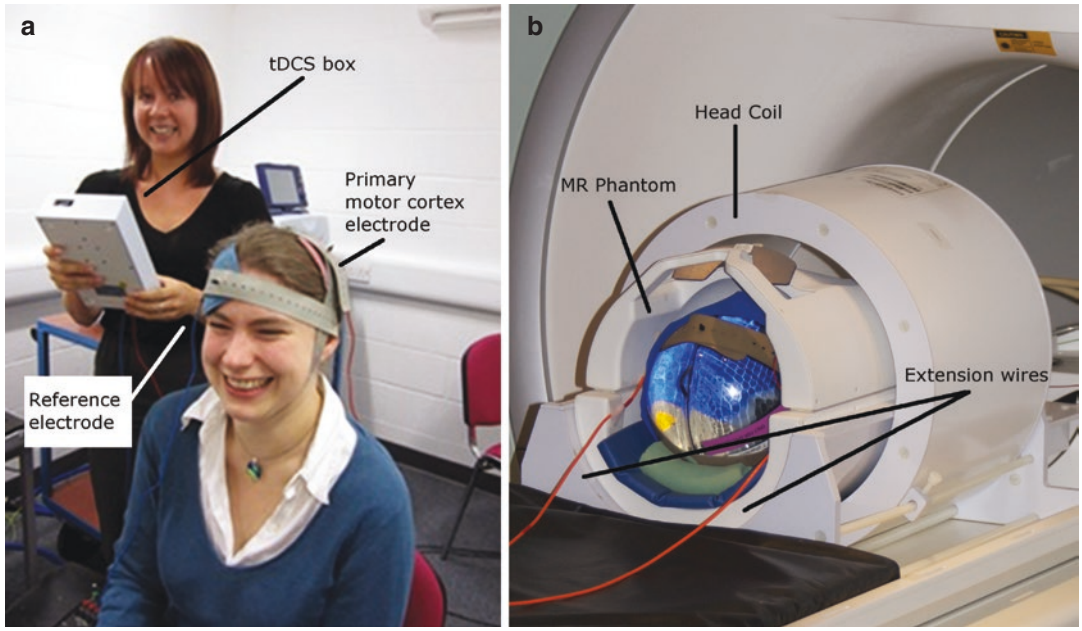

Fig. 8.1 (**a**) Overview of the 'conventional' tDCS electrode configuration most studied in the literature – one electrode over the left primary motor cortex and one over the right supraorbital ridge. (**b**) Example set-up of tDCS in the MR environment, showing careful placement of extension leads and the stimulator kept out of the magnetic field

motor cortex (M1) and one over the contralateral supraorbital ridge. We therefore concentrate here on studies using this montage, though we have highlighted important studies using different electrode placements where we believe that these will be of importance in the context of the potential treatment of psychiatric disorders. However, it is important to note that while some of the findings from studies involving an M1 montage will be applicable to other sites, this cannot be assumed and further studies are warranted with any electrode montage of interest.

8.2 Combining tDCS and MRI

tDCS can be combined with MRI either in a sequential or concurrent approach. In sequential acquisition, the stimulation is delivered outside of the scanner with the participant placed in the scanner before and immediately following the stimulation period. Alternatively, stimulation can be delivered within the bore of the scanner (concurrent acquisition) either at the same time as collecting MR data or during rest (Fig. 8.1b).

Both approaches have been used successfully, with concurrent acquisition the most favourable in most cases due to logistical issues associated with removing and replacing the participant before subsequent MR data can be collected. Concurrent acquisition also has the advantage that pre- and post-stimulation data can be controlled for reproducibility (in terms of placement for spectroscopy voxels or high-resolution fMRI slices). While there are obvious advantages to concurrent stimulation, integration of tDCS to MRI requires multiple extra considerations including MR-specific kit, additional setup criteria and potential adverse effects on MR acquisitions. The following should be seen only as a summary of the most significant risks of the approach, and given the inherent risks of the technique, tDCS should only be used in the scanner environment by trained individuals.

Concurrent tDCS/MRI requires a specialist kit that is MR compatible and rigorously tested. The

electrodes used in this case should be fitted with high-ohmic resistors to prevent induction of eddy currents within the stimulating leads. Additional care should be taken to keep the leads away from the participant to prevent RF burns and run parallel to the bore without loops to prevent eddy currents. The tDCS stimulator must be kept in the control room and monitored closely by a researcher for the duration of the stimulation.

In addition, and in contrast to tDCS outside of the scanner, electrodes must be carefully prepared with high conductance electrical paste (such as that used for EEG) as saline-soaked sponges will dry out over time, making their use unsuitable for MRI scans that ordinarily last around 60–90 minutes. Dry sponges result in poor conductance of the electrical current, which can be uncomfortable or even painful for the participant and may result in skin burning in severe cases. For more details on the use of tDCS in the MR environment, see [3].

8.3 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a versatile and non-invasive tool that can be used to inform our understanding of how tDCS can modulate activity within the brain. The majority of the studies discussed here rely on the quantification of the blood oxygen level-dependent (BOLD) contrast, the most widely used fMRI technique, although other fMRI techniques are available, of which arterial spin labelling (see later) is perhaps the most relevant in the context of psychiatric disease.

8.4 BOLD Functional MRI

The BOLD signal relies on relative changes of deoxygenated haemoglobin (DeoxyHb) and oxygenated haemoglobin (OxyHb) caused by local changes in brain activity and is therefore an indirect measure of neuronal activity. The BOLD signal is reliant on the magnetic properties of these two compounds. DeoxyHb contains an iron molecule making it paramagnetic, meaning it has a significant interaction with the applied magnetic field during MRI. By contrast, OxyHb is diamagnetic, so it has little effect on the magnetic field. Therefore, if the ratio of OxyHb:DeoxyHb changes within a localized region of tissue as a result of local neuronal activity, this can be detected using BOLD fMRI. However, the precise relationship between changes in neuronal activity and a detectable change in the BOLD signal is complex and not yet fully understood [4].

8.4.1 Resting-State fMRI

Functional MRI acquired while the subject is lying in the scanner at rest, and commonly following the instruction ‘not to think of anything in particular’, is an increasingly used method of studying the brain. Without a super-imposed task to perform, the ongoing physiological fluctuations in the BOLD signal associated with quiet wakefulness can be recorded. In any given brain region, the BOLD signal will vary across time as a function of on-going neural activity, and by studying the relationship of the BOLD signal from one brain region to that of others, regions where the timecourse of fluctuations are highly correlated can be identified, and these regions are said to be ‘functionally connected’. Studies of functional connectivity can be made using a wide array of statistical methods including those utilizing graph theory and independent component analysis (ICA) approaches (for more details, see [5]).

‘Resting-state networks’ (RSNs) are robust distributed networks that show coordinated and highly reproducible fluctuations in activity between spatially distinct but anatomically closely connected areas while subjects lie at rest [6–8]. RSNs are identified using an ICA approach and are being widely investigated due to observed differences during different cognitive and clinical states. RSNs are thought to reflect intrinsic functional architecture in the brain, and separable networks can be identified within resting fMRI data which closely reflect brain regions that are active during task performance [9, 10]. While the physiological underpinnings of changes in RSN

connectivity are not understood and are still very much the focus of investigation and open to often complex interpretation [11], it is clear that RSNs are highly sensitive to changes in connectivity in a wide range of diseases [12–14], and that resting-state fMRI is a potentially powerful approach for the study of a wide range of clinical conditions as it removes the confound of task performance [15].

tDCS Has Significant, but Somewhat Unclear, Effects on Resting Functional Connectivity

The absence of any confound of task performance, and the relative ease with which resting-state fMRI experiments can be performed, has meant the publication of a relatively large number of studies utilizing the combination of tDCS and rs-fMRI in recent years. tDCS has been demonstrated in a number of studies to modulate resting functional connectivity between a number of brain regions, although to date no clear consensus across the literature has emerged as to the specific pattern of stimulation-induced changes [16–21] (see Tables 8.1 and 8.2 for full details). This lack of agreement between studies as to the effects of tDCS most likely reflects differences in MR acquisition and stimulation parameters, as well as the likely sensitivities of different analysis approaches, but makes interpretation of the literature as it stands somewhat problematic.

tDCS As a Potential Tool to Understand the Basis of Resting Functional Connectivity

Recently, attempts have been made to understand the basis of the RSNs using magnetic resonance spectroscopy (see later), which allows the quantification of specific neurochemicals, particularly glutamate and GABA, within a region of interest. Two studies have now demonstrated a relationship between GABA levels in M1 and the degree of functional connectivity within the motor RSN [21, 23], such that higher levels of inhibition are related to lower connectivity within the network (see Fig. 8.2). However, although anodal tDCS applied to M1 has been shown to modulate both GABA levels [21, 37, 48] and RSN strength [20, 21], the degree to which GABA and RSN strength are modulated by tDCS does not seem to be related in the same individual [21]. In addition, other groups have demonstrated similar relationships between both GABA and glutamate and functional connectivity outside the motor system [49–51]. These findings, if replicated, may begin to shed light on the physiological basis the RSNs, and the ability of tDCS to modulate both GABAergic and glutamatergic activity may play an important part in answering this potentially very important question. However, it is important to note that the finding that tDCS modulates resting connectivity has only been established to any great extent in healthy subjects, and how these findings may translate to clinical populations is not yet clear.

8.4.2 Task-Based fMRI

Task-based fMRI is a versatile tool that can be used to inform our understanding of how tDCS can modulate activity within the brain while a task is being performed. Task-based fMRI is reliant on BOLD signal changes resulting from changing neural activity in task-based areas of the brain and can result in whole-brain data with a high spatial and reasonably high temporal resolution. The ability to combine concurrent tDCS stimulation and fMRI imaging has allowed studies to characterize the effects of stimulation on various cortical regions; however, the motor cortex is one of the most widely studied.

Studies in Healthy Controls

Behaviourally, anodal tDCS applied concurrently to M1 with a motor task has been shown to improve performance in a variety of domains, including motor speed and dexterity [52, 53] and motor learning and adaptation [52, 54, 55]. By contrast, cathodal tDCS has been shown to have little or no effect on learning [52, 55] or simple reaction time [52]. Task-based fMRI has been utilized in a number of studies to understand not only the activity changes underlying these behavioural effects within the stimulated cortex but also more anatomically distant neural changes.

Table 8.1 Summary of studies combining tDCS and resting-state fMRI

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Analysis method	Summary of main findings
Polanìa et al. [22]	13	BOLD	Healthy	Left M1/right frontopolar cortex	35cm^2 for both electrodes	Bipolar (real/ sham, within subject)	10 mins, 1 mA	Graph theory	· tDCS-induced neuroplastic alterations correlate with changes in functional connectivity
									· Voxel-based graph theoretical analysis is a powerful approach to track for functional alterations
Polanìa et al. [17]	14	BOLD	Healthy	Left M1/right supraorbital ridge	35 cm^2 for both electrodes	Anodal/ cathodal/sham	10 mins, 1 mA	Graph theory	In dorsolateral BA4 region, cathodal tDCS boosted local connections, while anodal tDCS enhanced long-distance functional communication within M1
									The more efficient the functional architecture of M1 was at baseline, the more efficient the tDCS-induced functional modulations were
Sehm et al. [19]	12	BOLD	Healthy	Unilateral: Right M1/left supraorbital ridge	35cm^2 for both electrodes	Unilateral/ bilateral/sham	20 mins, 1 mA	Eigenvector centrality mapping (ECM) – Graph-based method	·Bilateral tDCS modulated changes in primary and secondary motor and prefrontal regions
				Bilateral: Anode over right M1, cathode over left M1					· Unilateral tDCS affected prefrontal, parietal and cerebellar areas (no direct effect under stimulating electrode)

(continued)

Table 8.1 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Analysis method	Summary of main findings
Sehm et al. [18]	12	BOLD	Healthy	Unilateral: Anode over left M1, cathode over right supraorbital ridge	35 cm^2 for both electrodes	Unilateral (anodal)/ bilateral/sham	20 mins, 1 mA	Seed-based functional connectivity analysis	· Bilateral tDCS results in decreased inter-hemispheric functional connectivity during stimulation and an increase in intracortical functional connectivity within left M1 after termination of stimulation
				Bilateral: Anode over left M1, cathode over right supraorbital ridge					· Unilateral stimulation resulted in similar effects during stimulation, but no changes were observed after termination of tDCS
									· Conclusion that different tDCS montages affect the modulation of intra- and inter-hemispheric connectivity
Amadi et al. [20]	11	BOLD	Healthy	Left M1/right supraorbital ridge	35cm^2 for both electrodes	Anodal/ cathodal/sham	10 mins, 1 mA	Seed-based and ICA	· Cathodal tDCS increased in inter-hemispheric coherence of resting fMRI signal between the left and right supplementary motor area (SMA), and between the left and right-hand areas of M1. A similar trend was documented for the premotor cortex
									· Increased functional connectivity following cathodal stimulation was apparent within ICA-generated motor and default mode networks

Stagg et al. [23]	10	BOLD	Healthy	Left M1/right supraorbital ridge	35 cm^2 for both electrodes	Anodal	10 mins, 1 mA	ICA	Anodal tDCS increases resting motor network connectivity
Bachtiar et al. [21]	12	BOLD	Healthy	Left M1/right supraorbital ridge	35 cm^2 for both electrodes	Anodal/sham	20 mins, 1 mA	ICA	Anodal tDCS reduced GABA concentration and increased functional connectivity in the stimulated cortex; however, these changes are not correlated
Pereira et al. [24]	16	BOLD	Parkinson's disease patients	Configuration 1: Anode: Left DLPFC, cathode: Right SOR Configuration 2: Anode: Left tempo-parietal cortex (TPC), cathode: Right SOR	35 cm^2 for both electrodes	Anodal	20 mins, 2 mA	ICA	Functional connectivity was significantly more enhanced by tDCS to DLPFC than TPC
Minami et al. [25]	9 patients, 10 controls	BOLD	9 subjects with tinnitus, 10 healthy controls	Anode: Right primary auditory cortex (posterior superior temporal gyrus, pSTG) Cathode: Left primary auditory cortex (pSTG)	Not specified	Not specified	10mins, 1 mA	Seed-based analysis	Functional connectivity between left and right auditory cortex is significantly weaker in tinnitus patients than controls. tDCS over auditory cortex modulated auditory-based functional connectivity differently in control and tinnitus patients. More research required into how auditory functional connectivity is modulated in patients with tinnitus

(continued)

Table 8.1 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Analysis method	Summary of main findings
Meinzer et al. [26]	36 (18 MCI patients, 18 matched controls)	BOLD	Patients: Mild cognitive impairment due to Alzheimer's disease	Anode: Left ventral IFG, cathode: Right supraorbital ridge	Not specified	Anodal/sham	20 mins, 1 mA	Eigenvector centrality mapping (ECM)	Anodal stimulation led to widespread connectivity changes in patients compared to controls, including a reversal of an abnormal pattern in several regions including medial frontal and lateral fronto-temporal cortices, bilateral sensorimotor regions and right cerebellum
			Controls: Healthy age matched, no MCI						No major group differences or stimulation-induced differences to the default mode network, in which disruptions have previously been reported in MCI
Lindenberg et al. [27]	40 (20 elderly and 20 young)	BOLD	Healthy: Elderly and young	Active electrode: Left ventral IFG	Stimulating: 35 cm^2	Anodal/sham	20 mins, 1 mA	Eigenvector centrality mapping (ECM)	Anodal tDCS induced a more 'youth-like' connectivity pattern in older adults suggesting that a single session of anodal tDCS can temporarily reverse non-beneficial effects of ageing on cognition and connectivity
				Reference electrode: Right supraorbital ridge	Reference: 100 cm^2				
Park et al. [28]	39	BOLD	Healthy	Anode: Left DLPFC, cathode: Right supraorbital ridge	25 cm^2 for both electrodes	Anodal/sham	20 mins, 1 mA	Parametric random-effects analysis	Anodal tDCS of the left DLPFC increased inter-hemispheric connectivity at rest, which is hypothesized to be associated with tDCS effects on cognitive functions

Clemens et al. [29]	11	BOLD	Healthy	Anode: Right angular gyrus, cathode: Left SOR	35 cm^2 for both electrodes	Bipolar	20 mins, 2 mA	Probabilistic ICA	Bipolar tDCS results in large-scale changes of activity within several RSNs, as well as local changes under the stimulating electrode
									Increased ICA-generated functional connectivity in cerebellum, medial occipital, sensorimotor, right fronto-parietal and superior frontal gyrus
									Decreased functional connectivity in right putamen and lateral occipital areas
Peña-Gómez et al. [30]	10	BOLD	Healthy	Experiment 1: Anode: Left DLPFC, cathode: Right SOR	35 cm^2 for both electrodes	Anodal/sham for both configurations	20 mins, 2 mA	ICA	After active stimulation, functional network connectivity revealed increased synchrony with the anticorrelated (AN) network components and reduced synchrony with DMN components
				Experiment 2: Anode: Right DLPFC, cathode: Left SOR					

(continued)

Table 8.1 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Analysis method	Summary of main findings
Keeser et al. [31]	13	BOLD	Healthy	Anode: Left DLPFC, cathode: Right supraorbital ridge	35 cm^2 for both electrodes	Anodal/sham	20 mins, 2 mA	ICA	After real tDCS compared to sham tDCS, significant changes of regional brain connectivity were found for the DMN and fronto-parietal networks (FPN) close to the stimulation site and in connected brain regions
									Prefrontal tDCS modulated resting-state functional connectivity in distinct functional networks of the human brain
Meinzer et al. [32]	20	BOLD	Healthy	Active electrode over BA44/45 (Broca's area)	Stimulating: 35 cm^2	Anodal/sham	Approximately 17 minutes, 1 mA	Eigenvector centrality mapping (ECM)	Under anodal tDCS, resting-state fMRI revealed increased connectivity of the left IFG and additional major hubs overlapping with the language network
				Reference electrode: Right supraorbital ridge	Reference: 100 cm^2				
Alon et al. [33]	4	BOLD	Healthy	Anode: Right M1, cathode: Left SOR	31.5 cm^2 for both electrodes	Anodal/sham	12 min 48 s (split into two blocks), 2 mA	Seed-based analysis	Anodal tDCS reduced connectivity measures in the right and left regions of interest. Suggestion that non-invasive brain stimulation during fMRI may down regulate the motor cortex's resting-state network connectivity

Mondino et al. [34]	15	BOLD	Healthy	Anode: Left DLPFC, cathode: Right DLPFC	35 cm^2 for both electrodes	Bipolar (real/sham, within subject)	30 mins, 1 mA	Seed-based analysis	tDCS increased functional connectivity during and after stimulation compared with sham, between the left DLPFC and bilateral posterior parietal regions
Antonenko et al. [35]	48	BOLD	Healthy older adults	Left M1/right supraorbital ridge	35 cm2 for M1, 100 cm^2 for supraorbital ridge	Anodal/cathodal/sham	15 mins, 1 mA	Seed-based and ICA	Decreased functional connectivity after anodal tDCS
Abellaneda-Perez et al. [36]	44 (15 sham, 15 tDCS, 14 tACS)	BOLD	Healthy	Anode: Left DLPFC, cathode: Right supraorbital ridge	35 cm^2 for both electrodes	Anodal/sham	20 mins, 2 mA	Seed-based and ICA	Anodal tDCS increases resting default mode network connectivity

Table 8.2 Summary table of tDCS studies combining tDCS with task fMRI

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Task	Summary of main findings
Stagg et al. [37]	15	BOLD	Healthy	Left M1/right supraorbital ridge	35cm^2 for both electrodes	Anodal/ cathodal/ sham	10 minutes 1 mA	Visually cued serial reaction time task before and after tDCS	Anodal tDCS led to short-lived activation increases in M1 and SMA within stimulated hemisphere
									·Cathodal tDCS led to increase in activation in contralateral M1 and dorsal premotor cortex (PMd), as well, and increased functional connectivity between these areas and the stimulated left M1
Stagg et al. [38]	11	BOLD	Stroke patients (at least 6 months post stroke)	Anodal: Anode on ipsilesional M1, cathode on contralesional supraorbital ridge	35cm^2 for both electrodes	Anodal/ cathodal/ sham	10 minutes, 1 mA	Visually cued motor task with simple response time and choice response time conditions	·Significant behavioural improvements produced by anodal stimulation to ipsilesional hemisphere are associated with a functionally relevant increase in activity within ipsilesional M1 in patients following stroke
				Cathodal: Anode on contralesional M1, anode on ipsilesional supraorbital ridge					·Anodal stimulation to ipsilesional hemisphere led to 5–10% improvement in reaction time, with an associated increase in movement-related cortical activity in stimulated M1 and functionally interconnected areas
									·Cathodal stimulation to contralesional hemisphere let to functional improvement when compared to sham stimulation

Lindenberg et al. [39]	20	BOLD	Chronic stroke	Anode: Ipsilesional M1 Cathode: Contralesional M1	16.3 cm^2 for both electrodes	Bilateral	5 sessions of bi-hemispheric stimulation (30mins, 1.5 mA) or sham stimulation with simultaneous physical/occupational therapy	Alternating flexion and extension of elbow/wrist	· Stronger activation of intact ipsilesional motor regions found post intervention in real stimulation group, not change in the control group
Lindenberg et al. [40]	17	BOLD	Healthy, older participants	Unilateral anode: Left M1, cathode: Right SOR	Unilateral: Anode: 35 cm^2, cathode: 100 cm^2	Unilateral/ bilateral/ sham	30 mins, 1 mA	Motor choice reaction task (and overt semantic word retrieval task – reported in Meinzer et al. 2014)	Both anodal and dual tDCS can potentially be used to counteract age-related impairment of inter-hemispheric interactions
				Bilateral: Anode: Left M1, cathode, right M0	Bilateral: 35 cm^2 for both electrodes				Differential effects of bihemispheric compared to unihemispheric stimulation may not merely be mediated by an 'add-on' effect of anodal and cathodal stimulation, but rather due to complex bihemispheric network modulations
Meinzer et al. [41]	18	BOLD	Healthy, older participants	Unilateral anode: Left M1, cathode: Right SOR	Unilateral: Anode: 35 cm^2, cathode: 100 cm^2	Unilateral/ bilateral/ sham	20 mins, 1 mA	Overt semantic word retrieval task (and motor choice reaction task – reported in Lindenberg et al. [26])	M1 stimulation can improve word-retrieval in healthy older individuals, confirming language-motor interaction extend beyond action-specific material as previously shown
				Bilateral: Anode: Left M1, cathode, right M1	Bilateral: 35 cm^2 for both electrodes				Provide a rationale to explore the effectiveness of M1 stimulation as an alternative and clinically feasible adjunct therapy approach in post-stroke aphasia

(continued)

Table 8.2 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Task	Summary of main findings
Lindenberg et al. [27]	40 (20 elderly and 20 young)	BOLD	Healthy: Elderly and young	Stimulating electrode: Left ventral IFG	Stimulating: 35 cm^2	Anodal/ sham	20 mins, 1 mA	Overt semantic word retrieval task	During sham stimulation, task-related fMRI demonstrated that enhanced bilateral prefrontal ability in older adults was associated with reduced performance
				Reference electrode: Right supraorbital ridge	Reference: 100 cm^2				Anodal tDCS significantly improved performance of older adults up to the level of younger controls and significantly reduced task-related hyperactivity in pre-frontal cortices, anterior cingulate gyrus and precuneus
									Suggestion that a single session of anodal tDCS can temporarily reverse non-beneficial effects of ageing on cognition and brain activity. These findings may translate to novel treatments to ameliorate cognitive decline in normal ageing
Ulm et al. [42]	1	BOLD	Chronic aphasia (4.7 years post stroke)	Anode: Based on location of peak activity in baseline scan - ~75% upwards from F7 to F3 (target: Left inferior frontal gyrus)	Anode: 35 cm^2	Anodal/ sham	20mins, 1 mA	Picture naming task	Feasible to target an individualized stimulation site in post-stroke aphasia during simultaneous fMRI to assess the underlying neural signatures of tDCS-action in post-stroke aphasia

Holland et al. [43]	10	BOLD	Aphasic stroke patients	Anode: Left IFC, cathode: Right frontopolar cortex	35 cm^2 for both electrodes	Anodal/ sham	20 mins, 2 mA	Overt picture naming task	Anodal tDCS had significant behavioural and regionally specific neural facilitation effects. Faster naming responses correlated with decreased BOLD signal in Broca's area Could indicate that Broca's area could be a suitable candidate target site for tDCS in neurorehabilitation of anomic patients, whose brain damage spares this region
Meinzer et al. [26]	36 (18 MCI patients, 18 matched controls)	BOLD	Patients: Mild cognitive impairment due to Alzheimer's disease Controls: Healthy age matched, no MCI	Anode: Left ventral IFG, cathode: Right supraorbital ridge	Not specified	Anodal/ sham	20 mins, 1 mA	Overt semantic word-retrieval task	Anodal stimulation led to improved performance on the overt word retrieval task which was accompanied by reduced hyperactivity in bilateral prefrontal cortex
Alekseichuk et al. [44]	17	BOLD	Healthy	Anode over Oz and Cathode over Cz according to EEG system	25 cm^2 for both electrodes	Anodal/ sham	10mins, 1 mA	Visual stimuli: 'wedges' and 'rings' shown directly before and after stimulation	Anodal tDCS induced a small but significant increase in BOLD response evoked by a visual stimulus, with no after-effects. This study also used tACS (10 Hz) which resulted in no online, but a widespread offline effect of BOLD activity

(continued)

Table 8.2 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Task	Summary of main findings
Spiegel et al. 2013	5	BOLD	Amblyopic patients	Stimulating electrode over Oz and reference electrode over Cz according to EEG system	Stimulating electrode: 43.2 cm^2, reference electrode: 109.25 cm^2	Anodal/ sham	15mins, 2 mA	2-alternative force choice design (orientation discrimination: Horizontal/ vertical)	Anodal tDCS transiently improved contrast sensitivity in a subset of adults with amblyopia and equated the cortical response to inputs from the amblyopic and fellow eyes
									Suggest that anodal tDCS may be of use in the treatment of amblyopia alone or in combination with other interventions
Pereira et al. [24]	16	BOLD	Parkinson's disease patients	Configuration 1: Anode: Left DLPFC, cathode: Right SOR	35 cm^2 for both electrodes	Anodal	20 mins, 2 mA	Verbal fluency paradigm	tDCS to DLPFC increased performance on the phonemic fluency task, after adjusting for baseline phonemic performance
				Configuration 2: Anode: Left tempo-parietal cortex (TPC), cathode: Right SOR					tDCS to specific brain regions may be able to enhance phonemic fluency in PD
Meinzer et al. [32]	20	BOLD	Healthy	Stimulating electrode over BA44/45 (Broca's area)	Stimulating: 35 cm^2	Anodal/ sham	Approximately 17 minutes, 1 mA	Semantic word generation task	Anodal tDCS improved word retrieval and was paralleled by selectively reduced task-related activation in the left ventral IFG, an area specifically implicated in semantic retrieval processes
				Reference electrode: Right supraorbital ridge	Reference: 100 cm^2				

Alon et al. [33]	4	BOLD	Healthy	Anode: Right M1, cathode: Left SOR	31.5 cm^2 for both electrodes	Anodal/ sham	12 min 48 s (split into two blocks), 2 mA	Self-paced bilateral finger-thumb opposition task	Anodal tDCS reduced connectivity measures in the right and left regions of interest. Suggestion that non-invasive brain stimulation during fMRI may down regulate the motor cortex's resting-state network connectivity
Kwon et al. [45]	12	BOLD	Healthy	Anode: Left M1, cathode: Right SOR	35 cm^2 for both electrodes	Anodal/ sham	2mins, 1 mA	Grasp-release hand movements at metronome-guided frequency of 1 Hz	Significant differences in voxel count and peak intensity were observed between real tDCS and sham tDCS Anodal tDCS application during the motor task enhanced cortical activation on the underlying targeted motor cortex, seeming that tDCS induced more cortical activity and modulated brain function when concurrently applied with a motor task

(continued)

Table 8.2 (continued)

Reference	Number of subjects	fMRI contrast	Healthy subjects/ clinical population	Electrode montage	Electrode size	Type of stimulation	Length of stimulation	Task	Summary of main findings
Antal et al. [46]	20	BOLD	Healthy	Anode: Left M1, cathode: Right SOR	35 cm^2 for both electrodes	Anodal/ cathodal	Alternate blocks of 20s, 1 mA and no stimulation	Finger tapping	Neither anodal nor cathodal tDCS induced a detectable BOLD change. However, in comparison to a voluntary finger tapping task without stimulation, anodal tDCS during finger tapping resulted in a decrease in the BOLD response in the SMA.
									Cathodal stimulation did not result in a significant change in the BOLD response in the SMA, but a trend could be seen
Jang et al. [47]	14	BOLD	Healthy (7 in anodal, 7 in sham)	Anode: Left M1, cathode: Right SOR	35 cm^2 for both electrodes	Anodal/ sham	20 mins, 1 mA	Grasp-release hand movements at metronome-guided frequency of 1 Hz	Anodal tDCS increased cortical excitability of underlying motor cortex in the human brain

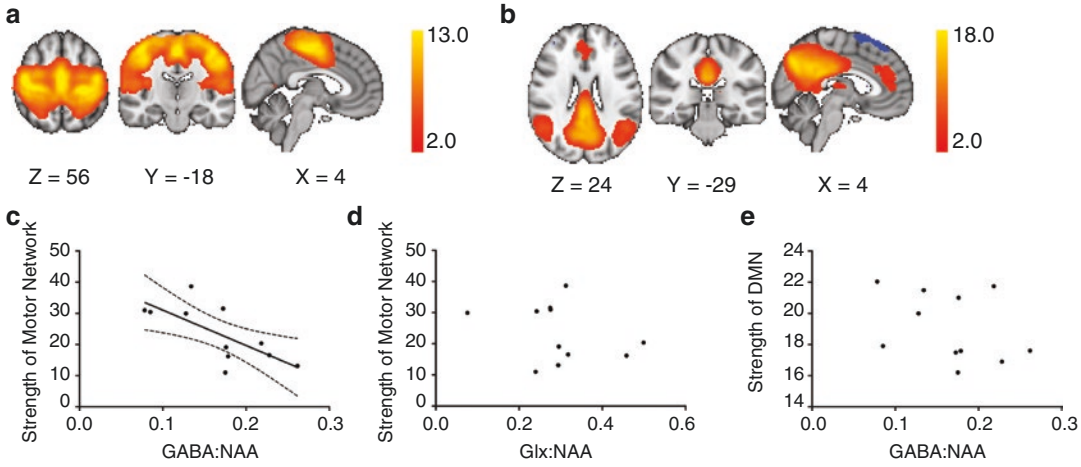

Fig. 8.2 The neurochemical basis of RSN strength. (**a**) Group mean motor RSN. (**b**) Group mean default mode RSN, which served here as a control network to assess the specificity of any relationships seen. (**c**–**e**) A significant relationship was demonstrated between M1-GABA and functional connectivity within the motor RSN ($r = -0.71$, $p = 0.01$; **c**) but neither between M1-Glx and motor network functional connectivity (**d**) nor between M1-GABA and functional connectivity within the DMN (**e**). (Figure reproduced with permission from Stagg et al. [23])

Baudewig and colleagues initially confirmed the feasibility of combining functional MRI and tDCS [56]. In this study, the BOLD signal was recorded in a sample of six subjects before and after 5 minutes of tDCS. The authors reported small stimulation-induced changes in activation in the supplementary motor area (SMA), an effect still noticeable 15 minutes after the end of stimulation.

Since this work, a number of imaging studies in healthy controls have investigated the effects of tDCS on motor-related activity [37, 40, 41, 46, 57]. Of these, one investigated the conventional electrode montage and a stimulation period of minutes, during the performance of a simple motor task [37]. Participants completed a simple visually cued serial reaction time task for 15 minutes before and immediately after 10 minutes of tDCS (anodal, cathodal or sham). The results indicated an expected increase in activation after anodal stimulation compared to sham in the stimulated (left) M1, ipsilateral dorsal premotor cortex (dPMC) and SMA. After cathodal stimulation, an increase in BOLD signal was observed under the stimulating electrode (left M1). Additionally, an increase in task-related activation was observed in the contralateral (right) M1, dPMC and SMA (Fig. 8.3).

8.4.3 Arterial Spin Labelling (ASL)

As discussed in some detail above, BOLD fMRI is the most common method of assessing neural activity changes during or following tDCS. However, while BOLD has a relatively high signal-to-noise ratio, meaning that data can be acquired over relatively short timescales, making is highly suitable for clinical use, the physiological underpinnings of the BOLD effect are complex and currently relatively poorly understood. This may be of particular importance in clinical populations, where changes in blood supply or neurovascular coupling may be expected.

An alternative approach is that of arterial spin labelling (ASL). ASL is a relatively novel fMRI technique that is able to quantify changes in tissue perfusion directly in the brain. It has a much lower signal-to-noise ratio than BOLD fMRI, which initially limited its use in clinical populations, but with the advent of ultra-high field imaging, it has become more widely used. ASL has two significant advantages over the BOLD signal: (1) it is primarily sensitive to low-frequency signals and is therefore the ideal modality to detect blood flow changes induced by the minutes-long tDCS protocols commonly used, and (2) the physiological basis of the con-

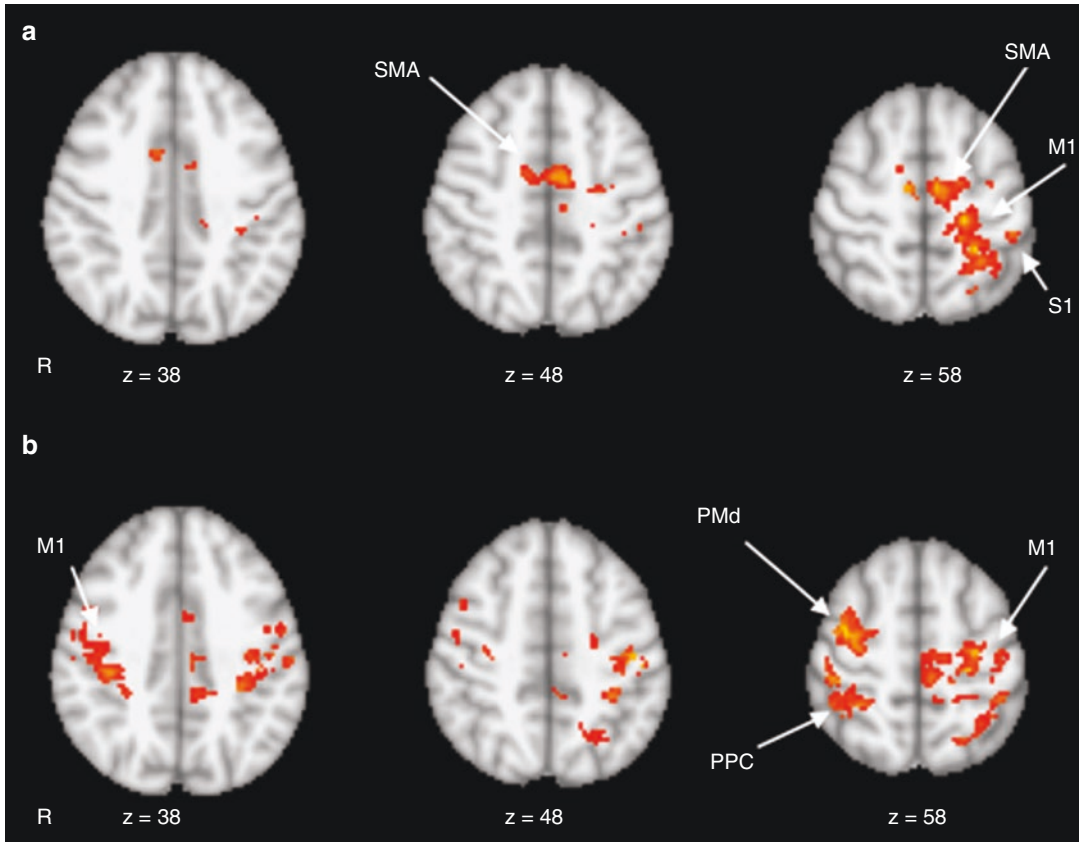

Fig. 8.3 (**a**) An increase in task-related BOLD signal was observed after anodal stimulation to the left M1 compared with sham stimulation in the left M1, left primary somatosensory cortex (S1), left posterior parietal cortex (PPC) and supplementary motor area (SMA). (**b**) An increase in BOLD signal was observed after cathodal stimulation to the left M1 compared with sham in the left M1, right M1, right PPC and right dorsal premotor cortex (PMd). (Figure adapted with permission from Stagg et al. [37])

trast is inherently simpler to understand than BOLD, a factor particularly important in clinical populations where many factors may change.

Zheng and colleagues performed the first tDCS/ASL study and showed non-polarity-specific effects, with an increase in perfusion in the stimulated M1 after short periods of both anodal and cathodal tDCS [58] (Fig. 8.4). A subsequent ASL study during concurrent tDCS to the left dorsolateral prefrontal cortex (DLPFC) found a polarity-specific effect of tDCS, with an increase in perfusion during and after anodal tDCS and a decrease in perfusion during and after cathodal tDCS [59], a finding in line with animal models [60]. This study also went on to analyse the tDCS-induced changes in perfusion across the whole brain and demonstrated significantly increased perfusion during anodal tDCS in those areas anatomically connected to the DLPFC [59] (Fig. 8.4). Interestingly, the same increased perfusion effects were not seen in the period immediately following stimulation, despite increased cortical excitability continuing post stimulation in similar studies over the motor cortex. It is not clear why this should be the case, but as discussed above, the effects of tDCS are likely highly dependent on the site of stimulation and electrode placement, and it is also possible that further excitability changes post stimulation are maintained by factors that do not in themselves induce an increase in cortical perfusion in

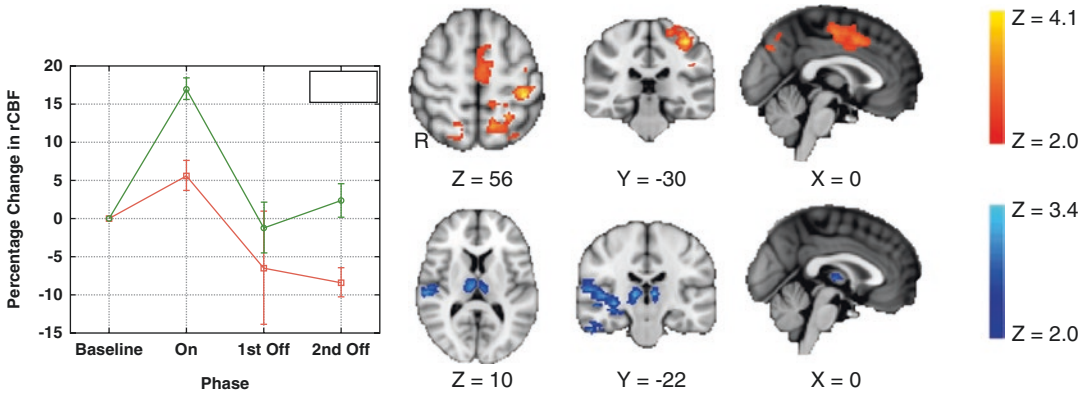

Fig. 8.4 Summary of arterial spin labelling (ASL) studies using tDCS. Anodal tDCS applied to the left M1 leads to an increase in perfusion under the stimulated electrode during stimulation (green line) and cathodal tDCS to a less substantial increase in the same region. (Figure reproduced from Zheng et al. [58] with permission). Anodal tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) leads to an increase in perfusion in the left primary sensory cortex, mid-cingulate cortex, paracingulate cortex and left parietal cortex during stimulation. Regions of decreased perfusion during cathodal stimulation. Decreases were seen in the thalami bilaterally and the right middle and inferior temporal gyri. (Figure adapted from Stagg et al. [59] with permission)

the resting brain. Outside the motor domain, ASL has more recently been used to explore the neural basis of emotional processing, demonstrating a reduction in cortical perfusion due to tDCS only in subjects who had experienced prior criticism [61].

8.5 Magnetic Resonance Spectroscopy

Understanding how transcranial direct current stimulation (tDCS) affects neuronal activity is of vital importance to discovering the mechanisms by which tDCS alters behaviour. As well as studying BOLD and ASL signals, we can also use magnetic resonance (MR) techniques to investigate the effects of tDCS at a deeper level, by examining how tDCS affects the neurochemicals which go on to cause these activity changes. We can achieve this by using magnetic resonance spectroscopy (MRS), a technique that enables us to detect and quantify concentrations of different metabolites within a volume of tissue.

MRS was first performed in the human brain in 1985 [62] and since then has been primarily used to investigate metabolic changes in pathological states. MRS relies on many of the same principles as magnetic resonance imaging (MRI); it measures signals produced by the behaviour of certain diamagnetic molecules within a magnetic field. While MRI focuses on the variations in signal across space, traditional MRS examines signals produced from only one or two large volumes of tissue [63]. However, recent sequence advances now allow MRS imaging (MRSI) of a slab of cortex, with comparable in-plane resolution to that used in MRI [64], though this has yet to be used to assess tDCS-induced neurochemical changes. A number of atomic nuclei have diamagnetic properties, including 1H, 31P and 13C MRS, of which 1H MRS is used most widely. The ability of MRS to discriminate between different molecules relies on the fact that the structure of the molecules within which these atoms are bound, and the environment surrounding these molecules, influence the behaviour of the atoms within the magnetic field. MRS focuses on very small differences in the signals produced by the atoms contained within different metabolites in a volume of interest (VOI).

The spectra produced by specific metabolites can be determined by performing spectroscopy on a specifically designed object or 'phantom' that contains that metabolite alone. The charac-

teristic peaks and frequencies of many neurochemicals are therefore known, meaning that these metabolites can be identified from sample spectra. The signal amplitudes of the peaks in a spectrum are directly proportional to the corresponding compound's concentration within the target volume of tissue (see Fig. 8.5 for an example spectrum). Typical SNR of MRS sequences allows detection of metabolites present in millimolar concentrations. Fortunately, many neurochemicals involved in neurotransmission and metabolism have concentrations above this threshold, but others (e.g. dopamine) are not, making their detection and quantification impossible with current MRS methods.

8.5.1 1H-MRS

Hydrogen atoms form a part of many of the molecules within the brain and body. The molecule with by far the highest concentration is water, but many of the brain's endogenous neurochemicals, controlling metabolism and neural firing, also contain hydrogen at concentrations high enough to allow detection by 1H MRS. The neurotransmitters glutamate and GABA (gamma-aminobutyric acid) are of most relevance and interest to research investigating the neurochemical effects of tDCS. Both of these neurotransmitters are involved in mechanisms that selectively alter synaptic strength, for example long-term potentiation-like (LTP-like) processes within the neocortex [66–70]. These LTP-like processes are thought to be the main mechanism controlling learning in the brain and therefore improvements across many tasks, particularly in the motor domain. Changed to LTP-like processes have been demonstrated with anodal tDCS (see [1] for a review), and it has therefore been proposed that modulation of GABA and glutamate levels may be the mechanism by which tDCS exerts its behavioural effects, an argument strengthened by studies showing that drugs acting on glutamatergic and GABAergic receptors can alter tDCS behavioural after-effects [71, 72].

Neurochemicals of Interest

A number of neurochemicals can be measured using 1H-MRS, of which the following are of most interest for tDCS-MRS studies.

Glutamate

Glutamate is the main excitatory neurotransmitter in the brain and is essential for the development of normal synaptic connections and learning. Glutamate is stored in synaptic vesicles before being released into the synaptic cleft. Once released at the synapse, glutamate can contact either post-synaptic ionotropic receptors (NMDA, AMPA or kainate) or metabotropic receptors linked to G-proteins. A critical mechanism of LTP is to increase the number of these post-synaptic receptors. This form of neuroplastic change is invisible to MRS; however, the process is dependent on glutamate release. This glutamate release may result in an overall increase in glutamate concentration within the volume, a change which may be detected by MRS, though the relationship between receptor density changes and the MRS glutamate signal is not yet clear.

After binding and unbinding with post-synaptic receptors, most glutamate is taken up by neighbouring astrocytes and metabolized into glutamine. The H1 resonances produced by glutamate and glutamine are difficult to separate, except at very high field strengths, due to the similarities in their molecular structures. Due to this, a composite Glx signal, made up of contributions from both glutamate and glutamine, is often reported. An additional challenge to the interpretation of these MRS signals is their summation across a large volume of tissue. It is therefore not possible to discriminate between levels of neurotransmitter within different pools, or to gain information about where in the cell molecules are located. Furthermore, while glutamate has a highly important role in neurotransmission, the significant majority of glutamate in the brain is involved in metabolism and not neurotransmission, making changes in this resonance somewhat difficult to link with changes in behaviour. For more, details see [73].

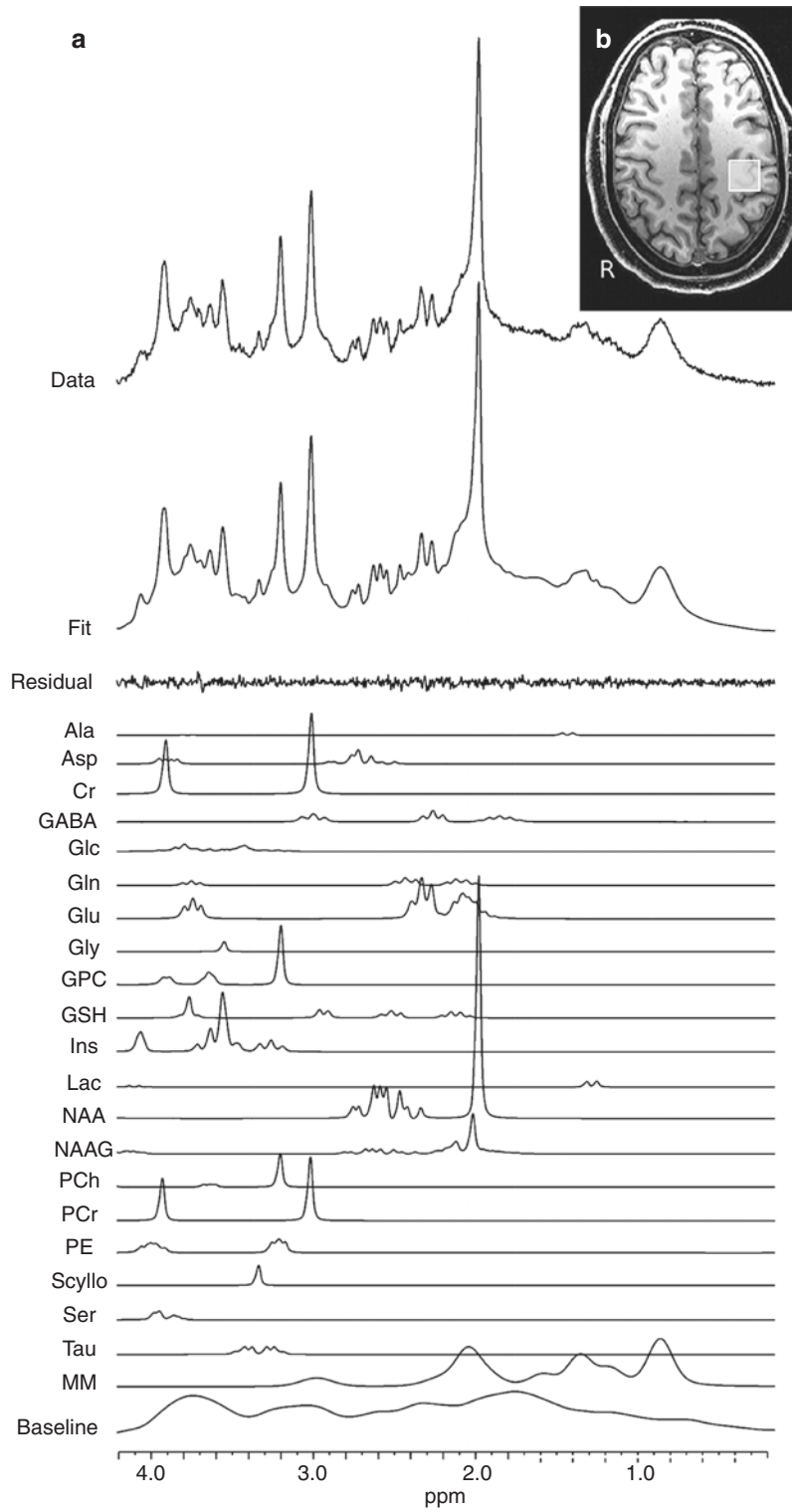

Fig. 8.5 (**a**) An example of a spectrum produced by 1H MRS at 3 Tesla using the SPECIAL sequence from a 2×2×2 cm M1 voxel. The original MRS data is shown in the top row. The next row is the full model fit produced from LCModel [65]. The high quality of the fit is demonstrated by the small residual signal remaining after fitting, shown by the row labelled 'residual'. Individual fits for all neurochemicals are also demonstrated – each neurochemical has multiple fitted peaks that reflect the individual protons within the molecule. Quantification of metabolites within a sample can be achieved by linear combination of these individual metabolite spectra. (**b**). Location of the left primary motor cortex (M1) voxel. (Figure reproduced with permission from [66])

GABA

GABA is the main inhibitory neurotransmitter within the brain, but it also has a role as a metabolite. It is metabolized from glutamate by the enzyme glutamic acid decarboxylase (GAD). 1H MRS has demonstrated a correlation between measures of GABA and glutamate [74], which is expected given their close relationship. GABA is found in three distinct pools within the brain: as a metabolite within the cytoplasm of GABAergic interneurons, within synaptic vesicles and extracellularly both in the synaptic cleft and in the surrounding intercellular fluid. Attempts have been made to correlate MRS measures of GABA with paired-pulse transcranial magnetic stimulation (ppTMS) measurements of GABA receptor activity. Neither GABAA nor GABAB receptor activity, nor a combination of the two, was able to describe the MRS GABA signal. One ppTMS measure, 1 ms SICI IO curves, which has been proposed to reflect the activity at extra-synaptic GABAA receptors [74], has however been shown to correlate with MRS GABA levels. Additionally, MRS-measured GABA levels have been shown to be closely related to CSF-GABA level [75], suggesting that in the resting state, MRS-assessed GABA probably most closely reflects extrasynaptic GABA tone. However, as extracellular GABA is derived from intracellular pools, it is still not clear what aspects of GABAergic processing a change in the GABA signal, as a result of neuromodulation, may represent. For more details, see [76].

N-Acetylaspartic Acid and Creatine

Other molecules which commonly produce peaks in 1H MRS spectra are N-Acetylaspartic acid (NAA) and creatine. NAA is one of the most concentrated molecules in the brain and is thought of as a marker for neuronal health, with reduced levels being indicative of disease [77, 78], brain injury [79–81] or psychiatric disorders [82]. Within healthy brains, however, it is thought to be present at a stable concentration, and so is often used as a reference chemical within MRS, where concentration of other molecules in the tissue volume is given as a ratio of NAA [83]. Total creatine, a measure made up of signal contributions from both creatine and phosphocreatine (Cr + PCr), can also be used for this purpose. Creatine and phosphocreatine are vitally important molecules for energy storage and transmission within cells.

8.5.2 31P-MRS

Phosphorus MR spectroscopy (31P MRS) can be performed in much the same way as 1H MRS but is tuned to the range of resonant frequencies of phosphorus atoms. Many molecules, which the body and brain depend on for energy transport and release, contain phosphorus. High-energy phosphates within the energy transportation molecules ATP and phosphocreatine create large peaks, and lower amplitude peaks are created by sugars, lipids and inorganic phosphates, which are all present at lower concentrations within the brain. By measuring the concentrations of ATP, inorganic phosphate and phosphocreatine simultaneously, the energy metabolism of the volume can be estimated. However, despite this potential utility, 31P MRS is less widely used than 1H MRS as it requires specialized hardware to record the resonance frequencies. Additionally, 31P MRS only has approximately 7% of the sensitivity of proton MRS, meaning it requires long acquisition times and has only a low spatial resolution.

8.5.3 Combining tDCS with MRS

The majority of studies investigating the effects of tDCS on 1H MRS-measured neurochemistry have focused on so-called ‘anodal’ and ‘cathodal’ tDCS applied to M1 (where one electrode is over M1, the other on the contralateral supraorbital ridge). Work by our group and others [21, 48, 84, 85] has demonstrated that anodal tDCS over M1 causes a decrease in MRS measured GABA levels in the stimulated area of cortex (Fig. 8.6a), which persist for at least 90 minutes following stimulation [86], and is associated

across individuals with the intensity of induced electric field [87]. Using a simultaneous two-voxel MRS sequence, our group also found a concurrent decrease in GABA concentration in the non-stimulated M1 [88].

The above studies indicate that a decrease in MRS-measured GABA may be a reliable effect of anodal M1 tDCS. It has been proposed that this GABA decrease may be responsible for the accelerated learning effects seen when tDCS is performed in conjunction with motor training (see above), an idea which is supported by multiple lines of evidence. Normal motor training, without stimulation, causes a decrease in GABA: MRS-measured GABA has been demonstrated to decrease in the primary sensorimotor cortex after training the contralateral hand on an isometric motor sequence learning task [89, 90]. The decrease in GABA seen with tDCS correlates with the degree of motor learning: inter-individual responsiveness in MRS-measured M1 GABA levels to ipsilateral, anodal tDCS correlated with individual's degree of motor learning on a serial reaction time task (performed without stimulation) and the amount of fMRI signal change [48] (Fig. 8.6b). Baseline levels of GABA in patients are correlated with the behavioural gains induced by stimulation: higher initial GABA levels within the ipsilesional M1 of stroke patients predicted greater percentage improvement on a reaction time task [91]. Finally, GABA decrease after training on a motor adaptation task with tDCS has been shown to correlate with improvements on the task: anodal tDCS induced changes in ipsilateral M1 MRS-GABA levels correlated with model-based motor adaptation learning [85, 92].

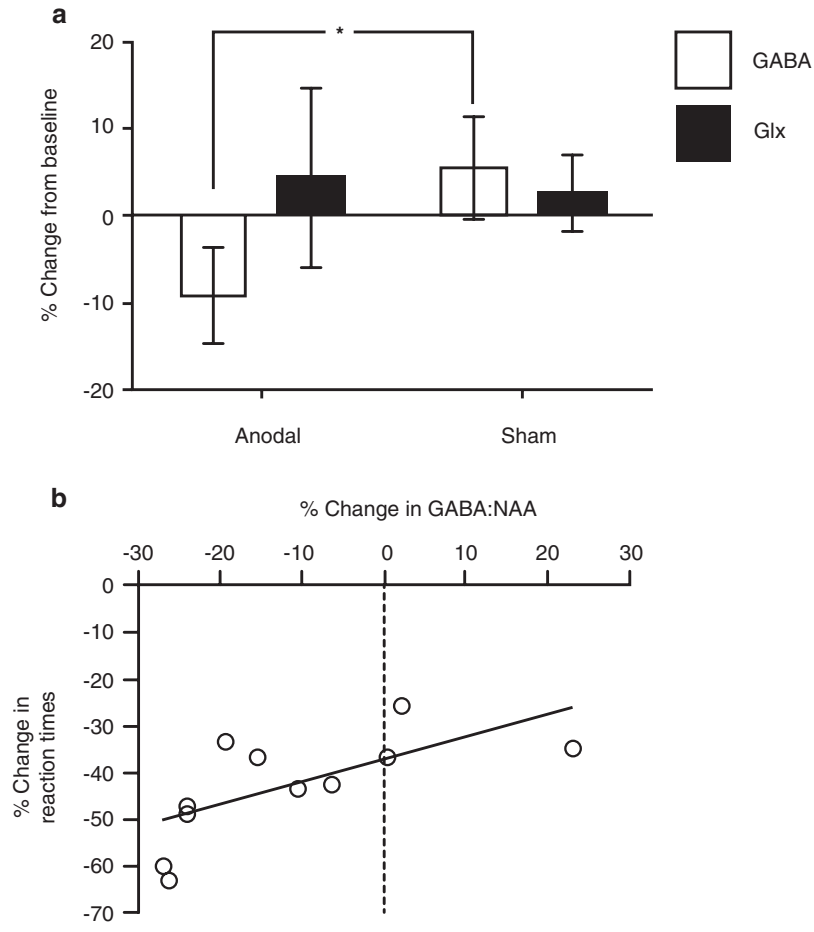

Fig. 8.6 (**a**) A decrease in MRS-assessed GABA concentration in the left M1 is observed after anodal tDCS applied to this region. No significant decrease in seen after sham stimulation. (Figure adapted from Stagg et al. [84] with permission; copyright 2009 Society for Neuroscience). (**b**) The degree of anodal tDCS-induced decrease in GABA on 1 day correlates with the decrease in reaction times in an explicit sequence learning task (a marker of motor learning) performed on a separate day, such that subjects who have a greater decrease in GABA due to anodal tDCS are also those who learn most. (Figure adapted from Stagg et al. [48] with permission)

Taken together, this indicates that the decrease in GABA as measured by MRS may be responsible for the behavioural effects of tDCS.

Decreases in MRS measured GABA levels after tDCS on M1 have been reliably demonstrated [21, 48, 84], but changes in levels of other metabolites have also been reported. For example, in a study by Rango and colleagues [93], a decrease in myoinositol concentration was the only change detected after 30 minutes of anodal tDCS over M1. However, the scanner sequence used in this study meant that the GABA signal was not examined, and this change in myoinositol has not been replicated [37].

Importantly, the effect of anodal M1 tDCS on neurochemistry varies depending on the location of the cathode. While the above studies place the cathode on the supraorbital ridge, altering this montage to place the cathode over the contralateral M1 does not result in altered metabolite concentrations in the 'anode-targeted' M1 [88, 94, 95]. It is not clear whether this difference in effect is due to differences in the direction of current flow through the cortex or due to changes in interactions between stimulated areas. However, these results highlight the fact that 'anodal' or 'cathodal' tDCS are not merely exciting or inhibiting the area underneath the electrodes and rather are stimulating multiple interacting brain areas, not necessarily in an intuitive manner, meaning the effects of one montage may not be generalizable to another.

The MRS-measured effects of tDCS on other brain areas have also been examined. Two studies from the same group targeting the parietal cortex found an increase in Glx beneath the anodal electrode, while finding no change in the same region of the contralateral cortex [50, 96]. One of these studies also demonstrated an increase in NAA beneath the anodal electrode [96]. These studies show markedly different findings than those examining tDCS over M1 where Glx increases in the anodally stimulated cortex have not been demonstrated. Another well-studied montage involves placing both electrodes over the prefrontal cortex, with papers reporting a decrease in Glu in the area under the cathode [51, 97], the magnitude of which depends on the intensity of induced electric field [51]. In contrast, Glu levels have been shown to increase in the PFC under the anode [98], and though group-level changes in GABA have not been reported, brain morphology in the DLPFC has been shown to correlate with GABA changes in the area under the anode [99].

As discussed, traditional MRS involves choosing one or two specific voxels of interest, but yet tDCS has been shown to induce an electric field which is dispersed across a large area [100], much of which may lie outside the examined volume or may be influenced by interactions with the target. Often a control region is tested to ensure that changes observed in the volume of interest are not in fact global changes. However, MRS still cannot tell us the whole story about the neurochemical implications of tDCS occurring in areas beyond the VOI. To be able to draw global conclusions on the effect of tDCS on neurochemistry across the whole brain, studies combining tDCS with MRS imaging are needed.

8.6 Current Density and Impedance Imaging

Recent years has seen the emergence of neuroimaging methods designed to measure the path that transcranially applied current takes through the head and brain. These methods can be used to assess how much current is entering the brain and the distribution of that current, either validating or being used in conjunction with computation current flow models. Understanding how current moves through the brain both at the group and individual level could guide the development of optimized montages, either targeting certain brain areas or standardizing current 'dose' across participants [101, 102].

Current density and impedance imaging methods require stimulation, either tDCS or transcranial alternating current stimulation (tACS), to be applied during scanning. Current density imaging (CDI) involves measuring the tDCS current-induced magnetic fields along the direction of the static MRI Bz field [103]. While this is a relatively simple to acquire these magnetic field measurements – even allowing for concurrent measure-

ment of fMRI BOLD signal [104] – the information gained from a single run of the sequence only obtains magnetic field changes in one direction. Therefore, in order to construct current density images, subjects need to be measured in at least three different orientations [105], which is clearly not possible in vivo with current MRI scanners.

Another method which can be used to construct current flow maps and measure the electrical impedance of brain tissues is known as diffusion tensor magnetic resonance electrical impedance tomography (DT-MREIT) [106]. For this technique, magnetic field images are obtained sequentially during current application in both the x and y scanner directions. These two Bz images are then combined with a basic computation model of current flow through a homogenous head, to create projected current densities. These current densities can then be combined with a diffusion-tensor image, assuming that electrical conductance is proportional to diffusion, to create a conductance tensor image. This method has been applied in humans in vivo and obtained conductance values in line with values reported from studies on excised tissues and values currently used in computation current flow models [65].

These imaging techniques are only beginning to be utilized in human research, and further refinement of sequences is needed. As well as providing detailed assessments of healthy tissue conductivities, these protocols could be used to explore current flow and conductance in lesioned and degenerating tissue, allowing stimulation protocols to be optimized and current flow models to be updated for these populations that we believe may benefit from tDCS-enhanced therapies.

8.7 Conclusions and Future Directions

tDCS is showing increasing promise as a therapeutic tool in the treatment of psychiatric disorders, but for that promise to be realized, more must be understood of the underlying effects on the brain, both in health and disease. However, while studies are beginning to increase our understanding of both the local and distant effects of tDCS, the combination of tDCS and MRI is within, at the moment, from the so-called infinite parameter space.

tDCS is a technique with a high number of degrees of freedom: there are several different stimulation types, multiple different electrode placement montages, varying stimulation intensities and lengths and important differences in its behavioural effects depending on whether stimulation is performed concurrently or prior to the task. The number of neuroimaging approaches utilized and the significant question over which results from studies in healthy controls can be translated into clinical populations mean that there is currently little consensus over the likely neural correlates underlying the promising behavioural effects of tDCS seen in a range of psychiatric disorders.

However, neuroimaging offers great potential to allow the study of the neural effects of tDCS, once the technical difficulties of combining tDCS and MR have been overcome. It is to be expected that as stimulation parameters with clear clinical significance are developed, neuroimaging will play a vital role in refining our stimulation approaches in clinical populations.

References

1. Stagg CJCJ, Nitsche MAA. Physiological basis of transcranial direct current stimulation. Neurosci [Internet]. 2011;17(1):37–53. Available from: http://nro.sagepub.com/cgi/content/abstract/17/1/37.
2. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(3):633–9.
3. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127(2).
4. Logothetis NK. What we can do and what we cannot do with fMRI. Nature [Internet]. 2008;453(7197):869–78. Available from: http://www.nature.com/nature/journal/v453/n7197/abs/nature06976.html.
5. Cole DM, Smith SM, Beckmann CF. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. Front Syst Neurosci [Internet]. 2010.; Available from: http://journal.frontiersin.org/article/10.3389/fnsys.2010.00008/abstract.

6. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci [Internet]. 2007;8(9):700–11. Available from: http://www.nature.com/doifinder/10.1038/nrn2201.
7. Snyder AZ, Raichle ME. A brief history of the resting state: the Washington University perspective. Neuroimage [Internet]. 2012;62(2):902–10. Available from: https://doi.org/10.1016/j.neuroimage.2012.01.044
8. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A [Internet]. 2001;98(2):676–82. Available from: https://doi.org/10.1073/pnas.98.2.676.
9. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc London Ser B, Biol Sci [Internet]. 2005 May 29;360(1457):1001–13. Available from: http://journals.royalsociety.org/content/xt925hertx30wfyp/
10. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A [Internet]. 2009;106(31):13040–5. Available from: http://www.pnas.org/content/106/31/13040.short.
11. Johansen-Berg H. Human connectomics — what will the future demand? Neuroimage [Internet]. 2013;80(C):541–4. Available from: https://doi.org/10.1016/j.neuroimage.2013.05.082
12. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A [Internet]. 2009;106(17):7209–14. Available from: http://www.pnas.org/content/106/17/7209.long.
13. Pievani M, de Hann W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. Lancet Neurol [Internet]. 2011;10(9):829–43. Available from: https://doi.org/10.1016/S1474-4422(11)70158-2
14. Pievani M, Filippini N, van den Heuvel MP, Cappa SF, Frisoni GB. Brain connectivity in neurodegenerative diseases—from phenotype to proteinopathy. Nat Rev Neurol [Internet]. 2014;10(11):620–33. Available from: https://doi.org/10.1038/nrneurol.2014.178
15. Fornito A, Zalesky A, Breakspear M. Graph analysis of the human connectome: promise, progress, and pitfalls. Neuroimage [Internet]. 2013;80(C):426–44. Available from: https://doi.org/10.1016/j.neuroimage.2013.04.087
16. Polanía R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp [Internet]. 2011;32(8):1236–49. Available from: http://doi.wiley.com/10.1002/hbm.21104.
17. Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp [Internet]. 2012;33(10):2499–508. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21922602&retmode=ref&cmd=prlinks.
18. Sehm B, Kipping J, Schäfer A, Villringer A, Ragert P. A Comparison between Uni- and Bilateral tDCS Effects on Functional Connectivity of the Human Motor Cortex. Front Hum Neurosci [Internet]. 2013;7:183. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23675337&retmode=ref&cmd=prlinks.
19. Sehm B, Schafer A, Kipping J, Margulies D, Conde V, Taubert M, et al. Dynamic modulation of intrinsic functional connectivity by transcranial direct current stimulation. J Neurophysiol [Internet]. 2012;108(12):3253–63. Available from: http://jn.physiology.org/cgi/doi/10.1152/jn.00606.2012.
20. Amadi U, Ilie AS, Johansen-Berg H, Stagg CJCJ. Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. Neuroimage [Internet]. 2014;88:155–61. Available from: https://doi.org/10.1016/j.neuroimage.2013.11.037
21. Bachtiar V, Near J, Johansen-Berg H, Stagg CJCJ. Modulation of GABA and resting state functional connectivity by transcranial direct current stimulation. Culham JC, editor. Elife [Internet]. 2015 Jan 1;4(September 2015):e08789. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26381352&retmode=ref&cmd=prlinks.
22. Polanía R, Paulus W, Antal A, Nitsche MA. Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. NeuroImage. 2011;54:2287–96.
23. Stagg CJJ, Bachtiar V, Amadi U, Gudberg CAA, Ilie ASS, Sampaio-Baptista C, et al. Local GABA concentration is related to network-level resting functional connectivity. Elife [Internet]. 2014;3(0):–e01465. Available from: http://elife.elifesciences.org/lookup/doi/10.7554/eLife.01465.011.
24. Pereira JB, Junqué C, Bartrés-Faz D, Martí MJ, Sala-Llonch R, Compta Y, Falcón C, Vendrell P, Pascual-Leone A, Valls-Sole J, Tolosa E. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. Brain Stimul. 2013;6:16–24.
25. Minami SB, Oishi N, Watabe T, Uno K, Kaga K, Ogawa K. Auditory resting-state functional connectivity in tinnitus and modulation with transcranial direct current stimulation. Acta Oto-Laryngologica. 2015;135:1286–92.
26. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Flöel A. Transcranial direct current stimulation in mild cognitive impairment: Behavioral effects and neural mechanisms. Alzheimer's Dementia. 2015;11:1032–40.
27. Lindenberg R, Nachtigall L, Meinzer M, Sieg MM, Floeel A. Differential effects of dual and unihemispheric motor cortex stimulation in older adults. J Neurosci. 2013;33:9176–83.

28. Park C-H, Chang H, Park J-Y, Shin Y-I, Kim ST, Kim Y-H. Transcranial direct current stimulation increases resting state interhemispheric connectivity. Neurosci Lett. 2013;539:7–10.
29. Clemens B, Jung S, Mingoia G, Weyer D, Domahs F. Influence of anodal transcranial direct current stimulation (tDCS) over the right angular gyrus on brain activity during rest. PLoS One. 2014;9:95984.
30. Peña-Gómez C, Sala-Lonch R, Junqué C, Clemente IC, Vidal D, Bargalló N, Falcón C, Valls-Sole J, Pascual-Leone A, Bartrés-Faz D. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul. 2012;5:252–63.
31. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Moller H-J, Reiser M, Padberg F. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31:15284–93.
32. Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, Flaisch T, Flöel A. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci. 2012;32:1859–66.
33. Alon G, Roys SR, Gullapalli RP, Greenspan JD. Non-invasive electrical stimulation of the brain (ESB) modifies the resting-state network connectivity of the primary motor cortex: a proof of concept fMRI study. Brain Res. 2011;1403:37–44.
34. Mondino M, Ghumman S, Gane C, Renauld E, Whittingstall K, Fecteau S. Effects of transcranial stimulation with direct and alternating current on resting-state functional connectivity: an exploratory study simultaneously combining stimulation and multiband functional magnetic resonance imaging. Front Human Neurosci. 2020;13:1–8.
35. Antonenko D, Schubert F, Bohm F, Ittermann B, Aydin S, Hayek D, Grittner U, Floel A. tDCS-induced modulation of GABA levels and resting-state functional connectivity in older adults. J Neurosci. 2017;37:4065–73.
36. Abellaneda-Pérez K, Vaqué-Alcázar L, Perellón-Alfonso R, Bargalló N, Kuo M-F, Pascual-Leone A, Nitsche MA, Bartrés-Faz D. Differential tDCS and tACS effects on working memory-related neural activity and resting-state connectivity. Front Neurosci. 2020;13:1440.
37. Stagg CJJ, O'Shea J, Kincses ZTT, Woolrich M, Matthews PMM, Johansen-Berg H. Modulation of movement-associated cortical activation by transcranial direct current stimulation. Eur J Neurosci [Internet]. 2009;30(7):1412–23. Available from: http://pubget.com/site/paper/19788568?institution=.
38. Stagg CJCJ, Bachtiar V, O'Shea J, Allman C, Bosnell RARA, Kischka U, Matthews PMPM, Johansen-Berg H. Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke. Brain J Neurol. 2012;135:276–84.
39. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010;75:2176–84.
40. Lindenberg R, Nachtigall L, Meinzer M, Sieg MM, Floeel A. Differential effects of dual and Unihemispheric motor cortex stimulation in older adults. J Neurosci [Internet]. 2013;33(21):9176–83. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23699528&retmode=ref&cmd=prlinks.
41. Meinzer M, Lindenberg R, Sieg MM, Nachtigall L, Ulm L, Flöel A. Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults. 2014;1–9. Available from: https://doi.org/10.3389/fnagi.2014.00253/abstract
42. Ulm L, Mcmahon K, Copland D, de Zubicaray GI, Meinzer M. Neural mechanisms underlying perilesional transcranial direct current stimulation in aphasia: a feasibility study. Front Human Neurosci. 2015;9:550.
43. Holland R, Leff AP, Josephs O, Galea JM, Desikan M. Speech facilitation by left inferior frontal cortex stimulation. Curr Biol. 2011; Available at: http://www.sciencedirect.com/science/article/pii/S0960982211008207
44. Alekseichuk I, Diers K, Paulus W, Antal A. Transcranial electrical stimulation of the occipital cortex during visual perception modifies the magnitude of BOLD activity: a combined tES-fMRI approach. 2015; https://doi.org/10.1016/j.neuroimage.2015.11.034.
45. Kwon YH, Jang SH. The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. Neurosci Lett. 2011;492:105–8.
46. Antal A, Polanía R, Schmidt-Samoa C, Dechent P, Paulus W. Transcranial direct current stimulation over the primary motor cortex during fMRI. Neuroimage [Internet]. 2011;55(2):590–6. Available from: https://doi.org/10.1016/j.neuroimage.2010.11.085
47. Jang SH, Ahn SH, Byun WM, Kim CS, Lee MY, Kwon YH. The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neurosci Lett. 2009;460:117–20.
48. Stagg CJ, Bachtiar V, Johansen-Berg H. The role of GABA in human motor learning. Curr Biol [Internet]. 2011;21(6):480–4. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0960982211001254.
49. Kapogiannis D, Reiter DA, Willette AA, Mattson MP. Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. Neuroimage [Internet]. 2013;64(C):112–9. Available from: https://doi.org/10.1016/j.neuroimage.2012.09.029
50. Hunter MA, Coffman BA, Gasparovic C, Calhoun VD, Trumbo MC, Clark VP. Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity. Brain Res [Internet]. 2015;1594:92–107. Available from: https://doi.org/10.1016/j.brainres.2014.09.066

51. Mezger E, Rauchmann BS, Brunoni AR, Bulubas L, Thielscher A, Werle J, et al. Effects of prefrontal cathodal tDCS on brain glutamate levels and resting state connectivity: a randomized, sham-controlled, crossover trial in healthy volunteers. Clin Neurophysiol. 2020;131(4):e127.
52. Nitsche M, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, et al. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci [Internet]. 2003;15(4):619–26. Available from: papers2://publication/uuid/B0168D10-4B45-434C-99EF-EE0904B3F2A2.
53. Stagg CJJ, Jayaram G, Pastor D, Kincses ZTT, Matthews PMM, Johansen-Berg H. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia [Internet]. 2011;49(5):800–4. Available from: https://doi.org/10.1016/j.neuropsychologia.2011.02.009
54. Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, et al. Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett [Internet]. 2006;404(1–2):232–6. Available from: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0G-4K9C5NM-2&_user=126524&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000010360&_version=1&_urlVersion=0&_userid=126524&md5=1898471adcbd92d18e573de753a713ed.
55. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A. 2009;106(5):1590–5.
56. Baudewig J, Nitsche MA, Paulus W, Frahm J. Regional Modulation of BOLD MRI Responses to Human Sensorimotor Activation by Transcranial Direct Current Stimulation. Magn Reson Med [Internet]. 2001;45:196–201. Available from: papers2://publication/uuid/23D1C1DF-A212–4489-BD8C-38FD281BFAA8.
57. Kwon YH, Ko M-H, Ahn SH, Kim Y-H, Song JC, Lee C-H, et al. Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett [Internet]. 2008;435(1):56–9. Available from: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T0G-4RTM34M-4&_user=126524&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000010360&_version=1&_urlVersion=0&_userid=126524&md5=c83fe3e8a3c4cede9fbb60c7430a9434.
58. Zheng X, Alsop DC, Schlaug G. Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. Neuroimage [Internet]. 2011;58(1):26–33. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1053811911006264.
59. Stagg CJCJ, Lin RLRL, Mezue M, Segerdahl A, Kong Y, Xie J, et al. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci [Internet]. 2013;33(28):11425–31. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23843514&retmode=ref&cmd=prlinks.
60. Wachter D, Wrede A, Schulz-Schaeffer W, Taghizadeh-Waghefi A, Nitsche MA, Kutschenko A, et al. Transcranial direct current stimulation induces polarity-specific changes of cortical blood perfusion in the rat. Exp Neurol [Internet]. 2011;227(2):322–7. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0014488610004279.
61. Baeken C, Dedoncker J, Remue J, Wu GR, Vanderhasselt MA, De Witte S, et al. One MRI-compatible tDCS session attenuates ventromedial cortical perfusion when exposed to verbal criticism: the role of perceived criticism. Hum Brain Mapp. 2018;39(11):4462–70.
62. Bottomley PA, Edelstein WA, Foster TH, Adams WA. In vivo solvent-suppressed localized hydrogen nuclear magnetic resonance spectroscopy: a window to metabolism? Proc Natl Acad Sci U S A. 1985;82(7):2148–52.
63. Lemke C, Hess A, Bachtiar V, Clare S, Stagg CJ, Jezzard P, et al. Two-voxel spectroscopy with dynamic B0 shimming and flip angles at ultra high field. Conf Proc 22nd Annu Meet ISMRM [Internet]. 2013;1. Available from: https://mail.google.com/mail/u/0/?shva=1.
64. Steel A, Chiew M, Jezzard P, Voets NL, Plaha P, Thomas MA, et al. Metabolite-cycled density-weighted concentric rings k-space trajectory (DW-CRT) enables high-resolution 1 H magnetic resonance spectroscopic imaging at 3-Tesla. Sci Rep. 2018;8(1).
65. Chauhan M, Indahlastari A, Kasinadhuni AK, Schär M, Mareci TH, Sadleir RJ. Low-frequency conductivity tensor imaging of the human head in vivo using DT-MREIT: first study. IEEE Trans Med Imaging. 2017;
66. Hess G, Aizenman CD, Donoghue JP, Aizenmann CD, Donoghue JP. Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. J Neurophysiol [Internet]. 1996;75(5):1765–78. Available from: papers2://publication/uuid/77E35AAD-40D2-4A58-BD3F-41D750688E2A.
67. Aroniadou VA, Keller A. Mechanisms of LTP induction in rat motor cortex in vitro. Cereb cortex (New York, NY 1991) [Internet]. 1995;5(4):353–62. Available from: http://cercor.oxfordjournals.org/cgi/content/abstract/5/4/353.
68. Trepel C, Racine RJ. GABAergic modulation of neocortical long-term potentiation in the freely moving rat. Synapse [Internet]. 2000 Jan 1;35(2):120–8. Available from: papers3://publication/uuid/926D22E9-B072-497E-9655-27CF2B-D8C40D.

69. Trepel C, Racine RJ. Long-term potentiation in the neocortex of the adult, freely moving rat. Cereb cortex (New York, NY 1991) [Internet]. 1998;8(8):719–29. Available from: http://cercor.oxfordjournals.org/cgi/reprint/8/8/719.
70. Castro-Alamancos MA, Donoghue JP, Connors BW. Different forms of synaptic plasticity in somatosensory and motor areas of the neocortex. J Neurosci [Internet]. 1995;15(7 Pt 2):5324–33. Available from: http://www.jneurosci.org/content/15/7/5324.long.
71. Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol [Internet]. 2004;29(8):1573–8. Available from: https://doi.org/10.1038/sj.npp.1300517.
72. Nitsche MA, Liebetanz D, Fricke K, Frommann K, Lang N, Paulus W, et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci [Internet]. 2004;19(10):2720–6. Available from: http://www3.interscience.wiley.com/journal/118790965/abstract?CRETRY=1&SRETRY=0.
73. Stagg C, Rothman D. No Title [Internet]. Elsevier Inc.; 2014. 1–376 p. Available from: http://elsevier.macops.com/Books/Ecomp.aspx.
74. Stagg CJ, Bestmann S, Constantinescu AO, Moreno Moreno L, Allman C, Mekle R, et al. Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex: investigating human motor cortical excitability and inhibition. J Physiol [Internet]. 2011;589(23):5845–55. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22005678&retmode=ref&cmd=prlinks.
75. Petroff OA, Rothman DL. Measuring human brain GABA in vivo: effects of GABA-transaminase inhibition with vigabatrin. Mol Neurobiol [Internet]. 1998;16(1):97–121. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9554704&retmode=ref&cmd=prlinks.
76. Stagg CJCJ. Magnetic resonance spectroscopy as a tool to study the role of GABA in motor-cortical plasticity. Neuroimage [Internet]. 2014;86(1):19–27. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23333699&retmode=ref&cmd=prlinks.
77. Watanabe T, Shiino A, Akiguchi I. Absolute quantification in proton magnetic resonance spectroscopy is superior to relative ratio to discriminate Alzheimer's disease from Binswanger's disease. Dement Geriatr Cogn Disord [Internet]. 2008;26(1):89–100. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18617735&retmode=ref&cmd=prlinks.
78. Stagg CJJ, Knight S, Talbot K, Jenkinson M, Maudsley AAA, Turner MRR, et al. Whole-brain magnetic resonance spectroscopic imaging measures are related to disability in ALS. Neurology [Internet]. 2013;80(7). Available from: http://www.neurology.org/cgi/doi/10.1212/WNL.0b013e318281ccec.
79. Wardlaw JM, Marshall I, Wild J, Dennis MS, Cannon J, Lewis SC. Studies of acute ischemic stroke with proton magnetic resonance spectroscopy: relation between time from onset, neurological deficit, metabolite abnormalities in the infarct, blood flow, and clinical outcome. Stroke [Internet]. 1998;29(8):1618–24. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9707203&retmode=ref&cmd=prlinks.
80. Signoretti S, Di Pietro V, Vagnozzi R. Transient alterations of creatine, creatine phosphate, N-acetylaspartate and high-energy phosphates after mild traumatic brain injury in the rat. Mol Cell … [Internet]. 2010.; Available from: http://link.springer.com/article/10.1007/s11010-009-0228-9.
81. Vagnozzi R, Signoretti S, Cristofori L, Alessandrini F, Floris R, Isgrò E, et al. Assessment of metabolic brain damage and recovery following mild traumatic brain injury: a multicentre, proton magnetic resonance spectroscopic study in concussed patients. Brain [Internet]. 2010;133(11):3232–42. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20736189&retmode=ref&cmd=prlinks.
82. Brugger S, Davis JM, Leucht S, Stone JM. Proton magnetic resonance spectroscopy and illness stage in schizophrenia–a systematic review and meta-analysis. BPS [Internet]. 2011;69(5):495–503. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21145039&retmode=ref&cmd=prlinks.
83. Bachtiar V, Stagg CJJ. The role of inhibition in human motor cortical plasticity. Neuroscience [Internet]. 2014;278:93–104. Available from: https://doi.org/10.1016/j.neuroscience.2014.07.059
84. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci [Internet]. 2009;29(16):5202–6. Available from: http://www.jneurosci.org/content/29/16/5202.short.
85. Kim S, Stephenson MC, Morris PG, Jackson SR. tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: A 7T magnetic resonance spectroscopy study. Neuroimage [Internet]. 2014 Jan 1;99:237–43. Available from: https://doi.org/10.1016/j.neuroimage.2014.05.070.
86. Patel HJ, Romanzetti S, Pellicano A, Nitsche MA, Reetz K, Binkofski F. Proton magnetic resonance spectroscopy of the motor cortex reveals long term GABA change following anodal transcranial direct current stimulation. Sci Rep. 2019;9(1):1–8.
87. Antonenko D, Thielscher A, Saturnino GB, Aydin S, Ittermann B, Grittner U, et al. Towards precise brain stimulation: is electric field simulation related to neuromodulation? Brain Stimul. 2019;

88. Bachtiar V, Johnstone A, Berrington A, Lemke C, Johansen-Berg H, Emir U, et al. Modulating regional motor cortical excitability with noninvasive brain stimulation results in neurochemical changes in bilateral motor cortices. J Neurosci [Internet]. 2018;38(33):7327–36. Available from: http://www.jneurosci.org/lookup/doi/10.1523/JNEUROSCI.2853-17.2018.
89. Floyer-Lea A, Wylezinska M, Kincses T, Matthews PM. Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. J Neurophysiol [Internet]. 2006;95(3):1639–44. Available from: https://doi.org/10.1152/jn.00346.2005.
90. Kolasinski J, Hinson EL, Divanbeighi Zand AP, Rizov A, Emir UE, Stagg CJ. The dynamics of cortical GABA in human motor learning. J Physiol. 2019;597(1):271–82.
91. O'Shea J, Boudrias M-HM-HMH, Stagg CJCJ, Bachtiar V, Kischka U, Blicher JUJU, et al. Predicting behavioural response to TDCS in chronic motor stroke. Neuroimage [Internet]. 2014;85(3):924–33. Available from: https://doi.org/10.1016/j.neuroimage.2013.05.096
92. Petitet P, O'Reilly JX, Goncalves AM, Salvan P, Kitazawa S, Johansen-Berg H, et al. Causal explanation of individual differences in human sensorimotor memory formation. bioRxiv. 2018;255091.
93. Rango M, Cogiamanian F, Marceglia S, Barberis B, Arighi A, Biondetti P, et al. Myoinositol content in the human brain is modified by transcranial direct current stimulation in a matter of minutes: a 1H-MRS study. Magn Reson Med [Internet]. 2008;60(4):782–9. Available from: http://www3.interscience.wiley.com/journal/121420961/abstract.
94. Tremblay S, LaFleur L-P, Proulx S, Beaulé V, Latulipe-Loiselle A, Doyon J, et al. The effects of bi-hemispheric M1-M1 transcranial direct current stimulation on primary motor cortex neurophysiology and metabolite concentration. Restor Neurol Neurosci. 2016;34(4):587–602.
95. Ryan K, Wawrzyn K, Gati JS, Chronik BA, Wong D, Duggal N, et al. 1H MR spectroscopy of the motor cortex immediately following transcranial direct current stimulation at 7 tesla. PLoS One. 2018;13(8):1–14.
96. Clark VP, Coffman BA, Trumbo MC, Gasparovic C. Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a 1H magnetic resonance spectroscopy study. Neurosci Lett [Internet]. 2011;500(1):67–71. Available from: https://doi.org/10.1016/j.neulet.2011.05.244
97. Mezger E, Rauchmann B, Wörsching J, Mortazavi M, Brunoni A, Ertl-Wagner B, et al. Modulation of brain metabolites by prefrontal transcranial direct current stimulation (tDCS) in healthy subjects – the double-blinded hypothesis. Encéphale. 2019;45:S77–8.
98. Hone-Blanchet A, Edden RA, Fecteau S. Online effects of transcranial direct current stimulation in real time on human prefrontal and striatal metabolites. Biol Psychiatry. 2016;80(6):432–8.
99. Bouchard AE, Dickler M, Renauld E, Lenglos C, Ferland F, Edden RA, et al. The impact of brain morphometry on tDCS effects on GABA levels. Brain Stimul Basic Transl Clin Res Neuromodulation. 2020;13(2):284–6.
100. Salvador R, Wenger C, Miranda PC. Investigating the cortical regions involved in MEP modulation in tDCS. Front Cell Neurosci [Internet]. 2015 Jan 1;9. Available from: http://www.frontiersin.org/Journal/Abstract.aspx?s=156&name=cellular_neuroscience&ART_DOI=10.3389/fncel.2015.00405.
101. Evans C, Bachmann C, Lee J, Gregoriou E, Ward N, Bestmann S. Dose-controlled tDCS reduces electric field intensity variability at a cortical target site. Brain Stimul. 2019;
102. Bestmann S, Ward N. Are current flow models for transcranial electrical stimulation fit for purpose? Brain Stimul. 2017;10(4):865–6.
103. Jog M V, Smith RX, Jann K, Dunn W, Lafon B, Truong D, et al. In-vivo imaging of magnetic fields induced by Transcranial Direct Current Stimulation (tDCS) in human brain using MRI. Sci Rep [Internet]. 2017 Jun 25;1–10. Available from: https://doi.org/10.1038/srep34385
104. Jog M, Jann K, Yan L, Huang Y, Parra L, Narr K, et al. Concurrent imaging of markers of current flow and neurophysiological changes during tDCS. Front Neurosci. 2020;14:374.
105. Joy M, Scott G, Henkelman M. In vivo detection of applied electric currents by magnetic resonance imaging. Magn Reson Imaging. 1989;7(1):89–94.
106. Jeong WC, Sajib SZK, Katoch N, Kim HJ, Kwon OI, Woo EJ. Anisotropic conductivity tensor imaging of in vivo canine brain using DT-MREIT. IEEE Trans Med Imaging. 2017;36(1):124–31.
107. Provencher SW. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed [Internet]. 2001;14(4):260–4. Available from: http://onlinelibrary.wiley.com/doi/10.1002/nbm.698/abstract.

tDCS and Functional Connectivity

9

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9.1 Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive transcranial brain stimulation (NTBS) technique in which the cortical excitability of the human brain is modulated by weak direct currents applied via scalp electrodes [37]. Numerous studies have been conducted with both healthy subjects and patients with neurological disorders (such as stroke and Parkinson's diseases) and psychiatric disorders (such as major depressive disorder [MDD] and schizophrenia) [36, 50, 72, 73]. However, the mechanisms of tDCS effect are not fully understood. Therefore, one way is to investigate the modulation of functional connectivity by combining tDCS with brain imaging techniques.

Functional magnetic resonance imaging (fMRI) measures the blood-oxygen-level-dependent (BOLD) signal which is a proxy of neuronal activation [58]. In order to evaluate the tDCS effect, functional connectivity is studied either task-based or during resting states. Task-based functional connectivity can be investigated by administering an appropriate task according to the respective research question during fMRI. The resting-state fMRI (rsfcMRI), on the other hand, is used to measure the functional integration of neural networks when participants are asked not to follow any particular thoughts or tasks. During the resting state, the human brain still exhibits organized activity across distant regions, and this activity can be recorded by changes in fluctuations of the BOLD signal [95]. In the resting state, previous studies have used seed-based analysis, independent component analysis (ICA), and graph analysis to extract major networks of activation, such as default mode network (DMN) [91], salience network [86], and central executive network [93]. The DMN is one of the most frequently investigated resting-state network in clinical research such as Alzheimer's disease [12], schizophrenia [62], and major depressive disorder [32]. The DMN locates its major hubs in medial prefrontal cortex, posterior cingulate cortex, and angular gyrus [3]. These regions are significantly less activated while performing cognitive tasks in comparison with resting state [85], and it has been suggested that they are related to self-referential thinking, theory of mind, and moral decisions [11, 80]. Wörsching et al. [102] from our group published a comprehensive review on prior research combining prefrontal tDCS and multimodal MRI.

In this chapter, we critically review the effects of motor cortex as well as prefrontal tDCS on functional connectivity in healthy subjects and patients with neurological and psychiatric disorders using both resting-state and task-based fMRI paradigms.

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9.2 Motor Cortex

9.2.1 Effects of Anodal tDCS

tDCS of motor regions may modulate motor cortex excitability including motor evoked potentials [51] and motor performance [47]. For example, anodal tDCS applied to the primary motor cortex (M1) shows an increase of neuronal activity in the ipsilateral hemisphere not only directly at M1 [49] but also in premotor regions [83] in the primary sensorimotor cortex (SM1) [40, 48] and in the supplementary motor area (SMA) [49]. However, the neuronal effect of motor tDCS is not only observed in regions close to the electrodes but also in distant areas via trans-synaptic paths. For example, tDCS with the anode over M1 modulates neuronal activity also at neighboring regions, that is, inducing an increase of activity within the parietal cortex [84]. Moreover, anodal M1 tDCS may reduce functional connectivity between SM1 and the rest of the brain [84] and increase functional connectivity between M1 and thalamus [83]. These findings suggest that tDCS exerts effects on corticocortical connectivity. Thus, tDCS appears to be an effective mediator for modulating brain function not only focally under the electrodes but also within networks involving distant intracortical as well as subcortical regions [38].

Finally, but importantly, it should be mentioned that the anodal stimulation side of tDCS does not always have a facilitating effect. For example, Amadi et al. [2] reported no significant changes in resting-state connectivity with anodal M1 tDCS. Furthermore, Antal et al. [4] found a reduced BOLD signal at the supplementary motor area (SMA) during finger tapping. Although tDCS with the anode over motor regions is a topic, which has been rather extensively studied compared to others, its effects are not yet fully understood and need further research.

9.2.2 Effects of Cathodal tDCS

Conversely, it is hypothesized that tDCS with the cathode over motor cortex regions exerts opposite effects to anodal tDCS, that is, reduces motor cortical excitability. Cathodal tDCS over the left motor cortex leads to a decrease in neuronal activity at the underlying area, as is the case with SMA [6]. Moreover, a global decrease in functional connectivity [6] as well as between the cortical and subcortical areas [82] are reported. However, as it was the case for anodal stimulation, the direction of the effect is not always the same. Cathodal tDCS on M1 could also increase resting-state functional connectivity on both motor and non-motor networks. For example, Amadi et al. [2] showed that cathodal left M1 tDCS leads to an increase of BOLD signal between the left- and right-hand regions of M1 and between left and right supplementary motor area (SMA). Additionally, increased functional connectivity within motor and default mode network was also observed, supporting the hypothesis that diminished top-down control may contribute to the impaired motor performance induced by cathodal tDCS [2]. Another study suggested that cathodal left M1 tDCS could enhance regional connectivity in the dorsolateral-M1 region [83].

9.2.3 Effects of Dual tDCS

In addition to unilateral stimulation of motor regions, bihemispheric or "dual" tDCS of left and right M1 has been investigated as well, for example, combined positioning of the anode over the nondominant motor cortex and of the cathode over the dominant motor cortex. This approach was found to improve performance significantly more than unihemispheric or sham tDCS [97] and facilitates motor recovery in chronic stroke patients [57]. Bihemispheric tDCS is thought to upregulate excitability of ipsilesional motor regions via anodal stimulation while concurrently downregulating contralesional motor regions via cathodal stimulation after stroke [57]. Therefore, Lindenberg et al. [56] investigated the effect of bihemispheric tDCS impacts on motor system activity and connectivity. Measuring neural correlates of dual and unihemispheric tDCS in healthy older subjects, they found that dual but not only anodal tDCS enhanced resting-state

connectivity of the left dorsal posterior cingulate cortex. Furthermore, dual tDCS showed stronger activations in bilateral M1 than anodal tDCS alone, regardless of whether participants used their left or right hand during the motor task. These results indicated that bihemispheric tDCS can induce complex networks modulations on left and right M1, including interhemispheric interactions and areas associated with motor control in the dorsal posterior cingulate cortex [56]. A further study showed that bilateral M1 tDCS (anode over right M1, cathode over left M1) induces the decrease in interhemispheric functional connectivity during stimulation. On the other hand, an increase in intracortical functional connectivity within right M1 was also observed [87]. These studies suggest that the dual tDCS is a potentially more powerful method in order to modulate functional connectivity.

9.3 Prefrontal tDCS

The prefrontal cortex plays a pivotal role in executing complex cognitive functions. Moreover, it is considered as a part of brain that, in addition to many functions, also determines the personality of individuals [67]. Previous studies have shown that anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) can improve performance in various cognitive domains, including verbal skills, executive functions, and working memory in healthy subjects [16, 30, 35, 99]. Though we can observe the effects of prefrontal tDCS on multiple functional levels, the understanding of its neurophysiological action is still limited.

9.3.1 Prefrontal tDCS and Cognitive/Executive Functions

Prefrontal tDCS has been shown to be effective in modulating higher cognitive and executive performance such as verbal fluency [15], decision-making [19], and risk behavior [23]. Nevertheless, the neural basis of functional improvement remains unclear. Several combined tDCS-fMRI studies have addressed this neurofunctional relationship. For example, it is known that tDCS over the DLPFC modulates risk-taking behavior [8, 23, 103]. Weber et al. [99] showed that dual DLPFC tDCS (anode over F4 and cathode over F3 according to the 10–20-EEG system) reduces connectivity between right ACC and the rest of the brain, and the right ACC activity is positively correlated with risk behavior. Another example is anodal tDCS over the inferior frontal gyrus (IFG), that is, a region controlling the semantic retrieval process [96], which improves verbal function [52, 64]. The neurofunctional correlation of verbal improvement seems to be related to the reduced activity observed in the prefrontal cortex, especially at IFG, during the semantic word generation task [66]. Interestingly, anodal IFG tDCS reduces the hyperactivity in bilateral frontal cortices in elderly subjects. This may be associated with a neuronal mechanism corresponding to the temporal reversal of age-related verbal functional decline [65]. Furthermore, increased connectivity between IFG and other major hubs in language networks (such as bilateral inferior parietal, dorsolateral, medial prefrontal regions, and the left middle temporal gyrus) may represent a neuronal mechanism of language performance enhancement [66].

Working memory (WM) in healthy subjects showed a small but significant improvement after anodal tDCS of the left DLPFC, as suggested by a recent meta-analysis of 31 studies in healthy volunteers, when stimulation was coupled with WM training [61]. In contrast, stimulation alone did not show a significant difference after correction of the publication bias. In an early neurophysiological study, we observed similar effects, that is, a significant reduction of mean current densities for the delta band in the left subgenual PFC, the anterior cingulate, and the left medial frontal gyrus, in parallel with effects on n-back performance at a higher working memory load (2-back), while the less challenging memory performance at 0- and 1-back did not show superiority over sham treatment [44, 45].

9.3.2 Prefrontal tDCS and Resting-State Network

Several researchers investigated whether prefrontal tDCS modulates resting-state network connectivity as well. For example, [44, 45] showed that anodal tDCS over the left DLPFC increases functional connectivity in both the default mode network (DMN) and in left and right frontoparietal network (FPN). Likewise, when anodal electrode was placed over either the left or right DLPFC, DMN components showed reduced synchrony, whereas the anticorrelated network (AN) showed increased synchrony [80]. The AN is associated with cognitive processing when attention to the external environment is required, and it is known to anticorrelate with DMN activity [28, 70]. Furthermore, Park et al. [79] also found that left DLPFC anodal tDCS increases DLPFC connectivity to the right hemisphere and decreases DLPFC connectivity to the brain regions around the stimulation site in the left hemisphere. These findings suggest that prefrontal tDCS modulates resting-state functional connectivity at the primary stimulation site and at connected brain regions. Wörsching et al. [100] investigated a priori hypotheses on specific effects of prefrontal tDCS montage using multimodal fMRI in 32 healthy participants. After tDCS with an F3 cathode/ F4 anode montage, functional MRI connectivity decreased in the medial part of the left PFC at rest [100]. In addition, regional brain activity during a delayed working memory-retrieval task (DWM) decreased in this area more strongly after negative than neutral distraction, and responses to DWM tasks were faster, regardless of distractor type [100] (Fig. 9.1).

9.4 Therapeutic Application of tDCS

tDCS has been proposed as an effective intervention in alleviating symptoms of neurological disorders such as Parkinson's disease [29] and chronic pain [5] as well as psychiatric disorders such as depression [71], schizophrenia [9], and addiction [59]. However, despite its enormous potential, tDCS still requires many efforts such as large randomized controlled clinical trials (RCTs) and individualized development of NTBS treatment to achieve a broader clinical implementation. Individualization of treatment is an important and challenging factor in this regard, as there are distinct individual response patterns to frontal tDCS due to, for example, individual anatomical features, gender, or age. One reason, among many others, is that we do not understand the neural underpinnings of stimulation-enhanced neuromodulation in relation to the individual pathology. Therefore, combined tDCS-fMRI studies need to be extended to clinical populations in order to investigate the mechanisms of tDCS treatment in comparison of health and disease.

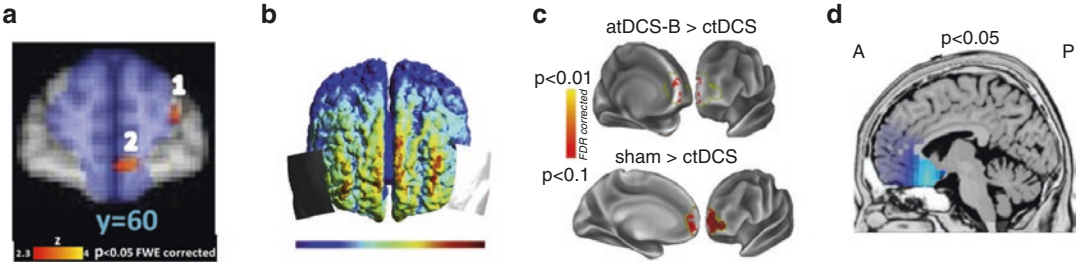

Fig. 9.1 In pilot studies, we observed direct effects of prefrontal tDCS on medial prefrontal areas. Shown here for (**a**) functional MRI connectivity at rest [45], (**b**) simulation in depressed patients using T1-weighted anatomies [14], (**c**) functional MRI connectivity at rest with different tDCS montages [100], and (**d**) EEG at rest [44]. Electrode localization for (**a**) F3-Fp2, (**b**) F3-F4, F4-F3, (**c**) F3-F4, and (**d**) F3-Fp2, 2 mA intensity, 20 minutes stimulation

9.4.1 Neurological Disorders

Stroke

tDCS over motor cortex can be used to treat neurological patients with motor disorders. For example, stroke patients benefit more from rehabilitation of motor skills when dual tDCS (anode over the lesion and cathode over the non-lesion hemisphere) is administered over M1 during motor training [53, 55]. Such effects were reported to be maintained for intervals of 1 week [55] up to several months [1], and improvement of performance may even reach out to an untrained task as well [55]. However, as to the neuronal mechanisms of this effect, Lefebvre et al. [55] suggested that the permanent behavioral enhancement induced by tDCS is associated with activity of the ipsilesional motor skill learning network, which has a main hub in premotor regions [27, 33]. More recently, it was reported that tDCS increases activity in the ipsilesional motor and premotor cortex during movement of the affected hand [1]. Additionally, Lefebvre et al. [54] showed that connectivity between M1 and the dorsal premotor cortex (PMd) is stronger in the lesioned hemisphere before dual tDCS treatment, but enhanced in the *non-lesion* site after treatment. Moreover, functional connectivity appears to increase between somatomotor network regions as well as within motor and premotor cortex [54]. Motor tDCS studies overall show both local effect within the motor cortex and network effect between motor regions and other areas as discussed.

Language Deficits

The interest in using tDCS for neurorehabilitation of stroke patients has led tDCS-fMRI research also to another target region, that is, Broca's area. Broca's area is located around the posterior region of left inferior frontal gyrus and is involved in speech production [7]. tDCS over Broca's area has been found to improve naming performance of aphasia patients [35, 43, 63]. Neuronal correlates of these functional changes were investigated by several researchers, leading to heterogeneous results at first glance. Holland et al. [35] observed that anodal tDCS over the left inferior frontal cortex during an overt picture-naming fMRI study reduced neuronal activity in Broca's area while performance in naming pictures improved in aphasic stroke patients. In contrast, Marangolo et al. [63] showed that bilateral tDCS (anode over left Broca) with simultaneous speech training increased functional connectivity in the left hemisphere of chronic stroke patients. These results may be explained by an interaction between neural priming and main effects [20]. In one study [35], the functional scan was obtained during task performance, whereas Marangolo et al. [63] investigated resting-state fMRI after a 3-week treatment period. One may hypothesize that neuronal activity decreased in the study by Holland et al. [35] due to repeated picture naming tasks, and this regional priming effect transcended the global hemispheric effect of anodal tDCS which was shown by Marangolo et al. [63]. Either way, these findings provide converging evidence from functional imaging and behavioral data that tDCS exerts effects on regional brain function at lesion sites, which may improve patients' cognitive recovery.

Patients with Parkinson's disease (PD) may also have verbal fluency problems such as phonemic and semantic fluency deficits due to dissociable processes mediated by different cortico-striatal circuits involving left frontal and temporal regions [94]. Therefore, Pereira et al. [81] investigated the differential effects induced by tDCS (2 mA, 20 min) over frontal and temporo-parietal areas on verbal fluency networks in patients with PD. Patients underwent a verbal fluency paradigm inside an fMRI scanner and received anodal tDCS over left DLPFC and temporo-parietal cortex (TPC) in a counterbalanced order with the cathode placed over the right supraorbital area. ICA showed that functional connectivity in verbal fluency and task-related deactivation networks is significantly better with tDCS over left DLPFC than with TPC. In addition, DLPFC tDCS also improved performance on the phonemic fluency task.

9.4.2 Psychiatric Disorders

Schizophrenia

tDCS has been demonstrated to exert therapeutic effects in a number of psychiatric disorders. Several research groups have combined tDCS with neuroimaging techniques to investigate the mechanisms of its putative therapeutic action. For example, the application of tDCS as treatment of negative symptoms and auditory verbal hallucination (AVH) in schizophrenia is a field that is relatively well tested. With regard to negative symptoms, Orlov et al. [76] showed that anodal tDCS over the left DLPFC (2 mA, 30 min, cathode over the right supraorbital area) in schizophrenia patients induces a positive correlation between increased activation in the medial frontal cortex and consolidated working memory (n-back) performance 24 hours after tDCS. Regarding executive functions, behavioral improvement with Stroop task was associated with reduced activity in the anterior cingulate cortex after prefrontal tDCS, which is known for response conflict processing [46, 68]. Auditory hallucinations, which are common positive symptoms of schizophrenia, are known to be associated with abnormal hyperactivity in the left temporo-parietal areas (Wernicke's area), left inferior frontal areas (Broca's area), and in their right homologues [41]. Several studies have shown that cathodal tDCS over the left temporo-parietal junction (TPJ) and anode over the left DLPFC may reduce AVH symptom in schizophrenia patients [24, 89, 90]. The neural representation of AVH reported by Mondino et al. [69] included specific areas for inner speech production and monitoring; in particular, a decrease in resting-state functional connectivity between left TPJ and left anterior insula as well as right inferior frontal gyrus and an increase between left TPJ and left angular gyrus, left DLPFC, and precuneus was observed. A study on the effect of prefrontal tDCS in schizophrenia with predominantly negative symptoms investigated the effect of prefrontal tDCS on both negative and positive symptoms under double-blind conditions. Clinically, there were remarkable effects in the group receiving active tDCS treatment [78]. The results of this proof-of-concept study show that prefrontal tDCS added to stable antipsychotic medication can improve negative symptoms of schizophrenia in severely affected patients, as demonstrated by the significant change in scores on the Scale for the Assessment of Negative Symptoms (SANS). These effects were associated with a change in intrinsic resting network activity, particularly an increase in functional connectivity in the insular cortex [78]. However, it must be added that the sample size was very small, and the gender distribution differed between active and sham tDCS.

Major Depressive Disorder

Numerous fMRI studies focused on functional connectivity at rest in major depressive disorder (MDD) patients. Bidirectional changes of connectivity in distinct regions, circuits, and networks have been reported compared to controls. For a therapeutic application of NIBS, that is, particularly rTMS as focal stimulation approach, these alterations were conceptualized as guidance for target sites on the group as well as on the individual level [21, 92]. In contrast, tDCS as nonfocal means for cortex stimulation may need another approach, where functional targeting is achieved by other specific interventions (e.g., cognitive tasks). For instance, working memory and sustained attention training are common cognitive tasks for depression treatment, since these tasks are associated with DLPFC activity [10]. In the first place, however, connectivity changes elicited by tDCS need to be better understood on the background of specific pathophysiological changes observed in MDD.

Some regions, such as the basal amygdala, show reduced functional connectivity with the medial orbitofrontal cortex, which is involved in reward; and the dorsolateral amygdala had relatively reduced connectivity with the lateral orbitofrontal cortex in MDD [17]. However, numerous studies suggest that the prefrontal cortex (PFC) is one of the most promising areas for connectivity-based target sites for NTBS. Among many findings, decreased whole brain functional connectivity homogeneity as proxy to voxel-wise changes of functional connectivity patterns

between the medial prefrontal cortex (MPFC) and the left angular gyrus has been reported in MDD [98], as well as a reduced default mode network (DMN) connectivity to the frontal pole in late-life depression [31]. Correlation coefficients also suggested an increased connectivity at the dorsomedial prefrontal cortex (DMPFC) in patients with MDD when compared to healthy subjects [88].

Very recently, two studies investigated gray matter (GM) volume as well as functional connectivity of the PFC in relation to the antidepressant response to tDCS within a large randomized placebo-controlled study, that is, the Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) [13, 14]. The main finding was a positive association between improvement of depression after treatment compared to baseline and the size of the GM volume in PFC subregions, which was only observed in the tDCS, but neither in the escitalopram nor in the placebo group [14].

In contrast, there was no significant association between resting-state connectivity within a priori defined regions of the PFC and the change in depression scores after tDCS treatment. A possible interpretation for these divergent findings would be that rsfcMRI rather reflects "brain states" [104] of the patients, while structural MRI data may provide trait measures. However, further interpretation is hampered by the small sample size of the cohort.

9.5 Effect Variability and Test-Retest Reliability of tDCS

Test-retest reliability (TRT) and variability of tDCS-induced effects has been one of the major topics of discussion. Opitz et al. [75] demonstrated the importance of precise tDCS electrode placement and suggested that less than 1 cm accuracy is required in order to achieve a sufficient reliability. Padberg et al. [77] employed a specially manufactured cap in order to assure the precise electrode placement over the DLPFC for a multicenter trial. However, even though accuracy of the electrode positions is ensured, inter- and intraindividual variability can be affected by many other factors too.

In order to measure the variability of tDCS effects on M1 excitability, standardized MEPs (i.e., peak-to-peak MEP amplitude of 1 mV prior to tDCS or fixed output of the stimulator) or recruitment curves were compared after each tDCS session. With this approach, a significant interindividual [18, 34] as well as intraindividual variability [18, 22] of MEP amplitudes were observed. However, Madhavan et al. [60] and Jamil et al. [39] reported a higher reliability (i.e., intraclass correlation coefficients [ICC] of 0.6–0.9) for intraindividual responses after 1 mA anodal tDCS.

For nonmotor regions, the assessment of intra- or interindividual variability is less established, and more complex measures, for example, modulation parameters for functional connectivity, had to be introduced. For example, Wörsching et al. [101] assessed individual responses to an active prefrontal tDCS over the three test sessions. This study showed a low test-retest reliability for the effects of 2 mA tDCS in terms of voxel-wise ICC of post-tDCS maps between sessions. Moreover, the distribution of voxel-wise ICC in the region of interest (ROI) analysis was shifted to lower TRT reliability after active, but not after sham tDCS. This result indicates that the neuromodulatory effects evoked by active tDCS are intra- and interindividually variable and may depend on brain state affected by various components such as time, mood, and hormone level. In sum, intra- as well as interindividual variation of tDCS effects have been reported and the underpinnings of this variability should be a focus for future research. This variation also hinders the use of tDCS paradigms for longitudinal assessment and a direct comparison of protocols [42]. Moreover, it emphasizes the need for even more standardized methods (e.g., by including electric field parameters) to account for this uncertainty. Notably, Madhavan et al. [60] reported that even lower interindividual variability and high test-retest reliability does not account for the reliability of tDCS clinical efficacy.

In order to account for these variabilities and to improve reproducibility, the importance of

open science needs to be emphasized. As technology improves, Platform as a Service (PaaS) products enable to convey software in a package (called container) using an open-source standard data interchange format, such as JSON. By sharing all available data, such as the version of the used analysis software and the exact computational method through the frame of open science, we may expect higher reproducibility of the each tDCS effect in the future.

9.6 Association Between Response Patterns and Baseline MRI Markers

Structural and functional MRI measures have been used to identify markers of clinical response to tDCS as individual prediction of therapeutic effects as an unmet need in the field. As outlined above, examples include gray matter volumes, cortical thickness, and DLPFC activation. The findings of Bulubas et al. [14] demonstrated that the antidepressant response to tDCS in the ELECT-TDCS trial was related to GM volumes of a left-sided PFC region at baseline. This relationship was intervention-specific for tDCS, that is, neither observed for escitalopram nor placebo. This finding converges with data from other pilot studies investigating such associations. The relationship with cortical thickness was also assessed by implementing a disruptive left prefrontal stimulation during a decision-making task [25, 26]. Filmer et al. [26] showed that an increased cortical thickness at the middle frontal sulcus and inferior frontal gyrus as well as a decreased thickness at the inferior frontal triangular gyrus were related to a higher disruption of the learning task after prefrontal anodal, but not cathodal stimulation. Furthermore, Filmer et al. [25] showed that performance inconsistency during anodal stimulation is not only related to cortical thickness in inferior frontal gyrus but also to prefrontal neurochemical response patterns measured by magnetic resonance spectroscopy. These studies show that both cortical anatomy and neurochemical difference influence individual variability in the effect of tDCS to the behavior.

Another example is the study by Nord et al. [74] who conducted task fMRI prior to prefrontal tDCS treatment in MDD. Greater activation of the left PFC during a working memory task (i.e., n-back) at baseline was correlated with a larger improvement of depression scores after tDCS treatment. This research line may develop tDCS toward a personalized treatment with individual adjustment of tDCS parameters, such as electrode localization and stimulation intensity, and thus improve its therapeutic effectiveness.

9.7 Conclusions and Future Directions

This chapter has given an overview on experimental and clinical studies that investigated changes of functional MRI connectivity in relation to nonfocal brain stimulation with tDCS. In the majority of studies, tDCS was used to induce changes in functional connectivity both at primary stimulation sites and connected brain regions. The results of these studies provide us with a better understanding of the brain's intrinsic networks and may serve to improve therapeutic effects of NTBS.

While most studies have focused on motor cortex and PFC regions, data for other brain areas (e.g., visual cortex) or other functional domains or systems (e.g., memory, executive, and visual) are very limited. In numerous studies, tDCS has been found to lead to an amelioration of clinical symptoms in neurological and psychiatric disorders; however, very few studies have included neuroimaging in order to elucidate mechanisms of tDCS action on a neuronal and system level. Further limitations we have identified in the field of functional connectivity research on tDCS are small sample sizes together with a large intra- and inter-individual variability of effects, a lack of test-retest designs, and active control conditions for comparison as well as systematic studies on the impact of stimulation parameters for establishing

dose-response relationships. Nevertheless, combining tDCS with multimodal neuroimaging appears to be a promising avenue for developing NTBS toward an effective array of interventions for an individualized treatment in neuropsychiatric disorders.

References

1. Allman C, Amadi U, Winkler AM, Wilkins L, Filippini N, Kischka U, Stagg CJ, Johansen-Berg H. Ipsilesional anodal tDCS enhances the functional benefits of rehabilitation in patients after stroke. Sci Transl Med. 2016;8(330):330re1. https://doi.org/10.1126/scitranslmed.aad5651
2. Amadi U, Ilie A, Johansen-Berg H, Stagg CJ. Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. NeuroImage. 2014;88:155–61. https://doi.org/10.1016/j.neuroimage.2013.11.037
3. Andrews-Hanna JR, Smallwood J, Spreng RN. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann N Y Acad Sci. 2014;1316(1):29–52. https://doi.org/10.1111/nyas.12360
4. Antal A, Polania R, Schmidt-Samoa C, Dechent P, Paulus W. Transcranial direct current stimulation over the primary motor cortex during fMRI. NeuroImage. 2011;55(2):590–6. https://doi.org/10.1016/j.neuroimage.2010.11.085
5. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short Intracortical inhibition. J Pain Symptom Manag. 2010;39(5):890–903. https://doi.org/10.1016/j.jpainsymman.2009.09.023
6. Baudewig J, Nitsche MA, Paulus W, Frahm J. Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med. 2001;45(2):196–201. https://doi.org/10.1002/1522-2594(200102)45:2<196::AID-MRM1026>3.0.CO;2-1
7. Blank SC, Scott SK, Murphy K, Warburton E, Wise RJS. Speech production: Wernicke, Broca and beyond. Brain. 2002;125(8):1829–38. https://doi.org/10.1093/brain/awf191
8. Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug Alcohol Depend. 2010;112(3):220–5. https://doi.org/10.1016/j.drugalcdep.2010.06.019
9. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny M-F, Saoud M, Mechri A, Poulet E. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatr. 2012;169(7):719–24. https://doi.org/10.1176/appi.ajp.2012.11071091
10. Brunoni AR, Boggio PS, De Raedt R, Benseñor IM, Lotufo PA, Namur V, Valiengo LCL, Vanderhasselt MA. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–9. https://doi.org/10.1016/j.jad.2014.03.026
11. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008;1124:1–38. https://doi.org/10.1196/annals.1440.011
12. Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, Mintun MA. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci Off J Soc Neurosci. 2005;25(34):7709–17. https://doi.org/10.1523/JNEUROSCI.2177-05.2005
13. Bulubas L, Padberg F, Bueno P, Duran F, Busatto G, Amaro E Jr, Benseñor I, Lotufo P, Goerigk S, Gattaz W, Keeser D, Brunoni AR. Prefrontal resting state connectivity and antidepressant response: no associations in the ELECT-TDCS trial. Europ Arvh Psychiatr Clin Neurosci. 2020; https://doi.org/10.1007/s00406-020-01187-y. Epub ahead of print
14. Bulubas L, Padberg F, Bueno PV, Duran F, Busatto G, Amaro E, Benseñor IM, Lotufo PA, Goerigk S, Gattaz W, Keeser D, Brunoni AR. Antidepressant effects of tDCS are associated with prefrontal gray matter volumes at baseline: evidence from the ELECT-TDCS trial. Brain Stimul. 2019;12(5):1197–204. https://doi.org/10.1016/j.brs.2019.05.006
15. Cattaneo Z, Pisoni A, Papagno C. Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. Neuroscience. 2011;183:64–70. https://doi.org/10.1016/j.neuroscience.2011.03.058
16. Cerruti C, Schlaug G. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci. 2009;21(10):1980–7. https://doi.org/10.1162/jocn.2008.21143
17. Cheng W, Rolls ET, Qiu J, Xie X, Lyu W, Li Y, Huang C-C, Yang AC, Tsai S-J, Lyu F, Zhuang K, Lin C-P, Xie P, Feng J. Functional connectivity of the human amygdala in health and in depression. Soc Cogn Affect Neurosci. 2018;13(6):557–68. https://doi.org/10.1093/scan/nsy032
18. Chew T, Ho K-A, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. Brain Stimul. 2015;8(6):1130–7. https://doi.org/10.1016/j.brs.2015.07.031
19. Clark L, Cools R, Robbins TW. The neuropsychology of ventral prefrontal cortex: decision-making

and reversal learning. Brain Cogn. 2004;55(1):41–53. https://doi.org/10.1016/S0278-2626(03)00284-7
20. de Zubicaray GI, McMahon KL. Auditory context effects in picture naming investigated with event-related fMRI. Cogn Affect Behav Neurosci. 2009;9(3):260–9. https://doi.org/10.3758/CABN.9.3.260
21. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ, Liston C. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28–38. https://doi.org/10.1038/nm.4246
22. Dyke K, Kim S, Jackson GM, Jackson SR. Intra-subject consistency and reliability of response following 2 mA transcranial direct current stimulation. Brain Stimul. 2016;9(6):819–25. https://doi.org/10.1016/j.brs.2016.06.052
23. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci. 2007;27(46):12500–5. https://doi.org/10.1523/JNEUROSCI.3283-07.2007
24. Ferrucci R, Bortolomasi M, Tessari E, Bellomo E, Trabucchi L, Gainelli G, Priori A. EPA-1392 – transcranial direct-current stimulation (tDCS) in patients with schizophrenia. Eur Psychiatry. 2014;29:1. https://doi.org/10.1016/S0924-9338(14)78600-6
25. Filmer HL, Ballard T, Ehrhardt SE, Bollmann S, Shaw TB, Mattingley JB, Dux PE. Dissociable effects of tDCS polarity on latent decision processes are associated with individual differences in neurochemical concentrations and cortical morphology. Neuropsychologia. 2020;141:107433. https://doi.org/10.1016/j.neuropsychologia.2020.107433
26. Filmer HL, Ehrhardt SE, Shaw TB, Mattingley JB, Dux PE. The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology. NeuroImage. 2019;196:41–8. https://doi.org/10.1016/j.neuroimage.2019.04.026
27. Floyer-Lea A, Matthews PM. Distinguishable brain activation networks for short- and long-term motor skill learning. J Neurophysiol. 2005;94(1):512–8. https://doi.org/10.1152/jn.00717.2004
28. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005;102(27):9673. https://doi.org/10.1073/pnas.0504136102
29. Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, Silva MTA, Barbosa ER, Nitsche MA, Pascual-Leone A. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov Disord. 2006;21(10):1693–702. https://doi.org/10.1002/mds.21012
30. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MTA, Paulus W, Pascual-Leone A. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005;166(1):23–30. https://doi.org/10.1007/s00221-005-2334-6
31. Gandelman JA, Albert K, Boyd BD, Park JW, Riddle M, Woodward ND, Kang H, Landman BA, Taylor WD. Intrinsic functional network connectivity is associated with clinical symptoms and cognition in late-life depression. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4(2):160–70. https://doi.org/10.1016/j.bpsc.2018.09.003
32. Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. Biol Psychiatry. 2011;70(4):327–33. https://doi.org/10.1016/j.biopsych.2011.02.003
33. Hikosaka O, Nakamura K, Sakai K, Nakahara H. Central mechanisms of motor skill learning. Curr Opin Neurobiol. 2002;12(2):217–22. https://doi.org/10.1016/S0959-4388(02)00307-0
34. Horvath JC, Vogrin SJ, Carter O, Cook MJ, Forte JD. Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials found to be highly variable within individuals over 9 testing sessions. Exp Brain Res. 2016;234(9):2629–42. https://doi.org/10.1007/s00221-016-4667-8
35. Holland R, Leff AP, Josephs O, Galea JM, Desikan M, Price CJ, Rothwell JC, Crinion J. Speech facilitation by left inferior frontal cortex stimulation. Curr Biol. 2011;21(16):1403–7. https://doi.org/10.1016/j.cub.2011.07.021
36. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol. 2006;5(8):708–12. https://doi.org/10.1016/S1474-4422(06)70525-7
37. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology. 2005;64(5):872–5. Scopus. https://doi.org/10.1212/01.WNL.0000152986.07469.E9
38. Jamil A, Batsikadze G, Kuo HI, Meesen RLJ, Dechent P, Paulus W, Nitsche MA. Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: an fMRI study. Hum Brain Mapp. 2020;41(6):1644–66. https://doi.org/10.1002/hbm.24901
39. Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, Nitsche MA. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol. 2017;595(4):1273–88. https://doi.org/10.1113/JP272738

40. Jang SH, Ahn SH, Byun WM, Kim CS, Lee MY, Kwon YH. The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neurosci Lett. 2009;460(2):117–20. https://doi.org/10.1016/j.neulet.2009.05.037
41. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatr. 2011;168(1):73–81. https://doi.org/10.1176/appi.ajp.2010.09101522
42. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42(9):1791–800. https://doi.org/10.1017/S0033291711003059
43. Kang EK, Kim YK, Sohn HM, Cohen LG, Paik N-J. Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. Restor Neurol Neurosci. 2011;29(3):141–52. https://doi.org/10.3233/RNN-2011-0587
44. Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, Karch S, Möller H-J, Nitsche MA, Mulert C. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. NeuroImage. 2011a;55(2):644–57. https://doi.org/10.1016/j.neuroimage.2010.12.004
45. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, Brunelin J, Möller H-J, Reiser M, Padberg F. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011b;31(43):15284–93. https://doi.org/10.1523/JNEUROSCI.0542-11.2011
46. Kerns JG, Cohen JD, MacDonald AW, Johnson MK, Stenger VA, Aizenstein H, Carter CS. Decreased conflict- and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. Am J Psychiatry. 2005;162(10):1833–9. https://doi.org/10.1176/appi.ajp.162.10.1833
47. Kidgell DJ, Goodwill AM, Frazer AK, Daly RM. Induction of cortical plasticity and improved motor performance following unilateral and bilateral transcranial direct current stimulation of the primary motor cortex. BMC Neurosci. 2013;14(1):64. https://doi.org/10.1186/1471-2202-14-64
48. Kwon YH, Jang SH. The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. Neurosci Lett. 2011;492(2):105–8. https://doi.org/10.1016/j.neulet.2011.01.066
49. Kwon YH, Ko M-H, Ahn SH, Kim Y-H, Song JC, Lee C-H, Chang MC, Jang SH. Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett. 2008;435(1):56–9. https://doi.org/10.1016/j.neulet.2008.02.012
50. Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci. 2005;22(2):495–504. Scopus. https://doi.org/10.1111/j.1460-9568.2005.04233.x
51. Lang N, Nitsche MA, Paulus W, Rothwell JC, Lemon RN. Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. Exp Brain Res. 2004;156(4):439–43. https://doi.org/10.1007/s00221-003-1800-2
52. Lee SY, Cheon H-J, Yoon KJ, Chang WH, Kim Y-H. Effects of dual transcranial direct current stimulation for aphasia in chronic stroke patients. Ann Rehabil Med. 2013;37(5):603–10. https://doi.org/10.5535/arm.2013.37.5.603
53. Lefebvre S, Laloux P, Peeters A, Desfontaines P, Jamart J, Vandermeeren Y. Dual-tDCS enhances online motor skill learning and long-term retention in chronic stroke patients. Front Hum Neurosci. 2013;6. https://doi.org/10.3389/fnhum.2012.00343
54. Lefebvre S, Dricot L, Laloux P, Desfontaines P, Evrard F, Peeters A, Jamart J, Vandermeeren Y. Increased functional connectivity one week after motor learning and tDCS in stroke patients. Neuroscience. 2017;340:424–35. https://doi.org/10.1016/j.neuroscience.2016.10.066
55. Lefebvre S, Dricot L, Laloux P, Gradkowski W, Desfontaines P, Evrard F, Peeters A, Jamart J, Vandermeeren Y. Neural substrates underlying stimulation-enhanced motor skill learning after stroke. Brain. 2015;138(1):149–63. https://doi.org/10.1093/brain/awu336
56. Lindenberg R, Nachtigall L, Meinzer M, Sieg MM, Floel A. Differential effects of dual and Unihemispheric motor cortex stimulation in older adults. J Neurosci. 2013;33(21):9176–83. https://doi.org/10.1523/JNEUROSCI.0055-13.2013
57. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010;75(24):2176–84. https://doi.org/10.1212/WNL.0b013e318202013a
58. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001;412(6843):150–7. https://doi.org/10.1038/35084005
59. Lupi M, Martinotti G, Santacroce R, Cinosi E, Carlucci M, Marini S, Acciavatti T, di Giannantonio M. Transcranial direct current stimulation in substance use disorders: a systematic review of scientific literature. J ECT. 2017;33(3):203–9. https://doi.org/10.1097/YCT.0000000000000401
60. Madhavan S, Sriraman A, Freels S. Reliability and variability of tDCS induced changes in the lower limb motor cortex. Brain Sci. 2016;6(3) https://doi.org/10.3390/brainsci6030026
61. Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ. Does transcranial direct current stimulation

improve healthy working memory?: a meta-analytic review. J Cogn Neurosci. 2016;28(8):1063–89. https://doi.org/10.1162/jocn_a_00956
62. Mannell MV, Franco AR, Calhoun VD, Cañive JM, Thoma RJ, Mayer AR. Resting state and task-induced deactivation: a methodological comparison in patients with schizophrenia and healthy controls. Hum Brain Mapp. 2010;31(3):424–37. https://doi.org/10.1002/hbm.20876
63. Marangolo P, Fiori V, Sabatini U, De Pasquale G, Razzano C, Caltagirone C, Gili T. Bilateral transcranial direct current stimulation language treatment enhances functional connectivity in the left hemisphere: preliminary data from aphasia. J Cogn Neurosci. 2016;28(5):724–38. https://doi.org/10.1162/jocn_a_00927
64. Mayseless N, Shamay-Tsoory SG. Enhancing verbal creativity: modulating creativity by altering the balance between right and left inferior frontal gyrus with tDCS. Neuroscience. 2015;291:167–76. https://doi.org/10.1016/j.neuroscience.2015.01.061
65. Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Flöel A. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci. 2013;33(30):12470–8. https://doi.org/10.1523/JNEUROSCI.5743-12.2013
66. Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, Flaisch T, Floel A. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci. 2012;32(5):1859–66. https://doi.org/10.1523/JNEUROSCI.4812-11.2012
67. Miller EK. The prefrontal cortex: complex neural properties for complex behavior. Neuron. 1999;22(1):15–7. https://doi.org/10.1016/s0896-6273(00)80673-x
68. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009;66(8):811–22. https://doi.org/10.1001/archgenpsychiatry.2009.91
69. Mondino M, Jardri R, Suaud-Chagny M-F, Saoud M, Poulet E, Brunelin J. Effects of Fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left Temporo-parietal junction in patients with schizophrenia. Schizophr Bull. 2016;42(2):318–26. https://doi.org/10.1093/schbul/sbv114
70. Newton AT, Morgan VL, Rogers BP, Gore JC. Modulation of steady state functional connectivity in the default mode and working memory networks by cognitive load. Hum Brain Mapp. 2011;32(10):1649–59. https://doi.org/10.1002/hbm.21138
71. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 2009;219(1):14–9. https://doi.org/10.1016/j.expneurol.2009.03.038
72. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. Suppl Clin Neurophysiol. 2003;56:255–76. https://doi.org/10.1016/s1567-424x(09)70230-2
73. Nitsche MA. Transcranial direct current stimulation: a new treatment for depression? Bipolar Disord. 2002;4(s1):98–9. https://doi.org/10.1034/j.1399-5618.4.s1.43.x
74. Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, Leibowitz J, Pilling S, Roiser JP. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology. 2019;44(9):1613–22. https://doi.org/10.1038/s41386-019-0401-0
75. Opitz A, Yeagle E, Thielscher A, Schroeder C, Mehta AD, Milham MP. On the importance of precise electrode placement for targeted transcranial electric stimulation. NeuroImage. 2018;181:560–7. https://doi.org/10.1016/j.neuroimage.2018.07.027
76. Orlov ND, O'Daly O, Tracy DK, Daniju Y, Hodsoll J, Valdearenas L, Rothwell J, Shergill SS. Stimulating thought: a functional MRI study of transcranial direct current stimulation in schizophrenia. Brain. 2017;140(9):2490–7. https://doi.org/10.1093/brain/awx170
77. Padberg F, Kumpf U, Mansmann U, Palm U, Plewnia C, Langguth B, Zwanzger P, Fallgatter A, Nolden J, Burger M, Keeser D, Rupprecht R, Falkai P, Hasan A, Egert S, Bajbouj M. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;267(8):751–66. https://doi.org/10.1007/s00406-017-0769-y
78. Palm U, Keeser D, Hasan A, Kupka MJ, Blautzik J, Sarubin N, Kaymakanova F, Unger I, Falkai P, Meindl T, Ertl-Wagner B, Padberg F. Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. Schizophr Bull. 2016;42(5):1253–61. https://doi.org/10.1093/schbul/sbw041
79. Park C, Chang WH, Park J-Y, Shin Y-I, Kim ST, Kim Y-H. Transcranial direct current stimulation increases resting state interhemispheric connectivity. Neurosci Lett. 2013;539:7–10. https://doi.org/10.1016/j.neulet.2013.01.047
80. Peña-Gómez C, Sala-Lonch R, Junqué C, Clemente IC, Vidal D, Bargalló N, Falcón C, Valls-Solé J, Pascual-Leone Á, Bartrés-Faz D. Modulation of large-scale brain networks by transcranial direct

current stimulation evidenced by resting-state functional MRI. Brain Stimul. 2012;5(3):252–63. https://doi.org/10.1016/j.brs.2011.08.006
81. Pereira JB, Junqué C, Bartrés-Faz D, Martí MJ, Sala-Llonch R, Compta Y, Falcón C, Vendrell P, Pascual-Leone Á, Valls-Solé J, Tolosa E. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. Brain Stimul. 2013;6(1):16–24. https://doi.org/10.1016/j.brs.2012.01.006; https://doi.org/10.1016/j.neuroimage.2010.09.085
82. Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp. 2012a;33(10):2499–508. https://doi.org/10.1002/hbm.21380
83. Polanía R, Paulus W, Nitsche MA. Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. PLoS One. 2012b;7(1):e30971. https://doi.org/10.1371/journal.pone.0030971
84. Polanía R, Paulus W, Antal A, Nitsche MA. Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. NeuroImage. 2011;54(3):2287–96.
85. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci. 2001;98(2):676–82. https://doi.org/10.1073/pnas.98.2.676
86. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007;27(9):2349–56. https://doi.org/10.1523/JNEUROSCI.5587-06.2007
87. Sehm B, Kipping J, Schäfer A, Villringer A, Ragert P. A comparison between Uni- and bilateral tDCS effects on functional connectivity of the human motor cortex. Front Hum Neurosci. 2013;7. https://doi.org/10.3389/fnhum.2013.00183
88. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A. 2010;107(24):11020–5. https://doi.org/10.1073/pnas.1000446107
89. Shiozawa P, da Silva ME, Cordeiro Q, Fregni F, Brunoni AR. Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. Brain Stimul. 2013;6(5):831–3. https://doi.org/10.1016/j.brs.2013.03.003
90. Shivakumar V, Bose A, Rakesh G, Nawani H, Subramaniam A, Agarwal SM, Kalmady SV, Narayanaswamy JC, Venkatasubramanian G. Rapid improvement of auditory verbal hallucinations in schizophrenia after add-on treatment with transcranial direct-current stimulation. J ECT. 2013;29(3):e43–4. https://doi.org/10.1097/YCT.0b013e318290fa4d
91. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci. 1997;9(5):648–63. https://doi.org/10.1162/jocn.1997.9.5.648
92. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatry. 2020;177(5):435–46. https://doi.org/10.1176/appi.ajp.2019.19090915
93. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci U S A. 2008;105(34):12569–74. https://doi.org/10.1073/pnas.0800005105
94. Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia. 2000;38(5):596–612. https://doi.org/10.1016/S0028-3932(99)00103-7
95. Takamura T, Hanakawa T. Clinical utility of resting-state functional connectivity magnetic resonance imaging for mood and cognitive disorders. J Neural Transm. 2017;124(7):821–39. https://doi.org/10.1007/s00702-017-1710-2
96. Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci. 1997;94(26):14792–7. https://doi.org/10.1073/pnas.94.26.14792
97. Vines BW, Cerruti C, Schlaug G. Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neurosci. 2008;9(1):103. https://doi.org/10.1186/1471-2202-9-103
98. Wang L, Yu L, Wu F, Wu H, Wang J. Altered whole brain functional connectivity pattern homogeneity in medication-free major depressive disorder. J Affect Disord. 2019;253:18–25. https://doi.org/10.1016/j.jad.2019.04.040
99. Weber MJ, Messing SB, Rao H, Detre JA, Thompson-Schill SL. Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: a tDCS-fMRI study. Hum Brain Mapp. 2014;35(8):3673–86. https://doi.org/10.1002/hbm.22429
100. Wörsching J, Padberg F, Goerigk S, Heinz I, Bauer C, Plewnia C, Hasan A, Ertl-Wagner B, Keeser D. Testing assumptions on prefrontal transcranial direct current stimulation: comparison of electrode montages using multimodal fMRI. Brain Stimul. 2018;11(5):998–1007. https://doi.org/10.1016/j.brs.2018.05.001
101. Wörsching J, Padberg F, Helbich K, Hasan A, Koch L, Goerigk S, Stoecklein S, Ertl-Wagner B, Keeser D. Test-retest reliability of prefrontal transcranial Direct Current Stimulation (tDCS) effects on func-

tional MRI connectivity in healthy subjects. 2017. https://opus.bibliothek.uni-augsburg.de/opus4/frontdoor/index/index/docId/70563.

102. Wörsching J, Padberg F, Ertl-Wagner B, Kumpf U, Kirsch B, Keeser D. Imaging transcranial direct current stimulation (tDCS) of the prefrontal cortex-correlation or causality in stimulation-mediated effects? Neurosci Biobehav Rev. 2016;69:333–56. https://doi.org/10.1016/j.neubiorev.2016.08.001
103. Ye H, Chen S, Huang D, Wang S, Luo J. Modulating activity in the prefrontal cortex changes decision-making for risky gains and losses: a transcranial direct current stimulation study. Behav Brain Res. 2015;286:17–21. https://doi.org/10.1016/j.bbr.2015.02.037
104. Zhang X, Liu B, Li N, Li Y, Hou J, Duan G, Wu D. Transcranial direct current stimulation over prefrontal areas improves psychomotor inhibition state in patients with traumatic brain injury: a pilot study. Front Neurosci. 2020;14. https://doi.org/10.3389/fnins.2020.00386

10 The Value of Neuroimaging for Treating Depression with Brain Stimulation

Verena Sarrazin and Jacinta O'Shea

Abbreviations

ACC	Anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
NIBS	Non-invasive brain stimulation
PET	Positron emission tomography
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation

10.1 Introduction

This chapter reviews studies that combine non-invasive brain stimulation (NIBS) with neuroimaging in neuropsychiatry. The goal is to evaluate how neuroimaging can inform and improve the clinical application of NIBS. Since depression is the psychiatric condition that has most often been treated and investigated using NIBS, this chapter focusses on NIBS treatment of depression.

Since 2008, transcranial magnetic stimulation (TMS) is an FDA-approved treatment for depression. It has been investigated extensively using neuroimaging. By contrast, transcranial direct current stimulation (tDCS) is currently under investigation as a potential antidepressant, and only very few studies combining tDCS and neuroimaging in depression have been published to date. The scientific and clinical questions that arise in the fields of tDCS and TMS (combined with neuroimaging) are conceptually very similar. Hence, this chapter addresses both stimulation modalities together, highlighting issues that are specific to one modality or the other as they arise.

We address four key questions about the potential value of neuroimaging: (1) Does neuroimaging-guided target localization improve treatment? (2) How has neuroimaging advanced understanding of NIBS treatment action? (3) Can neuroimaging help to predict who will respond to NIBS treatment? (4) How can neuroimaging be used to personalize NIBS treatment?

For this review, we searched for studies combining TMS or tDCS with functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or single photon emission computed tomography in the context of depres-

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sion. Owing to methodological heterogeneity, it was not possible to conduct a systematic review of the existing combined NIBS/neuroimaging literature. Across studies, stimulation parameters vary greatly, including frequency, intensity, number of sessions and overall dose. Moreover, older studies are characterized by very small sample sizes and low statistical power. So instead, this chapter provides a narrative review that outlines the conceptual framework within which research combining NIBS and neuroimaging in depression is conducted and reviews the current state of progress in this field.

10.1.1 Non-invasive Brain Stimulation to Treat Depression

In 1996, Alvaro Pascual-Leone and colleagues performed the first blinded and controlled study of TMS to treat depression [1]. The rationale built on PET findings that depressed individuals had hypometabolism in the left dorsolateral prefrontal cortex (DLPFC) compared to healthy controls [2]. The authors hypothesized that excitatory stimulation of the left DLPFC might normalize this aberrant hypometabolism and thus improve symptoms. As predicted, 5 daily sessions of 10 Hz TMS applied in 20 trains of 10s had antidepressant effects compared to sham TMS and also compared to stimulation of control brain regions (vertex and right DLPFC). This pioneering proof-of-principle work laid the foundations for the scientific and clinical fields of NIBS treatment of depression. Following a series of pivotal clinical trials [3–5], in 2008, the US Food and Drug Administration approved the clinical use of TMS to treat drug-resistant depression. Other jurisdictions have followed suit (e.g. UK NICE [6]). High-frequency TMS (3000 pulses per session at a frequency of 10 Hz and 120% of resting motor threshold [7]) of the left DLPFC is the FDA-approved and most commonly used protocol, as recommended by the Clinical TMS Society [8]. Recently, the non-inferiority of intermittent theta burst stimulation has been demonstrated, significantly shortening daily clinical treatment time from 37.5 to 3 minutes [9].

Response and remission rates to high-frequency TMS treatment to the left DLPFC are around 47% (Number Needed to Treat (NNT) 6) and 27% (NNT 8), respectively [9, 10]. Importantly, these clinical trials were conducted on patients classified as "treatment-resistant", that is, more severe cases of depression that failed to respond to previous drug treatments.

Over the past 15 years, tDCS has been proposed as a safer and cheaper alternative to TMS. Unlike TMS, tDCS does not trigger action potentials, so it does not carry the same risk of inducing seizures. It is also significantly less expensive, is light and mobile compared to TMS and thus expands the potential reach of treatment to a larger number of patients and to a wider range of treatment settings, including home use [11, 12]. Since the eighteenth century, it was known that electric current applied to the scalp can induce neurophysiological effects (see [13] for a review). However, in the treatment of depression, tDCS did not show reliable results (e.g. [14]). TDCS was "rediscovered" in the late twentieth century, around the time that the first successful TMS treatment attempts were reported. Pioneering studies in human volunteers by Alberto Priori [15], Michael Nitsche, Walter Paulus [16] and colleagues showed that tDCS can induce sustained changes in cortical excitability that vary with stimulation polarity. Using the same rationale as for TMS treatment, Andre Brunoni and colleagues pioneered the use of anodal tDCS in depression targeting the left DLPFC to try and increase its excitability [17]. Subsequent clinical trials have shown mixed evidence for efficacy of this approach, some reporting effect sizes for tDCS that are comparable [18, 19] and others inferior [20] to other antidepressant treatments. Hence, while evidence for efficacy is emerging, tDCS for depression is currently for investigational use (e.g. UK NICE review [21]). In contrast to TMS, which is indicated for patients with drug treatment resistant depression (TRD), tDCS studies often include a wider range of patients, notably less severe cases and those without a formal diagnosis of TRD. Response and remission rates for tDCS treatment of depression in studies to date are 34% (NNT = 7) and 23.1% (NNT = 9) [19].

The next section outlines two complementary theories of depression that offer a useful framework for appraising potential applications of NIBS in depression.

10.1.2 Network Theories of Depression

Neuroimaging studies have had significant influence on reconceptualizing mental disorders as manifestations of altered structure and function of dysfunctional networks distributed across the brain, rather than localized dysfunction of single brain regions [22]. Contemporary neuropsychiatric theories emphasize that depression reflects dysfunction within multiple interacting brain networks. This network perspective can help to explain heterogeneity, whereby individuals with the same diagnosis ("depression") can have non- or only partially overlapping symptoms, potentially reflecting partially shared and partially distinct brain network dysfunction.

Boxes 10.1 and 10.2 highlight two current network theories of depression: the *triple network model of psychopathology* [22] and the *neurobiological model of biased processing of negative stimuli* [23]. The models are mutually compatible but highlight different aspects of the same underlying theory. While the triple network model emphasizes *pathophysiology*, the biased processing model focuses on dysfunctional *information processing*. Together, they offer a useful framework for understanding depression as dysfunctional brain network interactions that lead to negatively biased information processing.

Box 10.1 Triple Network Model of Psychopathology [22]

- Most mental disorders can be explained by dysfunctional interplay of three brain networks (Fig. 10.1):
  - *Default mode network:*
    Involved in self-referential thinking and episodic memory retrieval; deactivated during task performance
    Regions: medial prefrontal cortex, medial parietal regions, angular gyrus, precuneus, posterior cingulate cortex and posterior hippocampus
  - *Executive control network:*
    Activated during task performance; responsible for executive control processes (such as planning or inhibition of task-irrelevant functions) and emotion regulation
    Regions: bilateral DLPFC and lateral posterior parietal regions
  - *Salience network:*
    Detection of salient stimuli in the environment; enables switching between default mode network and executive control network [24]
    Regions: dorsal anterior cingulate cortex, amygdala, anterior insula and anterior hippocampus
- In a healthy brain, the salience network reacts to external stimuli and initiates switching appropriately between internal (default mode network) and external (executive control network) goal-directed behaviour; pathological disturbance of the balance between the three systems can lead to excessive internal (e.g. depressive rumination) or external focus (e.g. threat vigilance in anxiety) [25].
- In depression, the salience network seems to be more strongly connected to the default mode network than to the executive control network (salience network – default mode network hyperconnectivity), which could cause difficulties in guiding attention away from internal processes and towards external stimuli (salience network – executive control network hypoconnectivity), which could lead to depressive symptoms such as rumination and loss of interest in daily life activities [25, 26].

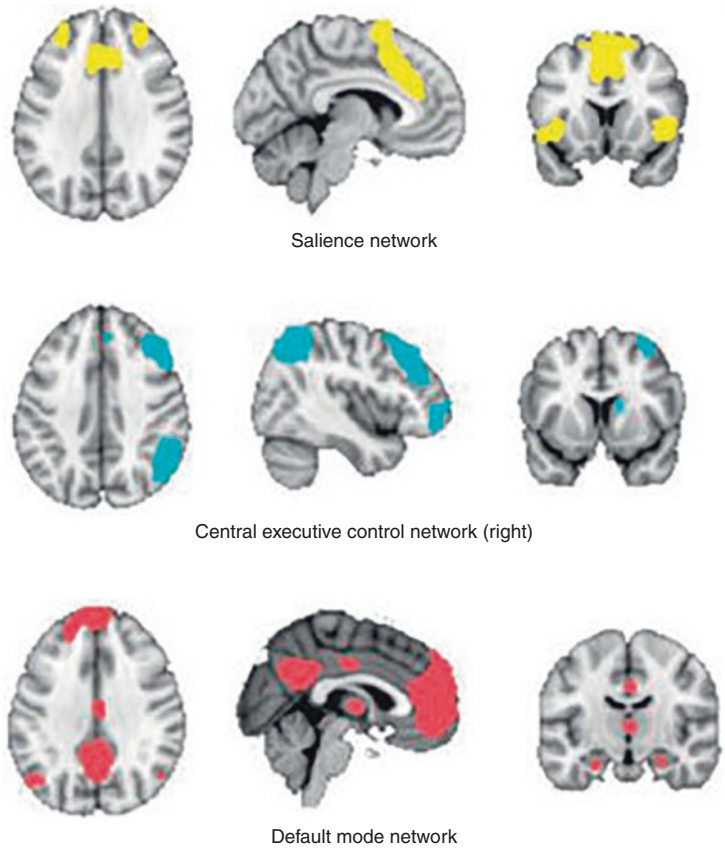

Fig. 10.1 Illustration of the three brain networks whose interactions play a major role in the psychopathology of most mental disorders according to the triple network theory of psychopathology [22]. According to the triple network model, the salience network, which reacts to external stimuli, enables switching between the default mode network and executive control network. In depression, the salience network is more strongly connected to the default mode network, which is hypothesized to lead to increased attention towards internal processes at the cost of attention to external stimuli [25]. (Reproduced from Ref. [22] with permission)

Box 10.2 Neurobiological Model of Biased Processing of Negative Stimuli in Depression [23]

- Based on Beck's cognitive model of depression [27].
- This model outlines how dysfunctional interactions between the executive control network (DLPFC), the salience network (dorsal anterior cingulate cortex, amygdala) and the default mode network (which the subgenual anterior cingulate cortex is connected to) are hypothesized to contribute to the development and maintenance of depressive symptoms (Fig. 10.2):
  - Negative stimuli evoke a *hyperactive* response in the thalamus [28].
  - This signal induces a (pathological) increase in activity in the amygdala and the *subgenual anterior cingulate cortex (subgenual ACC),* a way station connecting the limbic system to higher cortical areas [28–30].
  - The dorsolateral prefrontal cortex (DLPFC), a cortical region associated with cognitive control, is *hypoactive* in depression [31] – this contributes indirectly to depressive symptoms by decreasing the regulating influence of the dorsal anterior cingulate cortex on the amygdala.

➔ *Increased attention towards and increased processing of negative stimuli*

- Core pathophysiological features common to both models include hyper-active bottom-up emotional drive from the limbic system (and subgenual ACC), reflected in salience network – default mode network hyper-connectivity, combined with hypometabolism in DLPFC leading to reduced top-down cortical regulatory influence on limbic emotional drive.

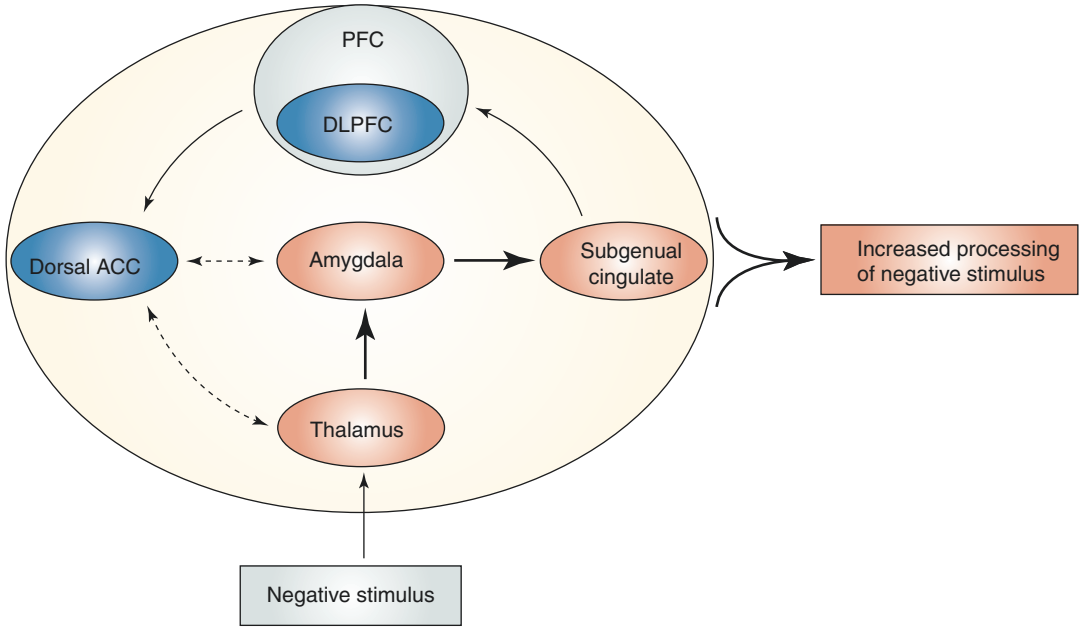

Fig. 10.2 Cognitive neurobiological model of biased processing of negative stimuli. In depression, increased processing of negative stimuli is hypothesized to arise from increased activity in the thalamus, amygdala (salience network) and subgenual cingulate (which is connected to the default mode network) in response to negative stimuli, accompanied by decreased regulatory influence from the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC) on these interconnected subcortical regions. Hyperactive areas are shown in red, hypoactive areas in blue. Dashed arrow indicates attenuated connectivity, thicker arrows indicate increased connectivity. (Reproduced from Ref. [23] with permission)

These two network theories of depression frame the current conceptual approach to NIBS treatment in depression: (1) Depression does not arise from dysfunction of discrete brain regions, but from dysfunctional interplay within and between distributed cortico-subcortical brain networks. This perspective suggests several potential alternative novel brain targets for stimulation, a topic which will be discussed in more detail later. (2) A key feature of depression pathophysiology is abnormal functional interactions between cortical and subcortical areas. More precisely, subcortical limbic regions seem to overreact in response to negative stimuli, while prefrontal cortical areas show impaired down-regulation of those negative emotional responses [23]. Hence, restoring normal functional interactions within cortico-limbic circuits may be an important mechanism of effective treatment action. (3) Within the triple network perspective, hyperconnectivity between subgenual ACC and the default mode network, which is associated with rumination, seems to be a key psychopathological feature of depression [28].

This third point has gained increasing attention and has had a significant influence on how NIBS is applied in depression treatment. Resting-state connectivity between the subgenual ACC and default mode network is increased in depressed compared to healthy participants, and connectivity strength has been shown to correlate with the length of the current depressive episode and with rumination and brooding [28, 32]. In patients with severe treatment-resistant depression, invasive deep brain stimulation targeting the subgenual ACC has been shown to both decrease subgenual ACC hyperactivity and successfully treat symptoms [33] (but see [34, 35]). In treatment responders, deep brain stimulation also restored healthy brain activity by decreasing activity in other subcortical areas, such as the hypothalamus, and increasing activity in cortical

prefrontal regions. This invasive brain stimulation work has strongly influenced thinking about desired brain changes to induce in order to ameliorate symptoms: suppress subcortical limbic (hyper)activity and restore cortical regulatory (hypo)activity. In the context of DLPFC-targeted NIBS, this network perspective has led to normalization of subgenual ACC-default mode network hyperconnectivity being hypothesized as a key potential mechanism of TMS treatment action [36], and efforts to specifically engage this target have been associated with better treatment outcomes [36, 37].

10.1.3 Why Combine NIBS and Neuroimaging?

By providing a window on the brain to both localize and characterize aberrant brain changes in depression, neuroimaging has provided the data that underpin the conceptual rationale for using stimulation to treat depression. The original work of Pascual-Leone, George and colleagues was informed and inspired by PET and aimed to use TMS to normalize a discrete region of cortical hypometabolism that differed between depressed patients and controls. Positive efficacy trials have provided apparent validation of this mechanistic rationale. Subsequent imaging case-control findings have led to an expansion of this stimulation intervention approach, informed by brain changes observed in other brain regions as a consequence of TMS treatment. Hence, in addition to exciting left DLPFC, other protocols in common use target and inhibit right DLPFC [38], or combine both manipulations [39], with a goal of "re-balancing" inter-hemispheric excitability [40]. There is evidence for efficacy of all of these approaches [38, 39]. Thus, the primary mode of treatment intervention has been to excite and/or inhibit left and/or right DLPFC, in order to restore normal excitability, metabolism and presumably function. Imaging has inspired this rationale and confirmed it.

Neuroimaging has led to the development of network theories of the psychopathology of depression, which in turn suggest how NIBS could or should be applied to restore healthy brain function. From a network perspective, the antidepressant efficacy of TMS is unlikely to reflect brain changes that are confined solely to the local DLPFC stimulation target. Instead, network models emphasize the key role of inter-areal brain interactions, in particular between hyper-active subcortical regions signalling negative stimuli and hypo-active cortical regions emotional regulation. These theories identify hyperactive limbic drive as key for negative affect, indicating that to be effective NIBS treatment should aim at inhibiting subcortical hyperactivity.

This raises the question of how NIBS can reach these deeper target regions, given it is applied transcranially to the cortex. The analysis of electric field distributions induced by stimulation, based on anatomical brain scans, has contributed to answering this question. Theoretically, there are two possibilities: (1) NIBS reaches subcortical regions directly by passing through the skull and cortical brain tissue. (2) Stimulation causes indirect changes in deeper regions via anatomical and functional connectional spread.

How Can NIBS Reach Deep Brain Regions?

In the case of TMS, there is evidence for both routes. Using a standard figure-of-eight-shaped coil, routinely used to deliver treatment under the conventional FDA protocol, the maximum induced current density is within the cubic centimetres of superficial cortical layers immediately underlying the centre of the coil. However, newer coil designs can reach deeper brain regions (e.g. H-coil, [41]). Electric field modelling suggests that these coils (with the halo circular assembly coil reaching the deepest regions) can induce an electric field in deep brain regions with a maximum of 30–50% of the electric field strength on the cortical surface [41]. A drawback of deep TMS is the trade-off between depth and focality, that is, stimulation reaching deep brain regions is also less focal. Despite the development of newer coils reaching deeper regions, most studies to date have used the conventional figure-8-shaped coil. Hence, observed changes in subcortical areas induced by TMS in those studies are likely to instead reflect connectional spread of cortical effects. TMS pulses depolarize neurons, induc-

ing action potentials. Thus, local stimulation spreads to distal regions via anatomical connections and functional inter-areal brain interactions. Treatment protocols require daily doses over several weeks. Thus, TMS-induced excitatory/inhibitory effects accumulate gradually over time with brain changes stabilized through plasticity.

Unlike TMS, which induces a local electrical field in the superficial cortical layers immediately underlying the centre of the figure-8-shaped coil, tDCS uses a dipole arrangement of two electrodes placed at distance across the scalp, which induces a diffuse electrical field to flow from the anode to the cathode, polarizing the tissue in between and thus affecting excitability across a large area of the brain [42]. Electric field modelling of the bipolar tDCS montages commonly used in depression studies has revealed that the highest e-field strength is actually found *between* the electrodes, rather than locally underneath each [43]. This means that the highest field strength induced is not in the DLPFC but rather in the medial prefrontal cortex [44, 45]. Although the original rationale for tDCS montages in depression was to stimulate the DLPFC, as for TMS, recent network theories suggest that stimulating the medial prefrontal cortex might actually prove more effective – since the medial prefrontal cortex is part of the default mode network [45]. This example highlights how important neuroimaging is for understanding and improving the clinical application of NIBS.

Unlike TMS, TDCS does not induce action potentials. Instead, it polarizes tissue, modulating neuronal excitability by changing the resting membrane potential in a direction that depends on the current polarity (anodal-excitatory, cathodal-inhibitory). Work in animals has shown that tDCS can induce long-term brain and behavioural changes via neuroplasticity, resembling long-term potentiation-like effects [46]. Treatment protocols, involving daily stimulation over weeks, are likely to engage and alter network-level functional interactions via plasticity, including subcortical areas. Apart from these indirect effects on subcortical regions, recent reports indicate that tDCS might also reach deeper regions more directly [47].

A recent novel approach in tDCS is the concept of network-targeted stimulation using multielectrode arrays [48]. This approach embraces the insight that brain functions (and dysfunctions) rely on the distributed activity of functionally interacting brain networks. Instead of targeting a single region (node in a network) using a conventional dipole electrode montage, and obtaining network-level changes as a by-product, this approach uses multiple electrodes to simultaneously target several nodes to more directly engage the distributed network target. For instance, multifocal tDCS targeting the primary motor cortex and additional interconnected regions within the distributed motor network increased motor cortex excitability compared to a traditional dipole montage targeting primary motor cortex alone [49]. In Parkinson's disease, multifocal tDCS simultaneously targeting both the primary motor cortex and DLPFC led to symptom improvement, whereas conventional dipole tDCS over the motor cortex or sham tDCS did not [50]. In depression treatment, this approach could be applied by positioning electrodes to engage multiple regions of the default mode network, which might yield larger modulation effects than using only a single electrode dipole.

Contributions of Neuroimaging to the Clinical Application of NIBS

One of the most important uses of imaging is that it provides a means to confirm "target engagement" – for example, whether DLPFC stimulation aimed at altering subgenual ACC metabolism has effectively done so. The importance of imaging for verifying target engagement is reflected in recent requirements from the US NIMH to include such verification data in psychiatry treatment trials [51]. This promises to increase the information gain from clinical trials (notably including negative trials), by enabling efficacy outcomes to be better interpreted, based on the degree to which the intended stimulation target was successfully engaged [52].

Neuroimaging also provides an opportunity to identify new and potentially more effective targets for stimulation. While there is significant focus on DLPFC-subgenual ACC interactions,

these two regions are not directly anatomically interconnected. Instead, engaging frontal regions more directly connected to subgenual ACC, such as dorsomedial prefrontal cortex (DMPFC), might be more effective. Indeed, TMS of DMPFC has been shown to have antidepressant effects, including in patients who did not respond to DLPFC stimulation [53]. Alternatively, the default mode network, which is implicated in depressive rumination, includes a lateral cortical component in the left angular gyrus. TMS targeted at left angular gyrus has been shown to induce neurotransmitter changes in the default mode network [54] and functional changes in hippocampal-dependent memory [55] both via anatomical and functional connectional spread. To date, few novel targets are under serious clinical investigation as alternatives for depression, with notable exceptions of DMPFC and lateral orbitofrontal cortex, both pioneered by Jonathan Downar's laboratory [53, 56, 57].

10.2 Does Neuroimaging-Guided Brain Target Localization Improve Treatment?

Prior to the ready availability of neuroimaging and frameless stereotaxy, scalp measurements relative to the hand motor "hotspot" were used to target TMS to stimulate the DLPFC. The more recent development of neuronavigation allows for precision targeting based on individual anatomical brain images. Given the cost and time of scanning procedures, the key question is whether this actually improves the clinical effects of NIBS treatment compared to standard localization methods using motor hotspot or EEG-based scalp coordinates that have been applied successfully in treatment protocols for many years.

10.2.1 TMS

In one of the first single-case studies using TMS for depression treatment, George and colleagues aimed to stimulate the left DLPFC, to remediate local hypometabolism [2, 58]. They identified the motor hotspot, the region in the primary motor cortex that elicited the strongest motor response to TMS in the contralateral hand and stimulated a region 5 cm anterior to this motor hotspot, the putative "DLPFC". This localization method was derived based on the inferred distance between the central sulcus (the putative motor hotspot) and the DLPFC in the Talairach atlas, a brain map created for neurosurgery. This "5-cm rule" became the standard method for targeting the DLPFC and is still used in clinical trials today.

The precise subregion of the DLPFC that is the intended target in most studies is Brodmann Area 46. There are two general approaches to target localization – applying a heuristic method based on scalp measurements or localizing an area more precisely using neuronavigation.

Regarding heuristic approaches, the accuracy of the 5-cm rule has been criticized since it does not take differences in head size into account, such that the anatomical area identified by this method varies considerably between participants [59–62]. An alternative that does take head size into account uses the EEG 10–20 system, in which the F3 electrode position is proposed to correspond to the left DLPFC. This method has been shown to be more accurate than the 5-cm rule [59, 62] but still lacks the individualized precision obtainable from MRI-guided localization [63].

Does Localization Accuracy Matter?

A number of studies have been conducted to investigate to what extent accuracy in target localization actually matters and what is the most efficient target subregion of DLPFC. In one study [64], TMS was targeted at left DLPFC as identified by the 5-cm rule. Across participants there was a relationship between the stimulated brain area and treatment response. A more lateral and anterior stimulation position – overlapping with the anatomical region Brodmann Area 46 – was associated with higher treatment success, suggesting that small differences in the target location do matter. One study investigated directly if stimulating a region identified by neuronavigation leads to a better clinical outcome than stimulating a region identified by the 5-cm rule [65]. The group that received stimulation to the neuronavigation-based target showed greater

symptom reduction than the group whose target region was localized with the 5-cm rule. These studies suggest that the antidepressant effectiveness of TMS treatment varies with the precision of the DLPFC subregion target location.

A seminal study by Fox and colleagues [36] (see Box 10.3 for a more detailed description)

Box 10.3 Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate

(Michael D. Fox, Randy L. Buckner, Matthew P. White, Michael D. Greicius, and Alvaro Pascual-Leone)

Based on findings highlighting the role of the subgenual ACC in depression [28, 33], Fox and colleagues [36] hypothesized that differences in the clinical efficacy of different TMS target regions within the DLPFC are related to differences in connectivity of the target region to the subgenual ACC. They retrospectively analysed data from several previous TMS studies by comparing connectivity of the target region with clinical efficacy across studies. Resting-state connectivity of each target region was estimated based on group-averaged connectivity in a large sample of healthy individuals.

They found that more effective target regions displayed a stronger negative correlation to the subgenual ACC in the sample of healthy participants. Direct comparisons between more and less effective target regions showed clear differences in connectivity to the subgenual ACC, as illustrated in Fig. 10.3, for the study by Fitzgerald and colleagues [65].

The meaning of targeting a region of *negative* functional coupling between the DLPFC-subgenual ACC becomes clear in the context of the triple network model [22] outlined in the introduction. The DLPFC is part of the executive control network, and the subgenual ACC is strongly connected to the default mode network. The executive control network and default mode network are opposing networks; the executive control network is activated during active brain states whereas the default mode network is activated at rest, that is, their activity tends to be negatively correlated. Depression is characterized by hyperactivity of the default mode network. Targeting *negative* functional connectivity between the DLPFC and subgenual ACC indicates that excitatory stimulation of the DLPFC is likely to have inhibitory effects on the subgenual ACC and the connected default mode network, which would be expected to have a beneficial effect in depression treatment.

Three major conclusions can be drawn from this study:

1. The antidepressant effect of TMS applied to the DLPFC might rely on downregulation of the subgenual ACC and default mode network via negative connectivity between the subgenual ACC and the DLPFC stimulation site.
2. The strength of the negative functional connectivity between stimulation site and subgenual ACC could predict treatment response.
3. Treatment efficacy could be enhanced by stimulating each patient's *individual* subregion within the DLPFC that shows the strongest negative correlation to the subgenual ACC.

Limitations: It should be kept in mind that these findings are based on the retrospective analysis of pre-existing datasets. The connectivity between the DLPFC target region and subgenual ACC was *not* calculated based on individual patient data. The connectivity was estimated based on the group-averaged connectivity in a sample of healthy participants. This means that the findings from this study need to be validated in a sample of patients with individual resting-state data. Prospective clinical trials are needed to test whether individualizing treatment based on individual resting-state connectivity profiles actually improves clinical outcome.

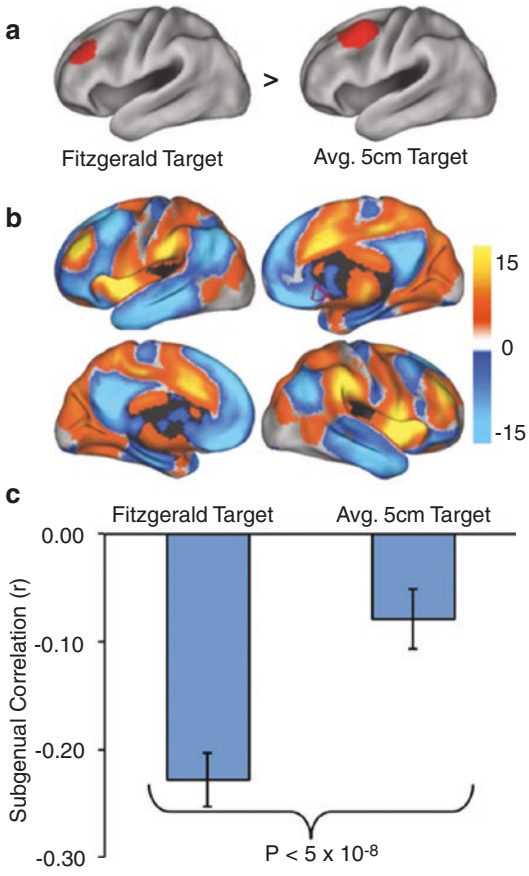

Fig. 10.3 Fox and colleagues [36] reanalysed the data from the study by Fitzgerald and colleagues [65] described in Sect. 10.2.1. This study tested the efficacy of TMS applied to the DLPFC based on neuronavigation versus the 5-cm rule. (**a**) Average target location determined by neuronavigation or 5-cm rule. Treatment was more effective in the neuronavigation condition ("Fitzgerald target"). (**b**) Difference of resting-state connectivity of the target regions (red areas: connectivity to target region was more positive in neuronavigation group; blue areas: connectivity to target regions was more negative in neuronavigation group). Connectivity to the subgenual ACC (indicated by red circle) was more negative in the neuronavigation group. (**c**) Correlation of the two stimulation sites with the subgenual ACC. The more effective target region (neuronavigation) showed a stronger negative connectivity to the subgenual ACC. (Reproduced from Ref. [36] with permission)

revealed that the clinical effectiveness of a DLPFC target relates not so much to its local properties as to its distributed functional connectivity with subgenual ACC. Within DLPFC, those TMS target locations that had stronger negative connectivity to subgenual ACC were associated with better treatment outcome. This suggests that patients might respond better to TMS if stimulation is targeted individually at the subregion within the DLPFC with the strongest negative functional connectivity to the subgenual ACC. For future use of neuroimaging-guided target localization, this suggests that in addition to the use of structural scans for frameless stereotaxy, resting-state functional scans to localize the DLPFC target will improve treatment outcome [37].

10.2.2 tDCS

In the more recent field of investigating tDCS for depression treatment, not much evidence is available yet to answer the question how far imaging-guided target localization can improve clinical outcome. Given that in tDCS induced current is distributed much less focally than in TMS, electric field modelling is essential to investigate how tDCS leads to clinical changes and how to target stimulation to optimize efficacy. Recent evidence comes from the first study correlating electric field strength to symptom improvement. Suen and colleagues [66] found that the field strength in the ACC correlated with symptom improvement, indicating that the ACC might be a key region that needs to be stimulated in order to induce antidepressant effects.

Recent e-field modelling studies have provided insights into the complexity of tDCS effects and target optimization. As outlined above, the field strength for bifrontal montages is maximal between the electrodes, not underneath them [43]. A standard montage with the electrodes placed on the left and right DLPFC thus induces the highest field strength in the medial prefrontal cortex. Second, modelling studies have found that the current induced by this montage produces a speckled pattern of anodal (inflowing current) and cathodal (outflowing current) effects since the current often enters a gyrus on one side and leaves it on the other side [43]. This indicates that the assumption that the areas underneath the anode or cathode only receive anodal or cathodal

stimulation is oversimplified. For the bilateral montages applied in depression treatment, it has been observed that the medial frontal part of the brain actually experiences the opposite polarity of the electrode placed on that hemisphere (Fig. 10.4b, d). Finally, modelling studies have demonstrated that the shape and strength of the electric field induced by tDCS depend on aspects of head and brain anatomy, so that there is large variability in the electric field experienced by different individuals [42]. Together, these findings indicate that the tDCS effects are far more complex than initially expected with high interindividual variability.

Neuroimaging Is Necessary to Test for Target Engagement

The most important use for neuroimaging in tDCS research on depression is to test for target engagement. The electric fields induced by tDCS are complex, and it is not yet clear what physiological changes they induce or how these relate to clinical improvement. For example, the finding that the medial prefrontal cortex mainly experiences the opposite polarity compared to the lateral cortex of the same hemisphere [43] is difficult to interpret. To understand and improve the clinical application of tDCS, it is key to investigate how complex electric fields translate into physiological changes. Electric field modelling on its own can be used to determine where the highest electric field strength is reached, but not what physiological changes this induces. For instance, the field strength in a specific area might not be high enough to induce physiological or functional changes, such as improved emotion regulation, that are necessary precursors for clinical gains. Therefore, future studies will need to calculate the electric fields induced across individuals, based on anatomical brain scans, and relate these to functional measures (e.g. fMRI) to better understand the functional relevance of induced electric field patterns. Physiological changes, in turn, will need to be correlated to clinical scores

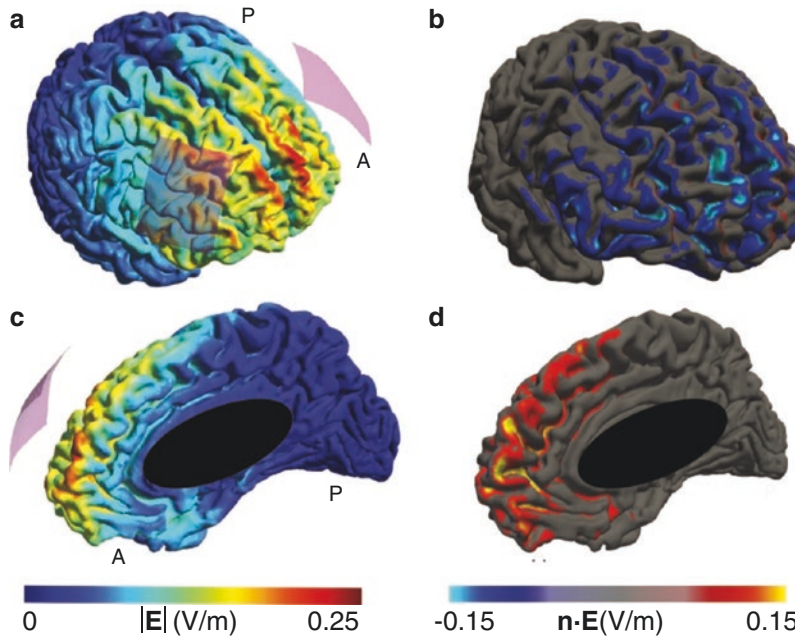

Fig. 10.4 Electric field of prefrontal tDCS predicted by electric field modelling. (**a**, **c**) illustrate the electric field induced by a bilateral electrode montage commonly used for depression treatment. The field strength is highest between the electrodes in the medial prefrontal cortex. (**b**, **d**) Current flow from the anode on the left DLPFC to the cathode on the right DLPFC leads to opposite polarities experienced by the cortical structures underneath the electrode (cathodal) and frontal midline structures (anodal) in the same (right) hemisphere. (Reproduced from Ref. [43] (CC BY 4.0))

to better understand which physiological changes are associated with beneficial effects for depressive symptoms. In future, such data should allow for imaging-based target localization to optimize stimulation montages to better drive physiological changes thought to cause clinical gains. Due to the large interindividual variability in head and frontal cortex anatomy and induced electric fields, stimulation montages should ideally be personalized for each individual.

These findings from electric field modelling studies offer important insights into the physiological effects of tDCS and should be considered when choosing an electrode montage. Electric field modelling software such as SimNIBS [67] can be used to determine the optimal electrode position based on a standard brain image or individual brain scans. Electric field models should be used to test for target engagement, as has recently been required by the US NIMH for clinical trials [51]. This is especially important for tDCS since evidence for the clinical efficacy of tDCS is mixed and its mechanisms of putative treatment action are unclear. While the targeting aim of the first tDCS studies was to stimulate the DLPFC, electric field evidence has since shown that the highest field strength is induced in the medial (not dorsolateral) prefrontal cortex, serendipitously suggesting that the default mode network may be modulated more directly by "DLPFC" tDCS montages compared to DLPFC TMS.

10.2.3 Summary

Summary: Does Neuroimaging-Guided Brain Target Localization Improve Treatment?

- Small differences in the target region within DLPFC have an influence on treatment efficacy.
- Treatment efficacy appears related to connectivity of the stimulated DLPFC with the subgenual ACC.
  ➔ Importance of neuronavigation based on functional brain images.
- In the field of tDCS, current research aims at understanding which brain areas are engaged by different montages and how the engagement of different brain regions relates to clinical effects.

10.3 Mechanisms of NIBS Treatment

This section evaluates studies investigating the effects of NIBS on brain activity and connectivity in the context of depression treatment. Understanding the mechanisms of stimulation action should help to improve future treatment effectiveness. For instance, identifying brain changes associated with clinical improvement opens up the possibility of engaging these regions more directly, as de novo stimulation targets, which could improve upon existing treatment strategies.

10.3.1 Effects on Brain Metabolism

The first insights about the physiological effects of TMS came from studies in which the primary motor cortex was targeted. It was observed that high frequencies (>5 Hz) increase whereas low frequencies (≤1 Hz) decrease motor evoked potentials [68, 69]. This was interpreted as high-frequency TMS having excitatory and low-frequency TMS having inhibitory effects on cortical excitability. However, since the brain is not homogenous in its structure or function, it was not clear whether stimulating other "non-eloquent" brain regions outside motor cortex, such as the DLPFC, with these same protocols would cause comparable excitatory and inhibitory effects.

Hence, some of the early TMS/PET studies were conducted to determine whether different TMS frequencies applied to the DLPFC did in fact cause excitatory versus inhibitory effects. Speer and colleagues acquired PET scans before and after 10 daily sessions of 20 Hz and 1 Hz TMS, using a within-subject design [70]. Both types of stimulation led to changes in regional

cerebral blood flow in prefrontal and subcortical regions. 20 Hz TMS was associated with increases of blood flow whereas 1 Hz stimulation was associated with decreases in blood flow, effects on metabolism that are consistent with the hypothesis of high-frequency/excitatory and low-frequency/inhibitory TMS effects.

Loo and colleagues measured acute effects of stimulation after one session [71]. They applied high- or low-frequency TMS and injected a radiotracer at the beginning of stimulation onset, acquiring a PET scan directly after the end of the stimulation session. Compared to sham stimulation, both high- and low-frequency TMS induced increases and decreases of regional cerebral blood flow in focal regions throughout the whole brain. A region-of-interest analysis of the left DLPFC showed that 15 Hz increased, whereas 1 Hz slightly decreased, the mean blood flow in this region. This study contributed significantly to the field by demonstrating the complexity of TMS effects, with both high and low frequencies causing increases and decreases of blood flow throughout the brain.

Other studies have used PET to test specific hypotheses about the mechanisms of TMS treatment. Based on the observation that some patients show hypermetabolism whereas others show hypometabolism in prefrontal cortex, Kimbrell and colleagues hypothesized that TMS improves depressive symptoms by bringing brain metabolism back within normal range, that is, the clinical efficacy of high- versus low-frequency TMS should depend on baseline metabolism [72]. They observed a correlation between baseline metabolism and clinical improvement for high-frequency but not low-frequency TMS. Given their limited sample size, an unambiguous conclusion cannot be drawn.

Based on the observation that high-frequency TMS to left DLPFC and low-frequency TMS to right DLPFC induce similar clinical effects, it has been hypothesized that the antidepressant effect reflects normalization of the ratio of activity in the left versus right frontal hemispheres [73]. In baseline single photon emission computed tomography scans, a left-right asymmetry, with larger activity in the right hemisphere, was observed in depressed patients. This asymmetry is commonly observed in depression across different imaging modalities, consistent with the right hemisphere association with negative emotions and thinking patterns [74, 75]. After 2 weeks of high-frequency TMS treatment, blood flow in the right hemisphere decreased to the same level as in the left hemisphere in treatment responders.

Physiological Effects of the Two Standard TMS Approaches

Several PET studies have investigated physiological effects of the two most common treatment protocols: high-frequency TMS to left DLPFC and low-frequency TMS to right DLPFC. Baeken and colleagues [76] observed that left DLPFC stimulation increased metabolism in the dorsal anterior cingulate cortex in responders. This is in line with the idea that TMS increases activity in hypoactive frontal regions. In a second study, the same group conducted a region-of-interest analysis focusing on the subgenual ACC in which they observed a decrease in metabolism [77]. The reduction in subgenual ACC metabolism correlated with symptom improvement, consistent with the triple network theory that inhibition of the subgenual ACC and default mode network is a key component to restore healthy brain function. Kito and colleagues conducted two studies using left-sided high-frequency and right-sided low-frequency TMS [78, 79]. In response to putatively inhibitory stimulation to the right DLPFC, they observed decreased metabolism in the right DLPFC, as well as in limbic regions including the subgenual ACC and amygdala, consistent with the importance of cortico-limbic connections and the idea that TMS might reduce the left-right hemisphere activation asymmetry commonly observed in depression and associated with negative emotions [74, 75]. Unfortunately, no relationship between brain changes and symptom improvement was reported, which limits the conclusions that can be drawn from this study. In response to putatively excitatory left-sided stimulation, there were increases in blood flow in the stimulated DLPFC, as well as a positive correlation between activity increases in prefrontal regions, the subgenual ACC and limbic regions

and symptom improvement. While increased activity in the prefrontal cortex and ACC might suggest improved emotion regulation, increases in activity in limbic regions might suggest a counterproductive effect on emotion processing, which contradicts most other studies. Both treatment approaches were compared by Richieri and colleagues [80]. They found that responders versus non-responders showed decreases in perfusion in the left perirhinal cortex, a region strongly connected to the hippocampus and amygdala, independent of stimulation type.

Critical Assessment of the Reported Literature

These early studies have contributed significantly to our understanding of the physiological effects of TMS in depression treatment. Nonetheless, the information value of most studies is limited due to aspects of the study design. The following points apply to the vast majority of imaging studies to date, including the methods discussed in next sections. First, these studies measured physiological changes and changes in depression symptoms but did not include tasks assessing cognitive or affective functions. These would be helpful to test what cognitive changes are induced by the physiological changes. Second, all of these studies used a similar experimental design – they all acquired neuroimaging data before and after the treatment to identify changes associated with mood improvement. One problem with this approach is that two very different states are compared, that is, the depressed state at baseline versus the non-depressed state after successful treatment. With this contrast, it is unclear whether observed changes are caused by stimulation, or simply reflect differences between a depressed versus a non-depressed brain. In order to evaluate how TMS induces changes in the brain that lead gradually to clinical improvement over time, several brain scans would need to be acquired to track stimulation-induced changes over the course of the treatment period. Third, most studies reported above lack a control group with sham stimulation. Sham stimulation is expected to act like a placebo, that is, some patients should improve over the "treatment" period despite receiving sham stimulation (e.g. owing to weeks of daily social interaction with clinic staff). A comparison of the effects of real versus sham stimulation would be helpful to differentiate between effects induced by the stimulation and changes occurring over time independently of TMS. Fourth, changes observed in the neuroimaging data should ideally be correlated to symptom improvement – to identify which changes are clinically meaningful. This test is missing in some studies. Finally, some studies report contrasts between responders versus non-responders, but symptom improvement is a continuous variable, so a correlation between brain changes and symptom improvement would arguably be more informative.

Taken together, these studies suggest that TMS treatment induces short-term physiological effects in prefrontal cortical areas as well as in subcortical limbic areas, that is, the regions associated with dysfunctional emotion regulation in the neurobiological model of depression. TMS is also associated with long-term changes in prefrontal and limbic areas; however, the directions of the effects reported in different studies partly disagree. For subcortical regions such as the subgenual ACC, increases and decreases have been reported, which suggests that the relationship between activity changes in single brain regions and symptom reduction is complex. Discrepancies in the findings might also be caused by methodological differences and different characteristics of the patient groups, given that depression is a heterogenous disorder and most studies report small sample sizes. In general, due to the design of these studies, it is not possible to conclude if the changes reported are caused by TMS or whether they simply reflect spontaneous clinical mood improvements over time.

10.3.2 Effects on Brain Networks in the Resting State

Consistent with the field of depression research moving towards network approaches, more recent imaging studies have focused on con-

nectivity analyses. Most have used resting-state functional connectivity – brain networks with correlated patterns of spontaneous fluctuations in activity over time measured while participants simply rest in the scanner. Connectivity is relevant to TMS since the magnetic field induced by TMS is focal, so changes in remote regions can only occur indirectly through connections from the stimulated brain region. Resting-state functional connectivity analyses can be used to investigate how focal stimulation to a cortical target is propagated within and across interconnected networks. Since depression is associated with limbic dysfunction, induced change in corticolimbic functional connectivity is likely to play an important role in NIBS treatment action.

Regions coactivated in a task-active state also tend to correlate at rest, which has been shown for several networks such as visual, auditory and language networks [81]. Resting-state fMRI has some advantages over task-related fMRI, including better signal-to-noise ratio, no confounds from task-related aspects, short acquisition time and higher participant compliance [82]. Moreover, it is a whole-brain approach, that is, networks and regions distributed across the entire brain can be observed simultaneously, making it possible to visualize the propagation of stimulation effects within and across networks.

Resting-state connectivity measures may be particularly important in treatment studies of depression. The default mode network, normally deactivated during task states, becomes active at rest. In depression, it is hyperactive at rest and this is associated with rumination [28, 32]. Dampening down default mode network hyperactivity is a candidate mechanism underlying NIBS treatment, similar to other treatment modalities that have been shown to have this effect (e.g. pharmacological [83]).

TMS Effects on Resting-State Networks

In a recent study, TMS-induced changes in resting-state functional connectivity of the cortical stimulation target, the left DLPFC, were analysed [84]. At baseline, global connectivity of the DLPFC was reduced in depressed patients compared to healthy controls. In response to TMS, connectivity increased, which correlated with clinical improvement. More detailed analyses showed that, consistent with a normalization mechanism, TMS induced negative connectivity between DLPFC and amygdala, which was absent in their sample of depressed patients at baseline and which is usually observed in healthy controls.

Another study used single photon emission computed tomography data to analyse connectivity and found that TMS decreased functional connectivity between the stimulated DLPFC and some regions of the default mode network, and this change correlated with symptom improvement [85]. In response to stimulation of the dorsomedial prefrontal cortex, connectivity between the stimulated region and the amygdala and insula decreased, while connectivity to the thalamus increased [56]. These changes were also associated with clinical response.

These studies support the hypothesis that TMS not only stimulates the cortical target region, but that the effects are also transmitted indirectly via structural and functional connectivity to subcortical regions. The correlations with symptom improvement indicate that the antidepressant effects might rely on the interaction between prefrontal and subcortical regions, especially regions related to emotion regulation. Moreover, these findings suggest that the clinical effect of brain stimulation could be enhanced if cortical regions with strong connections to specific subcortical regions were specifically targeted.

The Clinical Effect of TMS Is Associated with Connectivity Changes in the Subgenual ACC

Fox and colleagues' influential study used the DLFPC TMS target coordinates from several treatment trials and computed the strength of resting-state connectivity with the subgenual ACC for each [36] (see Box 10.3 for a more detailed description of the study). They found that stimulation sites with a stronger negative connectivity to the subgenual ACC were associated with better clinical outcome. Their findings, in line with the triple network model of depression, suggest that downregulation of the subgenual ACC and

the default mode network might be a potential mechanism of TMS treatment. Based on these findings, subsequent studies directly investigated connectivity changes of the subgenual ACC in response to stimulation. Baeken and colleagues found that TMS changed the negative functional coupling of the subgenual ACC with the perigenual anterior cingulate cortex and superior medial frontal gyrus into a positive coupling [86]. In a study using accelerated intermittent theta burst stimulation, a speeded treatment protocol, clinical improvement correlated with induced changes in connectivity between subgenual ACC and medial orbitofrontal cortex [87]. Connectivity changes between the subgenual ACC and regions of the default mode network have also been observed in several other studies [56, 88, 89, 90], suggesting that this might be an important mechanism underlying the antidepressant effect of TMS.

These findings have direct clinical implications, since they suggest that TMS treatment could be improved by targeting individual subregions within the DLPFC that have the highest anticorrelation with the subgenual ACC. This is further discussed in Sect. 10.5. However, some limitations remain. As discussed previously, it is often unclear if changes in neuroimaging markers after treatment are specifically induced by the stimulation. The results of studies often diverge in terms of the specific connections and the directionality of connectivity changes (increased or decreased) observed, which might be due to methodological differences. Most research has focused on subgenual ACC connectivity, which seems to be a promising approach. Nonetheless, other connections are likely to be equally or even more important and such data are lacking.

TMS Effects on the Three Major Resting-State Networks

Based on findings that depression is associated with disturbed interactions between brain networks, a few studies have investigated how TMS treatment changes connectivity within and between the three key networks implicated in depression – default mode network, executive control network and salience network. Liston and colleagues correlated signal within two seed regions, the DLPFC and subgenual ACC, with regions in the default mode network and executive control network [90]. They found that TMS reduced hyperconnectivity of the subgenual ACC to the default mode network and induced negative connectivity between DLPFC and medial prefrontal cortex. In another study, positive clinical outcome was associated with decreased connectivity between subgenual ACC and default mode network regions, as well as reduced connectivity between the hippocampus and regions of the salience network [88]. In a third study, symptom improvement was associated with decreased connectivity of the subgenual ACC to the default mode network, executive control network and a network related to affective processes [89]. However, similar changes were observed in the sham stimulation condition, suggesting that these brain changes were associated with symptom improvement in general rather than specifically with TMS treatment.

Similar to the PET studies reported in the previous section, a major limitation is that the absence of a sham control condition and the comparison of neuroimaging markers before versus after treatment makes it unclear whether observed changes are induced by NIBS or are more generally associated with clinical improvement. Nonetheless, such studies are valuable as their findings can be used to infer what imaging markers are associated with better mental health, and to guide the application of non-invasive brain stimulation to try and induce this desired brain state. Another important limitation in this research field is methodological heterogeneity. Overall, there is a substantial overlap in the networks implicated in depression and treatment response, but the exact regions as well as the direction of brain signal change often differs between studies. These methodological differences, especially the choice of regions of interest, make comparisons across studies very difficult, such that it is currently unclear how well results replicate across studies.

tDCS Effects on Resting-State Networks

Effects of tDCS on resting-state networks are reviewed in Chap. 9. Here, we therefore limit our text to highlighting just a few points.

TDCS Effects on the Three Major Resting-State Networks

tDCS has been shown to induce physiological changes in networks associated with depression. Two pre-clinical studies investigated the effects of prefrontal tDCS on resting-state fMRI in healthy participants. In both studies, participants underwent fMRI directly after the application of a single tDCS session. In the first study, real compared to sham tDCS induced changes in connectivity close to the electrodes as well as in more remote regions – the default mode network and bilateral fronto-parietal network [91]. In the second study, active tDCS led to increased synchrony in the executive control network and decreased synchrony in the default mode network [92]. Another study investigated the effects of prefrontal tDCS on resting-state networks using arterial-spin labelling [93]. During anodal stimulation, tDCS induced increases in areas close to the stimulation site. After the stimulation, a decrease in regions associated with the default mode network was observed. These studies demonstrate that DLPFC-targeted tDCS induces metabolic changes in networks implicated in depression. More precisely, tDCS decreased activity in the default mode network and increased activity in the executive control network, consistent with the triple network theory of antidepressant effects. However, these studies were conducted in healthy participants and measured the effects of a single tDCS session. Hence, it remains unclear both what the long-term effects of a daily tDCS treatment protocol over several weeks would be and how those physiological effects would be related to clinical improvement. There are a number of ongoing clinical trials investigating the effects of tDCS on fMRI, which should cast light on these questions, including: "Imaging-Guided tDCS Therapy in Major Depression" (NCT03556124), "Disorder-Tailored Transcranial Direct Current Stimulation (tDCS) of the Prefrontal Cortex: fMRI Study on Major Depression and Schizophrenia" (NCT02715128) and "Functional MRI Study of Transcranial Electric Stimulation in Major Depression" (NCT04031547).

Resting-State Analysis Suggests Alternative Target Regions

Resting-state studies of tDCS network effects have value in suggesting potential alternative treatment targets. The antidepressant effects of TMS and other treatment modalities seem to rely importantly on modulation of the default mode network. Hence, cortical areas closely coupled with the default mode network, and that are easy to reach with NIBS (e.g. medial prefrontal cortex or angular gyrus), might be good alternative targets for depression treatment. One recent study investigated this potential using resting-state connectivity. Zhang and colleagues [94] conducted a meta-analysis to identify brain regions associated with depression. Next, in a sample of depressed patients, they analysed resting-state connectivity to identify cortical regions connected to those brain areas identified by the meta-analysis. Figure 10.5 depicts the resulting maps, which indicate a number of cortical regions that could be targeted by NIBS and potentially serve as a "gateway" to modulate depression networks. This study highlights that the DLPFC is only one out of several possible target regions.

This is further supported by a study that compared effective target regions across invasive and non-invasive stimulation modalities [95]. Deep brain stimulation for depression targets the subgenual ACC directly and reduces hyperconnectivity of the default mode network. NIBS targets DLPFC, which has negative functional coupling with the subgenual ACC, and there is evidence that the effect of NIBD might rely on reducing hyperconnectivity of the subgenual ACC and default mode network [88, 90]. These findings suggest shared mechanisms of treatment action, despite the stimulation modality and target regions (DLPFC vs. sgACC) differing. It further supports the idea that stimulating different subregions of the same network (e.g. default mode network) might induce similar clinical effects.

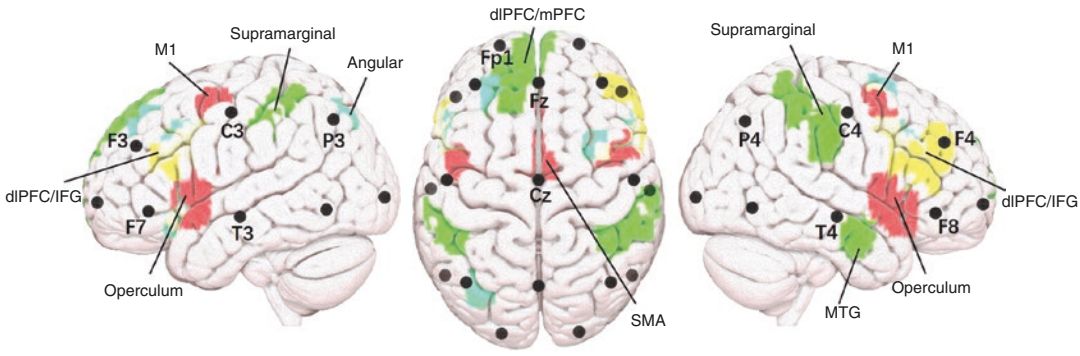

Fig. 10.5 Map of potential cortical target regions connected to areas associated with depression. The different colours refer to three different analysis pipelines. Yellow: cortical regions that are part of the clusters associated with depression. Light blue: cortical areas most strongly correlated to the regions associated with depression (positive correlation). Red and green: Cortical regions correlated with the highest number of depression-associated areas (red: positive correlation, green: negative correlation). (Figure provided by Binlong Zhang, adapted from Ref. [94])

10.3.3 Physiological Effects During Concurrent NIBS and fMRI

Most studies investigating the effects of NIBS have analysed changes in neuroimaging markers after the treatment period. While this kind of design can reveal what has changed in a depressed brain after treatment, it does not illuminate how these changes develop over the course of the treatment. This could be addressed by designs that measure repeatedly throughout the treatment period. For instance, the simultaneous use of NIBS and fMRI offers the opportunity to measure the direct physiological effects of the stimulation. This offers the potential to characterize dynamic treatment-induced changes over time.

To date, only a few studies have combined TMS and fMRI concurrently, and these have focused on the effects of single TMS pulses, enabling brain changes to be linked straightforwardly to stimulation without intervening complications (such as plasticity or mood change associated with chronic repetitive protocols). These studies have aimed to confirm hypotheses derived from previous PET and fMRI studies that could only provide correlative evidence. For instance, two TMS-fMRI studies have confirmed that single TMS pulses applied to the DLPFC can reach subcortical regions relevant to emotion regulation, such as the subgenual ACC and amygdala [96, 97]. Similar work has also shown that TMS pulses applied to the DLPFC can modulate activity and connectivity of the default mode network [97, 98]. Collectively, such studies have provided direct evidence that TMS can indeed induce effects in deep regions and distributed networks implicated in the pathophysiology of depression, such as the default mode network and the subgenual ACC.

The Value of Measuring the Direct Physiological Effects of NIBS

Information about the direct physiological effects of TMS pulses could be leveraged to improve the future clinical application of TMS. For example, stimulation protocols could be optimized to select those that induce greater physiological responses in regions thought to be core to depression pathophysiology or to underlie treatment effects, followed by tests to determine if this causes better clinical improvement. TMS/fMRI can be used to advance personalization, such as by targeting the subject-specific subregion of DLPFC with the highest anticorrelation to the subgenual ACC [36] or the subregion that induces the strongest physiological change in subgenual ACC. Oathes and colleagues stimulated DLPFC subregions with particularly strong connections to subcortical regions of interest and found that stimulation

reliably modulated activity in these subcortical targets [97]. Future studies could test the degree to which personalized connectivity-guided TMS leads to greater physiological engagement of subcortical targets. Clinical studies using personalized stimulation sites are discussed in Sect. 10.5.1.

Differences in the response to single TMS pulses are relevant to understanding heterogeneity in treatment response to TMS. Across healthy participants, Vink and colleagues [96] found large variability in the brain changes induced by TMS to the left DLPFC. Significant effects in the subgenual ACC were observed in only four out of nine participants. Understanding the sources of variation in physiological response is an important precursor to understanding why some patients respond to TMS treatment whereas others do not. Known sources of variability in the response to NIBS include cortical thickness [99], hormones [100] and genetic factors [101] (see [102] for a meta-analysis).

Regarding tDCS, in a recent study anodal, cathodal or sham tDCS was applied during resting-state and task-related fMRI during a simple choice reaction task [103]. This study demonstrated that stimulating the right inferior frontal gyrus, a cortical region of the salience network modulates functional connectivity within that network and between the salience and default mode network, regions implicated in the psychopathology of depression. The changes in functional connectivity induced by tDCS varied not only with stimulation polarity but also with brain state (i.e. changes differed during task performance vs. at rest). The effects of NIBS are known to vary with brain state [104]. Typically NIBS treatment is applied during rest, but brain-state dependency suggests that stimulating during a task that engages cognitive and affective processes relevant to depression could potentially enhance antidepressant effects. For instance, stimulation during a task designed to counteract the negative cognitive biases that maintain depressive symptoms [105] or combining NIBS with cognitive therapy [106, 107] could induce better long-term clinical gains. Cognitive effects of tDCS are reviewed in the Chaps. 17 and 29.

10.3.4 Effects on Task fMRI

Task-related imaging characterizes brain activity (or connectivity) during the performance of a behavioural task. In the analysis of data, brain activity is usually contrasted between two different task conditions (one of which might be rest) so that the resulting contrast images display brain regions that are activated to a greater or lesser extent in one condition compared to the other. In contrast to resting-state imaging, which visualizes the whole brain, task-related imaging is focused on brain regions where there are differences in activity between task conditions.

Therefore, the greatest challenge of investigating task-related effects is the choice of behavioural paradigm. The chosen task should engage brain circuits associated with depression, ideally prefrontal cortical regions as well as limbic areas. One possible approach for task selection would be to pilot cognitive and affective tasks in participants with varying levels of depressive symptoms and test for task parameters that are associated with depression. Neuroimaging could then be used to assess differences in task-related brain activity in healthy versus depressed participants and, for example, test whether TMS treatment normalizes task performance and related imaging markers.

To date, most research combining NIBS and imaging has focused on resting state for two good reasons: the practical advantages, such as short acquisition time and good comparability of data across studies, and because rumination, a cardinal feature of depression, is associated with the default mode network, which is activated during rest. However, in everyday life, the difficulties caused by depressive symptoms manifest in situations where patients interact with others and their environment, and such behaviours depend on brain circuits that are recruited during cognitive and affective processing [108]. For instance, patients with depression commonly exhibit a negative cognitive bias in which they focus more on negative than positive information. Effective antidepressant treatments, such as drugs and cognitive behavioural therapy, have been shown to reduce negative biases, and this has been shown to precede and predict clinical response [109].

This suggests the hypothesis that depression treatments may share common cognitive mechanisms of treatment action, such as reducing negative bias, which may also contribute to effective NIBS treatment [23, 110, 111]. Task-related imaging could be used to investigate this.

A number of proof-of-concept studies have investigated the effects of NIBS on task-related imaging in healthy volunteers. In one study, healthy women were presented with positively or negatively valenced baby faces after one TMS session. Right-sided (but not left-sided) high-frequency stimulation resulted in blunted responses of the amygdala to negative faces [112]. In a second study in healthy women using the same task, sham stimulation compared to left-sided high-frequency prefrontal TMS increased activity in the left superior frontal cortex and right inferior parietal cortex in response to positive faces, and decreased activity in the right insula in response to negative faces [113].

With respect to tDCS, two studies showed that prefrontal tDCS can reduce vigilance to threatening stimuli in healthy participants and individuals with high state anxiety, suggesting a potential cognitive mechanism that could contribute to symptom improvement [110, 111]. This behavioural effect was associated with a reduced response of the amygdala to negative stimuli and increased activity in cortical control regions [110]. Another study analysed the influence of tDCS targeting the medial prefrontal cortex on the processing of negative or neutral video clips [114]. Compared to sham stimulation, real tDCS reduced participants' intensity ratings and self-reported stress levels in response to negative stimuli. tDCS also increased activity in the medial prefrontal cortex in response to negative stimuli, a possible correlate of enhanced regulation of negative affect. There was a trend-level increase in subgenual ACC activity, which would normally be associated with increased experience of negative emotions and might thus indicate an unfavourable effect. The stimulation also modulated connectivity in a network related to emotion regulation, comprising the ventromedial prefrontal cortex, subgenual ACC, amygdala and ventral striatum. In another study, anodal compared to cathodal tDCS targeting the ventromedial prefrontal cortex led to increased activity in occipital, temporal and frontal areas in response to pleasant scenes [115]. Two studies analysed tDCS effects on women scoring high on perceived criticism. In response to real compared to sham tDCS, decreased perfusion in the perigenual anterior cingulate cortex and medial prefrontal cortex was observed after being criticized, which might indicate a downregulation of negative emotion processing [116]. In a second study, reduced connectivity between the left DLPFC and insula were observed in response to tDCS, indicating modulation of the interplay between executive control network and salience network [117]. Neither study on perceived criticism found effects of tDCS on mood.

These studies suggest that NIBS has effects on networks relevant to processing of affective stimuli and emotion regulation. Overall, the physiological effects seem to be in the direction beneficial for depression treatment, that is, increased processing of positive stimuli and downregulation of negative emotions. Corresponding behavioural changes have not always been observed, potentially because more than one stimulation session might be necessary to induce such changes. These studies also investigated the effects of a single stimulation session in healthy participants, so that it is unclear what effects repeated stimulation sessions would have on patients suffering from depression.

Two studies investigated the effects of TMS treatment on task-related imaging in patients suffering from depression. In one study, single photon emission computed tomography was used to investigate brain perfusion related to a verbal fluency task before and after the first TMS session of a 10-day treatment [118]. Verbal fluency tasks have been shown to induce wide-spread activity in areas relevant to depression, such as the prefrontal cortex and subcortical regions [119]. The task was performed directly after injection of a radiotracer. TMS led to increased activation of the ACC and increased connectivity of dorsolateral and medial prefrontal to limbic regions. In

another study [120], differences in fMRI activation in relation to a planning task before and after 3 weeks of TMS treatment were analysed. Responders showed significant changes in task-related activity in prefrontal areas, depending on the stimulation frequency applied.

The value of both studies is limited by their small sample sizes, especially regarding the fact that different frequencies were applied within the studies. The observed connectivity changes between cortical control regions and limbic areas are in line with the hypothesis that TMS improves processes involved in emotion regulation. However, no convincing relationship between the physiological effects and symptom improvement was observed. More research is needed to evaluate how the physiological effects of NIBS treatment relate to clinically relevant cognitive changes. Future studies could try to use behavioural paradigms that are more closely associated with depression than verbal fluency or planning tasks, for example a task testing for negative attentional or cognitive biases (such as the one used in the studies on vigilance to threat [110, 111]), since changes in such tasks are more likely to have clinical relevance (see Chaps. 17 and 29 for a review of cognitive effects of tDCS).

10.3.5 Structural Changes in Response to NIBS Treatment

Depression has been associated with structural brain change, especially in fronto-limbic networks involved in emotion regulation [121]. Animal models have demonstrated that TMS can induce structural changes by increasing neurogenesis in the hippocampus [122]. In humans, structural changes have been observed in response to electro-convulsive therapy [123, 124], suggesting the possibility that this might also contribute to TMS treatment effects.

A few studies have tested whether TMS treatment induces structural changes in medial temporal lobe areas. In one study, treatment responders showed a trend-level increase in the volume of the left amygdala, but not the hippocampus [125]. Another study observed the opposite pattern, that is, significant volume increases in the left hippocampus, but not in the amygdala [126]. Volume increases in the hippocampus were also observed by Noda and colleagues [127] although neither of these two studies found a correlation between volume increase in the hippocampus and clinical improvement. Similar structural changes in the temporal lobe have been observed in response to electro-convulsive therapy, also without any association with clinical improvement [128].

One study focused on whole-brain grey matter to test whether TMS can induce structural changes in brain areas that show abnormal structure in depression [129]. They found that increases in grey matter volume in the left ACC, a region which showed reduced volume in depressed patients compared to healthy controls at baseline, correlated with symptom improvement.

Another study investigated whether TMS alters structural connectivity by inducing changes in white matter microstructure [130]. The authors compared white matter integrity between patients and healthy controls and found reductions in patients in the left middle frontal gyrus. Compared to sham, TMS increased white matter integrity in this area and this correlated with symptom improvement. These results suggest increases in white matter integrity in the left middle frontal gyrus might be a structural correlate of TMS treatment effects.

All of these studies compared structural neuroimaging data before versus after treatment. In most studies, no relationship between structural changes and symptom improvement was found. In general, it is unclear how structural changes relate to functional changes. Nonetheless, these studies support the hypothesis that NIBS has an effect on subcortical, especially limbic areas, which might mediate antidepressant effects. Further research on structural effects might help to understand how these relate to clinical change and hence how TMS parameters could be improved to maximize the relevant effects.

10.3.6 Summary

Summary: Imaging Insights into Mechanisms of NIBS Treatment Action

- The modulation of subcortical limbic areas related to emotional response seems to play an important role in the antidepressant effect of NIBS treatment.
- Therefore, connectivity between the cortical target area and subcortical regions (in particular, the subgenual ACC) is especially relevant.
- Resting-state network analysis suggests several potential novel NIBS target regions (cortical regions of the default mode network) of which very few have been investigated so far.

10.4 Predictors of Treatment Response

The central clinical challenge in treating depression is to find the right treatment for the right individual. For NIBS, as for other treatments, clinical response varies a lot between patients, so it would be very beneficial to be able to predict in advance whether an individual is likely to respond to a given treatment or not. Neuroimaging treatment predictors are analysed by acquiring structural or functional brain images at baseline and relating brain characteristics to the clinical outcome after the treatment period. The most common approach is to categorize patients into "responders" versus "non-responders" and then analyse differences in baseline brain imaging markers between these two groups. Treatment response is typically defined as a reduction of at least 50% in a standard clinical depression questionnaire after 4–6 weeks of treatment.

The prediction of treatment response is still a young field of research. The current state of the field is at the beginning of testing the first algorithms for prediction in prospective clinical trials.

10.4.1 Predictors Based on PET

One of the first studies to investigate treatment predictors was by Kimbrell and colleagues [72] in which they hypothesized that global brain metabolism at baseline could predict clinical response to high- versus low-frequency stimulation. The results of the study were not convincing, but nonetheless this early study had value in suggesting that baseline neuroimaging markers might have predictive utility.

Later studies focused on the metabolism in mainly frontal regions that had previously been associated with treatment effects. Kito and colleagues hypothesized that treatment response depends on relative metabolism in dorsolateral prefrontal regions associated with top-down control versus ventromedial regions related to emotional response [131, 132]. Therefore, they calculated a ratio metric, by dividing the average metabolism in the DLPFC by the metabolism in the ventromedial prefrontal cortex. They found that the response to high-frequency left-sided TMS correlated with the ratio of DLPFC/ventromedial prefrontal cortex activity, with a smaller ratio predicting better response [131]. With respect to low-frequency stimulation to the right hemisphere, better treatment outcome was associated with higher ventromedial prefrontal cortex baseline activity [132]. Taken together, for both types of TMS treatment, high baseline activity in the ventromedial prefrontal cortex seemed to be associated with successful improvement. With respect to the triple network model of psychopathology, this is consistent with the theory that depression is associated with hyperactivity in the default mode network, and that this is reduced by effective treatment.

Based on the findings that TMS modulates activity in frontal cortical and related subcortical areas, other studies have conducted region-of-interest analyses of these areas. Baeken and colleagues tested whether baseline metabolism in the DLPFC and ACC could predict treatment response [76]. They found that higher levels of metabolism in both areas were associated with better clinical outcome. Higher ACC metabolism

was also found to be predictive of better response in another study [133]. In response to accelerated high-frequency treatment, patients with higher subgenual ACC metabolism showed better clinical improvement [77].

The importance of the ACC has also been highlighted in the general literature on psychopathology. Reduced grey matter volume in the dorsal ACC has been shown to be a common neurobiological substrate across several mental disorders, including depression, addiction and schizophrenia [134]. The predictive potential of ACC neuroimaging markers in depression has also been reported in other treatment modalities. For instance, activity and connectivity of the ACC has been found to predict treatment response to selective serotonin reuptake inhibitors [135, 136]. Therefore, the ACC might be a general predictor of treatment response in depression across different treatment modalities including NIBS.

There are some methodological problems that make conclusions about the predictive potential of baseline metabolism difficult. First, some studies only contrast responders versus non-responders, whereas clinical improvement is a continuous variable (patients improve to a certain extent) and so correlations between baseline metabolism and degrees of improvement could arguably be more informative. Second, many studies use region-of-interest approaches, that is, they restrict their analysis to certain pre-defined brain regions. This is a useful approach to test specifically whether a certain brain area might have predictive value, but it does not allow for comparison of predictive potential across brain regions. This also hinders comparison across studies that use different regions of interest. Finally, most studies do not report the prediction accuracy of the neuroimaging markers found to have predictive potential. This is a major problem, since prediction accuracy is the metric that allows for quantification of the predictive value and for relative comparison across studies and different potential predictors.

One positive example is a study conducted by Richieri and colleagues, who used a whole-brain approach [137]. They found that non-responders compared to responders showed decreased perfusion in four clusters, the left and right prefrontal cortices, the left parahippocampal cortex and the right thalamus. Based on these four clusters, a discriminant analysis was performed which yielded an *area under the curve* (a standardized measure for prediction accuracy) of 0.89 (sensitivity = 0.94, specificity = 0.73). This study is worth highlighting, since it used a whole-brain approach and reported a standardized measure of prediction accuracy.

10.4.2 Predictors Based on Resting-State Connectivity

The majority of studies investigating resting-state connectivity as a predictor of treatment response have focused on subgenual ACC functional connectivity and have built upon a seminal study by Fox and colleagues [36] (for details see Box 10.3). Based on findings highlighting the role of the subgenual ACC in depression [28, 33] that study tested the hypothesis that variation in TMS clinical efficacy would be related to differences in the precise location of the TMS target within DLPFC. Specifically, stronger clinical response would be associated with stronger negative functional coupling between DLPFC and subgenual ACC. They used a large sample of healthy participants to calculate group-averaged resting-state connectivity between the subgenual ACC and the different DLPFC target coordinates used in previous treatment studies. They confirmed the hypothesis both for the group-averaged DLPFC coordinates as well as for the coordinates from individual patients.

This same study suggests a model of treatment action: that DLPFC TMS reduces the hyperactivity in the default mode network typically observed in depression. The negative functional connectivity between DLPFC (part of the executive control network) and subgenual ACC (connected to the default mode network) suggests that exciting DLPFC would induce inhibitory effects in the default mode network, and this would be expected to have antidepressant effects. Further, this study suggests that DLPFC-subgenual ACC

functional connectivity strength might predict treatment outcome, thus indicating a personalization approach: to improve efficacy, apply TMS to the subregion of the DLPFC with the strongest negative correlation to the subgenual ACC in each individual.

A number of studies have been conducted to replicate and extend these findings. It has been shown that measures of connectivity strength between parts of the DLPFC and subgenual ACC can be reproduced across sessions [138]. Subgenual ACC connectivity has also been found to correlate with improvements in affective and cognitive but not somatic symptoms, suggesting that the clinical efficacy of this approach might depend on individuals' symptom profile [139].

This line of work is a positive example of a research finding that has been replicated and extended by other groups. While these studies above have aimed at identifying the optimal (individual) target region, other studies have analysed connectivity features to predict who will respond to a given treatment.

For instance, Baeken and colleagues tested in two studies whether whole-brain subgenual ACC connectivity could predict response to TMS treatment [86, 87]. Negative connectivity between subgenual ACC and superior middle frontal gyrus predicted better response to accelerated high-frequency stimulation while positive connectivity between subgenual ACC and medial OFC predicted better response to accelerated intermittent theta burst TMS. Ge and colleagues tested the predictive value of connectivity of the subgenual ACC and rostral ACC to all other areas of the brain [140]. They found that decreased connectivity between subgenual ACC and right DLPFC and increased connectivity between rACC and inferior parietal lobe predicted clinical improvement. These two connectivity features reached classification accuracies of 84% and 76%, respectively.

While most studies have focused on subgenual ACC connectivity, it is important to also consider connectivity between other regions, since taking multiple connectivity features into account is likely to improve prediction accuracy. For instance, one study found that not only subgenual ACC but also perigenual ACC connectivity to the stimulation site was predictive of clinical effectiveness, indicating that subgenual ACC connectivity is not the only potentially useful predictor [141].

Other studies have focused on connectivity between networks, rather than discrete regions, thereby considering a larger number of areas throughout the brain. Liston and colleagues [90] analysed connectivity from the DLPFC and subgenual ACC to the default mode and executive control networks and found that higher connectivity of the subgenual ACC to the default mode and executive control networks predicted better treatment outcome. Another study [88] found that more negative connectivity of the subgenual ACC to the default mode network and stronger connectivity between the amygdala and ventromedial prefrontal cortex was associated with better treatment response. Unfortunately, neither of these studies reported prediction accuracy, so it is difficult to judge whether prediction based on these connectivity features would have significant clinical value, or how these connectivity markers compare to other potential predictors from other studies. To achieve prediction accuracy high enough to be applied in clinical practice, it will likely prove useful to combine multiple imaging biomarkers.

With respect to multivariate analyses, a study by Cash and colleagues [142] is worth highlighting. They compared patients and healthy controls at baseline and found that patients showed decreased BOLD power in the medial prefrontal cortex and some subcortical regions and decreased functional connectivity within a network involved in emotion regulation. Better clinical improvement in response to TMS was associated with three imaging markers: lower BOLD signal power in the medial prefrontal cortex and subcortical regions including the ACC and decreased functional connectivity within the emotion regulation network and the default mode network. The authors developed multivariate classifiers based on these three imaging markers and reached an accuracy level of 85% (sensitivity = 75%, specificity = 92%). When they included "clinical improvement after one

week of treatment" as a fourth predictor variable, classification accuracy improved to 93% (sensitivity = 95%, specificity = 92%). Individual improvement in depressive symptoms score could be predicted with an average error of 16%. The results of this study need to be validated in a larger clinical sample, but they nonetheless illustrate how machine learning can be used to identify and combine different potential outcome predictors. Another positive aspect is that the authors applied a regression method to predict the expected amount of clinical improvement, rather than classifying patients into responder versus non-responder categories. This is relevant since clinical improvement is a continuous variable, and classification into a binary outcome is less precise and less meaningful than predicting the degree of clinical improvement.

10.4.3 Predictors Based on Task-Related Activity

Only a small number of studies have investigated task-related activity as a treatment response predictor. One TMS study [143] used a word generation task, chosen because the task activates a distributed network of areas relevant to depression, such as the prefrontal cortex and subcortical regions, thus providing a measure of functional recruitment of these networks [119]. Patients performed the word generation task in the scanner prior to treatment onset. Symptom improvement was correlated with baseline characteristics of smaller task-induced deactivations in the perigenual cortex, medial orbitofrontal cortex and middle frontal cortex and larger task-induced activations in parts of the putamen. These results suggest that task-related activity in regions associated with emotion processing, such as prefrontal and limbic regions, might have predictive value.

One study examined imaging predictors of clinical response to a treatment involving tDCS and psychotherapy [106]. At baseline, greater activation of the stimulation target, the left DLPFC, during a working memory task was associated with better clinical improvement in the active but not in the sham tDCS group, suggesting that DLPFC activity specifically predicted improvement in response to combined tDCS/psychotherapy rather than psychotherapy alone. This suggests baseline activation of the DLPFC as a candidate predictor of response to tDCS treatment.

Further research is needed to evaluate how far task-related imaging markers can contribute to outcome prediction relative to resting-state measures.

10.4.4 Structural Predictors

To date, only a small number of studies have explored structural predictors of TMS treatment response. Some indicate that structural characteristics might have predictive value, including cortical thickness of the left rACC [144], the volume of medial temporal lobe structures [145], structural connectivity between the individual stimulation site and parts of the cingulate cortex [146] as well as structural integrity, an alternative measure of network connectivity, of the executive control network [147]. More research is needed to evaluate the relative predictive value of structural markers versus resting-state connectivity markers.

With respect to tDCS, brain anatomy seems to be an important factor determining the physiological effects. Opitz and colleagues [42] showed that the distribution and strength of electric fields induced by tDCS depend strongly on individual anatomical features, including skull thickness and composition, thickness of cerebral spinal fluid and sulcal depth. The brain regions stimulated by the same electrode montage can differ considerably across individuals. The influence of anatomical factors is so strong that, in some individuals, different stimulation hotspots in the brain can arise that will receive a high field strength even if the electrode position is varied. This implies that adjusting the electrode position to target a specific brain region might be more difficult than expected. Therefore, structural features might be particularly relevant features for predicting clinical response to tDCS treatment.

To date, only one clinical tDCS trial involving neuroimaging has been completed [148]. There were two important findings regarding structural predictors. First, prefrontal grey matter volume at baseline was found to correlate with clinical improvement [44]. The region associated with clinical improvement was located medial to the electrode placed on the left DLPFC, in line with the finding that the e-field strength induced by a bilateral electrode montage is highest in the medial prefrontal cortex [45, 43]. Second, correlations between the simulated electric field strength in the ACC and DLPFC with reduction in negative affect and between field strength in the left ACC and depressive symptom improvement were found [66]. Although these findings need to be replicated in future clinical trials, they suggest that anatomical aspects might play an essential role in the prediction of clinical response to tDCS treatment and highlight the importance of the combined use of individual structural imaging and electric field modelling.

10.4.5 Summary

Summary: Predictors of Treatment Response

- Activity and connectivity in several brain regions have been proposed as potential predictors for clinical response to TMS treatment.
- The most promising predictor seems to be connectivity between the stimulated region and subcortical areas related to the default mode network.
- Rather than predicting a binary outcome (i.e. response vs. non-response), the degree of symptom improvement could be predicted on a continuous scale.
- Future studies should test what prediction accuracies can be achieved by combining multiple biological markers.
- Prospective clinical studies are needed to test how proposed predictors would perform in practice.

10.5 Individualized Treatment

Depression is a very heterogenous disease – symptoms and brain dysfunctions vary widely across patients. Consequently, it is unlikely that all patients will respond to the same treatment. A potential solution is to tailor treatment to individuals. With regard to brain stimulation, such research has mostly focused on individualizing the target region.

The idea of personalizing TMS treatment is not new, but successful approaches have only been reported in recent years. The earliest studies attempted to personalize treatment by identifying individual prefrontal cortical regions displaying hyper- or hypometabolism and applying a TMS frequency in order to "normalize" metabolism in this area. These failed attempts include a study in which the target region was personalized by applying the stimulation to the less active side of the DLPFC, as determined by PET [149]. In another study [150], the personalized group received high-frequency TMS to a hypoactive region and low-frequency TMS to a hyperactive region. In a third study [151], TMS was applied to the least active region of the left or right prefrontal cortex. None of these studies observed a significant difference between personalized and standard stimulation. In a more recent study [152], personalizing the target region based on hypometabolism showed a better response rate. In the personalized condition, TMS was applied to a hypometabolic prefrontal region, and this was more effective than standard treatment. However, due to the small sample size (13 patients in the personalized group, 7 patients in the standard group), the generalizability of this finding is questionable.

One general problem of these studies is the use of small sample sizes, since this increases the risk of false positive findings and at the same time reduces the likelihood of detecting differences between conditions, particularly given the heterogeneity of patient populations [153]. More recent findings have suggested that the antidepressant effect of TMS relies on induced changes in activity and connectivity of subcortical areas (see previous sections), such that adjusting TMS

treatment based on metabolism in prefrontal cortical areas, as above, is unlikely to be key to improving treatment outcome.

In recent literature, two general approaches to treatment individualization have emerged. One approach is to optimize stimulation targeting at the cortical level to take account of individual differences in structural and functional anatomy. Another is to categorize patients into different subgroups and tailor stimulation differently for each group based on what the imaging data indicates is likely to be the most effective stimulation target.

10.5.1 Adjusting the Target Region Based on Individual Anatomy

Most effort has aimed to optimize coil placement to the coordinates that overlap with DLPFC-sgACC negative functional coupling, based on Fox and colleagues' influential finding that this connectivity strength measure relates to clinical improvement [36] (see Box 10.3). Their finding suggests that coil targeting could be personalized by stimulating in each individual that subregion within DLPFC with the strongest anticorrelation to subgenual ACC. However, the study used group-averaged connectivity, precluding direct conclusions about the relationship between individual connectivity and treatment response. Two studies have tried to replicate the findings on an individual-patient level. One study [154] found that treatment outcome could be predicted based on individual DLPFC-sgACC connectivity. In another study [155], no such relationship was found. Therefore, it is currently unclear whether this approach to personalization is likely to enhance treatment effectiveness. Translating neuroimaging analyses based on group averages to individuals is often difficult due to methodological problems such as low signal-to-noise ratio in the areas of interest or low retest reliability of functional connectivity measures.

A point that highlights that treatment individualization is still in early stages is the fact that all of these studies that built on the findings by Fox and colleagues [36] used retrospective analyses. None has yet attempted to personalize the stimulation site in advance of treatment. A notable exception is one ongoing clinical trial [37] in which personalized prospective targeting of DLPFC-subgenual ACC based on maximal functional connectivity anticorrelation is being combined with a new accelerated high-dose iTBS protocol. With this protocol, a response rate of 90% was observed in the open-label pilot study. However, there was no control group, so it is currently unclear whether the high response rate was a consequence of the personalized target position, the accelerated stimulation protocol or both. Further conclusions await the results of the placebo-controlled double-blinded clinical trial.

10.5.2 Categorization into Different Subtypes of Depression

An alternative approach is to categorize patients into different depression subtypes and target stimulation at the brain regions thought to best engage the relevant dysfunctional brain circuitry. Downar and colleagues [53] used this approach to retrospectively investigate potential predictors of treatment response to dorsomedial prefrontal cortex TMS. Non-responders had significantly stronger anhedonia at baseline and lower connectivity in a reward pathway comprising the ventral tegmental area, the striatum and lateral orbitofrontal cortex. The authors suggested the existence of two different depression subtypes, one with preserved hedonic function that responds to dorsomedial prefrontal cortex TMS treatment and one with pronounced anhedonia that is unresponsive to dorsomedial prefrontal TMS. This latter group had abnormal connectivity in lateral orbitofrontal cortex, suggesting that region as a potential alternative personalized TMS treatment target.

In that study, the categorization into subtypes was based on the clinical response to TMS treatment. In contrast, Drysdale and colleagues [156] hypothesized that depressed patients could be grouped into subtypes based on correlated clinical and imaging markers. They found four distinct "biotypes" of depression – patterns of

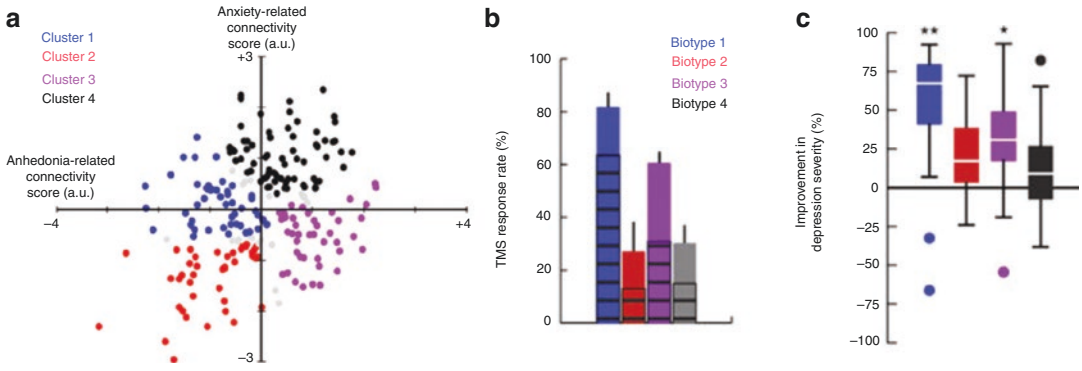

Fig. 10.6 The four different biotypes of depression identified by Drysdale and colleagues [156] based on connectivity profiles. (**a**) The clusters of the four biotypes plotted along the two connectivity scores. (**b**) Percentage of TMS response for each of the four biotypes. (**c**) Percent of improvement in depression score in response to TMS. (Reproduced from Ref. [156] with permission)

abnormal functional connectivity in limbic and fronto-striatal networks (Fig. 10.6a) that covaried with differing levels of anhedonia and anxiety symptoms. These four biotypes also differed in their responsiveness to TMS treatment applied to the dorsomedial prefrontal cortex (Fig. 10.6b, c), which suggested that the different subtypes may have different optimal TMS treatment targets. Because of the potential clinical implications, this study has attracted a lot of attention but needs to be interpreted with caution since it has also earned criticism regarding methodological shortcomings [157, 158].

While the previous studies aimed at identifying subcategories of depression, another study investigated how target regions are associated with improvement in specific symptom clusters [159]. The authors created connectivity maps for the TMS targets of individual patients based on the resting-state data of a large connectome database. Across patients, each voxel's connectivity to the target region was correlated to improvement in each depressive symptom, so that each of the resulting maps corresponded to the degree to which each voxel's connectivity with the target region predicted improvement in a specific symptom. Since there were similarities between these symptom-response maps, they were categorized into two clusters. The "dysphoric" cluster included symptoms such as sadness, decreased interest and suicidality, whereas the "anxiosomatic" cluster was associated with irritability, sexual disinterest and insomnia (Fig. 10.7). In further analysis steps, symptom-response maps for the two clusters were combined, which resulted in a map indicating to what extent stimulating a region would result in the reduction of "dysphoric" or "anxiosomatic" symptoms. This map retrospectively explained improvements in different symptoms across 14 different TMS studies. The results of this study have potential clinical value since the map could be used to personalize the target region based on the symptom profile of a given patient. This needs to be validated in a prospective clinical trial to test whether individually tailored treatment does improve outcomes.

10.5.3 Summary

Summary: Individualized Treatment

- Approaches for personalizing NIBS treatment can be grouped into two categories:
  - Categorize patients into different subgroups based on symptoms and/or neuroimaging markers and apply the treatment that this patient category should respond best to adjust stimulation positioning to accommodate individual anatomical variation, such as the optimal scalp location for stimulation to engage specific cortico-limbic circuits.

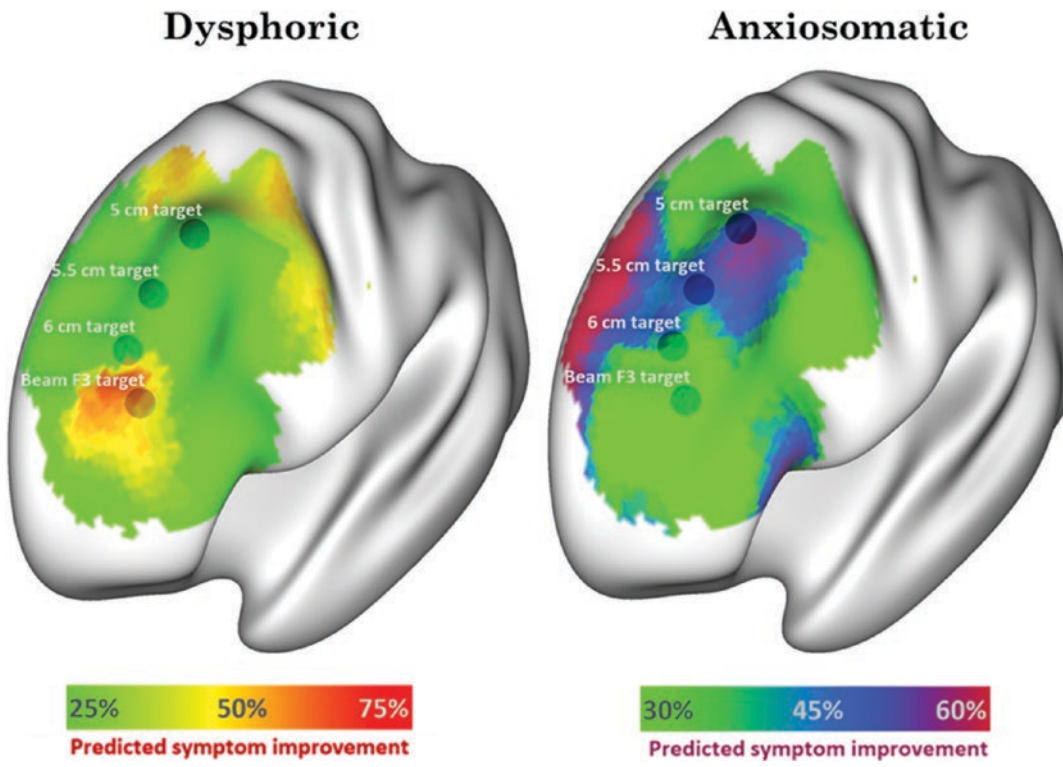

Fig. 10.7 Association between potential target regions and improvement in two different symptom clusters as proposed by Siddiqi and colleagues [159]. The two maps the predicted improvement in dysphoric or anxiosomatic symptoms for potential TMS target regions. The overlaid dots represent common target areas. (Figure provided by Shan Siddiqi, adapted from Ref. [159])

- Although there are promising findings in retrospective analyses, all findings reviewed here still need to be validated in large prospective clinical trials to compare their efficacy to standard treatment.
- Personalizing other protocol parameters such as stimulation frequency or intensity is likely to further optimize treatment.

10.6 Conclusions and Challenges

This chapter, especially the last sections, clearly highlights the progress that has been made in this field over the course of the last decade. The field of combined NIBS/neuroimaging research in psychiatry has moved from simply contrasting brain activity before versus after treatment to more sophisticated approaches aimed at treatment prediction and personalization using connectivity analyses and machine learning.

The most important methodological barrier to progress in this field at present is lack of comparability across studies. Most studies differ in their methods, including stimulation and imaging parameters, as well as analysis approaches, which makes comparisons across studies very difficult. To enable the comparison of predictive values across studies, criteria of prediction accuracy need to be reported, which is now being done more frequently than in the past.

Several issues remain that need to be addressed in the future. For instance, large intra-individual variability in the response to tDCS has been observed both behaviourally and in resting-state connectivity [160]. More research is needed to understand what factors underlie variability and how the treatment can be adjusted to induce more reliable effects.

Another challenge is to move the analyses from the group level to the individual patient level. Most studies have analysed group-averaged data so that it is unclear how claims translate to the individual level. For instance, the influential findings of the study by Fox and colleagues [36] were in group-averaged data and were not replicated in a study of individual patient data [155].

Although various approaches for predicting treatment outcome and personalizing treatment have been proposed, large-scale clinical trials have not yet been conducted. These are necessary to determine how accurate predictions for individual patients are and to what extent individualized treatment improves clinical improvement compared to standard treatment.

Ongoing clinical trials include the "DepressionDC" trial using tDCS as add-on therapy to an antidepressant drug [161], the "PsychotherapyPlus" trial combining tDCS and psychotherapy [162] and a clinical trial investigating the antidepressant effect of tACS [163]. All of these trials include the acquisition of neuroimaging data which will help to gain a better understanding of the effects and predictors of tDCS treatment.

Another factor worth considering with regard to clinical translation is that time, effort, analysis expertise and costs limit the practicability of advanced neuroimaging procedures in altering routine clinical practice. From this point of view, a treatment predictor based on clinical or behavioural data would be easier to translate than one based on functional neuroimaging data. Therefore, practicability is an important consideration in the development of predictors and treatment personalization.

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References

1. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet. 1996;348(9022):233–7. https://doi.org/10.1016/s0140-6736(96)01219-6.
2. George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. Depression. 1994;2(2):59–72. https://doi.org/10.1002/depr.3050020202.
3. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62(11):1208–16. https://doi.org/10.1016/j.biopsych.2007.01.018.
4. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010;67(5):507–16.
5. Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry. 2015;14(1):64–73.
6. National Institute for Clinical Excellence. Repetitive transcranial magnetic stimulation for depression. 2015. https://www.nice.org.uk/guidance/ipg542. Accessed Aug 2020.
7. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79(1). https://doi.org/10.4088/JCP.16cs10905.
8. Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul. 2016;9(3):336–46. https://doi.org/10.1016/j.brs.2016.03.010.
9. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018;391(10131):1683–92. https://doi.org/10.1016/s0140-6736(18)30295-2.
10. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014;44(2):225–39. https://doi.org/10.1017/S0033291713000512.

11. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–83. https://doi.org/10.1016/j.jad.2019.04.041.
12. Shaw MT, Kasschau M, Dobbs B, Pawlak N, Pau W, Sherman K, et al. Remotely supervised transcranial direct current stimulation: an update on safety and tolerability. J Vis Exp. 2017;(128). https://doi.org/10.3791/56211.
13. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95. https://doi.org/10.1016/j.brs.2011.03.002.
14. Arfai E, Theano G, Montagu J, Robin A. A controlled study of polarization in depression. Br J Psychiatry. 1970;116(533):433–4.
15. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9(10):2257–60.
16. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633.
17. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006;8(2):203–4.
18. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91. https://doi.org/10.1001/2013.jamapsychiatry.32.
19. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31. https://doi.org/10.1192/bjp.bp.115.164715.
20. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376(26):2523–33. https://doi.org/10.1056/NEJMoa1612999.
21. National Institute for Clinical Excellence. Transcranial direct current stimulation (tDCS) for depression. 2015. http://nice.org.uk/guidance/ipg530. Accessed Aug 2020.
22. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483–506. https://doi.org/10.1016/j.tics.2011.08.003.
23. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci. 2011;12(8):467–77. https://doi.org/10.1038/nrn3027.
24. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010;214(5–6):655–67. https://doi.org/10.1007/s00429-010-0262-0.
25. Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci. 2013;7:930. https://doi.org/10.3389/fnhum.2013.00930.
26. Cooney RE, Joormann J, Eugene F, Dennis EL, Gotlib IH. Neural correlates of rumination in depression. Cogn Affect Behav Neurosci. 2010;10(4):470–8. https://doi.org/10.3758/CABN.10.4.470.
27. Beck AT. Depression: clinical, experimental, and theoretical aspects. New York: Hoeber Medical Division, Harper & Row; 1967.
28. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry. 2007;62(5):429–37. https://doi.org/10.1016/j.biopsych.2006.09.020.
29. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol. 2001;11(2):240–9.
30. Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biol Psychiatry. 2002;51(9):693–707.
31. Gotlib IH, Hamilton JP. Neuroimaging and depression. Curr Dir Psychol Sci. 2008;17(2):159–63. https://doi.org/10.1111/j.1467-8721.2008.00567.x.
32. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J. Depression, rumination and the default network. Soc Cogn Affect Neurosci. 2011;6(5):548–55. https://doi.org/10.1093/scan/nsq080.
33. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651–60. https://doi.org/10.1016/j.neuron.2005.02.014.
34. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. Lancet Psychiatry. 2017;4(11):839–49. https://doi.org/10.1016/s2215-0366(17)30371-1.
35. Merkl A, Aust S, Schneider GH, Visser-Vandewalle V, Horn A, Kuhn AA, et al. Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a double-blinded randomized controlled study and long-term follow-up in eight patients. J Affect Disord. 2018;227:521–9. https://doi.org/10.1016/j.jad.2017.11.024.

36. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry. 2012;72(7):595–603. https://doi.org/10.1016/j.biopsych.2012.04.028.
37. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. Am J Psychiatry. 2020:appi-ajp201919070720. https://doi.org/10.1176/appi.ajp.2019.19070720.
38. Chen J, Zhou C, Wu B, Wang Y, Li Q, Wei Y, et al. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. Psychiatry Res. 2013;210(3):1260–4. https://doi.org/10.1016/j.psychres.2013.09.007.
39. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatr. 2006;163(1):88–94.
40. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry. 2008;63(4):369–76. https://doi.org/10.1016/j.biopsych.2007.05.033.
41. Gomez-Tames J, Hamasaka A, Hirata A, Laakso I, Lu M, Ueno S. Group-level analysis of induced electric field in deep brain regions by different TMS coils. Phys Med Biol. 2020;65(2):025007. https://doi.org/10.1088/1361-6560/ab5e4a.
42. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. NeuroImage. 2015;109:140–50. https://doi.org/10.1016/j.neuroimage.2015.01.033.
43. Karabanov AN, Saturnino GB, Thielscher A, Siebner HR. Can transcranial electrical stimulation localize brain function? Front Psychol. 2019;10:213. https://doi.org/10.3389/fpsyg.2019.00213.
44. Bulubas L, Padberg F, Bueno PV, Duran F, Busatto G, Amaro E Jr, et al. Antidepressant effects of tDCS are associated with prefrontal gray matter volumes at baseline: evidence from the ELECT-TDCS trial. Brain Stimul. 2019;12(5):1197–204. https://doi.org/10.1016/j.brs.2019.05.006.
45. Csifcsák G, Boayue NM, Puonti O, Thielscher A, Mittner M. Effects of transcranial direct current stimulation for treating depression: a modeling study. J Affect Disord. 2018;234:164–73. https://doi.org/10.1016/j.jad.2018.02.077.
46. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204. https://doi.org/10.1016/j.neuron.2010.03.035.
47. Gomez-Tames J, Asai A, Hirata A. Significant group-level hotspots found in deep brain regions during transcranial direct current stimulation (tDCS): a computational analysis of electric fields. Clin Neurophysiol. 2020;131(3):755–65. https://doi.org/10.1016/j.clinph.2019.11.018.
48. Ruffini G, Wendling F, Sanchez-Todo R, Santarnecchi E. Targeting brain networks with multichannel transcranial current stimulation (tCS). Curr Opin Biomed Eng. 2018;8:70–7. https://doi.org/10.1016/j.cobme.2018.11.001.
49. Fischer DB, Fried PJ, Ruffini G, Ripolles O, Salvador R, Banus J, et al. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. NeuroImage. 2017;157:34–44. https://doi.org/10.1016/j.neuroimage.2017.05.060.
50. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord. 2018;33(4):642–6. https://doi.org/10.1002/mds.27300.
51. Bikson M, Brunoni AR, Charvet LE, Clark VP, Cohen LG, Deng ZD, et al. Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul. 2018;11(3):465–80. https://doi.org/10.1016/j.brs.2017.12.008.
52. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial direct current stimulation in depression. Brain Stimul. 2018;11(1):125–33. https://doi.org/10.1016/j.brs.2017.10.011.
53. Downar J, Geraci J, Salomons TV, Dunlop K, Wheeler S, McAndrews MP, et al. Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. Biol Psychiatry. 2014;76(3):176–85. https://doi.org/10.1016/j.biopsych.2013.10.026.
54. Vidal-Pineiro D, Martin-Trias P, Falcon C, Bargallo N, Clemente IC, Valls-Sole J, et al. Neurochemical modulation in posteromedial default-mode network cortex induced by transcranial magnetic stimulation. Brain Stimul. 2015;8(5):937–44. https://doi.org/10.1016/j.brs.2015.04.005.
55. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, et al. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science. 2014;345(6200):1054–7.
56. Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, et al. Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. Neuropsychopharmacology. 2014;39(2):488–98. https://doi.org/10.1038/npp.2013.222.

57. Feffer K, Fettes P, Giacobbe P, Daskalakis ZJ, Blumberger DM, Downar J. 1Hz rTMS of the right orbitofrontal cortex for major depression: safety, tolerability and clinical outcomes. Eur Neuropsychopharmacol. 2018;28(1):109–17. https://doi.org/10.1016/j.euroneuro.2017.11.011.
58. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport. 1995;6:1853–6.
59. Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, et al. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Hum Brain Mapp. 2010;31(11):1643–52. https://doi.org/10.1002/hbm.20964.
60. Ahdab R, Ayache SS, Brugieres P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. Neurophysiol Clin. 2010;40(1):27–36. https://doi.org/10.1016/j.neucli.2010.01.001.
61. Herwig U, Padberg F, Unger J, Spitzer M, Schoenfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. Biol Psychiatry. 2001;50:58–61.
62. Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ. Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. Brain Stimul. 2009;2(4):234–7. https://doi.org/10.1016/j.brs.2009.03.002.
63. De Witte S, Klooster D, Dedoncker J, Duprat R, Remue J, Baeken C. Left prefrontal neuronavigated electrode localization in tDCS: 10-20 EEG system versus MRI-guided neuronavigation. Psychiatry Res Neuroimaging. 2018;274:1–6. https://doi.org/10.1016/j.pscychresns.2018.02.001.
64. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, et al. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. Biol Psychiatry. 2009;66(5):509–15. https://doi.org/10.1016/j.biopsych.2009.04.034.
65. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuronavigation in treatment-resistant depression. Neuropsychopharmacology. 2009;34(5):1255–62. https://doi.org/10.1038/npp.2008.233.
66. Suen PJC, Doll S, Batistuzzo MC, Busatto G, Razza LB, Padberg F, et al. Association between tDCS computational modeling and clinical outcomes in depression: data from the ELECT-TDCS trial. Eur Arch Psychiatry Clin Neurosci. 2020; https://doi.org/10.1007/s00406-020-01127-w.
67. Thielscher A, Antunes A, Saturnino GB, editors. Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? 2015 37th annual international conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2015.
68. Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain. 1994;117(4):847–58.
69. Chen R, Classen J, Gerloff C, Celnik P, Wassermann E, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997;48(5):1398–403.
70. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry. 2000;48(12):1133–41. https://doi.org/10.1016/s0006-3223(00)01065-9.
71. Loo CK, Sachdev PS, Haindl W, Wen W, Mitchell PB, Croker VM, et al. High (15 Hz) and low (1 Hz) frequency transcranial magnetic stimulation have different acute effects on regional cerebral blood flow in depressed patients. Psychol Med. 2003;33(6):997–1006. https://doi.org/10.1017/s0033291703007955.
72. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry. 1999;46(12):1603–13. https://doi.org/10.1016/s0006-3223(99)00195-x.
73. Mottaghy FM, Keller CE, Gangitano M, Ly J, Thall M, Parker JA, et al. Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. Psychiatry Res. 2002;115(1–2):1–14. https://doi.org/10.1016/s0925-4927(02)00032-x.
74. Hecht D. Depression and the hyperactive right-hemisphere. Neurosci Res. 2010;68(2):77–87. https://doi.org/10.1016/j.neures.2010.06.013.
75. Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. J Abnorm Psychol. 2006;115(4):715–29. https://doi.org/10.1037/0021-843X.115.4.715.
76. Baeken C, De Raedt R, Van Hove C, Clerinx P, De Mey J, Bossuyt A. HF-rTMS treatment in medication-resistant melancholic depression: results from 18FDG-PET brain imaging. CNS Spectr. 2009;14(8):439–48. https://doi.org/10.1017/s1092852900020411.
77. Baeken C, Marinazzo D, Everaert H, Wu GR, Van Hove C, Audenaert K, et al. The impact of accelerated HF-rTMS on the subgenual anterior cingulate cortex in refractory unipolar major depression: insights from 18FDG PET brain imaging. Brain Stimul. 2015;8(4):808–15. https://doi.org/10.1016/j.brs.2015.01.415.

78. Kito S, Fujita K, Koga Y. Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. J Neuropsychiatry Clin Neurosci. 2008;20(1):74–80. https://doi.org/10.1176/jnp.2008.20.1.74.
79. Kito S, Fujita K, Koga Y. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. Neuropsychobiology. 2008;58(1):29–36. https://doi.org/10.1159/000154477.
80. Richieri R, Boyer L, Padovani R, Adida M, Colavolpe C, Mundler O, et al. Equivalent brain SPECT perfusion changes underlying therapeutic efficiency in pharmacoresistant depression using either high-frequency left or low-frequency right prefrontal rTMS. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;39(2):364–70. https://doi.org/10.1016/j.pnpbp.2012.07.012.
81. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11. https://doi.org/10.1038/nrn2201.
82. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Syst Neurosci. 2010;4:19. https://doi.org/10.3389/fnsys.2010.00019.
83. Brakowski J, Spinelli S, Dorig N, Bosch OG, Manoliu A, Holtforth MG, et al. Resting state brain network function in major depression – depression symptomatology, antidepressant treatment effects, future research. J Psychiatr Res. 2017;92:147–59. https://doi.org/10.1016/j.jpsychires.2017.04.007.
84. Eshel N, Keller CJ, Wu W, Jiang J, Mills-Finnerty C, Huemer J, et al. Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. Neuropsychopharmacology. 2020; https://doi.org/10.1038/s41386-020-0633-z.
85. Richieri R, Jouvenoz D, Verger A, Fiat P, Boyer L, Lançon C, et al. Changes in dorsolateral prefrontal connectivity after rTMS in treatment-resistant depression: a brain perfusion SPECT study. Eur J Nucl Med Mol Imaging. 2017;44(6):1051–5. https://doi.org/10.1007/s00259-017-3640-5.
86. Baeken C, Marinazzo D, Wu GR, Van Schuerbeek P, De Mey J, Marchetti I, et al. Accelerated HF-rTMS in treatment-resistant unipolar depression: insights from subgenual anterior cingulate functional connectivity. World J Biol Psychiatry. 2014;15(4):286–97. https://doi.org/10.3109/15622975.2013.872295.
87. Baeken C, Duprat R, Wu GR, De Raedt R, van Heeringen K. Subgenual anterior cingulate-medial orbitofrontal functional connectivity in medication-resistant major depression: a neurobiological marker for accelerated intermittent theta burst stimulation treatment? Biol Psychiatry Cogn Neurosci Neuroimaging. 2017;2(7):556–65. https://doi.org/10.1016/j.bpsc.2017.01.001.
88. Philip NS, Barredo J, van't Wout-Frank M, Tyrka AR, Price LH, Carpenter LL. Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. Biol Psychiatry. 2018;83(3):263–72. https://doi.org/10.1016/j.biopsych.2017.07.021.
89. Taylor SF, Ho SS, Abagis T, Angstadt M, Maixner DF, Welsh RC, et al. Changes in brain connectivity during a sham-controlled, transcranial magnetic stimulation trial for depression. J Affect Disord. 2018;232:143–51. https://doi.org/10.1016/j.jad.2018.02.019.
90. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry. 2014;76(7):517–26. https://doi.org/10.1016/j.biopsych.2014.01.023.
91. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, et al. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31(43):15284–93. https://doi.org/10.1523/JNEUROSCI.0542-11.2011.
92. Pena-Gomez C, Sala-Lonch R, Junque C, Clemente IC, Vidal D, Bargallo N, et al. Modulation of large-scale brain networks by transcranial direct current stimulation evidenced by resting-state functional MRI. Brain Stimul. 2012;5(3):252–63. https://doi.org/10.1016/j.brs.2011.08.006.
93. Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, et al. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci. 2013;33(28):11425–31. https://doi.org/10.1523/JNEUROSCI.3887-12.2013.
94. Zhang B, Liu J, Bao T, Wilson G, Park J, Zhao B, et al. Locations for noninvasive brain stimulation in treating depressive disorders: a combination of meta-analysis and resting-state functional connectivity analysis. Aust N Z J Psychiatry. 2020;54(6):582–90. https://doi.org/10.1177/0004867420920372.
95. Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc Natl Acad Sci U S A. 2014;111(41):E4367–75. https://doi.org/10.1073/pnas.1405003111.
96. Vink JJT, Mandija S, Petrov PI, van den Berg CAT, Sommer IEC, Neggers SFW. A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. Hum Brain Mapp. 2018;39(11):4580–92. https://doi.org/10.1002/hbm.24307.
97. Oathes DJ, Zimmerman J, Duprat R, Cavdaroglu S, Scully M, Rosenberg B, et al. Individualized non-invasive brain stimulation engages the subgenual anterior cingulate and amygdala. bioRxiv. 2018; https://doi.org/10.1101/503441.
98. Chen AC, Oathes DJ, Chang C, Bradley T, Zhou ZW, Williams LM, et al. Causal interactions between

fronto-parietal central executive and default-mode networks in humans. Proc Natl Acad Sci U S A. 2013;110(49):19944–9. https://doi.org/10.1073/pnas.1311772110.
99. Conde V, Vollmann H, Sehm B, Taubert M, Villringer A, Ragert P. Cortical thickness in primary sensorimotor cortex influences the effectiveness of paired associative stimulation. NeuroImage. 2012;60(2):864–70. https://doi.org/10.1016/j.neuroimage.2012.01.052.
100. Rogers LM, Dhaher YY. Female sex hormones modulate the response to low-frequency rTMS in the human motor cortex. Brain Stimul. 2017;10(4):850–2. https://doi.org/10.1016/j.brs.2017.02.010.
101. Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol. 2008;586(23):5717–25. https://doi.org/10.1113/jphysiol.2008.159905.
102. Pellegrini M, Zoghi M, Jaberzadeh S. Biological and anatomical factors influencing interindividual variability to noninvasive brain stimulation of the primary motor cortex: a systematic review and meta-analysis. Rev Neurosci. 2018;29(2):199–222. https://doi.org/10.1515/revneuro-2017-0048.
103. Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp. 2019;40(3):904–15. https://doi.org/10.1002/hbm.24420.
104. Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci. 2008;12(12):447–54. https://doi.org/10.1016/j.tics.2008.09.004.
105. Clarke PJ, Browning M, Hammond G, Notebaert L, MacLeod C. The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: evidence from transcranial direct current stimulation. Biol Psychiatry. 2014;76(12):946–52. https://doi.org/10.1016/j.biopsych.2014.03.003.
106. Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, et al. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology. 2019;44(9):1613–22. https://doi.org/10.1038/s41386-019-0401-0.
107. Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: clinical outcomes and predictors from a large naturalistic study. Brain Stimul. 2018;11(2):337–45. https://doi.org/10.1016/j.brs.2017.11.004.
108. Scholl J, Klein-Flugge M. Understanding psychiatric disorder by capturing ecologically relevant features of learning and decision-making. Behav Brain Res. 2018;355:56–75. https://doi.org/10.1016/j.bbr.2017.09.050.
109. Godlewska BR, Browning M, Norbury R, Cowen PJ, Harmer CJ. Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. Transl Psychiatry. 2016;6(11):e957. https://doi.org/10.1038/tp.2016.130.
110. Ironside M, Browning M, Ansari TL, Harvey CJ, Sekyi-Djan MN, Bishop SJ, et al. Effect of prefrontal cortex stimulation on regulation of amygdala response to threat in individuals with trait anxiety: a randomized clinical trial. JAMA Psychiat. 2019;76(1):71–8. https://doi.org/10.1001/jamapsychiatry.2018.2172.
111. Ironside M, O'Shea J, Cowen PJ, Harmer CJ. Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety. Biol Psychiatry. 2016;79(10):823–30. https://doi.org/10.1016/j.biopsych.2015.06.012.
112. Baeken C, De Raedt R, Van Schuerbeek P, Vanderhasselt MA, De Mey J, Bossuyt A, et al. Right prefrontal HF-rTMS attenuates right amygdala processing of negatively valenced emotional stimuli in healthy females. Behav Brain Res. 2010;214(2):450–5. https://doi.org/10.1016/j.bbr.2010.06.029.
113. Baeken C, Van Schuerbeek P, De Raedt R, De Mey J, Vanderhasselt MA, Bossuyt A, et al. The effect of one left-sided dorsolateral prefrontal cortical HF-rTMS session on emotional brain processes in women. Psychiatr Danub. 2010;22(Suppl 1):S163.
114. Abend R, Sar-El R, Gonen T, Jalon I, Vaisvaser S, Bar-Haim Y, et al. Modulating emotional experience using electrical stimulation of the medial-prefrontal cortex: a preliminary tDCS-fMRI study. Neuromodulation. 2019;22(8):884–93. https://doi.org/10.1111/ner.12787.
115. Junghofer M, Winker C, Rehbein MA, Sabatinelli D. Noninvasive stimulation of the ventromedial prefrontal cortex enhances pleasant scene processing. Cereb Cortex. 2017;27(6):3449–56. https://doi.org/10.1093/cercor/bhx073.
116. Baeken C, Dedoncker J, Remue J, Wu GR, Vanderhasselt MA, De Witte S, et al. One MRI-compatible tDCS session attenuates ventromedial cortical perfusion when exposed to verbal criticism: the role of perceived criticism. Hum Brain Mapp. 2018;39(11):4462–70. https://doi.org/10.1002/hbm.24285.
117. Dedoncker J, Vanderhasselt MA, Remue J, De Witte S, Wu GR, Hooley JM, et al. Prefrontal TDCS attenuates medial prefrontal connectivity upon being criticized in individuals scoring high on perceived criticism. Brain Imaging Behav. 2019;13(4):1060–70. https://doi.org/10.1007/s11682-018-9927-8.
118. Shajahan PM, Glabus MF, Steele JD, Doris AB, Anderson K, Jenkins JA, et al. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2002;26(5):945–54. https://doi.org/10.1016/s0278-5846(02)00210-5.

119. Gourovitch ML, Kirkby BS, Goldberg TE, Weinberger DR, Gold JM, Esposito G, et al. A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology. 2000;14(3):353–60. https://doi.org/10.1037//0894-4105.14.3.353.
120. Fitzgerald PB, Sritharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. J Clin Psychopharmacol. 2007;27(5):488–92. https://doi.org/10.1097/jcp.0b013e318151521c.
121. Peng W, Chen Z, Yin L, Jia Z, Gong Q. Essential brain structural alterations in major depressive disorder: a voxel-wise meta-analysis on first episode, medication-naive patients. J Affect Disord. 2016;199:114–23. https://doi.org/10.1016/j.jad.2016.04.001.
122. Ueyama E, Ukai S, Ogawa A, Yamamoto M, Kawaguchi S, Ishii R, et al. Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats. Psychiatry Clin Neurosci. 2011;65(1):77–81. https://doi.org/10.1111/j.1440-1819.2010.02170.x.
123. Ota M, Noda T, Sato N, Okazaki M, Ishikawa M, Hattori K, et al. Effect of electroconvulsive therapy on gray matter volume in major depressive disorder. J Affect Disord. 2015;186:186–91. https://doi.org/10.1016/j.jad.2015.06.051.
124. Sartorius A, Demirakca T, Bohringer A, von Hohenberg C, Aksay SS, Bumb JM, et al. Electroconvulsive therapy increases temporal gray matter volume and cortical thickness. Eur Neuropsychopharmacol. 2016;26(3):506–17. https://doi.org/10.1016/j.euroneuro.2015.12.036.
125. Furtado CP, Hoy KE, Maller JJ, Savage G, Daskalakis ZJ, Fitzgerald PB. An investigation of medial temporal lobe changes and cognition following antidepressant response: a prospective rTMS study. Brain Stimul. 2013;6(3):346–54. https://doi.org/10.1016/j.brs.2012.06.006.
126. Hayasaka S, Nakamura M, Noda Y, Izuno T, Saeki T, Iwanari H, et al. Lateralized hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. Psychiatry Clin Neurosci. 2017;71(11):747–58. https://doi.org/10.1111/pcn.12547.
127. Noda Y, Zomorrodi R, Daskalakis ZJ, Blumberger DM, Nakamura M. Enhanced theta-gamma coupling associated with hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. Int J Psychophysiol. 2018;133:169–74. https://doi.org/10.1016/j.ijpsycho.2018.07.004.
128. Sartorius A, Demirakca T, Bohringer A, von Hohenberg C, Aksay SS, Bumb JM, et al. Electroconvulsive therapy induced gray matter increase is not necessarily correlated with clinical data in depressed patients. Brain Stimul. 2019;12(2):335–43. https://doi.org/10.1016/j.brs.2018.11.017.
129. Lan MJ, Chhetry BT, Liston C, Mann JJ, Dubin M. Transcranial magnetic stimulation of left dorsolateral prefrontal cortex induces brain morphological changes in regions associated with a treatment resistant major depressive episode: an exploratory analysis. Brain Stimul. 2016;9(4):577–83. https://doi.org/10.1016/j.brs.2016.02.011.
130. Peng H, Zheng H, Li L, Liu J, Zhang Y, Shan B, et al. High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. J Affect Disord. 2012;136(3):249–57. https://doi.org/10.1016/j.jad.2011.12.006.
131. Kito S, Hasegawa T, Koga Y. Cerebral blood flow ratio of the dorsolateral prefrontal cortex to the ventromedial prefrontal cortex as a potential predictor of treatment response to transcranial magnetic stimulation in depression. Brain Stimul. 2012;5(4):547–53. https://doi.org/10.1016/j.brs.2011.09.004.
132. Kito S, Hasegawa T, Koga Y. Cerebral blood flow in the ventromedial prefrontal cortex correlates with treatment response to low-frequency right prefrontal repetitive transcranial magnetic stimulation in the treatment of depression. Psychiatry Clin Neurosci. 2012;66(2):138–45. https://doi.org/10.1111/j.1440-1819.2011.02312.x.
133. Langguth B, Wiegand R, Kharraz A, Landgrebe M, Marienhagen J, Frick U, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). Neuro Endocrinol Lett. 2007;28(5):633–8.
134. Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, et al. Identification of a common neurobiological substrate for mental illness. JAMA Psychiat. 2015;72(4):305–15. https://doi.org/10.1001/jamapsychiatry.2014.2206.
135. Godlewska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ. Predicting treatment response in depression: the role of anterior cingulate cortex. Int J Neuropsychopharmacol. 2018;21(11):988–96. https://doi.org/10.1093/ijnp/pyy069.
136. Vai B, Bulgarelli C, Godlewska BR, Cowen PJ, Benedetti F, Harmer CJ. Fronto-limbic effective connectivity as possible predictor of antidepressant response to SSRI administration. Eur Neuropsychopharmacol. 2016;26(12):2000–10. https://doi.org/10.1016/j.euroneuro.2016.09.640.
137. Richieri R, Boyer L, Farisse J, Colavolpe C, Mundler O, Lancon C, et al. Predictive value of brain perfusion SPECT for rTMS response in pharmacoresistant depression. Eur J Nucl Med Mol Imaging. 2011;38(9):1715–22. https://doi.org/10.1007/s00259-011-1850-9.
138. Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connec-

tivity. NeuroImage. 2013;66:151–60. https://doi.org/10.1016/j.neuroimage.2012.10.082.
139. Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective validation that subgenual connectivity predicts antidepressant efficacy of transcranial magnetic stimulation sites. Biol Psychiatry. 2018;84(1):28–37. https://doi.org/10.1016/j.biopsych.2017.10.028.
140. Ge R, Downar J, Blumberger DM, Daskalakis ZJ, Vila-Rodriguez F. Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. Brain Stimul. 2020;13(1):206–14. https://doi.org/10.1016/j.brs.2019.10.012.
141. Jing Y, Zhao N, Deng XP, Feng ZJ, Huang GF, Meng M et al. Pregenual or subgenual anterior cingulate cortex as potential effective region for brain stimulation of depression. Brain Behav. 2020:e01591. https://doi.org/10.1002/brb3.1591.
142. Cash RFH, Cocchi L, Anderson R, Rogachov A, Kucyi A, Barnett AJ, et al. A multivariate neuroimaging biomarker of individual outcome to transcranial magnetic stimulation in depression. Hum Brain Mapp. 2019;40(16):4618–29. https://doi.org/10.1002/hbm.24725.
143. Hernandez-Ribas R, Deus J, Pujol J, Segalas C, Vallejo J, Menchon JM, et al. Identifying brain imaging correlates of clinical response to repetitive transcranial magnetic stimulation (rTMS) in major depression. Brain Stimul. 2013;6(1):54–61. https://doi.org/10.1016/j.brs.2012.01.001.
144. Boes AD, Uitermarkt BD, Albazron FM, Lan MJ, Liston C, Pascual-Leone A, et al. Rostral anterior cingulate cortex is a structural correlate of repetitive TMS treatment response in depression. Brain Stimul. 2018;11(3):575–81. https://doi.org/10.1016/j.brs.2018.01.029.
145. Furtado CP, Hoy KE, Maller JJ, Savage G, Daskalakis ZJ, Fitzgerald PB. Cognitive and volumetric predictors of response to repetitive transcranial magnetic stimulation (rTMS) – a prospective follow-up study. Psychiatry Res. 2012;202(1):12–9. https://doi.org/10.1016/j.pscychresns.2012.02.004.
146. Klooster DC, Vos IN, Caeyenberghs K, Leemans A, David S, Besseling RM, et al. Indirect frontocingulate structural connectivity predicts clinical response to accelerated rTMS in major depressive disorder. J Psychiatry Neurosci. 2020;45(2):190088. https://doi.org/10.1503/jpn.190088.
147. Ge R, Downar J, Blumberger DM, Daskalakis ZJ, Lam RW, Vila-Rodriguez F. Structural network integrity of the central executive network is associated with the therapeutic effect of rTMS in treatment resistant depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2019;92:217–25. https://doi.org/10.1016/j.pnpbp.2019.01.012.
148. Brunoni AR, Sampaio-Junior B, Moffa AH, Borrione L, Nogueira BS, Aparício LV, et al. The Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS): rationale and study design of a non-inferiority, triple-arm, placebo-controlled clinical trial. Sao Paulo Med J. 2015;133(3):252–63. https://doi.org/10.1590/1516-3180.2014.00351712.
149. Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M, et al. Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. J Psychiatr Res. 2003;37(4):267–75. https://doi.org/10.1016/s0022-3956(03)00042-6.
150. Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. Psychiatry Res. 2006;146(1):53–7. https://doi.org/10.1016/j.pscychresns.2004.08.005.
151. Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. Int J Neuropsychopharmacol. 2010;13(1):45–59. https://doi.org/10.1017/s146114570900008x.
152. Jha S, Chadda RK, Kumar N, Bal CS. Brain SPECT guided repetitive transcranial magnetic stimulation (rTMS) in treatment resistant major depressive disorder. Asian J Psychiatr. 2016;21:1–6. https://doi.org/10.1016/j.ajp.2016.02.003.
153. Christley R. Power and error: increased risk of false positive results in underpowered studies. Open Epidemiol J. 2010;3(1).
154. Cash RFH, Zalesky A, Thomson RH, Tian Y, Cocchi L, Fitzgerald PB. Subgenual functional connectivity predicts antidepressant treatment response to transcranial magnetic stimulation: independent validation and evaluation of personalization. Biol Psychiatry. 2019;86(2):e5–7. https://doi.org/10.1016/j.biopsych.2018.12.002.
155. Siddiqi SH, Weigand A, Cooke D, Pascual-Leone A, Fox MD. Abstract #155: Individualized connectivity between rTMS targets and the subgenual cingulate is unrelated to antidepressant response. Brain Stimul. 2019;12(2). https://doi.org/10.1016/j.brs.2018.12.162.
156. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28–38. https://doi.org/10.1038/nm.4246.
157. Dinga R, Schmaal L, Marquand AF. A closer look at depression biotypes: correspondence relating to Grosenick et al. (2019). Biol Psychiatry Cogn Neurosci Neuroimaging. 2020; https://doi.org/10.1016/j.bpsc.2019.09.011.
158. Dinga R, Schmaal L, Penninx B, van Tol MJ, Veltman DJ, van Velzen L, et al. Evaluating the evidence for biotypes of depression: methodological replication and extension of. Neuroimage Clin. 2019;22:101796. https://doi.org/10.1016/j.nicl.2019.101796.

159. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatry. 2020:appiajp201919090915. https://doi.org/10.1176/appi.ajp.2019.19090915.
160. Worsching J, Padberg F, Helbich K, Hasan A, Koch L, Goerigk S, et al. Test-retest reliability of prefrontal transcranial direct current stimulation (tDCS) effects on functional MRI connectivity in healthy subjects. NeuroImage. 2017;155:187–201. https://doi.org/10.1016/j.neuroimage.2017.04.052.
161. Padberg F, Kumpf U, Mansmann U, Palm U, Plewnia C, Langguth B, et al. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;267(8):751–66. https://doi.org/10.1007/s00406-017-0769-y.
162. Bajbouj M, Aust S, Spies J, Herrera-Melendez AL, Mayer SV, Peters M, et al. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. Eur Arch Psychiatry Clin Neurosci. 2018;268(8):797–808. https://doi.org/10.1007/s00406-017-0859-x.
163. Wang HX, Wang K, Zhang WR, Zhao WF, Yang XT, Wang L, et al. Protocol on transcranial alternating current stimulation for the treatment of major depressive disorder: a randomized controlled trial. Chin Med J. 2019; https://doi.org/10.1097/cm9.0000000000000589.

11 Target Engagement with Transcranial Current Stimulation

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Transcranial electric stimulation (tES) applies a weak electric current to the scalp which causes an electric field in the brain that can modulate neuronal activity and behavior. Despite the rapidly growing number of studies that report successful modulation of behavior by tES, comparably little is known about how tES modulates brain activity. In this chapter, we discuss what we know and what we do not know about the targeting of brain networks with tES. We provide an in-depth review of studies that use computational models, in vitro and in vivo animal models, and human participants to elucidate the mechanism of action of tES. The main emerging themes are that (1) the stimulation interacts with endogenous network dynamics resulting in state-dependent target engagement, (2) spatial and temporal targeting of specific neuronal network oscillations can be used to modulate and restore cognitive function, (3) low-frequency cortical oscillations during sleep represent a promising network target to elucidate the mechanisms of tES, and (4) that transcranial alternating current stimulation (tACS) has shown promise as a safe and potentially efficacious strategy to modulate impaired neuronal network oscillations and associated symptoms in psychiatry.

It has been known for a long time that electricity interacts with both the central and peripheral nervous systems. Today, electric brain stimulation is used both as a research tool for the study of brain function and as a clinical tool for the treatment of neurological and psychiatric disorders. In this chapter, we focus on one form of

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noninvasive brain stimulation, transcranial electric stimulation (tES, also referred to as transcranial current stimulation, tCS), which has recently attracted broad attention due to a large number of promising study results.

TES applies a weak electric current to the scalp. There are two main types of tES: transcranial direct current stimulation (tDCS) applies a constant current and transcranial alternating current stimulation (tACS) uses a sine-wave stimulation waveform. The aim of tES is to modulate brain function; the *target* of tES is the electrical activity in brain circuits. Most tES studies, however, only use behavioral outcomes and do not measure the changes in brain activity caused by stimulation. Therefore, the questions of how and by what mechanism tES engages network-level targets in the brain have remained mostly unanswered.

Here, we review the research that is aimed at uncovering the mechanisms by which tES modulates neuronal network dynamics and behavior. As we see, the mechanisms of action by which weak electric fields modulate neuronal activity have been studied with a range of different methods. In vitro studies using live brain slices have contributed to a mechanistic understanding of the effect of weak electric fields on neuronal activity at the cellular and microcircuit levels. In vivo animal studies have enabled the characterization of the effects of tES on intact brains with invasive recording methods with microscale spatial resolution. Noninvasive electrophysiology and imaging studies in humans have contributed insights into how stimulation interacts with endogenous network activity. In addition to these experimental approaches, computational modeling studies have provided important insights into targeting specific networks and their endogenous network dynamics. The combination of these methods has proven to be very useful to understand how a weak electric field can change brain function by vertical integration.

In this chapter, we provide an overview of the potential mechanisms of tES that have been uncovered using these diverse methodological approaches. First, we review in vitro and in vivo studies. This is followed by a discussion of computational modeling studies, which provide mechanistic insights on the effects of tES at a cellular and network level. Next, we focus on human studies that measured changes in brain activity by tES. Then, we turn our attention to the future and delineate what we believe are the rising new areas of tES research that deserve particular attention by the field. First, we discuss recent innovative strategies to target brain network oscillations in time and space for restoring and enhancing cognitive function. Second, we look at one promising network target where the different methodological approaches discussed here have come together in a synergistic way: low-frequency oscillations during sleep. Third, we provide a brief outlook toward mechanism-based clinical trials. Together, this chapter aims to equip the reader with a comprehensive understanding of how tES engages network targets.

11.1 Mechanistic Insights from Animal Studies

Although tES is a noninvasive stimulation modality with an outstanding safety track record for the use in humans, studies in animal models are of high importance. They play a crucial role in understanding the mechanisms by which tES modulates brain activity. First, animal experiments allow for the use of invasive electrophysiology such as the insertion of recording microelectrodes into the brain. This enables the investigation of how neuronal spiking is modulated by external electric fields. Second, reduced in vitro preparations such as the slice preparation offer the opportunity to study the effects of weak electric fields under controlled experimental conditions, which bypass the questions about delivery of the electric field through the scalp and the skull in the intact animal.

11.1.1 Effect of Electric Fields on Individual Neurons

One of the first observations of the effect of electric fields on neurons goes back many decades when Terzuolo and Bullock [1] applied a 1 mV/mm field to spontaneously active cardiac ganglion

neurons of a lobster. The spontaneous firing rate of the cells was increased by the electric field. Similar modulation of neuronal firing rates by constant electric fields was also reported for other species [2, 3]. In 1988, Chan and colleagues [4] demonstrated that an applied electric field depolarizes the membrane voltage even when action potentials were blocked with the sodium-channel blocker tetrodotoxin. This demonstrated that the membrane depolarization caused by electric fields was a passive event, that is, no opening or closing of ion channels was required. The underlying mechanism of fields altering the membrane voltage is that the ions within neurons change position in the presence of an external electric field. As the charge carriers redistribute within the cell to compensate for the applied field, the intracellular potential changes. As a result, the membrane voltage that is defined as the difference between the intracellular and extracellular potentials changes. The two distal poles of the structure aligned with electric field exhibit a depolarization and a hyperpolarization, respectively. This process is called *polarization* and depends on the overall length of the neuron as measured along the direction of the applied electric field. Specifically, there is a concomitant change in the membrane voltage in the apical dendrites of cortical pyramidal cells of opposite polarity to the effect in the soma [5, 6]. Therefore, the orientation, morphology, and size of the cell play a role in the response to the application of electric fields.

In addition, the change in the membrane voltage also depends on both the amplitude and frequency of the applied field. To demonstrate that the change in membrane voltage is dependent on the strength of the electric field, fields ranging from −40 to +60 mV/mm were applied along the somato-dendritic axis of CA1 cells and the change in membrane voltage at somata was recorded in acute hippocampal slices [7]. The resulting polarization linearly depended on the strength of the applied electric field. This work was then extended to sine-wave (AC) electric fields in CA3 pyramidal cells [8]. The change in membrane potentials resulting from AC electric fields was less than those of DC fields of the same strength. The relationship between the field strength and the membrane depolarization was still linear but the slope, which quantifies the change in membrane voltage for every V/m of electric field, was decreased with increased frequency. Frequencies ranging from 5 to 100 Hz were applied and the change in the slope exponentially decays with the frequency of the applied electric field. This frequency dependence is caused by the low-pass filtering property of the passive cell membrane. Further, computational models demonstrate that AC-induced, frequency-dependent resonance in neurons (especially apical dendrites) is shaped by the dynamic interaction of the somato-dendritic morphology and the high-pass filtering property of the hyperpolarization-activated depolarizing cation current (I_h) [5, 6].

11.1.2 TES Effect on Neuronal Firing Rate and Spike Timing

To understand the neuronal mechanism of tES, in vivo animal research with invasive recordings of the neuronal spiking activity is essential. The modulation of both neuronal firing rate and spike timing are two candidate mechanisms through which tES may shape neuronal network dynamics. Using intracellular and extracellular recordings in rats, Vöröslakos et al. showed that at least 1 mV/mm EF is necessary to affect the neuronal spiking rate [9]. Another mechanism through which tACS affects neuronal activity is through entrainment (spike timing modulation such that spikes lock to a preferred phase of the sine-wave electric field), especially when tACS is too weak to induce firing rate changes. Krause et al. applied tACS (4 mA peak to peak, similar to human studies) through two scalp electrodes in two rhesus macaques and measured the effect on single-unit neural entrainment in the hippocampus and basal ganglia via depth electrodes. They found that tACS consistently influences the timing, but not the rate, of spiking activity [10]. TACS applied on awake ferrets also showed entrainment of cortical neurons but no change in firing rate [11].

An alternative hypothesis is that the tES effect may be mediated by the stimulation of peripheral nerves in the scalp. Single neuron activity recordings in the rat motor cortex have shown that transcranial and transcutaneous electrical stimulation can entrain neuronal oscillations (~1 Hz), and that anesthetizing the scalp significantly decreases the effect of tACS on tremor in humans [12]. This particular study caused quite some discussion but was ultimately recognized as limited in implications due to lack of construct validity (human tremor as a marker of cortical oscillations) and statistical conclusion validity (lack of statistical significance due to low sample size). Follow-up work that employed appropriate neurophysiological strategies showed that, when somatosensory input was blocked (by topical anesthesia), tACS (2 mA) entrained hippocampal and visual cortex neurons, suggesting that peripheral input is not required for tACS to entrain neurons [13]. Nevertheless, it cannot be excluded at this point that the two mechanisms have a combined effect on neuronal entrainment and behavioral performance, and more research is needed.

11.1.3 Interactions of Network Oscillations and Electric Fields

The change in membrane voltage of a single neuron by tES electric fields is too small to evoke action potentials in a cell at its resting potential in absence of synaptic input. Therefore, the effects of tDCS and tACS depend on the interaction of the applied stimulation and the endogenous network dynamics. In particular, slice experiments have provided important insights on the interactions between the ongoing network activity and the applied electric fields. Few slice preparations exhibit spontaneous network oscillations, presumably because of (1) the relative lack of synaptic inputs due to the deafferentation inherent to this preparation and (2) impaired neuromodulatory tone in tissue slices in comparison to the intact brain. However, oscillations may occur spontaneously in the slice preparation in more in vivo–like ionic conditions [14] and in response to pharmacological activation [15]. More recently, optogenetic stimulation has uncovered in vivo–like activity patterns in the slice preparation [16]. Therefore, these experimental strategies can be combined with the application of external electric fields for the study of the mechanisms of tES. For example, pharmacological activation of hippocampal slices caused the emergence of gamma oscillations that were susceptible to weak DC electric fields [17]. Interestingly, the effect of the DC field was asymmetric with regards to the polarity. Hyperpolarizing fields were more effective at suppressing this network oscillation than depolarizing fields were at enhancing the same activity pattern. This asymmetry is supportive of the framework where ongoing activity shapes the response to stimulation. In the case of AC fields, for sufficiently low stimulation frequency, the amplitude of the gamma oscillation was periodically modulated, reminiscent of the theta-nested gamma oscillation [18]. The most complex effect occurred if the stimulation frequency was similar to the frequency of the endogenous oscillation. In this case, three simultaneous frequencies were observed. The endogenous oscillation was reduced (but still present) while oscillations half a harmonic above and below the endogenous frequency appeared. However, in vivo, tACS entrains neural oscillations in a triangular Arnold tongue pattern – with only a small amplitude needed to entrain at the endogenous frequency and higher amplitudes needed for frequencies further away from the endogenous frequency [11]. The Arnold tongues refer to the parameter space where phase locking appears in a coupled oscillators system [19]. This model-driven prediction supports the mechanistic understanding of AC stimulation effects.

The interaction of electric field stimulation and endogenous oscillations appear to not only depend on the frequencies of both but on their relative amplitudes as well. In a study of low-frequency (1 Hz) oscillations evoked by optogenetic stimulation, it was observed that electric fields of a mismatched frequency would enhance the power of the endogenous oscillation often without increasing power at the frequency of the electric field [20]. This occurred when the

optogenetic drive, and therefore, the "endogenous" oscillations, were strong and the electric field was relatively weak. However, the power of the oscillations at the stimulation frequency was enhanced when the magnitude of the endogenous oscillation was reduced (lower light intensity for optogenetic stimulation) or the strength of the electric field was increased. Taken together, the response of neural networks depends both on the frequency and the power (relative to the endogenous oscillation) of the electric field used for stimulation. Furthermore, these results suggest that the response of cortical networks to tES may be nonlinear in nature.

So far, we have focused on the response to stationary stimulation waveforms; however, endogenous neural activity is not stationary. To this end, endogenous activity may be better manipulated with feedback control algorithms than with static preprogrammed stimulation waveforms. One such example is the modulation of seizure-like, epileptiform electric events in slices. The application of DC fields can suppress epileptiform activity in hippocampal slices which exhibit spontaneous seizure-like activity; however, the network quickly adapted to the stimulation and epileptiform activity returned [21]. In a follow-up study, nonstationary electric stimulation was applied to suppress seizure-like activity [22]. The authors were able to suppress seizure activity for 16 min using a negative feedback stimulation paradigm in a hippocampal slice which exhibited electrographic seizure events every 40 s. Critically, spontaneous activity still occurred while epileptiform activity was suppressed. Thus, in the case of suppression of epileptiform activity with tES, these studies show that adaptive feedback stimulation may have greater effect on network dynamics than constant stimulation. Indeed, there is also evidence that feedback stimulation has uses outside of suppression of aberrant activity. In spontaneously oscillating slices of ferret visual cortex, positive feedback stimulation with electric field was shown to decrease the length of time between cortical up states and increase the strength of the endogenous oscillation [23]. Conversely, the application of negative feedback stimulation to the slices reduced strength of the endogenous oscillation. Interestingly, this effect was accomplished with stimulation amplitudes similar to the amplitude of endogenous electric fields recorded in vivo (1 mV/mm). These results are at the core of our current understanding of how weak endogenous electric fields act as an amplifier of endogenous rhythmic activity [24].

11.1.4 Outlasting Effects of Electric Fields

One of the most exciting aspects of tES is that the effects of stimulation can outlast the stimulation as demonstrated by sustained modulation of motor evoked potentials after completion of stimulation [25]. This "outlasting effect" of tDCS has been studied in animal models and slice preparations. In contrast, most in vitro studies have reported no outlasting effects of weak electric fields. However, the stimulation duration in these studies was typically short. With a longer stimulation duration, outlasting effects were observed more than 10 min after the end of 10 min DC stimulation with higher field amplitudes (i.e., 10 V/m and higher) than what can be expected to occur with tES in humans [26]. In vivo, tDCS over somatosensory cortex applied to rabbits modulated eye blink conditioning; however, an outlasting effect of tDCS only occurred for cathodal stimulation [27]. The underlying mechanism was probed by paired pulse experiments, which revealed that spike time-dependent long-term depression (LTD) was activated by tDCS. Moreover, the resulting LTD was suppressed by pharmacological blockade of adenosine receptors by a local injection. Similarly, evoked potentials were enhanced by application of electric fields in vivo in anesthetized rats with effects that outlasted the stimulation for hours [28]. Both long-term potentiation (LTP) and paired-pulse facilitation (PPF) were increased after DC field application in hippocampal slices [29]. Intriguingly, LTP (but not PPF) was also enhanced in hippocampal slices of rats which had received anodal tDCS 24 h earlier. Application of an NMDA antagonist prevented LTP induction but not paired pulse facilitation. In slices of mouse motor cortex, the application of DC field enhanced

synaptic strength when paired with a low-frequency electric stimulation of afferent pathways [30]. Importantly, this observed form of LTP depended on NMDA receptors and brain-derived neurotrophic factor (BDNF). Today's limited evidence, therefore, suggests that tDCS activates multiple, diverse plasticity mechanisms, both pre- and postsynaptic, depending on the brain region, polarity (anodal vs. cathodal) of stimulation, and other poorly understood factors. In addition, enhancement of oscillation following tACS have also been attributed to plasticity [31]; however, direct experimental evidence for such a mechanism is lacking. More recently, it was reported that the enhancement of alpha oscillations with tACS depended on BDNF genotype [32], which suggests a role for synaptic plasticity in enabling "outlasting effects."

11.1.5 Interaction of Cellular and Network Mechanisms

The main targets of tES are cortical networks due to their positions closest to the stimulation electrodes. The circuits in neocortex are composed of different cell types that exhibit distinct morphology and electrophysiological properties. Importantly, not all cell types respond equally to weak electric fields. This was demonstrated by the combination of patch recordings of the somatic membrane voltage with careful reconstruction of cell morphology [33]. Layer 5 (L5) pyramidal cells had largest change in membrane voltage in response to externally applied electric fields due to their morphology and orientation within cortex. These cells exhibit an elongated somato-dendritic axis that spans from L5 to L1. In addition, the somato-dendritic axis is approximately perpendicular to the surface of the brain meaning that the cells are properly aligned to receive energy from an external electric field orthogonal to the skull. Note that the folding of cortex may introduce additional complexity. Since L5 pyramidal neurons are the likely primary targets of tES, we can expect that their response to stimulation play a critical role in the modulation of cortical network dynamics. Therefore, considering the intrinsic dynamics of this cell type will provide clues with regards to the network-level effects of stimulation. The response of L5 pyramidal cells to subthreshold changes in membrane voltages, particularly in the prefrontal cortex, has been well studied by current-clamp whole-cell patch clamp experiments; these cells respond best to subthreshold perturbations in the theta-frequency (4–8 Hz) band [34, 35]. This suggests that electric fields of a given strength will cause the largest subthreshold oscillations in the theta band and that AC field stimulation preferentially modulates low-frequency oscillation in cortex. However, in vivo study has shown that tACS more strongly entrains narrow-spiking neurons (presumed fast-spiking inhibitory interneurons) than broad-spiking neurons (presumed pyramidal cells), which can be explained by the tighter phase locking of the former to the endogenous rhythmic network activity [11]. More direct experimental evidence confirming this link among single cell excitability, cell morphology, and network level effects is needed. In addition, non-neuronal cells have also been shown to be activated by tES. For example, both anodal and cathodal tDCS applied to the awake mouse brain induce microglia activation and neurogenesis from the subventricular zone [36].

11.2 Computational Models

Despite the extensive investigation of cognitive and clinical applications of tES, the exact mechanisms of tES in modulating neuronal activity in humans have remained only partially understood. In the above section, we have discussed key findings on mechanisms of tES from animal experiments. Here, we provide an up-to-date review of computational models of tES, focusing on recent advances in modeling techniques and their applications.

11.2.1 Forward Models

Computational forward models determine the current flow in biological tissue and can predict the resulting electric field during tES. The current

density distribution in the head depends on a number of dose parameters, including electrode number, position, size, shape, and electric current amplitude and waveform. Different electrode *montages*, positioning of the stimulation electrodes, result in distinct current flow through the brain. Although such flexibility allows for customization and optimization of tES paradigms, it also renders the optimal choice for engaging a specific brain circuit more difficult to identify. Perhaps most importantly, forward models allow us to relate the amount of current applied to the scalp to the magnitude and the direction of the resulting electric field in the targeted brain areas [37]. By calculating current density distributions, forward models provide accurate and detailed description of current flow patterns, thus greatly facilitating the rational design and optimization of tES parameters.

Computational forward models of tES have evolved from the simple concentric sphere models assuming simplified geometries to low-resolution anatomy-based models to high-resolution anatomically accurate models based on individual structural magnetic resonance imaging (MRI) scan. Lacking regional anatomical differences, the concentric sphere models were successfully used to determine the main effects of different electrode montages [37]. Such simplified models are particularly beneficial for initial evaluation of the effects of different electrode configurations. For example, a finite-element concentric sphere human head model for simulating a range of different electrode configurations showed that concentric ring electrodes cause electric field distributions with higher spatial focality than more commonly used electrode types and montages [38]. In contrast, low-resolution anatomy-based models incorporate both anatomical structure and individual patient-specific features, but the anatomical accuracy is limited because cortical folding, ventricles, and tissue anisotropy are usually not taken into account. Consequently, such models are not able to capture local nonuniformities in electrical field distribution [39]. Despite these limitations, low-resolution models have offered valuable insights in informing tES montage design and how pathological changes in brain and skull anatomy affect current density distribution. A number of low-resolution models developed by Wagner et al. (2004, 2006 and 2007) serve this purpose. In one tDCS study [40], the comparison of several electrode montages commonly used in clinical application showed that smaller electrodes led to greater current shunting through the scalp. In the same study, the analysis of the current density distribution between healthy and stroke head models under tDCS demonstrated that lesions substantially altered spatial targeting, which may interfere with the treatment outcome. Finally, high-resolution anatomically accurate models based on MRI scans have become a promising tool in assisting the design of customized and individualized tES protocols as they allow for accurate representation of current density distribution in the brain (for a comprehensive review, see [41]). These high-resolution models advance our understanding of tES effects and may eventually lead to improved stimulation for optimized and customized therapy. Below we review a few examples to illustrate the potential merit and utility of high-resolution models in the design and analysis of tES. It is important to note that most of these modeling results are awaiting physiological proof, but see [42, 43] for experimental validation (at the macroscopic scale).

The actual pattern of current flow produced by tES is greatly shaped by anatomy and tissue properties [37]. To achieve similar treatment outcome despite patient-to-patient variability in head and brain anatomy, it is important to know the sensitivity of electrical field distributions to normal anatomy variation for a given electrode montage. High-resolution models provide an ideal tool to analyze the underlying basis for individual variation during tES. For example, a detailed analysis of the influence of cerebrospinal fluid (CSF) showed that electric fields may be clustered at distinct gyri/sulci sites due to details of CSF flow [44]. Together with other high-resolution models [45–47], this study suggested that individual variability in dosing of tES could arise primarily due to gyri-specific dispersion of current flow more than differential skull dispersion as previously thought.

High-resolution models have contributed significantly to the design of new tDCS montages. The conventional tDCS applies weak direct currents to the scalp via sponge-based rectangular pads. High-definition tDCS (HD-tDCS) uses arrays small scalp electrodes for stimulation [27]. A high-resolution MRI-based finite-element model of the human head demonstrated that the 4 × 1 ring electrode configuration (four "return" [cathode] disc electrodes arranged in a circular fashion around an "active" [anode] center electrode) resulted in significant improvement of spatial focality [44]. To what extent such increased spatial focality improves treatment outcomes remains an open question. In fact, the number of direct comparisons of the effects of "conventional" tDCS and "multi-electrode tDCS" on (network) neurophysiology remains limited.

Furthermore, high-resolution models allow for safety analysis of tES application in populations at increased risk of negative side effects. For example, there is a growing interest in applying tES in children for the treatment of disorders such as autism spectrum disorder and epilepsy. However, due to anatomical differences, the same stimulation dose that is safe for adults may be hazardous to children. In order to establish the comparable safety and tolerability dose in children, cortical electric field maps at different stimulation intensities and electrode configurations were determined [48] using a high-resolution, MRI-derived, finite-element model of a typically developing, anatomically normal, 12-year-old child. Simulation results indicated that, for a given stimulus intensity, the maximal electric fields in the adolescent brain were twice as high as in the adult brain for conventional tDCS and nearly four times as high as for a 4 × 1 high-definition tDCS electrode configuration. Thus, special caution needs to be taken when applying tES to the pediatric population. Another vulnerable population is patients with traumatic brain injury or decompressive craniectomy, who often have skull defects or surgically implanted plates. To safely apply tES in these patients, safety guidelines needed to be established. In order to evaluate the impact of skull defect on current density distribution under tDCS, a MRI-derived finite-element head model with several conceptualized skull injuries including two types of skull defects and two types of skull plates was developed [49]. Interestingly, simulation results indicated that skull defect provided a preferential pathway for current flow to concentrate in the brain. Under such conditions, the underlying cortex would be exposed to a higher intensity of focused current flow, raising important clinical and safety considerations. Together, these studies show that computational forward models are an essential tool for safe (and optimal) targeting of the brain structure of interests.

11.2.2 Computational Neural Models

Different from computational forward models, computational neural models of tES focus on the effects of electrical stimulation on neuronal excitability and network dynamics. Neural models of tES are desirable since they provide a solid computational framework to readily explore the neural mechanisms underlying tES-induced behavioral/treatment outcome and the effects of stimulation parameters such as frequency and amplitude in the case of tACS. Although there exists a number of cellular and network models of electrical stimulation [50–58], few are dedicated to the study of tES. Below, we focus on three neuronal network models that specifically investigate the effects of tES on cortical activity [56–58].

During neural activity, the superimposition of electrical currents from a large population of neurons that have similar spatial orientation gives rise to a potential in the extracellular medium. This electric field is the source of the electroencephalogram (EEG) recorded from the scalp [59, 60]. Scalp EEG activity shows oscillations in a variety of frequency bands which reflect the synchronous activity of thousands (up to millions) of cortical neurons [61] and are associated with different behavioral states (e.g., waking and sleep [62]). Abnormal or disrupted cortical oscillations are a hallmark of a number of neurological and psychiatric disorders including schizophrenia and depression [63]. The mechanisms by which externally applied fields modulate the activity of

cortical neurons remain unclear. The three computational studies [56–58] aim to elucidate how cortical dynamics are modulated by tES.

The computational study by Molaee-Ardekani and colleagues [58] analyzed in detail how cortical neuronal assemblies are affected by the electrical field induced by tDCS and how local field potentials (LFPs) respond to the applied electrical field. The authors constructed a macroscopic computational model (neural mass model) of the cerebral cortex including subpopulations of pyramidal cells and inhibitory interneurons connected with realistic models of synapses. Model parameters were adjusted to reproduce evoked potentials (EPs) recorded from the somatosensory cortex of the rabbit in response to air puffs applied to the whiskers. The application of tDCS was modeled as a perturbation on the mean membrane potentials of pyramidal cells and/or interneurons. Simulation results demonstrated (1) that a feedforward inhibition mechanism must be included in the model to accurately replicate the actual EP and (2) that electric fields had to modulate interneurons to replicate the experimental findings.

EEG signals usually contain oscillations in multiple frequency bands that can be analyzed by power spectrum. To capture the origin of tDCS-induced alterations in the EEG power spectrum, Dutta and Nitsche [57] developed a thalamo-cortical neural mass model that contained four subpopulations of cortical cells (excitatory pyramidal cells, excitatory interneurons, slow inhibitory interneurons, and fast inhibitory interneurons) and two subpopulation of thalamic neurons (excitatory thalamo-cortical cells and inhibitory reticular thalamic neurons). This thalamo-cortical network model was used to simulate the subject-specific EEG power spectrum changes during and following tDCS by varying synaptic parameters. Model simulation showed that anodal tDCS enhanced activity and excitability of the excitatory pyramidal neurons at a population level in a nonspecific manner and led to mu-rhythm (9–11 Hz) desynchronization. The model further showed that the tDCS effects on mu-rhythm desynchronization depended on the stimulation polarity, consistent with experimental observations [64].

Recent human studies have demonstrated that sine-wave stimulation waveforms (tACS) induce frequency-specific effects on brain dynamics measured by EEG [65–67], suggesting that tACS may present a targeted stimulation paradigm for the enhancement of cortical oscillations. However, it remains unknown how periodic, weak global electric fields alter the spatiotemporal dynamics of large-scale cortical networks. To address this question, Ali and colleagues [56] developed a large-scale two-dimensional cortical network consisting of 160,000 (400 × 400) pyramidal cells and 40,000 (200 × 200) interneurons modeled by Izhikevich neural dynamics [68, 69]. Simulations revealed distinct roles of the depolarizing and hyperpolarizing phases of tACS in oscillation entrainment, which entailed moving network activity toward and away from a strong nonlinearity provided by the local excitatory coupling of pyramidal cells. Interestingly, the model demonstrated that recovery of synaptic depression played an important role in entrainment of network activity by tACS and that sparse global stimulation was more effective than spatially localized stimulation. The simulations further revealed that entrainment by tACS was mediated by "network resonance" dynamics so that stimulation frequency matched with the endogenous frequency was most effective in entraining the oscillating network. Entrainment effects were centered on the endogenous network frequency and expanded to neighboring frequencies with increasing stimulation amplitude (Arnold tongue). These findings were subsequently replicated in other computational simulation studies (e.g., [11, 70]). These findings provide a detailed mechanistic understanding of tACS at the level of large-scale network dynamics and give support for tACS as a targeted stimulation paradigm for the treatment of neuropsychiatric illnesses with impaired cortical oscillations.

11.2.3 Future Directions

Together, computational models of tES play a critical role in visualizing the electrical field distribution, understanding the mechanistic action of

tES on neuronal network dynamics, and optimizing stimulation parameters to guide the design of the next-generation tES. While anatomically accurate high-resolution MRI-based forward models guide the rational design and optimization of tES electrode montages, neuronal models constrained by neurophysiological measurements provide a mechanistic understanding of the effects of tES on cellular and network dynamics and thereby provide guidance for the rational design of the stimulation waveform. As most existing neural models of tES are either neural mass models or simplified spiking models that lack accurate ion channel dynamics, it is desirable to construct biophysically realistic neuronal models of tES. We anticipate that such models will further illustrate at both the cellular and network levels how the stimulation dynamics interact with the intrinsic neuronal dynamics to give rise to the state-dependent effects of tES. Furthermore, there is an increasing demand for the incorporation of neural models into computational forward models of electric current flow to thoroughly explore how tES-induced electric fields modulate cellular excitability and network dynamics as a function of time and space.

11.3 Effects of Weak Electric Fields on the Human Brain

Even before observations of interactions between electricity and brain activity, electrical currents have been used for treating various disorders like headache and epilepsy. Initial treatments involved using live electric rays and electric catfishes [71]. Efforts by a number of pioneers including Walsh, Galvani, Volta, and Aldini led to the establishment of the field of bioelectricity and subsequently the development of *electrotherapy* [72]. Interest in electrically polarizing brain regions using transcranial weak current stimulation for treating symptoms of psychiatric disorders increased in the 1960s and 1970s with a number of studies showing positive outcomes [73–76]. However, development of drugs which appeared to be more effective in treating psychiatric disorders led to waning interest in transcranial stimulation.

During this period, the predominant understanding of how stimulation produces such effects was based on evoked potentials observed in animal studies. When a positive polarization is applied across the cortex, there is an increase in evoked response amplitude and conversely, there is decrease in evoked potential amplitude when a negative polarization is applied [77, 78]. In essence, stimulation was thought to affect the excitability of neurons. In humans, one of the first studies to look at excitability change after transcranial direct current stimulation (tDCS) was performed by Priori et al. [79]. Weak DC current (<0.5 mA) was applied over motor cortex and excitability was tested using single-pulse transcranial magnetic stimulation (TMS) to trigger an evoked response. The resulting motor evoked potential (MEP) amplitudes served as a physiological measure of change in excitability. Anodal and cathodal stimulation indeed modulated the MEP amplitude, however, perhaps surprisingly, factors such as the temporal order of the stimulation paradigm appeared to matter. A clearer result emerged from a more comprehensive study by Nitsche and Paulus [25] where they showed that anodal stimulation led to an increase in MEP amplitude and conversely cathodal stimulation led to a decrease in MEP amplitude. Interestingly, the change in amplitude lasted for a few minutes after completion of tDCS and returned to baseline after 5 min. Also, the size and duration of the after-effect depended on the stimulation duration and current intensity. This landmark study provided the foundation for the field of tDCS. This result has been replicated several times, including a recent study that combined tDCS with rigorous double-blind placebo-controlled trial design and sophisticated source localization of transcranial evoked potentials [80].

11.3.1 Neurophysiology of tDCS in Humans

Increasing interest in tDCS has led to an exploration of possible modalities that can provide more insight into neurophysiological effects. Consequently, tDCS has been used in conjunc-

tion with other neurophysiological approaches. Electroencephalography (EEG) was also one of the earliest modalities used in studying the effect of current stimulation [81].

Analogous to the approach of using MEPs for evaluating excitability change in motor cortex, Antal et al. [82] used visual evoked potentials (VEPs) to study excitability change caused by tDCS. They found that the amplitude of N70 component of the VEP in EEG was increased by anodal stimulation and, conversely, decreased by cathodal stimulation over visual cortex. In another study [83], tDCS was found to affect the P100 component (anodal tDCS caused decrease in amplitude while cathodal tDCS caused increase in amplitude) of the VEP and the duration of the after-effect of tDCS dependent on the duration of stimulation. Of note, as so often in this literature, the choice of return electrode was different. This may explain the different findings across studies. In both studies, stimulation did not affect the latency of the VEP. Similarly, the effects of tDCS on somatosensory evoked potentials (SEPs) have been studied. A 9-minute application of cathodal tDCS to somatosensory cortex decreased the N20 component of the SEP for up to an hour after stimulation while there was no significant change with anodal tDCS [84]. In another study, tDCS applied over motor association areas produced changes in SEP amplitudes as well as MEP amplitudes. Interestingly, the effects were inversely related. Anodal stimulation decreased amplitudes of MEPs while amplitudes of SEP components increased compared to cathodal stimulation [85]. Other studies have evaluated pain perception using laser evoked potentials (LEPs) after tDCS and found that only cathodal stimulation produced a change in the amplitudes of N2 and P2 components of LEPs [86, 87]. The effects of tDCS on auditory evoked potentials (AEPs) have also been evaluated and significant effects of stimulation polarity and stimulation locations (temporal vs. temporo-parietal) have been found [88].

Apart from evoked potentials, EEG oscillations have also been investigated for elucidating the effect of tDCS. In a study accompanying the previously mentioned study by Antal et al., cathodal tDCS was found to decrease power in the beta band (15.625–31.25 Hz) as well as the gamma band (31.25–62.5 Hz) related to VEPs [89]. A study by Ardolino et al. [90] evaluated the changes in spontaneous EEG activity following application of cathodal tDCS over motor cortex and found increases in power in the delta and theta bands. In another study, the effect of tDCS on mu event-related desynchronization (ERD) caused by imagined hand movements was studied [64]. The change in power of mu-rhythms was used as a measure of ERD. Anodal tDCS increased mu ERD while cathodal tDCS decreased mu ERD. The changes were attributed to the change in excitability caused by tDCS. There have also been studies which evaluated tDCS-induced changes in EEG activity patterns observed during sleep. These are covered in detail in the last section of this chapter.

The use of tDCS and EEG can be divided into two approaches – the *offline* approach, where EEG is collected after tDCS application, and the *online* approach, where EEG is collected concurrently with tDCS application. The former approach allows evaluation of the after-effects of stimulation while the latter approach allows study of the effect of stimulation on ongoing dynamics. Most of the studies described above fall in the category of offline investigations. In addition, a few of the studies have attempted to concurrently record EEG signals when stimulating with tDCS and have found noise to be the limiting factor. In a study assessing the efficacy of tDCS as a treatment for epilepsy, tDCS produced high-frequency artifacts that contaminated the EEG [91]. These artifacts were removed using an independent component analysis (ICA) algorithm. In another study [92], tDCS electrodes were placed between EEG electrodes and a band-pass filter between 0.5 Hz and 70 Hz was found sufficient to remove the artifacts produced by tDCS.

Magnetoencephalography (MEG), which records brain activity by measuring magnetic fields produced by neuronal activity, is a similar modality that has been used with tDCS. MEG (at least partially) overcomes the main limitation of using tDCS concurrently with EEG, namely the

limited source localization capability due to volume conduction. Soekadar et al. [93] applied tDCS over motor cortical areas of healthy volunteers performing a button-press task and assessed task-related changes in alpha- and beta-frequency bands from concurrently recorded MEG. Using a mathematical approach that provided spatially selective noise reduction and source localization, they were able to successfully isolate the stimulation current as a source. By separating this identified source from other sources that corresponded to brain oscillations, they were able to remove the stimulation artifacts.

Functional magnetic resonance imaging (fMRI) which relies on blood oxygenation levels (BOLD) to detect changes in activity in different brain regions is another commonly used approach to measure neurophysiological changes associated with tDCS. Compared to EEG and MEG, fMRI provides higher spatial resolution in terms of identifying the anatomical regions affected by stimulation. However, the temporal resolution is poorer as the changes in BOLD are observed a few seconds after neuronal activation. In one of the earliest studies, cathodal tDCS over motor cortex was shown to produce decreased activation [94]. As in the case with early tDCS–EEG studies, this study used an offline approach, that is, there was no stimulation during fMRI data acquisition. This was due to the potential safety hazard caused by magnetic fields from the MRI scanner inducing currents in the stimulation electrodes. Once this concern was resolved by the addition of current-limiting resistors, it became possible to perform concurrent fMRI-tDCS studies [95]. Overall, such studies have helped to understand the spatial distribution of the effects of tDCS in terms of motor and visual functions as well as functional connectivity between different regions.

11.3.2 Mechanisms of tDCS in Humans

A common observation in most neurophysiological studies discussed above is that tDCS produces a change in excitability of the region being stimulated. Alterations in membrane potential changes are thought to be the main mechanism underlying the change in excitability in both anodal and cathodal stimulation. Blocking sodium and calcium channels using pharmacological agents led to decrease or complete abolition of the effects of anodal tDCS in humans. While there was no change in the effects of cathodal tDCS, this still supported the hypothesized hyperpolarization effect of cathodal tDCS [96]. The outlasting effects of stimulation have been attributed to synaptic plasticity such as LTP that depends on NMDA receptors. Indeed, an NMDA antagonist suppressed the outlasting effects of tDCS [97]. The effect of cathodal tDCS is likely also the result of synaptic plasticity since it is also abolished by blockade of NMDA receptors [96]. Synaptic long-term depression [98] is, thus, a strong candidate mechanism. Further supporting the idea that synaptic plasticity underlies the outlasting effects is the observation that individuals with brain-derived neurotrophic factor (BDNF) Val66Met polymorphism showed lower effect of tDCS-induced change in MEP compared to individuals without the polymorphism [30].

Moreover, studies involving magnetic resonance spectroscopy have shown that tDCS polarity affects local accumulation of neurotransmitters. Stagg et al. [99] showed that anodal tDCS reduced concentrations of GABA while cathodal tDCS reduces concentration of glutamate (with a correlated decrease in GABA concentrations as well). Given the fact that increased firing rates have been shown to decrease GAD-67 activity and decreased firing rate is correlated with decreased glutamate/glutamine cycling, the idea that anodal tDCS increases and cathodal tDCS decreases excitability (and consequently firing rate) is, therefore, further supported by these spectroscopy results. In another study by Clark et al. [100], application of anodal tDCS over parietal cortex led to an increase in glutamate and glutamine levels. The effect was local as only the region in the ipsilateral hemisphere showed an increase compared to the same region in the contralateral hemisphere. The relation between reduction in GABA levels and motor learning suggests that modulation of

GABA levels is another possible mechanism which explains the observed effects of tDCS. This idea has received further support in a recent study [101] which showed that the effect of anodal tDCS over primary motor cortex produced a local decrease in the GABA concentrations and the tDCS-induced concentration change predicted motor learning performance.

11.3.3 Neurophysiology of tACS in Humans

The growing interest of the scientific community in tDCS has led to the recent development of novel tES paradigms. One particular approach, transcranial alternating current stimulation (tACS), has garnered considerable interest is now the topic of a large and rapidly growing number of scientific studies [102–104]. Transcranial alternating current stimulation is a type of noninvasive electrical brain stimulation where oscillating (typically), sinusoidal currents are applied to the scalp and underlying brain tissue of an individual. Many different frequencies have been used throughout the literature, but it is the most common to apply currents in the frequency range of observed periodic phenomena in the brain such as local field potentials and EEG oscillations. This follows from the assumption that mimicking the structure of endogenous electrical brain activity is the best way to interact with and influence the sources of such activity. Various studies have combined neurophysiological measurements with tACS in attempts to show that oscillatory noninvasive brain stimulation indeed influences the activity of the human brain. Most of these studies have found outlasting effects of tACS when examining EEG before and after stimulation, providing the first evidence that approximately matching the stimulation frequency to the frequency of prominent endogenous oscillatory brain activity yields effects on EEG activity at that frequency. A smaller number of studies have also measured the effects of tACS during its administration.

One of the first studies to record EEG and apply tACS found no effect of tACS on EEG activity or motor evoked potentials [105], but several subsequent studies found outlasting effects of theta-frequency tACS on EEG theta power [106], alpha-frequency tACS on EEG alpha power [31, 67, 107], and gamma-frequency tACS on EEG gamma coherence [108, 109] and alpha power [108]. The first evidence for outlasting effects of tACS on EEG was found by [67]. In this study, participants performed a vigilance monitoring task for the stimulation portion of a single 16-min session (3 min of EEG recording, 10 min of stimulation, and 3 min of EEG recording). During the task, participants were required to fixate on a crosshair on a computer monitor and press a button whenever the crosshair rotated 45 degrees. At the beginning of the session, the authors determined the peak individual alpha frequency (IAF) from the single-channel EEG data by calculating the spectral peak in the alpha band during a 1 min closed-eyes recording. Either sham tACS or ~1 mAmp tACS at the IAF was applied under the assumption that matching the stimulation frequency would best enhance endogenous alpha power. The tACS amplitude was titrated just below the thresholds of visual phosphene induction or skin sensation. They compared the average amplitude spectrum of 1-s windows between the baseline and the poststimulation epochs for both stimulation conditions and found a significant increase in alpha power relative to baseline in the IAF-tACS condition and not for the sham stimulation condition. Specifically, this increase was found to be in the neighborhood of the IAF across participants (IAF ± 2 Hz). Neuling et al. then investigated if the effects of tACS were also dependent on the brain state of participant [107]. They utilized the well-known alpha power difference between the eyes-open and eyes-closed conditions to test the hypothesis that the state of endogenous alpha oscillations would in part determine the EEG response to alpha-frequency tACS. The authors recorded 5 min of whole-head EEG activity, then applied the sham or verum IAF-tACS during an auditory oddball task, and finally recorded EEG for 30 min after the task. The protocol for the other experimental group was exactly the same except participants had their eyes closed for the

entirety of the experiment. In this study, tACS enhanced the alpha power for the entire 30-min post-tACS recording window. This effect was specific to the eyes-open (low endogenous alpha power) experiment, and no such power enhancement occurred during the eyes-closed (high endogenous alpha power) experiment. They also found that IAF-tACS enhanced coherence between P3 and P4 alpha activity for the eyes-closed condition, but not the eyes-open condition. These electrophysiological changes did not result in a change in oddball task performance as measured by reaction time and sensitivity. While the authors argue that the effects seen in these studies result from the entrainment of endogenous alpha oscillators to the tACS frequency, Vossen et al. found similar alpha power enhancements in the absence of evidence for entrainment [31]. The authors conducted a four-session within-participant study with three active tACS conditions and one sham tACS condition. During each session, participants performed a basic visual detection task for 22–30 min with a 2-min EEG recording before and after. During the task, the authors administered tACS at IAF (determined in the first session and used for all subsequent sessions) with individually adjusted intensity (1.35 mAmp to 2 mAmp). Each tACS protocol consisted of intermittent bursts of tACS, two of which were 80 cycles on followed by 80 cycles off and the other 30 cycles on followed by 30 cycles off. The difference between the two 80 cycles on/off conditions was whether or not the tACS phase was continuous throughout the experiment relative to the phase of a virtual sine wave at the tACS frequency for the full duration of the task. This was termed the "long continuous condition." The "long discontinuous condition" shifted the start of each tACS burst such that the phase difference between the virtual sine wave and the administered tACS changed by a randomly selected 0, 90, 180, or 270 degrees. For the 30 cycles burst condition, the onset phase was not disrupted (short continuous). The comparison of the prestimulation and poststimulation EEGs showed significant alpha power enhancement for both the long conditions and long discontinuous conditions relative to sham stimulation, but no significant difference between the two conditions. For the uncontaminated EEG epochs during the stimulation protocols, they assessed the degree of phase locking present after each burst of stimulation in terms of intertrial phase coherence (ITPC) in the alpha band. They hypothesized that entrainment "echoes," or brief periods of phase consistency in the alpha oscillation across trials, would likely be present if each tACS burst entrained the endogenous alpha oscillation to its phase. However, they found no difference in ITPC between the stimulation conditions or the sham condition (essentially measuring spontaneous phase consistency in the alpha oscillation). These results have been interpreted in favor of a spike timing-dependent plasticity framework to explain outlasting elevation of alpha power after tACS.

While studies that observe the after-effects of tACS have elucidated a robust set of neurophysiological changes attributable to oscillatory noninvasive brain stimulation, they can merely speculate about the changes that occur during stimulation to achieve the observed results. This is why studies that performed tACS while acquiring neurophysiological data such as EEG [110] and MEG [111] are of particular interest. Helfrich et al. [110] devised an artifact removal method that allowed them to measure EEG during a visual oddball task accompanied by the administration of 10 Hz tACS. In this study, participants performed a standard color-mismatch visual oddball paradigm where the presentation of each stimulus was aligned to one- of four-phase bins of the tACS waveform. The authors recorded 59-channel whole-head EEG while administering the 1 mApp current. To remove the artifact potential from the EEG, which is approximately, but not exactly, a sine wave at 10 Hz due to fluctuations in scalp impedance and various other sources of nonstationarity, the authors first constructed artifact templates from moving neighborhoods of recording epochs by a moving average approach. These artifact templates were then subtracted from their respective artifact-contaminated EEG segments to yield semi-cleaned EEG data. The remaining tACS artifacts were captured by decomposing each EEG time

series into its principal component subspace via principal component analysis (PCA). Components that were clearly artifactual in nature were removed and the time series reconstructed from the remaining components in this final step. The authors assessed the validity of this approach by contaminating artifact-free data with similar artifacts found when they applied tACS (somewhat nonstationary 10 Hz sine waves 2–4 orders of magnitude greater than typical EEG potentials). The study of the preprocessed EEG showed an enhancement of mainly occipital alpha power during tACS application, and the enhancement was strongest at the stimulation frequency. The phase-locking value (PLV) between the tACS waveform and alpha-band frequencies of the EEG was significantly greater during tACS application than that during sham stimulation, and this PLV enhancement was constrained to occipital brain regions. Interestingly, the authors found a phasic modulation of oddball target detection accuracy as a function of the tACS phase during target presentation. Given that the phase of the alpha oscillation is known to influence the perception of visual stimuli [112–114], combined with the observed enhancement in endogenous alpha power, this study provides compelling evidence that 10 Hz tACS over occipital brain regions may entrain disparate endogenous alpha oscillations to a similar phase, resulting in an increase in occipital alpha synchronization. While this approach is a promising direction for the study of the neurophysiology of tACS, it has caused quite some debate in the field due to potential nonlinear distortion of the recorded signal during stimulation [115, 116].

More recently, a study by Neuling et al. detailed a different approach to study the "online" effects during stimulation [111] based on MEG. The authors applied IAF-tACS at weak (50 μApp) and strong (between 100 μApp and 1.5 mApp) current levels while acquiring 306-channel MEG. Participants performed several tasks well established to induce alpha modulations and each participant completed three blocks consisting of sham stimulation, weak tACS, or strong tACS. The authors found substantial contamination of the sensor-level signals by tACS-induced magnetic artifacts but were able to recover meaningful event responses by using linearly constrained minimum variance (LCMV) beam forming to project the measured magnetic fields into a grid of dipolar sources within the Montreal Neurological Institute (MNI) coordinate system. The source signals determined with this method showed alpha activations/suppressions and auditory/visual average event responses that were surprisingly similar to those obtained during sham stimulation. Importantly, these effects are all within condition and localized to the same regions as seen during sham tACS, whether or not that happened to be near or away from the stimulation electrodes. Furthermore, the presence of similar enhancements *and* reductions in alpha power during all three tACS conditions strongly supports that measured source activity is physiological in nature during all three conditions.

Additionally, as with tDCS [25, 79], the combination of tACS and TMS over the motor cortex has provided a useful model to identify the influence of oscillatory electric fields on network dynamics. By pairing tACS with causal probes of motor cortex excitability (i.e., TMS), researchers can causally test the instantaneous and additive influences of specific frequency modulations across the phase-frequency parameter space. The earliest investigations of tACS applied to the motor cortex found no effects of stimulation [105]; however, shortly thereafter, several studies that followed demonstrated a slowing of movements [117] as well as an increase in the amplitude of TMS motor evoked potentials (MEP) [118] by beta-frequency tACS. These investigations inspired Fuerra and colleagues (2013) [119] to test the state dependency frequency modulations in the motor cortex. The researchers applied tACS at 5, 10, 20, and 40 Hz to the left motor cortex and to the parietal cortex as an active control region. In addition, MEPs were tested under conditions of rest or while performing a motor imagery task (imagined finger pinching). MEPs collected during the motor imagery task were on average higher when compared to rest. After controlling for this overall effect, a frequency-specific double dissociation was identified where

5 Hz tACS facilitated MEPs during motor imagery and 20 Hz tACS facilitated MEPs at rest. Indeed, the resting facilitation effect of beta tACS has become a well-substantiated finding. A recent meta-analysis of studies applying beta tACS (15–25 Hz) to modulate corticospinal excitability calculated the effects of various tACS study parameters (i.e., amplitude, montage, and online/offline testing) [120]. The authors found that stimulation intensities greater than 1 mA most consistently showed significantly increased MEP amplitudes with beta tACS. Furthermore, the classic M1-Pz/Oz montage and high-density montages were also associated with increased MEP amplitudes. No differences were observed as a function of whether testing was online or offline; MEPs were increased under both conditions. These findings run contrary to the intuition that motor cortex beta oscillations reflect a resting maintenance signal [121]. Furthermore, alpha-tACS also increased MEP amplitudes during motor imagery in Fuerra [119], albeit to a lesser extent and contrary to the typical interpretation that alpha is an inhibitory signal [122].

To address this topic, Fuerra et al. [123] had participants view a hand making a pinching movement during tACS presented at 5, 10, 20, or 40 Hz and during an active sham condition (tRNS with a 30 s ramp up and ramp down). These conditions were also tested observing a hand at rest. MEPs were recorded from hand muscles involved in the observed pinching movement (index finger) and from muscles not involved (pinky finger). As in [119], the authors found that 20 Hz tACS induced a nonselective facilitation of MEPs in both muscles at rest. However, 10 Hz tACS only increased MEPs in the muscle involved in the observed hand motion (index finger) leading the researchers to conclude that alpha rhythms in the motor cortex serve a role in selective action; possibly through surround inhibition for nonselected muscle groups. By contrast, 40 Hz tACS facilitated MEPs in both muscles during movement observation.

While several studies have used 40 Hz as a standard frequency for the gamma-band, movement-related gamma oscillations tend to appear at frequencies between 60 and 90 Hz [124, 125]. Joundi and colleagues [125] compared the effects of 20 and 70 Hz tACS on performance of a go/no-go task. Under the go condition, 20 Hz tACS slowed the time to peak force exerted in response, replicating prior results [117]. This effect was much more pronounced in no-go error trials where a participant is required to inhibit a prepotent response but fails to do so, supporting the notion of beta as an antikinetic "hold" signal [121].

How then does one reconcile the role of motor cortex beta oscillations with reports demonstrating an increase in corticospinal output? A preliminary answer can be deduced from studies investigating the impact of tACS phase on TMS-MEPs. Nakazono et al. [126] and Schilber et al. [127] both sought to address this question by analyzing the changes in MEP amplitudes as a function of the phase of ongoing tACS. Nakazono et al. [126] found that both 10 Hz and 20 Hz tACS demonstrated phase-specific effects whereby 10 Hz tACS attenuated MEPs and 20 Hz tACS facilitated MEPs at the same preferred phase (identified as 90 degrees by the authors). A few years later, Schilberg et al. [127] approached the same question using individually defined alpha- and beta-frequency tACS. As before, MEP amplitudes significantly modulated with respect to beta phase, but these effects were larger for participants with lower natural beta frequencies. Alpha tACS had no effect. Though, in a secondary experiment, Nakazono et al. [126], alpha tACS at the preferred 90 degree phase was not significantly different from a sham condition while 20 Hz tACS still significantly increased MEP amplitudes. These studies demonstrate a cyclical modulation of cortical excitability showing a net excitatory effect at preferred phases of beta tACS which presents as an overall elevated MEP in online studies due to trial averaging. Collectively, tACS-TMS protocols have provided causal evidence that tACS alters cortical excitability in ways predicted by correlational EEG studies.

11.3.4 Mechanism of tACS in Humans

The interest in tACS as a tool for manipulating cortical dynamics as well as a therapeutic option for treating CNS disorders with aberrant cortical

and thalamo-cortical oscillations is relatively recent when compared to tDCS. Correspondingly, the mechanisms by which tACS produce change are also less certain.

The primary targets for tACS in humans are oscillations observed in EEG and different studies have shown that tACS indeed alters the strength of oscillations [31, 67, 107, 110]. Given the periodic nature of stimulation as well as the stimulation target, concepts from dynamical systems are generally used to explain the mechanism of action of tACS. The different cortical oscillations are considered to be generated by self-sustained oscillators with phase as a free parameter [128]. Depending on the level of abstraction, neurons or networks of neurons or individual brain regions are treated as these oscillators. One leading hypothesis is that the brain region targeted by tACS is composed of many oscillators and tACS produces a realignment of the phase of the oscillators to the phase of stimulation waveform. This is defined as entrainment [129]. Once the oscillators are aligned, it is assumed that oscillations continue even after the removal of stimulation until entropy of the system pulls them back to the initial state. An alternate hypothesis is that tACS preferentially strengthens synapses between neurons by spike timing-dependent plasticity (STDP) and this facilitates the effects of stimulation to be present after the removal of stimulation.

Studies involving tACS and EEG in humans have attempted to elucidate which of the above-mentioned mechanisms might be prevalent. The study by Helfrich et al., where healthy volunteers were stimulated with 10 Hz tACS during a visual oddball task, found an increase in phase-locking value between stimulation waveform and EEG waveform (after stimulation artifact removal) during stimulation [110]. This was postulated as evidence for entrainment as the results satisfied the key requirements for entrainment as proposed by Thut et al. [129]. In another study, tACS applied at the individual alpha frequency produced an enhancement in alpha power when the participants had their eyes open compared to the condition where they had their eyes closed [107]. This result provides additional support to the entrainment hypothesis. In the eyes-closed condition, the phases of the oscillators within the region targeted by tACS can be considered to be aligned to each other resulting in a strong endogenous alpha oscillation. In the eyes-open condition, however, the phases of the oscillators are not aligned with each other and tACS is able to cause synchronization of the phases of the oscillators resulting in stronger alpha oscillations. However, in the study where tACS was applied in an intermittent manner, scrambling the phase of stimulation current between consecutive trials did not produce effects different from the stimulation where the phase of the stimulation current was maintained to be continuous across all trials [31]. The authors argue that the results imply entrainment is not the underlying mechanism as the enhancement produced by stimulation with scrambled intertrial phases should have been lesser than that produced by stimulation with continuous phase. Also, enhancement was stronger when stimulation frequency was closer to the individual alpha frequency. If entrainment was true, the enhancement should have been higher at stimulation frequency and not individual alpha frequency. Additionally, as mentioned before, the absence of difference in intertrial phase coherence between sham and stimulation conditions suggested that the outlasting effects of stimulation were not caused by entrainment. The authors propose a simplified STDP model to account for the effects of stimulation. Plasticity is a plausible mechanism underlying the outlasting effects of tACS and recent tACS-TMS studies of the motor cortex are providing preliminary support for this hypothesis.

As discussed in the section *Neurophysiology of tACS in Humans*, the online effects of tACS on the human brain is likely via recruitment of cortical circuits that are modulated by the application of electric fields that mimic endogenous rhythms. As such, the likelihood of STDP-related mechanisms is plausible insofar as cortical oscillations shape STDP. In that vein, McNickle and Carson [130] tested modified paired associative stimulation (PAS) protocol to use tACS instead of TMS. In TMS-PAS, electrical stimulation of the median nerve is paired with TMS applied to

the motor cortex at a fixed latency matched to individual corticospinal conduction latencies [131]. If the TMS pulse precedes the arrival of the median nerve signal, the MEP is depressed. If the TMS pulse is timed to the arrival of the median nerve signal, the MEP is potentiated. McNickle and Carson [130] leveraged a similar protocol by pairing 500 ms of 10 Hz peripheral nerve stimulation with 500 ms of tACS at 80, 140, and 250 Hz. The onset of both trains was lagged by 25 ms to mimic the expected conduction delay. Paired associative tACS at 80 Hz elicited the strongest and fastest potentiation of MEPs, but all frequencies resulted in potentiation at 30-min poststimulation. The 80 Hz tACS potentiation effects were further enhanced when the tACS duration was longer (1 s) and when using an 80 Hz vibratory stimulus instead of electrical stimulation. The potentiation observed by Nickle and Carson demonstrates that tACS can induce STDP-like effects in the human motor cortex. Future studies will need to determine whether lower-frequency tACS (i.e., <80 Hz) can induce PAS-like effects or if the aftereffects observed at those frequencies rely on some other mechanism.

Pharmacological manipulation offers a more traditional method to study the relationship of STDP to tACS effects. However, to date, only one study has used this approach in humans to identify the cellular mechanisms implicated in tACS. Wischnewski et al. [132] conducted a double-blind, placebo-controlled study of the NMDA receptor antagonist, dextromethorphan (DMO), to measure the degree to which tACS-induced changes in cortical excitability are mediated by NMDA receptors. Participants were administered DMO or placebo prior to receiving 20 Hz tACS over the motor cortex in a high-density montage. MEP amplitudes increased during the placebo visit as expected from prior literature. DMO blocked these aftereffects, suggesting that NMDA-related plasticity mechanisms likely underlie the typical increases associated with 20 Hz tACS. The lack of further cellular mechanistic studies emphasizes the need for investigators to leverage pharmacological methods in conjunction with tACS. In the meantime, we must rely on animal studies and computational modeling to infer the neural drivers of such effects.

Nevertheless, several researchers have leveraged the wide literature of pharmaco-TMS studies [133] to infer the active mechanisms underlying tACS. Returning to the topic of phase dependency of beta tACS effects, Guerra and colleagues [134] used a variety of paired-pulse TMS techniques applied at multiple phases of 7 Hz and 20 Hz tACS. Guerra et al. [134] applied short-latency and long-latency intracortical inhibition (SICI and LICI), which are considered to index GABA-A and GABA-B receptor-mediated inhibition [133, 135, 136]. In addition, the researchers indexed glutamatergic tone by measuring intracortical facilitation (ICF; [133, 135]) and cholinergic inhibition through short afferent inhibition (SAI; [137, 138]), in which a conditioning electrical stimulation to the median nerve is applied before applying a test TMS pulse to the cortex. TACS at 20 Hz significantly modulated MEP amplitudes from single-pulse TMS, ICF (i.e., glutamatergic), SICI (i.e., GABA-Aergic), and SAI (i.e., cholinergic). SAI was blunted during 20 Hz tACS but did not demonstrate phase-specific effects. By contrast, ICF and SICI followed antiphase relationships to each other—when SICI was up, ICF was reduced, and vice versa. These findings present compelling evidence that the application of tACS modulates existing cellular mechanisms underlying neuronal circuits in a manner that mimics endogenous oscillations. Finally, the nonphase specificity of the SAI findings emphasizes the presence of both phase (i.e., momentary) and continuous effects of stimulation which indicates that tACS recruits neuromodulatory circuits as well.

We are now seeing converging evidence that tACS modulates brain activity and excitability through multiple mechanisms. While the ideas of entrainment and plasticity seem mutually exclusive, it is apparent that this is not necessarily true. A realignment of phase may lead to strengthening of synaptic connections between the neurons because of STDP. Conversely, strengthening of synapses may lead to increased phase locking and consequently entrainment. Future studies

trying to answer this question will be well served to include this consideration when designing the study as well as when trying to interpret the results.

11.4 Spatial and Temporal Targeting to Improve Cognition

Deficits in cognitive capacity are now realized to be ubiquitous across psychiatric illness and commonly experienced in aging. Thus, novel interventions to improve cognitive function are of critical need. However, a meta-analysis of the impact of transcranial magnetic stimulation on performance finds an overall cognitive detriment from online stimulation [139] (but see [140–142]). The relatively weaker influence of tACS to modulate, but not dominate, brain activity (see Effect of Electric Fields on Individual Neurons) may prove to be the optimal technique for improving cognition. Recent advances in the spatial localization of stimulation effects using high-density tACS and temporal localization using custom waveforms designed to mimic cross-frequency coupling provide greater controllability of brain dynamics. As cognitive neuroscience elucidates the neural correlates of higher-order cognition, tACS will continue to causally probe their mechanistic role and build a foundation of evidence that tACS can be utilized to improve cognition when properly targeted.

11.4.1 Frequency-Specific Effects of tACS

Working memory, or the ability to maintain and manipulate information over time, is the foundation of higher-order cognitive abilities [143], and deficits in working memory appear in a variety of illnesses [144–146]. A better understanding of the neural basis of working memory provides refinement of the targets for neurostimulation to engage in order to improve working memory. Theoretical models on how the brain implements working memory suggest that higher-frequency activity is nested within lower-frequency activity [147]. The higher-frequency activity (gamma oscillations [30–50 Hz]) encodes the individual items of memory and the lower-frequency oscillations (theta oscillations [4–8 Hz]) support the maintenance and sequencing of these items [148]. A consequence of this model is that slower theta oscillations are able to contain a greater number of gamma cycles, which may support greater working memory capacity. Indeed, invasive recordings of the human hippocampus during working memory found that slower theta oscillations coupled to high-frequency gamma oscillations as the load of a working memory task was increased [149]. A recent study provided causal evidence for the speed of theta oscillations in working memory [150]. Wolinski et al. delivered tACS at the slower end of the theta band (4 Hz) or at the faster end of the theta band (7 Hz) as participants performed a visuospatial working memory task. Participants that received tACS in the slower theta frequency demonstrated improved working memory capacity relative to those that receive faster theta-frequency stimulation. These data provide evidence that the particular frequency of stimulation is critically important, and that stimulation may need to be delivered offset to the endogenous peak frequency.

While the previous section on the Arnold tongue explained that the efficacy of stimulation is strongest at the endogenous frequency, some studies found that the specific frequency of peak resonance was consequential for performance [151] and could even be manipulated by task demands [152]. Individual differences in pain perception were found to correlate with peak alpha frequency of sensorimotor cortex [153]. In patients with chronic pain, the peak frequency of the alpha oscillations is slower with greater experience of chronic pain [154]. Thus, stimulation for the treatment of chronic pain might be more effective when delivered at the canonical peak frequency of the alpha oscillation rather than the individual alpha frequency. In a recent clinical trial on the treatment of chronic pain, symptoms of chronic pain were reduced when stimulation was delivered targeted to sensorimotor cortex at

the canonical alpha frequency [155]. These effects might not have been observed if stimulation was delivered at the individual alpha frequency, although this study did not compare stimulation at individual frequency to canonical frequency.

11.4.2 High-Density Spatial Targeting

As current enters the scalp from the stimulation electrodes, the skull shunts the majority of electric current through the skin. Thus, stimulation techniques historically focused on using large electrodes placed on opposite sides of the scalp. However, recent availability of electric field modeling toolboxes allowed scientists to design novel electrode montages that optimized for focality of stimulation of effects rather than magnitude. High-density tACS is the application of many small electrodes, typically with a central electrode encircled by three or four electrodes. The central electrode is the current source, and the encircling electrodes are the current sink. Thus, the current enters the brain maximally under the central electrode and returns in a more diffused manner. Unlike other forms of current stimulation, high-density tACS can be used to target a single brain region. For example, Alekseichuk et al. used high-density tACS to target a relatively focal region of left lateral prefrontal cortex during a working memory task and found an improvement in working memory performance from theta-frequency stimulation [156].

High-density tACS can also be used to investigate functional connectivity between regions. In traditional tACS montages using two electrodes, the two regions targeted by stimulation receive current antiphase to each other. As the current depolarizes one region, the other region is hyperpolarized. Thus, stimulation with two electrodes is unable to investigate functional connectivity, except by way of disruption. In order to increase functional connectivity, tACS must be delivered with a minimum of three electrodes. Current is delivered in sync to two regions, and out of sync with the third region. However, the three-electrode montage introduces a third location that is necessarily in antiphase. The potential nuisance of a desynchronized region is minimized by using a larger electrode for the current sink. High-density tACS introduces a novel approach for manipulating connectivity as the two regions can be targeted independently, each with their own high-density arrangement. Two recent publications utilized high-density tACS to two regions. In one study, participants received stimulation to either both lateral and medial prefrontal cortex in-phase using high-density tACS or the electrodes were rigged such that the regions received canonical-like antiphase tACS [157]. When stimulation was delivered in phase, performance in a cognitive task was improved and when stimulation was delivered antiphase, performance decreased.

In another study, Reinhart and Nguyen used two high-density tACS montages to target lateral prefrontal cortex and temporal cortex during performance of a working memory task [158]. When stimulation was delivered to both sites in phase at theta frequency, working memory performance was improved in older adults. However, when stimulation was delivered to only lateral prefrontal cortex or only the temporal cortex, there was no benefit to performance. This study leveraged the unique capabilities afforded by tACS to target individual regions and to deliver in-phase stimulation to two sites.

11.4.3 Cross-Frequency tACS

Cross-frequency coupling increases during tasks that demands higher levels of cognitive control [159]. Low-frequency oscillations, typically in prefrontal cortex, couple to high-frequency activity. One form of cross-frequency coupling is phase-amplitude coupling where the phase of the low-frequency oscillations is locked to the amplitude of high-frequency oscillations. This pattern of activity was first discovered in the hippocampus between the theta and gamma oscillations (see [147] for review). The electrical waveform of tACS can be customized to simulate phase-

amplitude coupling [156, 160]. A high-frequency waveform is superimposed on a low-frequency waveform such that a high-frequency modulation occurs at a particular phase of the low-frequency component. In a previous experiment, cross-frequency tACS that mimicked theta-gamma coupling was delivered to left lateral prefrontal cortex using high-density tACS during performance of a working memory task [156]. When the gamma component was delivered at the peak of the theta phase, then working memory performance was increased. However, when the gamma component was at the trough of the theta phase, performance did not improve. These findings provide causal evidence for the role of theta-gamma phase-amplitude coupling in working memory. Furthermore, the authors included a condition with theta-frequency tACS only. Theta-only stimulation also improved working memory performance, but the benefit to performance was improved further with theta-gamma cross-frequency tACS. This experiment demonstrates the unique ability for tACS to enhance cross-frequency coupling with the use of customized waveforms.

11.5 Application of tES to Sleep Oscillations

A complete understanding of the effects of tES on human brain activity and behavior will require linking the findings of the microscopic domains (cellular recordings and computational models) to the discoveries from the macroscopic domains (human studies with EEG, MEG, and fMRI). Sleep is a promising frontier in terms of bringing these different levels of analysis together. More specifically, the slow oscillation (<1 Hz) represents a strong candidate for such an undertaking for several reasons. First, we have an advanced understanding of the cellular and synaptic mechanisms underlying slow oscillations (SO). Second, weak electrical fields with frequencies mimicking the frequency of cortical SO have been applied in brain slices in vitro, in rats in vivo, and humans, and also studied in computational models. We discuss these two points in more detail.

11.5.1 Mechanisms of Slow Oscillations

In order to understand the effects of DC, oscillatory DC (rhythmic stimulation with a DC offset), or AC stimulation, we need to understand the mechanisms underlying different endogenous brain rhythms. SO are prevalent during slow-wave sleep and can be observed under anesthesia in vivo and in vitro, when the medium mimics in vivo conditions of the cerebrospinal fluid. Mechanistically, SO have been very well studied and have been suggested to be generated and sustained in the neocortex [161–163], although thalamic circuits may also contribute [164]. This allows for investigating these rhythms in cortical slices [14]. The SO represents a low-frequency oscillation (~1 Hz) in the membrane potential of cortical neurons [165, 166] with the neurons alternating between so-called up and down states [163, 167]. The up state is associated with the depolarized, that is, active, phase of cortical neurons and most cortical neurons fire action potentials during the up state [168]. During the down state, neurons are silent and do not fire action potentials. These down states can last for several hundreds of milliseconds and represent the prolonged hyperpolarizing phases of cortical neurons [168]. The synchronization of the slow oscillation of many neurons leads to the characteristic slow waves (<4 Hz) seen in depth and surface EEG [166, 167, 169]. Of note, the prolonged silent or hyperpolarized phase, synchronized across many neurons, is unique to the slow oscillation during natural sleep and anesthesia [170, 171].

Internal dynamics need to be taken into account to understand which aspects of the slow oscillation can be modulated by weak electrical fields [172]. Specifically, for SO, the transition to the down state is associated with activity-dependent reduction in synaptic strength that is maximal at the end of the up state [172–175]. Thus, modulating the termination of up states that are intrinsically determined [172] may be difficult. In contrast, the transition from down to up state is driven by slight depolarizations that shorten the down

state [172]. This idea of differential susceptibility of different phases of the SO cycle has been supported by an in vitro study of ferret slices [23] and a computational model [176].

11.5.2 Modulating the Slow Oscillation with Weak Electric Fields

Modulation of SO using AC, DC, and oscillatory DC has gained significant interest in the last decade for the following reasons. First, SO have been implicated in coordinating other sleep rhythms (e.g., sleep spindles), providing a restorative function and promoting memory consolidation. Thus, applying electrical stimulation to further boost SO will help to prove their causal role in the proposed processes [177]. Second, SO induce very pronounced endogenous electric fields and are, therefore, ideally suited to study the importance of those extracellular fields in entraining physiological neocortical network activity [23]. Thus, manipulation of SO with weak electrical stimulation has been probed in slices, in vivo in rats and ferrets, in humans, and in computational models.

Frohlich and McCormick [23] used the in vitro neocortical slow oscillations from acute slices of ferret visual cortex to demonstrate that externally applied weak electrical fields (physiological amplitudes that are found in vivo) and endogenous electric fields can directly modulate neuronal dynamics. Recorded oscillations are, therefore, not only a mere epiphenomenon of the underlying neuronal activity but rather actively modulate neuronal activity. The application of constant depolarizing currents (corresponding to anodal tDCS in humans) accelerated the slow-oscillation frequency by shortening the duration of the down states (with no concurrent modulation of the up-state duration). Frohlich and McCormick [23] further highlighted the importance of ongoing network activity for weak electrical fields to have an effect. They applied sine-wave electrical fields that approximately matched the frequency of the spontaneous network oscillation and found that the SO became more periodic and entrained to the applied field. Importantly, weak external electrical fields preferentially enhanced the slow oscillation when their frequency was matching the intrinsic frequency. Along this line, Schmidt et al. [20] used an optogenetic approach to further confirm that weak alternating electric fields only enhanced endogenous oscillations when the stimulation frequencies were matched to the endogenous oscillations. In addition, ongoing network activity is necessary to amplify the effect of weak electrical fields by bringing the membrane voltage of neurons close to the threshold [23]. These important in vitro results hint at the fact that the amplification of network-wide weak perturbations by synaptic interaction may be an important aspect of the mechanism of tES.

Frohlich and McCormick [23] provided further support for this hypothesis with a computational network model showing that neuronal activity modulations by weak electric fields can be explained by small but simultaneous somatic depolarization of all neurons in the network. In a multiscale computational model, Reato et al. [176] showed that that intrinsic network dynamics of slow-oscillatory activity can rectify mixed polarizations leading to a unidirectional increase in firing rates in case a monophasic alternating current is used (on/off periods with ramp-up/ramp-down properties). Due to the cortical folding of the cortex, the applied electric fields show bi-directional polarities throughout the cortex, thus some regions might receive anodal stimulation while others experience cathodal stimulation. Thus, applying a constant DC would lead to both an increase and decrease in firing rates. In contrast when using monophasic alternating DC, the computational model predicts that entrainment occurs regardless of polarity (this applies for monophasic stimulation) via a modulation of the duration of the endogenous up and down state. Specifically, up states will align with the on phase of the anodal stimulation and the down states with the on states of the cathodal stimulation and, therefore, only a rectified increase but no decrease in firing rate will be obtained [176]. However, this model only holds true if the off period of the alternating current field has a cur-

rent strength of zero. Collectively, the findings in in vitro and computational studies emphasize that if and how tES affects neuronal activity depends on the intrinsic network activity (and on the applied field parameters).

To fully understand how tES affects SO in humans, we need a comprehensive physiological understanding of tES-induced effects on neuronal activity in the intact brain. This issue has been investigated by applying tES at frequencies of cortical slow oscillations to multiple cortical regions in both anesthetized and awake rats [178, 179], and anesthetized ferrets [56]. Ozen et al. [178] placed the stimulation electrodes on the surface of the skull or on the dura. Extra- and intracellular recordings showed an entrainment (phase locking) of neurons to the externally applied sinusoidal electrical field. This effect was more pronounced if the network already exhibited intrinsic slow oscillations (anesthesia), further emphasizing that effectiveness of tES rests upon the internal network dynamics. Considering that rodents have lissencephalic brains and the human cortex exhibits pronounced folding, which leads to uncontrolled and mixed field orientations, it is difficult to directly interpolate in vivo findings in rodents to humans. The ferret represents a model species with a gyrencephalic brain that at least partially helps overcome this limitation. Applying tACS at different slow-oscillatory frequencies (0.5–3.5 Hz), Ali et al. [56] showed that multiunit activity in anesthetized ferrets is entrained to the specific applied frequency. Whether this effect is restricted to a stimulated network that already exhibits intrinsic slow-oscillatory activity remains unknown because only anesthetized ferrets were investigated.

Slow oscillations have been proposed to play a key role in sleep-dependent memory consolidation [180]. Marshall et al. [177] were the first to demonstrate causality in this memory process by applying monophasic, slow-oscillatory tDCS (0.75 Hz, also compare [176]) during the first half hour of NREM sleep in healthy sleeping subjects. They found a significant increase in declarative memory along with increased slow-oscillatory and slow-spindle activity (8–12 Hz) in stimulation-free EEG intervals (1 min intervals without stimulation in alternation with five 5-min stimulation periods). As mentioned in previous parts of this book chapter, the pronounced stimulation artefacts in the EEG prevent an accurate analysis of the EEG during tES application. Along this line, Reato et al. [176] predicted with their computational model (approximating the stimulation settings from [177]) that the rectified increase in firing rate leads to a faster downscaling of synaptic strength. Convincing evidence exists that slow oscillation is involved in downscaling synaptic connections to ensure the synaptic homeostasis of the brain [181] with high firing rates favoring synaptic depression [182, 183]. In addition, this downscaling process might lead to an increased synaptic signal-to-noise ratio that could explain the beneficial effect of sleep on memory consolidation [181, 184, 185]. Assuming that stimulation accelerates synaptic downscaling by increasing the firing rate, the rate of downscaling should be decelerated after the stimulation has stopped [176]. Their assumption was confirmed in the human dataset recorded by Lisa Marshall et al. [177]. Marshall et al. were further able to replicate the behavioral and EEG findings in rats [186, 187]. In addition, some studies were able to replicate, at least partially, the findings from Marshall et al. (2006) in both healthy humans and patients with neurologic or neurodevelopmental disorders [188–194]. However, other groups found contradicting results on EEG and memory consolidation when applying monophasic slow-oscillatory tDCS [195–198]. One of the differences between the studies was the waveform of the used tDCS pulse; for example, Marshall et al. (2006) were using ramp-up, ramp-down shaped pulses, and Sahlem et al. [195] were applying square waves. Whether and how the tDCS pulse shape is critical for the effectiveness of oscillatory tDCS needs to be further investigated with the interdisciplinary toolkit discussed in the previous sections of this chapter. Koo and colleagues [193] also bring up the importance of interindividual difference in the susceptibility to slow-oscillatory tDCS for which they hypothesize to strongly depend on the network state, for example, on task-induced (pre-

sleep period) endogenous network activity during sleep. Along these lines tES approaches use weak fields and, therefore, the success of modulating brain oscillations will rely on the extent of endogenous oscillations, that is, if the modulated system has an ongoing oscillation at the frequency of interest and is close to threshold according to the principle of the Arnold tongue [11, 56, 70]. Thus, for a rational design of electrical stimulation approaches during sleep (e.g., oscillatory tDCS or tACS), feedback-controlled systems that consider endogenous activity patterns when stimulating might increase effectiveness of the stimulation (reviewed in [199]). Specifically for slow oscillations, individually and dynamically matching the stimulation frequency to the endogenous slow wave to optimally target the on and off periods is of interest. A few studies have established feedback-controlled tACS in the slow-oscillatory frequency range [200–202], yet only two report effects in human participants [200, 201]. Ketz et al. (2018) and Jones et al. (2018) report results from the same experiment in healthy young volunteers, in which they used frequency matching of the stimulation waveform (sine-wave AC at the frequency of slow oscillations) to a short prestimulation window before. They used a dynamic approach matching a sine wave to the endogenous slow wave for a few cycles and then applied stimulation for a few cycles following this matched sine wave. This process was repeated during nocturnal NREM sleep allowing for an online matching/updating in short intervals. They found a significant increase in EEG power in the slow-wave frequency range (poststimulation interval) and a superior overnight effect on memory consolidation (target detection task). Besides slow oscillations, a feedback-controlled approach during sleep is also attractive to modulate sleep spindles due to their transient nature. These thalamo-cortically generated NREM oscillations (11–16 Hz) only occur for 0.5–3 s and then vanish again for a certain amount of time (reviewed in [203]). Keeping in mind that tES paradigms resembling the temporal structure of endogenous activity patterns are likely the most effective approaches, we applied spindle-like tACS during online detected sleep spindles [204]. This approach significantly enhanced spindle activity in the poststimulation window and improved overnight finger-tapping performance, revealing for the first time their functional role in motor memory consolidation.

To date, one major drawback of assessing the direct effects of tES on sleep oscillations noninvasively in humans is the pronounced artifact of the stimulation. Currently, new and potentially promising avenues have been proposed to remove the artifact, yet other factors like breathing and heartbeat that nonlinearly affect the artifact render its removal a particular challenge [115]. Therefore, for all the abovementioned human sleep studies, it remains unclear what effects the stimulation had on sleep oscillations for the whole duration of the sleep period. Lafon et al. (2018) assessed the effect of slow-oscillatory tACS in patients with intracranial EEG recordings [205]. They indirectly estimated the efficiency of slow-oscillatory tACS by taking advantage of the nesting behavior of sleep spindles to specific phases of slow oscillations. Therefore, if the stimulation were effective, one would expect that sleep spindles align to the externally applied slow-oscillatory phase. They failed to find a significant effect. Together with the discrepancies in previous studies and the inability to directly assess the stimulation effect on the EEG, efficacy of tES in modulating sleep (brain) oscillations has been heavily criticized. Therefore, rational designs of the stimulation paradigms by taking underlying endogenous activity into account (e.g., feedback-controlled approaches as described above) may indeed be essential for more effective stimulation outcomes when weak electrical fields are applied [24, 199].

11.6 Clinical Trials of tACS

More recently, tACS has been considered in the context of modulating pathophysiological brain rhythms in psychiatric disorders. Initial findings of tACS in clinical trials support continued investigations into how tACS frequency and electrode placement alter network connectivity in multiple

disorders such as schizophrenia and major depressive disorder. Crucially, studies that use tACS often do not investigate target engagement in the form of changes in oscillation and power network connectivity but solely focus on behavioral or symptom outcomes, limiting their usefulness in understanding the mechanisms by which tACS alters physiology. As such, we will limit our discussion to trials that include target engagement outcomes.

Our group published the first study of tACS on symptoms of major depressive disorder and EEG oscillations [206]. In this double-blind, randomized pilot trial, participants received daily 40-min sessions of 10 Hz tACS, 40 Hz tACS, or active sham stimulation for 5 consecutive days. Two electrodes (delivering together in-phase 2 mA (zero-to-peak) sine-wave electric current) were placed on bilateral frontal sites (F3 and F4) with a centrally located third electrode (CZ). Symptom changes on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale and changes in alpha power at 2- and 4-week post -treatment were assessed in 32 patients. Ten-Hz tACS significantly reduced alpha power over the left frontal regions, in agreement with the overall model that synchronization of alpha oscillations can restore pathologically altered hemispheric asymmetries of alpha oscillations in depression [207]. While we found no significant group effect on symptom changes at 4 weeks post treatment, those who did experience a reduction in symptoms 2 weeks post treatment were more likely to be in the group receiving 10 Hz tACS. We used a similar design to investigate the effects of both tACS and tDCS on auditory hallucinations in treatment-resistant schizophrenia and found alterations in alpha power for the tACS group [208, 209]. Participants were clinically stable, but with persistent auditory hallucinations (≥3 per week). Treatment sessions were extended to twice daily for 2 weeks, with 1-week and 1-month post-treatment study visits. Symptom changes were assessed with the auditory hallucination rating scale, and physiological changes were measured as alpha oscillations and functional connectivity in the alpha-frequency band. Stimulation electrodes were placed on the left side between F3 and Fp1 (targeting dorsolateral prefrontal cortex) and between T3 and P3 (temporoparietal junction), with a return electrode placed centrally at CZ. For tACS, the former two electrodes delivered an in-phase sinusoidal waveform with 1 mA (zero-to-peak) amplitude, while +2 mA current was delivered to the frontal site and −2 mA current was delivered to the posterior site in the tDCS condition. Compared to tDCS and active sham, alpha power was increased on day 5 ($p < 0.05$) and at the 1-week and 1-month follow-up sessions (though not statistically significant). Additionally, global functional connectivity strength was shifted to 10 Hz (frequency of 10 Hz waveform) and the auditory response to click trains was enhanced in the tACS group, but not in the other conditions. Enhanced alpha oscillations were correlated with both auditory responses and negatively associated with auditory hallucinations. Another lab reported a decrease in residual delusions after 5 days of alpha tACS, with even greater improvement after an additional 5 days [210], although they did not report the physiological effects of treatment and did not use a randomized controlled trial (RCT) design leading to concerns about statistical conclusion validity. In our ongoing trials, we hope to clarify the promising relationship between symptom reductions and alterations in alpha power by delivering 10 Hz tACS and measuring the resulting behavioral and physiological changes.

11.7 Outlook

In this chapter, we have attempted to pull together results from a vast set of different neuroscience methods to delineate how tES engages network targets in the brain. By necessity, this chapter is incomplete despite our best efforts and we express our apologies to authors of other important work that did not fit this current chapter. Briefly, we have first introduced basic results on changes in excitability of individual neurons, followed by a discussion of modulation of network dynamics in vitro and in vivo. We then considered computational models as a comple-

mentary strategy to investigate the spatial targeting (forward models) and the targeting of neuronal dynamics (neural models). Next, we reviewed studies in humans that used noninvasive monitoring of brain activity (EEG, MEG, and fMRI) to demonstrate targeting of brain network dynamics by tES. In particular, we focused on the underlying dynamic principles that guide the interaction between tES and endogenous network dynamics. We then provide three unique perspectives that we believe will be central to furthering our understanding of targeting brain networks with tES. First, we look at how targeted stimulation waveforms can be used to understand the causal role of oscillations in cognition and the potential of tACS for restoring cognitive deficits. Second, we consider low-frequency rhythms during sleep as a case study for how the different methods discussed in earlier sections of the chapter can come together not only for understanding the mechanisms of tES but also for the design of effective tES strategies to modulate memory consolidation. Third, we briefly summarized the first clinical trials of tACS in psychiatry. We hope that this tour de force provides an integrated overview of today's research on how tES targets network dynamics and inspires a new area of rational design of brain stimulation to target physiological and pathological network states.

Given the noninvasive nature and the low cost combined with the promising behavioral results of tES, it is imperative to understand what the underlying mechanisms of tES are. The various levels of investigation described in this chapter, from microscopic to macroscopic and from in silico to in vivo domains, are essential to arrive at a holistic understanding of the mechanisms of tES. Once this is achieved, rational design of tES paradigms to target specific network dynamics will become the norm. Ultimately, this will help to usher in a new area of neuroscience in which tES serves as a broadly used, effective research tool for probing and understanding functional networks of the human brain as well as a transformative therapeutic tool for treating disorders of brain networks.

References

1. Terzuolo CA, Bullock TH. Measurement of imposed voltage gradient adequate to modulate neuronal firing. Proc Natl Acad Sci U S A. 1956;42(9):687–94.
2. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
3. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol. 1962;5:436–52.
4. Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. J Physiol. 1988;402:751–71.
5. Aspart F, Remme MWH, Obermayer K. Differential polarization of cortical pyramidal neuron dendrites through weak extracellular fields. PLoS Comput Biol. 2018;14(5):e1006124.
6. Toloza EHS, Negahbani E, Fröhlich F. Ih interacts with somato-dendritic structure to determine frequency response to weak alternating electric field stimulation. J Neurophysiol. 2018;119(3):1029–36.
7. Bikson M, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol. 2004;557(Pt 1):175–90.
8. Deans JK, Powell AD, Jefferys JG. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J Physiol. 2007;583(Pt 2):555–65.
9. Vöröslakos M, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9(1):483.
10. Krause MR, et al. Transcranial alternating current stimulation entrains single-neuron activity in the primate brain. Proc Natl Acad Sci. 2019;116(12):5747–55.
11. Huang W, Stitt I, et al. Transcranial alternating current stimulation entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform. Nat Commun. 2021;12(1):3151. https://doi.org/10.1038/s41467-021-23021-2. PMID: 34035240.
12. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat Commun. 2019;10(1):266.
13. Vieira PG, Krause MR, Pack CC. tACS entrains neural activity while somatosensory input is blocked. PLOS Biology 18(10): e3000834. https://doi.org/10.1371/journal.pbio.3000834.
14. Sanchez-Vives MV, McCormick DA. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nat Neurosci. 2000;3(10):1027–34.
15. Williams JH, Kauer JA. Properties of carbachol-induced oscillatory activity in rat hippocampus. J Neurophysiol. 1997;78(5):2631–40.
16. Beltramo R, et al. Layer-specific excitatory circuits differentially control recurrent network dynamics in the neocortex. Nat Neurosci. 2013;16(2):227–34.

17. Reato D, et al. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30(45):15067–79.
18. Canolty RT, et al. High gamma power is phase-locked to theta oscillations in human neocortex. Science. 2006;313(5793):1626–8.
19. Pikovsky A, et al. Synchronization: a universal concept in nonlinear sciences, vol. 12. Cambridge: Cambridge University Press; 2003.
20. Schmidt SL, et al. Endogenous cortical oscillations constrain neuromodulation by weak electric fields. Brain Stimul. 2014;7(6):878–89.
21. Gluckman BJ, et al. Electric field suppression of epileptiform activity in hippocampal slices. J Neurophysiol. 1996;76(6):4202–5.
22. Gluckman BJ, et al. Adaptive electric field control of epileptic seizures. J Neurosci. 2001;21(2):590–600.
23. Frohlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67(1):129–43.
24. Fröhlich F. Endogenous and exogenous electric fields as modifiers of brain activity: rational design of noninvasive brain stimulation with transcranial alternating current stimulation. Dialogues Clin Neurosci. 2014;16(1):93–102.
25. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
26. Reato D, Bikson M, Parra LC. Lasting modulation of in vitro oscillatory activity with weak direct current stimulation. J Neurophysiol. 2015;113(5):1334–41.
27. Marquez-Ruiz J, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. Proc Natl Acad Sci U S A. 2012;109(17):6710–5.
28. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
29. Rohan JG, et al. Modulating hippocampal plasticity with in vivo brain stimulation. J Neurosci. 2015;35(37):12824–32.
30. Fritsch B, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
31. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (alpha-tACS) reflects plastic changes rather than entrainment. Brain Stimul. 2015;8(3):499–508.
32. Riddle J, et al. Brain-derived neurotrophic factor (BDNF) polymorphism may influence the efficacy of tACS to modulate neural oscillations. Brain Stimul. 2020;13(4):998–9.
33. Radman T, et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul. 2009;2(4):215–28, 228 e1–3.
34. Hu H, Vervaeke K, Storm JF. Two forms of electrical resonance at theta frequencies, generated by M-current, h-current and persistent Na+ current in rat hippocampal pyramidal cells. J Physiol. 2002;545(Pt 3):783–805.
35. Hutcheon B, Yarom Y. Resonance, oscillation and the intrinsic frequency preferences of neurons. Trends Neurosci. 2000;23(5):216–22.
36. Pikhovych A, et al. Transcranial direct current stimulation modulates neurogenesis and microglia activation in the mouse brain. Stem Cells Int. 2016;2016:2715196.
37. Bikson M, Rahman A, Datta A. Computational models of transcranial direct current stimulation. Clin EEG Neurosci. 2012;43(3):176–83.
38. Datta A, et al. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. J Neural Eng. 2008;5(2):163–74.
39. Bai S, Loo C, Dokos S. A review of computational models of transcranial electrical stimulation. Crit Rev Biomed Eng. 2013;41(1):21–35.
40. Wagner T, et al. Transcranial direct current stimulation: a computer-based human model study. NeuroImage. 2007;35(3):1113–24.
41. Bikson M, et al. High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. Neuromodulation. 2012;15(4):306–15.
42. Huang Y, et al. Correction: measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. elife. 2018;7:e35178.
43. Huang Y, et al. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. elife. 2017;6:e18834.
44. Datta A, et al. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2(4):201–7, 207 e1.
45. Salvador R, et al. Modeling the electric field induced in a high resolution realistic head model during transcranial current stimulation. 2010 Annual International Conference of the Ieee Engineering in Medicine and Biology Society (Embc), 2010: 2073–2076.
46. Opitz A, et al. How the brain tissue shapes the electric field induced by transcranial magnetic stimulation. NeuroImage. 2011;58(3):849–59.
47. Thielscher A, Opitz A, Windhoff M. Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. NeuroImage. 2011;54(1):234–43.
48. Minhas P, et al. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:859–62.
49. Datta A, Bikson M, Fregni F. Transcranial direct current stimulation in patients with skull defects

and skull plates: high-resolution computational FEM study of factors altering cortical current flow. NeuroImage. 2010;52(4):1268–78.
50. Rattay F. Analysis of the electrical excitation of CNS neurons. IEEE Trans Biomed Eng. 1998;45(6):766–72.
51. McIntyre CC, et al. Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol. 2004;91(4):1457–69.
52. Esser SK, Hill SL, Tononi G. Modeling the effects of transcranial magnetic stimulation on cortical circuits. J Neurophysiol. 2005;94(1):622–39.
53. Anderson WS, et al. Studies of stimulus parameters for seizure disruption using neural network simulations. Biol Cybern. 2007;97(2):173–94.
54. Manola L, et al. Anodal vs cathodal stimulation of motor cortex: a modeling study. Clin Neurophysiol. 2007;118(2):464–74.
55. Birdno MJ, et al. Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation. J Neurophysiol. 2012;107(1):364–83.
56. Ali MM, Sellers KK, Frohlich F. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. J Neurosci. 2013;33(27):11262–75.
57. Dutta A, Nitsche MA. Neural mass model analysis of online modulation of electroencephalogram with transcranial direct current stimulation. 2013 6th International IEEE/EMBS Conference on Neural Engineering (Ner), 2013: 206–210.
58. Molaee-Ardekani B, et al. Effects of transcranial direct current stimulation (tDCS) on cortical activity: a computational modeling study. Brain Stimul. 2013;6(1):25–39.
59. Dutta A. Bidirectional interactions between neuronal and hemodynamic responses to transcranial direct current stimulation (tDCS): challenges for brain-state dependent tDCS. Front Syst Neurosci. 2015;9:107.
60. Berger H. Uber das Elektrenkephalogramm des Menschen. Arch Psychiatr Nervenkr. 1929;87(1):527–70.
61. Buzsaki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents--EEG, ECoG, LFP and spikes. Nat Rev Neurosci. 2012;13(6):407–20.
62. Harris KD, Thiele A. Cortical state and attention. Nat Rev Neurosci. 2011;12(9):509–23.
63. Uhlhaas PJ, Singer W. Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. Neuron. 2012;75(6):963–80.
64. Matsumoto J, et al. Modulation of mu rhythm desynchronization during motor imagery by transcranial direct current stimulation. J Neuroeng Rehabil. 2010;7:27.
65. Kirov R, et al. Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. Proc Natl Acad Sci U S A. 2009;106(36):15460–5.
66. Kanai R, Paulus W, Walsh V. Transcranial alternating current stimulation (tACS) modulates cortical excitability as assessed by TMS-induced phosphene thresholds. Clin Neurophysiol. 2010;121(9):1551–4.
67. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One. 2010;5(11):e13766.
68. Izhikevich EM. Simple model of spiking neurons. IEEE Trans Neural Netw. 2003;14(6):1569–72.
69. Izhikevich EM. Which model to use for cortical spiking neurons? IEEE Trans Neural Netw. 2004;15(5):1063–70.
70. Negahbani E, et al. Targeting alpha-band oscillations in a cortical model with amplitude-modulated high-frequency transcranial electric stimulation. NeuroImage. 2018;173:3–12.
71. Kellaway P. The part played by electric fish in the early history of bioelectricity and electrotherapy. Bull Hist Med. 1946;20(2):112–37.
72. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol. 2003;114(4):589–95.
73. Costain R, Redfearn JW, Lippold OCJ. Controlled trial of therapeutic effects of polarization of brain depressive-illness. Br J Psychiatry. 1964;110(469):786.
74. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry. 1964;110:768–72.
75. Redfearn JW, Costain R, Lippold OCJ. Preliminary account of clinical effects of polarizing brain in certain psychiatric-disorders. Br J Psychiatry. 1964;110(469)):773.
76. Rosenthal SH, Wulfsohn NL. Electrosleep–a clinical trial. Am J Psychiatry. 1970;127(4):533–4.
77. Bishop GH, O'Leary JL. The effects of polarizing currents on cell potentials and their significance in the interpretation of central nervous system activity. Electroencephalogr Clin Neurophysiol. 1950;2(4):401–16.
78. Bindman LJ, Lippold OCJ, Redfearn JW. Action of brief polarizing currents on cerebral cortex of rat.1. During current flow + 2. In production of long-lecting after-effects. J Physiol. 1964;172(3):369.
79. Priori A, et al. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9(10):2257–60.
80. Ahn S, Fröhlich F. Pinging the brain with transcranial magnetic stimulation reveals cortical reactivity in time and space. Brain Stimulation. 2021;14(2):304–15. https://doi.org/10.1016/j.brs.2021.01.018.
81. Pfurtscheller G. Spectrum analysis of EEG: before, during and after extracranial stimulation in man. Elektromed Biomed Tech. 1970;15(6):225–30.
82. Antal A, et al. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysi-

ological evidence. Invest Ophthalmol Vis Sci. 2004;45(2):702–7.
83. Accornero N, et al. Visual evoked potentials modulation during direct current cortical polarization. Exp Brain Res. 2007;178(2):261–6.
84. Dieckhofer A, et al. Transcranial direct current stimulation applied over the somatosensory cortex - differential effect on low and high frequency SEPs. Clin Neurophysiol. 2006;117(10):2221–7.
85. Kirimoto H, et al. Transcranial direct current stimulation over the motor association cortex induces plastic changes in ipsilateral primary motor and somatosensory cortices. Clin Neurophysiol. 2011;122(4):777–83.
86. Antal A, et al. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain. 2008;24(1):56–63.
87. Csifcsak G, et al. Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. Pain Med. 2009;10(1):122–32.
88. Zaehle T, et al. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. Exp Brain Res. 2011;215(2):135–40.
89. Antal A, et al. Oscillatory brain activity and transcranial direct current stimulation in humans. Neuroreport. 2004;15(8):1307–10.
90. Ardolino G, et al. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J Physiol. 2005;568(Pt 2):653–63.
91. Faria P, et al. Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy. Epilepsy Behav. 2012;25(3):417–25.
92. Accornero N, et al. EEG mean frequency changes in healthy subjects during prefrontal transcranial direct current stimulation. J Neurophysiol. 2014;112(6):1367–75.
93. Soekadar SR, et al. In vivo assessment of human brain oscillations during application of transcranial electric currents. Nat Commun. 2013;4:2032.
94. Baudewig J, et al. Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med. 2001;45(2):196–201.
95. Saiote C, et al. Combining functional magnetic resonance imaging with transcranial electrical stimulation. Front Hum Neurosci. 2013;7:435.
96. Nitsche MA, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553(Pt 1):293–301.
97. Liebetanz D, et al. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(Pt 10):2238–47.
98. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci U S A. 1992;89(10):4363–7.
99. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29(16):5202–6.
100. Clark VP, et al. Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a (1)H magnetic resonance spectroscopy study. Neurosci Lett. 2011;500(1):67–71.
101. Kim S, et al. tDCS-induced alterations in GABA concentration within primary motor cortex predict motor learning and motor memory: a 7 T magnetic resonance spectroscopy study. NeuroImage. 2014;99:237–43.
102. Frohlich F, Sellers KK, Cordle AL. Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. Expert Rev Neurother. 2015;15(2):145–67.
103. Frohlich F. Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. Prog Brain Res. 2015;222:41–73.
104. Herrmann CS, et al. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci. 2013;7:279.
105. Antal A, et al. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 2008;1(2):97–105.
106. Vosskuhl J, Huster RJ, Herrmann CS. Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. Front Hum Neurosci. 2015;9:257.
107. Neuling T, Rach S, Herrmann CS. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front Hum Neurosci. 2013;7:161.
108. Helfrich RF, et al. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. 2014;12(12):e1002031.
109. Struber D, et al. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. Brain Topogr. 2014;27(1):158–71.
110. Helfrich RF, et al. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol. 2014;24(3):333–9.
111. Neuling T, et al. Friends, not foes: magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. NeuroImage. 2015;118:406–13.
112. Busch NA, Dubois J, VanRullen R. The phase of ongoing EEG oscillations predicts visual perception. J Neurosci. 2009;29(24):7869–76.
113. Mathewson KE, et al. To see or not to see: prestimulus alpha phase predicts visual awareness. J Neurosci. 2009;29(9):2725–32.
114. Romei V, Gross J, Thut G. On the role of prestimulus alpha rhythms over occipito-parietal areas in

visual input regulation: correlation or causation? J Neurosci. 2010;30(25):8692–7.
115. Noury N, Hipp JF, Siegel M. Physiological processes non-linearly affect electrophysiological recordings during transcranial electric stimulation. NeuroImage. 2016;140(Supplement C):99–109.
116. Neuling T, et al. Faith and oscillations recovered: On analyzing EEG/MEG signals during tACS. NeuroImage. 2017;147(Supplement C):960–3.
117. Pogosyan A, et al. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr Biol. 2009;19(19):1637–41.
118. Feurra M, et al. Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. J Neurosci. 2011;31(34):12165–70.
119. Feurra M, et al. State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. J Neurosci. 2013;33(44):17483–9.
120. Wischnewski M, Schutter D, Nitsche MA. Effects of beta-tACS on corticospinal excitability: a meta-analysis. Brain Stimul. 2019;12(6):1381–9.
121. Engel AK, Fries P. Beta-band oscillations–signalling the status quo? Curr Opin Neurobiol. 2010;20(2):156–65.
122. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev. 2007;53(1):63–88.
123. Feurra M, et al. State-dependent effects of transcranial oscillatory currents on the motor system during action observation. Sci Rep. 2019;9(1):12858.
124. Ball T, et al. Movement related activity in the high gamma range of the human EEG. NeuroImage. 2008;41(2):302–10.
125. Joundi RA, et al. Driving oscillatory activity in the human cortex enhances motor performance. Curr Biol. 2012;22(5):403–7.
126. Nakazono H, et al. Phase and frequency-dependent effects of transcranial alternating current stimulation on motor cortical excitability. PLoS One. 2016;11(9):e0162521.
127. Schilberg L, et al. Phase of beta-frequency tACS over primary motor cortex modulates corticospinal excitability. Cortex. 2018;103:142–52.
128. Pikovsky A, Rosenblum M, Kurths J. Synchronization : a universal concept in nonlinear sciences. The Cambridge nonlinear science series. Cambridge: Cambridge University Press; 2001. p. xix, 411 p.
129. Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. Front Psychol. 2011;2:170.
130. McNickle E, Carson RG. Paired associative transcranial alternating current stimulation increases the excitability of corticospinal projections in humans. J Physiol. 2015;593(7):1649–66.
131. Stefan K, et al. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain. 2000;123:572–84.
132. Wischnewski M, et al. NMDA receptor-mediated motor cortex plasticity after 20 Hz transcranial alternating current stimulation. Cereb Cortex. 2019;29(7):2924–31.
133. Ziemann U, et al. TMS and drugs revisited 2014. Clin Neurophysiol. 2015;126(10):1847–68.
134. Guerra A, et al. Phase dependency of the human primary motor cortex and cholinergic inhibition cancelation during Beta tACS. Cereb Cortex. 2016;26(10):3977–90.
135. Kujirai T, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993;471(510–9):21–9.
136. Valls-Solé J, et al. Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol. 1992;85(6):355–64.
137. Di Lazzaro V, et al. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp Brain Res. 2000;135(4):455–61.
138. Di Lazzaro V, et al. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. Neurology. 2002;59(3):392–7.
139. Beynel L, et al. Effects of online repetitive transcranial magnetic stimulation (rTMS) on cognitive processing: a meta-analysis and recommendations for future studies. Neurosci Biobehav Rev. 2019;107:47–58.
140. Sauseng P, et al. Brain oscillatory substrates of visual short-term memory capacity. Curr Biol. 2009;19(21):1846–52.
141. Albouy P, et al. Selective entrainment of theta oscillations in the dorsal stream causally enhances auditory working memory performance. Neuron. 2017;94(1):193–206, e5.
142. Riddle J, et al. Causal evidence for a role of theta and alpha oscillations in the control of working memory. Curr Biol. 2020;30(9):1748–54.
143. D'Esposito M, Postle BR. The cognitive neuroscience of working memory. Annu Rev Psychol. 2015;66:115–42.
144. Rose EJ, Ebmeier K. Pattern of impaired working memory during major depression. J Affect Disord. 2006;90(2–3):149–61.
145. Owen AM, et al. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia. 1997;35(4):519–32.
146. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry. 1992;49(12):975–82.
147. Lisman JE, Jensen O. The theta-gamma neural code. Neuron. 2013;77(6):1002–16.
148. Bahramisharif A, et al. Serial representation of items during working memory maintenance at letter-selective cortical sites. PLoS Biol. 2018;16(8):e2003805.
149. Axmacher N, et al. Cross-frequency coupling supports multi-item working memory in

the human hippocampus. Proc Natl Acad Sci. 2010;107(7):3228–33.
150. Wolinski N, et al. The speed of parietal theta frequency drives visuospatial working memory capacity. PLoS Biol. 2018;16(3):e2005348.
151. Samaha J, Bradley R. Postle, the speed of alpha-band oscillations predicts the temporal resolution of visual perception. Curr Biol. 2015;25(22):2985–90.
152. Wutz A, Melcher D, Samaha J. Frequency modulation of neural oscillations according to visual task demands. Proc Natl Acad Sci. 2018;115(6):1346–51.
153. Furman AJ, et al. Cerebral peak alpha frequency predicts individual differences in pain sensitivity. NeuroImage. 2018;167:203–10.
154. Sarnthein J, et al. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. Brain. 2006;129(1):55–64.
155. Ahn S, et al. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. J Pain. 2019;20(3):277, e1–277. e11.
156. Alekseichuk I, et al. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr Biol. 2016;26(12):1513–21.
157. Reinhart RM. Disruption and rescue of interareal theta phase coupling and adaptive behavior. Proc Natl Acad Sci. 2017;114(43):11542–7.
158. Reinhart RM, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci. 2019;22(5):820–7.
159. Canolty RT, Knight RT. The functional role of cross-frequency coupling. Trends Cogn Sci. 2010;14(11):506–15.
160. Riddle J, McFerren A, Frohlich F. Causal role of cross-frequency coupling in distinct components of cognitive control. Prog Neurobiol. 2021;202:102033.
161. Amzica F, Steriade M. Disconnection of intracortical synaptic linkages disrupts synchronization of a slow oscillation. J Neurosci. 1995;15(6):4658–77.
162. Shu Y, Hasenstaub A, McCormick DA. Turning on and off recurrent balanced cortical activity. Nature. 2003;423(6937):288–93.
163. Steriade M, Nunez A, Amzica F. A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci. 1993;13(8):3252–65.
164. Crunelli V, Hughes SW. The slow (<1 Hz) rhythm of non-REM sleep: a dialogue between three cardinal oscillators. Nat Neurosci. 2010;13(1):9–17.
165. Amzica F, Steriade M. Electrophysiological correlates of sleep delta waves. Electroencephalogr Clin Neurophysiol. 1998;107:69–83.
166. Contreras D, Steriade M. Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. J Neurosci. 1995;15(1 Pt 2):604–22.
167. Vyazovskiy VV, et al. Cortical firing and sleep homeostasis. Neuron. 2009;63(6):865–78.
168. Timofeev I. Local origin of slow EEG waves during sleep. Zh Vyssh Nerv Deiat Im I P Pavlova. 2013;63(1):105–12.
169. Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. Sleep. 2007;30(12):1617–30.
170. Chauvette S, et al. Properties of slow oscillation during slow-wave sleep and anesthesia in cats. J Neurosci. 2011;31(42):14998–5008.
171. Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol. 2001;85(5):1969–85.
172. Reato D, et al. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci. 2013;7:687.
173. Contreras D, Timofeev I, Steriade M. Mechanisms of long-lasting hyperpolarizations underlying slow sleep oscillations in cat corticothalamic networks. J Physiol. 1996;494(Pt 1):251–64.
174. Timofeev I, Contreras D, Steriade M. Synaptic responsiveness of cortical and thalamic neurones during various phases of slow sleep oscillation in cat. J Physiol. 1996;494:265–78.
175. Timofeev I, Grenier F, Steriade M. Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. Proc Natl Acad Sci U S A. 2001;98(4):1924–9.
176. Reato D, et al. Transcranial electrical stimulation accelerates human sleep homeostasis. PLoS Comput Biol. 2013;9(2):e1002898.
177. Marshall L, et al. Boosting slow oscillations during sleep potentiates memory. Nature. 2006;444(7119):610–3.
178. Ozen S, et al. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci. 2010;30(34):11476–85.
179. Greenberg A, Whitten TA, Dickson CT. Stimulating forebrain communications: slow sinusoidal electric fields over frontal cortices dynamically modulate hippocampal activity and cortico-hippocampal interplay during slow-wave states. NeuroImage. 2016;133:189–206.
180. Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93(2):681–766.
181. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron. 2014;81(1):12–34.
182. Turrigiano G. Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol. 2012;4(1):a005736.
183. Turrigiano GG, et al. Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature. 1998;391(6670):892–6.
184. Hill S, Tononi G, Ghilardi MF. Sleep improves the variability of motor performance. Brain Res Bull. 2008;76(6):605–11.

185. Nere A, et al. Sleep-dependent synaptic down-selection (I): modeling the benefits of sleep on memory consolidation and integration. Front Neurol. 2013;4:143.
186. Binder S, et al. Transcranial slow oscillation stimulation during sleep enhances memory consolidation in rats. Brain Stimul. 2014;7(4):508–15.
187. Binder S, et al. Transcranial slow oscillation stimulation during NREM sleep enhances acquisition of the radial maze task and modulates cortical network activity in rats. Front Behav Neurosci. 2014;7:220.
188. Del Felice A, Magalini A, Masiero S. Slow-oscillatory transcranial direct current stimulation modulates memory in temporal lobe epilepsy by altering sleep spindle generators: a possible rehabilitation tool. Brain Stimul. 2015;8(3):567–73.
189. Munz MT, et al. Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. Front Cell Neurosci. 2015;9:307.
190. Saebipour MR, et al. Slow oscillating transcranial direct current stimulation during sleep has a sleep-stabilizing effect in chronic insomnia: a pilot study. J Sleep Res. 2015;24(5):518–25.
191. Westerberg CE, et al. Memory improvement via slow-oscillatory stimulation during sleep in older adults. Neurobiol Aging. 2015;36(9):2577–86.
192. Ladenbauer J, et al. Brain stimulation during an afternoon nap boosts slow oscillatory activity and memory consolidation in older adults. NeuroImage. 2016;142:311–23.
193. Koo PC, Mölle M, Marshall L. Efficacy of slow oscillatory-transcranial direct current stimulation on EEG and memory – contribution of an inter-individual factor. Eur J Neurosci. 2018;47(7):812–23.
194. Ladenbauer J, et al. Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. J Neurosci. 2017;37(30):7111–24.
195. Sahlem GL, et al. Oscillating square wave transcranial direct current stimulation (tDCS) delivered during slow wave sleep does not improve declarative memory more than sham: a randomized sham controlled crossover study. Brain Stimul. 2015;8(3):528–34.
196. Eggert T, et al. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul. 2013;6(6):938–45.
197. Paßmann S, et al. Boosting slow oscillatory activity using tDCS during early nocturnal slow wave sleep does not improve memory consolidation in healthy older adults. Brain Stimul. 2016;9(5):730–9.
198. Bueno-Lopez A, et al. Slow oscillatory transcranial direct current stimulation (so-tDCS) during slow wave sleep has no effects on declarative memory in healthy young subjects. Brain Stimul. 2019;12(4):948–58.
199. Fröhlich F, Lustenberger C. Neuromodulation of sleep rhythms in schizophrenia: towards the rational design of non-invasive brain stimulation. Schizophr Res. 2020;221:71–80.
200. Jones AP, et al. Dose-dependent effects of closed-loop tACS delivered during slow-wave oscillations on memory consolidation. Front Neurosci. 2018;12:867.
201. Ketz N, et al. Closed-loop slow-wave tACS improves sleep-dependent long-term memory generalization by modulating endogenous oscillations. J Neurosci. 2018;38(33):7314–26.
202. Wilde C, et al. Closed-loop transcranial alternating current stimulation of slow oscillations. Curr Directions Biomed Eng. 2015;1(1):85.
203. Fernandez LMJ, Lüthi A. Sleep spindles: mechanisms and functions. Physiol Rev. 2020;100(2):805–68.
204. Lustenberger C, et al. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr Biol. 2016;26(16):2127–36.
205. Lafon B, et al. Low frequency transcranial electrical stimulation does not entrain sleep rhythms measured by human intracranial recordings. Nat Commun. 2017;8(1):1199.
206. Alexander ML, et al. Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). Transl Psychiatry. 2019;9(1):106.
207. Leuchter A, et al. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci. 2013;7:37.
208. Ahn S, et al. Targeting reduced neural oscillations in patients with schizophrenia by transcranial alternating current stimulation. NeuroImage. 2019;186:126–36.
209. Mellin JM, et al. Randomized trial of transcranial alternating current stimulation for treatment of auditory hallucinations in schizophrenia. Eur Psychiatry. 2018;51:25–33.
210. Sreeraj VS, et al. Effect of add-on transcranial alternating current stimulation (tACS) on persistent delusions in schizophrenia. Psychiatry Res. 2020;290:113106.

Cerebellar and Spinal tDCS

12

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12.1 Cerebellar Transcranial Direct Current Stimulation: Technique's Overview and Clinical Applications

The cerebellum has been considered for a long time to play a role in motor function (in the control of balance and intentional voluntary movement). However, neuroimaging [1], clinical/lesional [2], and neuromodulation [3] studies have shown that the cerebellum also plays a key role in many motor, cognitive, and emotional processes. In addition, studies have also shown that the cerebellum is implicated in many psychiatric disorders including attention-deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders [4].

The cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways allow the cerebellum to affect information processing in cortical areas responsible for cognitive and emotional processes [4]. These intricate connections between the cerebellum and other structures can explain why cerebellar damage can lead to various psychiatric disorders.

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A recent possible way of gathering insights into the functional role of the human cerebellum in psychiatric and neurological disorders may be provided by transcranial direct current stimulation (tDCS) [5].

The need for a noninvasive tool to influence cerebellar function in normal and pathological conditions led researchers to develop cerebellar tDCS [3]. Cerebellar tDCS depends on the principle that weak direct currents delivered at around 2 mA for minutes over the cerebellum through surface electrodes induce prolonged changes in cerebellar function [6]. Usually, the stimulating electrode is placed over one or two cerebellar hemispheres and the other (return electrode) over the buccinator muscle, over the scalp, or over the right shoulders [6].

Though current evidence leaves open possible (transsynaptic or antidromic) changes in other brain or brainstem structures, the physiological effects elicited by cerebellar tDCS arise mainly from functional changes in the cerebellum itself. Cerebellar tDCS could interfere with membrane polarization in Purkinje cells and in other neurons, fibers (mossy fibers and climbing fibers), and glial cells. DC stimulation applied to the cerebellar cortex in the decerebrated cat influences Purkinje and granular cell activity in a polarity-specific manner; while anodal DC flowing in the dendrite–axonal direction increases tonic neuronal activity, cathodal DC decreases it [7].

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Cerebellar tDCS modulates several cerebellar skills in humans including motor control, learning, and emotional processing [3]. Several studies suggest that tDCS may be a valuable tool for the treatment of neuropsychiatric conditions such as depression, schizophrenia, addiction, and chronic pain [8, 9]. Research has also demonstrated cognitive improvement in some patients undergoing tDCS [10].

For instance, tDCS treatments for depression have used bifrontal montages with anodal (excitatory) stimulation targeting the left dorsolateral prefrontal cortex (DLPFC) [11]. There is limited research examining the effects of alternative electrode montages.

The first study aimed to examine the feasibility, tolerability, safety, and efficacy of two alternative electrode montages was conducted by Ho and colleagues [12]. They studied two different montages, fronto-occipital (F-O) and fronto-cerebellar (F-C), to target respectively midline brain structures and the cerebellum in 14 depressed participants. For F-O montage, the anode electrode was placed over the left supraorbital area and the cathode over the occipital area; for F-C montage, the anode electrode was placed over the cerebellum and the cathode over the occipital area. The intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. Mood and neuropsychological functions (memory and frontal lobe functions) were assessed at baseline and after 4 weeks of tDCS. Using a computational modeling based on one healthy participant, they demonstrated that the novel montages resulted in greater activation in the anterior cingulated cortices and cerebellum than the bifrontal montage. They also showed that after 4 weeks of tDCS, overall mood improvement was observed under the F-O and F-C conditions and no significant neuropsychological changes were found. Results of this open-label pilot study found both montages safe and feasible. The small sample size and the absence of a sham control group are major limitations of the study.

Successively, Minichino and colleagues [13] aimed to improve sleep quality of 25 euthymic outpatients with a diagnosis of bipolar disorder (BD) type I or II through the administration of prefronto-cerebellar tDCS. They placed the cathode electrode over the right cerebellar cortex and anode over the left dorsolateral prefrontal cortex (DLPFC); the intensity of stimulation was set at 2 mA and delivered for 20 min/die for 3 consecutive weeks. The sleep quality was assessed at baseline and after the tDCS treatment using Pittsburgh Sleep Quality Index (PSQI). They demonstrated that PSQI total score and all PSQI subdomains significantly improved after treatment.

Furthermore, Minichino and colleagues [14], using the same previous protocols [13], studied the effects of tDCS applied to cerebellar and prefrontal cortices on neuropsychological functioning of 25 euthymic patients with BD. All participants were assessed through the Rey Complex Figure Test delay and copy and the Neurological Examination Scale at baseline and after therapy with tDCS. The results of the present research suggest that concomitant prefrontal-excitatory and cerebellar-inhibitory tDCS might have a positive effect on visuospatial memory and executive functioning in euthymic BD patients, quantified through neuropsychological and neurological measures. The small sample size and the absence of a sham control group are major limitations of these two studies.

More recently, Bation and colleagues [15], in an open-label pilot study, assessed the efficacy and the safety of orbitofrontal cortex (OFC) cathodal tDCS coupled with cerebellum anodal-tDCS in eight patients with treatment-resistant obsessive–compulsive disorder (OCD). Cathode electrode was placed over the left OFC and the anode over the right cerebellum for ten sessions (twice a day) of 2 mA. Patients were assessed four times, once before tDCS and three times after: immediately after the ten sessions of tDCS, 1 and 3 months later. The effect of tDCS on the severity of obsessive and compulsive symptoms was assessed using the Yale–Brown Obsessive and Compulsive Scale score (Y-BOCS) and a self-reporting OCD Visual Analog Scale (OCD-VAS) given to the participant. The effect of tDCS on the severity of depressive symptoms was assessed using the Montgomery and Asberg Depression Rating Scale (MADRS).

They reported a significant 26.4% decrease of Y-BOCS score, and the beneficial effect lasted during the 3-month follow-up. No effect of tDCS was observed on depressive symptoms. This open-label pilot study demonstrates for the first time the clinical interest of orbitofrontal and cerebellar tDCS in combination with SSRI in patients with treatment-resistant OCD. These promising results should be confirmed in large placebo-controlled trials.

The few cerebellar tDCS studies in psychiatric patients we reviewed here taken together, despite their heterogeneities, show that cerebellar tDCS is safe, feasible, and might improve psychiatric symptoms. Cerebellar tDCS probably could influence psychiatric symptoms through highly complex mechanisms; it could induce neuroplasticity throughout a distributed cortico-subcortical network. Premised that the clinical efficacy of cerebellar tDCS in patients with psychiatric disorders remains to be ultimately established by large, controlled clinical studies, future research work should systematically assess the clinical patient features predicting the optimal response: type and site of stimulation, time since the pathology occurred, age, gender, concurrent drug treatments, and comorbidities can all influence the tDCS effect.

Future research directions should include studies to clarify whether cerebellar tDCS could be combined with behavioral therapy, and whether these noninvasive techniques could be used to stimulate multiple brain sites. A study in a larger homogeneous population is needed to further investigate the possible therapeutic benefit of cerebellar tDCS.

12.2 Transcutaneous Spinal Direct Current Stimulation: Technique's Overview

As for the cerebellum, a new and fascinating target for noninvasive current stimulation has emerged in the recent years. Spinal cord is a critical, yet less understood, final pathway for motor control, but also acts a "highway" for modifying brain and brainstem function. Transcutaneous spinal direct current stimulation (tsDCS) is a noninvasive technique for modulating spinal cord activity in animals and humans [16–20]. DC stimulation intensity ranges from 1.5 to 2.5 mA, with effects lasting for minutes to hours [21]. After the first reports [19], this technique has come into increasingly widespread use, especially for modulating conduction along lemniscal pathways and nociceptive spinal system [22–24]. The device is the same used for transcranial direct current stimulation, but no conclusive remark has been reached so far regarding the position of electrodes over the spinal cord, ultimately influencing current density and distribution in biological tissues [25]. This remains a critical issue, together with interindividual variability due to genetic polymorphisms, thus modifying neurophysiological and psychophysical response in an unpredictable way [26].

For lumbar spinal cord stimulation, the active electrode is commonly placed over the spinous process of the tenth thoracic vertebra and the reference above the right shoulder [19, 20], while for cervical modulation, the active electrode is positioned on the seventh cervical vertebra and the reference either on the right shoulder [27] or on the anterior neck [28]. By analogy with the tDCS, placing the return electrode over the shoulder is the preferred montage, as it reduces interference between anodal and cathodal effects.

12.3 Mechanisms of Action

12.3.1 Putative Mechanisms of Action at a Spinal Level

Recent modeling studies have proved that, despite some interindividual differences due to age and anatomical variability, the electrical field induced by tsDCS is longitudinally directed along all the vertebral column, especially when the return electrode is placed over the right arm or over Cz [25], confirming that both ventral (motor) and dorsal (sensitive) spinal tracts undergo identical electric field strength. Different from transcranial direct current stimulation (tDCS), anodal tsDCS has probably an overall inhibitory effect on spinal cord activity [19, 20, 28, 29]. Particularly, while

anodal polarization could act directly on corticospinal descending pathways, without changes in postsynaptic motor neuronal excitability, the cathodal one seems to interfere with interneuronal networks [17, 27, 30]. By analogy with the effects of direct currents on peripheral nerves, it has been hypostasized that anodal tsDCS leads to a hyperpolarizing "anodal block" [31]. Conversely, there is an extensive debate whether cathodal tsDCS has or not polarity-specific effects on segmental activity [28]. Overall, as suggested for tDCS [32], rather than be simply specular, anodal and cathodal tsDCS may have quite similar effects on different targets. That widens the field of therapeutic applications, raising at the same time the possibility of a combined use of transcranial and spinal polarization in a number of clinical conditions, as proved in chronic stroke [33]. From a practical point of view, the same DC device could be used to simultaneously stimulate the cerebellum spinal cord and cerebral cortex, thus enhancing the tDCS aftereffects.

12.3.2 Putative Mechanisms of Action at a Supraspinal Level

Many studies have proved possible supraspinal mechanisms of action of spinal direct current stimulation, both in animal [34] and human models [30, 35], possibly synchronizing the activity among different cortical areas and inducing neuroplasticity [36]. That is not surprising also considering the literature about invasive current stimulation (SCS), suggesting a possible modulation of glutamatergic cortical interneurons in patients with neuropathic pain [37]. Moreover, it is known that alternating currents epidurally delivered to the posterior columns of the spinal cord are able to modify sensory processing at thalamic relays and cortical levels [38]. Recently, studies from our laboratories have explored two main no-spinal targets, (a) the GABA(a) cortical interneurons, mediating the so-called short intracortical inhibition (SICI) [30] and (b) the interhemispheric processing [35]. Other groups did not confirm data about GABA(a); nonetheless, they studied a different anatomical region, with different recording montage and stimulation intensity [39].

12.4 Perspective on Clinical Studies

Different from cerebellar tDCS, only few studies have been published to date about the application of tsDCS in human disorders, and little is known about its spinal and long-range (supraspinal) effects both in health and disease. Although elusive, the possibility to interfere with cognitive processes by using spinal polarization is intriguing. First studies showed that tsDCS modulates somatosensory potentials evoked by stimulation of posterior tibial nerve, the post-activation H-reflex dynamics [23, 24], and the flexion reflex in the human lower limb [40]. In this view, Truini and colleagues [29] have proved that anodal spinal polarization leads to a significant decrease of the amplitudes of laser-evoked potentials (LEPs) derived from lower limb, thus modulating both the sensory-discriminative and affective-emotional dimension of pain. More recently, tsDCS has been successfully used for both interfering with maladaptive phenomena taking place in spinal cord-injured patients [22] and improving symptoms in patients with restless legs syndrome [41]. Mechanisms of action of tsDCS have only partly been elucidated, but likely rely on both local (spinal) and supraspinal effects. The later aspect is particularly attracting; in spinal cord injury (SCI), tsDCS may interfere with the maladaptive reorganization of cortical sensorimotor maps, thus improving motor output and preventing central pain sensitization [36]. That implies that tsDCS could be useful also as an early rehabilitation strategy in patients with acute brain lesions, such as stroke, when other NIBS tools are not indicated due to safety concerns.

Theoretically, spinal DC may be also used to improve the effects of tDCS in a number of neuropsychiatric disorders likely characterized by impaired interhemispheric balance, ranging from schizophrenia and obsessive–compulsive disorder [42, 43] to major depression [44].

Putative ways to nonspinal targets are to date only speculative, but evidence in animals showed that supraspinal effects of invasive spinal polarization could be induced by the modulation of indirect spinal projections to noradrenergic locus coeruleus (LC) neurons, which has widespread projections to the neocortical brain [45–47]. Alternatively, a critical role in brain plasticity after an SCI seems to be played by a reorganization of the serotonergic ascending pathways [48–51]; serotonergic system interferes also with bottom-up and top-down modulation of motor responses, especially through parallel and partially overlapping projections arising from the median and dorsal raphe nuclei [52–54]. As the serotonergic projections seem to participate in the regulation of different functional systems (motor, somatosensory, limbic), tsDCS may ultimately modulate this connectivity.

tsDCS could be of particular interest as a noninvasive, safe promising therapeutic tool in managing a number of human diseases. This technique could be useful also as a rehabilitation strategy in patients with brain lesions or even in the treatment of neurological disorders characterized by abnormal interhemispheric processing. In addition, the possibility to modulate supraspinal and intracortical processing of motor inputs makes tsDCS a useful approach, complementary to either SCS or noninvasive brain stimulation techniques, to modify spinal drive through nonspinal mechanisms.

12.5 Why Should Psychiatrists Be Interested in Cerebellar/Spinal DC Stimulation?

Despite the uncertainties, cerebellar and spinal tDCS for its simplicity, low cost, and possibility of online use has a great potential in the field of restorative psychiatry symptoms. This potential must however be developed through strictly controlled and methodologically sound experimental and clinical research work [55].

Delivering DC currents for few minutes over the cerebellum or spinal cord can induce persistent, polarity-dependent excitability changes persisting several minutes after the current offset. Cerebellar DC stimulation can elicit neurophysiological and behavioral changes both in the motor functions and in cognitive-behavioral domain. Spinal cord DC stimulation elicits not only neurophysiological and behavioral changes related to spinal cord functions, but, interestingly, also changes in the brain functions that may arise from the activation of tonic afferent systems to the brain.

Future studies should endeavor to assess whether experimental data translate into benefits in real life, lengthen behavioral benefits, investigate how changing stimulation variables influences tDCS-induced effects, determine possible interactions with other treatments, and improve patients' selection.

References

1. Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron. 2013;80(3):807–15.
2. Koziol LF, et al. Consensus paper: the cerebellum's role in movement and cognition. Cerebellum. 2014;13(1):151–77.
3. Ferrucci R, Priori A. Transcranial cerebellar direct current stimulation (tcDCS): motor control, cognition, learning and emotions. Neuroimage. 2014;85(Pt 3):918–23.
4. Phillips JR, et al. The cerebellum and psychiatric disorders. Front Public Health. 2015;3:66.
5. Grimaldi G, et al. Cerebellar transcranial direct current stimulation (ctDCS): a novel approach to understanding cerebellar function in health and disease. Neuroscientist. 2011;22(1):83–97.
6. Ferrucci R, Cortese F, Priori A. Cerebellar tDCS: how to do it. Cerebellum. 2015;14(1):27–30.
7. Brookhart JM. A study of corticospinal activation of motor neurons. Res Publ Assoc Res Nerv Ment Dis. 1952;30:157–73.
8. O'Connell NE, et al. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev. 2014;4:CD008208.
9. Tortella G, et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry. 2015;5(1):88–102.
10. Kuo MF, Nitsche MA. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. Neurosci Bull. 2015;31(2):198–206.
11. Meron D, et al. Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. Neurosci Biobehav Rev. 2015;57:46–62.

12. Ho KA, et al. A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression. J Affect Disord. 2014;167:251–8.
13. Minichino A, et al. Prefronto-cerebellar transcranial direct current stimulation improves sleep quality in euthymic bipolar patients: a brief report. Behav Neurol. 2014;2014:876521.
14. Minichino A, et al. Prefronto-cerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder. Neuropsychiatr Dis Treat. 2015;11:2265–70.
15. Bation R, et al. Transcranial direct current stimulation in treatment-resistant obsessive-compulsive disorder: an open-label pilot study. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;65:153–7.
16. Ahmed Z. Trans-spinal direct current stimulation modulates motor cortex-induced muscle contraction in mice. J Appl Physiol (1985). 2011;110(5):1414–24.
17. Ahmed Z. Effects of cathodal trans-spinal direct current stimulation on mouse spinal network and complex multijoint movements. J Neurosci. 2013;33(37):14949–57.
18. Cogiamanian F, et al. Transcutaneous spinal direct current stimulation. Front Psych. 2012;3:63.
19. Cogiamanian F, et al. Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol. 2008;119(11):2636–40.
20. Cogiamanian F, et al. Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings. Pain. 2011;152(2):370–5.
21. Woods AJ, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2015;127(2):1031–48.
22. Hubli M, et al. Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. Clin Neurophysiol. 2013;124(6):1187–95.
23. Lamy JC, et al. Modulation of soleus H reflex by spinal DC stimulation in humans. J Neurophysiol. 2012;108(3):906–14.
24. Winkler T, Hering P, Straube A. Spinal DC stimulation in humans modulates post-activation depression of the H-reflex depending on current polarity. Clin Neurophysiol. 2010;121(6):957–61.
25. Parazzini M, et al. Modeling the current density generated by transcutaneous spinal direct current stimulation (tsDCS). Clin Neurophysiol. 2014;125(11):2260–70.
26. Lamy JC, Boakye M. Seeking significance for transcutaneous spinal DC stimulation. Clin Neurophysiol. 2013;124(6):1049–50.
27. Bocci T, et al. Cathodal transcutaneous spinal direct current stimulation (tsDCS) improves motor unit recruitment in healthy subjects. Neurosci Lett. 2014;578:75–9.
28. Lim CY, Shin HI. Noninvasive DC stimulation on neck changes MEP. Neuroreport. 2011;22(16):819–23.
29. Truini A, et al. Transcutaneous spinal direct current stimulation inhibits nociceptive spinal pathway conduction and increases pain tolerance in humans. Eur J Pain. 2011;15(10):1023–7.
30. Bocci T, et al. Transcutaneous spinal direct current stimulation modulates human corticospinal system excitability. J Neurophysiol. 2015;114(1):440–6.
31. Bhadra N, Kilgore KL. Direct current electrical conduction block of peripheral nerve. IEEE Trans Neural Syst Rehabil Eng. 2004;12(3):313–24.
32. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29(16):5202–6.
33. Picelli A, et al. Combined effects of transcranial direct current stimulation (tDCS) and transcutaneous spinal direct current stimulation (tsDCS) on robot-assisted gait training in patients with chronic stroke: a pilot, double blind, randomized controlled trial. Restor Neurol Neurosci. 2015;33(3):357–68.
34. Aguilar J, et al. Spinal direct current stimulation modulates the activity of gracile nucleus and primary somatosensory cortex in anaesthetized rats. J Physiol. 2011;589(Pt 20):4981–96.
35. Bocci T, et al. An unexpected target of spinal direct current stimulation: interhemispheric connectivity in humans. J Neurosci Methods. 2015;254:18–26.
36. Song W, et al. Transspinal direct current stimulation immediately modifies motor cortex sensorimotor maps. J Neurophysiol. 2015;113(7):2801–11.
37. Schlaier JR, et al. Effects of spinal cord stimulation on cortical excitability in patients with chronic neuropathic pain: a pilot study. Eur J Pain. 2007;11(8):863–8.
38. Paradiso C, et al. Cervical and scalp recorded short latency somatosensory evoked potentials in response to epidural spinal cord stimulation in patients with peripheral vascular disease. Electroencephalogr Clin Neurophysiol. 1995;96(2):105–13.
39. Nierat MC, Similowski T, Lamy JC. Does trans-spinal direct current stimulation alter phrenic motoneurons and respiratory neuromechanical outputs in humans? A double-blind, sham-controlled, randomized, cross-over study. J Neurosci. 2014;34(43):14420–9.
40. Meyer-Friessem CH, et al. Transcutaneous spinal DC stimulation reduces pain sensitivity in humans. Neurosci Lett. 2015;589:153–8.
41. Heide AC, et al. Effects of transcutaneous spinal direct current stimulation in idiopathic restless legs patients. Brain Stimul. 2014;7(5):636–42.
42. Goncalves OF, et al. Obsessive compulsive disorder as a functional interhemispheric imbalance at the thalamic level. Med Hypotheses. 2011;77(3):445–7.
43. Innocenti GM, Ansermet F, Parnas J. Schizophrenia, neurodevelopment and corpus callosum. Mol Psychiatry. 2003;8(3):261–74.
44. Bajwa S, et al. Impaired interhemispheric interactions in patients with major depression. J Nerv Ment Dis. 2008;196(9):671–7.
45. Condes-Lara M. Different direct pathways of locus coeruleus to medial prefrontal cortex and centrolateral

thalamic nucleus: electrical stimulation effects on the evoked responses to nociceptive peripheral stimulation. Eur J Pain. 1998;2(1):15–23.
46. Tanaka M, et al. The origins of catecholaminergic innervation in the rostral ventromedial medulla oblongata of the rat. Neurosci Lett. 1996;207(1):53–6.
47. Voisin DL, et al. Nociceptive stimulation activates locus coeruleus neurones projecting to the somatosensory thalamus in the rat. J Physiol. 2005;566(Pt 3):929–37.
48. Azmitia EC, et al. 5-HT1A agonist and dexamethasone reversal of para-chloroamphetamine induced loss of MAP-2 and synaptophysin immunoreactivity in adult rat brain. Brain Res. 1995;677(2):181–92.
49. Bachatene L, et al. Fluoxetine and serotonin facilitate attractive-adaptation-induced orientation plasticity in adult cat visual cortex. Eur J Neurosci. 2013;38(1):2065–77.
50. Maya Vetencourt JF, et al. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science. 2008;320(5874):385–8.
51. Ramos AJ, et al. The 5HT1A receptor agonist, 8-OH-DPAT, protects neurons and reduces astroglial reaction after ischemic damage caused by cortical devascularization. Brain Res. 2004;1030(2):201–20.
52. Cotel F, et al. Serotonin spillover onto the axon initial segment of motoneurons induces central fatigue by inhibiting action potential initiation. Proc Natl Acad Sci U S A. 2013;110(12):4774–9.
53. Hornung JP. The human raphe nuclei and the serotonergic system. J Chem Neuroanat. 2003;26(4):331–43.
54. Ptak K, et al. Raphe neurons stimulate respiratory circuit activity by multiple mechanisms via endogenously released serotonin and substance P. J Neurosci. 2009;29(12):3720–37.
55. Brunoni AR, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95.

13 Precision Targeting of Neural Networks with tDCS Informed by Brain Mapping

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13.1 Introduction

Transcranial direct current stimulation (tDCS) is applied via surface electrodes attached to the scalp. The induced electrical field in the targeted cortex is thought to cause tonic shifts in the membrane potentials of cortical neurons that remain below firing threshold. This subthreshold effect on axonal excitability is thought to alter the intrinsic firing rate of the stimulated neurons in the brain and thereby the signaling in neural networks. By reversing aberrant signaling in those neural networks that are affected by neurological and neuropsychiatric conditions, tDCS offers a low-cost treatment option. The current state of evidence suggests moderate treatment effects in mental disorders, for example, depression [1], and in ameliorating motor and cognitive symptoms in nonprogressive (e.g., stroke [2, 3]) and progressive neurological disorders ([4]; see also [5] for review). The treatment effects of tDCS show substantial interindividual but also intraindividual variations. This variability hampers the clinical application of tDCS as therapeutic intervention [6]. In this chapter, we argue that the personalization of tDCS is critical to the future advancement of tDCS as a scientific and therapeutic tool. By tailoring the tDCS intervention to the individual brain, one can render tDCS more precise and induce more reliable and robust aftereffects. Taking a brain network perspective, we highlight how the combination of tDCS and brain imaging can reveal basic insights into the mechanism of action of tDCS and inform the personalization of tDCS.

13.1.1 Identifying and Targeting Dysfunctional Large-Scale Brain Networks

Genetic, environmental, and neurodevelopmental factors play important roles in the manifestation of psychiatric syndromes [7]. The interplay and extent of these factors are thought to alter molecular pathways in the cell as well as the functional interplay between neurons and surrounding glia at the micro-circuit level, for instance by altering

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neurotransmitter release or neuronal firing patterns. However, it is the resulting large-scale circuit dysfunction that ultimately causes mental dysfunction and psychiatric symptoms [8] (Fig. 13.1). Emotional, cognitive, and self-reflective mental functions critically rely on the integrated activity and connectivity of large-scale brain circuits. This implies that a clinically relevant mental dysfunction (e.g., excessive anxiety or fear) first emerges, when aberrant processes at the cellular and micro-circuit level produce a significant dysfunction of the macro-scale brain circuit that underpins the affected brain function (e.g., affective limbic brain circuit of emotional processing). This implies that the way a psychiatric disorder affects large-scale functional brain networks determines which behavioral dimensions are impaired and how they are impaired.

Figure 13.1 illustrates the complex etiology of psychiatric disorders. Polygenetic and neurodevelopmental factors lead to changes in multiple neurotransmitter systems and alters micro-circuit activity in multiple brain regions. The spatial expression of these micro-scale changes affects to a varying extent the activity and connectivity of several large-scale brain networks. The individual profile of large-scale brain circuit dysfunction determines the type and severity of symptoms that characterize the patient's clinical phenotype (i.e., the specific expression of symptoms and course of the disorder in an individual patient).

Pharmaceutical therapies with molecular and cellular targets are currently the first-in-line treatment but inherently lack "circuit specificity," impacting on all large-scale brain networks that express the molecular target structure (Fig. 13.1).

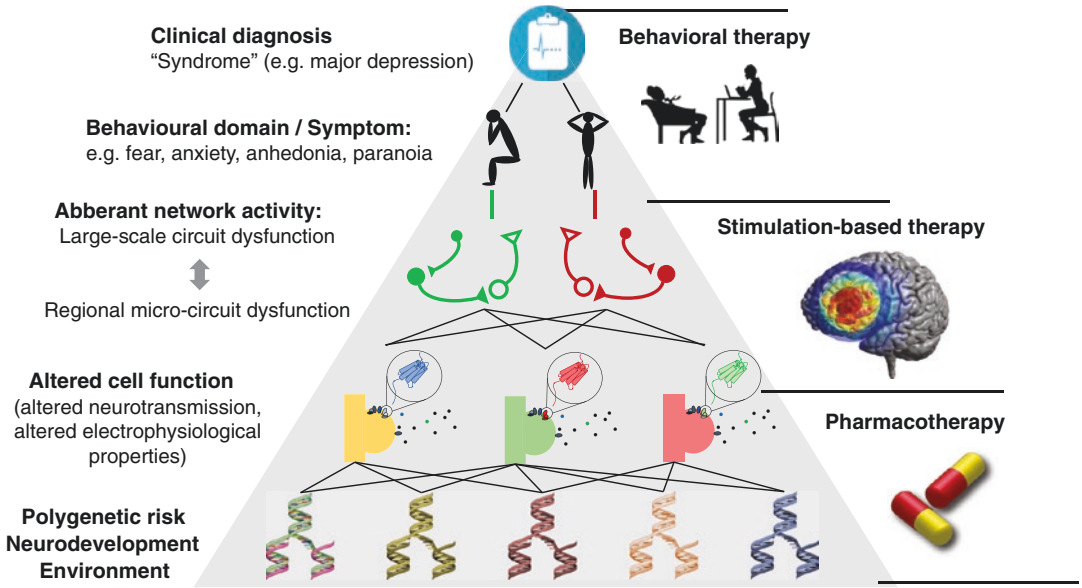

Fig. 13.1 Multilevel neurobiological framework of the pathogenesis and treatment of brain disorders
Psychiatric and neurologic disorders have a poly-causal origin. Multiple genetic factors and environmental exposures lead to multiple alterations of cellular pathways. The molecular changes at the cell level give rise to dysfunction in neuronal micro-circuits and large-scale brain circuits. The disease-related circuit dysfunctions (network level) are ultimately causing a range of symptoms in a given patient which leads to a clinical diagnosis (syndrome level). The black lines illustrate the polygenetic contribution to changes in neurotransmission and the polycausative molecular background leading to abnormal signaling in neural networks. The vertical green and red lines denote the close relationship between network signaling and a behavioral expression within specific domains of functions or cluster of symptoms. While pharmacological therapies have molecular targets and aim at improving cellular biology, therapeutic interventions are tailored to the symptoms expressed in a given patient. Brain stimulation therapies have an intermediate target, because they primarily are geared to improve the regional and network dysfunction that leads to a clinical dysfunction

Furthermore, the causative relation between their molecular targets and the therapeutic effect is often blurred. This is illustrated by the delayed clinical response to antidepressant pharmacotherapy which contrast with the immediate action at the cellular level (e.g., inhibition of serotonin reuptake from the synaptic cleft) [9]. Behavioral interventions such as cognitive behavioral therapy or motor training are also relatively non-selective. They usually engage multiple brain networks to a variable degree, and the magnitude of functional engagement of the various networks can be expected to vary from patient to patient. Transcranial brain stimulation techniques, such as tDCS, complement pharmacological and behavioral therapies, because they offer the opportunity to selectively target large-scale circuit dysfunction in a symptom-causing brain network, opening up interesting possibilities for a patient-specific "personalized" treatment. Of note, tDCS can be combined with pharmacological and behavioral interventions to manipulate circuit activity in the stimulated target network (see below).

The classical approach to investigate circuit-dysfunction in mental disorders is to identify syndrome-related changes in functional brain circuit activity and connectivity based on group comparisons between "affected" and "healthy" persons. The last decades have witnessed a paradigm shift away from grouping patients according to clinical diagnosis toward focusing on general domains of human functioning in order to enable a better mechanistic understanding of mental health and illness. The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc) has been proposed as an open, matrix-like framework, which aims to identify the varying degrees of dysfunction in general psychological and neurobiological systems, currently focusing on six domains: negative valence systems, positive valence systems, cognitive systems, systems for social processes, regulatory (arousal) systems, and sensorimotor systems. The RDoC framework links genetic, molecular, and cellular aspects of neural systems with behavioral dimensions. Critically, circuit abnormalities in large-scale neuronal networks are seen as the causal link between aberrant neural systems and the resulting dysfunctional behavior. The RDoC framework has important implications for the therapeutic use of tDCS in mental disorders [10]. If one has identified a specific property of the brain network that causes a specific symptom, the individual expression of this circuit-biotype can guide the stratification and personalization of neuromodulatory tDCS.

13.1.2 Neuromodulation of Large-Scale Brain Circuits with tDCS

The traditional view is that tDCS has immediate polarity-dependent effects on intrinsic neural excitability. When given continuously for several minutes, tDCS may produce longer lasting polarity-specific shifts in intrinsic neuronal activity in the stimulated brain regions. Such polarizing effects have been shown in invasive recordings of cortical neuronal activity, while the cortex was exposed to a DC current running perpendicular to the cortical layers [11]. In humans, polarity-dependent, neuromodulatory effects of tDCS on cortical excitability were first demonstrated in the human motor cortex [12]. Placing one electrode over the motor hand area and the other electrode over the contralateral supraorbital region, bipolar tDCS can induce lasting changes in corticospinal excitability [12].

How Does tDCS Stimulate Neurons in the Brain?

The mechanisms through which tDCS affects neural spiking and patterns of network activity are still to be determined, but they are likely to be dose dependent. Current tDCS protocols produce relatively low currents in the cortical tissue. Approximately, 75% of the current that is applied to the scalp is shunted along low-resistance pathways (e.g., fluid, bone, skin, and subcutaneous tissue), while only 25% of the current pass through the brain [13–15]. Therefore, tDCS does only cause subtle effects on the membrane potential of cortical axons. These subtle polarizing effects may add stochastic noise to ongoing

activity (see [16]) and "tune" the level of ongoing (intrinsic) neuronal activity but are too weak to trigger action potentials. Thus, the weak intracranial currents cannot evoke synchronized extra activity in the stimulated cortex.

The intensity of the intracranially induced electrical field is highest at the gyral crowns and relatively weak in the gyral sulci [14]. Neuromodulatory effects of tDCS on the excitability and activity of cortical neurons are therefore more likely to occur in cortical regions close to the surface [17]. Depending on the orientation of the electrical field with respect to the axon, tDCS induces slight changes in the membrane potential, which in turn can alter neuronal excitability. The direction of polarization depends on the orientation of the axonal structures with respect to the orientation of the induced electrical field and is illustrated in Fig. 13.2. Changing the orientation of the induced electrical field relative to the main neuron's soma-dendritic axis, from parallel to perpendicular, substantially changes which axonal structures are polarized as well as the strength and direction of the polarizing effects. The immediate or acute effects on axonal excitability may change how efficient the neuron interacts with connected neurons, for instance by changing synaptic or ephaptic couplings or the interaction of both (see [18] for review). Due to the complex biophysical-neurophysiological interactions, the functional impact of tDCS on the targeted brain networks cannot be simply accounted for by polarity-dependent increase or decrease in neuronal excitability and consequently neural activity.

From a network perspective, tDCS can modulate not only task-specific activity below the electrodes, but also the connectivity within large-scale network [19]. The polarization of neurons during tDCS not only changes how they process information but also their propensity to undergo plastic changes (see [20]). The common notion is that tDCS evokes lasting after-effects at the site of stimulation by inducing prolonged changes in intrinsic circuit activity in the stimulated regional microcircuits [21]. In addition, tDCS may also change the integration of neuronal activity in large-scale bran networks by changing inter-regional functional coupling of the stimulated brain region with other remote network nodes [22].

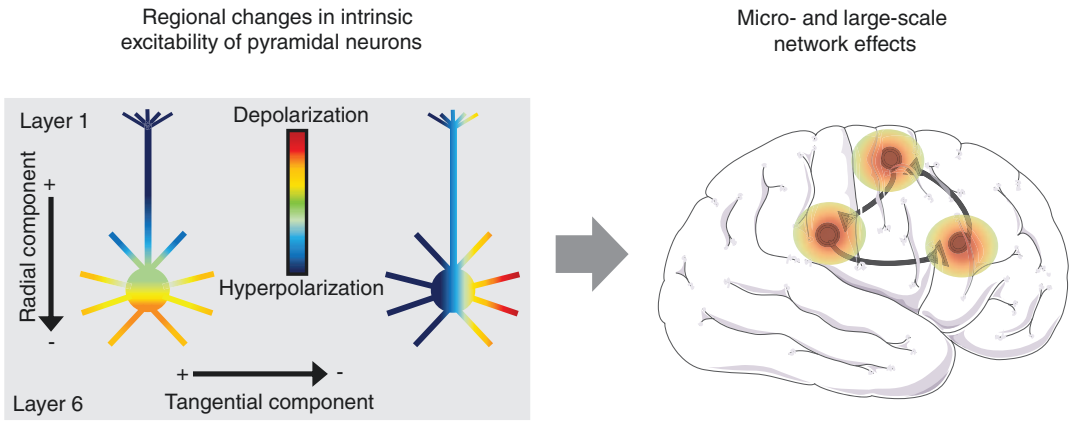

Fig. 13.2 Interactions of tDCS with brain function: from the single-cell level to signal integration in large-scale brain networks
Exposed neuronal compartments are depolarized or hyperpolarized dependent on orientation relative to the electric field. The left panel illustrates the polarization of a pyramidal cell depending on a current flow. Below the anode, the radial component of the electric field depolarizes basal neural compartments and hyperpolarized apical dendrites, whereas a radial component excites axonal kinks and bends. The neuronal effects, that is, on membrane potential, are miniscule but augment and tune ongoing activity in neural networks (left panel), which leads to behavioral and clinical effects

13.2 Precision tDCS: How to Tailor tDCS-Based Research to the Individual Brain

The vast majority of tDCS research applies the same tDCS regime to a group of individuals to study and modulate brain function, matching the electrode positions and current intensity across individuals (Fig. 13.3). Such one-size-fits-all approach is inherently imprecise as it does not consider interindividual variations in brain structure and function (brain-trait features) and ignores the fact that tDCS effects critically depend on the "brain state" at the time of stimulation (brain-state features). We therefore argue that the tDCS community should thrive toward a personalization of tDCS that tailors the tDCS intervention to the individual brain anatomy and function. Personalization and precision can only be achieved by leveraging the explanatory potential offered by brain imaging techniques. This applies equally to the neuroscientific and therapeutic use of tDCS in humans. Only a comprehensive use of neuroimaging can unravel the underlying neuromodulatory mechanisms of tDCS at the brain circuit level. The combination of tDCS and brain mapping can lead to neurobiologically informed, causal models that can predict how tDCS will change the function of targeted brain networks and thereby improve target symptoms. The potential contributions of brain mapping to the personalization and optimization of tDCS interventions are illustrated in Fig. 13.4. We elaborate in the following sections how brain mapping can guide precision tDCS providing illustrative examples from the literature. This

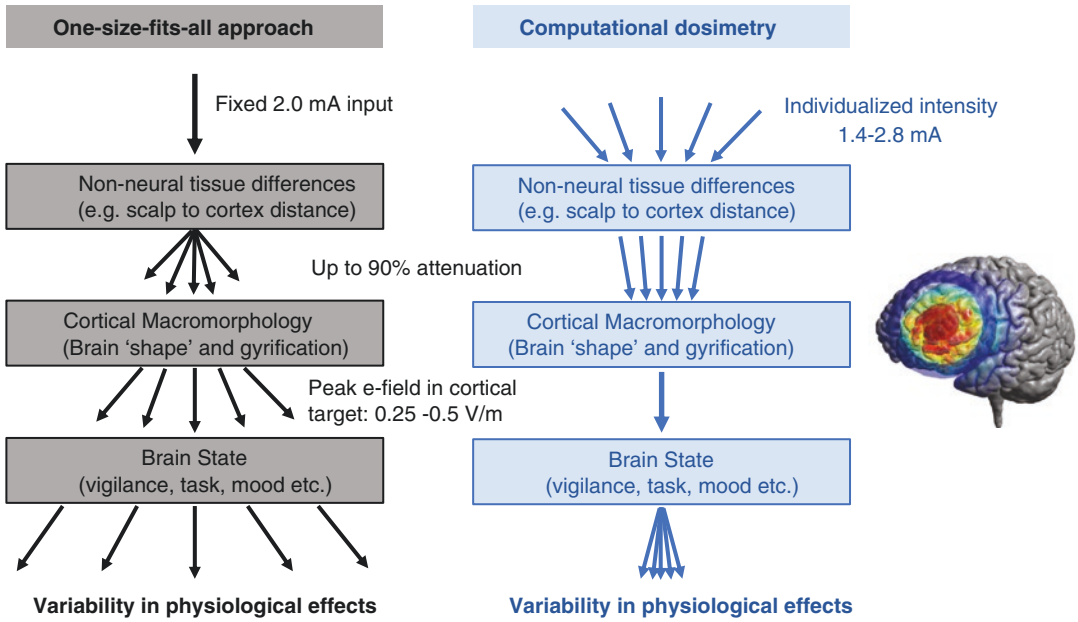

Fig. 13.3 The impact of individualized computational dosimetry
The left panel illustrate the variability in the physiological outcome when applying a *one-size-fits-all* tDCS protocol. Both stabile individual traits such as nonneural tissue properties (top boxes) and cortical anatomy (middle boxes) as well as rapidly changing brain states (bottom boxes) contribute to the variability. The right panel depicts the effect of individualizing the dose using sMRI-based computational models of the electric field. The variability caused by interindividual differences in stable anatomical traits can be accounted for by adjusting the individual tDCS setup (montage, current intensity), but variability caused by differences in the state of targeted and interconnected neural networks are still present. To minimize these, online imaging-based state control is needed (not illustrated here). Values for input intensity, attenuation, and electric field strength are taken from [26, 47]

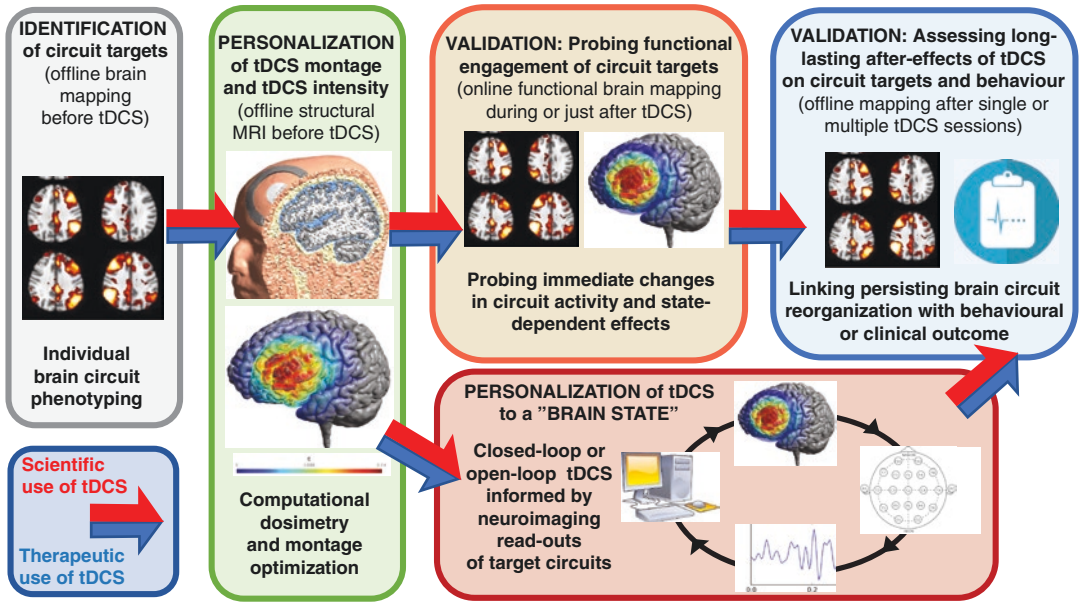

Fig. 13.4 Brain mapping informs precision tDCS
Brain imaging is necessary and sufficient to enable and ensure precision tCDS stimulation. Identifying the circuitry phenotype and adjusting stimulation intensity to the individual brain increases the likelihood of changing signaling (exclusively) in the affected networks. Only through online validation as well as state-informed and controlled stimulation can target engagement be ensured. Offline validation provides mechanisms of actions underlying the therapeutic effects of tDCS, which informs future application

does not only entail neuroimaging informed planning of a tDCS intervention at the individual level (i.e., personalization), but also identifying intrinsic brain states that are more susceptible to the neuromodulatory effects of tDCS (i.e., state dependency).

13.2.1 Identification of Brain Circuit Targets with Offline Brain Mapping Before tDCS

Task-related and task-free functional MRI (fMRI) or EEG/MEG studies can reveal spatiotemporal patterns of functional integration in large-scale networks that are consistent at the group level. Hence, researchers can use this information to identify cerebral regions that constitute a promising target for a tDCS intervention, for instance, because a given region shows strong functional engagement in an experimental task that probes the brain function of interest (Fig. 13.4). However, not only regional brain *activity* and inter-regional *functional connectivity* (identified with fMRI, EEG/MEG or PET) but also *structural connectivity* (revealed by structural MRI, diffusion sensitive MRI, and changes in the neurochemical profile, evidenced by magnetic resonance spectroscopy (MRS) or PET can assist researchers in the decision on which brain region to target with tDCS. Since reproducibility of functional brain mapping studies is often poor, one may apply meta-analytical tools such as activation likelihood estimation (ALE) to identify brain regions that express a brain activity profile consistently across many studies [23]. An illustrative example for neuroimaging-guided target selection is the left dorsal prefrontal cortex (dlPFC) as cortical target for transcranial stimulation therapies in major depression disorder (MDD). This region is chosen because it expresses local functional (hypoactivity) and structural (reduced gray matter volume) abnormalities as well changes in functional connectivity to anterior cingulate cortex in MDD [24]. Moreover, local metabolic changes in the shape of reduced regional GABA

and glutamine (GLX) have been revealed in several prefrontal cortical regions with MRS [25].

How can the knowledge provided by brain mapping studies be used in practice when planning a tDCS study? Let us assume that a range of task-related fMRI studies point to an abnormality "X" in cortical region "Y," and the hypothesis is that by applying anodal tDCS to region "Y," a symptom "Z" will improve. One option is to extract the peak location derived from the group-based activation maps, at which abnormality "X" is maximally expressed in region "Y" and use this peak as "hot spot" for tDCS targeting. An alternative option is to perform task-related fMRI in the participants before the tDCS intervention and use the individual activation pattern in cortical region "Y" as individual "hotspot" for tDCS targeting.

13.2.2 Personalization of tDCS: Computational Dosimetry and Montage Optimization

Modeling of the tDCS-induced electrical field can be used to reduce individual differences in current field distribution and intensity. The effects of individualized dosing are illustrated in Fig. 13.3. Modeled e-fields corresponds well to intracranial measurements and are preferable to both one-size-fits-all approaches and unifactorial corrections based on, for example, scalp to gray matter distance (see [26]). A recent post-hoc analyses of the clinical outcome following 10 weeks of tDCS treatment in the ELECT trial underscores the clinical potential of electrical field modeling to inform the dosing of tDCS [27]. Improvements in negative affect scaled positively and linearly with the modeled electrical field strength in bilateral DLFPC and ACC. In contrast, no relation between the induced electrical field strength and positive affect or anxiety was found. The results suggest the existence of a therapeutic range that is associated with positive outcomes, and future studies may use this knowledge to prospectively adjust the necessary dose (i.e., current intensity) to reach the target range with the help of electrical field modeling.

A precise model of the tDCS-induced electrical field is contingent on the ability to segment both neural and nonneural head tissues precisely. Hereinto, segmentations based on both T1- and T2-weighted sMRI have been demonstrated to outperform segmentations from T1 alone in terms of DICE scores and variability. Recent developments in automated segmentation pipelines have improved T1-based segmentations substantially [28], but the inclusion of T2-weighted brain scans is recommended to minimize fat-shift artifacts.

Modeling the tDCS-induced electrical field based on high-resolution anatomical head models can reveal interindividual and between-group variability in the tDCS-induced electric fields [29]. This has been shown for tDCS of the left dlPFC, a common target in brain stimulation studies designed to treat MDD. A recent study applied computational modeling to simulate the spatial distribution of tDCS-induced electric fields in 20 frontal regions, considering several bi-hemispheric, bi-polar tDCS and left-hemispheric, multielectrode tDCS montages [30]. Bi-hemispheric, bi-polar tDCS montages placed electrodes symmetrically over right and left dlPFC and produced comparable e-field strength in the left dlPFC and medial prefrontal cortex. In contrast, the multielectrode tDCS montages with a central electrode placed over left dlPFC produced a more local e-field in the targeted dlPFC. Depending on stimulation parameters, the magnitude and focality of tDCS-induced electrical fields varied considerably [30]. These findings suggest that individual modeling of tDCS protocols may substantially improve individual cortical targeting as well as standardizing therapeutic tDCS interventions across subjects. This also applies to scientific tDCS studies of human brain function that lack a therapeutic context. Here, electric field calculations can be used to compare and optimize different tDCS strategies for selective spatial targeting of the cortical region of interest [31].

Choosing the optimal montage for selective engagement of a specific region can be difficult. Concentric electrode or multielectrode montages with a central anode (or cathode) and surrounding cathodes (anodes) can increase the spatial

specificity at the expense of a reduced strength of the induced electrical field [32] which further increases the need for spatial guidance. Several automatized pipelines exist that enables reversed e-field modeling; that is, based on an anatomical target and a predefined electrical field intensity, the optimal montage within the safety limitation can be found (see [17]). An important notion is that even with careful brain imaging-guided electrode placement and individual computed dosing, the effect of ongoing activity in the target and interconnected network can still shape the neuronal effects of tDCS. Hence, modeling the tDCS-induced electrical fields in the brain is only a first step. Future work will need to implement anatomically realistic biophysical models that can be used to predict the effects of the induced electrical fields on axonal structures in terms of depolarization or hyperpolarization as well as the dependency of these de- or hyperpolarizing effects on physiological factors.

13.2.3 Probing Functional Engagement of Brain Circuit Targets by tDCS

As evident from early studies targeting the pericentral cortex, the effects of tDCS substantially depend on the functional state of the cortex at the time of stimulation, changing radically when stimulation is given when subjects are relaxed (idling state) or while they generate motor activity (active state) [33]. Both immediate- and after-effects of tDCS are emergent properties of the applied current (extrinsic variable) and the ongoing neuronal activity (intrinsic variable). The interaction between these variables explains the state dependency of the functional responses of both neural networks and individual neuronal compartments exposed to the e-field. In general, it is assumed that tDCS only engage those axonal compartments that are already active by adding stochastic noise to the system. However, opposing mechanisms may operate. Ongoing activity changes the biophysical properties of membranes such as decreased resistance, which in terms may augment hyperpolarization and antagonize depolarization by anodal stimulation (see [34] for discussion). This implies that regional and network effects most likely scale nonlinearly with the intensity of the locally induced electrical field strength and that this relationship depends on the brain state.

These uncertainties regarding the functional impact of tDCS on the target region motivate the need to assess the functional engagement of circuit targets with online functional brain mapping during or shortly after tDCS and to validate efficacy of stimulation as demonstrated in a recent study by Li et al. [35]. Using concurrent tDCS and fMRI, they found tDCS of inferior prefrontal gyrus to cause polarity-specific and state-dependent activity changes in remote cortical nodes of the default mode (DMN) and salience (SN) networks [35]. In regions active during a choice reaction time task, the largest accentuation of activity was found with cathodal stimulation that conversely attenuated regional activity across both networks when delivered during rest. Functional connectivity in the interrogated networks also changed with tDCS in a polarity- and task-specific manner. Whereas these results showcase the potential of brain imaging to probe the immediate impact of tDCS and thereby confirm functional engagement of the targeted brain networks. This is particularly important in all tDCS studies that do not stimulate motor cortex and thus cannot use MEP measurements as functional readout.

We wish to emphasize that the absence of changes in a neuroimaging readout during concurrent brain imaging and tDCS cannot be interpreted as a failure to engage the target node or network. Regarding BOLD-fMRI, the BOLD signal in a single voxel is an average signal that reflect the net effect of tDCS on a wide range of different neural compartments with different orientations and different neuronal populations, including excitatory and inhibitory neurons. The multitude of regional tDCS effects might very well oppose each other in terms of changing the BOLD signal and thereby cancel each other out, leaving the BOLD signal in that voxel unchanged. In addition, artifacts below the electrode may be mistaken as changes in neural activity, as evi-

dent from the BOLD signal changes under the stimulation electrodes observed during tDCS in cadavers [36] (but see also [37]). Independent of the imaging modality, non-transcranial off-target effects of tDCS may also confound the neuroimaging readout (see below).

13.2.4 Mapping tDCS-Induced After-Effects with Brain Imaging

Brain imaging conducted (before and) after tDCS can delineate functional changes at the regional and inter-regional level that underpin the behavioral and clinical after-effects of tDCS interventions. In basic science, this is a critical step toward establishing causal relationship between brain network features and behavioral variation in health (e.g., abilities) or disease (e.g., disabilities). The characterization of longer lasting (hours to weeks) after-effects on circuit targets and behavior is key to validation of tDCS efficacy (Fig. 13.4). Offline mapping after single or multiple tDCS sessions has the potential to link long-lasting brain circuit reorganization with behavioral or clinical outcomes at the single-person level. If a tDCS-induced reversal of aberrant brain activity predicts a mitigation of a preexisting disability, this corroborates a causal relation and validates the tDCS protocol and confirms efficient modulation of the tDCS target at the brain network level.

13.2.5 State-Informed tDCS to Achieve Contextual Precision

It is well known that the neuromodulatory effects of tDCS critically depend on the functional state of the targeted brain networks (i.e., the neuronal context) [35, 38], but the mechanistic rules that govern the state dependency of tDCS are poorly understood. Given the importance of state dependency, it should be a priority of tDCS research in the coming years to systematically study how the "neuronal context" of the targeted brain circuits frames the efficacy of tDCS and how tDCS can be aligned to the expression of a favorable brain state to achieve conceptual precision.

Modeling of the tDCS-induced electrical fields in the brain can be used to optimize spatial precision and standardize the electrical field in the target region across persons. Functional brain mapping can indicate functional engagement of the targeted brain network and its outlasting modulation by tDCS. While these are major milestones in the pursuit to realize precision tDCS, they cannot contribute to advance the contextual precision of tDCS. This requires the use of techniques that can extract information about the current brain state at high temporal resolution without significant temporal delay. One experimental strategy is to "standardize" the brain state during tDCS by asking the subjects to perform a well-defined task during tDCS. Another option is to record measures of the bodily state (respiration, pupillometry, sympathetic skin response) and use these bodily signals to adjust tDCS for instance by online tuning tDCS intensity according to fluctuations of these bodily signals. A third option is to directly record brain activity with electroencephalography (EEG). Because of its excellent temporal resolution, EEG can instantaneously extract fluctuations in the brain state of interest, and this information can be used to inform precision tDCS. The optimal hardware solution would be an integrated tDCS-EEG system that can record brain activity and apply tDCS simultaneously. For therapeutic applications, such integrated tDCS-EEG systems should be easy to operate and should allow home-based use and remote, web-based control.

Two control principles can be used for state-informed EEG-tDCS (Fig. 13.4). Firstly, one may adopt an open-loop approach that uses an EEG-based readout of the brain state of interest to ensure contextual precision of tDCS. For instance, subjects can be instructed to engage in a specific task that previously has been demonstrated to increase the neuromodulatory (after) effects of tDCS and treatment efficacy. In this setting, EEG could be used to monitor whether the task-related brain state is sufficiently increasing contextual precision of tDCS. Secondly, one

may adopt a closed-loop approach, in which the EEG-based readout of the brain state of interest is used in a rule-based adaptive fashion. For instance, if the oscillatory power expressed in the target network does not shift toward the target frequency, a closed-loop system could adjust tDCS variables to improve target engagement. If focal stimulation of one node does not achieve the desired state change in the target network, one may increase intensity stimulus intensity or increase the number of targeted brain regions by altering the weighting of current in a multielectrode tDCS setup (see [39]).

13.2.6 Mind Peripheral Effects When Personalizing tDCS!

When applying transcutaneous electric current, less than a quarter reaches the brain. Most of the current is shunted through more conductive superficial tissue which causes simultaneous costimulation of peripheral components of the nervous system in the head, including peripheral nerve fibers and peripheral receptors in the skin, eye (retina), or inner ear [40–42]. Peripheral costimulation is a relevant issue when using tDCS as a scientific or therapeutic tool, because it may contribute to the behavioral effects of tDCS and should be controlled for by "sham" stimulation [31]. Especially when using pseudo-monopolar (multielectrode or center-ring) montages, tDCS-induced excitation of the peripheral somatosensory system leads to sensory side effects, including itching, tingling, and burning sensations under the electrode. Depending on the electrode positions, bi-polar tDCS setups may cause vertigo or visual phenomena such as phosphenes during the ramping-up and ramping-down phase of tDCS (for further details on side effects, see [40]).

Peripheral costimulation during tDCS may contribute to therapeutic or behavioral aftereffects of tDCS and should be controlled for by "sham" tDCS that matches the peripheral costimulation without causing neurobiologically relevant brain stimulation [31]. The somatosensory effects of tDCS render it possible for the subjects to recognize when the tDCS is applied. This may unintentionally change their brain state during the intervention by, for instance, introducing expectancy or changing the emotional state. Even if somatosensory costimulation does not cause conscious perception, it may induce indirect brain modulation through a tonic change in afferent input to sensory brain networks.

Since conscious perception of costimulation may change overall alertness to a task and induce placebo effects, a realistic "sham tDCS" condition should be included in the experimental design. This is however challenging, because it is difficult in practice to match subjective experiences. Accordingly, real tDCS can often be distinguished from sham tDCS. When asked directly, subjects frequently report the strongest experience of, for example, skin sensations to be at the beginning of stimulation, corresponding with the ramping phase of the current. It cannot be excluded that some sensory receptors are more susceptible to the change in voltage gradient, rather than the gradient alone, meaning a shorter range between ramp-up and -down phase (as used in sham conditions) can be detected by the subject. It would therefore be too simplistic to assume that the sham stimulation induces the exact same peripheral effects as the real tDCS.

Some studies have tested the effect of applying numbing cream before stimulation, and found a reduction in the sensation of pain and other sensory modalities associated with nociceptive processing, such as tingling, sharpness, and pinching (specific receptor or fiber type has however not been reported) [43, 44]. Even though numbing cream can alleviate some mechanistic properties of pain and discomfort, there are still issues with the apparent ability to distinguish between tDCS and sham stimulation (placebo) [45, 46].

Modeling the tDCS-induced electrical field in the scalp may contribute to minimize peripheral effects. As mentioned previously in this chapter, recent developed computational models of current flow provide accurate estimations of induced electrical fields from tDCS. Toolboxes, such as SimNIBS, use individual MRI head anatomy for precise modeling of peripheral costimulation, for example, cutaneous stimulation. Electrical field

simulations can show how the field distribution differs in the cortex and skin depending on the electrode type, the number of electrodes and their position on the scalp. This, in terms, can help to minimize peripheral costimulation or to design sham tDCS conditions that only stimulate the peripheral extracranial neuronal structures, while sparing the cortex, thereby avoiding unwanted direct modulation of the target network. This might be achieved by placing smaller electrodes in proximity to each other. In conclusion, there is no simple solution that can fix the methodological issues caused by peripheral costimulation during tDCS. The inherent methodological challenges should not prevent one to take proper precautions to minimize peripheral costimulation and to ensure optimal sham-tDCS conditions based on individual simulation of the induced electrical fields outside the brain.

13.3 Conclusion and Perspectives

The combination of tDCS with a wide range of brain mapping techniques offers powerful opportunities to advance the scientific and therapeutic use of tDCS. The computational modeling of the tDCS-induced electrical field distribution in the brain is already well established and an important step toward personalization of dosing and increased spatial precision (Fig. 13.3). Future research will expand the precision tDCS approach by mapping and modeling the biophysical-neurobiological interactions and their state dependency. This research will yield insights which can be used to ensure functional precision and to personalize tDCS to the individual properties of the stimulated functional brain networks (Fig. 13.4).

Conflict of Interest Hartwig R. Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and Lundbeck AS, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, the Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark.

References

1. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, Brunoni AR. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020;37:594.
2. Bai X, Guo Z, He L, Ren L, McClure MA, Mu Q. Different therapeutic effects of transcranial direct current stimulation on upper and lower limb recovery of stroke patients with motor dysfunction: a meta-analysis. Neural Plast. 2019;2019:1372138.
3. Yan R-B, Zhang X-L, Li Y-H, Hou J-M, Chen H, Liu H-L. Effect of transcranial direct-current stimulation on cognitive function in stroke patients: a systematic review and meta-analysis. PLoS One. 2020;15:e0233903.
4. Liu M, Fan S, Xu Y, Cui L. Non-invasive brain stimulation for fatigue in multiple sclerosis patients: a systematic review and meta-analysis. Mult Scler Relat Disord. 2019;36:101375.
5. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, Brunelin J, Nakamura-Palacios EM, Marangolo P, Venkatasubramanian G. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int J Neuropsychopharmacol. 2020;24:256.
6. Ziemann U, Siebner HR. Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? Brain Stimul. 2015;8:662–3.
7. Charney DS, Manji HK. Life stress, genes, and depression: multiple pathways lead to increased risk and new opportunities for intervention. Sci STKE. 2004;2004:re5.
8. Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety. 2017;34:9–24.
9. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? Int Clin Psychopharmacol. 2014;29:185.
10. Deng Z-D, Luber B, Balderston NL, Afanador MV, Noh MM, Thomas J, Altekruse WC, Exley SL, Awasthi S, Lisanby SH. Device-based modulation of neurocircuits as a therapeutic for psychiatric disorders. Annu Rev Pharmacol Toxicol. 2020;60:591–614.
11. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol. 1965;28:166–85.
12. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
13. Antonenko D, Grittner U, Saturnino G, Nierhaus T, Thielscher A, Flöel A. Inter-individual and age-dependent variability in simulated electric fields

induced by conventional transcranial electrical stimulation. NeuroImage. 2020;224:117413.
14. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. NeuroImage. 2015;109:140–50.
15. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, Kozák G, Kincses ZT, Iványi B, Buzsáki G, Berényi A. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9:483.
16. Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist. 2017;23:109–23.
17. Saturnino GB, Siebner HR, Thielscher A, Madsen KH. Accessibility of cortical regions to focal TES: dependence on spatial position, safety, and practical constraints. NeuroImage. 2019;203:116183.
18. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, Opitz A, Mehta A, Pack CC, Krekelberg B. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9:1–12.
19. Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, Flaisch T, Flöel A. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci. 2012;32:1859–66.
20. Bindman LJ, Lippold O, Redfearn J. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369.
21. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist. 2011;17:37–53.
22. Bachtiar V, Near J, Johansen-Berg H, Stagg CJ. Modulation of GABA and resting state functional connectivity by transcranial direct current stimulation. elife. 2015;4:e08789.
23. Herz DM, Eickhoff SB, Løkkegaard A, Siebner HR. Functional neuroimaging of motor control in Parkinson's disease: a meta-analysis. Hum Brain Mapp. 2014;35:3227–37.
24. George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. Depression. 1994;2:59–72.
25. Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and γ-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Arch Gen Psychiatry. 2007;64:193–200.
26. Evans C, Bachmann C, Lee JS, Gregoriou E, Ward N, Bestmann S. Dose-controlled tDCS reduces electric field intensity variability at a cortical target site. Brain Stimul. 2020;13:125–36.
27. Suen PJ, Doll S, Batistuzzo MC, Busatto G, Razza LB, Padberg F, Mezger E, Bulubas L, Keeser D, Deng Z-D. Association between tDCS computational modeling and clinical outcomes in depression: data from the ELECT-TDCS trial. Eur Arch Psychiatry Clin Neurosci. 2020;271:101.
28. Puonti O, Van Leemput K, Saturnino GB, Siebner HR, Madsen KH, Thielscher A. Accurate and robust whole-head segmentation from magnetic resonance images for individualized head modeling. NeuroImage. 2020;219:117044.
29. Boayue NM, Csifcsák G, Puonti O, Thielscher A, Mittner M. Head models of healthy and depressed adults for simulating the electric fields of non-invasive electric brain stimulation. F1000Res. 2018;7:704.
30. Csifcsák G, Boayue NM, Puonti O, Thielscher A, Mittner M. Effects of transcranial direct current stimulation for treating depression: a modeling study. J Affect Disord. 2018;234:164–73.
31. Karabanov AN, Saturnino GB, Thielscher A, Siebner HR. Can transcranial electrical stimulation localize brain function? Front Psychol. 2019;10:213.
32. Saturnino GB, Antunes A, Thielscher A. On the importance of electrode parameters for shaping electric field patterns generated by tDCS. NeuroImage. 2015;120:25–35.
33. Antal A, Terney D, Poreisz C, Paulus W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci. 2007;26:2687–91.
34. Paulus W, Rothwell JC. Membrane resistance and shunting inhibition: where biophysics meets state-dependent human neurophysiology. J Physiol. 2016;594:2719–28.
35. Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, Rothwell JC, Carmichael DW, Sharp DJ. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp. 2019;40:904–15.
36. Antal A, Bikson M, Datta A, Lafon B, Dechent P, Parra LC, Paulus W. Imaging artifacts induced by electrical stimulation during conventional fMRI of the brain. NeuroImage. 2014;85:1040–7.
37. Esmaeilpour Z, Shereen AD, Ghobadi-Azbari P, Datta A, Woods AJ, Ironside M, O'Shea J, Kirk U, Bikson M, Ekhtiari H. Methodology for tDCS integration with fMRI. Hum Brain Mapp. 2020;41:1950–67.
38. Nozaki D, Yokoi A, Kimura T, Hirashima M, de Xivry J-JO. Tagging motor memories with transcranial direct current stimulation allows later artificially-controlled retrieval. elife. 2016;5:e15378.
39. Fischer DB, Fried PJ, Ruffini G, Ripolles O, Salvador R, Banus J, Ketchabaw W, Santarnecchi E, Pascual-Leone A, Fox MD. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. NeuroImage. 2017;157:34–44.
40. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen L, Dowthwaite G, Ellrich J, Flöel A. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128:1774–809.

41. Kar K, Krekelberg B. Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. J Neurophysiol. 2012;108:2173–8.
42. Schutter DJ. Cutaneous retinal activation and neural entrainment in transcranial alternating current stimulation: a systematic review. NeuroImage. 2016;140:83–8.
43. Guleyupoglu B, Febles N, Minhas P, Hahn C, Bikson M. Reduced discomfort during high-definition transcutaneous stimulation using 6% benzocaine. Front Neuroeng. 2014;7:28.
44. McFadden JL, Borckardt JJ, George MS, Beam W. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. Brain Stimul. 2011;4:38–42.
45. Greinacher R, Buhôt L, Möller L, Learmonth G. The time course of ineffective sham-blinding during low-intensity (1 mA) transcranial direct current stimulation. Eur J Neurosci. 2019;50:3380–8.
46. Turi Z, Csifcsák G, Boayue NM, Aslaksen P, Antal A, Paulus W, Groot J, Hawkins GE, Forstmann B, Opitz A. Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 min in young healthy adults. Eur J Neurosci. 2019;50:3261–8.
47. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, Kozák G, Kincses ZT, Iványi B, Buzsáki G. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9:1–17.

14 Clinical Research and Methodological Aspects for tDCS Research

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14.1 Introduction

Transcranial direct current stimulation (tDCS) was reintroduced as a modern method for noninvasive brain stimulation (NIBS) in humans approximately 20 years ago, in 1998–2000 [1, 2]. Since its reintroduction to the scientific and clinical community, the application of tDCS across a variety of healthy, psychiatric, and neurological populations has increased exponentially. However, like many nascent fields, methods used to apply tDCS have varied over the past 20 years. This variation, together with a lack of standardized reporting methods for the field, have likely played a role in issues of reproducibility for certain effects previously demonstrated with tDCS [3]. Specifically, variability in tDCS application methodology, design, stimulation parameters, and other factors have undermined the ability to reproducibly apply tDCS within and between patients and healthy subjects. For example, inconsistent placement of electrodes alters the location and intensity of stimulation to various brain regions [4]. In contrast, different levels of stimulation intensity (e.g., 1 vs. 2 mA) result in partially nonlinear changes in depolarizing versus hyperpolarizing resting membrane potentials under anode versus cathode electrodes, respectively [5]. Furthermore, certain medications can alter excitability effects of tDCS on resting membrane potentials (e.g., serotonin selective reuptake inhibitors, SSRIs [6]) relative to effects previously shown in healthy adults not taking these medications. These are only a few examples of methodological and design factors that significantly alter the potential outcomes of clinical or research applications of tDCS. However, studies often do not provide the level of methodological detail required to guide neither clinicians and researchers new to the field of tDCS nor experienced researchers attempting to replicate study effects. These details are of critical importance for not only reproducing effects from a given study and consistent clinical outcomes, but also for educating new tDCS researchers and clinicians.

In this chapter, we will provide guidance on methodological and design aspects of tDCS, covering basic methodological issues, effective approaches, and reproducible methods for the application of tDCS in both clinical and research settings. These materials are intended to provide easily implemented and reproducible methods for both new and experienced tDCS researchers and clinicians.

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14.2 Clinical/Research Trial Designs

14.2.1 Protocol Intensity/Duration/Repetition

When designing an experimental or intervention protocol, it is important to choose tDCS parameters (i.e., stimulation intensity, electrode locations, duration, and repetition) based on the outcome being investigated (i.e., neurophysiological, cognitive, or behavioral), as well as the clinical population being studied. This is because findings with the use of particular parameters for one outcome may not directly correspond with another similar or different outcome, or in a different subject population. Neurophysiological responses (e.g., MEP amplitudes) to tDCS and other noninvasive brain stimulation techniques, for example, have been shown to have little or no correspondence to motor learning capacity [7]. As such, stimulus parameters chosen based on findings of effects on MEP amplitudes measured in the motor cortex in healthy participants may not produce equivalent effects on alternative outcomes (e.g., cognitive or behavioral) when assessed following stimulation of the same or different brain regions. This principle also can apply to the administration of stimulus parameters found effective for healthy subjects to clinical populations. While 1 mA stimulation intensity given to the left dorsolateral prefrontal cortex for 10 min improved working memory performance in healthy participants [8], 2 mA but not 1 mA stimulation intensity for 20 min was necessary to produce similar effects in patients with schizophrenia [9]. Prior research using TMS evoked MEPs consistently suggests that 1 mA tDCS produces increased excitability under the anode electrode and decreased excitability under the cathode electrode [10]. However, recent research suggests that 2 mA stimulation may result in increases in excitability under both anode and cathode electrodes [5, 11–13]. In contrast, a recent study suggests that higher doses of 3 mA tDCS (e.g., 3 mA or more) results in increased excitability under the anode and reduced excitability under the cathode, similar to 1 mA stimulation [11]. Thus, selection of stimulation intensity should be chosen carefully based on the desired change in excitability for a given application of tDCS.

Similarly, this principle may equally apply when choosing the interval for repeated tDCS administrations, for example, in intervention protocols. This appears to be the case, as both the stimulus polarity and interval between sessions can interact to cause different effects on outcomes. In healthy subjects, differently spaced intervals (i.e., 0 min to 24 h) between consecutively applied tDCS given with the cathode electrode over the motor cortex has been shown to directly affect both the magnitude and duration of post-stimulation neurophysiological effects [14]. Similar differential behavioral effects due to both the polarity and duration of the spaced interval on cognitive outcomes have been found, with improvement in working memory performance following two sessions of tDCS with the cathode electrode over the left prefrontal cortex, although not when the anode electrode was placed over the same region, given 10 min apart [15]. This latter finding additionally highlighted the potential role of metaplastic effects within the stimulated region on outcomes (i.e., when tDCS is administered again during the aftereffects of a previous tDCS administration).

Unlike other noninvasive brain stimulation methods (e.g., TMS, ECT), tDCS typically applies a fixed dose of tDCS parameters across participants rather than individual dosing titration. Recent computational modeling research suggests that titration of stimulation intensity may serve as a significant factor contributing to interindividual variability of response to tDCS. Indahlastari et al. demonstrated significant variability in the distribution of current density in the brain as a function of age-related atrophy, as estimated through MRI-derived finite element computational modeling of current in a cohort of 587 older adults [16]. This work suggested that for those with the greatest signs of atrophy, the intensity of current would need to be increased by almost twofold to reach equivalent levels of current intensity induced in younger adults with-

out atrophy. Wang et al. have proposed an initial method for titrating the generated E-field generated by tDCS as a possible method for individual titration of tDCS intensity dose [17]. While robust methods for individual dose titration in tDCS is still in development, this area represents an important evolution in tDCS approaches for future studies.

Taken together these collective findings thus suggest that if no prior reference study exists when designing an experimental or intervention protocol, titration of tDCS parameters in relation to stimulus intensity, duration, and repetition should be considered. This can be achieved, for example, through a pilot study. Such piloting can also be invaluable for informing future studies.

14.2.2 Methodological Aspects of Online and Offline Protocols

A potentially important methodological consideration when designing an intervention or study using tDCS is the timing of tDCS administration in relation to task execution. That is, when tasks are given, it is important to determine whether these are performed during the application of tDCS (i.e., "online") or following tDCS administration (i.e., "offline"). This consideration is based on evidence indicating that both the physiological and behavioral effects of tDCS are different during and after stimulation. For example, functional neuroimaging has shown that while an increase in regional blood activity occurs during stimulation, activity is reduced immediately following stimulation [18]. Different behavioral outcomes have also been demonstrated with "online" compared to "offline" protocols. While improved motor learning was found to occur with "online" stimulation, decreased learning was found when the same task was performed "offline" [19]. Similarly, better performance on a cognitive training task was found with "online" compared to "offline" tDCS, with greater maintenance of learning found the following day [20]. When evaluating outcomes in interventions involving repeated tDCS administrations, these effects should also be considered as "offline" or "after"effects immediately following tDCS administration may affect task performance and/or other measurements, for example, cognitive or neurobiological changes following a course of tDCS for depression. While these after-effects have primarily been shown in the context of research studies [1, 21, 22], their impact should be carefully considered in multisession treatment studies.

A further methodological consideration is the relative effect of task related activity within stimulated regions, as this has also been shown to affect outcomes. For example, different effects on post-stimulation cortical excitability have been found depending on whether subjects were sitting passively at rest during tDCS, paying attention to a cognitive task, or actively engaging the stimulated region with performance of a motor task [23]. Further, the relative level of task-related activity has also been found to be relevant. While performance of a slow motor task during anodal stimulation over the motor cortex significantly improved learning and increased cortical excitability, poorer learning and decreased cortical excitability was found when subjects performed a fast motor task [24]. Relative activity levels during tDCS have further been shown to affect whether neuroplastic changes occur following stimulation, with ongoing background activity shown to be necessary to induce long-term potentiation in an in vitro animal model [25].

As such, both the timing of task execution together with the relative state of stimulated regions in relation to tDCS administration together are potentially important considerations when assessing outcomes for a particular study or intervention. Correspondingly, attempts should be made to control for potential brain state effects whenever behavioral or physiological outcomes are examined during or after tDCS administration. This could be achieved, for example, by requiring subjects to sit at rest for a given period prior to commencement of tDCS and implementing methods to standardize or restrict behavioral activity (e.g., talking) during and following stimulation.

14.2.3 Blinding, Sham, and Active Control

Appropriate blinding methods is a critical feature for interpretability of non-invasive brain stimulation studies and trials. The usual approach for blinding subjects is to apply a "sham" stimulation protocol which typically involves ramping the stimulation up and down similar to active stimulation, although only providing constant stimulation for a few seconds. The advantage of this methodology is while subjects will feel the initial itching/tingling sensation suggestive of active stimulation, the overall stimulation duration is too short to induce aftereffects, providing the stimulator is turned off after the ramping down period. If this latter step is not done, there is the potential for undesired neuromodulatory effects from the delivery of a constant very low level current with some devices when left on or in standby mode [26]. For 1 mA tDCS with an electrode size of 25 cm2, this method has been shown to reliably blind subjects [27]. As stronger stimulation intensities induce larger sensations, providing a brief constant stimulation at the maximum intensity, however, may compromise blinding [28]. An alternative approach is to apply topical anesthetics to abolish skin sensations [29]. Care should be given if this approach is taken, as local anesthetics may reduce cutaneous sensations indicative of skin damage which could in turn increase the risk for adverse side effects. However, prior research found no relationship between increased skin sensation and probability of skin burns, suggesting that the use of topical anesthetics may be a safe alternative in the sham procedure [30]. Nonetheless, care should be taken when considering the use of topical anesthetics. In recent years, the efficacy of tDCS blinding approaches has been called into question. This has been driven, in part, by insufficient assessment of blinding efficacy within studies, lack of consistent assessment of blinding efficacy across studies, and variation in sham techniques applied serving as potential sources of variability between studies [31]. To date, the most commonly used approach is the brief sham approach described above (ramp up, on for a few seconds, ramp down, and machine off).

Experimenter blinding is accomplished by use of tDCS stimulators, which include a sham stimulation function that enables the experimenter to remain unaware of the stimulation condition. However, even in this situation, it is important to note that the presence of skin erythema due to vasodilation, as well as sensations reported by subjects during and following stimulation, can nevertheless compromise experimenter blinding. Skin erythema can be reliably reduced by acetylsalicylate or topical application of ketoprofen [32]. Having one experimenter recording side effects following tDCS (e.g., skin reddening), while another one only assessing efficacy measures can further blind the primary interventionist to study conditions. Alternatively, allowing electrodes to remain in place on the participant's head for a period (e.g., 10 minutes) after stimulation has stopped can enable any skin erythema to dissipate and electrodes to return to room/body temperature levels prior to removal. This approach addresses both potential unblinding features potentially notable by experimenters. For reliable double blinding in sham/placebo-controlled studies, several different approaches should thus be considered. Any blinding procedures implemented must be accurately reported in scientific papers to facilitate replication in future studies.

On a related note, assessment of stimulation sensation and blinding efficacy is an important consideration for both clinical trials and research studies comparing active to a placebo/sham stimulation condition. Assessments of sensation should ideally evaluate a range of sensation types (e.g., tickling, burning, pain, warming, etc.) before, during, and after stimulation. This data can provide important information for direct comparison of the sensation experience between active and sham/placebo conditions of relevance for assessing sham/placebo blinding. Further, direct assessment of blinding of both participants and experimenters should occur at the end of the last stimulation session. While some studies simply inquire as to which condition the participant and experimenter believe was applied, expand-

ing this to include assessment of the confidence in their selection can provide additional useful information for assessing the integrity of blinding [33]. While a study/trial may show a significant difference in a selected outcome between active and sham/placebo conditions, this finding should be considered viable only in the context of a direct demonstration of sham/placebo-blinding efficacy within the trial/study.

Alternatively, or in addition, the inclusion of an active control condition may be considered. This may be useful to determine specificity if the overall goal is to demonstrate that stimulation applied over one cortical region induces a particular effect. Application of tDCS over an alternative brain region (i.e., as an active control) therefore may provide a stronger foundation for interpretation of results. For such designs, use of high-definition tDCS electrode montages (e.g., 4 × 1) could be considered, as this enables better localization of the stimulation effects particularly for cortical regions [34–37]. Notwithstanding, the choice of the control (i.e., sham or active) should be hypothesis driven, as this can have a profound impact on study conclusions.

14.3 Patient/Participant Screening

Using modern stimulation parameters, tDCS given either over a single treatment session or over several sessions spaced apart has been safely administered to healthy subjects and patients with diverse psychiatric (e.g., schizophrenia, attention deficit hyperactivity disorder, anorexia) and neurological conditions (e.g., stroke, epilepsy, traumatic brain injury) in experimental protocols [38]. Increasingly, tDCS has also been given over multiple repeated sessions to patients as a therapeutic intervention. Careful screening, however, is critical for minimizing the risk for adverse side effects for all protocols using tDCS in both healthy and patient populations.

Prior to stimulation, it is necessary to conduct formal screening for potential comorbid neuropsychiatric and neurological conditions as well as structural abnormalities. This is important both to accurately characterize the particular patient/participant population being investigated and to determine the relative risk for unexpected side effects for particular subjects. For example, mood switching in patients with major depressive disorder and bipolar disorder have been reported in several case reports [39]. For neuropsychiatric conditions, this can be achieved using published formal structured interviews, for example, the Structured Clinical Interview for DSM-5 (SCID-5: [40]) or the M.I.N.I.6. International Neuropsychiatric Interview (M.I.N.I. 6.0: [41]). Potential neurological conditions can be screened either through either patient interview or self-report questionnaires (e.g., Transcranial Magnetic Stimulation Adult Safety Screen; TASS; [42]). Due to the potential for local enhancement of current density as a result of anatomical abnormalities (e.g., to the skull), exclusion criteria for tDCS (i.e., metal in the head, no stimulation over fissures, or cranial holes) are also typically implemented. Recent research suggests that cardiac pacemakers are not affected by tDCS [43].

Screening for concurrent medication use is also important, as particular psychoactive medications can interact with tDCS effects. For example, D-Cycloserine, a common treatment for tuberculosis, has been shown to prolong the neuromodulatory effects of tDCS [44]. Other common medications, including selective serotonin reuptake inhibitors (SSRIs; [45]), mood stabilizers (i.e., sodium and calcium channel blockers; [6]), antipsychotics (i.e., dopamine antagonists; [46]), and common pain killers and sedatives (e.g., benzodiazepines; [47]), have also been shown to interact with tDCS. Concomitant medication use should therefore be kept stable throughout the study period and ideally for at least 4–6 weeks prior to tDCS administration in therapeutic interventions. Furthermore, the experimenter should be notified immediately of any medication changes during any tDCS study, as this may affect outcomes.

Lastly, as tDCS is administered using electrodes place upon on the scalp, it is necessary to inspect the skin where the electrodes will be

placed. Skin damage to these areas (e.g., disease, irritation, or lesion) during administration of tDCS can potentially increase the likelihood of further skin damage or skin burns [48].

14.4 Electrodes and Contact Medium

The role of electrodes in tDCS is to facilitate delivery of current from the stimulation device to the scalp. Teams of clinical trial researchers have reported application of thousands of tDCS sessions without any skin injury using rigorous control of electrode selection and preparation, along with adherence to established tDCS protocols, operator training, and use of certified devices [45, 49–52]. The tDCS electrode assembly most commonly comprises (1) a metal or conductive rubber (e.g., biocarbon) electrode, (2) an electrode sponge, (3) an electrolyte-based contact medium (e.g., saline, gel, or conductive cream) to facilitate current delivery to the scalp, and (4) any materials used to shape these components or otherwise direct current flow (plastic casing, rivets).

The metal or conductive rubber electrode is the site of electrochemical reactions during tDCS [53] and should never directly contact the skin. An electrolyte must be used as a buffer between the electrode assembly and the skin. Sufficient electrolyte volume prevents chemicals formed at the electrode during the electrochemical reaction occurring during stimulation from reaching the skin [54]. The electrolyte can be placed in a sponge encasing the electrode (i.e., saline) or, in the case of electrode cream, placed directly on the electrode surface. For saline, oversaturation of the electrode sponge can significantly undermine reproducibility of tDCS application and effects. When sponges are over-saturated, saline is evacuated from the sponge and covers an area of the scalp outside of the surface area electrode sponge. Rather than delivering current through a specified surface area on the scalp under the electrode (e.g., 5 × 5 cm), the electrode surface area and area of current delivery now encompasses the entire area of the scalp that is covered in saline. This creates an unreproducible and amorphous area of current delivery within and between subjects. It is important to obtain good contact under, and only under, the electrode with the electrode sufficiently, but not overly saturated. Methods allowing quantification of saline (e.g., syringes) can assist in achieving a consistent and appropriate amount of contact medium.

Consistent with issues introduced by oversaturation of sponges, the shape/size of electrodes/sponges significantly alter the distribution of current delivered to the scalp and the brain [55, 56]. At a constant current intensity level (e.g., 1 mA), increases in electrode size or differences in electrode assembly shape result in differences in the distribution of the current across the surface area of the scalp, resulting in differences in the distribution of current throughout the brain [55, 56]. Thus, it is critical for investigators to consistently report not only the current intensity applied and the amount of contact medium used, but also the shape and size of the electrode assembly.

14.5 Electrode Location

Another critical consideration for tDCS is determining where to place electrodes on the head. Studies monitoring physiological changes following tDCS and computational modeling studies of predicted current flow demonstrate that the relative location of electrodes results in significant differences in where and how much current is delivered to the brain [4, 57, 58]. For example, Nitsche and Paulus [1] demonstrated that relative differences in electrode locations altered whether or not tDCS impacted TMS-generated motor-evoked potentials (MEPs). Numerous modeling studies have demonstrated significant differences between relative locations of electrodes, with results varying from stimulation of the whole brain to more selective stimulation of particular lobes of the brain [4, 57, 58]. Woods et al. [59] further demonstrated that as little as 1 cm of movement in electrode position significantly altered the distribution of predicted current flow in the brain, as well as the intensity of stimulation in specific brain regions. Recent research using intracranial recording and careful manipulation

of electrode positioning on the scalp directly demonstrated that a 1 cm shift in electrode positioning significantly alters the underlying E-field generated by tDCS [60]. Computational modeling of electric current through the brain can be a useful tool for the a priori design of tDCS electrode positions for a given study. In this same context, the importance of electrode location also highlights yet another critical consideration, preparation of a stable electrode placement on the head.

Head size and shape vary from person to person. Thus, it is necessary to use a method for common localization of electrode position. There are several methods for addressing this issue: (1) International 10-20 (or 10-5) Electrode Placement System [61, 62], or another gross anatomical coordinate system [63], (2) neuronavigation systems (e.g., MRI guided), or (3) physiology-based placement (e.g., TMS-generated MEPs). Each method can be used to consistently center each electrode on the head, accommodating varied head shape or size, and has relative strengths and weaknesses (e.g., accuracy vs. time and cost).

For example, even when using a method like the 10–20 Electrode placement, inaccuracy of electrode placement can occur due to human error in the measurement process or in placing the EEG cap over the head. Recent work provides methods for direct measurement of electrode placement using 3D scanning of the scalp using inexpensive hardware (e.g., iPad with an attached 3D scanning camera) to capture accurate models of electrode positioning on the scalp [64]. Prior work also provides for less technologically dependent methods for capturing errors in electrode positioning using physical measurements taken on the scalp [4]. Regardless of method, these techniques provide valuable information regarding the consistency of electrode location on the scalp both within and between participants. As prior work has demonstrated that electrode locations play a central role in the distribution of the E-field generated by tDCS, these measures provide a form of quality control measurement for studies and can provide metrics for inclusion in statistical analyses to assess or control for application variability in electrode location.

14.6 Electrode Placement

Once desired locations are identified based on specific study design needs, the electrode assembly must be affixed to the head for delivery of current. Nonconductive headgear used to position the electrodes on the body or scalp (e.g., elastic straps) are not typically included in the electrode assembly but are critical for appropriate electrode placement [4]. For tDCS using sponge-covered electrodes, elastic straps are the most commonly used headgear for electrode placement. If these straps are under- or over-tightened, electrodes have a strong tendency to move/shift over the course of a tDCS session. Thus, the distribution of current delivery changes over the duration of a tDCS session [4]. This too undermines tDCS replicability. Furthermore, if electrode straps are over-tightened, there is an increase in the probability of evacuation of saline from the electrode sponges. Regardless, the contour at the base of the skull below the inion and the flat of forehead provide for stable placement of a strap around the head. For participants with long hair, placement of the back of the strap under the hairline also improves stability of the strap preparation, whereas placement over the hair leads to a high probability of upward drift of the strap and the electrodes placed on the head. Use of cross straps over the head should also avoid over-tightening of the cross-strap to avoid this same issue. Use of a cross-strap under the chin can counteract this tendency, but may be uncomfortable to participants. If under-chin straps are used, these should be used for all participants to maintain consistency of participant experience in the study.

As the field of tDCS has progressed, a wider array of electrode positioning systems has become available. Some of these systems provide rigid systems for placement of electrodes on the scalp, while others are individually adjustable. Other approaches have worked to integrate electrodes within EEG-like cap systems. Thus, a variety of electrode placement methods now exist. Regardless of selected electrode positioning approach, the user must evaluate whether the selected system provides a stable and consistent positioning and placement of the electrodes on

the scalps of participants/patients—evaluating these methods across different head sizes.

In addition, at-home based approaches to delivery of tDCS has significantly advanced over the past 5 years [65]. At present, there are a number of different available options for at-home approaches. Typically, at-home approaches involve a remote-supervision component where staff can remotely observe self-application of tDCS head-gear by the participant/patient. These systems typically involve a head strapping system with integrated electrodes that stretch to fit the electrodes over the desired target locations. Some of these available options require participants to individually prepare electrodes for each session, while others come with pre-prepped electrodes that are attached to the placement headgear. Commonly, participants will receive at least one or more in-clinic/lab or home visit training sessions on self-placement of at-home equipment prior to remotely supervised sessions. In addition, at-home systems typically involve controlled access to stimulation features on the at home device. For example, some systems provide single use stimulation cartridges while other involve input of a stimulation code that is only active for a dedicated period of time (e.g., 1 day) to activate a stimulation session. This provides the clinic/study staff with a level of control in terms of the interval at which participants/patients can deliver stimulation to themselves. At-home methods continue to advance, but may provide a viable remote option for delivery of multisession stimulation treatment in the future—for example, for depression [66].

14.7 tDCS Stimulator Selection

A limited but growing number of certified tDCS-stimulators are currently available [67]. These devices are designed to deliver constant current through two or more electrodes [68, 69]. Available stimulators differ based on specific features, such as: suitability for alternative stimulation protocols (e.g., transcranial alternating current stimulation, transcranial random noise stimulation, transcranial pulsed current stimulation), custom programming capabilities, number of stimulation channels, available stimulation intensity level, stimulator size, stimulator weight, stimulator portability, compatibility with magnetic resonance imaging (MRI), blinding options, and sham options. Certified tDCS stimulators provide the basic features required to deliver tDCS. Thus, selection of a stimulator depends on the planned application and study protocol (e.g., number of electrodes, requirements for blinding, desired stimulation intensity, sham options, etc.). In any case, exactness of delivered current, as programmed, is of crucial importance and should be tested at a regular interval (e.g., by aid of an oscilloscope), as minor deviances can result in prominent alterations of experimental outcomes. Thus, while a certified stimulator from a manufacturer may be delivered performing to exact specifications, repeated stimulation may result in alteration of the exactness of delivered current (i.e., delivery of less than or more than 2 mA when stimulator set to 2 mA) and should be tested for consistent delivery of tDCS to patients and participants. Certified tDCS stimulators also have the advantage of limiting the intensity of current to, typically, less than 3 mA, and limiting the duration of stimulation. In contrast, many stimulation devices repurposed for tDCS (e.g., iontophoresis stimulators) provide the ability to deliver stimulation up to and beyond 1 mA. This is a significant safety concern regarding skin lesions/burns, for example, if an error is made with stimulation settings. Stimulators should be chosen that provide optimal safety for participants and patients, as well as based on the specific features required for a given stimulation protocol.

14.8 Assessment of Safety/Adverse Events and Monitoring During Stimulation

It is important to make the distinction between tolerability and safety aspects in relation to tDCS. While tolerability refers to the presence of uncomfortable and unintended effects (e.g., tin-

gling and itching sensation under the electrodes), safety refers to damaging effects. Using modern protocols, comfort ratings for tDCS have generally shown a favorable tolerability profile [70, 71]. The most frequently reported side effects are tingling and itching sensations under the electrodes, headache, and tiredness [52]. The sensation of phosphenes elicited by abrupt current on- or offset is avoided by ramping current intensity in both active and sham conditions. Erythema under the electrodes is caused by tDCS-induced vasodilation and hence is not a safety issue [72].

In relation to safety aspects, no structural damage of brain tissue as examined with diffusion-weighted and contrast-enhanced MRI [73] or neural damage as assessed using neuron-specific enolase [73, 74]have been reported using the modern protocols introduced by Nitsche and colleagues. Nevertheless, caution should be taken to systematically assess safety when using protocols with stimulation settings beyond those typically used in modern research studies (e.g., higher current intensities), including those involving prolonged multisession treatment in clinical settings. To date only one seizure, which potentially may be attributed to tDCS, has been reported since the introduction of modern tDCS protocols. This occurred when repeated tDCS sessions in combination with administration of escitalopram was given to a 4-year-old boy who had a prior history of epileptic activity and a recent adjustment to his antiepileptic medication regime [75]. This report thus further highlights the importance for careful patient screening and monitoring, as well as titration with the use of both novel tDCS protocols and established protocols used in different clinical populations.

Another potentially relevant aspect to safety is the application of tDCS using an extracephalic reference electrode based on adverse side effects reported in an early study [76]. Computer modeling of the use of an extracephalic electrode placed upon the shoulder suggests that cardiac or brainstem activities should not be affected [77, 78]. Data in healthy subjects suggests that using an extracephalic electrode reference does not modulate brainstem autonomic activity [79]. Notwithstanding, this assumption does not necessarily apply for any tDCS protocol, independent from current intensity, and stimulation duration, and without regard for inclusion/exclusion criteria. Hence, careful patient monitoring to demonstrate safety is recommended particularly for novel protocols.

The most immediate safety risk for tDCS is the potential for skin lesions or burns following repeated treatments [30, 80]. Risk to subjects, however, can be substantially ameliorated through the implementation of several previously outlined recommendations [81, 82]. (1) Subjects should be screened for skin disease, irritation, or lesions underneath where the electrodes will be placed to minimize focalization of current density. Skin should also be checked prior to every tDCS administration. (2) A single-use sponge should be placed between the electrode and the scalp, as repeated use of sponges may lead to the build-up of substances, which could cause electrochemical reactions [80]. (3) Sponges should be evenly saturated with contact medium (e.g., saline) so that no dry portion of the sponge is in contact with the skin. If using electrolyte cream directly on an electrode, the thickness of the cream application should be consistent (~5 mm) and should cover the electrode completely, preventing direct contact of the electrode with the skin [82]. (4) Care should be taken to ensure adequate and even contact of the electrode skin interface is achieved. (5) Finally, standardized monitoring of patient comfort (e.g., discomfort/pain during stimulation) and side effects following stimulation should be implemented [81, 83], to regularly assess subjects' skin condition and risk for burns.

14.9 Monitoring Functional Effects of tDCS

There are several possible approaches to monitoring the functional effects of tDCS. Effects on motor cortex plasticity and motor cortex excitability, for example, are typically examined through experimental designs which involve firstly determining the motor cortex hotspot for a targeted muscle (e.g., first dorsal interosseous)

using single pulse TMS, obtaining a measure of baseline excitability, and then measuring physiological changes following tDCS stimulation [74, 84]. Another commonly used approach is to examine cognitive effects either during or following tDCS administration (for review, see [85]).

Increasingly, investigators are additionally employing neuroimaging tools (e.g., EEG and fMRI) to further explore functional effects. EEG, while lacking the spatial resolution of other techniques, has the advantage of allowing for enhanced temporal resolution for assessing tDCS-related functional effects. EEG measures voltage fluctuations resulting from ionic current flow via scalp recorded activity and thus is useful for elucidating changes in processing over time within specific regions or across circuits [24]. Similar to the assessment of functional cognitive changes, functional effects can be measured "online" or "offline" following stimulation. Both methods, however, are associated with methodological challenges. Firstly, the tDCS electrodes will need to be integrated together with the EEG electrodes, so as to avoid both types of electrodes being in direct contact and potential bridging between tDCS and nearby EEG electrodes via spreading of the conductive medium. The latter can be potentially avoided through the use of small-sized electrodes, similarly to those used with HD-tDCS [34]. Secondly, for "online" protocols, as tDCS involves the application of an electrical current and EEG directly measures very small electrical changes within the brain, there is the potential for direct interference from tDCS. This can thus result in saturation of an EEG recording amplifier that does not have sufficient range. Artifacts related to the tDCS device can also introduce external noise. Such effects may potentially be accounted for by the use of a phantom head so as to identify potential artifacts introduced by the tDCS device [86]. Recent research on the integration of tDCS and EEG has also evidenced that tDCS during EEG can produce local changes in skin impedance around the site of stimulation electrodes [87]. This, in turn, may significantly alter the amplitude of EEG data through improvement of impedance for the recording electrodes—which may be entirely unrelated to effects of tDCS on the brain and EEG signal therein. Continuous recording of impedance from recording electrodes may provide for methods to covary out artificial changes in impedance and recover interpretability of EEG data during tDCS. In addition, prior work also demonstrates that recording electrodes are able to detect a significant and variable heartbeat artifact around the site of stimulation electrodes [87]. This artifact is presumably produced by changes in local blood flow response under the stimulating electrodes and appears as a variable ~1 Hz signal within EEG data. Filtration/processing methods have been proposed as a possible method for addressing this artifact source. Nonetheless, EEG provides a promising method for integrated assessment of tDCS effects on the brain, but special considerations are required for production of interpretable data.

Functional effects may further be investigated using magnetic resonance imaging (MRI), which incorporates several methods including blood-oxygen-level-dependent (BOLD) fMRI [88, 89], arterial spin labeling [18], as well as proton and nonproton MR spectroscopy [90]. tDCS can be applied within the bore of the magnet, with the option of assessing effects either during "online" or "offline" stimulation, where subjects are removed from the scanner, have tDCS applied, and then are returned in the scanner. There are several methodological considerations in regards to the use of tDCS within the MR bore [91]. Firstly, due to the potential for premature drying out of the electrodes during concurrent scanning (which may last up to or over an hour), biocarbon electrodes should be attached to the participant using thick electrical conductance paste (e.g., Ten-20 paste), rather than saline soaked sponges or low viscosity electrode gel. Secondly, electrodes should be marked with oil capsules, so their position can be checked on the resulting images. It is also very important that electrodes are not in contact with the head coil, or sound attenuating headphones, to prevent electrode displacement and unexpected interactions between the stimulator and the scanner. Specially designed MRI-compatible (nonferrous or appropriately shielded) tDCS cables and electrodes passed

through the magnet suite waveguide and into the magnet bore are also necessary, with loops avoided and placed away from subjects to avoid the risk of eddy current induction and potential RF burns. Lastly, when analyzing data, consideration should also be given to the potential warping of the magnetic field due to the introduction of tDCS resulting in false positive findings.

14.10 Concluding Remarks

In this chapter, we deliver guidance for technically sound application of tDCS. Although the technique is seemingly simple and easy to apply, specific aspects must be taken into careful consideration to perform reproducible application and obtain reliable results. In the absence of careful consideration for the topics covered in this chapter, it is difficult, if not impossible, to interpret study findings, and difficult to facilitate attempts to replicate prior findings. In addition to other available technical guides to tDCS [92], this chapter will arm researchers and clinicians new to tDCS with insight into methodological considerations necessary for consistent application of tDCS in both clinical and research settings. For experienced researchers, this chapter provides a critical review of methodological aspects of tDCS important for consideration in attempts to replicate existing effects in the literature and important for inclusion in reports of tDCS effects. In summary, with careful consideration of the topics covered in this chapter, clinicians and researchers should be well equipped to perform consistent and reproducible tDCS in clinical and research settings.

References

1. Nitsche MA, Nitsche MA, Paulus W, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
2. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9:2257.
3. Horvath JC, Forte JD, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul [Internet]. 2015 [cited 2015 Jan 19];8(3):535–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25701175.
4. Woods AJ, Bryant V, Sacchetti D, Gervits F, Hamilton R. Effects of electrode drift in transcranial direct current stimulation. Brain Stimul. 2015;8(3):515–9.
5. Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche M. a. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol. 2013;591(Pt 7):1987–2000.
6. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293.
7. López-Alonso V, Cheeran B, Fernández-Del-Olmo M. Relationship between non-invasive brain stimulation-induced plasticity and capacity for motor learning. Brain Stimul [Internet]. 2015 [cited 2015 Sep 21]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26319358.
8. Fregni F, Fregni F, Boggio PS, Boggio PS, Nitsche M, Nitsche M, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res [Internet]. 2005;166(1):23–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15999258.
9. Hoy KE, Arnold SL, Emonson MRL, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res [Internet]. 2014 [cited 2015 Oct 13];155(1–3):96–100. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24703529.
10. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. [Internet]. J Physiol. 2000;527(Pt 3):633–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10990547%5Cn, http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2270099&tool=pmcentrez&rendertype=abstract.
11. Mosayebi Samani M, Agboada D, Jamil A, Kuo M-F, Nitsche MA. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. Cortex [Internet]. 2019 [cited 2020 Jun 25];119:350–61. Available from: https://www.sciencedirect.com/science/article/pii/S0010945219301844?via%3Dihub.
12. Nissim NR, O'Shea A, Indahlastari A, Telles R, Richards L, Porges E, et al. Effects of in-scanner bilateral frontal tDCS on functional connectivity of the working memory network in older adults. Front Aging Neurosci [Internet]. 2019 [cited 2020 Jun 25];11:51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30930766.

13. Nissim NR, O'Shea A, Indahlastari A, Kraft JN, von Mering O, Aksu S, et al. Effects of transcranial direct current stimulation paired with cognitive training on functional connectivity of the working memory network in older adults. Front Aging Neurosci [Internet]. 2019 [cited 2020 Jun 25];11:340. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31998111.
14. Monte-Silva K, Kuo M-F, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol. 2010;103:1735.
15. Carvalho S, Boggio PS, Gonçalves ÓF, Vigário AR, Faria M, Silva S, et al. Transcranial direct current stimulation based metaplasticity protocols in working memory. Brain Stimul [Internet]. 2014 [cited 2015 Jan 29];8(2):289–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25550147.
16. Indahlastari A, Albizu A, Forbes MA, Nissim NR, Kraft JN, Evangelista ND, et al. Modeling transcranial electrical stimulation in the aging brain. Brain Stimul [Internet]. 2020 [cited 2020 Jun 19];13:664–74. Available from: https://doi.org/10.1016/j.brs.2020.02.007.
17. Caulfield KA, Badran BW, DeVries WH, Summers PM, Kofmehl E, Li X, et al. Transcranial electrical stimulation motor threshold can estimate individualized tDCS dosage from reverse-calculation electric-field modeling. Brain Stimul [Internet]. 2020 [cited 2020 Jun 19];13(4):961–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32330607.
18. Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, et al. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. J Neurosci [Internet]. 2013;33(28):11425–31. Available from: http://www.jneurosci.org/content/33/28/11425.long.
19. Stagg CJ, Jayaram G, Pastor D, Kincses ZT, Matthews PM, Johansen-Berg H. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia [Internet]. 2011 [cited 2015 Aug 3];49(5):800–4. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3083512&tool=pmcentrez&rendertype=abstract.
20. Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp Brain Res [Internet]. 2014 [cited 2015 Sep 17];232(10):3345–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24992897.
21. Woods AJ, Hamilton RH, Kranjec A, Minhaus P, Bikson M, Yu J, et al. Space, time, and causality in the human brain. NeuroImage. 2014;92:285–97.
22. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul [Internet]. 2014 [cited 2015 Jan 29];8(2):253–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25465291.
23. Antal A, Terney D, Poreisz C, Paulus W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci [Internet]. 2007 [cited 2015 Oct 3];26(9):2687–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17970738.
24. Bortoletto M, Veniero D, Thut G, Miniussi C. The contribution of TMS–EEG coregistration in the exploration of the human cortical connectome. Neurosci Biobehav Rev [Internet]. 2014 [cited 2014 Dec 27];49C:114–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25541459.
25. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
26. Nikolin S, Martin D, Loo CK, Boonstra TW. Effects of TDCS dosage on working memory in healthy participants. Brain Stimul [Internet]. 2018 [cited 2020 Jun 24];11(3). Available from: https://pubmed.ncbi.nlm.nih.gov/29361442/.
27. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in - short stimulation - fade out approach to sham tDCS - reliable at 1 mA for naïve and experienced subjects, but not investigators. Brain Stimul. 2012;5(4):499–504.
28. O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, Moseley GL, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. PLoS One. 2012;7(10):e47514.
29. Guleyupoglu B, Febles N, Minhas P, Hahn C, Bikson M. Reduced discomfort during high-definition transcutaneous stimulation using 6% benzocaine. Front Neuroeng [Internet]. 2014 [cited 2015 Mar 27];7:28. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4093654&tool=pmcentrez&rendertype=abstract.
30. Palm U, Keeser D, Schiller C, Fintescu Z, Reisinger E, Padberg F, et al. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul. 2008;1:386–7.
31. Fonteneau C, Mondino M, Arns M, Baeken C, Bikson M, Brunoni AR, et al. Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul [Internet]. 2019 [cited 2020 Jun 25];12(3):668–73. Available from: https://www.sciencedirect.com/science/article/pii/S1935861X18313962?via%3Dihub.
32. Guarienti F, Caumo W, Shiozawa P, Cordeiro Q, Boggio PS, Benseñor IM, et al. Reducing transcranial direct current stimulation-induced Erythema with skin pretreatment: considerations for Sham-controlled clinical trials. Neuromodulation. 2014;18:261.
33. Woods AJ, Cohen R, Marsiske M, Alexander GE, Czaja SJ, Wu S. Augmenting cognitive training in older adults (the ACT study): design and methods of a phase III tDCS and cognitive training trial. Contemp Clin Trials. 2018;65:19.

34. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul [Internet]. 2009 [cited 2015 Jan 28];2(4):201–7, 207.e1. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2790295&tool=pmcentrez&rendertype=abstract.
35. Nikolin S, Loo CK, Bai S, Dokos S, Martin DM. Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. Neuroimage [Internet]. 2015 [cited 2015 Jul 17];117:11–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25987365.
36. Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Conf Proc IEEE Eng Med Biol Soc [Internet]. 2012;2012:859–62. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3641645&tool=pmcentrez&rendertype=abstract.
37. Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112.
38. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9(5):641.
39. Gálvez V, Alonzo A, Martin D, Mitchell PB, Sachdev P, Loo CK. Hypomania induction in a patient with Bipolar II disorder by transcranial direct current stimulation (tDCS). J ECT [Internet]. 2011 [cited 2015 Oct 9];27(3):256–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21206371.
40. First MB, Williams JBW, Spitzer RL, Gibbon M. Structured clinical interview for DSM-IV-TR Axis I disorders, clinical trials version (SCID-CT). New York: New York State Psychiatric Institute; 2007.
41. Sheehan D V, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry [Internet]. 1998 [cited 2014 Jul 10];59 Suppl 2:22–33;quiz 34–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9881538.
42. Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol [Internet]. 2001 [cited 2015 Oct 13];112(4):720. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11332408.
43. Roncero C, Mardigyan V, Service E, Singerman J, Whittaker KC, Friedman M, et al. Investigation into the effect of transcranial direct current stimulation on cardiac pacemakers. Brain Stimul [Internet]. 2020 [cited 2020 Jun 24];13(1):89–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31481297.
44. Nitsche MA, Jaussi W, Liebetanz D, Lang N, Tergau F, Paulus W. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology [Internet]. 2004 [cited 2015 Oct 13];29(8):1573–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15199378.
45. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, Oliveira AC, Goulart AC, et al. The sertraline versus electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91.
46. Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur J Neurosci [Internet]. 2006 [cited 2015 Oct 13];23(6):1651–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16553629.
47. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the major depressive episode: findings from a naturalistic study. Eur Psychiatry. 2013;28(6):356–61.
48. Loo CK, Martin DM, Alonzo A, Gandevia S, Mitchell PB, Sachdev P. Avoiding skin burns with transcranial direct current stimulation: preliminary considerations. Int J Neuropsychopharmacol [Internet]. 2010 [cited 2015 Oct 13];14(03):425–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20923600.
49. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35(1):96–101.
50. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9.
51. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42:1791–800.
52. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol [Internet]. 2015 [cited 2015 Jul 18]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/25922128.
53. Merrill DR, Bikson M, Jefferys JGR. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods. 2005;141(2):171–98.
54. Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. J Neurosci Methods. 2010;190(2):188–97.
55. Minhas P, Datta A, Bikson M. Cutaneous perception during tDCS: role of electrode shape and sponge salinity. Clin Neurophysiol. 2011;122(4):637–8.

56. Kronberg G, Bikson M. Electrode assembly design for transcranial direct current stimulation: a FEM modeling study. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2012;2012:891–5.
57. Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Conf Proc IEEE Eng Med Biol Soc [Internet]. 2012;2012:859–62. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3641645&tool=pmcentrez&rendertype=abstract.
58. Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112.
59. Woods AJ, Bryant V, Sacchetti D, Gervits F, Hamilton R. Effects of electrode drift in transcranial direct current stimulation. Brain Stimul [Internet]. 2014 [cited 2015 Mar 27]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/25583653.
60. Opitz A, Yeagle E, Thielscher A, Schroeder C, Mehta AD, Milham MP. On the importance of precise electrode placement for targeted transcranial electric stimulation. Neuroimage [Internet]. 2018 [cited 2019 Jan 22];181:560–7. Available from: https://www.sciencedirect.com/science/article/pii/S1053811918306426.
61. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl [Internet]. 1999 [cited 2015 Apr 2];52:3–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10590970.
62. Oostenveld R, Praamstra P. The five percent electrode system for high-resolution EEG and ERP measurements. Clin Neurophysiol [Internet]. 2001 [cited 2015 Apr 17];112(4):713–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11275545.
63. Seibt O, Brunoni AR, Huang Y, Bikson M. The Pursuit of DLPFC: Non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic Transcranial Direct Current Stimulation (tDCS). Brain Stimul [Internet]. Jan [cited 2015 Jul 24];8(3):590–602. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25862601.
64. Indahlastari A, Albizu A, Nissim NR, Traeger KR, O'Shea A, Woods AJ. Methods to monitor accurate and consistent electrode placements in conventional transcranial electrical stimulation. Brain Stimul [Internet]. 2019 [cited 2020 Jun 19];12(2):267–74. Available from: https://www.sciencedirect.com/science/article/pii/S1935861X18303644?via%3Dihub.
65. Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. Front Syst Neurosci [Internet]. 2015;9(March):26. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4362220&tool=pmcentrez&rendertype=abstract.
66. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord [Internet]. 2019 1 [cited 2020 Jun 24];252:475–83. Available from: https://www.sciencedirect.com/science/article/pii/S0165032718318329?via%3Dihub.
67. Bikson M, Paneri B, Mourdoukoutas A, Esmaeilpour Z, Badran BW, Azzam R, et al. Limited output transcranial electrical stimulation (LOTES-2017): engineering principles, regulatory statutes, and industry standards for wellness, over-the-counter, or prescription devices with low risk. Brain Stimul. 2017;11:134.
68. Agnew WF, McCreery DB. Considerations for safety in the use of extracranial stimulation for motor evoked potentials. Neurosurgery. 1987;20(1):143–7.
69. Bronstein JM, Tagliati M, McIntyre C, Chen R, Cheung T, Hargreaves EL, et al. The rationale driving the evolution of deep brain stimulation to constant-current devices. Neuromodulation. 2015;18(2):85–9.
70. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14(8):1133–45.
71. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9:641.
72. Durand S, Fromy B, Bouyé P, Saumet JL, Abraham P. Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. J Physiol. 2002;540(Pt 1):261–9.
73. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol [Internet]. 2003 [cited 2015 Oct 13];114(11):2220–2; author reply 2222–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14580622.
74. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899–901.
75. Ekici B. Transcranial direcet current stimulation-induced seizure: analysis of a case. Clin EEG Neurosci [Internet]. 2015 [cited 2015 Oct 15];46(2):169–169. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25869110.
76. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry [Internet]. 1964 [cited 2015 Oct 15];110:768–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14211693.
77. Parazzini M, Rossi E, Rossi L, Priori A, Ravazzani P. Evaluation of the current density in the brainstem during transcranial direct current stimulation with extra-cephalic reference electrode. Clin Neurophysiol [Internet]. 2013 [cited 2015 Jul 24];124(5):1039–

40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23084663.
78. Parazzini M, Rossi E, Rossi L, Priori A, Ravazzani P. Numerical estimation of the current density in the heart during transcranial direct current stimulation. Brain Stimul [Internet]. 2013 [cited 2015 Jul 24];6(3):457–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22704793.
79. Vandermeeren Y, Jamart J, Ossemann M. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci [Internet]. 2010 [cited 2015 Oct 13];11:38. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2844382&tool=pmcentrez&rendertype=abstract.
80. Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul [Internet]. 2010 [cited 2015 Oct 13];3(1):58–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20633432.
81. Loo CK, Martin DM, Alonzo A, Gandevia S, Mitchell PB, Sachdev P. Avoiding skin burns with transcranial direct current stimulation: preliminary considerations. Int J Neuropsychopharmacol [Internet]. 2010 [cited 2015 Oct 13];14(03):425–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20923600.
82. Bikson M, Brunoni AR, Charvet LE, Clark VP, Cohen LG, Deng Z-D, et al. Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul. 2018;11:465.
83. Martin DM, Alonzo A, Ho K-A, Player M, Mitchell PB, Sachdev P, et al. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J Affect Disord [Internet]. 2013 [cited 2015 Oct 5];144(3):274–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23146197.
84. Ho K-A, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, et al. The effect of Transcranial Direct Current Stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. Brain Stimul [Internet]. 2015 [cited 2015 Sep 9]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/26350410.
85. Berryhill ME, Martin D. Cognitive effects of transcranial direct current stimulation in healthy and clinical populations. J ECT [Internet]. 2018 [cited 2020 Jun 24];34(3):e25–35. Available from: http://journals.lww.com/00124509-201809000-00010.
86. Veniero D, Bortoletto M, Miniussi C. On the challenge of measuring direct cortical reactivity by TMS-EEG. Brain Stimul [Internet]. Jan [cited 2015 Feb 20];7(5):759–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24974077.
87. Gebodh N, Esmaeilpour Z, Adair D, Chelette K, Dmochowski J, Woods AJ, et al. Inherent physiological artifacts in EEG during tDCS. Neuroimage [Internet]. 2019 [cited 2018 Dec 9];185:408–24. Available from: https://www.sciencedirect.com/science/article/pii/S1053811918319840.
88. Baudewig J, Siebner HR, Bestmann S, Tergau F, Tings T, Paulus W, et al. Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). Neuroreport. 2001;12(16):3543–8.
89. Woods AJ, Hamilton RH, Kranjec A, Minhaus P, Bikson M, Yu J, et al. Space, time, and causality in the human brain. NeuroImage. 2014;92:285–97.
90. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist. 2011;17(1):37–53.
91. Esmaeilpour Z, Shereen AD, Ghobadi-Azbari P, Datta A, Woods AJ, Ironside M, et al. Methodology for tDCS integration with fMRI. Hum Brain Mapp [Internet]. 2020 [cited 2020 Jun 19];41(7):1950–67. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.24908.
92. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127(2):1031–48.

Part III

tDCS in the Life Cycle

tDCS in Child and Adolescent Psychiatry

15

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15.1 Introduction

Since the introduction of tDCS in its modern form in the last two decades, it has been exponentially applied in humans for studying and modifying brain physiology that underlies cognition as well as for improving symptoms in clinical populations that suffer from plasticity-related symptoms/deficits. The number of currently available studies in children and adolescents is still limited compared to adults and according to a review of tDCS studies conducted until 2015, less than 2% of subjects who underwent tDCS interventions were under 18 years of age [1]. In the last couple of years, however, tDCS has been increasingly used in children and adolescents, which warrants specific attention to its application in the developing population. What makes the use of tDCS worth further investigation in these populations is the developmental aspect of brain physiology. The brain undergoes pervasive neuronal changes during development. While this makes the brain more permeable to neuroplastic changes and thus could be potentially an advantageous feature especially in clinical pediatric populations, it raises safety and ethical considerations concerning stimulation dosage.

Standard and safe application of tDCS in the developing population, especially children and adolescents, requires a comprehensive and updated overview of the currently available studies. In this chapter, we attempt to approach this by first providing a conceptual overview of the underlying physiological mechanisms of tDCS effects on the brain, considering developmental aspects. Next and in the major section of this chapter, we discuss the findings of tDCS studies conducted to date in child and adolescent psychiatric disorders in line with the DSM-5 organizational structure of disorders to *internalizing* and *externalizing* categories. Importantly, we also discuss tDCS stimulation parameters from a developmental perspective highlighting the need to

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adapt stimulation protocols to the developmental age. In the final section of this chapter, we discuss other promising but understudied approaches of transcranial electrical stimulation that might be promising in the developing population. Safety aspects of tDCS use in children and adolescents are exclusively covered in Chap. 38 of this book.

15.2 Cortical Excitability and Neuroplasticity in the Developing Brain

Cortical excitability and neuroplasticity are two central concepts that have been increasingly mentioned in noninvasive brain stimulation (NIBS) research, including tDCS studies over the past two decades. The *acute* and *longer-lasting* effects induced by tDCS are linked to these concepts. Cortical excitability refers to responsiveness and response selectivity of cortical neurons to an input processed by the brain and is, therefore, a fundamental aspect of human brain functioning and cognition. Glutamate-mediated cortical facilitation and GABA-mediated cortical inhibition are major aspects of neuronal excitability and thereby synaptic plasticity [2, 3]. Neuroplasticity is an intrinsic property of the nervous system that allows an individual to adapt to a changing environment through strengthening, weakening, pruning, or adding of synaptic connections. The latter is specifically important for learning and memory formation, including during development [4, 5]. The therapeutic effects of NIBS techniques, including tDCS, rely on these basic physiological mechanisms of the human brain [6, 7] whose functionality differs across developmental stages [8]. It is, therefore, essential to understand these mechanisms in the developing brain and design and adapt stimulation protocols in children and adolescents accordingly.

Our knowledge about cortical excitability and neuroplasticity in the developing brain mostly comes from preclinical research in animal models and a limited number of physiological studies in children. Physiological studies in immature rodent brains show that *N*-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, which are important units for brain neuroplasticity, and involved in tDCS effects [9, 10], are more sensitive in early development, enhancing the effects of excitatory neurotransmitters (e.g., glutamate) in the developing brain [11, 12]. This developmental overweight of cortical excitation can make the immature brain vulnerable to NMDA receptor overstimulation [11] and can affect the brain potential for neuroplasticity induction as well. Cortical excitability in the brain depends on the balance between both excitatory and inhibitory processes. GABA is the major inhibitory neurotransmitter in the brain and involved in the observed tDCS after-effects too [6, 13]. The GABAergic inhibitory system reaches its full functionality in the adult brain and is normally compromised in the developing brain [14, 15]. TMS studies in children, in this line, show a low level of GABA-mediated intracortical inhibition in the motor cortex [16].

Neuroplasticity of the brain depends on long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength, which can be induced by tDCS [7]. Synaptic plasticity in the developing brain has a heterogeneous pattern, but in general, it seems more malleable than the adult brain. For example, synapses are produced at a rapid rate in the postnatal period, which provides an excess of synapses to be selected by external demands of the environment, and reach a density that is twice of that of the adult brain by the age of 2 years, and then is reduced to the adult level until early adolescence [8]. This enhanced plasticity in the developing brain allows it to be influenced more strongly by environmental experience and external modulation [8, 17]. Synaptic LTP- and LTD-like plasticity have not been studied systematically across pediatric ages in humans, but preclinical animal studies deliver valuable information. It has been shown that LTP and LTD are age dependent [18], but the results of available studies are somewhat heterogeneous. It has been reported that LTP induction is facilitated in the visual cortex and hippocampus of adult mice, compared to 4–5-week mice (4–11 years in humans) [19]. In contrast, hippocampal LTD induction was shown to be enhanced and requires a lower threshold in immature rats compared to older ones [20]. While these studies compared LTP/

LTD in immature versus adult animal brains in general, there are critical or "sensitive" periods during development of the brain, in which both LTP and LTD induction are facilitated [21, 22]. These critical developmental changes of neuroplastic responses in the developing brain are in line with the observation that the developing brain is characterized by periods, where the effects of interventions affecting the brain are unusually strong [23] and thus should be considered in stimulation protocols aimed to affect the developing brain.

In sum, cortical excitability, and its underlying neurotransmitter systems (glutamate-related facilitation, GABAergic-related inhibition), which are fundamental aspects of behavior and cognition, differ in the developing, as compared to the adult brain. Findings from animal studies suggest that the brain is prone to higher facilitation and lower inhibition in the developing period [14]. Furthermore, induction of neuroplasticity (LTP/LTD), as another core mechanism underlying learning and cognition, differs in the developing, as compared to the adult brain, and specific differences might depend on sensitive periods of the developing brain. The effects of tDCS on behavior and cognition are achieved via its modulatory effects on cortical excitability and neuroplasticity, and these developmental differences in brain physiology can affect tDCS effects. It is therefore important to consider that stimulation parameters from adult studies cannot be transferred one to one to children and adolescents. The amount of neurophysiological studies (in both, animals, and humans) exploring neurophysiological aspects of tDCS effects in children and adolescents is still limited at present but required for the development of safe and effective NIBS-based therapeutic interventions.

15.3 Physiology of tDCS—The Developmental Perspective

The potential of tDCS in effectively modulating a wide range of clinical and cognitive symptoms and functions depends on its underlying physiological mechanism, the modulation of cortical excitability. Modulation of cortical excitability with tDCS can induce both primary acute effects and secondary longer-lasting neoplastic effects. The primary effects of tDCS during stimulation are polarity-dependent shifts in the resting membrane potential of neurons [24]. In standard protocols, anodal stimulation is assumed to induce its excitability-enhancing effects due to depolarization of the membrane potential of the soma and basal dendrite of respective neurons, while cathodal stimulation, which generates a negative current flow pointing outward from the cortex, results in an inhibitory effect due to hyperpolarization respective neuronal compartments [25]. Acute effects of tDCS have been confirmed in both animal [26] and human studies where polarity-dependent changes of cortical excitability are monitored via motor-evoked potentials (MEPs) generated by transcranial magnetic stimulation [24, 27]. Pharmacological studies further confirmed that these acute effects of tDCS are likely the result of membrane potential polarization, since administration of voltage-dependent calcium and sodium channel blockers abolished anodal tDCS-induced excitability changes, while modulation of NMDA and GABA receptor activity was without effects [9].

The primary effects of tDCS can turn into longer-lasting neuroplastic effects in the central nervous system if the stimulation duration is sufficiently long [28–30]. Physiological studies in humans based on the motor cortex model have shown that tDCS can induce after-effects in the range of early-phase LTP- and LTD-like plasticity (after-effects lasting for 60–90 min following stimulation) [29, 30]. Pharmacological studies revealed an abolishment of these after-effects by NMDA receptor block, and a prolongation of LTP-like plasticity induced by anodal tDCS under an NMDA receptor agonist, suggesting that these after-effects depend on the glutamatergic system [10, 31]. GABA is another major neurotransmitter relevant for plasticity which is also involved in tDCS-induced plasticity. Results of a magnetic resonance spectroscopy (MRS) study showed that GABA is reduced by anodal and cathodal tDCS, which might gate glutamatergic plasticity [32].

Taken together, the modulatory effect of tDCS on cortical excitability and plasticity, which is the suggested mechanism for its pro-cognitive and symptom-improving effects, depends on a complex interaction of glutamate-related cortical facilitation, GABA-dependent cortical inhibition, and LTP/D-like plasticity. Importantly, the activity of respective transmitters and receptors differ in developing and adult brains. The concentration of synaptic glutamate concentration, calcium influx, and AMPA receptor permeability is higher in the immature rat brain, implicating that the brain is overexcitable in the developmental stage as compared to the adult brain [14]. Furthermore, the concentration of GABA and its tDCS-dependent modulation in the developing brain might differ from the adult brain. A recent tDCS study using MRS in children showed that neither conventional nor high-definition (using a smaller electrode size) stimulation protocols changed GABA concentration in the sensorimotor cortex after 5 consecutive days anodal tDCS over the right motor cortex applied concurrently with a motor task [33]. Although in this study the concentration of GABA was not examined during stimulation, which could at least partially explain the different results, as compared to a related study in humans (see above), the observed effect could also be related to the delayed maturation of the GABAergic system in the developing brain [14]. These physiological differences between adult and developing brains highlights (1) the need for further investigations of acute and neuroplastic effects of tDCS on the developing brain physiology, and (2) the importance to systematically explore the specific impact of stimulation parameters on tDCS after-effects, which may not be directly transferrable from adult studies. In this respect, physiological studies in children have shown a "paradoxical excitatory" effect of cathodal stimulation with 1 mA on MEP amplitudes, which was associated with a suppressed inhibitory TMS-EEG-generated N100 amplitude component [34, 35]. These results differ from the typical MEP changes in adults following identical protocols. Interestingly, cathodal tDCS with 0.5 mA intensity, which has no effects in adults [36], resulted in LTD-like effects in the same group of children, suggesting that stimulation parameter-dependent tDCS effects differ in children compared to adults. This topic is discussed in more detail from a developmental perspective later in this chapter.

15.4 Overview of tDCS Studies in Child and Adolescent Psychiatry

In this section, we provide an overview of the available tDCS studies conducted in child and adolescent psychiatric populations to date. We present the disorders in two broad categories of "*neuropsychiatric disorders*" and "*neurodevelopmental disorders.*" For each category, we discuss the disorders according to the new organizational structure introduced in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DMS-5), which is based on a model of internalization-externalization [37] that has gained increasing support over the last years [38].

15.4.1 Child and Adolescent Neuropsychiatric Disorders

According to the DSM-5 organizational structure, psychiatric disorders of children and adolescents are organized in the *internalization-externalization* structure. *Internalizing* disorders include schizophrenia spectrum disorders, mood disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma, and stress-related disorders, and feeding and eating disorders. *Externalizing* disorders include disruptive, impulse control, and conduct disorders. Here we provide an overview of those disorders that have been examined with tDCS interventions in child and adolescent populations so far and summarize details of each study in Table 15.1. We limited the scope of this section

Table 15.1 Summary of available tDCS studies conducted in child and adolescent psychiatry (neuropsychiatric disorders, neurodevelopmental disorders)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
Neuropsychiatric disorders											
Schizophrenia spectrum											
1	Mattai et al. (2011)	RCT double blind (sham controlled)	13	15.4 ± 2.21 [10–17]	(1) Bilateral DLPFC (F3) (2) bilateral STG (T3,T4)	Forearms /5 × 5 cm	2 mA	10 × 20 min (daily[a])	Anodal	tDCS side effects	No significant difference in reported adverse effects. No change in mood, mental status, MRI, EEG, ECG
Eating disorder											
1	Khedr et al. (2014)[b]	Open label (no control)	7	NR [16–39]	Left DLPFC (F3)	Right arm/5 × 5 cm	2 mA	10 × 20 min (daily)	Anodal	Eating attitude and behavior	Improved eating attitude, behavior, and depression state after tDCS and for up to 1 month post stimulation
Anxiety and OCD symptoms											
1	Francis et al. (2020)	Case report, randomized double blind (sham controlled)	Twins [ASD, ADHD, OCD]	15 years old	Right inferior frontal gyrus (F8)	Fp1/NR	1 mA	10 × two times daily tDCS (13 min) with 40 min interval	Anodal	Compulsivity, OCD symptoms, attention, hyperactivity	Compulsivity scores (based on parent report) and OCD symptoms decreased in the twin under active treatment (tDCS+cognitive training). No changes in ADHD symptoms

(continued)

Table 15.1 (continued)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
Alcohol/substance use disorders											
1	Khayyer et al. (2019)	Case report (sham controlled)	1	18 years old	Left motor area (C3)	Fp2/10.5 cm^2	1.5	12 × 20 min (twice weekly) with MBPR	Anodal	Nicotine dependence, aggression, stress, craving, EEG	Reduction in cigarette consumption, craving, stress, and anxiety, alpha and beta bands after the intervention up to 3-month follow-up
Neurodevelopmental disorders (internalizing)											
Learning disorder—dyslexia											
1	Costanzo et al. (2016a)	RCT double blind cross over (sham controlled)	19	13.7 ± 2.4 [10–17]	Left parietotemporal (mid P7-TP7)	Right parietotemporal /5 × 5 cm	1 mA	20 min (3 single sessions)	Anodal/ cathodal	Reading abilities	Improved accuracy in text reading after anodal left cathodal right protocol. Decreased accuracy after cathodal left anodal right
2	Costanzo et al. (2016b)	RCT double blind (sham controlled)	18	13.2 ± 2.6 [10–17]	Left parietotemporal (mid P7-TP7)	Right parietotemporal /5 × 5 cm	1 mA	18 × 20 min	Anodal	Reading abilities	Reduced reading errors and increased reading speed after active tDCS vs. sham up to 1 month
3	Costanzo et al. (2019)	RCT double blind (sham controlled)	26	13.6 ± 2.4 [10–17]	Left parietotemporal (mid P7-TP7)	Right parietotemporal /5 × 5 cm	1 mA	18 × 20 min	Anodal	Reading abilities	Improved nonword and low-frequency word reading after active tDCS vs. sham up to 6 months
4	Rios et al. (2018)	Pre/posttest (baseline control, no sham)	12	12.5 ± 3.18 [8–17]	Left STG (between T3, T4)	Fp2/7 × 5 cm	2 mA	10 × 30 min (daily)	Anodal	Reading performance tasks	Significant increase in correct answers for nonwords and text tasks

5	Rahimi et al. (2019a)	RCT single blind (sham controlled)	17	10.35 ± 1.36 [9–12]	(1) Bilateral STG (T7, T8) (2) left STG (T3, T4)	Right shoulder /5 × 5 cm	1 mA	20 min (single session)	Anodal	Auditory processing and ERP correlates	Improved visual attention processing in active tDCS vs. sham
6	Lazzaro et al. (2021)	RCT single blind (no sham control)	10	13.89 ± 2.4 [10–16]	(1) Left temporo-parietal region (2) Right temporo-parietal region	(1) Right temporo-parietal region (2) Left temporo-parietal region /5 × 5 cm	1 mA	20 min (single session)	Anodal/ cathodal	Reading abilities, visuo-spatial working memory and attention	Left anodal-right cathodal tDCS on temporoparietal improved text accuracy, word recognition speed, motion perception, and modified attentional focusing
7	Moslemi et al. (2021)	RCT single blind parallel group (sham controlled)	24	NR [8–10]	Left DLPFC (F3)	Right supraorbital / 5 × 5 cm	1.5 mA	15 × 20 min (daily)	Anodal	Reading abilities, working memory, attention	Visual working memory and attention significantly improved in the active stimulation group
Learning disorders-specific learning disorders											
1	Rahimi et al. (2019b)	RCT single blind (sham controlled)	45 (tDCS group = 15)	Primary school age 2–5 grade [7–10]	Left DLPFC (F3)	NR/5 × 5 cm	1.5 mA	10 × 20 min (daily)	Anodal	Visual sustained attention	Improved visual attention processing in active tDCS vs. sham
Learning disorders—dyscalculia											
1	Arjmandnia et al. (2016)	RCT single blind (sham controlled)	10	23.1 ± 3.7 [7–14]	Left DLPFC (F3)	NR/5 × 5 cm	1 mA	10 × 10 min (daily)	Anodal	Working memory	Improved working memory in active tDCS vs. sham
Learning disorders—language disorder											
1	Andrade et al. (2014)[c]	Open label (no control)	14	[5–12]	Broca's area (F5)	Fp2/7 × 5 cm	2 mA	10 × 30 min (daily)	Anodal	Feasibility of tDCS	Feasibility and tolerability of tDCS in all patients

(continued)

Table 15.1 (continued)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
Neurodevelopmental disorders (externalizing)											
Autism spectrum disorder											
1	Schneider & Hopp (2011)[d]	Open label (no control)	10	9.8 ± 4.4 [6–21]	Left DLPFC (F3)	Fp2/5 × 5 cm	2 mA	30 min (single session)	Anodal	Syntax acquisition	Improved syntax acquisition and vocabulary scores after tDCS
2	Amatachaya et al. (2014)	RCT double blind, cross over (sham controlled)	20	6.4 ± 1.1 [5–8]	Left DLPFC (F3)	Right shoulder /7 × 5 cm	1 mA	5 × 20 min (daily)	Anodal	Symptoms (psychosocial, cognition)	Improved social function, behavioral, sensory/ cognitive, ATEC scores) after active tDCS vs. sham
3	Amatachaya et al. (2015)	RCT double blind, cross over (sham controlled)	20	6.4 ± 1.1 [5–8]	Left DLPFC (F3)	Right shoulder /7 × 5 cm	1 mA	20 min (single session)	Anodal	Symptoms (psychosocial, cognition), EEG correlates	Improved social behavior and behavioral ATEC scores after active tDCS associated with increased alpha frequency
4	Costanzo et al. (2015)	Case report	1	14	Anodal left cathodal right DLPFC (F3-F4)	F4/5 × 5 cm	1 mA	28 × 20 min (daily)	Anodal/ cathodal	Catatonic symptoms	Reduced catatonia symptoms, recovery of eating and drinking, improvement maintained for up to 1 month
5	D'Urso et al. (2015)[b]	Open label (no control)	12	[18–26]	Left DLPFC (F3)	Right arm/40, 5 × 5 cm	1.5 mA	10 × 20 min (daily)	Cathodal	Overall functioning	Reduced irritability and aggression, improved social withdrawal and hyperactivity after tDCS

6	Gómez et al. (2017)	Nonrandomized, single blind (sham controlled)	24	12.2 [NR]	Left DLPFC (F3)	Right arm/NR	1 mA	20 × 20 min (daily)	Cathodal	Connectivity, ERP components, behavioral and social functioning	Increased functional connectivity. Shorter P300 latency, but no change in amplitude. Behavioral and social improvement for up to 6 months
7	Toscano et al. (2019)[e]	RCT (sham controlled)	16	NR [9–14]	Left DLPFC (F3)	Right cerebellum/NR	(1)1 mA age < 10 (2)1.5 mA age > 11	20 × 20 min (daily)	Anodal	Behavioral symptoms, treatment evaluation	Significant decrease in the behavior and treatment evaluation checklist in the active tDCS vs sham condition
8	Mahmoodifar & Sotoodeh (2020)	RCT (sham controlled)	18	10.17 ± 2.75 [6.14]	Left motor cortex (M1)	Fp2/7 × 5 cm	1.5 mA	10 × 20 min + motor training	Anodal	Motor skill learning, movement balance	Both anodal/sham tDCS combined with motor training improved balance. Active tDCS+training showed a significantly higher improvement compared to sham+training
9	Hadoush et al. (2020)	RCT double blind (sham controlled)	50	7.8 ± 2.5 [4–15]	Left and right frontocentral (FC1-FC2)	Left and right supraorbital (Fp1-Fp2) /8 cm^2	1 mA per electrode	10 × 20 min (daily)	Bilateral anodal	Symptoms (by ATEC)	Bilateral anodal tDCS significantly improved sociability, behavior, health, and physical conditions measured by ATEC with no reported side effects

(continued)

Table 15.1 (continued)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
10	Salehinejad et al. (2021)	RCT (sham controlled)	14	10.7 ± 1.9	(1) Right temporoparietal junction (CP6) / (2) vmPFC (Fpz)	Left shoulder / 5 × 5 cm	1 mA	20 min (single session)	Anodal	Theory of Mind Test (TOMT)	Activation of the vmPFC with anodal tDCS significantly improved ToM in children with ASD compared with both, rTPJ tDCS, and sham stimulation
ADHD											
1	Prehn-Kristensen et al. (2014)	RCT double blind (sham controlled)	12	12 ± 1.4, [10–14]	1. Left DLPFC (F3) 2. Right DLPFC (F4)	Lateral mastoid 0.503 cm^2 (Ag/AgCl electrodes)	(0–250 μA 0.75 Hz)	5 × 5 min (single session)	Anodal	Declarative memory	Enhanced memory consolidation and retrieval following active tDCS vs. sham tDCS
2	Munz et al. (2015)	RCT double blind (sham controlled)	14	12.3 ± 1.39, [10–14]	(1) Left DLPFC (F3) (2) Right DLPFC (F4)	Lateral mastoid 0.503 cm^2 (Ag/AgCl electrodes)	(0–250 μA 0.75 Hz)	5 × 5 min (single session)	Anodal	Response inhibition	Faster response time after active vs. sham tDCS in Go/No-Go task. No effect on accuracy
3	Soltaninejad et al. (2015a)	RCT single blind (sham controlled)	20	16.40 ± 1.09 [15–17]	Left DLPFC (F3)	Fp2/7 × 5 cm	1.5 mA	15 min (single session)	Anodal/ cathodal	Response inhibition, selective attention	Cathodal F3, but not anodal F3, improved response inhibition. No effect on selective attention
4	Soltaninejad et al. (2015b)	RCT single blind (sham controlled)	20	16.40 ± 1.09 [15–17]	Right inferior frontal gyrus (F8)	Fp1/7 × 5 cm	1.5 mA	15 min (single session)	Anodal	Response inhibition, selective attention	No effect on response inhibition (No-Go) and selective attention. Improved execution (Go) accuracy in active vs sham tDCS

5	Bandeira et al. (2016)	Open label (no control)	9	11.1 ± 2.08 [6–16]	Left DLPFC (F3)	Fp2/7 × 5 cm	2 mA	5 × 30 min (daily)	Anodal	Symptoms, attention, working memory, response inhibition	Reduced errors in selective attention, shorter RT and reduced switching errors, slight clinical improvement after intervention
6	Breitling et al., (2016)	RCT parallel group single blind (sham controlled)	21	14.33 [NR]	Right inferior frontal gyrus (F8)	Left mastoid	1 mA	20 min (single session)	Anodal/ cathodal	Response inhibition, interference control	No effect on interference control after anodal/ cathodal tDCS, diminished commission errors in the ADHD group vs healthy controls after anodal tDCS
7	Nejati et al. (2017)(Exp 1)	RCT double blind (sham controlled)	15	10 ± 2.3 [8–15]	Bilateral DLPFC (anodal left)	Right DLPFC (F4)/5 × 5 cm	1 mA	15 min (single session)	Anodal	Response inhibition, working memory, executive functions	Improved executive control functions (working memory, interference control) but not response inhibition and cognitive flexibility after active vs. sham
8	Nejati et al. (2017)(Exp 2)	RCT double blind (sham controlled)	10	9 ± 1.8 [7–12]	Left DLPFC (F3)	Fp2/5 × 5 cm	1 mA	15 min (single session)	Anodal/ cathodal	Response inhibition, working memory, cognitive flexibility	Improved working memory after anodal tDCS over F3, improved response inhibition after cathodal tDCS over F3, improved cognitive flexibility after both protocols vs. sham

(continued)

Table 15.1 (continued)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
9	Soff et al. (2017)	RCT double blind (sham controlled)	15	14.20 ± 1.2 [12–16]	Left DLPFC (F3)	Vertex (Cz)/7 × 5 cm	1 mA	5 × 20 min (daily)	Anodal	ADHD symptoms	Reduced inattention and hyperactivity symptoms in the active tDCS vs. sham condition
10	Sotnikova et al. (2017)	RCT double blind cross over (sham controlled)	13	14.33 ± 1.2 [12–16]	Left DLPFC (F3)	Vertex (Cz)/7 × 5 cm	1 mA	20 min (single session)	Anodal	Quantified behavior test	Reduced RT and variability, reduced accuracy and increased omission errors, increased connectivity in left DLPFC in the active tDCS vs. sham
11	Breitling et al. (2020)	RCT double blind (sham controlled)	14	13.3 ± 1.9 [10–16]	Right inferior frontal gyrus (F8)	1. Fp1/7 × 5 cm 2. 1 cm electrodes (HD)	1 mA conventional, 0.5 mA (4 × 1 montage)	20 min (single session)	Anodal	2-back working memory task	No effect of conventional or HD-tDCS on working memory. Higher responder rate for 4 × 1 (50%) than conventional (35%) tDCS. Higher N200 and P300 amplitudes after both protocols
12	Nejati et al. (2020)	RCT single blind (sham controlled)	20	8.60 ± 1.56	1. Left DLPFC (F3) 2. Right VMPFC (Fp2)	1. Right VMPFC (Fp2) 2. Left DLPFC (F3) /6 × 4 cm	1 mA	15 min (single session)	Anodal/ cathodal	Reward processing, risky decision-making	Anodal right VMPFC-cathodal left DLPFC reduced risky decision-making and delay discounting

13	Salehinejad et al. (2020)	RCT single blind (sham controlled)	17	9.33 ± 1.50	Right posterior parietal cortex (r-PPC) (P4)	Left shoulder /7 × 5 cm	1 mA	15 min (single session)	Anodal	Attentional functioning	Anodal r-PPC tDCS specifically improved attention orienting network but had a deteriorating effect on the top-down attentional control
14	Berger et al. (2021)	RCT single blind (sham controlled)	19	13.3 ± 1.9 [7–12]	Left DLPFC (F3)	Right supraorbital (Fp2) /	0.75 mA	5 × 20 min (daily)	Anodal	ADHD symptoms, Working memory, attentional performance	Bilateral DLPFC tRNS reduced ADHD rating-scale score and working memory from baseline compared to tDCS. tRNS effects was larger than tDCS
Tourette's syndrome and tic disorder											
1	Carvalho et al. (2015)	Case study	1	16	pre SMA	Right deltoid /5 × 5 cm, 10 × 10 cm	0.75 mA	5 × 20 min (daily)	Anodal	ADHD symptoms, Working memory, attentional performance	Anodal r-PPC tDCS specifically improved attention orienting network but had a deteriorating effect on the top-down attentional control

(continued)

#	Author	Design (control condition)	*N*	Mean age ± SD [age range]	Target electrode site	Return electrode/size	Intensity	Duration	Polarity	Measure	Outcome
2	Dyke et al. (2017)[b]	RCT double blind (sham controlled)	10	[16–33]	Pre-SMA	Fp2/7 × 5 cm	1 mA	20 min (single session)	Cathodal	Motor excitability, tics monitoring	Bilateral DLPFC tRNS reduced ADHD rating-scale score and working memory from baseline compared to tDCS. tRNS effects was larger than tDCS

Note: *tDCS* transcranial direct current stimulation, *SD* standard deviation, *RCT* randomized, controlled trials, *MBPR* Mindfulness-based relapse prevention, *DLPFC* dorsolateral prefrontal cortex, *VMPFC* ventromedial prefrontal cortex, *STG* superior temporal gyrus, *F3* left dorsolateral prefrontal cortex, *F4* right dorsolateral prefrontal cortex, *F5* Broca's area, *F8* right inferior frontal gyrus, *M1* left primary motor cortex, *Fp2* right supraorbital area, *P7* parietal-temporal region, *TP7* parietal-central region, *CP1/2* left and right frontocentral area, *pre-SMA* pre-supplementary motor area, *RCT* randomized controlled trial, *ERP* event-related potential, *ATEC* Autism Treatment Evaluation Checklist, *NR* not reported or available

[a]Daily refers to one tDCS session per day unless described otherwise

[b]samples of these studies include both adolescents (<21) and young adults [Khedr et al. (2014) = 4 of 7, D'Urso et al. (2015) = 9 of 12, Dyke et al. (2017) = 6 of 10]

[c]patients in this study included neurodevelopmental disorders including learning disorder, expressive language disorder, and autism spectrum disorder

[d]patients in this study had comorbid language disorders in addition to autism spectrum disorder

[e]findings of these works are based on proceeding reports

to neuropsychiatric disorders; neurological disorders and intellectual disabilities are not covered.

Internalizing Disorders

Schizophrenia Spectrum

Schizophrenia is one of the widely targeted neuropsychiatric populations in tDCS studies in the adult population. Due to the executive dysfunctions and frontal-prefrontal abnormalities in the pathophysiology of schizophrenia, tDCS has been applied in schizophrenic patients [39, 40]. In childhood-onset schizophrenia, however, only a very limited number of studies is available. In the only available tDCS study in childhood-onset schizophrenia, 12 children underwent repeated 2 mA of anodal tDCS (10 sessions, 20 min) (see Table 15.1) [41]. The study was designed to examine safety and tolerability of tDCS in the clinical pediatric population. No clinical/symptomatic decompensation or worsening of psychotic/cognitive symptoms were described due to tDCS.

In an animal study using a neurodevelopmental rodent model of schizophrenia, the efficacy of tDCS during adolescence for prevention of the development of positive symptoms and related neurobiological alterations of the disease was investigated [42]. This study showed that anodal tDCS over the prefrontal cortex during adolescence, prior to any overt schizophrenia-related behavioral abnormalities, successfully prevented the manifestation of sensorimotor gating deficits and abnormal rapid reversal. The results of this study provide supportive evidence for the application of tDCS during adolescence for prevention of schizophrenia symptoms, given that the onset of the disease is typically in early adulthood [43].

Mood Disorders

No studies have been published about the use of tDCS in child and adolescent depression. However, at present an ongoing, randomized, sham-controlled tDCS study investigates whether tDCS targeting the dorsolateral prefrontal cortex (DLPFC) can enhance the therapeutic effect of mindful breathing training (MBT) in adolescent depression. This study also aims to investigate the connectivity between the DLPFC with the amygdala and default mode network (DMN) circuits via electroencephalographic (EEG) and magnetic resonance imaging (MRI) (clinicaltrials.gov, NCT03897699; no results posted at this time).

Although studies of tDCS in adolescent depression are lacking, tDCS- and NIBS-based interventions might be promising considering the pathophysiology of adolescent depression [44] and the promising results from adult depression studies [45, 46]. Current interventions for adolescent depression (e.g., pharmacotherapy and psychotherapy) are not consistently effective [47, 48] with poor adherence [49, 50], which could be the case because these interventions might not target the relevant pathophysiology of adolescent depression in an ideal way [44]. Adolescent depression involves altered medial prefrontal cortical connectivity with brain regions involved in executive functioning, emotion regulation, attention, and reward processing [51, 52]. Accordingly, tDCS as a neuromodulatory intervention might be used to modulate and/or balance cortical activity in these regions and thus develop as a novel intervention for adolescent depression.

Eating Disorders

Only one tDCS study in adolescents is available for the treatment of anorexia nervosa. In this open-label study, 7 patients were recruited, including 4 adolescents, and patients received anodal tDCS (2 mA) for 25 minutes over the left dorsolateral prefrontal cortex once daily for 10 days [53]. TDCS significantly improved scores of Eating attitudes and behavior in 6 patients and the Beck Depression Inventory scores in all patients. Due to the very limited number of patients, and study design, these results should be interpreted with caution and warrant further investigation.

Anxiety Disorders, Obsessive-Compulsive and Related Disorders, Trauma, and Stress-Related Disorders

Recently, a case report was published about application of tDCS in two adolescent twins diagnosed with multiple neurodevelopmental disorders (autism, ADHD), anxiety states, and compulsive symptoms with an additional OCD

diagnosis in one of the twins. The authors investigated the impact of 10 sessions anodal tDCS over the right inferior frontal gyrus paired with cognitive training on compulsivity in a double-blind, between-subject, sham-controlled design (Table 15.1) [54]. One twin received ten sessions of active (1 mA) tDCS paired with cognitive training tasks over 1 week and the second twin received sham stimulation combined with the same tasks. Compulsive symptoms (measured by parent report, but not clinician-rated impulsivity) decreased in the twin that received active tDCS, and a significant reduction of OCD symptoms was observed as well. These preliminary findings suggest that tDCS might be useful for the treatment of compulsive symptoms in adolescents. Beyond this case report, no studies of tDCS in children and adolescents with OCD, anxiety, and stress-related disorders are available so far. Functional imaging studies on pediatric OCD patients indicate altered functional activation of affective and cognitive cortico-striatal-thalamic (CST) circuits, similar to those reported for adult OCD patients [55], which could be relevant targets for tDCS studies. Moreover, a recent systematic review showed that patients with early-onset OCD may not respond well to pharmacological interventions [56], indicating the need for alternative therapeutic approaches. Similar cortical regions (prefrontal and cingulate cortices), subcortical areas (e.g., amygdala), and brain networks (e.g., default mode, executive control, and salience networks), though with different activation patterns, are involved in the pathophysiology of anxiety and trauma-related disorders in both adults and children/adolescent populations [57, 58]. Based on promising results of NIBS application in these disorders in the adult population [59, 60], tDCS over respective target areas could be a promising intervention also in child and adolescent populations.

Externalizing Disorders

Disruptive, Impulse-Control, and Conduct Disorders

Disruptive, impulse-control, and conduct disorders include oppositional defiant disorder (ODD), conduct disorder (CD), pyromania, and alcohol-related and other substance use disorders (SUDs) according to the DSM-5 new classification [61]. So far, only one case study is available which reports positive effects of repeated anodal tDCS over the left DLPFC concurrent with mindfulness-based prevention treatment on smoking cessation in an 18-year-old adolescent [62]. The clinical assessment showed reduced nicotine dependence, aggression and stress, subjective craving, and cigarette consumption after the treatment for up to a 3-month follow-up (Table 15.1). Besides this case report, which leaves the question open if tDCS, the mindfulness training, or a combination of both interventions caused the clinical effects, no tDCS studies have been published in these disorders in children and adolescent populations, which is surprising. A high comorbidity rate, as well as shared brain activity alterations, are present in ODD/CD and attention-deficit hyperactive disorder (ADHD) [63, 64], which is the most-studied disorder of children and adolescents with respect to tDCS intervention [65, 66]. Furthermore, recent findings of functional neuroimaging studies show that these disorders show similar alterations of brain physiology that might benefit from neuromodulation interventions. Alterations of four major neurocognitive systems have been described in individuals with conduct problems (i.e., CD, ODD, SUD, or antisocial/impulsive behavior), including empathy (medial PFC, temporoparietal junction), acute response to stress and distress (amygdala, VMPFC), reinforcement-based decision-making, and response inhibition (prefrontal and cingulate cortices, inferior frontal gyrus) systems [67]. Application of tDCS over respective areas might thus be promising in these disorders but remains to be explored.

15.4.2 Neurodevelopmental Disorders

Internalizing Neurodevelopmental Disorders

Language and Learning Disorders

Most of the tDCS studies on learning disorders focus on dyslexia (7 of 10 studies). In the first

study conducted on dyslexia [68], the effect of single-session tDCS (1 mA, 20 min) was investigated on reading and reading-related skills of 19 children and adolescents. The authors compared the effects of three stimulation protocols (left anodal/right cathodal, right anodal/left cathodal, and sham stimulation) over the parietotemporal region (in the midway between P7/8 and TP7/8) in counterbalanced order, with a 24-hour or larger interval between sessions. They found a polarity-dependent effect of tDCS. Reading accuracy improved after left anodal/right cathodal stimulation (compared with baseline, sham, and right anodal/left cathodal tDCS), and errors increased after right anodal/left cathodal stimulation (compared with baseline, sham, and left anodal and right cathodal stimulation).

The next study was an extension of the previous one. In this study, the effect of *repeated* stimulation on enhancing reading abilities of children and adolescents with dyslexia was investigated [69]. 18 children and adolescents (aged 10–17 years) with dyslexia underwent 18 sessions of tDCS (3 sessions per week over 6 weeks) with the same protocol that yielded an performance-improving effect in the previous study (1 mA, 20 min, left anodal/right cathodal), and concurrent with cognitive training. The outcome measures for reading abilities were accuracy and speed in reading aloud low- and high-frequency word and nonword stimuli. The results show reduced low-frequency word reading errors and improved nonword reading time (speed) in the active tDCS groups, as compared to sham stimulation. These positive effects were stable for at least 1 month after the end of intervention. Using the same tDCS parameters, the same researchers investigated the long-lasting effects of the intervention in 26 children and adolescents with dyslexia (aged 10–17 years) in a double-blind, sham-controlled trial [70]. They replicated the findings of the previous study for a 6-month follow-up.

Another tDCS study investigated the impact of 5 consecutive once-daily sessions of 2 mA anodal tDCS on reading skills of 12 children and adolescents with dyslexia (12.5 years ±3.18, 8–17 years age range) [71]. In this study, the anodal electrode was placed over the left superior temporal gyrus (between T3 and T5) and the cathode was placed over the contralateral supraorbital area (5 × 7 cm^2). The finding from this study shows a significant increase in correct responses for nonword and word reading after transcranial direct current stimulation. Importantly, this was an open-label study without sham condition. Another study conducted in dyslexia investigated the effect of single-session tDCS (1 mA, 20 min) on auditory processing and its electrophysiological correlates in 17 children and adolescents (10.35 years ±1.36, 9–12 years age range) [72]. tDCS conditions were (1) anodal left/cathodal right superior temporal gyrus, (2) anodal left superior temporal gyrus/cathodal right shoulder, and (3) sham tDCS. Both active protocols significantly improved temporal information processing and its electrophysiological correlates (larger P1, P2, N1 components) in this patient population. Two recently published studies in 2021 also confirm improving effects of anodal tDCS over the left temporoparietal region [73] and left DLPFC [74] on both reading abilities and neuropsychological functioning (e.g., working memory, attention) of children with dyslexia (see Table 15.1).

In addition to dyslexia, a very limited number of studies conducted in children with other learning disabilities is available. A recent study compared the efficacy of tDCS and cognitive training to improve sustained attention in 45 children with specific learning disorders. The tDCS groups (N = 15) received 10 daily secessions of anodal tDCS over the left DLPFC (1.5 mA, 20 min) [75] and showed significantly improved visual attention processing following the intervention, as compared to the control group. In another study, the effect of 10 sessions of anodal tDCS over the left DLPFC (1 mA, 10 min) was investigated with respect to its effect on working memory in 10 children with dyscalculia (7–14 years old range) [76]. The active tDCS group showed improved working memory performance immediately following the intervention. No follow-up data are available for this study (Table 15.1).

In sum, available evidence suggests promising effects of tDCS in learning disorders, especially

developmental dyslexia. Nevertheless, randomized, clinical trials with long-term follow-up measurements are required to establish the clinical efficacy of this intervention. Based on current evidence, improving visuospatial attention and modulation of neural oscillations are suggested as novel potential targets for remediation in dyslexia [77]. Finally, for other DSM-5-based neurodevelopmental disorders of the internalizing spectrum (e.g., developmental arithmetic, intellectual disabilities, social communication disorders), tDCS has not been probed as a therapeutic intervention. These disorders have similar genetic risk factors, shared neural substrates, and similar clinical features as compared to syndromes in which an impact of tDCS has been shown [78], which encourages to explore tDCS as treatment option also in these disorders.

Externalizing Neurodevelopmental Disorders

The neurodevelopmental disorders most frequently studied with tDCS so far belong to the externalizing group according to the DSM-5 classification. Externalizing neurodevelopmental disorders include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), Tourette's and tic disorders, and developmental coordination disorder (DCD) [61]. ADHD is the most studied neurodevelopmental disorder with a rapidly increasing number of studies in the last couple of years [65, 66], and ASD is the second most studied neurodevelopmental disorder [79]. In contrast, there are very few or no published tDCS studies in Tourette's and tic disorders and DCD in child and adolescent populations. Details of the tDCS studies conducted in ADHD and ASD are summarized in Table 15.1. In what follows, we briefly discuss recent tDCS findings and potential applications of this technique in these disorders.

Autism Spectrum Disorder (ASD)

ASD is characterized by deficits in social communication (including verbal and nonverbal communication) and restricted, repetitive patterns of behavior [80]. ASD affects 1 out of 68 children in the USA, and <1% to 52% across outpatient and inpatient populations [81], imposing a significant burden on families and society. Increasing evidence for atypical brain structure and function [82], imbalanced cortical facilitation and inhibition [83], and impaired functional domains (e.g., language, social cognition, motor behavior) make NIBS a potential promising treatment strategy for this disorder. While application of repetitive TMS (r-TMS) in ASD has shown promising results [84], tDCS has been less frequently explored so far, but early findings are also encouraging. A recent review of studies ($N = 5$) published in 2018 suggests a potential usefulness of tDCS for treatment of ASD in children and adolescents, although evidence is sparse and studies have heterogeneous quality [79]. More studies became available during the last 2 years. We identified ten reports of tDCS application in children and adolescents with ASD up to May 2021, spanning from case reports and open-label trials to single- and double-blind randomized-controlled trials. Details of these reports are summarized in Table 15.1. Anodal tDCS over the left DLPFC (in 6 out of 10 studies) [85–90] and cathodal stimulation over the same region (in 2 out of 10 studies) [91, 92] are the most often applied protocols in ASD. Two recent studies also report improving effect of frontocerebellar tDCS on behavioral symptoms [87] and anodal stimulation over the primary motor cortex on motor skill training in children with ASD [93]. A recent tDCS study has also reported promising effect of tDCS over the right temporoparietal junction on improving theory of mind abilities in children with ASD [94]. All of these studies reported an improving effect of tDCS, and repeated daily sessions resulted in improved behavioral and social functioning for up to 1 [85] and 6 months [91] after the intervention. Hadoush et al. (2020) conducted a study in 50 children with ASD, the largest sample reported thus far, in a double-blind, parallel-group design and found a significant improving effect of bilateral anodal stimulation over the DLPFC on overall behavioral symptoms. A novel aspect of this study was the application of bilateral anodal stimulation over both left and right DLPFC, with a 4x1 electrode arrangement.

Polarity of stimulation (anodal vs. cathodal) of the respective target regions (e.g., left DLPFC) should be considered with respect to target symptoms, stimulation parameters (intensity, duration, and repetition rate), and the excitatory/inhibitory dysbalance in ASD. Cathodal stimulation of the left DLPFC was theoretically motivated to mitigate hyperactive behavior and restore inhibition [91, 92], while left DLPFC anodal stimulation was applied to compensate for left hemispheric hypoactivity. Nonetheless, the classical concept of anodal-excitatory/cathodal-inhibitory has been questioned by recent studies on the human motor cortex in both adults [95] and children. In this line, it has been shown that 1 mA cathodal stimulation, like 1 mA anodal stimulation, has an excitatory effect on motor cortical excitability in children and adolescents [34, 35]. The beneficial effect of cathodal tDCS over the left DLPFC reported in autism studies should thus be interpreted carefully with respect to mechanisms of action, as these stimulation protocols might indeed have an excitability-enhancing effect. Because of increasing evidence for an involvement of the cerebellum in autistic-like behavior [96], investigating the efficacy of cerebellar tDCS as a treatment option is worth to be investigated in the future. In conclusion, from a clinical standpoint, future studies should investigate long-term effects of tDCS on ASD symptom reduction and optimize intervention protocols including stimulation polarity and site in ASD patients.

ADHD

Since ADHD is fully covered in Chap. 28 of this handbook, here we only briefly discuss recent tDCS findings. ADHD is the disorder most-widely studied with respect to tDCS interventions in children and adolescents [66]. The hallmark symptoms of ADHD are inattention, hyperactivity/impulsivity [80], and executive dysfunctions [97, 98]. We found 14 tDCS studies conducted on ADHD patients in the developing age [99–111]. Cognitive deficits and executive dysfunctions were the primary targets in 11 of the studies, and one study specifically targeted clinical core symptoms. Details of these studies are summarized in Table 15.1. Overall, the results of these studies suggest partially improving effects of tDCS on cognitive deficits (response inhibition, working memory, attention, cognitive flexibility, reward processing) or clinical symptoms (e.g., inattention), but the clinical utility of tDCS in ADHD cannot yet be concluded and requires further investigation in larger sample sizes [65, 66]. Left and right DLPFC were the most often targeted regions, and anodal tDCS—the most often applied protocol—showed promising results. The promising, yet preliminary, findings of DLPFC tDCS in ADHD encourages the exploration of other stimulation parameters that might further enhance efficacy. Additional cortical regions (e.g., lateral vs. medial PFC, inferior frontal gyrus) involved in the pathophysiology of ADHD and specific symptoms, stimulation parameters (e.g., intensity, duration, polarity, and electrode size), and types of symptoms/deficits are potential determinants of tDCS efficacy in ADHD to be explored in the future.

Tourette's and Tic Disorders

The application of tDCS in children and adolescents with Tourette's and tic disorders is at a very early stage. The first publication was a case report that applied 10 daily sessions of cathodal tDCS over the pre-supplementary motor area (pre-SMA) in a 16-year-old boy with refractory and severe Tourette's syndrome [112]. Both motor and vocal tics were improved with a 41% decrease in tic severity immediately after the intervention and 39% at the 3- and 6-month follow-ups. Dyke and coworkers [113] conducted the only available randomized sham-controlled study of tDCS in adolescents and young adults with Tourette's syndrome. The sample included 10 participants, and 6 of them were adolescents (21 years old or younger, age range = 16–20.5). In this cross-over study, the effects of tDCS on the occurrence of tics and motor cortical excitability were investigated. Tic occurrence and motor cortex excitability were monitored before and after 20 min of cathodal tDCS (1 mA) over the pre-SMA. Tic impairment scores were significantly lower following cathodal tDCS compared to the sham stimulation, but motor cortical excitability (measured by single-pulse TMS of the motor cortex) did not significantly change. These preliminary findings are encouraging for the application

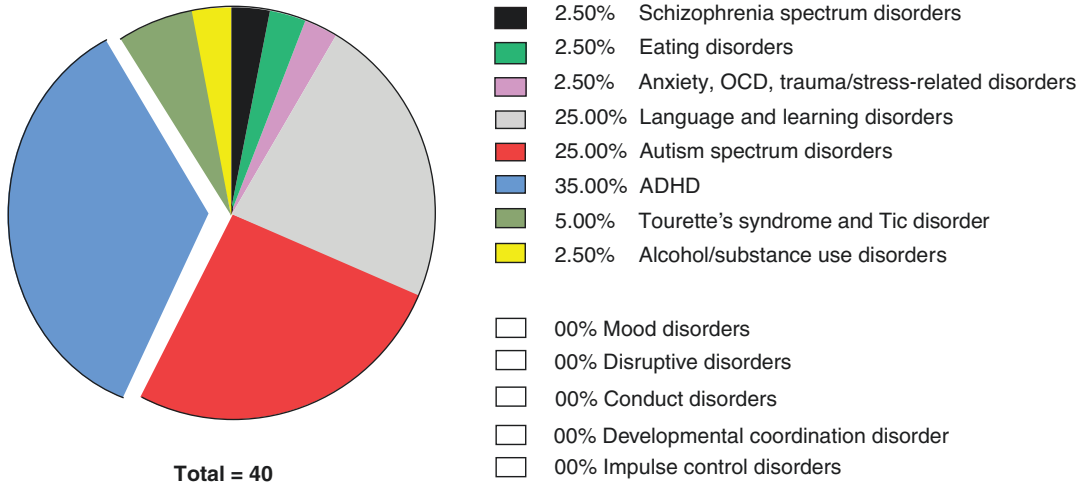

Fig. 15.1 Proportion of tDCS studies in child and adolescent psychiatry (updated April 2021)

of tDCS for the treatment of Tourette's syndrome and tic disorders. Future randomized controlled trials are needed to support these conclusions.

Developmental Coordination Disorder (DCD)

DCD is a relatively underrecognized neurodevelopmental disorder that affects 5–6% of all school-aged children [114]. It is characterized by poorly coordinated motor abilities and motor challenges during performing daily living tasks [80]. Neuroimaging findings show that the pathophysiology of motor learning deficits in DCD is related to motor regions of the brain, including the premotor and motor cortical regions, cerebellum, and basal ganglia as well as prefrontal regions such as the DLPFC and orbitofrontal cortex [115, 116]. These findings, along with the promising effects of tDCS on motor learning, and other NIBS techniques on motor-related disorders, make tDCS an appealing option to modulate neural activity and augment motor learning in children with DCD [117]. No tDCS studies have been conducted however in DCD yet. There is an ongoing randomized, sham-controlled clinical trial in 30 children aged 10 to 15 years with DCD (NCT03453983), which examines the effect of 1 mA anodal tDCS over the primary motor cortex on motor and sensorimotor functioning. The results from this study will give valuable information about the efficacy and promises of tDCS in DCD.

Future Directions: Child and Adolescent Neuropsychiatric Disorders

There has been a significant increase in tDCS studies conducted in child and adolescent psychiatric disorders since 2015. Overall, current research provides preliminary evidence that tDCS has therapeutic potential for the treatment of several disorders in children and adolescents. The distribution and frequency of disorders targeted by tDCS are quite heterogeneous, and some disorders have remained less or widely unexplored (Fig. 15.1). The number of tDCS studies in child/adolescent neuropsychiatric disorders is considerably limited as compared to application of tDCS for treatment of neurodevelopmental disorders in the same population. In light of recent evidence from large datasets that confirm the safety of tDCS in children and adolescents [118], substantial promise for research and clinical application in the adult population, and pathophysiological alterations of the brain in these diseases that are modifiable with neuromodulatory interventions, application of this technique in child and adolescent psychiatric disorders appears to be promising. Lines of research needed to be addressed in future studies to establish tDCS as a clinical intervention are multifold. First, the literature lacks double-blind, sham-controlled trials that are required to improve the interpretation of the

current results. Secondly, the use of objective physiological measures (e.g., EEG correlates, neurophysiological parameters), complementary to primary behavioral measures, is needed to improve understanding of the underlying mechanism of effects. Finally, stimulation protocols should be adapted to the developmental aspects of pathophysiology, including specific activation patterns in the child and adolescent brain and adaptation of respective stimulation parameters (e.g., stimulation intensity, polarity, duration, electrode size). We discuss this in detail in the next section.

15.5 Developmental Aspects of Stimulation Parameters

The acute and neuroplastic effects of tDCS depend on the stimulation protocol parameters, including stimulation polarity, intensity, duration, repetition rate, and interval. There are unique practical considerations about the application of tDCS in the developing brain with respect to these parameters. It is believed that the developing brain in childhood and adolescence is more plastic than the adult brain especially in the critical periods of brain development [17, 119], and thus the effects of plasticity-inducing interventions might be stronger, especially during sensitive developmental periods [23]. Moreover, the smaller head size of children and adolescents likely results in a stronger electrical field, as compared to adults [66, 120]. Adapting stimulation parameters to the developing brain is therefore essential in tDCS studies. But in order to adapt stimulation parameters, first, an understanding of stimulation parameters and mechanism of their impact on modulating brain physiology is needed. In this section, we briefly discuss developmental aspects of tDCS with a specific focus on the above-mentioned stimulation parameters.

The modulatory effect of tDCS on cortical excitability is polarity-specific, with anodal stimulation and cathodal stimulation increasing and decreasing cortical excitability respectively within certain parameters of stimulation. In recent years, however, nonlinear effects have been observed and replicated, especially for cathodal tDCS, and it was shown that the direction of plasticity is determined by parameters like stimulation duration, intensity, and repetition interval [121, 122] (for a brief review, see [123]). Previous studies in the adult population have shown a nonlinearity of tDCS-induced after-effects for cathodal tDCS depending on stimulation intensity. Specifically, a conversion of excitability-diminishing after-effects of cathodal tDCS to excitability-enhancing after-effects has been observed and replicated in adults when stimulation intensity was enhanced to 2 mA from 1 mA [95]. A similar conversion of the directionality of effects is observed in children where cathodal tDCS with 1 mA intensity, which has excitability-diminishing effects in adults, had excitatory effects in children and adolescents and reduced cortical inhibition markers [34, 35]. This conversion of after-effects should be considered, especially if an excitability-diminishing effect is expected from the intervention.

Regarding stimulation intensity, computational modeling of electrical current flow shows that the electrical field induced by the same stimulation intensity is different in a developing compared to an adult brain. In a recent study [66], it was shown that the required stimulation intensity to generate an electrical field comparable to that achieved in adults (2 mA, 0.8 V/m) is almost half in children (1 mA, 0.6 V/m), under otherwise identical conditions (Fig. 15.2a, b). Previous computational studies had similar results and suggest that on average, children will be exposed to higher peak electrical fields for a given applied current intensity than adults [120]. Therefore, stimulation intensity might have to be adjusted in children, to achieve similar effects as in adults. In this line, higher stimulation intensities might modulate areas beyond the target electrode, with possibly nonintended effects on the tackled clinical symptoms. However, a reduction of stimulation intensity might not be warranted for all targets. It is possible that the stimulation intensity that modulates surface-near cortical regions such as DLPFC might not be sufficient to reach deeper regions such as the inferior frontal gyrus [66]. A priori modeling of electrical current flow

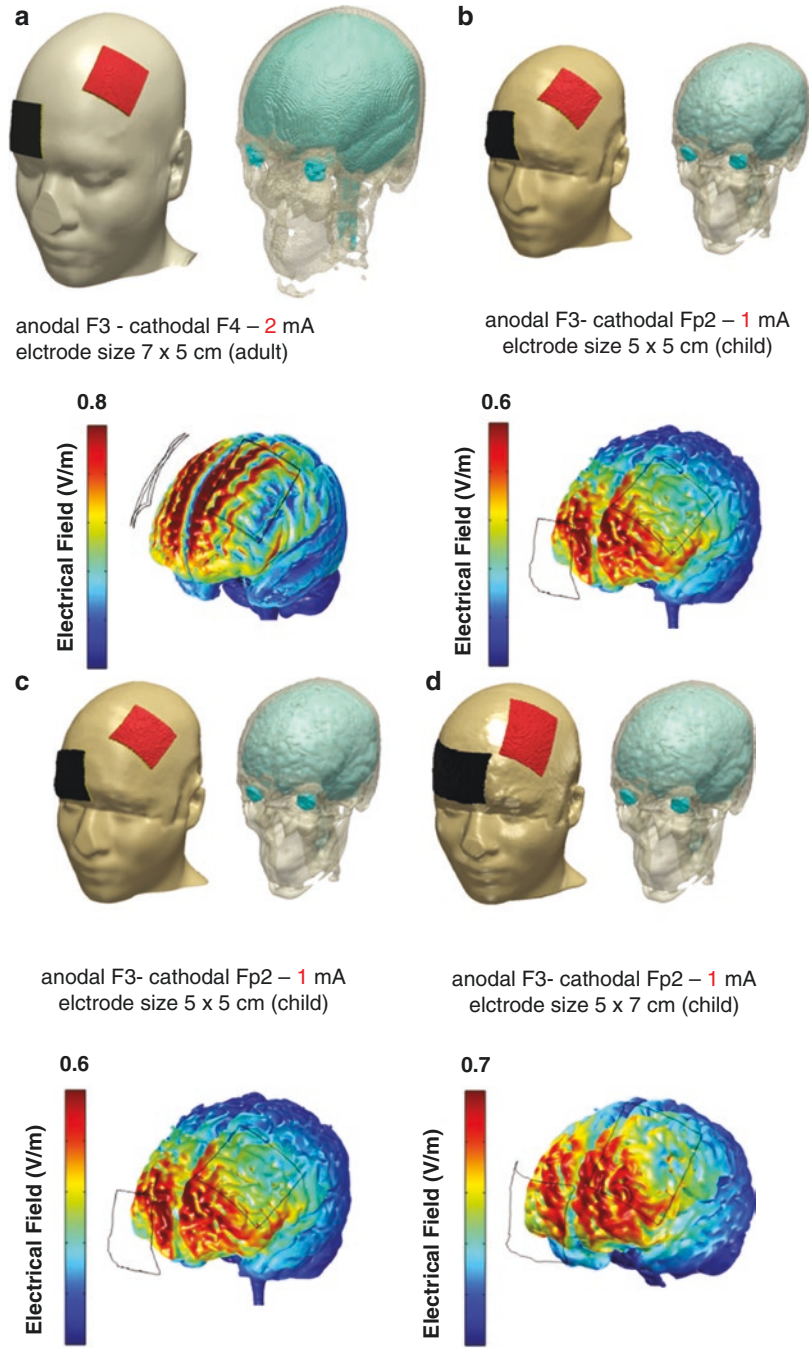

Fig. 15.2 Three-dimensional models of electrical current flow in the head induced by common stimulation montages with the head sizes of an adult (1 and 2; the New York (ICBM-NY) head [128]) and a 9-year-old child (3 and 4; open-source ABIDEII-OHSU child MR datasets). (*Note:* Pictures are adopted from Salehinejad et al. [66] with the permission of the publisher)

induced by the target protocol might be helpful to solve this problem.

Electrode size is also an important aspect in this respect. A smaller electrode size has the principal advantage to generate the current density aimed for at the brain level with less current intensity [124], and with higher focality, which is relevant for tDCS application in pediatrics because of the smaller head size, as compared to adults. The distance between electrodes should be sufficient to minimize current shunting through the skin, which requires attention espe-

cially if target regions are close. For example, the use of electrodes with 35 cm^2 over frontal target regions (e.g., left DLPFC and right orbitofrontal area) does not in each case guarantee the required minimum distance between the electrodes and can result in an unintended high amount of current shunting. Therefore, in these case, smaller electrodes are preferable. As shown in Fig. 15.2c, d, the current intensity of 2 mA with 35 cm^2 electrode size results in an induced electrical field of ~0.7 V/m, while 1 mA with 25^2 cm electrode size induces an electrical field of 0.6 V/m in the same target regions with the same electrode arrangement. In this respect, differences in electrode shape can also result in differences in the distribution of the current across the surface area of the scalp, and in turn, different distribution of current throughout the brain [125], which needs to be considered.

In addition to stimulation intensity, parameters like stimulation duration, repetition rate, and repetition interval are other determinant factors for the direction and duration of tDCS after-effects so far not systematically addressed in children and adolescents. The efficacy of prolonged stimulation for improving efficacy of the intervention needs to be investigated in different cortical regions; however, similar to stimulation intensity, prolonged stimulation duration might induce nonlinear effects [28, 126], which should be considered in children and adolescents as well. Repeated session tDCS approaches are reported to be safe [127] and are expected to lead to cumulative effects especially in clinical populations. In order to evaluate the efficacy of tDCS in child and adolescent psychiatry, especially in disorders that have been addressed by previous tDCS studies (e.g., ADHD, ASD), trials with repeated stimulation sessions are needed. In ADHD studies, the effects of repeated tDCS were explored in two studies [103, 106]. Similarly, in ASD, studies with multisession approaches reported improving effects of the intervention on autism symptoms [85–87, 91–93]. In learning disorders, studies with multisession approaches showed an improving effect of tDCS on reading abilities as well [68, 70, 71, 75]. The results of these studies suggest that indeed repeated tDCS is valuable to obtain clinically useful effects.

15.6 Other NIBS Approach in Child and Adolescent (tRNS, tACS)

While most of the transcranial electrical stimulation studies have focused on tDCS, we would like to also highlight the potential of other NIBS approaches that are underused but could allow further exciting possibilities. tDCS delivers a direct current to the scalp. However, other methods that use alternating current, such as transcranial alternating current stimulation (tACS) and random noise stimulation (tRNS), have been also used to modulate neural activity [129] with promising preliminary results in some neurodevelopmental disorders [111].

In tACS, electrical current is alternated between electrodes, usually in a sinusoidal wave. The prevalent suggestion is that instead of altering neuronal excitability as in tDCS, tACS entrains neuronal firing from a large number of underlying neurons to the exogenous frequency [130]. Neuronal entrainment is achieved by the applied current altering the transmembrane potential of the neurons. The polarization of the neurons reflects the current applied to it, leading to a sinusoidal fluctuation of the membrane potential. As this fluctuation is both frequency dependent and linearly proportional to the applied current, lower frequency stimulation induces larger polarization than higher frequencies [131]. The ability to entrain the neurons in a specific brain region to fire at a predetermined frequency can be attractive to alter pathophysiology that is associated with different psychiatric conditions. However, one of the caveats with tACS is that currently when it is applied during wakefulness, it does not show long-term effects beyond a couple of hours post stimulation.

Similar to tACS, also tRNS uses an alternating current. However, instead of stimulating at a fixed frequency throughout the stimulation period, tRNS alternates at a random frequency and amplitude within a specific range. The

frequency of stimulation used is normally distributed between 0.1 and 640 Hz [132], although it seems to be more effective at high frequency stimulation (101–640 Hz) [132, 133]. Similar to tACS, short durations of tRNS have also been shown to be effective in modulating behavior [134].

While the mechanisms behind tRNS are not clearly understood in humans, in the rat, periods of repetitive high frequency stimulation have been shown to cause inward sodium currents within the neuron as well as weak depolarization [135]. In humans, the excitability-enhancing effects of tRNS are significantly decreased by blocking voltage-gated sodium channels [136].

A dominant explanation for the effect of tRNS is based on stochastic resonance. Stochastic resonance describes the phenomenon of introducing an appropriate level of random noise to enhance the output of subthreshold signals. With respect to tRNS, it suggests that the application of weak electric currents amounts to an introduction of neural noise [137]. Information processing at the neuronal level is sensitive to stochastic resonance [138]. tRNS at different intensities over the visual cortex has been shown to lead to behavioral changes in a manner that corresponds to an inverted-U function, a characteristic of stochastic resonance [139]. Alternatively, it was suggested that the mechanism of action of tRNS is based on repeated subthreshold stimulations, which may prevent homeostasis of the system and potentiate task-related neural activity [133].

Research using tRNS has shown long-lasting effects, similar to those observed with tDCS [140–143]. In addition, compared to other NIBS methods, such as tDCS and tACS, tRNS is the most comfortable intervention technique, which is also a key advantage for effective blinding (i.e., placebo/sham vs. active tRNS) [144] and application in children [145]. tRNS is also polarity independent, so that both electrodes can induce excitatory effects [132]. In addition, tRNS is less sensitive to cortical folding than other stimulation methods [132], reducing the impact of anatomical variations between participants.

tRNS during 5-day executive functions training improved clinical outcomes in children with attention deficit hyperactivity disorder (ADHD), and this improvement was significant compared to the clinical symptoms reported before the intervention started. Moreover, tRNS yielded greater effect in comparison to the same duration of executive functions training coupled with tDCS [146]. This improvement was also associated with improvement in working memory, which was part of the components in the executive functions training, and is one of the cognitive core deficits in ADHD [147].

To the best of our knowledge, tACS has not been used so far in minors with psychiatric disorders, although it has been used in minors with developmental learning difficulties [148]. In this study, the authors also used tRNS [148]. However, the efficacy of tACS and tRNS on task performance (phoneme categorization) differed as a function of age, with tACS at 40 Hz showing improvement for minors, while tRNS showing improvement for adults. These results highlight how a successful stimulation protocol in one age group might not have a straightforward extrapolation to another age group.

While the application of non-tDCS methods is sparse as indicated by our chapter, we believe that further research into tDCS and non-tDCS methods and the comparison between different methods is required. In addition, further understanding of the mechanisms behind these stimulation methods could contribute to better understanding and greater rationale of which methods should be applied in a given age group and psychiatric condition.

15.7 Conclusion

In this chapter, we first discussed the physiology of the developing brain especially with respect to the parameters that determine tDCS acute and neuroplastic after-effects. We then provided the most up-to-date findings of tDCS studies in child and adolescent psychiatric disorders, which remarkably increased since 2015. At the end of this chapter, we discussed the importance of adapting stimulation parameters in the developing population and provided an overview of other

tES techniques with promising use in children and adolescents. Taken together, current research provides preliminary evidence for the therapeutic potential of tDCS in several disorders in childhood and adolescence. However, we still have a long way ahead to establish tDCS-based interventions in the developing population.

But what should be the approach for future studies conducted in developing populations? The answer to this question is not easy at present, considering the lack of large-scale, sham-controlled studies, and translational studies covering the range from basic neurophysiology to application in cognitive-clinical neuroscience. However, some aspects relevant for future approaches should be highlighted. As with the NIBS studies in adult populations, the "one-size-fits-all" approach might not dominate future studies. Stimulation protocols applied in the most-studied neurodevelopmental disorders (e.g., ASD, ADHD) show that we need to develop symptom-specific stimulation protocols that take disorder-specific conditions into account. In this line, interindividual variabilities should be also considered, in line with a "personalized" approach in NIBS research. This is even more important in the developing brain, which undergoes vast physiological changes. Adopting a personalized approach would allow us to purposefully target deficits and symptoms and apply tDCS in individuals that will likely respond to the treatment.

The following lines of research are needed to be systematically explored in order to reach a clear and comprehensive picture of tDCS efficacy, safety, and application in child and adolescent psychiatry in future: (1) preference for double-blind, sham-controlled trials, (2) systematic investigation of stimulation parameters in order to identify adaptive stimulation protocols, (3) conduction of multisession studies in tDCS applications which showed promising effects in single-session approaches for examining clinical relevance of these interventions, (4) longitudinal studies dedicated to safety aspects of tDCS in children, (5) use of other NIBS techniques with potential effects in children and adolescents (e.g., tACS, tRNS), (6) and finally use of tDCS in those disorders that might respond to tDCS but remained unexplored so far, such as pediatric and early-onset psychosis, disruptive, impulse-control, and conduct disorders, Tourette's syndrome, anxiety and mood disorders, and eating disorders.

References

1. Bikson M, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9(5):641–61.
2. Chevaleyre V, Castillo PE. Heterosynaptic LTD of hippocampal GABAergic synapses: a novel role of endocannabinoids in regulating excitability. Neuron. 2003;38(3):461–72.
3. Kolaj M, Renaud LP. Metabotropic glutamate receptors in median preoptic neurons modulate neuronal excitability and glutamatergic and GABAergic inputs from the subfornical organ. J Neurophysiol. 2010;103(2):1104–13.
4. Lamprecht R, LeDoux J. Structural plasticity and memory. Nat Rev Neurosci. 2004;5(1):45–54.
5. Bavelier D, et al. Brain plasticity through the life span: learning to learn and action video games. Annu Rev Neurosci. 2012;35(1):391–416.
6. Stagg CJ. The physiological basis of brain stimulation. In: Kadosh RC, editor. The stimulated brain. San Diego: Academic Press; 2014. p. 145–77.
7. Stagg CJ, Antal A, Nitsche MA. Physiology of transcranial direct current stimulation. J ECT. 2018;34(3):144–52.
8. Johnston MV. Plasticity in the developing brain: implications for rehabilitation. Dev Disabil Res Rev. 2009;15(2):94–101.
9. Nitsche M, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553(1):293–301.
10. Nitsche MA, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology. 2004;29(8):1573–8.
11. Johnston MV. Neurotransmitters and vulnerability of the developing brain. Brain Dev. 1995;17(5):301–6.
12. Sanchez RM, Jensen FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. Epilepsia. 2001;42(5):577–85.
13. Nitsche MA, et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci. 2004;19(10):2720–6.
14. Hameed MQ, et al. The developing brain—relevance to pediatric Neurotechnology. In: Oberman LM, Enticott PG, editors. Neurotechnology and brain stimulation in pediatric psychiatric and neurodevelopmental disorders. Academic Press; 2019. p. 9–30.
15. Luján R, Shigemoto R, López-Bendito G. Glutamate and GABA receptor signalling in the developing brain. Neuroscience. 2005;130(3):567–80.
16. Mall V, et al. Low level of Intracortical inhibition in children shown by transcranial magnetic stimulation. Neuropediatrics. 2004;35(02):120–5.

17. Johnston MV, et al. Plasticity and injury in the developing brain. Brain Dev. 2009;31(1):1–10.
18. Kirkwood A, Lee H-K, Bear MF. Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. Nature. 1995;375(6529):328–31.
19. Kirkwood A, Silva A, Bear MF. Age-dependent decrease of synaptic plasticity in the neocortex of αCaMKII mutant mice. Proc Natl Acad Sci. 1997;94(7):3380–3.
20. Dudek S, Bear M. Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. J Neurosci. 1993;13(7):2910–8.
21. Feldman DE, Nicoll RA, Malenka RC. Synaptic plasticity at thalamocortical synapses in developing rat somatosensory cortex: LTP, LTD, and silent synapses. J Neurobiol. 1999;41(1):92–101.
22. Munakata Y, Pfaffly J. Hebbian learning and development. Dev Sci. 2004;7(2):141–8.
23. Knudsen EI. Sensitive periods in the development of the brain and behavior. J Cogn Neurosci. 2004;16(8):1412–25.
24. Nitsche M, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(3):633–9.
25. Bikson M, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol. 2004;557(1):175–90.
26. Rahman A, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol. 2013;591(10):2563–78.
27. Priori A, et al. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9(10):2257–60.
28. Monte-Silva K, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul. 2013;6(3):424–32.
29. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899–901.
30. Nitsche M, et al. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114(4):600–4.
31. Liebetanz D, et al. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(10):2238–47.
32. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29(16):5202–6.
33. Nwaroh C, et al. Effects of transcranial direct current stimulation on GABA and Glx in children: a pilot study. PLoS One. 2020;15(1):e0222620.
34. Moliadze V, et al. 1 mA cathodal tDCS shows excitatory effects in children and adolescents: Insights from TMS evoked N100 potential. Brain Res Bull. 2018;140:43–51.
35. Moliadze V, et al. Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. Clin Neurophysiol. 2015;126(7):1392–9.
36. Jamil A, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol. 2017;595(4):1273–88.
37. Akram F, Kawa S, Giordano J. Diagnosis in American psychiatry: a brief history of the diagnostic and statistical manual. In: Goldstein S, DeVries M, editors. Handbook of DSM-5 disorders in children and adolescents. Cham: Springer International Publishing; 2017. p. 3–15.
38. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol. 2006;2(1):111–33.
39. Kostova R, et al. Targeting cognition in schizophrenia trough transcranial direct current stimulation: a systematic review and perspective. Schizophr Res. 2020;220:300.
40. Papazova I, et al. Improving working memory in schizophrenia: effects of 1 mA and 2 mA transcranial direct current stimulation to the left DLPFC. Schizophr Res. 2018;202:203–9.
41. Mattai A, et al. Tolerability of transcranial direct current stimulation in childhood-onset schizophrenia. Brain Stimul. 2011;4(4):275–80.
42. Hadar R, et al. Prevention of schizophrenia deficits via non-invasive adolescent frontal cortex stimulation in rats. Mol Psychiatry. 2019;25:896.
43. Clemmensen L, Vernal DL, Steinhausen H-C. A systematic review of the long-term outcome of early onset schizophrenia. BMC Psychiatry. 2012;12(1):150.
44. Lee JC, et al. Transcranial direct current stimulation: considerations for research in adolescent depression. Front Psych. 2017;8:91.
45. Moffa AH, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;99:109836.
46. Razza LB, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020;37:594.
47. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. Psychol Bull. 2006;132(1):132–49.
48. Cheung AH, Emslie GJ, Mayes TL. Review of the efficacy and safety of antidepressants in youth depression. J Child Psychol Psychiatry. 2005;46(7):735–54.
49. Fontanella CA, et al. Factors associated with antidepressant adherence for Medicaid-enrolled children and adolescents. Ann Pharmacother. 2011;45(7-8):898–909.
50. Krivoy A, et al. The impact of age and gender on adherence to antidepressants: a 4-year population-based cohort study. Psychopharmacology. 2015;232(18):3385–90.
51. Kerestes R, et al. Functional brain imaging studies of youth depression: a systematic review. NeuroImage Clin. 2014;4:209–31.

52. Rakesh D, Allen NB, Whittle S. Balancing act: neural correlates of affect dysregulation in youth depression and substance use – a systematic review of functional neuroimaging studies. Dev Cogn Neurosci. 2020;42:100775.
53. Khedr EM, et al. Anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex improves anorexia nervosa: a pilot study. Restor Neurol Neurosci. 2014;32(6):789–97.
54. Francis SM, et al. Transcranial direct current stimulation for compulsivity in adolescent fraternal twins with neurodevelopmental disorders. Brain Stimul. 2020;13(4):1153–5.
55. Brem S, et al. Neuroimaging of cognitive brain function in paediatric obsessive compulsive disorder: a review of literature and preliminary meta-analysis. J Neural Transm. 2012;119(11):1425–48.
56. Skapinakis P, et al. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. Health Technol Assess. 2016;20(43):1.
57. Sheynin J, et al. Altered resting-state functional connectivity in adolescents is associated with PTSD symptoms and trauma exposure. NeuroImage Clin. 2020;26:102215.
58. Andrea L. Gold, et al., Age differences in the neural correlates of anxiety disorders: an fMRI study of response to learned threat. Am J Psychiatr, 2020. 0(0): p. appi.ajp.2019.19060650.
59. Vicario CM, et al. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. Neurosci Biobehav Rev. 2019;96:219–31.
60. da Silva RDMF, et al. Transcranial direct current stimulation for obsessive-compulsive disorder: patient selection and perspectives. Neuropsychiatr Dis Treat. 2019;15:2663–9.
61. Goldstein S, DeVries M. Handbook of DSM-5 disorders in children and adolescents. Springer; 2017.
62. Khayyer Z, et al. Transcranial direct current stimulation combining mindfulness based relapse prevention for smoking cessation: a case report. Int Clin Neurosci J. 2019;6(3):5.
63. Noordermeer SDS, Luman M, Oosterlaan J. A systematic review and meta-analysis of neuroimaging in Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) taking Attention-Deficit Hyperactivity Disorder (ADHD) into account. Neuropsychol Rev. 2016;26(1):44–72.
64. Rubia K. Cognitive neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and its clinical translation. Front Hum Neurosci. 2018;12:100.
65. Salehinejad MA, et al. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. PLoS One. 2019;14(4):e0215095.
66. Salehinejad MA, et al. Transcranial direct current stimulation in ADHD: a systematic review of efficacy, safety, and protocol-induced electrical field modeling results. Neurosci Bull. 2020;36:1191.
67. Blair RJR, Veroude K, Buitelaar JK. Neurocognitive system dysfunction and symptom sets: a review of fMRI studies in youth with conduct problems. Neurosci Biobehav Rev. 2018;91:69–90.
68. Costanzo F, et al. Reading changes in children and adolescents with dyslexia after transcranial direct current stimulation. Neuroreport. 2016;27(5):295–300.
69. Costanzo F, et al. Evidence for reading improvement following tDCS treatment in children and adolescents with dyslexia. Restor Neurol Neurosci. 2016;34:215–26.
70. Costanzo F, et al. Long-lasting improvement following tDCS treatment combined with a training for reading in children and adolescents with dyslexia. Neuropsychologia. 2019;130:38–43.
71. Rios DM, et al. Impact of transcranial direct current stimulation on reading skills of children and adolescents with dyslexia. Child Neurol Open. 2018;5:2329048X18798255.
72. Rahimi V, et al. Modulation of temporal resolution and speech long-latency auditory-evoked potentials by transcranial direct current stimulation in children and adolescents with dyslexia. Exp Brain Res. 2019;237(3):873–82.
73. Rahimi M, et al. Comparison of cognitive training method and transcranial direct current stimulation (tDCS) on the visual attention processes in the students with special learning disorders. Int J Behav Sci. 2019;12(4):162–8.
74. Lazzaro G, et al. Beyond reading modulation: temporo-parietal tDCS alters visuo-spatial attention and motion perception in dyslexia. Brain Sci. 2021;11(2):263.
75. Moslemi, B, et al. The effectiveness of transcranial direct current stimulation (tDCS) on attention and visual-auditory working memory in children with dyslexia. J Except Child. 2021;20(4):104–93.
76. Arjmandnia AA, et al. The effect of transcranial direct current stimulation (TDCS) on improving working memory performance in children with mathematical disorder. J Learn Disabil. 2016;6(1(20)):7.
77. Vidyasagar TR. Visual attention and neural oscillations in reading and dyslexia: are they possible targets for remediation? Neuropsychologia. 2019;130:59–65.
78. Gillam RB, et al. Language disorder in children. In: Goldstein S, DeVries M, editors. Handbook of DSM-5 disorders in children and adolescents. Cham: Springer International Publishing; 2017. p. 57–76.
79. Osório AAC, Brunoni AR. Transcranial direct current stimulation in children with autism spectrum disorder: a systematic scoping review. Dev Med Child Neurol. 2019;61(3):298–304.
80. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.

81. Kincaid DL, et al. What is the prevalence of autism spectrum disorder and ASD traits in psychosis? A systematic review. Psychiatry Res. 2017;250:99–105.
82. Cardinale RC, et al. Pervasive rightward asymmetry shifts of functional networks in autism Spectrum disorder. JAMA Psychiat. 2013;70(9):975–82.
83. Uzunova G, Pallanti S, Hollander E. Excitatory/inhibitory imbalance in autism spectrum disorders: implications for interventions and therapeutics. World J Biol Psychiatry. 2016;17(3):174–86.
84. Barahona-Corrêa JB, et al. Repetitive transcranial magnetic stimulation for treatment of autism spectrum disorder: a systematic review and meta-analysis. Front Integr Neurosci. 2018;12:27.
85. Costanzo F, et al. Transcranial direct current stimulation treatment in an adolescent with autism and drug-resistant catatonia. Brain Stimul: Basic, Translational, and Clinical Research in Neuromodulation. 2015;8(6):1233–5.
86. Hadoush H, et al. Therapeutic effects of bilateral anodal transcranial direct current stimulation on prefrontal and motor cortical areas in children with autism Spectrum disorders: a pilot study. Autism Res. 2020;13(5):828–36.
87. Toscano E, et al. Fronto-cerebellar tDCS in children with autism Spectrum disorder. L'Encéphale. 2019;45:S79–80.
88. Schneider HD, Hopp JP. The use of the bilingual aphasia test for assessment and transcranial direct current stimulation to modulate language acquisition in minimally verbal children with autism. Clin Linguist Phon. 2011;25(6-7):640–54.
89. Amatachaya A, et al. Effect of anodal transcranial direct current stimulation on autism: a randomized double-blind crossover trial. Behav Neurol. 2014;2014:173073.
90. Amatachaya A, et al. The short-term effects of transcranial direct current stimulation on electroencephalography in children with autism: a randomized crossover controlled trial. Behav Neurol. 2015;2015:928631.
91. Gómez L, et al. Non-invasive brain stimulation for children with autism Spectrum disorders: a short-term outcome study. Behav Sci. 2017;7(3):63.
92. D'Urso G, et al. Transcranial direct current stimulation for hyperactivity and noncompliance in autistic disorder. World J Biol Psychiatry. 2015;16(5):361–6.
93. Mahmoodifar E, Sotoodeh MS. Combined transcranial direct current stimulation and selective motor training enhances balance in children with autism Spectrum disorder. Percept Mot Skills. 2020;127(1):113–25.
94. Salehinejad MA, et al. Contribution of the right temporoparietal junction and ventromedial prefrontal cortex to theory of mind in autism: A randomized, sham-controlled tDCS study. Autism Res. 2021;n/a(n/a):1–13. https://doi.org/10.1002/aur.2538.
95. Batsikadze G, et al. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol. 2013;591(7):1987–2000.
96. Stoodley CJ, et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci. 2017;20(12):1744–51.
97. Castellanos FX, et al. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci. 2006;10(3):117–23.
98. Nigg JT, et al. Working memory and vigilance as multivariate Endophenotypes related to common genetic risk for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2018;57(3):175–82.
99. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of anodal and cathodal transcranial direct current stimulation on DLPFC on modulation of inhibitory control in ADHD. J Atten Disord. 2015;23:325.
100. Prehn-Kristensen A, et al. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimul. 2014;7(6):793–9.
101. Munz MT, et al. Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. Front Cell Neurosci. 2015;9:307.
102. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of transcranial direct current stimulation on remediation of inhibitory control on right inferio frontal gyrus in attention deficit and hyperactivity symptoms. Rehabil Med. 2015;3(4):1–9.
103. Bandeira ID, et al. Transcranial direct current stimulation in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD):a pilot study. J Child Neurol. 2016;31(7):918–24.
104. Breitling C, et al. Improving interference control in ADHD patients with transcranial direct current stimulation (tDCS). Front Cell Neurosci. 2016;10:72.
105. Sotnikova A, et al. Transcranial direct current stimulation modulates neuronal networks in attention deficit hyperactivity disorder. Brain Topogr. 2017;30(5):656–72.
106. Soff C, et al. Transcranial direct current stimulation improves clinical symptoms in adolescents with attention deficit hyperactivity disorder. J Neural Transm. 2017;124(1):133–44.
107. Nejati V, et al. Transcranial direct current stimulation improves executive dysfunctions in ADHD: implications for inhibitory control, interference control, working memory, and cognitive flexibility. J Atten Disord. 2017;0(0):1087054717730611.
108. Breitling C, et al. Comparison between conventional and HD-tDCS of the right inferior frontal gyrus in children and adolescents with ADHD. Clin Neurophysiol. 2020;131:1146.
109. Nejati V, Sarraj Khorrami A, Nitsche MA. Transcranial direct current stimulation improves

reward processing in children with ADHD. J Atten Disord. 2020;0(0):1087054720923094.
110. Salehinejad MA, et al. Domain-specific involvement of the right posterior parietal cortex in attention network and attentional control of ADHD: A Randomized, Cross-over, Sham-controlled tDCS Study. Neurosci. 2020;444:149–59.
111. Berger I, et al. Scaffolding the attention-deficit/hyperactivity disorder brain using transcranial direct current and random noise stimulation: A randomized controlled trial. Clin Neurophysiol. 2021;132(3):699–707.
112. Carvalho S, et al. Sustained effects of a neural-based intervention in a refractory case of Tourette syndrome. Brain Stimul: Basic, Translational, and Clinical Research in Neuromodulation. 2015;8(3):657–9.
113. Dyke K, et al. Effects of single-session cathodal transcranial direct current stimulation on tic symptoms in Tourette's syndrome. Exp Brain Res. 2019;237(11):2853–63.
114. Missiuna C, Rivard L, Campbell W. Developmental coordination disorder. In: Goldstein S, DeVries M, editors. Handbook of DSM-5 disorders in children and adolescents. Cham: Springer International Publishing; 2017. p. 431–50.
115. Fuelscher I, et al. Differential activation of brain areas in children with developmental coordination disorder during tasks of manual dexterity: an ALE meta-analysis. Neurosci Biobehav Rev. 2018;86:77–84.
116. Biotteau M, et al. Neural signature of DCD: a critical review of MRI neuroimaging studies. Front Neurol. 2016;7:227.
117. Grohs MN, Hilderley A, Kirton A. The therapeutic potential of non-invasive Neurostimulation for motor skill learning in children with neurodevelopmental disorders. Curr Dev Disord Rep. 2019;6(1):19–28.
118. Zewdie E, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: prospective single center evidence from 3.5 million stimulations. Brain Stimul. 2020;13(3):565–75.
119. Qin Y, et al. The change of the brain activation patterns as children learn algebra equation solving. Proc Natl Acad Sci U S A. 2004;101(15):5686–91.
120. Kessler SK, et al. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112.
121. Monte-Silva K, et al. Shaping the optimal repetition interval for cathodal Transcranial Direct Current Stimulation (tDCS). J Neurophysiol. 2010;103(4):1735–40.
122. Samani MM, et al. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. Cortex. 2019;119:350.
123. Salehinejad MA, Ghanavati E. Complexity of cathodal tDCS: relevance of stimulation repetition, interval, and intensity. J Physiol. 2020;598(6):1127–9.
124. Faria P, Hallett M, Miranda PC. A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. J Neural Eng. 2011;8(6):066017.
125. Woods AJ, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127(2):1031–48.
126. Monte-Silva K, et al. Dosage-dependent non-linear effect of l-dopa on human motor cortex plasticity. J Physiol. 2010;588(18):3415–24.
127. Nikolin S, et al. Adverse events associated with repeated sessions of tDCS: a systematic review and meta-analysis. Brain Stimul. 2019;12(2):483.
128. Huang Y, Parra LC, Haufe S. The New York Head-A precise standardized volume conductor model for EEG source localization and tES targeting. NeuroImage. 2016;140:150–62.
129. Reed T, Cohen Kadosh R. Transcranial electrical stimulation (tES) mechanisms and its effects on cortical excitability and connectivity. J Inherit Metab Dis. 2018;41(6):1123–30.
130. Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast. 2016;2016:3616807.
131. Reato D, et al. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30(45):15067–79.
132. Terney D, et al. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28:14147–55.
133. Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci. 2011;31(43):15416–23.
134. van der Groen O, Mattingley JB, Wenderoth N. Altering brain dynamics with transcranial random noise stimulation. Sci Rep. 2019;9(1):4029.
135. Schoen I, Fromherz P. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak capacitive currents on a silicon Chip. J Neurophysiol. 2008;100(1):346–57.
136. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci. 2015;9:125.
137. Fertonani A, Miniussi C. Transcranial electrical stimulation: what we know and do not know about mechanisms. Neuroscientist. 2017;23(2):109–23.
138. McDonnell MD, Ward LM. The benefits of noise in neural systems: bridging theory and experiment. Nat Rev Neurosci. 2011;12:415–25.
139. van der Groen O, Wenderoth N. Transcranial random noise stimulation of visual cortex: stochastic resonance enhances central mechanisms of perception. J Neurosci. 2016;36(19):5289–98.
140. Cappelletti M, et al. Transfer of cognitive training across magnitude dimensions achieved with concurrent brain stimulation of the parietal lobe. J Neurosci. 2013;33(37):14899–907.

141. Frank B, et al. Learning while multitasking: short and long-term benefits of brain stimulation. Ergonomics. 2018;61(11):1454–63.
142. Pasqualotto A. Transcranial random noise stimulation benefits arithmetic skills. Neurobiol Learn Mem. 2016;133:7–12.
143. Snowball A, et al. Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. Curr Biol. 2013;23(11):987–92.
144. Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol. 2010;121(11):1908–14.
145. Looi CY, et al. Transcranial random noise stimulation and cognitive training to improve learning and cognition of the atypically developing brain: a pilot study. Sci Rep. 2017;7(1):4633.
146. Berger I, et al. Scaffolding the attention-deficit/hyperactivity disorder brain using random noise stimulation. medRxiv. 2019:19005983.
147. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 1997;121(1):65.
148. Rufener KS, et al. Transcranial electrical stimulation improves phoneme processing in developmental dyslexia. Brain Stimul. 2019;12(4):930–7.

Transcranial Direct Current Stimulation in the Perinatal Period

16

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16.1 Definition of Perinatal Mental Mood and Anxiety Disorders

Perinatal or peripartum mental illness encompasses all mental health disorders that are frequent during pregnancy and/or up to 12 months after childbirth [1], from mild depression to psychosis. Among the most common complications are the perinatal mood and anxiety disorders (PNMAD). These include, for example, anhedonia, and major unipolar and bipolar depression (MDD and BD), panic disorder (PD), social anxiety disorder (SAD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and postpartum psychosis (PP), with a prevalence of 10–20% of women in the perinatal period [2]. While not all symptoms or clusters of symptoms reach mild-to-moderate levels, these are nevertheless experienced by women with significant impairment and distress in daily activities.

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PNMAD affects the mother but also the antenatal and postnatal neurodevelopment. For example, antenatal depression increases the risk of delayed intrauterine growth, premature birth, and lower birth weight [3]. In the postpartum period, PNMAD clinically significant symptoms can lead to less effective, less sensitive, and less contingent serve-and-return interactions. The negative impact of PNMAD on mothers' visual and verbal communication ultimately compromises the quality of the mother-baby dyad bonding, with deleterious consequences on the infant sleep, breastfeeding routine or feeding disturbances, avoidance behavior, difficulties in affect regulation, and failure to thrive [4]. In the long term, such consequences are associated with child avoidant attachment and decreased cognitive, verbal, and social competencies [5].

Persistent sadness, anhedonia, lethargy, guilt, irritability, psychomotor agitation, and sleep, weight, and appetite disturbances are common manifestations of depression in the perinatal period [6]. Estimates of peripartum minor and major (non-psychotic) depression range between 7% and 15% in high-income countries and 19% and 25% in low-income countries [7]. A meta-analysis across 56 countries showed that the global prevalence of depression during pregnancy can escalate as high as 38% [8].

The first months postpartum are particularly vulnerable. Studies suggest that the highest incidence of depression in the peripartum

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period occurs during pregnancy (33%) [9] or in the acute postpartum period (18.4% and 19.3%) [2, 10, 11]. For some authors, the most critical postpartum period can be extended to up to 5 to 9 months after delivery [12–14]. However, 27% of diagnosed depression in the peripartum period may have its onset earlier than pregnancy. Therefore, previous history of depression out of the peripartum period is a predictive factor for the future development of postnatal depression [11]. Of importance, the moment of onset of symptoms, symptoms severity, and the phenotype are the three core variables that currently support the literature on the existence of distinctive patterns of the disorder [10, 15].

Although peripartum depression shares phenomenological similarities with major depression disorder [2], peripartum depression has two distinguishing features. Firstly, the comorbidity with anxiety-related symptoms [6, 16] in the peripartum period occurs approximately in 50–60% women during the first 12 months after delivery [16–19]. However, because depression and anxiety share several transdiagnostic processes, such distinction is subtle. Secondly, the association between non-perinatal diagnosis of depression and anxiety with the experience of anxiety symptoms during childhood or adolescence is not frequent in PNMAD [11].

The rate of formal diagnosis for anxiety disorders during pregnancy is set to 6.6% [20], and the prevalence of anxiety symptoms without formal diagnosis in antenatal women is 15.6%, ranging from excessive worry to panic episodes [21]. A recent study confirmed previous data that suggested anxiety to be more frequent than depression during pregnancy (35.3%) with a decreasing tendency toward the first week after birth and stabilizing around 17.3% across the first year postpartum [16, 22].

In contrast with the consensual distinctiveness between perinatal depression and non-perinatal depression, the field is unclear regarding whether former anxiety disorders differ from those with perinatal onset [23]. However, antenatal anxiety is a clear risk factor for the development of postnatal depression and this association is independent of the presence of depressive symptoms before delivery [17]. For in-depth review, we suggest the systematic review and meta-analysis by Furtado and colleagues [23].

The third most common PNMAD is bipolar depression with 14% of women seeking psychiatric support for the first time within the 30 days postpartum converting into bipolar disorder within the following 15 years [24]. Additionally, according to Wisner and colleagues' large-scale study, up to 22.6% of women screening positive in the Edinburgh Postnatal Depression Scale (EPDS) [25] were later diagnosed with bipolar disorder [11]. However, the prevalence of bipolar disorder might be even higher, because EPDS is not designed to screen bipolar depression as there are no items questioning for (hypo)maniac symptoms. Women diagnosed with bipolar disorder I or II are particularly vulnerable to experience a psychotic episode during the first months postpartum. The so-called puerperal or postpartum psychosis is described as a sudden maniac, severe depressive, or mixed episode, which includes delusional thoughts and/or hallucinations, and is characterized by a rapid onset, usually immediately after delivery [26].

16.2 Transdiagnostic Mechanisms of Perinatal Mood and Anxiety Disorders: The Central Role of Rumination

Transdiagnostic mechanisms have been accounted as vulnerability factors for the development of depression, anxiety, and psychotic disorders across the lifespan [27, 28]. Excessive worry or rumination, defined as repetitive thinking about negative self-relevant information [29], is one of such mechanisms that has been associated with increased severity of perinatal illness [30]. Moreover, anticipatory worry and rumination are suggested as predictors of delusion and

hallucinations which in turn exacerbate experienced stress [31]. In the perinatal period, brooding, in particular, seems to be associated with depression [32].

A common cognitive process that is denominator to the pervasiveness of ruminative thinking, worry, and obsessions across disorders is cognitive control—the capacity to adjust cognitive and behavioral processes to current context demands [33]. Attention (e.g., attentional switching and attentional flexibility shifting), inhibitory control (e.g., overriding prepotent responses and thoughts), and working memory updating are especially relevant and present a bidirectional association with rumination and depression [34]. Whereas decreased attentional control leads to the inability to detach from persistent negative thoughts, increased attentional control leads to enhanced inhibition of prevailing thoughts, contributing to increased cognitive flexibility and the effective implementation of emotion regulation strategies.

Impaired executive functioning associated to ruminative thinking negatively impacts not only women wellness and perception of self-efficacy but also the uniqueness of the mother-baby relationship, which during the first year of life strongly supports child neurodevelopment [35]. For example, anxiety symptoms may lead to intrusive interactions from the mother that are associated with infant protest behavior [36]. Such an asynchronous pattern of interaction with the baby is well described in the depression model of rumination and its effects on parenting behavior [34]. According to DeJong's model, deficits in top-down cognitive control (e.g., impaired working memory and short-term memory and compromised task switching) and bottom-up cognitive bias (e.g., memory bias to negative events, negative attention, and negative interpretation) can contribute to rumination and worry, which in turn may compromise accurate information processing of baby cues, ultimately leading to ineffective parenting behaviors.

16.3 The Neural Underpinnings of Perinatal Mood and Anxiety Disorders

The maternal brain results from the interplay between environmental experiences and genetic expression, impacting a complex system that combines fluctuating reproductive hormones [37], the hypothalamic-pituitary-adrenal Axis (HPA) function [38], and the neuroimmune changes that occur during pregnancy and postpartum [39]. This multifactorial system and its bidirectional associations with the maternal brain lead to altered morphology and function in particular brain regions directly and indirectly related to motherhood behaviors [40].

At the network level, the maternal brain refers to changes in overlapping regions that participate in the maternal caregiving network [41]. This network combines the motivational/reward system, the salience/fear system (SN), the dorsal attention network (DAN), the central executive network (CEN), the frontoparietal network (FP), the default-mode network (DMN), and regions responsible for social attachment and empathic and theory of mind driven behavior [41, 42].

Structural brain changes happening during the perinatal period have been found to be both hormonal and experience dependent. From the side of hormonal-driven changes, Carmona and colleagues found that the monthly rate of decreased gray matter volume observed during pregnancy is equivalent to that happening during adolescence [43]. From the experience-dependent side, the brain specialization toward caregiving tasks increases in the postpartum period and corresponds to the increase of the grey matter volume of some regions involved in motivation, somatosensory processing and executive functions [44].

The neural activity of the motivational and reward system involved in maternal grooming (e.g., the medial preoptic area, the bed nucleus of the stria terminalis, the ventral tegmental area, and the nucleus accumbens) is unsurprisingly

enhanced in the perinatal period [45]. Hence, the motivation network is closely interconnected with the executive system involved in planning (e.g., the dorsal striatum) and cognitive and emotional regulation, overlapping with the SN (the amygdala, the hippocampus, and the prefrontal cortex) [40]. In fact, several studies have found an increased neuronal activity in the right amygdala, and in the middle frontal and inferior frontal gyrus, in postpartum vs non-postpartum women when processing emotional stimuli [46]. However, contrasting evidence suggests a generalized diminished activity of the ventrolateral prefrontal cortex characterizing the postpartum period [47], and a decreased spontaneous and task-based neural activity in the left posterior cingulate and in the prefrontal frontal region that seem to be unrelated with psychopathology [48, 49]. In sum, such as any other period of enhanced brain plasticity, the abovementioned changes that prepare woman's brains during pregnancy and support motherhood skills during the early postpartum period represent simultaneously a highly adaptive stage, but also an increased risk to develop perinatal mental illness.

So far, unipolar depression is the peripartum psychiatric disorder that has attracted the highest interest amongst the PNMAD. Thus, most functional neuroimaging data available today concerns peripartum depression (PPD). fMRI studies found that women diagnosed with PPD, when compared to healthy controls, showed a decreased activity in the thalamus, the nucleus accumbens, the caudate, the anterior cingulate cortex, the amygdala, the hippocampus, the dorsolateral prefrontal cortex, and the orbitofrontal areas [50, 51]. This altered activity is in turn associated with reduced responsiveness of depressed mothers to their babies' calls [51].

Enhanced anxiety in the perinatal period was found to be associated with decreased brain activity in regions of the reward system [52]. In fact, the dysfunctional reward system in postpartum depressed women leads to the rapid habituation to reward and the unsustained activity of the ventral striatum compared to non-depressed postpartum women [53].

Resting state fMRI studies showed decreased homogeneity in frontal and temporal regions in women diagnosed with depression in the postpartum when processing their own baby crying [54]. Another study found that depressive symptoms and anxiety-related cognitive processes were positively associated with an increased activity in the left medial prefrontal cortex [55], similar to the pattern that is typically found in depressed patients across the life span.

Cortical and corticolimbic connectivity, in particular the projections between the posterior cingulate and the amygdala, and the projections between the amygdala and the dorsolateral prefrontal cortex, are impaired in postpartum depression [50, 56]. These data show that, as happens with depression outside the peripartum period, the altered connectivity between the SN, the DMN, and the CEN may have a central role in depressive states of young mothers. Hence, this altered connectivity negatively impacts processes of self-perception, and self-referential and emotional appraisal. For an in-depth review on the altered connectivity in PPD, we suggest the review by Duan and colleagues [57].

Particularly important to the complexity of the clinical decision and the potential of tDCS regarding the management of mood and anxiety in the perinatal period are the distinctions between the depressed brain and the anxious brain, inside and outside the perinatal period. For example, the typical hyperactivity observed in the middle line and limbic regions that characterizes MDD is not always present in PND. Similarly, the increased connectivity between the amygdala and the insula in response to emotional salient stimuli that is typically observed in generalized anxiety disorder (GAD) patients is not present in postpartum women that report anxiety-related symptoms [40].

In postpartum psychosis (PP) several brain dysfunctions have been presented as neural substrates candidates of the pathophysiological mechanisms associated with the development of the disorder. fMRI data shows that reduced volume in the anterior cingulate cortex (involved in decision-making and emotional regulation) [58],

along with reduced activity in the orbitofrontal cortex and altered ventricular/brain ratios and lesions in the corpus callosum [59, 60] may play a central role in the development of PP. However, data is disperse and further and updated research is needed to better understand the specificities of PP so that the most adequate treatment alternatives are chosen. For in-depth reading on the neural changes occurring in the postpartum period, we recommend the review by Pawluski and colleagues [40]. For an overall view of the neurobiological underpinnings of postpartum depression we recommend the review by Payne and Maguire [41].

16.4 tDCS Applications in Perinatal Mood and Anxiety Disorders and Psychosis

Health interventions implemented to address the impact of PNMAD aim to improve the environment of the newborn, as well as mothers' clinical symptoms, boosting maternal self-efficacy and functional status in the peripartum period. Choosing for the most adequate treatment to symptoms of PNMAD depends on many factors, such as individual characteristics (e.g., the peripartum period, quality and severity of symptoms, the mother willingness to breastfeed, previous history of psychiatric disorders, previous successful and unsuccessful treatments and, of course, the women preferences). Furthermore, interventions designed to decrease psychiatric symptoms or aiming at improving sensitive and high-quality parental skills must observe the distinctive phenotypes of PNMAD [10].

For mild to moderate peripartum depression and mild to moderate anxiety disorders, psychotherapy is the most commonly recommended treatment and has been shown to be the women's preference during pregnancy and after delivery [61] while frequently disregarded due to stigma [62]. For new depressive episodes and non-severe cases, most guidelines consider cognitive behavioral therapy and interpersonal therapy as the preferred treatments [63]. However, the availability of psychotherapy across countries is limited due to the high cost per session and its non-universal accessibility in public health care services. Thus online or phone-based interventions seem to be a promising alternative with evidence of efficacy being found across studies, particularly those applying CBT programs in the postpartum period [64].

Based on a reduced number of clinical trials conducted with small samples, overall clinicians suggest that antidepressants are safe to use in the peripartum period, particularly during pregnancy. So, it is common practice that, regardless the severity of symptoms, women are treated with medication [65, 66]. However, besides recent systematic reviews suggesting caution about the use of medication during pregnancy [67, 68], 49% of medicated pregnant women show low adherence to pharmacotherapy (from antidepressants to anxiolytics/sedatives and antipsychotics) [69]. In the postpartum period, due to the absence of teratogenic effects, most guidelines encourage breastfeeding even when antidepressant medication is used, being particularly favorable to sertraline due to its low levels found in breast milk [63]. Notwithstanding, adherence to antidepressants seems to be associated with lower rates of breastfeeding (although other factors such as mothers psychiatric illness and neonatal outcomes status may be involved as well) [70]. Additionally, in the postpartum period medication seems to present no extra benefit over psychotherapy as stand-alone or in combination [71]. Of interest, according to the latest available meta-analysis, the effect size of interventions (from distinctive modalities of psychotherapy to medication) is equivalent to what is found in general depressive patients ($g = 0.65$) [72].

Of importance, psychotherapy alone is not recommended when symptoms of depression are severe [68] and although medication combined with psychotherapy could be more frequently suggested to women, evidence of its efficacy is scarce and outdated [72]. Electroconvulsive therapy is the third-line treatment for psychotic or treatment-resistant postpartum women, but

again, few studies fully confirm its evidence [73, 74]. For an in-depth review on peripartum treatments we recommend Nillni and colleagues' publication [71].

The clinical decision about the most adequate treatment in PNMAD should be defined individually, according to women characteristics, the clinical setting conditions, the best clinical evidence, accessible treatments, and women preferences. Due to current limited options, new evidence-based alternatives that support woman needs and values in the peripartum period and inform treatment decisions are deemed necessary.

Given the negative impact of PPD, the lack of consensus concerning the use of pharmacotherapy, the low adherence to treatment, and current knowledge about tDCS efficacy, tolerability and safety profile in MDD [75], the upscale of tDCS for the treatment of pre- and postnatal depression has been suggested [76].

tDCS has a subthreshold effect on neurons resting membrane potential, inducing depolarization or hyperpolarization according to the direction of the current. The effects of longer and repeated stimulation sessions lead to local and distal neuroplastic changes [77]. Local tDCS effects target calcium-dependent synaptic plasticity and distal effects alter the networks' connectivity, synchronicity, and oscillatory patterns [78]. tDCS applications to reduce depressive symptoms are aimed to counteract the hypoactivity of the FP network and the left sided hyperactivity of the DMN. This pattern of brain activity is known to be associated with depressive symptoms [79], ruminative thinking, and negative bias, which are typically observed in PNMAD and to which we referred to in previous sections [57]. This pattern of brain activity is particularly associated with negative thoughts and self-referencing processes, as well as with avoidance and withdrawal behaviors outside [80] or inside the perinatal period [40].

The antidepressant effect of tDCS is well described in the literature with studies showing superiority to placebo, and antidepressant effect comparable to medication and transcranial magnetic stimulation [81], leading to greater and faster response to treatment [82]. On the contrary, the anxiolytic effect of tDCS is far from confirmed, both due to the reduced number of studies up to now conducted, as well as because the small number of studies show conflicting findings. For example, Movahed and colleagues [83] described the benefits of 10 sessions of cathodal tDCS over the right PFC in GAD patients. On the contrary, de Lima study [84] observing the effect of five sessions of bilateral stimulation in GAD (with the anode placed over the left DLPFC and the cathode over the right supraorbital area) did not confirm the expected improved mood and anxiety symptoms though showing improved physical stress symptoms. As for results from preclinical studies, tDCS seems to contribute to reduced negative bias [85, 86]. For an overview of the state-of-the-art about tDCS anxiolytic effects, we suggest Stein et al. [87].

In what concerns the application of tDCS in severe depression or psychosis, current literature recommends caution, due to the risk of tDCS-induced hypomania/mania (two of which refer to patients diagnosed with bipolar disorder and five refer to patients that started tDCS simultaneously to sertraline) observed in some studies. Of importance, despite the fact that the highest number of tDCS-induced psychotic episodes was reported in active stimulation groups, differences between active and sham groups were not statistically significative [88].

16.4.1 Summary of Findings of tDCS Studies in Perinatal Depression and Anxiety Disorders (and Psychosis)

The likelihood of obtaining clinically significant antidepressant effects using tDCS in perinatal depression is supported by previous work involving other noninvasive neuromodulatory approaches, such as repetitive transcranial magnetic stimulation (rTMS). To date, 16 studies were published on the rTMS antidepressant effect during pregnancy, enrolling 87 women and showing promising results [89–104]. Similarly,

five studies were published to tackle depression in the postpartum period, which enrolled 49 women and showed rTMS antidepressant benefits [105–109]. The latest systematic review on the application of rTMS/iTBS in the peripartum, found medium to large effect sizes in pregnancy (d = 0.40–2.18) and large effect sizes in the postpartum period (d = 2.27; [110]). However, interpretation of results warrant caution as those are mostly non-randomized controlled studies and thus suffer from common bias.

In what concerns tDCS, seven studies were conducted so far to observe tDCS effect in psychiatric disorders during pregnancy, but no report exists on the tDCS effects in the postpartum period. Four studies about tDCS in PNMAD concern the management of major depression disorder [76, 111–113] and two case studies observe tDCS effect in auditory hallucinations in the perinatal period (potentially not postpartum psychosis; [114, 115]. Finally, one study observed the effect of transcranial alternating current stimulation (tACS; [113]. Of these, only one study was a randomized controlled trial [116], one was open-label study [111], and four were case studies [112, 113].

Sreeraj and colleagues [112] published the first case report that observed the effect of tDCS in recurrent moderate depressive and anxious symptoms, starting tDCS protocol at the 6th week of pregnancy. The tDCS course consisted of 10 daily tDCS sessions, of 30 min at 2 mA, using the bifrontal dorsolateral prefrontal cortex montage (F3-F4) and electrode sponges of 25 cm^2. One week after treatment an 11th boost session was delivered. The patient achieved remission, and depression and anxiety scores were kept bellow clinical significance at one-month follow-up.

Palm et al. [111] published an abstract proceeding for an open-label study protocol aiming at observing the efficacy of 10 tDCS sessions of 30 minutes at 2 mA, to be delivered twice daily during an inpatient stay. After the first inpatient stay, a second optional tDCS course would follow in outpatient regime which included 10 sessions of 30 min tDCS delivered once daily. The dorsolateral prefrontal cortex montage was again adopted (F3-F4). Although the study goal was to recruit 10 pregnant women diagnosed with MDD, the available data concerns just three patients between the 19th and the 31st gestational week who have completed the second course of treatment. Whereas no statistically significant results were reported, cognitive performance and depressive symptoms decreased for all three patients and one achieved remission.

In Vigod et al. study [76], the authors observed the effects of 3 weeks (15 sessions) of 30-minute daily tDCS sessions at 2 mA, in an outpatient setting. The study included 10 depressed pregnant women in the active treatment group and 10 patients in the sham control group. Participants were enrolled between the 20th and the 26th week gestation, had several comorbid anxiety disorders (GAD, PD, OCD), and were medication free. The same bifrontal montage was adopted with the anode electrode placed over the left and the cathode electrode placed over the right DLPFC (35 cm^2 soaked sponges were used). The authors reported a remission rate of 75% at week 4 postpartum, maintained at 1-year follow-up. Clinical improvement was extended to anxiety-related symptoms. As this was a pilot study, it was not properly sampled, so that despite its encouraging results the effect size was small (d = .48).

Overall, these are encouraging findings. Besides confirming tDCS safety profile, the data suggest that 10 to 15 daily sessions of tDCS at 2 mA, using the F3-F4 montage and electrode between 25 to 35 cm^2 has a potential antidepressant effect across the three trimesters of pregnancy, extending its benefits to the typically comorbid anxiety symptoms. Additionally, tDCS may contribute to improve cognitive performance in depressed women. The clinical option regarding once or twice a day session should be discussed according to the available conditions.

Wilkening and colleagues [113] reported the first case study of a pregnant woman that presented moderate symptoms of depression that were managed with transcranial alternating current stimulation (tACS). The treatment course started at the 6th week of her second pregnancy. The authors aimed at altering endogenous oscil-

lations by applying nine sessions of Gamma tACS for 20 min (at 40 Hz, 48,000 cycles, 2 mA range, and offset at 1 mA). The F3-F4 montage was used and the electrodes were placed inside saline soaked sponges of 35 cm^2. The authors reported the safeness and positive results with complete remission achieved at 3 months follow-up (27 weeks pregnancy). No other studies report results concerning tACS which leads to the need for further research on the benefits of targeting particular patterns of brain function toward increased precision treatments.

The study of Shenoy et al. [114] reported the first case study on the use of tDCS as add-on to daily 12 mg iloperidone aimed to treat auditory verbal hallucinations during pregnancy. Starting treatment at the 18th week gestation, the tDCS montage used placed the anode at the left dorsolateral prefrontal cortex and the cathode at the left temporo-parietal junction (TP3). The patient completed 10 twice daily 20 min tDCS sessions at 2 mA intensity, with 3 h-interval in between, for 5 consecutive days. The hallucinations reduced progressively during the course of treatment and in the following weeks with no adverse effects for the mother nor for the fetus and no changes nor abnormalities across the remaining gestation weeks were reported.

Following these promising effects, Strube and colleagues [115] reported the first case study of stand-alone tDCS treatment in schizophrenia during pregnancy. The authors used a similar tDCS protocol as Shenoy et al. (2015), administering twice daily 30 min tDCS sessions with 3-hours interval at 2 mA, but extended the treatment duration to two weeks. The patient was in her 32nd gestational week, registered one previous episode of paranoia 2 years earlier, and by the time of the report presented relapsed persecutory delusions, vocal auditory hallucinations, and thought insertions. The anode electrode was positioned over the left dorsolateral prefrontal cortex (F3), and the cathode was positioned over the left temporoparietal junction (TP3). At 2 weeks of treatment the auditory hallucinations were remitted and remained so at 5 weeks follow-up. Global clinical and daily functioning assessment was markedly improved with overall enhanced quality of life. Together, these two case reports suggest tDCS can be effective to decrease auditory hallucinations, with global improvement of the mother functioning and positive impact in the future mother-baby dyad.

Overall, among studies during pregnancy, tDCS seems to be well tolerated, and no adverse or unexpected effects were found for the mother besides transient mild phosphenes [113] and minor burning sensations [112]. Of the utmost importance, no teratogenic effects or physiological impact was observed on the normal course of the pregnancy. Moreover, tDCS acceptability across studies seems favorable as suggested by dropout rates. All women enrolled in case studies completed the prescribed protocol and their extensions when available. Hence, whereas the RCTs reported a dropout rate of 10% (suggesting that withdrawal of patients is due to the negative impact that the daily visits to the clinic have on individuals and family's routines) [116], the open-label study was unclear as to the expected seven patients that were not reported [111].

Despite the encouraging findings, the quality of the data is still low as it is characterized by critical risk of biases due to attrition, absence of blinding procedures regarding intervention and assessments, incomplete reports, failure to establish a priori outcomes, and due to the short follow-up periods, which hamper the observation of important adverse events and negative outcomes that may occur during pregnancy (e.g., medical complications or teratogenic effects), the partum (e.g., premature delivery), or postpartum (e.g., low weight at birth). Considering these promising data, and the secure postpartum period (during which fear of adverse effects to the newborn have to be considered), it would be expected to find studies regarding the effect of tDCS during the postpartum period.

16.4.2 Safety Issues

Women in the peripartum period are considered a vulnerable population, and fetal safety is a core concern to researchers designing tDCS related studies and to clinicians deciding on the adequate

treatments in the perinatal mental health. This means that besides considering cumulative efficacy, researchers and clinicians must account for evidence on cumulative safety data.

The most common adverse effects after tDCS sessions are mild, and disappear short after stimulation [117]. Bikson and colleagues [118], in their review of more than 33,200 repeated tDCS sessions and 1000 subjects, spotted that when conventional tDCS protocols are followed (current intensity below or equal to 4 mA, for 40 minutes or less and 7.2 or less Coulombs), no serious adverse effects were found.

To show that the application of tDCS in the mother's scalp does not affect the baby, we may rely on full body finite element method (FEM) studies to understand the current field and the peaks it may reach in fetal volume. Evidence shows that, when using tDCS cephalic montages, peak current densities occur on the edges of the pad or between the pads [119]. Thus, it is not expected to have current passing beneath the neck and no current is expected to impact the fetal volume. From the six articles published so far observing tDCS in PNMAD and psychosis (all conducted during pregnancy), half reported no evidence of negative neonatal physiological impact. The remaining three failed to report neonatal safety outcomes. Regarding mothers' safety, three studies reported mild and temporary adverse effects (16% reported burning, buzzing, or tingling sensations at the electrode site, and 33.3% reported fleeting phosphenes) and no study reported serious adverse effects suggesting that tDCS is well tolerated.

As home-based tDCS seems to be a promising option for tDCS in mood and anxiety disorders, it is important to consider not only the ease of use of portable devices but also the safety specificities associated to its use in at-home settings [120]. For that, and to prevent over use and over dosage, the home-based devices must have a blocking system and in-built automatic systems to end stimulation if impedance levels are too high [121]. Moreover, for a responsible use of home-based tDCS devices, educating users, supervising the application process and adverse effects inspection should be implemented as part of the clinical protocol routine [120, 122, 123]. These should include the systematic (1) assessment of fetal and baby development and (2) reporting of potential side effects related to tDCS both in mothers and babies [124].

16.5 The Future of tDCS in Perinatal Mental Health

The decreased adherence to medication by pregnant women and women breastfeeding, the limitations of psychotherapy, and the absence of other evidence-based treatments to peripartum mental health disorders, suggest the need to urgently develop adjusted alternatives for the treatment of peripartum depression and anxiety disorders. tDCS safety profile and its potential efficacy strongly support tDCS scalability to the perinatal mental healthcare system, in particular to peripartum depression and akin phenotypes, as safety protocols have been tested and data strongly suggests its antidepressant benefits.

According to the literature, tDCS protocols could be implemented in PNMAD as stand-alone treatments (addressing the need for the development of medication-free alternatives) or as add-on to medication as suggested by evidence in psychosis—to reduce medication dosage and eventually boost treatment response. In particular, in depression-related phenotypes of PNMAD, the collection of further evidence is deemed necessary. The validation of the efficacy of traditional tDCS protocols targeting the dorsolateral prefrontal cortex and aiming to alter extant regional networks that participate in maternal brain functioning should be on the spotlight for the following years. This is especially true for the networks involved in transdiagnostic emotional and cognitive processes such as ruminative thinking.

Albeit the available data concerning the F3-F4 montage efficacy in peripartum depression and its extended effect to anxiety symptoms, other electrodes positioning await further investigation. Aiming at shaping current intensity targeting the dorsolateral prefrontal cortex, high-resolution FEM models showed that the OLE-system may be a strong candidate for future studies, as it offers

reduced electric field variability while maintaining the advantage of being easy to handle and use at the home setting [125].

Hence, in what regards perinatal depression the field is now ready for properly sampled randomized controlled studies, informed by the data regarding phenotypes and neuroendocrinal underpinnings and finally achieve the next leap on defining biomarkers toward precision tDCS. As for postpartum psychosis though, the field is still on its first stages and proof-of-concept studies should be the next step to confirm the benefits of tDCS in this particular diagnosis.

Although currently, tDCS is starting to be accessible in general psychiatric/mental health units, tDCS treatments are still limited to specialized medical centers, and its treatment courses of 10–20 sessions across 5–20 daily visits are too intensive and costly for patients and families. To address tDCS intensiveness, progress has been made toward remotely supervised, home-based, portable, preprogramed devices that guarantee the correct electrode positioning and avoid over dosage. So far, one home-based tDCS trial was successfully conducted for depression [122] with response and remission rates equivalent to clinic-based systems and large effect size (d = 1.53; [122]). Additionally, no evidence of adverse events was reported in this particular study or across distinctive studies in different neuropsychiatric disorders [126]. Following the trend of at-distance technological medical care, home-based tDCS devices may as well be added by virtual care systems and app-based psychological interventions promoting self-management of symptoms, increasing patient's engagement and perception of self-efficacy, and ultimately empowering patients in the management of their health condition. However, for the responsible uptake of home-based tDCS systems to perinatal disorders, further research is needed, and new studies should be implemented to test home-based programs efficacy and feasibility.

To our knowledge, so far, no cost-effectiveness study regarding tDCS in the peripartum depression was conducted. A cost-utility analysis study in non-resistant depression comparing treatment as usual vs treatment as usual add-on with tDCS is currently ongoing and its findings are expected by 2022 [127]. This study will further advance knowledge about the benefits of implementing tDCS in the pathways of care in perinatal mental health.

Finally, research on women's health is underdeveloped across biomedical fields. Particularly in the perinatal period, women, fetus, and newborns fall into the concept of vulnerable population. While acknowledging women in the peripartum and their babies as vulnerable groups have protected them from harmful interventions, it has also prevented faster progress in perinatal mental health care. In this sense, gender focused studies are needed to boost the understanding of the pathophysiological mechanisms in PNMAD. Recognizing the importance of investigating the psychological, neurocognitive, endocrinal, and epigenetic changes in the perinatal period will advance knowledge toward the development of novel therapies that may be translated into the clinical practice, improving high-quality perinatal pathways of care.

References

1. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Howard LM, Molyneaux E, Dennis C-L, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. Lancet Lond Engl. 2014;384:1775–88. https://doi.org/10.1016/S0140-6736(14)61276-9.
3. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry. 2010;67:1012. https://doi.org/10.1001/archgenpsychiatry.2010.111.
4. Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. Infant Behav Dev. 2010;33:1–6. https://doi.org/10.1016/j.infbeh.2009.10.005.
5. Kaplan PS, Danko CM, Everhart KD, Diaz A, Asherin R, Vogeli J, et al. Maternal depression and expressive communication in one-year-old infants. Infant Behav Dev. 2014;37:398–405. https://doi.org/10.1016/j.infbeh.2014.05.008.

6. Frieder A, Fersh M, Hainline R, Deligiannidis KM. Pharmacotherapy of postpartum depression: current approaches and novel drug development. CNS Drugs. 2019;33:265–82. https://doi.org/10.1007/s40263-019-00605-7.
7. Gelaye B, Rondon MB, Araya R, Williams MA. Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. Lancet Psychiatry. 2016;3:973–82. https://doi.org/10.1016/S2215-0366(16)30284-X.
8. Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and health predictors of national postpartum depression prevalence: a systematic review, meta-analysis, and meta-regression of 291 studies from 56 countries. Front Psych. 2017;8:248. https://doi.org/10.3389/fpsyt.2017.00248.
9. Biaggi A, Conroy S, Pawlby S, Pariante CM. Identifying the women at risk of antenatal anxiety and depression: a systematic review. J Affect Disord. 2016;191:62–77. https://doi.org/10.1016/j.jad.2015.11.014.
10. Putnam KT, Wilcox M, Robertson-Blackmore E, Sharkey K, Bergink V, Munk-Olsen T, et al. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry. 2017;4:477–85. https://doi.org/10.1016/S2215-0366(17)30136-0.
11. Wisner KL, Sit DKY, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiat. 2013;70:490–8. https://doi.org/10.1001/jamapsychiatry.2013.87.
12. Ban L, Gibson JE, West J, Fiaschi L, Oates MR, Tata LJ. Impact of socioeconomic deprivation on maternal perinatal mental illnesses presenting to UK general practice. Br J Gen Pract. 2012;62:e671–8. https://doi.org/10.3399/bjgp12X656801.
13. Munk-Olsen T, Laursen TM, Pedersen CB, Mors O, Mortensen PB. New parents and mental disorders: a population-based register study. JAMA. 2006;296:2582–9. https://doi.org/10.1001/jama.296.21.2582.
14. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry. 2008;65:805–15. https://doi.org/10.1001/archpsyc.65.7.805.
15. Denckla CA, Mancini AD, Consedine NS, Milanovic SM, Basu A, Seedat S, et al. Distinguishing postpartum and antepartum depressive trajectories in a large population-based cohort: the impact of exposure to adversity and offspring gender. Psychol Med. 2018;48:1139–47. https://doi.org/10.1017/S0033291717002549.
16. Radoš SN, Tadinac M, Herman R. Anxiety during pregnancy and postpartum: course, predictors and comorbidity with postpartum depression. Acta Clin Croat. 2018;57:39–51. https://doi.org/10.20471/acc.2018.57.01.05.
17. Heron J, O'Connor TG, Evans J, Golding J, Glover V, ALSPAC Study Team. The course of anxiety and depression through pregnancy and the postpartum in a community sample. J Affect Disord. 2004;80:65–73. https://doi.org/10.1016/j.jad.2003.08.004.
18. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095–105. https://doi.org/10.1001/jama.289.23.3095.
19. Lancaster CA, Gold KJ, Flynn HA, Yoo H, Marcus SM, Davis MM. Risk factors for depressive symptoms during pregnancy: a systematic review. Am J Obstet Gynecol. 2010;202:5–14. https://doi.org/10.1016/j.ajog.2009.09.007.
20. Andersson L, Sundström-Poromaa I, Bixo M, Wulff M, Bondestam K, åström M. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. Am J Obstet Gynecol 2003;189:148–154. https://doi.org/10.1067/mob.2003.336.
21. Rubertsson C, Hellström J, Cross M, Sydsjö G. Anxiety in early pregnancy: prevalence and contributing factors. Arch Womens Ment Health. 2014;17:221–8. https://doi.org/10.1007/s00737-013-0409-0.
22. Wenzel A, Haugen EN, Jackson LC, Brendle JR. Anxiety symptoms and disorders at eight weeks postpartum. J Anxiety Disord. 2005;19:295–311. https://doi.org/10.1016/j.janxdis.2004.04.001.
23. Furtado M, Chow CHT, Owais S, Frey BN, Van Lieshout RJ. Risk factors of new onset anxiety and anxiety exacerbation in the perinatal period: a systematic review and meta-analysis. J Affect Disord. 2018;238:626–35. https://doi.org/10.1016/j.jad.2018.05.073.
24. Munk-Olsen T, Laursen TM, Meltzer-Brody S, Mortensen PB, Jones I. Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders. Arch Gen Psychiatry. 2012;69:428–34. https://doi.org/10.1001/archgenpsychiatry.2011.157.
25. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. Br J Psychiatry. 1987;150:782–6. https://doi.org/10.1192/bjp.150.6.782.
26. Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. Lancet Lond Engl. 2014;384:1789–99. https://doi.org/10.1016/S0140-6736(14)61278-2.
27. De Raedt R, Koster EHW. Understanding vulnerability for depression from a cognitive neuroscience perspective: a reappraisal of attentional factors and a new conceptual framework. Cogn Affect Behav Neurosci. 2010;10:50–70. https://doi.org/10.3758/CABN.10.1.50.
28. Mellings TM, Alden LE. Cognitive processes in social anxiety: the effects of self-focus, rumi-

nation and anticipatory processing. Behav Res Ther. 2000;38:243–57. https://doi.org/10.1016/s0005-7967(99)00040-6.
29. Hsu KJ, Beard C, Rifkin L, Dillon DG, Pizzagalli DA, Björgvinsson T. Transdiagnostic mechanisms in depression and anxiety: the role of rumination and attentional control. J Affect Disord. 2015;188:22–7. https://doi.org/10.1016/j.jad.2015.08.008.
30. Miller ES, Hoxha D, Wisner KL, Gossett DR. Obsessions and compulsions in postpartum women without obsessive compulsive disorder. J Womens Health 2002. 2015;24:825–30. https://doi.org/10.1089/jwh.2014.5063.
31. Hartley S, Haddock G, Sa DVe, Emsley R, Barrowclough C. An experience sampling study of worry and rumination in psychosis. Psychol Med. 2014;44:1605–14. https://doi.org/10.1017/S0033291713002080.
32. Tester-Jones M, O'Mahen H, Watkins E, Karl A. The impact of maternal characteristics, infant temperament and contextual factors on maternal responsiveness to infant. Infant Behav Dev. 2015;40:1–11. https://doi.org/10.1016/j.infbeh.2015.02.014.
33. Medaglia JD. Clarifying cognitive control and the controllable connectome. WIREs Cogn Sci. 2019;10:e1471. https://doi.org/10.1002/wcs.1471.
34. DeJong H, Fox E, Stein A. Rumination and postnatal depression: a systematic review and a cognitive model. Behav Res Ther. 2016;82:38–49. https://doi.org/10.1016/j.brat.2016.05.003.
35. Lucassen N, Tharner A, Van IJzendoorn MH, Bakermans-Kranenburg MJ, Volling BL, Verhulst FC, et al. The association between paternal sensitivity and infant–father attachment security: a meta-analysis of three decades of research. J Fam Psychol. 2011;25:986–92. https://doi.org/10.1037/a0025855.
36. Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child Dev. 1996;67:2512–26.
37. Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. CNS Spectr. 2015;20:48–59. https://doi.org/10.1017/S1092852914000480.
38. Almanza-Sepulveda ML, Fleming AS, Jonas W. Mothering revisited: a role for cortisol? Horm Behav. 2020;121:104679. https://doi.org/10.1016/j.yhbeh.2020.104679.
39. Posillico CK, Schwarz JM. An investigation into the effects of antenatal stressors on the postpartum neuroimmune profile and depressive-like behaviors. Behav Brain Res. 2016;298:218–28. https://doi.org/10.1016/j.bbr.2015.11.011.
40. Pawluski JL, Lonstein JS, Fleming AS. The neurobiology of postpartum anxiety and depression. Trends Neurosci. 2017;40:106–20. https://doi.org/10.1016/j.tins.2016.11.009.
41. Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. Front Neuroendocrinol. 2019;52:165–80. https://doi.org/10.1016/j.yfrne.2018.12.001.
42. Payne JL, Osborne LM. Biomarkers of postpartum psychiatric disorders. Academic Press; 2019.
43. Carmona S, Martínez-García M, Paternina-Die M, Barba-Müller E, Wierenga LM, Alemán-Gómez Y, et al. Pregnancy and adolescence entail similar neuroanatomical adaptations: a comparative analysis of cerebral morphometric changes. Hum Brain Mapp. 2019;40:2143–52. https://doi.org/10.1002/hbm.24513.
44. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat Rev Neurosci. 2006;7:697–709. https://doi.org/10.1038/nrn1970.
45. Numan M. Motivational systems and the neural circuitry of maternal behavior in the rat. Dev Psychobiol. 2007;49:12–21. https://doi.org/10.1002/dev.20198.
46. Gingnell M, Bannbers E, Moes H, Engman J, Sylvén S, Skalkidou A, et al. Emotion reactivity is increased 4-6 weeks postpartum in healthy women: a longitudinal fMRI Study. PLoS One. 2015;10 https://doi.org/10.1371/journal.pone.0128964.
47. Moses-Kolko EL, Horner MS, Phillips ML, Hipwell AE, Swain JE. In search of neural endophenotypes of postpartum psychopathology and disrupted maternal caregiving. J Neuroendocrinol. 2014;26:665–84. https://doi.org/10.1111/jne.12183.
48. Bannbers E, Gingnell M, Engman J, Morell A, Sylvén S, Skalkidou A, et al. Prefrontal activity during response inhibition decreases over time in the postpartum period. Behav Brain Res. 2013;241:132–8. https://doi.org/10.1016/j.bbr.2012.12.003.
49. Zheng J-X, Chen Y-C, Chen H, Jiang L, Bo F, Feng Y, et al. Disrupted spontaneous neural activity related to cognitive impairment in postpartum women. Front Psychol. 2018;9 https://doi.org/10.3389/fpsyg.2018.00624.
50. Deligiannidis KM, Sikoglu EM, Shaffer SA, Frederick B, Svenson AE, Kopoyan A, et al. GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: a preliminary study. J Psychiatr Res. 2013;47:816–28. https://doi.org/10.1016/j.jpsychires.2013.02.010.
51. Laurent HK, Ablow JC. The missing link: mothers' neural response to infant cry related to infant attachment behaviors. Infant Behav Dev. 2012;35:761–72. https://doi.org/10.1016/j.infbeh.2012.07.007.
52. Kim P. Human maternal brain plasticity: adaptation to parenting. New Dir Child Adolesc Dev. 2016;2016:47–58. https://doi.org/10.1002/cad.20168.
53. Moses-Kolko EL, Fraser D, Wisner KL, James JA, Saul AT, Fiez JA, et al. Rapid habituation of ventral striatal response to reward receipt in postpartum depression. Biol Psychiatry. 2011;70:395–9. https://doi.org/10.1016/j.biopsych.2011.02.021.
54. Xiao-juan W, Jian W, Zhi-hong L, Yan M, Shi-wei Z. Increased posterior cingulate, medial frontal and decreased temporal regional homogeneity

in depressed mothers. A resting-state functional magnetic resonance study. Procedia Environ Sci. 2011;8:737–43. https://doi.org/10.1016/j.proenv.2011.10.112.
55. Swain JE, Tasgin E, Mayes LC, Feldman R, Constable RT, Leckman JF. Maternal brain response to own baby-cry is affected by cesarean section delivery. J Child Psychol Psychiatry. 2008;49:1042–52. https://doi.org/10.1111/j.1469-7610.2008.01963.x.
56. Chase HW, Moses-Kolko EL, Zevallos C, Wisner KL, Phillips ML. Disrupted posterior cingulate–amygdala connectivity in postpartum depressed women as measured with resting BOLD fMRI. Soc Cogn Affect Neurosci. 2014;9:1069–75. https://doi.org/10.1093/scan/nst083.
57. Duan C, Cosgrove J, Deligiannidis KM. Understanding peripartum depression through neuroimaging: a review of structural and functional connectivity and molecular imaging research. Curr Psychiatry Rep. 2017;19:70. https://doi.org/10.1007/s11920-017-0824-4.
58. Fusté M, Pauls A, Worker A, Reinders AATS, Simmons A, Williams SCR, et al. Brain structure in women at risk of postpartum psychosis: an MRI study. Transl Psychiatry. 2017;7 https://doi.org/10.1038/s41398-017-0003-8.
59. Lanczik M, Fritze J, Hofmann E, Schulz C, Knoche M, Becker T. Ventricular abnormality in patients with postpartum psychoses. Arch Womens Ment Health. 1998;1:45–7. https://doi.org/10.1007/s007370050005.
60. Udaya SC, Chauhan BN, Philip VJ. Bright splenium of a psychotic mind. Ann Indian Acad Neurol. 2015;18:80–3. https://doi.org/10.4103/0972-2327.145287.
61. Hübner-Liebermann B, Hausner H, Wittmann M. Recognizing and treating Peripartum depression. Dtsch Aerzteblatt Online. 2012; https://doi.org/10.3238/arztebl.2012.0419.
62. Guille C, Newman R, Fryml LD, Lifton CK, Epperson CN. Management of Postpartum Depression. J Midwifery Womens Health. 2013;58:643–53. https://doi.org/10.1111/jmwh.12104.
63. Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal depression with antidepressants: an international review. Aust N Z J Psychiatry. 2018;52:320–7. https://doi.org/10.1177/0004867418762057.
64. Milgrom J, Danaher BG, Gemmill AW, Holt C, Holt CJ, Seeley JR, et al. Internet cognitive behavioral therapy for women with postnatal depression: a randomized controlled trial of MumMoodBooster. J Med Internet Res. 2016;18:e54. https://doi.org/10.2196/jmir.4993.
65. Olfson M, Blanco C, Marcus SC. Treatment of adult depression in the United States. JAMA Intern Med. 2016;176:1482. https://doi.org/10.1001/jamainternmed.2016.5057.
66. Verhaak PFM, van Dijk CE, Nuijen J, Verheij RA, Schellevis FG. Mental health care as delivered by Dutch general practitioners between 2004 and 2008. Scand J Prim Health Care. 2012;30:156–62. https://doi.org/10.3109/02813432.2012.688707.
67. Bellantuono C, Vargas M, Mandarelli G, Nardi B, Martini MG. The safety of serotonin-noradrenaline reuptake inhibitors (SNRIs) in pregnancy and breastfeeding: a comprehensive review. Hum Psychopharmacol Clin Exp. 2015;30:143–51. https://doi.org/10.1002/hup.2473.
68. Mohammed AA. The adverse effects of antidepressant medication treatments on the offspring of women with perinatal depression. Sci J Res Rev. 2019:1. https://doi.org/10.33552/SJRR.2019.01.000509.
69. Lupattelli A, Spigset O, Björnsdóttir I, Hämeen-Anttila K, Mårdby A-C, Panchaud A, et al. Patterns and factors associated with low adherence to psychotropic medications during pregnancy--a cross-sectional, multinational web-based study. Depress Anxiety. 2015;32:426–36. https://doi.org/10.1002/da.22352.
70. Leggett C, Costi L, Morrison JL, Clifton VL, Grzeskowiak LE. Antidepressant use in late gestation and breastfeeding rates at discharge from Hospital. J Hum Lact. 2017; https://journals.sagepub.com/doi/10.1177/0890334416678209. Accessed 26 June 2020
71. Nillni YI, Mehralizade A, Mayer L, Milanovic S. Treatment of depression, anxiety, and trauma-related disorders during the perinatal period: a systematic review. Clin Psychol Rev. 2018;66:136–48. https://doi.org/10.1016/j.cpr.2018.06.004.
72. Sockol LE, Epperson CN, Barber JP. A meta-analysis of treatments for perinatal depression. Clin Psychol Rev. 2011;31:839–49. https://doi.org/10.1016/j.cpr.2011.03.009.
73. Rundgren S, Brus O, Båve U, Landén M, Lundberg J, Nordanskog P, et al. Improvement of postpartum depression and psychosis after electroconvulsive therapy: a population-based study with a matched comparison group. J Affect Disord. 2018;235:258–64. https://doi.org/10.1016/j.jad.2018.04.043.
74. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder. Can J Psychiatry Rev Can Psychiatr. 2016;61:588–603. https://doi.org/10.1177/0706743716659276.
75. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128:56–92. https://doi.org/10.1016/j.clinph.2016.10.087.
76. Vigod SN, Murphy KE, Dennis C-L, Oberlander TF, Ray JG, Daskalakis ZJ, et al. Transcranial direct current stimulation (tDCS) for depression in pregnancy: a pilot randomized controlled trial. Brain Stimul. 2019;12:1475–83. https://doi.org/10.1016/j.brs.2019.06.019.

77. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.
78. Bennabi D, Haffen E. Transcranial direct current stimulation (tDCS): a promising treatment for major depressive disorder? Brain Sci. 2018;8 https://doi.org/10.3390/brainsci8050081.
79. Borrione L, Bellini H, Razza LB, Avila AG, Baeken C, Brem A-K, et al. Precision non-implantable neuromodulation therapies: a perspective for the depressed brain. Braz J Psychiatry. 2020; https://doi.org/10.1590/1516-4446-2019-0741.
80. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3:472–80. https://doi.org/10.1016/s2215-0366(15)00579-9.
81. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiat. 2017;74:143–52. https://doi.org/10.1001/jamapsychiatry.2016.3644.
82. Padberg F, Kumpf U, Mansmann U, Palm U, Plewnia C, Langguth B, et al. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;267:751–66. https://doi.org/10.1007/s00406-017-0769-y.
83. Sadeghi Movahed F, Alizadeh Goradel J, Pouresmali A, Mowlaie M. Effectiveness of transcranial direct current stimulation on worry, anxiety, and depression in generalized anxiety disorder: a randomized, single-blind pharmacotherapy and sham-controlled clinical trial. Iran J Psychiatry Behav Sci. 2018;12 https://doi.org/10.5812/ijpbs.11071.
84. de Lima AL, Braga FMA, da Costa RMM, Gomes EP, Brunoni AR, Pegado R. Transcranial direct current stimulation for the treatment of generalized anxiety disorder: a randomized clinical trial. J Affect Disord. 2019;259:31–7. https://doi.org/10.1016/j.jad.2019.08.020.
85. Heeren A, Billieux J, Philippot P, De Raedt R, Baeken C, de Timary P, et al. Impact of transcranial direct current stimulation on attentional bias for threat: a proof-of-concept study among individuals with social anxiety disorder. Soc Cogn Affect Neurosci. 2016;12:251–60. https://doi.org/10.1093/scan/nsw119.
86. Ironside M, O'Shea J, Cowen PJ, Harmer CJ. Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety. Biol Psychiatry. 2016;79:823–30. https://doi.org/10.1016/j.biopsych.2015.06.012.
87. Stein DJ, Fernandes Medeiros L, Caumo W, Torres IL. Transcranial direct current stimulation in patients with anxiety: current perspectives. Neuropsychiatr Dis Treat. 2020;16:161–9. https://doi.org/10.2147/NDT.S195840.
88. Brunoni AR, Moffa AH, Sampaio-Júnior B, Gálvez V, Loo CK. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. Brain Stimul. 2017;10:260–2. https://doi.org/10.1016/j.brs.2016.11.005.
89. Burton C, Gill S, Clarke P, Galletly C. Maintaining remission of depression with repetitive transcranial magnetic stimulation during pregnancy: a case report. Arch Womens Ment Health. 2014;17:247–50. https://doi.org/10.1007/s00737-014-0418-7.
90. Cohen RB, Ferreira MS, Ferreira MJL, Fregni F. Use of repetitive transcranial magnetic stimulation for the management of bipolar disorder during the postpartum period. Brain Stimul Basic Transl Clin Res Neuromodulation. 2008;1:224–6. https://doi.org/10.1016/j.brs.2008.05.002.
91. Ferrão YA, da Silva R de MF, Ferrão YA, da Silva R de MF. Repetitive transcranial magnetic stimulation for the treatment of major depression during pregnancy. Braz J Psychiatry. 2018;40:227–8. https://doi.org/10.1590/1516-4446-2017-2522.
92. Gahr M, Blacha C, Connemann BJ, Freudenmann RW, Schönfeldt-Lecuona C. Successful treatment of major depression with electroconvulsive therapy in a pregnant patient with previous non-response to prefrontal rTMS. Pharmacopsychiatry. 2012;45:79–80. https://doi.org/10.1055/s-0031-1297936.
93. Kim DR, Wang E, McGeehan B, Snell J, Ewing G, Iannelli C, et al. Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder. Brain Stimul. 2019;12:96–102. https://doi.org/10.1016/j.brs.2018.09.005.
94. Kim DR, Epperson N, Paré E, Gonzalez JM, Parry S, Thase ME, et al. An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. J Women's Health. 2011;20:255–61. https://doi.org/10.1089/jwh.2010.2353.
95. Klirova M, Novak T, Kopecek M, Mohr P, Strunzova V. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. Neuro Endocrinol Lett. 2008;29:69–70.
96. Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. J Clin Psychiatry. 1999;60:50–2. https://doi.org/10.4088/jcp.v60n0111.
97. Özten EE, Sayar GH, Karamustafalıoğlu KO. Antidepressant effect of 58 sessions of rTMS in a pregnant woman with recurrent major depressive disorder: a case report. Prim Care Companion J Clin Psychiatry. 2013;2:22.
98. Hizli Sayar G, Ozten E, Tufan E, Cerit C, Kagan G, Dilbaz N, et al. Transcranial magnetic stimulation during pregnancy. Arch Womens Ment

Health. 2014;17:311–5. https://doi.org/10.1007/s00737-013-0397-0.
99. Tan O, Tarhan N, Coban A, Baripoglu SK, Guducu F, Izgi HB, et al. Antidepressant effect of 58 sessions of rTMS in a pregnant woman with recurrent major depressive disorder. Prim Care Companion J Clin Psychiatry. 2008;10:69–71. https://doi.org/10.4088/PCC.v10n0113a.
100. Tarhan N, Sayar FGH, Tan O, Kağan G. Efficacy of high-frequency repetitive transcranial magnetic stimulation in treatment-resistant depression. Clin EEG Neurosci. 2012; https://doi.org/10.1177/1550059412449752.
101. Trevizol AP, Vigod SN, Daskalakis ZJ, Vila-Rodriguez F, Downar J, Blumberger DM. Intermittent theta burst stimulation for major depression during pregnancy. Brain Stimul Basic Transl Clin Res Neuromodulation. 2019;12:772–4. https://doi.org/10.1016/j.brs.2019.01.003.
102. Xiong W, Lopez R, Cristancho P, Xiong W, Lopez R, Cristancho P. Transcranial magnetic stimulation in the treatment of peripartum bipolar depression: a case report. Braz J Psychiatry. 2018;40:344–5. https://doi.org/10.1590/1516-4446-2018-0037.
103. Zhang X, Liu K, Sun J, Zheng Z. Safety and feasibility of repetitive transcranial magnetic stimulation (rTMS) as a treatment for major depression during pregnancy. Arch Womens Ment Health. 2010;13:369–70. https://doi.org/10.1007/s00737-010-0163-5.
104. Zhang D, Hu Z. RTMS may be a good choice for pregnant women with depression. Arch Womens Ment Health. 2009;12:189–90. https://doi.org/10.1007/s00737-009-0058-5.
105. Brock DG, Demitrack MA, Groom P, Holbert R, Rado JT, Gross PK, et al. Effectiveness of NeuroStar transcranial magnetic stimulation (TMS) in patients with major depressive disorder with postpartum onset. Brain Stimul Basic Transl Clin Res Neuromodulation. 2016;9:e7. https://doi.org/10.1016/j.brs.2016.06.023.
106. Garcia KS, Flynn P, Pierce KJ, Caudle M. Repetitive transcranial magnetic stimulation treats postpartum depression. Brain Stimul. 2010;3:36–41. https://doi.org/10.1016/j.brs.2009.06.001.
107. Myczkowski ML, Dias AM, Luvisotto T, Arnaut D, Bellini BB, Mansur CG, et al. Effects of repetitive transcranial magnetic stimulation on clinical, social, and cognitive performance in postpartum depression. Neuropsychiatr Treat. 2012;8:491–500. https://doi.org/10.2147/ndt.s33851.
108. Ogden M, Lyndon W, Pridmore S. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode with postpartum onset - a case study. Ger J Psychiatry. 1999;2:43.
109. Cox EQ, Killenberg S, Frische R, McClure R, Hill M, Jenson J, et al. Repetitive transcranial magnetic stimulation for the treatment of postpartum depression. J Affect Disord. 2020;264:193–200. https://doi.org/10.1016/j.jad.2019.11.069.
110. Cole J, Bright K, Gagnon L, McGirr A. A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression. J Psychiatr Res. 2019;115:142–50. https://doi.org/10.1016/j.jpsychires.2019.05.015.
111. Palm U, Kirsch B, Leitner B, Popovic D, Padberg F. P017 transcranial direct current stimulation (tDCS) for the treatment of depression during pregnancy: a pilot study. Clin Neurophysiol. 2017;128:e17–8. https://doi.org/10.1016/j.clinph.2016.10.146.
112. Sreeraj VS, Bose A, Shanbhag V, Narayanaswamy JC, Venkatasubramanian G, Benegal V. Monotherapy with tDCS for treatment of depressive episode during pregnancy: a case report. Brain Stimul Basic Transl Clin Res Neuromodulation. 2016;9:457–8. https://doi.org/10.1016/j.brs.2016.03.007.
113. Wilkening A, Kurzeck A, Dechantsreiter E, Padberg F, Palm U. Transcranial alternating current stimulation for the treatment of major depression during pregnancy. Psychiatry Res. 2019;279:399–400. https://doi.org/10.1016/j.psychres.2019.06.009.
114. Shenoy S, Bose A, Chhabra H, Dinakaran D, Agarwal SM, Shivakumar V, et al. Transcranial direct current stimulation (tDCS) for auditory verbal hallucinations in schizophrenia during pregnancy: a case report. Brain Stimul. 2015;8:163–4. https://doi.org/10.1016/j.brs.2014.10.013.
115. Strube W, Kirsch B, Padberg F, Hasan A, Palm U. Transcranial direct current stimulation as monotherapy for the treatment of auditory hallucinations during pregnancy: a case report. J Clin Psychopharmacol. 2016;36:534–5. https://doi.org/10.1097/JCP.0000000000000554.
116. Vigod SN, Murphy KE, Dennis CL, Oberlander TF, Ray JG, Daskalakis ZJ, et al. Transcranial direct current stimulation (tDCS) for depression in pregnancy: a pilot randomized controlled trial. Brain Stimul. 2019; https://doi.org/10.1016/j.brs.2019.06.019.
117. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14:1133–45. https://doi.org/10.1017/S1461145710001690.
118. Bikson M, Grossman P, Thomas C, Zannou AL, Adnan T, Mourdoukoutas AP, et al. Safety of transcranial direct current stimulation: evidence based update 2016. 2016;9:641–61. https://doi.org/10.1016/j.brs.2016.06.004.Safety.
119. Noetscher GM, Yanamadala J, Makarov SN, Pascual-Leone A. Comparison of cephalic and extracephalic montages for transcranial direct current stimulation-a numerical study. IEEE Trans Biomed Eng. 2014;61:2488–98. https://doi.org/10.1109/TBME.2014.2322774.
120. Carvalho F, Brietzke AP, Gasparin A, Dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device develop-

ment: an updated protocol used at home in healthy subjects and fibromyalgia patients. J Vis Exp JoVE. 2018; https://doi.org/10.3791/57614.
121. Carvalho F, Brietzke AP, Gasparin A, dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. J Vis Exp. 2018:e57614. https://doi.org/10.3791/57614.
122. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–83. https://doi.org/10.1016/j.jad.2019.04.041.
123. Knotkova H, Nitsche M, Bikson M, Woods A. Home-based patient-delivered remotely supervised transcranial direct current stimulation. Pract. Guide Transcranial Direct Curr. Stimul. - Princ. Proced. Appl., Springer; 2019.
124. Kurzeck AK, Kirsch B, Weidinger E, Padberg F, Palm U. Transcranial direct current stimulation (tDCS) for depression during pregnancy: scientific evidence and what is being said in the media-a systematic review. Brain Sci. 2018;8:155. https://doi.org/10.3390/brainsci8080155.
125. Seibt O, Brunoni AR, Huang Y, Bikson M. The pursuit of DLPFC: non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS). Brain Stimul. 2015;8:590–602. https://doi.org/10.1016/j.brs.2015.01.401.
126. Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. Front Syst Neurosci. 2015;9:26. https://doi.org/10.3389/fnsys.2015.00026.
127. Sauvaget A, Lagalice L, Schirr-Bonnans S, Volteau C, Péré M, Dert C, et al. Cost-utility analysis of transcranial direct current stimulation (tDCS) in non-treatment-resistant depression: the DISCO randomised controlled study protocol. BMJ Open. 2020;10:e033376. https://doi.org/10.1136/bmjopen-2019-033376.

Modulating Cognition in Healthy Young Adults with tDCS

17

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Abbreviations

BART	Balloon analogue risk task
BOLD signal	Blood-oxygen-level-dependent signal
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
GNGT	Go/no-go task
IFC	Inferior frontal cortex
IFG	Inferior frontal gyrus
IGT	Iowa gambling task
IPS	Intraparietal sulcus
M1	Primary motor cortex
MMN	Mismatch negativity
MTL	Medial temporal lobe
PET	Positron emission tomography
preSMA	Pre-supplementary motor area
PT	Planum temporale
RGT	Risky-gains task
SST	Stop-signal task
SSRT	Stop-signal reaction time
tDCS	Transcranial direct current stimulation
TEP	TMS-evoked potential
TMS	Transcranial magnetic stimulation
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex
WM	Working memory

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17.1 Introduction

To date, most studies that have examined the effects of transcranial direct current stimulation (tDCS) on human cognition and the underlying neurophysiological principles assessed young healthy adults. We review the effects of tDCS on high-level cognitive functions in this population, specifically focusing on attention, executive functions, language, numerical cognition and general learning and memory. Additionally, we further address individual differences for stimulation outcomes. Given the observed heterogeneity, the standards for minimum participant numbers for study designs have evolved. Appreciating this issue while also attempting to provide a complete picture of the literature, references to earlier studies are integrated in the main body of the text, while we applied the current standards to the studies that are listed in the respective tables. Accordingly, only studies fulfilling the following criteria were included in the tables: number of participants per condition ≥15, information regarding age and gender was provided, age <40 years and >18 years. Further, studies with a wash-out period between conditions <1 day or without an appropriate control condition were excluded.

17.2 Effects of tDCS on Attention

Attention is a complex construct that can be divided into three distinct subcomponents: orienting, alerting and executive control, each of which has specific neural correlates in fronto-parietal networks [150, 153]. As attention is fundamental to cognition, many tDCS studies include attention paradigms in addition to their primary cognitive function of interest to exclude the possibility of general effects on attention. The present chapter, however, deals with the studies specifically modulating attentional processes through tDCS. Table 17.1 summarises the methodological parameters employed by the relevant studies to date.

Nikolin and colleagues [133] examined the effects of tDCS on the alerting component of attention, as assessed by a continuous performance task. They targeted the left dorsolateral prefrontal cortex (DLPFC) with high-definition (HD) anodal tDCS. With HD-tDCS, a centre electrode is surrounded by an array of return electrodes (typically four) or by a ring-shaped return electrode, providing more focal stimulation compared to conventional montages involving only two electrodes. The authors neither observed any difference on attentional performance between sham and anodal tDCS applied over the left DLPFC nor for tDCS applied over the planum temporale (PT) or left medial temporal lobe (MTL). This lack of an effect following left DLPFC stimulation is at odds with other studies, which used the more conventional two-electrode montage [34, 130]. Likewise, Fukai and colleagues [62] applied tDCS bilaterally to the DLPFC. Subsequently, participants performed a sustained visual attention task and the activation of their dopamine system was assessed with [^{11}C]-raclopride positron emission tomography (PET) scans. Active stimulation improved reaction times compared to sham. In agreement with the behavioural effect of the stimulation, PET measurements also found a significant release of dopamine in the right ventral striatum, which correlated with the behavioural improvement, thus corroborating the crucial role of dopamine in cognitive control.

A study by Stone and Tesche [177] constituted the first successful modulation of attentional orienting using tDCS. Therein, both anodal and cathodal tDCS over the left posterior parietal cortex (PPC) was associated with a diminished ability to shift the focus of attention (i.e. spatial orienting) from stimuli subtending narrow visual angles to those subtending wide visual angles (local-to-global attention shift). There was no change from baseline to active tDCS conditions in this study, but the relative difference between active and sham tDCS rested primarily on the increased performance in the sham condition relative to the baseline assessment. Two subsequent studies confirmed that the right PPC plays an important role in attentional orienting, while anodal tDCS applied to either the left PPC or the left DLPFC did not modulate the assessed attentional functions [110, 161].

Table 17.1 The effects of tDCS on attention

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Chechlacz et al. [29]	Crossover P4/P3 vs. P3/P4 vs. S	*lPPC, rPPC*	21 (11 f), 25.8 ± 5.3 y	A(P4): 5 × 5 cm/C(P3): 5 × 5 cm A(P3): 5 × 5 cm/C(P4): 5 × 5 cm	1.5 mA, 20 min, online	Online: visual attention compared to baseline	Accuracy: ↓ (P3/P4 compared to P4/P3 and S for left targets with similar distractors). RT: ↑ (less reduction of RTs compared to S for all distractors in P3/P4, for similar distractors only in P4/P3). No effect of session order.
Fukai et al. [62]	Crossover F3/F4 vs. S	*lDLPFC, rDLPFC*	20 (0 f), 20–26 y	A(F3): 35 cm^2/C(F4): 35 cm^2	2 mA, 2 × 13 min (20 min interval), offline	Offline: enhanced visual attention) and PET of dopamine system	Accuracy: ↑ (compared to S depending on age). Concentrations of [^{11}C]-raclopride BPND in right ventral striatum: ↓ [^{11}C]-raclopride BPND, demonstrating dopamine release = significant predictor of SD of RT.
Hanenberg et al. [76]	Crossover C6–T8/ext. vs. ext./C6–T8 vs. S	*Posterior superior temporal cortex*	20 (10 f), 24.3 ± 0.6 y, 18–30 y	A(C6–T8): 5 × 7 cm/C (*left shoulder*): 7 × 14 cm C(C6–T8): 5 × 7 cm/A(*left shoulder*): 7 × 14 cm	1 mA, 16 min, online/offline	Online/offline: auditory selective spatial attention and EEG	Errors (pre-normalised): ↓ (C6–T8/ext.), n.s. (ext./C6–T8, S), especially for ipsilateral (right) targets. Auditory ERPs amplitude: N1 and P2: n.s., N2: ↑ (C6–T8/ext. for contralateral targets). Corr: increase in accuracy with increasing amplitude for targets in ipsilateral hemispace.

(continued)

Table 17.1 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Lewald [106]	Crossover C5–T7 + C6–T8/2ext vs. S	*Auditory regions of temporal lobe*	24 (12 f), 22.6 ± 0.7 y, 18–29 y	2 × A(C5–T7, C6–T8): 5 × 7 cm/2 × C (*shoulders*): 7 × 14 cm	1 mA, 30 min, offline	Offline: pre-post auditory selective spatial attention	Performance (normalised): ↑ (C5–T7 + C6–T8/2ext vs. S) Effect mostly relying on first session. No dependence on baseline performance.
Li et al. [108]	Crossover F4/ext. vs. P4/ext. vs. Oz/ext.	*rDLPFC, rPPC, VC*	*Exp 1:* 27 (15 f), 22.15 ± 2.2 y *Exp 2:* 21 (13 f), 21.24 ± 1.9 y	A(F4): 5 × 5 cm/C(*left cheek*) A(P4): 5 × 5 cm/C(*left cheek*) A(Oz): 5 × 5 cm/C(*left cheek*)	1.5 mA, 15 min, offline	Offline: visual WM (change detection in bar orientation)	WM performance (attention scope): ↑ (P4/ext. compared to Oz/ext.). WM performance (attentional control): ↑ (F4/ext. compared to Oz/ext.). Same pattern for central and bilateral stimulus presentation.
Lo et al. [110]	Crossover P4/*cSOA* vs. S	*rPPC*	26 (13 f), 24.4 ± 4.0 y	A(P4): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1.5 mA, 20 min, offline	Offline: pre-post ANT	RT (orienting effect): ↑ (P4/*lSOA*). RT (alerting effect): n.s. RT (executive effect): n.s.

Mannarelli et al. [117]	Crossover *Cerebellum*/ext. vs. ext./*cerebellum* vs. S	*Cerebellum*	15 (7 f), 27 ± 3 y	A(1 cm below and 4 cm lateral to inion): 25 cm^2/C(*left deltoid*): 25 cm^2 C(1 cm below and 4 cm lateral to inion): 25 cm^2/A(*left deltoid*): 25 cm^2	2 mA, 20 min, offline	Offline: pre-post, novelty task and EEG	Error: ↑ (ext./*cerebellum*), n.s. (*cerebellum*/ext., S). P3 latency: n.s. P3 amplitude: ↓ (ext./*cerebellum*), n.s. (*cerebellum*/ext., S) N1 latency: ↓ (ext./*cerebellum*) n.s. (*cerebellum*/ext., S). N1 amplitude: ↓ (ext./*cerebellum*), n.s. (*cerebellum*/ext., S) N2 latency: n.s., N2 amplitude: ↓ (ext./*cerebellum*), n.s. (*cerebellum*/ext., S).
Mannarelli et al. [118]	Crossover *Cerebellum*/ext. vs. ext./*cerebellum* vs. S	*Cerebellum*	25 (13 f), 26.1 ± 2.1 y, 21–29 y	A(1 cm below and 4 cm lateral to inion): 25 cm^2/C(*left deltoid*): 25 cm^2 C(1 cm below and 4 cm lateral to inion): 25 cm^2/A(*left deltoid*): 25 cm^2	2 mA, 20 min, offline	Offline: pre-post ANT	Network efficiency (alerting network): n.s. Network efficiency (orienting network): n.s. Network efficiency (executive network): ↓ (ext./*cerebellum*), n.s. (*cerebellum*/ext., S). Accuracy: n.s. RT (overall): n.s. RT (congruent and incongruent targets): ↓ (*cerebellum*/ext., S). RT (congruent targets): ↓ (ext./*cerebellum*).

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Table 17.1 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
McDermott et al. [123]	Parallel Oz/*rSOA* vs. *rSOA*/Oz vs. S	*Occipital cortex*	48 (21 f), 24.13 y, 20–30 y	A(*midline occipital cortex*): 5 × 7 cm/C(*rSOA*): 5 × 7 cm C(*midline occipital cortex*): 5 × 7 cm/A(*rSOA*): 5 × 7 cm	2 mA, 20 min, offline	Offline: prior to visual selective attention and MEG	RT: ↑ (Oz/*rSOA* compared to *rSOA*/Oz and S). Task-related theta activity: ↓ (Oz/*rSOA* compared to *rSOA*/Oz and S in left insula and left/right DLPFC). Spontaneous theta activity: ↑ (Oz/*rSOA* compared to *rSOA*/Oz and S in left insula and left/right DLPFC). Negative corr between mean-centred RTs and mean-centred theta oscillations. Task-related alpha activity: n.s. Spontaneous alpha activity: ↑ (Oz/*rSOA* compared to *rSOA*/Oz and S in left/right occipital cortices). Corr n.s.

Miler et al. [127]	Parallel 1. F3/F4 2. S	*lDLPFC, rDLPFC*	Total: 30 (21 f) 1. 15 (10), 20.8 ± 1.8 y 2. 15 (11 f), 21.5 ± 2.9 y	A(F3): 4 × 4 cm/C(F4): 4 × 4 cm	2 mA, 20 min, offline	Offline: prior to ANT	RT: ↓ (in incongruent trials). Global RT and error rate: n.s. Executive attention control: ↑. Alerting attention control: n.s. Orienting attention control: n.s. No modulation of mood and anxiety levels.
Nikolin et al. [134]	Crossover HD-F3 vs. HD-CP5 vs. HD-P9 vs. S	*lDLPFC, PT, lMTL*	16 (8 f), 21.8 ± 2.4 y	HD A(F3)/4 × C(AF3,F1,FC3,F5) A(CP5)/4 × C(C5,CP3,P5,TP7) A(P9)/3 × C(Fp1,Fp2,FC4)	2 mA, 20 min, partially online	Partially online: auditory continuous performance task	Sustained attention performance: n.s.
Roe et al. [160]	Crossover P3/P4 vs. P4/P3 vs. S	*lPPC, rPPC*	34 (21 f), 24.7 ± 3.37 y, 21–35 y	A(P3): 5 × 7 cm/C(P4): 5 × 7 cm C(P3): 5 × 7 cm/A(P4): 5 × 7 cm	1 mA, 24 min, online	Online: multiple object tracking	Accuracy: ↓ ((P4/P3 vs. P4/P3 compared to S only in high load condition, no interaction with visual field). Additionally eye-tracking data shows that central fixation was maintained.
Roy et al. [161]	Crossover F3/*cSOA* vs. P3/Cz vs. P4/Cz vs. S	*lDLPFC, lPPC, rPPC*	24 (12 f), 25 ± 4 y, 18–35 y	A(F3): 25 cm^2/C(*cSOA*): 35 cm^2 A(P3): 25 cm^2/C(Cz): 35 cm^2 A(P4): 25 cm^2/C(Cz): 35 cm^2	1.5 mA, 20 min, online	Online: modified ANT	Spatial re-orienting ↑ (P4/Cz compared to S and other active conditions). Specifically for targets in contralateral left visual field.

(continued)

Table 17.1 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Weigl et al. [191]	Crossover F3/*cSOA* vs. *cSOA*/F3 vs. S	*lDLPFC*	18 (6 f); 20–29 y, median: 26	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm C(F3): 5 × 7 cm/A(*cSOA*): 5 × 7 cm	1 mA, 15 min, offline	Offline: pre-post active/passive auditory oddball and EEG	RT (active oddball): n.s. Novelty and target ERP: n.s. MMN (passive oddball, duration deviants): ↓ (F3/*rSOA* compared to *rSOA*/F3 and sham). MMN (passive oddball, frequency deviants): n.s. MMN (passive oddball, intensity deviants): ↓ (F3/*rSOA* compared to *rSOA*/F3 and sham). N100 for standards but not deviants: ↑ (F3/*rSOA* compared to *rSOA*/F3). Effect not due to altered early processing).

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. DLPFC = dorsolateral prefrontal cortex. MTL = medial temporal lobe. PPC = posterior parietal cortex. PT = planum temporale. SOA = supraorbital area. VC = visual cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]ANT = attention network test. WM = working memory. EEG = electroencephalography. MEG = magnetoencephalography. PET = positron emission tomography

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. Corr = correlation. MMN = mismatch negativity. RT = reaction time

Roy and colleagues [161] also demonstrated that the stimulation specifically enhanced mean network efficiency for targets presented in the contralateral hemispace (i.e. the left visual field), while weakening network efficiency for targets appearing in the ipsilateral hemispace (i.e. the right visual field). Likewise, Chechlacz and colleagues [29], who examined the influence of biparietal tDCS on a visual attention task, reported asymmetric results depending on visual field. In more concrete terms, left anodal/right cathodal tDCS relative to the reverse electrode montage and sham lowered the accuracy specifically in the detection of left targets with similar distractors. Along with a previous study by Sparing and colleagues [174], this result provided novel causal support for the classical concept of inter-hemispheric rivalry, which was originally proposed by Kinsbourne [99].

In contrast, Roe and colleagues [160] found an interaction between tDCS and task load in multiple object tracking. More precisely, accuracy was decreased in the high-load condition with left cathodal/right anodal tDCS over the PPC. The authors suggested that cognitive load needs to be carefully considered in the design of tDCS studies as the stimulation may undermine attentional capacity in an overtaxed system. Employing once more the attention network test that captures the performance in all three attentional subcomponents, Miler and colleagues [127] investigated the differential of tDCS on these subcomponents when targeting the left and right DLPFC in a bilateral montage. No effect of stimulation was found on alerting or orienting components or on global reaction times and error rates. However, executive attention control was enhanced compared to the sham condition. This finding suggests potential promise for using of tDCS to attenuate impairments in specific subcomponents of attention.

Weigl and colleagues [191] further tested whether attentive and pre-attentive stimulus discrimination can be modulated via tDCS to the left DLPFC. In an auditory oddball paradigm, they examined mismatch negativities (MMNs) for duration, intensity and frequency deviants as well as novelty and target ERPs to assess pre-attentive stimulus discrimination and attentive stimulus discrimination respectively. Whereas no tDCS effects were found in the active oddball paradigm for neither target reaction times nor ERPs, during the passive oddball paradigm, tDCS effects were observed for duration and intensity deviants on MMNs. In both cases, anodal tDCS, compared to cathodal and sham tDCS, was associated with decreased MMN amplitudes. No such reduction became evident for frequency deviants. Therefore, these results not only suggest that different kinds of sound deviants are processed in distinct cortical areas, but also that the DLPFC may be part of an inhibitory network that prevents allocation of attentional resources to auditory input that does not require a response.

Other studies indicated that the orienting component of attention could be modulated via tDCS. Hanenberg and colleagues [76] tested whether a single dose of 1 mA tDCS applied for 16 min unilaterally to the right posterior superior temporal cortex could modulate auditory selective spatial attention simulating a ‘cocktail party’ situation. As shown by a decreased error rate, participants profited from anodal tDCS in localising the target numeral out of four directions, particularly with regard to ipsilateral right targets. At the same time, neither cathodal nor sham stimulation led to any significant changes in attentional performance. Additionally, the significant correlation between increased accuracy and increased N2 amplitude after tDCS was restricted to ipsilateral targets. This account conflicts directly with the previously mentioned asymmetrical tDCS effect with a preference for targets at the contralateral side of the stimulation. The authors argue that their results may be attributable to an anodal tDCS-related enhanced suppression of irrelevant input as opposed to an improvement in coding of the target, thus also resulting in improved location coding. A complementary study from the same research group [106], using the same task but applying anodal tDCS in a double monopolar montage to both hemispheres of the temporal lobe, reproduced comparable performance gains derived from anodal tDCS. Focusing on the visual domain, McDermott and colleagues [123] explored the effect of anodal, cathodal and

sham tDCS over the occipital lobe on performance in an arrow-based version of the flanker task while simultaneously imaging oscillatory responses with MEG. Under anodal tDCS, participants demonstrated increased reaction times and elevated spontaneous activity in theta and alpha bands in prefrontal and occipital cortices, as well as decreased task-related theta activity in the left insula and bilateral DLPFC. Moreover, task-related theta activity in the three aforementioned brain regions was inversely related to reaction time, with lower task-related theta responses being associated with greater response latencies. These changes have been interpreted as an inhibitory impact of anodal tDCS on visual attention processing. Taken together, these studies indicate a supramodal tDCS-related effect on attention. The incongruence between these effects, however, merits further investigation.

Apart from cortical structures, the cerebellum has been suggested to control attentional processes. Indeed, Mannarelli and colleagues [118] found a decrease in the efficiency of the executive attention network (without a concurrent impact on other attentional subcomponents) when delivering cathodal tDCS to the left cerebellar hemisphere. No change relative to baseline was detected for anodal and sham conditions. Moreover, compared to baseline, reaction times were reduced for congruent and incongruent stimuli in anodal and sham conditions after 20 min of stimulation, whereas for cathodal tDCS, this reduction only persisted for the congruent but not for the incongruent stimuli. The role of the cerebellum in the function of attentional networks was further corroborated in another study by the same group [117] that additionally measured ERPs arising from an auditory novelty task. With cathodal tDCS leading to lower P3, N1 and N2 amplitudes as well as a reduced N1 latency post- compared to pre-stimulation, the authors propose that the application of cathodal tDCS perturbed the initial phase of attentional processing as well as the subsequent phase of attentional orienting. They further annotate that, similarly to the motor domain wherein the cerebellum is mainly assigned a coordinating function, the involvement of the cerebellum in attention may be indirect and restricted to the temporal coordination of cortical activity and inhibition.

Given the findings summarised here, it is apparent how tDCS-induced improvements in attention could have important implications for enhancing performance and safety in a multitude of real-world applications. Yet, more work is required still to determine whether these effects are reliable and whether they extend beyond formalised test settings.

17.3 Effects of tDCS on Executive Functions

17.3.1 Decision-Making

Decision-making describes the cognitive process of selecting one option from several possible alternatives after having weighted the potential outcomes against each other to choose the course of action in which potential gains exceed potential losses according to objective and/or subjective values and preferences [25, 49]. This section will exclusively consider individual decision-making, attending to personal profits and costs only. For an overview of the studies included in this section and their methodological parameters, see Table 17.2.

Often, not all variables that would ensure absolute certainty regarding the consequences of a choice are freely available, wherefore decision-making also involves a certain amount of risk-taking. To assess risk-taking behaviour in the laboratory, studies draw on a number of well-established tasks such as the risky-gains task (RGT [144]), the balloon analogue risk task (BART [103]) or the Iowa gambling task (IGT [8]), all of which require participants to develop and adapt their strategy to increase their (typically monetary) rewards. These tasks are known to activate frontal cortical areas that have consequently been chosen as target regions in tDCS studies.

Nejati and colleagues [129] investigated the impact of cathodal and anodal tDCS to the left DLPFC on risk-taking behaviour and risky decision-making. Compared to sham, both stimu-

Table 17.2 The effects of tDCS on decision-making

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age [3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Bogdanov et al. [16]	Parallel F4/Cz vs. Cz/F4 vs. S	*rDLPFC*	60 (30 f), 24.9 ± 3.6 y	A(F4): 5 × 5 cm/C(Cz): 10 × 10 cm C(F4): 5 × 5 cm/A(Cz): 10 × 10 cm	1.075 mA, max. 30 min, online	Online: investment task	Investment rate: ↑ (anodal compared to sham and cathodal after prior investment, sunk-cost effect, especially for options with low expected value).
Cheng and Lee [31]	Crossover F3/F4 vs. F4/F3 vs. S	*lDLPFC*, *rDLPFC*	16 (10 f), 20.9 ± 2.8 y	A(F3): 5 × 7 cm/C(F4): 5 × 7 cm C(F3): 5 × 7 cm/A(F4): 5 × 7 cm	2 mA, ~19 min, online	Online: risky-gains task and BART	Risky choices: ↓ (F4/F3 compared to S), n.s. (F3/F4 compared to S). Safe choices: ↑ (F4/F3 compared to S), n.s. (F3/F4 compared to S). BART: n.s.
Edgcumbe et al. [48]	Parallel F4/F3 vs. F3/F4 vs. S	*lDLPFC*, *rDLPFC*	54 (29 f), 24.63 ± 4.46 y	A(F4): 25 cm^2/C(F3): 25 cm^2 A(F3): 25 cm^2/C(F4): 25 cm^2	1.5 mA, 20 min, offline	Offline: heuristic thinking, belief bias syllogisms, cognitive reflection	Heuristic thinking: ↑ (F4/F3 compared to F3/F4 and S). Cognitive reflection: ↑ (F4/F3 compared to F3/F4 and S). Logic index: ↑ (F4/F3 compared to F3/F4 but not S), ↓ (F3/F4 compared to S).
Guo et al. [70]	Parallel HD-F3(anodal) vs. HD-F3(cathodal) vs. S	*lDLPFC*	58 (37 f), 20.4 ± 3.0 y	HD A(F3): 4 cm^2/4 × C(AF3, F1, F5, FC3): 4 cm^2 C(F3): 4 cm^2/4 × A(AF3, F1, F5, FC3): 4 cm^2	1.5 mA, 20 min, online	Online: BART	Earnings: n.s. but trend towards ↓ [HD-F3 (cathodal) compared to S]. Explosions: n.s. Adjusted number of pumps: n.s.

(continued)

Table 17.2 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age [3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Hämmerer et al. [75]	Crossover Fpz/below inion vs. F3/below inion vs. S	*VMPFC, lDLPFC*	16 (6 f), 25.6 ± 5.4 y, 20–37 y	A(Fpz): 5 × 5 cm/C(below inion): 5 × 5 cm A(F3): 5 × 5 cm/C(below inion): 5 × 5 cm	2 mA, 15 min, online	Online: similar value decision	Based on biophysical attractor model of cortical dynamics in decision-making. Choice accuracy: ↓ (Fpz compared to F3 and S), n.s. (F3 compared to S). Learning rate: trend towards ↑ (F3 compared to S).
Mengarelli et al. [126]	Parallel *cSOA*/F3 vs. *cSOA*/F4 vs. S	*lDLPFC, rDLPFC*	48 (24 f), 24 y, 20–38 y	A(*cSOA*): 35 cm^2/C(F3): 35 cm^2 A(*cSOA*): 35 cm^2/C(F4): 35 cm^2	1 mA, 15 min, offline	Offline: modified Brehm's free choice paradigm	Choice-induced preference change: ↓ (*cSOA*/F3, i.e. no difference in liking rating between phases 1 and 3).
Nejati et al. [129]	Crossover F3/Fp2 vs. Fp2/F3 vs. S	*lDLPFC/rOFC, rOFC/lDLPFC*	24 (0 f) 26.75 ± 1.89 y	A(F3): 5 × 7 cm/C(Fp2): 5 × 7 cm C(F3): 5 × 7 cm/A(Fp2): 5 × 7 cm	1.5 mA, 20 min, online, three sessions	Online: GNGT, TOH, BART and delay discounting tasks, 5 min after onset	BART (measure of risk-taking), number of pumps of non-exploding balloon: ↓ (F3/Fp2). BART, total number of pumps: ↓ (F3/Fp2, Fp2/F3). Delay discounting task (ability to delay gratification), temporal discounting rate: ↓ (smaller values indicative of preference for delayed as opposed to immediate rewards). Accuracy (GNGT): ↑ (F3/Fp2). RT (GNGT): ↓ (F3/Fp2). Total time (TOH): ↓ (F3/Fp2, Fp2/F3). Number of false moves (TOH): ↓ (F3/Fp2). Total number of moves (TOH): n.s. False action (TOH): n.s.

Ouellet et al. [141]	Parallel Fp1/Fp2 vs. Fp2/Fp1 vs. S	*lOFC*, *rOFC*	45 (29 f), 25.09 ± 7.10 y	A(Fp1): 5 × 7 cm/C(Fp2): 8.5 × 6.5 cm A(Fp2): 5 × 7 cm/C(Fp1): 8.5 × 6.5 cm	1.5 mA, 30 min, offline	Offline: IGT, BART, impulse control, stop-signal task, continuous performance task	Netscore (IGT): ↑ (both active conditions compared to S). Number of adjusted pumps (BART): n.s. Intereference index: ↓ (both active conditions compared to S). RT (stop signal): n.s. Omission errors (continuous performance): n.s.
Soutschek et al. [172]	Parallel LL1/Z7 vs. Z7/LL1 vs. S	*lFPC*	78 (0 f), 23.1 y, 18–38 y	A(LL1)5 × 5 cm/C(Z7): 10 × 10 cm C(LL1)5 × 5 cm/A(Z7): 10 × 10 cm	1 mA, 23 min, online	Online: decision/self-control task (small rewards sooner vs. large rewards later)	Precommitment: ↑ (LL1/Z7 compared to S), n.s. (Z7/LL1 compared to S).
Soutschek et al. [173]	Parallel *rFPC*/Z7 vs. Z7/*rFPC* vs. S	r*FPC*	141 (71 f), 22.78 y, 18–34 y	A(1 cm ventrally to electrode position R2): 5 × 5 cm/C(Z7): 10 × 10 cm C(1 cm ventrally to electrode position R2): 5 × 5 cm/A(Z7): 10 × 10 cm	1.5 mA, mean: 23 min, range 21–27 min), online	Online: decision task	Willingness to exert cognitive/physical effort for reward: ↑ (*rFPC*/Z7 compared to S), n.s. (Z7/*rFPC* compared to S).
Wen et al. [193]	Parallel HD-F3 vs. S	*lDLPFC*	60 (30 f), 19.73 ± 1.54 y	C(F3)/4 × A(F5, AF3, FC3, F1)	1.5 mA, 20 min, offline	Offline: everyday risky decisions	Risky attitude: ↓ (in risky but not control scenarios, larger in HD-F3).

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Table 17.2 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age [3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Ye et al. [200]	Parallel F4/F3 vs. F3/F4 vs. S	*lDLPFC, rDLPFC*	60 (36 f), 21.3 y, 17–28 y	A(F4):35 cm^2/C(F3): 35 cm^2 A(F3):35 cm^2/C(F4): 35 cm^2	2 mA, 15 min, offline	Offline: pre-post lottery choices task	Safe options: n.s. (more safe options post-tDCS for S in whole group and females, effect counteracted by active conditions).

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. DLPFC = dorsolateral prefrontal cortex. FPC = frontopolar cortex. OFC = orbitofrontal cortex. VMPFC = ventromedial prefrontal cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]BART = Balloon Analogue Risk Task. GNGT = Go/no-go task. IGT = Iowa Gambling Task. TOH = Tower of Hanoi

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. RT = reaction time

lation conditions decreased the number of pumps in the BART and decreased the discounting rate in a temporal discounting task, both indicative of a more risk-averse and disciplined response style. Cheng and Lee [31] measured the influence of bilateral tDCS over the left and right DLPFC on performance in two risk-taking tasks, RGT and BART. Interestingly, participants' risky attitude was influenced differentially depending on the task. While there were no significant differences between conditions in the BART, participants made significantly fewer risky choices combined with a larger number of safe choices in the RGT in the left cathodal/right anodal electrode configuration relative to sham. Effect sizes were particularly large in individuals exhibiting high baseline impulsivity, hinting at a therapeutic potential for tDCS in patients that engage in psychopathological risky behaviour such as addiction or deliberate self-harm. On the other hand, no effect emerged when the electrode montage was reversed. Employing the same electrode montage, Edgcumbe and colleagues [48] corroborate the role of the DLPFC in governing the analytical process in decision-making that inhibits initially more impulsive responses, thus, leading to more correct judgements. Given their bilateral application of tDCS, the latter two studies leave a particular question unanswered, namely, which of the two electrodes subserves the increase in self-reflection observed for the stimulation of the DLPFC, or whether this effect is specifically facilitated by the bilateral montage. This montage question was partially addressed by Guo and colleagues [70], who used an HD-tDCS setup targeting the left DLPFC with either anodal or cathodal tDCS. They found a trend towards smaller earnings in the BART when cathodal tDCS was applied, whereas there was no significant difference between anodal tDCS and sham. Furthermore, no significant differences between any of the conditions arose for number of balloon explosions or the adjusted number of pumps. Transferring these findings into real-world scenarios, Wen and colleagues [193] assessed university students' attitudes and intentions towards realistic everyday scenarios, which were either carrying minimal risk (e.g. visiting a webshop, engaging in social activities) or were considered risky (e.g. unsafe road crossing, unprotected intercourse, unethical academic conduct). In accordance with the aforementioned studies, the application of cathodal tDCS, once more employing an HD setup, resulted in a decline in risky behaviour in risky but not normal scenarios, whereas no change from baseline values was observed in the sham condition. Even though the discrepancies between tasks require further elucidation, these studies hint at a caution-inducing influence of cathodal tDCS over the left DLPFC, possibly by down-regulating its processing of positive aspects in choices, thus emphasising the risky side of choices.

Yet, these results are not entirely consistent across all studies. Specifically, Ye and colleagues [200] assessed whether bilateral tDCS to the DLPFC would modulate risk-taking behaviour. Comparing baseline and post-tDCS choices, they observed that in the sham condition participants preferred the safer options at the second time point, which was attributed to the wealth effect, that is, the reluctance to forsake previous gains. This wealth effect was counteracted by both active conditions in which no differences between baseline and post-tDCS assessments emerged. It remains to be shown whether this discrepancy is related to the involvement of strategic thinking based on prior knowledge, a component that was factored out in the study by Ye and colleagues, but was inherent in the tasks employed in other studies.

A set of four studies further investigated the influence of tDCS on different decision biases. Grounded in the framework of cognitive dissonance, which illustrates how people are aligning current choices to previous decisions, Mengarelli and colleagues [126] examined the impact of cathodal tDCS on choice-induced preference changes. Typically, a forced choice between equally desirable alternatives leads to a change in desirability judgements during the re-evaluation of the options in alignment with the forced choice. When applying the stimulation to the left, but not the right, DLPFC, this effect was reduced. In another bias known as the sunk-cost effect, people are reluctant to abandon an

option once they have invested in it. As shown by Bogdanov and colleagues [16], this bias was even further pronounced when anodal tDCS, but not sham or cathodal tDCS, was applied over the right DLPFC, especially in options with a low expected value. Thus, the latter two studies provide converging evidence that the DLPFC plays a role in sticking with a previous choice. However, the effect of anodal tDCS over the right DLPFC found by Bogdanov and colleagues in combination with the effect of cathodal tDCS over the left DLPFC observed by Mengarelli and colleagues, speak to the need to systematically assess the specificity of these behavioural findings in terms of both tDCS polarity and hemispheric lateralisation in future studies. Additionally, Soutschek and colleagues [172] probed the influence of both polarities of tDCS over the left frontopolar cortex on pre-commitment in a self-control task, in which participants either received a small reward sooner or a larger reward later. Anodal tDCS promoted pre-commitment to the larger reward later, whereas pre-commitment scores did not significantly differ between cathodal and sham stimulation, suggesting a possible application in enhancing self-control. At the same time, this study found no tDCS-related changes in impulsivity or reward preferences. The fourth study [173] applied anodal or cathodal tDCS over the right frontopolar cortex while participants had to decide whether to engage in cognitive or physical efforts to obtain a reward. Compared to sham, anodal tDCS reduced the discounting of rewards due to effort level without modulating the isolated sensitivity for gains and losses. In contrast, cathodal tDCS did not alter the willingness of participants to engage in rewarded efforts relative to sham. These findings support the notion that the right frontopolar cortex acts as a facilitator of motivation when weighing effort against rewards.

Moving the focus away from the DLPFC, Ouellet and colleagues [141] were interested in the involvement of the orbitofrontal cortices in decision-making and impulse control. Again, outcomes of the BART remained unaffected by bilateral application of tDCS for both electrode montages. Yet, both active conditions resulted in a higher net score in the IGT and an improved cognitive impulse control in the Stroop task, making it the first study to demonstrate the involvement of the OFC in these cognitive functions.

In a two-stage study, Hämmerer and colleagues [75] investigated the underlying mechanisms of decision-making, starting out with in silico simulations of perturbing neural dynamics. According to their simulation, depolarising a population of pyramidal neurons increases their sensitivity to background noise, ultimately resulting in a decreased choice accuracy at the behavioural level. These predictions were confirmed by the second part of their study, in which they applied anodal tDCS to either the ventromedial prefrontal cortex (VMPFC) or the left DLPFC. Choice accuracy was lower when targeting the VMPFC compared to the sham condition, while no such effect could be established when applying the stimulation to the left DLPFC. Additionally, anodal tDCS over the VMPFC also increased randomness in choices compared to sham, while stimulation of the left DLPFC was indistinguishable from the sham condition. On the other hand, relative to sham, only anodal tDCS over the left DLPFC, but not the VMPFC, increased the learning rate. With this identification of site-specific effects of anodal tDCS by means of a computational neurostimulation approach, this study contributes to a more nuanced understanding of stimulation effects that do not solely rely on electrode polarity. Future stimulation studies in the domain of decision-making should strive to integrate similar approaches in their experimental designs as this could enable the resolution of some of the discrepancies outlined above.

In summary, the studies in this section demonstrate that tDCS can modulate decision-making bi-directionally, bringing out more audacious or more cautious attitudes, depending on the chosen stimulation parameters. Always under the premise that the applied stimulation protocols are sufficiently reliable, bias in both directions could be advantageous in the clinical setting where patients show aberrations towards over-caution (e.g. in major depressive disorder or schizophrenia) or, conversely, excessive recklessness (e.g. in borderline personality disorder or substance abuse [105]).

17.3.2 Inhibitory Control

While cognitive function is oftentimes equated with the ability to produce an adequate response to a stimulus, response inhibition, that is, the ability to abort or suppress an inadequate response, is equally vital [185]. In the laboratory setting, the corresponding capacity to withhold a pre-potent response is principally assessed with one of the two paradigms. Developed by Logan and Cowan [111], the stop-signal task (SST) requires the participant to respond as quickly as possible to a go signal while aborting any response as soon as a stop signal is presented. Correspondingly, in the go/no-go task (GNGT), participants are likewise asked to promptly respond to the appearance of a go signal and withhold it upon the presentation of a less frequent no-go signal. The dual task demands of conflicting go and stop/no-go processes is also appreciated by the separate evaluation of accuracy and reaction times in the two types of trials. In line with other executive functions, engagement in these tasks activates frontal and parietal brain regions [64, 189]. With few exceptions [109, 115, 199], tDCS studies also focus on these cortical areas when attempting to influence inhibitory control processes (Table 17.3).

Cunillera and colleagues [38] used an adapted GNGT that incorporated components of an SST. By applying tDCS bilaterally with a right anodal/left cathodal montage to the inferior frontal cortex (IFC) during task performance, they demonstrated increased reaction times in go trials and decreased stop-signal reaction times (SSRTs). Based on these dual results, the authors conclude that the stimulation improved both proactive inhibition and reactive inhibition simultaneously. Two additional studies [164, 178] reported congruous findings regarding the positive influence of anodal tDCS over the right IFC on reactive inhibition but failed to corroborate the data concerning proactive inhibition. The designs of these studies do not permit deducing whether this discrepancy can be ascribed to the offline application of tDCS, the unilateral electrode montage or yet another factor.

However, Sandrini and colleagues [164] further strengthened the evidence for the facilitating role of the right IFC in response inhibition by acquiring complementary neuroimaging data. More precisely, anodal tDCS increased functional connectivity between the frontobasal ganglia inhibitory network at rest, while stop responses were accompanied by a significant increase in connectivity between the right pre-supplementary motor area (preSMA) and the subthalamic nuclei, both of which are regarded as integral nodes for rapid inhibitory responses. Indeed, a previous study by Liang and colleagues [109], in which they applied 10 min of anodal tDCS to the preSMA, also resulted in a beneficial impact on inhibitory control indicated by a shortening of SSRTs. This prompts the question whether the nodes within the frontobasal ganglia inhibitory network can be used as interchangeable targets for tDCS. Thus far, the effects observed when applying anodal stimulation to the IFC and the preSMA are similar, whereas stimulation of the right DLPFC fails to produce significant behavioural effects [178]. Nevertheless, additional exploratory analyses conducted by Sandrini and colleagues [164] revealed a decreased BOLD activity during go responses in the right DLPFC, which was predictive of SSRT, verifying the contribution of this cortical region to inhibitory control. Moreover, Friehs and Frings [60] corroborated this notion with their study, in which cathodal tDCS with a current intensity of only 0.5 mA applied to the right DLPFC lead to an increase in SSRT, indicating a declined capacity for response inhibition.

Deviating from the focus on the right hemisphere, two studies from the same research group [51, 120] selected the left DLPFC as the target region for tDCS prior to the execution of SSTs. While neither of the two reported significant effects on overall task performance, Fehring and colleagues [51] demonstrated that anodal stimulation effects depend on the level of expertise in an SST. To that effect, improvements in proactive and reactive inhibitory control within a session were restricted to week 1 in the anodal condition, while they occurred in both weeks 1 and 2 under sham. Furthermore, Mansouri and colleagues

Table 17.3 The effects of tDCS on inhibitory control

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Adelhöfer et al. [1]	Crossover Fz–T4–Cz–F8/*ext.* vs. S	*rDLPFC*	32 (18 f); 24.7 y, 20–30 y	A(Fz–T4–Cz–F8): 5 × 5 cm/C(*left deltoid muscle*): 5 × 5 cm	2 mA, 20 min, offline, two sessions	Offline: dichotic listening task EEG	IES: ↓ (in the high conflict condition when attention was focused on the left ear, that is, the most demanding situation for attentional control) EEG amplitudes in the N1 time window from the electrode at position C6: ↓ (in the high conflict condition when attention was focused on the left ear) EEG amplitudes in the N450 time window from the electrode at position FC4: ↑ (in the high conflict condition when attention was focused on the left ear)
Albein-Urios et al. [3]	Parallel Cathodal *VLPFC* tDCS vs. cathodal *DMPFC* tDCS vs. S	*VLPFC, DMPFC*	Overall: 52 (28f); 22.02 ± 2.19 y 1. 15 (N/S) 2. 15 (N/S) 3. 22 (N/S)	Overall dimensions: Outer Ø 20 mm vlPFC setup: C(T8, FT8)/A(FP2, F6, FC6) dmPFC setup: C(F2)/A(FZ, FCZ, CZ, AF4)	vlPFC setup: FP2 (0.9 mA), F6 (0.5 mA), FC6 (0.6 mA), T8 (0.9 mA), FT8 (1.1 mA) dmPFC setup: FZ (0.5 mA), FCZ (0.5 mA), CZ (0.5 mA), AF4 (0.5 mA), F2 (−2 mA) 20 min, offline, one session	Offline: probabilistic reversal learning task, 10 min after offset EEG	Accuracy: ↓ (*VLPFC* compared to *DMPFC* and S) EEG, feedback-related negativity: n.s.

Boudewyn et al. [18]	Crossover F3/Fp2 vs. S	*lDLPFC*	Overall (pre-exclusions): 21 (17 f); 21 y, 18–30 y Overall (post-exclusions): 20 (N/S)	A(F3): 5 × 7 cm/C(Fp2): 5 × 7 cm	2 mA, 20 min, online and offline, two sessions	Online: n-back task Offline: dot-pattern expectancy task, ~10 min after offset	False alarm rate: ↑ (cued non-targets). ↓ (non-cued targets). Low gamma (30–50 Hz) power: ↑ (non-cues vs. cues). High gamma (50–80 Hz) power: n.s. Accuracy, N-back task: n.s. Hit rate, N-back task: n.s. False alarm rate, N-back task: n.s.
Campanella et al. [27]	Parallel F8/*ext.* vs. S	*rIFC*	1. 15 (0 f); 21.9 ± 3.1 y 2. 16 (0 f); 21.3 ± 1.7 y	A(F8): 25 cm^2/C (*superior region of the trapezius muscle near base of neck*): 25 cm^2	2 mA, 20 min, offline, two sessions	Offline: GNGT, face detection task	Accuracy, both tasks: n.s. RT, both tasks: n.s. EEG P3d component amplitude, GNGT task: ↓ (at session 2 vs. session 1, for correctly inhibited trials).
Campanella et al. [28]	Parallel F8/*ext.* vs. S	*rIFC*	1. 18 (0 f); 22.2 ± 3.0 y 17 (0 f); 21.3 ± 1.7 y	A(F8): 25 cm^2/C(*left superior region of the trapezius muscle near the base of the participant's neck*): 25 cm^2	2 mA, 20 min, offline, one session	Offline: before GNGT task	Accuracy: n.s. RT: n.s. Drop in accuracy for fast responses: ↓ (first experimental block).

(continued)

Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Cunillera et al. [38]	Crossover T4–Fz–F8–Cz/ T3–Fz–F7–Cz vs. S	*rIFC, lIFC*	22 (18 f), 21.2 ± 2.7 y	A(T4–Fz–F8–Cz): 3 × 3 cm/C(T3–Fz–F7–Cz): 3 × 3 cm	1.5 mA, 18 min, online, two sessions	Online: GNGT-SST	Go RT: ↑ (indicating increased proactive inhibition). SSRT: ↓ (indicating improved reactive inhibition).
Dambacher et al. [39]	Parallel F8/F7 vs. F7/F8 vs. S	*lIFC, rIFC*	Overall: 64 (25 f), 21.89 ± 3.26 y 1. 22 (11 f); N/S 2. 22 (8 f); N/S 3. 20 (6 f) N/S	A(F8): 5 × 7 cm/C(F7): 5 × 7 cm C(F8): 5 × 7 cm/A(F7): 5 × 7 cm	1.5 mA, 21.75 min, online, one session	Online: GNGT, TAP	GNGT: n.s. TAP: n.s.

Di Rosa et al. [44]	*Exp 1:* Crossover P3/ *cSOA* vs. *cSOA*/P3 vs. S *Exp 2:* Crossover P4/ *cSOA* vs. *cSOA*/P4 vs. S	*Exp 1: lPPC* *Exp 2: rPPC*	*Exp 1:* 20 (14 f); 21.35 ± 1.84 y *Exp 2:* 20 (9 f); 24.58 ± 2.50 y	*Exp 1:* A(P3): 5 × 5 cm/C(*cSOA*): 5 × 7 cm C(P3): 5 × 5 cm/A(*cSOA*): 5 × 7 cm *Exp 2:* A(P4): 5 × 5 cm/C(*cSOA*): 5 × 7 cm C(P4): 5 × 5 cm/A(*cSOA*): 5 × 7 cm	*Exp 1:* 1.5 mA, 15 min, online, three sessions *Exp 2:* 1.5 mA, 15 min, online, three sessions	*Exp 1:* Online: parity judgement task *Exp 2:* Online: parity judgement task	*Exp 1:* Markedness Association of Response Codes (MARC) effect: n.s. Spatial Numerical Association of Response Codes (SNARC) effect: n.s. *Exp 2:* Markedness Association of Response Codes (MARC) effect, RT: ↓ (cathodal stimulation over rPPC). Spatial Numerical Association of Response Codes (SNARC) effect: n.s. MARC vs. SNARC: ↓ (cathodal stimulation over rPPC).
Fehring et al. [51]	Crossover F3/*cSOA* vs. S	*lDLPFC*	73 (37 f); 18–32 y	A(F3): 2.5 × 4 cm/C(*cSOA*): 4 × 6 cm	1.5 mA, 10 min, offline, two sessions	Offline: SST, 5 min after offset	Go RT (within session): ↑ (S in weeks 1 and 2, tDCS in week 1 only). SSRT (within session): ↑ (S in weeks 1 and 2, tDCS in week 1 only). This indicates a learning-level-dependant effect of tDCS.

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Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Filmer et al. [54]	Parallel *lDLPFC/cSOA* vs. *cSOA/lDLPFC* vs. S	*lDLPFC*	Overall: 59 (51 f); 21 ± 2 y 1. 20 (18 f); 21 y 2. 20 (18 f); 21 y 3. 19 (15 f); 21 y	A(*1 cm posterior to F3*): 5 × 5 cm/C(*cSOA*): 5 × 5 cm C(*1 cm posterior to F3*): 5 × 5 cm/A(*cSOA*): 5 × 5 cm	0.7 mA, 13 min, online, one session	Online: multi-tasking paradigm. Immediately prior to training, 1 day and 2 weeks after training, participants completed a battery of four tasks	1. Accuracy, visual search task: ↑ (set size 8). Accuracy, all other tasks: n.s. RT, visual search task: ↑ (set size 16, result consistent after 2 weeks follow-up). RT, trained multi-tasking paradigm: n.s. RT, untrained multi-tasking paradigm: ↑ RT, GNGT task: n.s. 2. Accuracy, visual search task: ↑ (set size 16). Accuracy, all other tasks: n.s. RT, visual search task: n.s. RT, trained multi-tasking paradigm: n.s. RT, GNGT: n.s. Group 1 vs. 2, RT, untrained multi-tasking paradigm: ↑ (both single and dual task trials). Group 1 vs. 2, RT, visual search task: ↑ (set size 16, result consistent after 2 weeks follow-up).

Friehs and Frings [60]	Parallel *ext.*/F4 vs. S	*rDLPFC*	1. 20 (12 f); 21.8 ± 2.39 y 2. 22 (19 f); 22.32 ± 2.75 y	C(F4): 3 × 3 cm/A(*left deltoid muscle*): 5 × 7 cm	0.5 mA, 19 min, offline, one session	Offline: SST	Accuracy: n.s. SSRT: ↑. Go RT: n.s. NSRT: n.s. SSD: n.s.
Gbadeyan et al. [66]	Parallel 1. HD-F3 vs. S 2. HD-F4 vs. S 3. HD-C3 vs. S 4. HD-C4 vs. S	*lDLPFC, rDLPFC, lM1, rM1*	1. 30 (15 f); 26.60 ± 4.52 y 2. 30 (13 f); 25.96 ± 5.10 y 3. 30 (17 f); 25.06 ± 4.34 y 4. 30 (16 f); 26.46 ± 4.48 y	Overall dimensions: Centre electrode: outer Ø 25 mm ring-shaped return electrode: outer Ø 115 mm, inner Ø 92 mm. 1. A(F3) 2. A(F4) 3. A(C3) 4. A(C4)	1 mA, 20 min, online, two sessions	Online: visual flanker task	1. Conflict adaptation effect (the modulation of the flanker effect as a function of previous response conflict): ↑. 2. Conflict adaptation effect: ↑. 3. Conflict adaptation effect: n.s. 4. Conflict adaptation effect: n.s. Group 1 vs. 2, mean RTs: ↑. Group 3 vs. 4, mean RTs: ↓.
Leite et al. [102]	Crossover *rIFG/lIFG* vs. *rIFG/lIFG* vs. S	*rIFG/lIFG, rIFG/lIFG*	16 (11 f); 21.5 ± 4.5 y	Bihemispheric setup: A(*rIFG*): 35 cm^2/C(*lIFG*): 35 cm^2 Unihemispheric setup: A(*rIFG*): 35 cm^2/C (*lIFG*): 100 cm^2	1 mA, ~30 min, online, one session	Online: pre-potent response inhibition task, GNGT, CRT	GNGT: n.s. CRT: n.s. Accuracy switch cost: ↓ (unilateral compared to S and bilateral). RT switch cost: ↑ (unilateral compared to S and bilateral).

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Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Liang et al. [109]	Crossover Fz/*ext.* vs. S	*preSMA*	18 (8 f), 25.4 y	A(Fz): 4 × 4 cm/C(*left cheek*): 4 × 4 cm	1.5 mA, 10 min, online, two sessions	Online: SST EEG	SSRT: ↓. Accuracy (non-cancelled) of stop trials: ↑. Accuracy, Go trials: n.s. NSRT: n.s. EEG, magnitude of multi-scale entropy: ↑ (at channel Fcz). EEG, magnitude of multi-scale entropy: ↑ (unsuccessful stop trials).

Maldonado et al. [115]	Crossover *Cerebellum* vs. S	*Cerebellum*	24 (12 f); 19.04 ± 1.60 y	Overall dimensions: N/S. Cathodal cerebellar setup: C(PO10, O10, Ex4)/A(P2, Ex3, Ex5, Ex12, Ex14, Nk1)	Cathodal cerebellar setup: P2(0.1135 mA), PO10(−0.1551 mA), O10(−0.3618 mA), Ex3(0.1956 mA), Ex4(−1.4832 mA), Ex5(0.4066 mA), Ex12(0.22 mA), Ex14(0.7886 mA), Nk1(0.2757 mA) 20 min, offline, two sessions	Offline: Stroop task, Sternberg task	n.s.
Mansouri et al. [120]	Parallel and crossover 1. F3/*cSOA* vs. *cSOA*/F3 vs. S 2. F3/*cSOA* vs. *cSOA*/F3 vs. S	*lDLPFC*	1. 19 (11 f). 19–28 y 2. 23 (11 f); 20–32 y	A(F3): 2.5 × 3 cm/C(*cSOA*): 4 × 5 cm C(F3): 2.5 × 3 cm/A(*cSOA*): 4 × 5 cm	1. 1 mA, 10 min, offline, three sessions 2. 1 mA, 10 min, offline, three sessions	1. Offline: WCST, 5 min after offset 2. Offline: SST, 5 min after offset	1. Accuracy (WCST): n.s. RT (WCST): ↓ (*cSOA*/F3, pre vs. post errors). 2. SSD: n.s. Accuracy go trials, SST: n.s. Post-error slowing: ↓ (F3/*cSOA* and *cSOA*/F3). Post-correct stop slowing: ↓ (F3/*cSOA* compared to S and *cSOA*/F3).

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Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Nejati et al. [129]	Crossover F3/Fp2 vs. Fp2/F3 vs. S	*lDLPFC/rOFC*, *rOFC/lDLPFC*	24 (0 f); 26.75 ± 1.89 y	A(F3): 5 × 7 cm/C(Fp2): 5 × 7 cm C(F3): 5 × 7 cm/A(Fp2): 5 × 7 cm	1.5 mA, 20 min, online, three sessions	Online: GNGT, TOH, BART, and delay discounting tasks, 5 min after onset	No-go accuracy: ↑ (F3/Fp2). No-go RT: ↓ (F3/Fp2). Total time (TOH): ↓ (F3/Fp2, Fp2/F3). Number of false moves (TOH): ↓ (F3/Fp2). Total number of moves (TOH): n.s. False action (TOH): n.s. BART (measure of risk-taking), number of pumps of non-exploding balloon: ↓ (F3/Fp2). BART, total number of pumps: ↓ (F3/Fp2, Fp2/F3). Delay discounting task (ability to delay gratification), temporal discounting rate: ↓ (smaller values indicative of preference for delayed as opposed to immediate rewards).
Nieratschker et al. [132]	Crossover *cSOA*/F3 vs. S	*lDLPFC*	41 (32 f), 24.0 ± 4.2 y	C(F3): 35 cm^2/A(*cSOA*): 35 cm^2	1 mA, 20 min, online, two sessions	Online: GNGT	Response inhibition: ↓ (*cSOA*/F3). Effect driven by COMT Val/Val homozygotes.

Pergolizzi and Chua [148]	Parallel F3/F4 vs. CP3/CP4 vs. S	*lDLPFC/rDLPFC, lPPC/rPPC*	Overall (pre-exclusions): 81 (54 f), 21.4 ± 4.25 y Overall (post-exclusions): 72 (N/S) 1. 24 (N/S) 2. 24 (N/S) 24 (N/S)	A(F3): 35 cm^2/C(F4): 35 cm^2 A(CP3): 35 cm^2/C(CP4): 35 cm^2	2 mA, 20 min, online (during retrieval)	Online: shallow verbal encoding inexplicit memory cueing paradigm	Correct rejection: ↑ (F3/F4 compared to sham when cued with 'likely new' but not with 'neutral' or 'likely old' cues). n.s. (P3/P4). Cue utilisation scores: ↑ (F3/F4 compared to S for 'likely new' and 'likely old'). ↑ (F3/F4 compared to P3/P4 with 'likely old' but not 'likely new').
Sallard et al. [163]	Crossover F6–FC6/*cSOA* vs. S	*rIFG/lOFC*	16 (9 f); 23.8 ± 3.9 y	A(F6–FC6): 5 × 7 cm/C(*cSOA*): 7 × 10 cm	1.5 mA, 20 min, offline, two sessions	Offline: GNGT fMRI	GNGT: n.s. BOLD (fMRI): ↑ (go vs. no-go, in rIFG, rMFG, lSMA and the left thalamus).
Sandrini et al. [164]	Parallel *rIFC/cSOA* vs. S	*rIFC*	1. 15 (8 f); 26 ± 4 y 2. 15 (8 f); 27 ± 6 y	A(*rIFC*, based on individual T1 image): 5 × 5 cm/C(*cSOA*): 5 × 5 cm	1.5 mA, 20 min, offline, one session	Offline: SST, 5 min after offset Resting state fMRI, after tDCS, before SST Event-related fMRI, during SST	SSRT: ↓. Go RT: n.s. Resting state fMRI (after tDCS, before SST), functional connectivity between rIFC and caudate: ↑. Event-related fMRI (during SST), functional connectivity, right pre-SMA and subthalamic nuclei: ↑ (during stop responses).

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Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Savic et al. [166]	*Exp 1:* Parallel 1. F3/*cSOA* 2. F4/*cSOA* 3. *cSOA*/F3 4. *cSOA*/F4 5. S, electrodes at F3/*cSOA* 6. S, electrodes at F4/*cSOA* *Exp 2:* 1. F3/*cSOA* 2. F4/*cSOA* 3. *cSOA*/F3 4. *cSOA*/F4 5. S, electrodes at F4/*cSOA*	*Exp 1:* 1. *lDLPFC* 2. *rDLPFC* 3. *lDLPFC* 4. *rDLPFC* *Exp 2:* 1. *lDLPFC* 2. *rDLPFC* 3. *lDLPFC* *rDLPFC*	*Exp 1:* Overall: 98 (76 f); 25 ± 4.5 y 1. 17 (N/S) 2. 17 (N/S) 3. 16 (N/S) 4. 16 (N/S) 5. 16 (N/S) 6. 16 (N/S) *Exp 2:* Overall: 80 (53 f); 25 ± 9 y 1. 15 (N/S) 2. 16 (N/S) 3. 16 (N/S) 4. 17 (N/S) 16 (N/S)	1. A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm 2. A(F4): 5 × 7 cm/C(*cSOA*): 5 × 7 cm 3. C(F3): 5 × 7 cm/A(*cSOA*): 5 × 7 cm C(F3): 5 × 7 cm/A(*cSOA*): 5 × 7 cm	1 mA, 30 min, online and offline, one session	Online: implicit task sequence, 15 min after onset Offline: implicit task sequence, continued after offset for a total of 50 min	*Exp 1:* RT: n.s. Switch cost: n.s. Follow-up session (24 h later): all n.s. Disruption scores: Significant decrease from session 1 to session 2 in S is counteracted by all active conditions. *Exp 2:* RT: n.s. Switch cost: n.s. Follow-up session (24 h later): all n.s.
Schroeder et al. [168]	Crossover F3/*ext.* vs. S	*lDLPFC*	24 (21 f); 24.3 ± 4.7 y	C(F3): 5 × 7 cm/A(*right upper arm*): 5 × 7 cm	1 mA, 25 min, online, two sessions	Online: Insect–flower evaluative IAT, 5 min after onset	RT: ↓ (congruent vs. incongruent). Accuracy: n.s.

Sdoia et al. [169]	Crossover F4/F3 vs. P4/P3 vs. S	*rDLPFC/lDLPFC, rPPC/lPPC*	20 (12 f); 26.3 ± 3.64 y	Overall dimensions: Ø 30 mm A(F4)/C(F3) A(P4)/C(P3)	1.5 mA, 25 min, online, three sessions	Online: magnitude task, parity task, position task	RT: ↓ (P4/P3, when switching back to a recently inhibited task). RT: ↓ (F4/F3 when switching back to a recently inhibited task or when engaging in a non-inhibited task).
Stramaccia et al. [178]	Parallel 1. T4–Fz–F8–Cz/*cSOA* 2. *cSOA*/T4–Fz–F8–Cz 3. F4/*cSOA* 4. *cSOA*/F4 5. S	*rIFG, rDLPFC*	Overall: 115 (86 f); 23.37 ± 2 y 1. 20 (14 f); 23.95 ± 2.26 y 2. 20 (12 f); 23.35 ± 1.53 y 3. 20 (17 f); 23.65 ± 2.08 y 4. 20 (17 f); 23.10 ± 2.57 y 5. 35 (26 f); 23.06 ± 1.61 y	1. A(T4–Fz–F8–Cz): 16 cm^2/C(*cSOA*): 16 cm^2 2. C(T4–Fz–F8–Cz): 16 cm^2/A(*cSOA*): 16 cm^2 3. A(F4): 16 cm^2/C(*cSOA*): 16 cm^2 C(F4): 16 cm^2/A(*cSOA*): 16 cm^2	1.5 mA, 20 min, offline, one session	Offline: SST	SSRT: ↓ (T4–Fz–F8–Cz/*cSOA* compared to S). n.s. (other active conditions compared to S). NSRT: n.s.

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Table 17.3 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Strobach et al. [180]	*Exp 1:* Crossover F4–C4/ *cSOA* vs. S *Exp 2:* Crossover *cSOA*/ F4–C4 vs. S	*IFJ*	*Exp 1:* 30 (20 f); 24.8 ± 3.1 y *Exp 2:* 28 (17 f); 22.6 ± 3.0 y	*Exp 1:* A(F4–C4): 5 × 7 cm/C(*cSOA*): 10 × 10 cm *Exp 2:* C(F4–C4): 5 × 7 cm/A(*cSOA*): 10 × 10 cm	1 mA, 20 min, online, two sessions	Online: dual-tasks	*Exp 1:* Accuracy, task 1: ↑ (at short stimulus onset asynchrony under the same-order condition). Accuracy, task 2: ↑ (at short stimulus onset asynchrony under the same-order condition). Lower accuracy at baseline positively correlated with improvements after tDCS for tasks 1 and 2. RT: n.s. *Exp 2:* Accuracy, task 1: ↓ (under the different-order condition). Accuracy, task 2: n.s. Corr between baseline performance and tDCS effect on accuracy, task 1: n.s. (after removing outlier). RT: n.s.

Weidacker et al. [190]	Crossover F4/*ext.* vs. *ext.*/F4 vs. S	*rDLPFC*	18 (9 f); 22.06 ± 0.98 y	A(F4): 5 × 5 cm/C(*left biceps*): 5 × 5 cm C(F4): 5 × 5 cm/A(*left biceps*): 5 × 5 cm	1.5 mA, 20 min, offline, three sessions	Offline: parametric GNGT Psychopathic Personality Inventory-Revised subscale of Coldheartedness	RT (GNGT): n.s. Accuracy (GNGT): n.s. Differential ↑ (*ext.*/F4) for individuals scoring high in coldheartedness in high load condition.
Wynn et al. [199]	Crossover *Cerebellum*/*ext.* vs. S	*Medial cerebellum*	26 (19 f); 23.48 ± 2.55 y	C(*2 cm below the inion*): 5 × 7 cm/A(*right deltoid muscle*): 5 × 7 cm	2 mA, 30 min, online, two sessions	Online: GNGT, delayed discounting tasks	Accuracy (GNGT): ↑. Delayed discounting task: n.s.

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. DLPFC = dorsolateral prefrontal cortex. DMPFC = dorsomedial prefrontal cortex. IFC = inferior frontal cortex. IFG = inferior frontal gyrus. IFJ = inferior frontal junction. M1 = primary motor cortex. OFC = orbitofrontal cortex. PPC = posterior parietal cortex. preSMA = pre-supplementary motor area. VLPFC = ventrolateral prefrontal cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]CRT = choice reaction time. GNGT = go/no-go task. IAT = Implicit Association Test. SST = stop-signal task. TAP = Taylor Aggression Paradigm. TOH = Tower of Hanoi. WCST = Wisconsin Card Sorting Test

EEG = electroencephalography. fMRI = functional magnetic resonance imaging

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. Corr = correlation. MMN = mismatch negativity. NSRT = no signal reaction time. RT = reaction time. SSD = stop-signal delay. SSRT = stop-signal reaction time

[120] revealed a differential effect of stimulation condition on the rule shift cost. When receiving anodal tDCS, compared to sham and cathodal tDCS, participants were significantly slower in a go trial after failing to suppress their response in the preceding no-go trial. Interestingly, this post-error slowing was also observed when subjects performed the Wisconsin Card Sorting Test (WCST, [69]), another test that is used to assess executive control, but only under cathodal tDCS. This generalisation of the effect to another paradigm corroborates the assumption that tDCS has successfully modulated the neural circuitry that supports inhibitory control as opposed to a more task-specific effect. In turn, this provides basis for being optimistic that these finding could have translational potential beyond laboratory test settings.

As argued by Raud and colleagues [156], tasks such as SST and GNGT, which are oftentimes employed interchangeably, do not necessarily tap into the same inhibitory processes. More specifically, an SST demands a stronger reactive inhibition compared to the more proactive inhibitory demands inherent in a GNGT. Consequently, their interchangeable use is also complicating the evidence base for tDCS results in this field. Acknowledging these subtle but significant differences between these tasks, Leite and colleagues [102] evaluated the distinct effects of tDCS on performance of different inhibitory control tasks in a single study. Applying uni- or bi-hemispheric tDCS to the inferior frontal gyrus (IFG), unilateral tDCS over the right IFG improved accuracy at the expense of response speed in a pre-potent response inhibition task, while at the same time no significant behavioural changes were elicited in the GNGT in either stimulation conditions. As opposed to the relatively consistent significant findings observed for SSTs, a number of studies using GNGT paradigms have not found any significant effects on overall inhibitory control performance [26, 28, 39, 163]. Again, a subset of these studies demonstrated that the adjuvant use of neuroimaging techniques might reveal more subtle tDCS-related changes, which fail to translate to the behavioural level. Even though the rate of commission errors did not differ pre-post anodal tDCS, Campanella and colleagues [26] detected a decrease in the P3d amplitude in response to correctly inhibited trials. This effect was specific for the application of anodal tDCS to the right IFC and did not emerge in the sham condition. Additionally, Sallard and colleagues [163] showed that right lateralised prefrontal anodal tDCS abolishes the discrepancy in BOLD activity in the ventrolateral prefrontal cortex (VLPFC) between go and no-go trials observed during sham stimulation by increasing BOLD activity during go trials. This observation hints at a possible brain-state-dependent effect (stimulation during go vs. no-go trials) of tDCS on BOLD activity. Choosing the left DLPFC, rather than the IFC, as a target region, Nejati and colleagues [129] demonstrated performance gains in a GNGT when applying anodal tDCS. Intriguingly, the improvements in accuracy and reaction times in the GNGT were associated with a better performance in the Tower of Hanoi, a more cautious approach to the BART as well as a preference for larger delayed as opposed to smaller immediate rewards in a temporal discounting task. In line with these results, another study [18] ascertained that anodal tDCS over the left DLPFC can also modulate performance in another proactive control paradigm. Participants were asked to respond to a specific target when this was preceded by a cue pattern and withhold the response in case of non-targets or non-cued targets. Results showed that participants in the anodal tDCS group relied more heavily on the target-preceding cues than their peers in the sham condition, exhibiting a higher rate of false alarms in the cued non-target condition and a lower rate of false alarms in the non-cued target condition. This effect was driven by an increased low gamma power following non-cues relative to cues in the delay period for the active stimulation condition. An increased use of contextual cues under tDCS was also shown in another study [148], which used a bilateral left anodal/right cathodal electrode montage over the DLPFC. While these results

collectively corroborate the multifaceted role of the DLPFC in various executive functions, a more recent study by Wynn and colleagues [199] also provided evidence that anodal stimulation of the medial cerebellum can positively influence response accuracy in a GNGT. As such, it would be of value for future research to systematically compare how the magnitude and the longevity of tDCS-related performance gains on the GNGT vary as a function of the specific cortical region that is targeted.

From the suppression of false responses in a single GNGT paradigm, Strobach and colleagues [180] directed their attention to the influence of tDCS on inhibitory control when switching between different tasks. In the dual-task setting, participants had to select the adequate response to the attributes of auditory and visual stimuli, which were presented with a short 200 ms or a longer 400 ms delay while receiving either anodal, cathodal or sham stimulation over the right inferior frontal junction. In line with previous observations by Savic and colleagues [165], anodal tDCS did not have an effect on task-switching performance as it only increased response accuracy at short stimulus delays in the same order condition compared to sham. Cathodal tDCS, however, impaired task-switching performance, as evidenced by a decrease in response accuracy towards the first task in the sequence in the different order condition. These results are complemented by another study [3], in which cathodal tDCS to the VLPFC decreased cognitive flexibility during probabilistic reversal learning. On the other hand, a reduction in task-switching costs was achieved in a study by Sdoia and colleagues [169]. They used a bilateral right anodal/left cathodal montage over the DLPFC and PPC. Both montages decreased reaction times when participants had to switch back to a previously inhibited task. Yet, gains derived from the bilateral stimulation of the PPC were less specific since performance was also enhanced in the non-inhibited task.

Building on promising findings in the working memory domain (see Sect. 17.4) that revealed that tDCS can further augment cognitive training gains, Filmer and colleagues [54] tested whether this observation held true for a multi-tasking paradigm. While multi-tasking training generally improved performance levels, especially in dual tasks as compared to single tasks, anodal tDCS over the left DLPFC did not further increase the benefit in the trained multi-tasking paradigm and no effect of cathodal tDCS was found. Instead, training combined with anodal tDCS, but none of the other stimulation conditions, improved performance in an untrained multi-tasking paradigm, as well as a visual search task. However, these transfer effects did not extend to a GNGT. In the absence of tDCS gains on the trained multi-tasking paradigm, the restriction of tDCS gains to untrained tasks is difficult to interpret. Nevertheless, these results indicate the wide scope of secondary benefits from tDCS that still require exploration.

Apart from inhibiting a competing set of rules that are introduced in a task, or a set of tasks, inhibitory control is also crucial to block task-irrelevant salience of stimuli that interfere with on-going task demands. A few studies have addressed the question whether tDCS also modulates the resolution of these types of conflicts. Using a visual flanker task, Gbadeyan and colleagues [66] showed that anodal HD-tDCS over the left and right DLPFC enhanced the conflict adaptation effect insofar as the flanker effect increased following congruent trials and decreased following incongruent trials. Given that no such enhancement was obtained with electrode montages targeting the left or right primary motor area, the authors also demonstrated that the effect was region specific. The role of the left DLPFC in evaluating implicit associations was also confirmed in a study by Schroeder and colleagues [168], in which the application of cathodal tDCS over the left DLPFC reduced the implicit bias in an implicit association test compared to the sham condition. Furthermore, Adelhöfer and colleagues [1] tested whether anodal stimulation over the right DLPFC would modulate an auditory perceptual-attentional

bias. Results from the dichotic listening task revealed that relative to sham, participants' ability to resolve the conflict was enhanced under anodal tDCS in the high conflict condition only when attention was focused on the left ear. Neurophysiologically, a decreased N1 amplitude at electrode position C6 and an increased N450 at electrode position FC4, which have been related to a decrease in early sensory conflict perception and an enhancement in conflict resolution, respectively, bolstered these behavioural results. Of note, source analysis of the N450 component retraced it to right frontal areas, corroborating the causal role of these cortical regions in cognitive inhibition. Di Rosa and colleagues [43] reported a reduction in salience processing in a parity judgement task when applying cathodal tDCS to the right PPC, in line with the importance of the frontoparietal network for cognitive control [202]. In contrast, cathodal cerebellar tDCS did not modulate performance in the Stroop task [115].

Whereas differences in experimental paradigms may explain incongruous results between studies, additional attention has been dedicated to the investigation of inter-individual determinants of behavioural tDCS benefits. In their study, Nieratschker and colleagues [131] reported a detrimental effect of cathodal tDCS to the left DLPFC on response inhibition in a GNGT. While this effect was statistically significant on the group level, additional analyses conducted on the individual level revealed that this effect was exclusive to *COMT* Val/Val homozygotes and not present in Met allele carriers. Beyond that, Weidacker and colleagues [190] determined that even personality traits that are easily accessible by means of questionnaires can have an impact on participants' responsiveness to tDCS in a GNGT (see Sect. 17.7).

This review of the tDCS-related effects on inhibitory control highlights the potential promise of tDCS for patients who exhibit poor self-control, such as in attention deficit hyperactivity disorder (ADHD) or addiction. Based on the presented studies, not only the IFC and DLPFC, but also the preSMA, appear to be promising target regions for this line of application. Yet, the interplay and distinct contributions of each of these regions, particularly with regard to differential task demands, merits further elucidation. This might be expedited in future tDCS studies by supplementing behavioural measurements with the acquisition of neural signals, for example, in the form of EEG or fMRI.

17.3.3 Working Memory

Working memory (WM) refers to the mental workspace that facilitates the temporary storage and online manipulation of goal-relevant information, while ignoring non-relevant information [6]. WM is required for a wide range of cognitive abilities such as problem-solving, reasoning, language and learning, and is accordingly critically involved in many aspects of daily functioning. WM also appears to be particularly vulnerable to disruption, as evidenced by several psychiatric and neurological conditions that are characterised by WM impairments. At the neural level, WM processes primarily rely on the frontoparietal network comprised of the DLPFC [171] and the PPC [142]. The DLPFC is particularly critical for updating goal representations based on context [7, 41, 42] and encoding task-relevant rules, associated responses, stimulus features and conflict [119]. The PPC, on the other hand, is primarily involved in the storage of perceptual attributes relating to spatial locations [138]. Consistent with this knowledge about the neural basis of WM, the vast majority of tDCS studies have targeted either the DLPFC or PPC. Even though there are slight variations between studies with regard to the employed paradigms, the *n*-back task is used in the majority of studies. This task requires the participants to monitor a string of visual or auditory stimuli and compare each stimulus to the stimulus presented *n* trials before. The task load typically varies between 0- and 3-back, which corresponds parametrically to the cognitive demands of the task. Performance on the *n*-back task is evaluated in terms of response times and accuracy of stimulus detection. The methodolog-

ical parameters for tDCS studies reviewed in this section can be found in Table 17.4.

Fregni and colleagues [58] were among the first to examine the effect of tDCS on WM. In their proof-of-concept study, they showed that after only 10 minutes of anodal tDCS over the left DLPFC, participants produced significantly fewer errors and more correct responses on a 3-back WM task. In a control experiment with only seven participants, they also demonstrated that these effects were polarity and site specific as neither cathodal tDCS over the same area nor anodal tDCS over the primary motor cortex had any effect. Using a very similar task, Ohn and colleagues [136] demonstrated that the beneficial effects of anodal tDCS on performance accuracy remained stable for up to 30 minutes after the end of stimulation, an observation that is of particular importance for the translational potential of these findings. Even longer lasting performance gains in *n*-back task performance substantiated in a similar study by Talsma and colleagues [181], wherein the beneficial effects of a single session of anodal tDCS persisted for 24 hours. However, contrary to the expectations of the authors, tDCS benefits were not augmented further in the following two sessions. Other than improving WM per se, Bogdanov and Schwabe [15] showed that anodal tDCS applied to the right DLPFC attenuates the disruptive impact of stressors on performance in a visuospatial WM task, as well as the digit span backwards task.

Another set of studies that investigated the effect of anodal tDCS over the left DLPFC on WM did not find changes in performance accuracy. Instead, cognitive improvements were restricted to response time parameters [86, 133, 201] or were completely absent on the group level [114]. The reasons for these disparate results are not clear. It is possible that in some cases different results may have been due to greater emphasis being placed on speed over accuracy when instructing participants [143]. Aside from that, ceiling effects in accuracy at baseline or in the sham condition may have prevented further improvement. Yet, many other differences in stimulation protocols may have played a role. For instance, Hoy and colleagues [86] showed that 1 mA resulted in more pronounced decreases in reaction time compared to 2 mA. Notably, this behavioural effect was also reflected in an increase in event-related theta synchronisation and alpha desynchronisation.

Indeed, given the heterogeneous effects of tDCS at the behavioural level, particular attention should be devoted to the additional collection of neurophysiological data to test for tDCS effects at the neural level that are a prerequisite for stimulation effects at the behavioural level. Performance on *n*-back tasks has been associated with differential theta and alpha band activity [149]. In line with this, Zaehle and colleagues [201] reported polarity-specific effects on oscillatory power in alpha and theta bands. More specifically, oscillatory activity in these bands was amplified after anodal tDCS to the left DLPFC and decreased after cathodal tDCS. These findings fit in with the assumed role of alpha band activity in the inhibition of task-irrelevant processes and the role of theta band activity in the executive aspects of WM. An increase in frontocentral theta power upon frontoparietal anodal tDCS (with HD montages targeting EEG positions F3 and P3 simultaneously), but not when applying HD-tDCS to the left DLPFC alone, was also demonstrated in a study by Hill and colleagues [85]. Further, they demonstrated the impact of the stimulation on cortical excitability as indexed by an enhanced P60 component in the transcranial magnetic stimulation (TMS) evoked potential in the wake of applying anodal tDCS in DLPFC and DLPFC+PC montages, thus replicating one of their previous findings [84]. Confirming the apparent subtlety of neurophysiological tDCS-related changes that do not necessarily translate to an altered performance, Nikolin and colleagues [135] found an increased frontal P3 amplitude for current intensities of 2 mA, 1 mA and 0.034 mA (the latter constituting a sham condition) compared to a condition in which there was no current flow at all. Of note, this effect was largest with 1 mA and moderately correlated with changes in WM accuracy from baseline to post-tDCS assessments, highlighting

Table 17.4 The effects of tDCS on working memory

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Au et al. [5]	Parallel 1. F3/Fp2 2. F4/Fp1 3. S	*lDLPFC, rDLPFC*	Total: 62 (38 f), 18–35 y 1. 20.91 ± 2.34 y 2. 21.55 ± 2.86 y 3. 20.52 ± 1.93 y	1. A(F3): 5 × 7 cm/C(Fp2): 5 × 7 cm 2. A(F4): 5 × 7 cm/C(Fp1): 5 × 7 cm	2 mA, 25 min, online, six sessions	Online: visuospatial WM	Gain scores: ↑ (combined active conditions). Greater effect in spaced group (weekend between third and fourth sessions). Differential transfer effects between active conditions. 3 month follow-up (range: 97–393 d, 221 ± 82 d): ↑ in trained task (combined active conditions).
Boehringer et al. [14]	Crossover *ext./Cerebellum* vs. S	*Cerebellum*	40 (20 f), 25 ± 3, 19–32	A(*right musculus buccinator*): 5 × 5 cm/C(2 cm below the inion and 1 cm posterior to the right mastoid process): 5 × 5 cm	2 mA, 25 min, offline	Offline: prior to digit span task	Digit span forward: ↓ (post *ext./cerebellum* compared to sham). Digit span backward: pre-post improvement blocked by *ext./cerebellum*.
Bogdanov et al. [15]	Parallel F4/Cz vs. Cz/F4 vs. S	*rDLPFC*	120 (60 f), 25.2 ± 0.31 y, 18–32 y	A(F4): 5 × 5 cm/C(Cz): 10 × 10 cm C(F4): 5 × 5 cm/A(Cz): 10 × 10 cm	1.075 mA, 6–10 min, online	Online: visuospatial WM and digit span backwards	Preventing stress-induced performance decline in both tasks (F4/Cz). n.s. (Cz/F4).
Fregni et al. [59]	Crossover F3/*cSOA* vs. S	*lDLPFC*	15 (11 f), 20.2 y, 19–22 y	A(F3):35 cm^2/C(*cSOA*):35 cm^2	1 mA, 10 min, online	Online: verbal 3-back	Accuracy: ↑ (F3/*cSOA* compared to sham). Error rate: ↓ (F3/*cSOA* compared to sham). RT: n.s.

Friehs and Frings [61]	Parallel 1. F3/*ext.* online 2. F3/*ext.* offline 3. S	*lDLPFC*	Total: 63 (43 f), 1. 23.76 ± 2.72 y 2. 24.62 ± 2.31 y 3. 24.1 ± 2.88 y	A(F3): 3 × 3 cm C(*left deltoid*): 5 × 7 cm	0.5 mA, 20 min, online/offline	Online: letter n-back Offline: letter n-back	Correct RT (offline): ↑. Accuracy (offline): ↑ (targets only).
Heinen et al. [81]	Parallel and crossover *Exp 1:* P4/P3 vs. S *Exp 2:* P3/P4 vs. S *Exp 3:* P4/*ext.* vs. *ext.*/P4 vs. S	*Exp 1: lPPC, rPPC* *Exp 2: lPPC, rPPC* *Exp 3: rPPC*	*Exp 1:* 16 (10 f), 19–37 y *Exp 2:* 16 (12 f), 19–38 y *Exp 3:* 19 (9 f), 19–33 y	*Exp 1:* A(P4): 6.5 × 4.5 cm/C(P3): 6.5 × 4.5 cm *Exp 2:* A(P3): 6.5 × 4.5 cm/C(P4): 6.5 × 4.5 cm *Exp 3:* A(P4): 6.5 × 4.5/C(*left arm*): 6.5 × 4.5 cm C(P4): 6.5 × 4.5/A(*left arm*): 6.5 × 4.5 cm	1.5 mA, 20 min, online	Online: visual WM (bar orientation)	Performance: ↑ (P4/P3 by decreasing random responses, especially in low-baseline performers). ↑ (P3/P4 by decreasing false positive rate, especially in low-baseline performers). n.s. in both unilateral conditions (beneficial effect of P4/*left arm* on low performers with decreased false positive).
Hill et al. [84]	Crossover HD-F3 vs. F3/Fp2 vs. S	*lDLPFC*	20 (12 f), 29.11 ± 12.31 y	A(F3): 3.14 cm^2/4xC(Fp1, Fz, C3, F7); 3.14 cm^2 A(F3): 12.56 cm^2/C(Fp2): 12.56 cm^2	1 mA, 20 min, offline	Offline: letter n-back and TMS-EEG	WM: n.s. (both active conditions). TEPs: P60 ↑ (both active conditions, 30 min after HD, 5 min after bipolar). Theta, alpha, beta, gamma power: n.s. Negative parietal-occipital clusters for theta and beta oscillations 30 min after HD respectively.

(continued)

Table 17.4 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Hill et al. [85]	Crossover HD-F3 vs. HD-F3 + P3 vs. S	*lDLPFC, lPPC*	16 (10 f), 32.81 ± 10.80 y	A(F3): 3.14 cm^2/4xC(Fp1, Fz, C3, F7); 3.14 cm^2 2xA(F3,P3)/6xC(Fp1, Fz, C3, F7, P7, Pz).	1.5 mA, 15 min, offline	Offline: TMS-EEG and letter n-back	WM: n.s. (both active conditions). P60: ↑ (both active conditions, 30 min). N100: ↑ (F3 + P3, 30 min). Frontocentral theta power: ↑ (F3 + P3, 5 min).
Hoy et al. [86]	Crossover F3/*cSOA*(1 mA) vs. F3/*cSOA*(2 mA) vs. S	*lDLPFC*	18 (11 f), 24.71 ± 6.97 y	A(F3): 35 cm^2/C(*cSOA*): 35 cm^2	1 and 2 mA, 20 min, offline	Offline: prior to verbal n-back and EEG	RT: ↓ (1 mA compared to 2 mA and S). Decrease of RT over time (1 mA and 2 mA compared to S). Theta event-related synchronisation: ↑ (1 mA and 2 mA, especially 1 mA immediately after stimulation). Alpha event-related desynchronisation: trend ↑ (1 mA).
Katz et al. [97] (follow-up of Au et al. [5])	Parallel F3/Fp2 vs. F4/Fp1 vs. S	*lDLPFC, rDLPFC*	67 (42 f), 18–35 y	A(F3): 5 × 7 cm/C(Fp2): 5 × 7 cm A(F4): 5 × 7 cm/C(Fp1): 5 × 7 cm	2 mA, 25 min, online, six sessions	Online: visuospatial WM	Gain scores: ↑ (combined active conditions). Long-term follow-up (range: 251–471 d, 355 ± 73 d): ↑ in trained task (combined active conditions).

Li et al. [108]	Crossover 1. F4/*ext.* vs. P4/*ext.* vs. Oz/*ext.* 2. F4/*ext.* vs. P4/*ext.* vs. Oz/*ext.*	*rDLPFC, rPPC, VC*	1. 27 (15 f), 22.15 ± 2.2 y 2. 21 (13 f), 21.24 ± 1.9 y	A(F4): 5 × 5 cm/C(*left cheek*) A(P4): 5 × 5 cm/C(*left cheek*) A(Oz): 5 × 5 cm/C(*left cheek*)	1.5 mA, 15 min, offline	Offline: visual WM (change detection in bar orientation)	WM performance (attention scope): ↑ (P4 compared to Oz). WM performance (attentional control): ↑ (P4 compared to Oz). Same pattern for central and bilateral stimulus presentation.
Luque-Casado et al. [114]	Crossover *lDLPFC*/*cSOA* vs. S	*lDLPFC*	30 (7 f), 21.6 ± 2.7 y	A(left DLPFC, 5 cm anterior to FDI hotspot): 35 cm^2/C(*cSOA*): 35 cm^2	1.5 mA, 15 min, offline	Offline: digit span backwards	Task performance: n.s.
Maldonado et al. [115]	Crossover *Cerebellum* vs. S	*Cerebellum*	24 (12 f), 19.04 ± 1.60 y	Overall dimensions: N/S. Cathodal cerebellar setup: C(PO10, O10, Ex4)/A(P2, Ex3, Ex5, Ex12, Ex14, Nk1)	Cathodal cerebellar setup: P2(0.1135 mA), PO10(−0.1551 mA), O10(−0.3618 mA), Ex3(0.1956 mA), Ex4(−1.4832 mA), Ex5(0.4066 mA), Ex12(0.22 mA), Ex14(0.7886 mA), Nk1(0.2757 mA) 20 min, offline, two sessions	Offline: Stroop task, Sternberg task	Task performance: n.s.
Nikolin et al. [134]	Crossover HD-F3 vs. HD-CP5 vs. HD-P9 vs. S		16 (8 f), 21.8 ± 2.4 y	HD A(F3)/4xC(AF3,F1,FC3,F5) A(CP5)/4x(C5,CP3,P5,TP7) A(P9)/3xC(Fp1,Fp2,FC4)	2 mA, 20 min, partially online	Partially online: letter n-back	RT: ↓ (HD-F3). Accuracy: n.s.
Nikolin et al. [135]	Parallel and crossover *Exp 1:* F3/F4 vs. S *Exp 2:* F3/F4 vs. S vs. off	*lDLPFC, rDLPFC*	*Exp 1:* 40 (20 f) *Exp 2:* 60 (32 f) 22.9 ± 4.3 y (overall)	A(F3): 4 × 4 cm/C(F4): 4 × 4 cm	1. 2 mA, S = 0.034 mA 2. 1 mA, S = 0.016 mA Off = disconnected electrodes 15 min, online/offline	Online: letter n-back and EEG Offline: letter n-back and EEG	RT and d' (3-back): n.s. P3: ↑ (1 mA), ↓ (0 mA), 2 mA > 0 mA, 1 mA > 0 mA, 0.034 > 0 mA. Corr: ΔP3 ~ Δd'.

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Table 17.4 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Ohn et al. [136]	Crossover F3/*cSOA* vs. S	*lDLPFC*	15 (10 f), 26.5 ± 3.5 y	A(F3): 5 × 5 cm/C(*cSOA*): 5 × 5 cm	1 mA, 30 min, online	Online: verbal 3-back	Accuracy: ↑ (F3/*cSOA* compared to S at 20 min and 30 min during stimulation and 30 min after stimulation). Error rate: n.s. RT: n.s.
Ruf et al. [162]	Parallel F3/*ext.* vs. F4/*ext.* vs. S	*lDLPFC, rDLPFC*	71 (57 f), 24.45 ± 5.16 y	A(F3): 5 × 7 cm/C(*right deltoid*): 5 × 7 cm A(F4): 5 × 7 cm/C(*left deltoid*): 5 × 7 cm	1 mA, 20 min, online, 3 WM training sessions [spatial (*N* = 36) or verbal (*N* = 35)]	Online/offline: spatial, verbal WM	Learning rates (during training sessions): ↑ (task-congruent tDCS). Greater benefit for low-baseline performers. Performance gains (at follow-up): ↑ (task-congruent tDCS). Transfer gains (after training): task-congruent tDCS > sham.
Talsma et al. [157]	Parallel 1. F3/*cSOA* 2. S	*lDLPFC*	1. 15 (11 f), 21.9 ± 2.8 y 2. 15 (10 f), 22.1 ± 2.3 y	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 20 min, online, three sessions	Online: letter n-back	Accuracy: ↑ (F3/*cSOA*, first session only, during tDCS, two blocks post-stimulation and 1 day later). RT: n.s. Transfer: n.s. (verbal WM with different stimuli, spatial WM, complex WM).

Trumbo et al. [183]	Parallel *Exp 1:* F3/*ext.* vs. F4/*ext.* vs. S *Exp 2:* F3/*ext.* vs. F4/*ext.* vs. S	*lDLPFC, rDLPFC*	*Exp 1:* 36 (18 f), 20.06 ± 3.43 y *Exp 2:* 36 (18 f), 20.89 ± 5.08 y	A(F3): 3.3 × 3.3 cm/C(*right arm*): 3.3 × 3.3 cm A(F4): 3.3 × 3.3 cm/C(*left arm*): 3.3 × 3.3 cm	2 mA, 30 min, online 1. Spatial WM training 2. Verbal WM training	Online/offline: spatial, verbal WM Offline: GFI	1. RT: n.s. d' ↑ (F4, but only in sessions 3 and 5). Accuracy: ↑ (F4, but only in sessions 3 and 5). Near transfer to verbal WM task: n.s. Near transfer to GFI: n.s. 2. RT: n.s. d': ↑ (F3, F4 to lesser degree). Accuracy: ↑ (F3, F4 to lesser degree). Near transfer to spatial WM: n.s. Near transfer to GFI: n.s.
Weintraub-Brevda and Chua [192]	Parallel HD-F7 vs. HD-F8 vs. S	*lVLPFC, rVLPFC*	60 (43 f), 18–35 y	A(F7): /4xC(F9, F5, FT7, Fc5) A(F8): /4xC(F10, F6, FT8, Fc6)	2 mA, 20 min, online	Online: remembering shapes	WM task: ↑ (HD-A7), n.s. (HD-A8). Greater portion of correct WM trials was also remembered in surprise episodic memory task.

(continued)

Table 17.4 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Zaehle et al. [201]	Crossover F3/lM vs. lM/F3 vs. S	*lDLPFC*	16 (10 f), 25 ± 21 y	A(F3): 5 × 7 cm/C(*lM*)	1 mA, 15 min, offline	Offline: prior to letter 3-back + EEG	RT: ↓ (F3/lM compared to lM/F3). Theta and alpha power: ↑ (F3/lM), ↓ (lM/F3).

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham. Tyr = tyrosine

[2]r = right. l = left. c = contralateral. i = ipsilateral. DLPFC = dorsolateral prefrontal cortex. PPC = posterior parietal cortex. SOA = supraorbital area. VC = visual cortex. VLPFC = ventrolateral prefrontal cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]GFI = general fluid intelligence. WM = working memory

EEG = electroencephalography. TEP = TMS-evoked potential. TMS = transcranial magnetic stimulation

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. Corr = correlation. RT = reaction time

how greater current intensities do not necessarily coincide with greater tDCS-related gains.

Earlier in this section, we mentioned that the translational potential of tDCS findings is contingent on the persistence of effects beyond the stimulation period [137]. In addition to this, the near- and far transfer of stimulation effects to untrained tasks, which rely on the same neural networks targeted during the stimulation, is another sought-after aspect in application-oriented contexts. Appreciating this consideration, Trumbo and colleagues [183] combined anodal tDCS over the left or right DLPFC with either spatial or verbal WM training. For the spatial WM training, only marginal effects of the active stimulation conditions compared to sham emerged and no gains arose in the transfer tasks, verbal WM and a matrix-reasoning task to measure general fluid intelligence, for near and far transfer respectively. At the same time, both left anodal and right anodal stimulation resulted in improved performances in the trained verbal WM task. Additionally, compared to baseline, significant numerical improvements were observed in the right anodal condition in both spatial WM and fluid intelligence performances, while only the latter improved in the sham condition. This suggests that cognitive benefits from pairing tDCS with WM training in a specific modality can be conferred to untrained tasks. Previous studies already revealed that stimulation effects can be further augmented by using multiple, as opposed to single, sessions of tDCS [121, 158]. Following up on this notion, Ruf and colleagues [162] examined the impact of three WM training sessions combined with anodal versus sham tDCS applied to the left or right DLPFC. Assigning participants to either spatial or verbal WM training, the study not only revealed that the stimulation boosted the learning rates during the online training sessions and performance gains at follow-up, but also that these effects relied on the application of anodal tDCS to the task-congruent hemisphere. Specifically, participants in the spatial WM training group profited from right anodal tDCS, while showing no significant difference in the left anodal condition compared to sham. Reciprocally, participants in the verbal training group exclusively scored higher in the left anodal tDCS condition. These effects lasted for up to 9 months and transferred to the respective untrained task. Further increasing the number of training sessions, another study [5] supplemented six sessions of visuospatial WM training with anodal tDCS to the left or right DLPFC compared to sham. Once again, the gain scores in the combined active conditions exceeded the ones observed in the sham condition. Interestingly, gain scores between training sessions 3 and 4, were found to be greater for the group of participants who had their fourth session following a weekend break as opposed to the consecutive day. This implies a crucial influence of offline stimulation effects, which have also been reported by others [61], but are not given much consideration in the literature at large. Returning to the study by Au and colleagues [5], right anodal, but not left anodal, tDCS resulted in cognitive improvements selectively in an untrained visual *n*-back as well as a backward block-tapping task. Furthermore, the authors demonstrated that the tDCS-derived gain in the trained task relative to the sham group was maintained at an approximately 3-month follow-up (221 ± 82 days, range: 97–393 days). Following up on the same participants after, on average, 12 months (355 ± 73 days, range: 97–471 days), the same research group [97] reported that participants in the active conditions continued to outperform their peers in the sham group. These observations suggest that repeated sessions of tDCS in conjunction with WM training, as opposed to either WM training or tDCS on their own, may hold particular promise for fostering lasting gains in WM performance.

A single study [192] chose the VLPFC as the target site for anodal HD-tDCS, testing the contribution of frontal regions other than the DLPFC on WM performance. In this sense, Weintraub-Brevda and Chua showed that the proportion of correct responses was greater in the left anodal condition compared to sham, whereas performance levels in the WM task did not differ between groups that received right anodal tDCS or sham.

Heinen and colleagues [81] explored the effect of parietal tDCS on a visual WM task. In three

separate experiments, they applied tDCS bilaterally or unilaterally to the PPC, while switching the positions of anode and cathode. Their results showed that independent of electrode polarity, bilateral tDCS improved performance levels, especially in initial low performers. These performance gains were, however, attributed to the suppression of different kinds of errors. While the right anodal/left cathodal configuration decreased the probability of random responses, performance gains in the reverse electrode configuration manifested as a lower rate of misbinding errors. With regard to the unilateral application of tDCS, the stimulation benefits were restricted to the cathodal condition and were solely observed in participants who exhibited a low performance at baseline. Thus, the latter experiment is yet another example of how cathodal tDCS rather than anodal tDCS can produce gains in cognitive performance.

Two tDCS studies also examined the role of the cerebellum in WM [14, 115]. Boehringer and colleagues [14] found that cathodal, relative to sham, tDCS over the cerebellum was associated with poorer performance on the digit span task, and additionally blocked a practice-dependent increase in digit span. In contrast, cathodal cerebellar tDCS did not modulate performance in a Sternberg task [115].

Potential indirect effects of tDCS on WM performance gains by way of modulating attentional processes also need to be considered. For instance, an elegant study conducted by Li and colleagues [108] provided evidence to suggest that the improvements in performance in a visual WM task may be traced back to the differential roles of the right DLPFC and the right PPC in attentional control and attentional scope, respectively.

In sum, a respectable body of evidence has accumulated to suggest that tDCS applied over DLPFC, PPC, VLPFC and cerebellum is capable of altering WM performance in young healthy adults. However, results are not entirely consistent, and discrepancies with regard to stimulation parameters and study designs are currently limiting the interpretation of results. Indeed, the same conclusions were drawn by two recent meta-analyses of the effects of tDCS on WM performance [21, 83] have drawn the same conclusions, and have emphasised the need for future studies to systematically probe the impact of various stimulation parameters with the view to both elucidating the factors that mediate inconsistent findings, and optimising performance gains. However, as will be discussed below, even when stimulation protocols are identical, inter-individual differences can also confound tDCS studies (Sect. 17.8).

17.4 Effects of tDCS on Language

Language refers to the complex capacity to understand as well as express mental contents with highly structured sets of sounds, manual gestures and written symbols. To date, most studies that investigated the effect of tDCS on language in healthy young adults have focused on picture naming, verbal fluency and reading comprehension. These functions rely predominantly on left lateralised, albeit distributed, frontal, temporal and parietal cortical regions. However, a few studies [46, 175] also appreciate the role of prefrontal-cerebellar loops in supporting language functions. Table 17.5 lists the studies reviewed in the section and their methodological parameters.

Applying 2 mA of anodal or cathodal tDCS to Wernicke's area, Sparing and colleagues [174] tested whether they could modulate the performance in picture naming. Subjects responded significantly faster with anodal tDCS over Wernicke's area when compared to sham and cathodal stimulation. Response times did not differ between cathodal stimulation and sham, nor did the application over the homologous region in the right hemisphere produce any significant effect. However, the authors observed that the facilitatory effect did not outlast the online stimulation. Applying anodal tDCS over Wernicke's area also proved to be beneficial during associative language learning, while cathodal stimulation did not have a significant impact on the acquisition of new vocabulary [57].

Based on the successful modulation of language production in earlier studies with smaller numbers of participants [53, 88], Wirth and col-

Table 17.5 The effects of tDCS on language

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Brückner and Kammer [20]	Parallel CP5/*ext.* vs. *ext.*/CP5 vs. S	*lPTC*	60 (30 f), 22.7 ± 2.8 y	A(CP5): 5 × 7 cm/C(left shoulder): 5 × 7 cm C(CP5): 5 × 7 cm/A(left shoulder): 5 × 7 cm	1 mA, 15 min, offline	Offline: prior to lexical decision task	RT: trend towards ↓ (CP5/*ext.*), ↓ (*ext.*/CP5). No difference between CP5/*ext.* and *ext.*/CP5. Accuracy: n.s. (CP5/*ext.* and *ext.*/CP5).
Choi and Perrachione [33]	Parallel HD-T7 + TP7 (anodal) vs. HD-T7 + TP7 (cathodal) vs. S	*lSTG*	60 (46 f), 20.4 y, 18–31 y	HD 2xA(T7, TP7)/4xC(C3, CP3, PO7, F7) 2xC(T7, TP7)/4xA(C3, CP3, PO7, F7)	2 mA, ~13 min, online	Online: speech adaptation	RT: n.s. Connected speech benefit in mixed talker condition: ↓ (both active conditions). Accuracy: n.s. (both active conditions).
Cummine et al. [37]	Parallel TP3/*ext.* vs. *ext.*/TP3 vs. S	*lAG*	77 (52 f), 21.6 ± 5.09 y	A(TP3): 4.5 × 5 cm/C(*right upper arm*): 4.5 × 5 cm C(TP3): 4.5 × 5 cm/A(*right upper arm*): 4.5 × 5 cm	1 mA, 13 min, offline	Offline: pre-post, semantic information in reading	RT: ↓ pre-post (*ext.*/TP3). Effect of imageability ↓ (TP3/*ext.* and *ext.*/TP3).
D'Mello et al. [46]	Parallel *Cerebellum*/*ext.* vs. S	*Cerebellum*	35 (23 f), 23.7 ± 2.7 y	A(1 cm down and 4 cm right of inion): 5 × 7 cm/C(*right clavicle*): 5 × 7 cm	1.5 mA, 20 min, offline	Offline: pre-post, sentence completion	RT: n.s. Activation in *right cerebellum*: ↑ (during semantic prediction). Resting state functional connectivity in reading/language networks: ↑.

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Table 17.5 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
de Vries et al. [187]	*Main exp:* Parallel *BA 44/45/cSOA* vs. S *Control exp:* Cz/*cSOA* vs. S	*Main exp: Broca's area* *Control exp):* Cz	*Main exp:* 44 (19 f), 22.6 ± 2.1 y 1. 22 (N/S) 2. 22 (N/S) *Control exp:* 10 (5 f), 23.7 ± 2.4 y	*Main exp:* A(*left BA 44/45*): 5 × 7 cm/C(*cSOA*): 10 × 10 cm *Control exp:* A(Cz): 5 × 7 cm/C(*cSOA*): 10 × 10 cm	1 mA, 20 min, online (acquisition phase, learning continued 5 min after tDCS), one session	Online: implicit artificial grammar learning (classification task) Offline: blood pressure, heart rate, mood ratings	Acquisition: n.s. Endorsement rate: ↓ (*BA 44/45/cSOA* compared to S for non-grammatical but not grammatical items). n.s. (Cz/*cSOA*). d': ↑ (*BA 44/45/cSOA* compared to S for low but not high chunk strength). Blood pressure: n.s. Heart rate: n.s. Mood: n.s.
Fiori et al. [56]	Crossover Fc5/*cSOA* vs. S	*lIFG*	28 (14 f), 26.96 y, 22–36 y	A(Fc5): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 24 min, online	Online: verb learning and fMRI	Correct responses: ↑ (Fc5/*cSOA* vs. S, fifth and sixth blocks). Task-related activity in left occipitofusiform gyrus, lIFG, rIFG: ↓. Differential effect for correct and incorrect responses. Coupling between lIFG and right insula: ↓. Negative corr between accuracy increase and connectivity strength.

Flöel et al. [57]	Crossover CP5/*cSOA* vs. *cSOA*/CP5 vs. S	*Wernicke's area*	19 (9 f), 25.6 ± 2.7 y, 22–32 y	A(CP5): 5 × 7 cm/C(*cSOA*): 5 × 7 cm C(CP5): 5 × 7 cm/A(*cSOA*): 5 × 7 cm	1 mA, 20 min, online (learning phase, learning continued 10 min after tDCS), three sessions	Online: associative language learning. Offline: immediate and delayed lexical knowledge test, blood pressure, heart rate, mood ratings	Correct responses: ↑ (CP5/*cSOA* compared to *cSOA*/CP5 and S at end of learning session). Response styles: n.s. Immediate lexical knowledge: ↑ (CP5/*cSOA* compared to *cSOA*/CP5 and S). Immediate lexical knowledge: n.s. RT: n.s. Blood pressure: n.s. Heart rate: n.s. Mood: n.s.
Giustolisi et al. [67]	Parallel F5/*cSOA* vs. S	*lIFG*	44 (32 f), 22 ± 2 y	A(F5): 3 × 3 cm/C(*cSOA*): 5 × 7 cm	0.75 mA, 30 min, online (sentence comprehension)	Online: sentence comprehension	Accuracy (picture matching previous sentence): ↑.
Herrmann et al. [82]	Parallel F3/F4 vs. F4/F3 vs. S	*lDLPFC, rDLPFC*	61 (30 f), 24.3 y	A(F3): 5 × 7 cm/C(F4): 5 × 7 cm C(F3): 5 × 7 cm/A(F4): 5 × 7 cm	1 mA, 26 min, online	Online: phonemic verbal fluency and NIRS	Number of words: n.s. Cortical activation: n.s.
Li et al. [107]	Crossover F4/*ext.* vs. *ext.*/F4 vs. S	*rDLPFC*	24 (15 f), 22.04 ± 2.3 y, 18–26 y	A(F4): 5 × 5 cm/C(right shoulder): 5 × 5 cm C(F4): 5 × 5 cm/A(right shoulder): 5 × 5 cm	1 mA, 25 min, offline	Offline: prior to language switching (bilinguals) and EEG	Late positive EEG component: ↑ (*ext.*/F4 when switching to weaker language compared to sham). Switch costs: ↓ (*ext.*/F4).
Lum et al. [113]	Parallel T3–Fz–F7–Cz/*rSOA* vs. S	*lIFG*	36 (20 f), 23.0 ± 2.1y, 22.7 ± 2.8 y	A(intersection T3–Fz–F7–Cz): 5 × 5 cm/C(*rSOA*): 5 × 7 cm	1 mA, 15 min, online	Online: sentence and word comprehension	Accuracy: n.s. RT: ↓ (T3–Fz–F7–Cz/*rSOA* in sentence comprehension), n.s. (word comprehension).

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Table 17.5 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Meinzer et al. [125]	Crossover AT3–Fz–F7–Cz/*rSOA* vs. *PMTG/STG* vs. S	*lIFG, PMTG/STG*	24 (14 f), 24.69 ± 4.61 y	A(intersection T3–Fz–F7–Cz): 5 × 7 cm/C(*rSOA*): 10 × 10 cm A(Talairach: $X = -50$; $Y = -46$; $Z = 1$) 5 × 7 cm/C(*rSOA*): 10 × 10 cm	1 mA, 20 min, online	Online: word production	RT: n.s. (AT3–Fz–F7–Cz/*rSOA*), interference effect: ↓ (AT3–Fz–F7–Cz/*rSOA* in second, third and fourth cycles). Interference effect: ↓ (*PMTG/STG* in second, third, fourth· fifth and sixth cycles due to latencies ↓ in related blocks).
Pisoni et al. [151]	Crossover *lIFG*/*cSOA* vs. S	*lIFG*	18 (10 f), 27.7 ± 5.3 y, 21–38 y	A(lIFG, MRI-neuronavigation): 16 cm^2/ C(*cSOA*): 25 cm^2	0.75 mA, 20 min, online/offline	Online: verbal fluency Offline: pre-post TMS-EEG	Verbal fluency: ↑. Cortical excitability: ↑ (TMS over BA6, early and middle latency components).
Price et al. [154]	Crossover HD-*lAG* vs. HD-*rAG* vs. S	*lAG, rAG*	18 (9 f), 25.3 y, 20–39 y	HD A(MNI: −52, −56, 22): diameter [in]: 0.6 cm, diameter [out]: 1.2 cm /4xC: diameter [in]: 0.6 cm, diameter [out]: 1.2 cm, 6 cm from A A(MNI: 52, −56, 22): diameter [in]: 0.6 cm, diameter [out]: 1.2 cm /4xC: diameter [in]: 0.6 cm, diameter [out]: 1.2 cm, 6 cm from A	2 mA, 20 min, offline	Offline: word pair task	RT: ↓ (HD-*lAG* compared to HD-*rAG* and S for meaningful relative to non-meaningful word pairs). Effect correlated with degree of semantic coherence of word pair.

Rodrigues de Almeida et al. [159]	Parallel 1. F5/*cSOA* 2. *cSOA*/F5 3. S	*lIFG*	60 (45 f), 1. 21.50 ± 2.19 y, 2. 19.90 ± 1.21 y, 3. 20.85 ± 2.66 y	A(F5): 5 × 7 cm/C(*cSOA*): 5 × 7 cm C(F5): 5 × 7 cm/A(*cSOA*): 5 × 7 cm	1.5 mA, 20 min, online	Online: categorical perception, lexical decision, word naming	RT (categorical perception): ↓ (F5/*cSOA* and *cSOA*/F5 even more for latter). Accuracy (categorical perception): ↑ (F5/*cSOA* only). RT (lexical decision): n.s. Accuracy (lexical decision): n.s. RT (word naming): ↓ [F5/*cSOA* and *cSOA*/F5, words (F5/*cSOA*), non-words (*cSOA*/F5)].
Sparing et al. [174]	Crossover CP5/Cz vs. Cz/CP5 vs. P6/Cz vs. S	*lPPR, rPPR*	15 (5 f), 26.9 ± 3.7 y	A(CP5): 5 × 7 cm/C(Cz): 5 × 7 cm C(CP5): 5 × 7 cm/A(Cz): 5 × 7 cm A(CP6): 5 × 7 cm/C(Cz): 5 × 7 cm	2 mA, 7 min, online	Online: picture naming task	RT: ↓ (CP5/Cz compared to Cz/CP5 and S, no difference between Cz/CP5 and S). ↑ (CP6/Cz compared to CP5/Cz).
Spielmann et al. [175] (replication of Pope)	Crossover *Ext./cerebellum* vs. S	*Cerebellum*	24 (18 f), 22 ± 2.36 y, 19–29 y	C(1 cm under, 4 cm lateral to inion): 25 cm^2/A(*right deltoid*): 25 cm^2	2 mA, 20 min, offline	Offline: pre-post noun reading, verb generation, verb reading	RT: n.s. Greater reduction when receiving S at first visit and *ext./cerebellum* at second visit (esp. in verb generation). Response variability: n.s. Greater reduction when receiving S at first visit and *ext./cerebellum* at second visit (esp. in verb generation). Learning: n.s.

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Table 17.5 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Westwood et al. [195]	Parallel and crossover 1. F7/*cSOA* vs. S 2. F7/*cSOA* vs. S 3. T3-T5/*ext.* vs. S 4. F7/*ext.* vs. S	*1. lIFG* *2. lIFG* *3. PMTG* *4. lIFG*	1. 18 (10 f), 21 ± 2.76 y 2. 20 (12 f), 21 ± 2.92 y 3. 18 (13 f), 19.8 ± 2.8 y 4. 17 (12 f), 21 ± 2.4 y	1. A(F7): 9 cm^2/C(*cSOA*): 35 cm^2 2. A(F7): 25 cm^2/C(*cSOA*): 35 cm^2 3. A(T3–T5): 25 cm^2/C(right cheek): 35 cm^2 4. A(F7): 25 cm^2/C(*cSOA*): 35 cm^2	1. 1 mA, 15 min, online 2. 1.5 mA, 25 min, online 3. 1.5 mA, 25 min, online 4. 1.5 mA, 25 min, online	1. Online: picture naming, reading 2. Online: picture naming, reading 3. Online: picture naming, reading 4. Online: blocked picture naming	1. Task performance: n.s. 2. Task performance: n.s. 3. Task performance: n.s. 4. Task performance: n.s.
Wirth et al. [196]	Crossover F3–AF3/*ext.* vs. S	*lDLPFC*	20 (10 f), 23.5 ± 3.7 y, 19–31 y	A(F3–AF3): 5 × 7 cm/C(*right shoulder*): 7 × 7 cm	1.5 mA, 37 min, online/offline	Online: semantic interference Offline: prior to picture naming task and EEG	Performance: ↑ with F3–AF3/*ext.* compared to S (in behavioural and neurophysiological correlates of the task).
Wong et al. [198]	Parallel F5/Fp2 vs. S	*lIFG*	30 (20 f), 27.36 ± 11.26 y	A(F5): 5 × 7 cm/C(Fp2): 5 × 7 cm	2 mA, 20 min, offline (after block 1)	Offline: after block 1 of tongue twister production	Speech rate: n.s. Response accuracy: n.s.

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. AG = angular gyrus. BA = Brodmann area. DLPFC = dorsolateral prefrontal cortex. IFG = inferior frontal gyrus. PMTG = posterior middle temporal gyrus. PPR = posterior perisylvian region. PTC = posterior temporal cortex. SOA = supraorbital area. STG = superior temporal gyrus

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]EEG = electroencephalography. fMRI = functional magnetic resonance imaging. NIRS = near-infrared spectroscopy. TMS = transcranial magnetic stimulation

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. Corr = correlation. RT = reaction time

leagues [196] selected the left DLPFC as their target region for anodal tDCS. Additionally, they sought to investigate the electrophysiological underpinnings of tDCS-induced changes in picture naming and a semantic interference task with EEG. In the latter task, semantic interference was defined as the difference in response time when subjects are required to respond to objects displayed in semantically homogeneous as opposed to heterogeneous contexts. At the behavioural level, the authors observed a reduction in semantic interference during online anodal tDCS. Similar to the study by Sparing and colleagues [174], no offline effect of anodal tDCS was found for picture naming. With regard to EEG results, it was found that the behavioural reduction of semantic interference correlated with an increase in amplitude of event-related potentials over left, but not right, temporal electrode sites. These results were interpreted as reflecting a superior tuning of neural responses within language-related substrates. Despite the absence of behavioural after effects on picture naming, delta activity was reduced during picture naming and at rest after the stimulation was terminated. This finding is consistent with the notion that anodal tDCS had an excitatory impact on frontally mediated neural processes and related language functions, which outlast the stimulation period. Further work is required to determine whether the electrophysiological aftereffects of the stimulation can be extended to behavioural results. It should, however, be noted that effects on task performance that outlast the effect of online stimulation does not equal effects of stimulation applied before task onset. Following a previous study [55] that indicated that the application of anodal tDCS to Broca's area was associated with more accurate and faster articulation of tongue twisters, Wong and colleagues [198] used an almost identical stimulation protocol with the exception of applying the stimulation at rest prior to the task. Contrary to the beneficial effects found in the online-tDCS study, neither speech rate nor response accuracy could be improved in the subsequent study by Wong and colleagues, which used an offline-tDCS paradigm. It should, however, be noted that a previous study [195] did not find a significant stimulation effect even though applying anodal tDCS concurrent with the task.

De Vries and colleagues [40] explored the effects of anodal tDCS over Broca's area when applied during an artificial grammar learning paradigm. Anodal tDCS was associated with an improved performance on a subsequent grammatical decision task, as compared to sham tDCS, and anodal tDCS over contralateral hemisphere. This tDCS-related improvement was particularly apparent for the detection of syntactic violations, a finding which may have future implications for facilitating recovery in some patients with post-stroke aphasia.

The acquisition of neurophysiological data in conjunction with cognitive measurements can prove helpful for interpreting null effects in tDCS studies. In line with this, Herrmann and colleagues [82] measured cortical activity in the prefrontal cortex with near-infrared spectroscopy (NIRS) while targeting the left and right DLPFC with bilateral tDCS during a phonemic verbal fluency task. Neither verbal fluency nor cortical activation was influenced by the stimulation, leading the authors to the conclusion that the left DLPFC is not involved in phonemic verbal fluency performance. The importance of the interaction between task-related brain activity and the tDCS-induced modulations of cortical excitability has been further elucidated by Pisoni and colleagues [151]. They applied anodal tDCS to the left IFG during a verbal fluency task while probing site-specific plasticity changes by means of TMS-EEG. Improvement in the task was positively correlated with increases in cortical excitability in terms of greater TEP amplitudes following anodal tDCS. This electrophysiological effect was restricted to the area involved in the functional network underlying verbal fluency (left BA6) and did not arise in an area uninvolved in this network (left BA7). Fiori and colleagues [56] targeted the same cortical area, the left IFG, with anodal tDCS and investigated the neural correlates of stimulation effect in a verbal learning task in an fMRI paradigm. Compared to sham stimulation, participants gave more correct responses in the anodal tDCS condition. This increase in accuracy was negatively correlated

with task-related functional coupling between the left IFG and the right insula. Moreover, anodal tDCS decreased task-related activity in the targeted left IFG as well as the homologous area of the right hemisphere. This reduction of the BOLD signal in Broca's area in relation to the tDCS-derived performance gains hints at a non-linear relationship between cortical activity and task performance, plausibly in the form of an inverted U curve.

A set of studies has corroborated how applying anodal tDCS over Broca's area reduced the interference effect in a word production task [125] while also elevating performance levels in the comprehension of sentences [67, 113]. Interestingly, both anodal and cathodal tDCS decreased reaction times in tasks on categorical perception and word naming in a study by Rodrigues de Almeida and colleagues [159]. The authors proposed that the beneficial effect of cathodal tDCS, which goes against common assumptions [89], is indicative of compensatory mechanisms shifting relative contributions of different nodes in the execution of the task.

Turning towards semantic processing, two studies selected the angular gyrus as a target region [37, 154]. In the former, Price and colleagues found that anodal tDCS to the left angular gyrus resulted in significantly shorter reaction times in the identification of meaningful compared to non-meaningful word pairs. This effect was graded on the single-item level such that greater semantic coherence of the word pair resulted in a larger stimulation effect. Neither cathodal nor sham stimulation resulted in a similar dissociation effect. A complementary interdependency between semantic content and stimulation effect was revealed in the study by Cummine and colleagues [37]. Therein, the positive effect of the imageability score on reading times of the respective word was reduced by both anodal and cathodal tDCS, particularly in participants who showed the largest imageability effect pre-stimulation. With the intention to likewise influence semantic processing, Brückner and Kammer [20] administered anodal or cathodal tDCS over Wernicke's area prior to a lexical decision task, in which participants had to decide whether the presented noun was a real word or not. While the accuracy of the responses was not altered by either of the two stimulation conditions compared to sham, cathodal tDCS significantly decreased reaction times, whereas anodal tDCS showed a trend in the same direction. These studies solidify the conclusion of a meta-analytical review [89] that the canonical assumption 'anodal excitatory, cathodal inhibitory', that was principally in the motor cortex, should not be transferred unseen to other cortical regions, especially not with the expectation to find a linear positive relationship between excitability and task performance. In fact, inhibitory control is often crucial to limit disruptive influences and thus ultimately improves cognitive performance. This notion is further reinforced by a study [107] in unbalanced Chinese-English bilinguals, in whom cathodal tDCS applied to the right DLPFC decreased language switching costs, supposedly by suppressing the interference of the non-target lemma. The analysis of late positive components of ERPs also revealed that cathodal tDCS reduced the asymmetry in switching costs between the two languages.

Choi and Perrachione [33] carried out an interesting study wherein they explored the effects of both anodal and cathodal tDCS to the left superior temporal lobe on speech processing. Participants had to identify whether they heard 'boat' or 'boot' while talker variability (single or mixed talkers) and speech context (isolated words or connected speech) where manipulated. Neither anodal nor cathodal tDCS had a significant impact on response times, whereas both stimulation conditions interfered with the beneficial effect derived from connected speech in the mixed talker condition. The authors argue that this outcome is consistent with the conjecture that superior temporal lobe structures are principally recruited when the phonetic category of a word is ambiguous. Hence, altering the excitability of this cortical region in the unambiguous condition may have produced the observed disruption in talker adaptation. This speaks to how the identification of target regions for tDCS, especially in the extensive language network, should take into account the fine-grained contributions of diverse

and distributed brain areas involved in executing the task under scrutiny.

Beyond the identification of an appropriate target region, there are numerous other parameters that must be determined when endeavouring to design efficacious stimulation protocols. Particularly in the language domain, there are conspicuous heterogeneities across studies, mainly regarding the use of diverse electrode montages to target the same brain region. This approach does little to advance the field as it reduces the likelihood that effects will be replicated, and hampers efforts to disentangle the influence of distinct brain regions in the chosen paradigm, as changes in montages lead to different distributions of current flow. Nevertheless, the studies reviewed in this section demonstrate the potential of tDCS to modulate neural functioning in language networks and associated behavioural indices in the healthy brain. Provided the necessary fine-tuning of stimulation protocols to increase their reliability, the findings also hold promise for promoting functional recovery in patients that suffer from language impairments.

17.5 Effects of tDCS on Numerical Cognition

Spanning representation and manipulation of quantities and numbers, numerical cognition is a key component of intellectual development. In the light of our society's increasing preoccupation with computation and data, it has become an ever more essential skill in everyday life. Accordingly, dyscalculia, a deficit in comprehending arithmetics, can pose serious personal, social and economic problems [9, 24]. So far, functional neuroimaging and TMS studies have consistently highlighted the importance of the intraparietal sulcus (IPS) and surrounding parietal lobe structures in numerical processing. Likewise, a small number of tDCS studies corroborate the role of the IPS in this capacity (Table 17.6).

In a study by Hauser and colleagues [78], targeting the left IPS with anodal tDCS prior to arithmetic operations significantly enhanced accuracy in a number comparison task and decreased reaction times in a subtraction task. Neither anodal stimulation of the right IPS, bilateral anodal nor bilateral cathodal stimulation resulted in any changes in performance compared to sham.

Consistent with these results, Kasahara and colleagues [96] corroborated the importance of the left IPS in their study wherein they also acquired fMRI measures. Here, additional attention was directed to the question whether individual differences in the laterality of parietal activity during mental calculation would moderate the extent to which participants would subsequently benefit from left anodal/right cathodal or left cathodal/right anodal tDCS. They found that left anodal/right cathodal tDCS was associated with reduced reaction times exclusively in those participants that had previously shown a left hemispheric dominance for brain activity when they solved the same arithmetic problems at baseline, whereas participants with a bilateral activation did not show this effect. As one of many, this finding highlights the critical role of individual differences in brain state and structure in determining tDCS outcomes (see Sect. 17.7).

Apart from subdividing the study population according to individual characteristics, the inclusion of neuroimaging measures in tDCS studies also contributes to a better understanding of the mechanisms underlying behavioural gains or their absence. In this regard, Hauser and colleagues [79] used concurrent fMRI to elucidate how the effect of tDCS on task-related neural network activity may mediate the effects on complex subtraction problems. While participants experienced no cognitive benefits from left anodal tDCS, relative to sham, in either repeated or novel arithmetic problems, tDCS exerted task-specific effects on neural activity. More precisely, the right IPS showed a decreased activation for novel relative to repeated problems in the sham group, whereas no such discrepancy emerged in the group who received 30 min of active tDCS to their left IPS concurrent with the task. The authors ascribed the effect to the impact of the excitability decreasing effect of the cathode. Placed over the right supraorbital area, the edges of the cathode bordered on the right IFC in which the

Table 17.6 The effects of tDCS on numerical cognition

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Artemenko et al. [4]	Crossover P4/*cSOA* vs. P3/*cSOA* vs. *cSOA*/P4 vs. *cSOA*/P3 vs. S	*lIPS, rIPS*	25 (22 f), 23.28 ± 4.51 y	A(P4): 5 × 5 cm^2/C(*cSOA*): 10 × 10 cm^2 A(P3): 5 × 5 cm^2/C(*cSOA*): 10 × 10 cm^2 C(P4): 5 × 5 cm^2/A(*cSOA*): 10 × 10 cm^2 C(P3): 5 × 5 cm^2/A(*cSOA*): 10 × 10 cm^2	1 mA, 20 min, online	Online: mental calculation task	RT: n.s. (overall), ↓ P4/*cSOA* (when carry-over operation needed).
Hauser et al. [78]	Crossover 1. P3/*cSOA* vs. P3 + P4/*cSOA* + *cSOA* vs. *cSOA* + *cSOA*/P3 + P4 vs. S 2. P4/*cSOA* vs. S	*1. lPPC, rPPC* *2. rPPC*	1. 21 (11f), 22.8 ± 3.1 y 2. 16 (9 f), 23.6 ± 2.4 y	1. A(P3): 35 cm^2/C(*cSOA*): 100 cm^2 2xA(P3,P4): 35 cm^2/2xC(*cSOA*,*cSOA*): 100 cm^2 2xC(P3,P4): 35 cm^2/2xA(*cSOA*,*cSOA*): 100 cm^2 2. A(P4): 35 cm^2/C(*cSOA*): 100 cm^2	1 mA, 25 min, offline	Offline: prior to number comparison, subtraction task	Accuracy (number comparison): ↑ P3/*cSOA* (compared to P3 + P4/*cSOA* + *cSOA*, *cSOA* + *cSOA*/P3 + P4, P4/*cSOA* and S). RT (number comparison): n.s. Accuracy (subtraction): n.s. RT: ↓ P3/*cSOA* (compared to P3 + P4/*cSOA* + *cSOA*, *cSOA* + *cSOA*/P3 + P4, P4/*cSOA* and S).

Hauser et al. [79]	Parallel 1. CP5–P5/*cSOA* 2. S	*lIPS/ lAG*	48 (20 f), 1. 22.4 ± 3.0 y 2. 22.4 ± 3.6 y	A (CP5–P5) 5 × 7 cm/C(*cSOA*): 5 × 10 cm	1 mA, 30 min, online	Online: subtraction task and fMRI	RT and solution rate (subtraction task): n.s. fMRI activation during novel problems: right inferior prefrontal cortex unresponsive (deactivation for novel but not repeated stimuli in sham).
Kasahara et al. [96]	Crossover P3/P4 vs. P4/P3 vs. S	*lPPC, rPPC*	16 (5 f), 21.1 y, 20–23 y	A(P3): 35 cm^2/C(P4):35 cm^2 C(P3): 35 cm^2/A(P4):35 cm^2	2 mA, 10 min, online	Online: mental calculation task	RT: ↓ P3/P4 (compared to P4/P3 and S for subjects with left hemispheric activation but not for bilateral activation assessed in fMRI)

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. AG = angular gyrus. IPS = intraparietal sulcus. = posterior parietal cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]fMRI = functional magnetic resonance imaging

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. RT = reaction time

fMRI effect was found and for which the current density simulations predicted the largest effect.

Employing a crossover design, Artemenko and colleagues [4] tested the impact of tDCS in five different electrode setups. They administered stimulation of both polarities (i.e. anodal or cathodal) unilaterally to either the right or the left IPS or a sham condition. Overall, reaction times in a subtraction task did not differ between stimulation conditions. However, tDCS over the right IPS modulated a specific task component, namely place-value integration, with anodal tDCS increasing the effect compared to cathodal stimulation.

For the most part, tDCS studies reviewed in this section converge on the notion that the parietal lobes are critical neural substrates for numerical cognition. Yet, discrepancies are likewise manifesting across studies. Currently, the origin of the latter cannot be unambiguously attributed to methodological irregularities, individual differences within and across study samples or the reliability of tDCS to modulate behavioural and neural indices of numerical cognition. While unilateral anodal tDCS may be sufficient to elicit improvements, effects observed with bilateral montages have prompted authors to speculate that a reduction in inter-hemispheric competition might mediate the effect on numerical processing. Hence, it would be of interest for future work to systematically compare the effect sizes produced with unilateral and bilateral montages that have been found to be effective.

17.6 Effects of tDCS on Learning and Memory

Studying his own processes of learning and forgetting, Ebbinghaus [47] set the research on memory rolling. Since then, different types of memory have been identified [36]. Alongside working memory (see Sect. 17.4), these are short-term and long-term memory that have been found to be closely linked to each other [77, 139, 140, 155]. Within these processes, the hippocampus is acknowledged as a crucial node in binding information from different sources [13, 19, 23] and may thus be considered an appropriate target for tDCS. While some studies argue that indirect stimulation of the hippocampus [11, 133], by way of its high connectivity to more accessible cortical regions, is possible, most studies on the effects of tDCS on learning and memory focus on cortical targets, prefrontal and parietal cortices in particular. In the following section, we provide a synopsis of studies investigating the impact of tDCS on short- and long-term memory (Table 17.7).

To date, only few, largely underpowered studies investigated the impact of tDCS on short-term memory. One study reported beneficial effects of tDCS over the left DLPFC when applied during a modified Sternberg task [68]. However, the authors observed significant improvements in reaction time only when additional distractor stimuli were presented during the delay period. Such a specific effect indicates that it might result from modulation of executive functions, such as inhibitory processes, which are known to involve frontal networks. No effects on accuracy were reported.

Studies that have targeted the parietal cortex additionally produced discrepant effects on short-term memory. Berryhill and colleagues [10] found that cathodal tDCS over the right parietal cortex applied during learning, impaired recognition, but not free recall in a visual short-term memory task. Contrarily, Heimrath and colleagues [80] found an improvement in a spatial delayed match-to-sample task when placing the cathode over the right parietal cortex. It should be noted, however, that in each study the anode was placed over the left cheek and the contralateral parietal cortex, respectively, which likely resulted in different current flow. For Heimrath and colleagues, the improvement was observed for stimuli that were presented in the left visual hemifield. On the other hand, short-term memory decreased when the anode was placed over the right parietal cortex (with the cathode over the contralateral parietal cortex). Electrophysiological measures obtained simultaneously showed a decrease in alpha power after cathodal stimulation, which has previously been associated with inhibitory

Table 17.7 The effects of tDCS on learning and memory

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Bjekić et al. [11, 12]	*Exp 1:* Crossover P3/*ext.* vs. S *Exp 2:* Crossover P4/*ext.* vs. S	*Exp 1: lPPC* *Exp 2: rPPC*	*Exp 1:* 20 (11 f); 26.40 ± 3.71 y *Exp 2:* 21 (12 f); 24.15 ± 2.74 y	*Exp 1:* A(P3): 5 × 5 cm/C(*contralateral cheek*): 5 × 5 cm *Exp 2:* A(P4): 5 × 5 cm/C(*contralateral cheek*): 5 × 5 cm	*Exp 1:* 1.5 mA, 20 min offline (computer game) *Exp 2:* 1.5 mA, 20 min offline (computer game)	*Exp 1:* Offline: associative memory: face-word, verbal fluency *Exp 2:* Offline: associative memory: object-location, verbal fluency	1. FR: ↑ (P3/*ext.*) verbal fluency: n.s. 2. FR: ↑ (P4/ext.) verbal fluency: n.s.
Bjekić et al. [11, 12]	Crossover P3/*ext.* vs. S	*lPPC*	40 (22 f); 21–35 y	A(P3): 5 × 5 cm/C(*contralateral cheek*): 5 × 5 cm	1.5 mA, 20 min, offline (computer game)	Offline: associative memory: face-word, verbal fluency	FR (immediate): ↑ (P3/*ext.*). No effect on simple face recognition. Effect particularly pronounced in initial low performers. FR (+ 1 day): ↑ (P3/*ext.*). Relying on performance in immediate FR rather than differences in retention rate. Similar effect for simple face recognition. FR (+ 4 days): ↑ (P3/*ext.*). Relying on performance in immediate FR rather than differences in retention rate. Similar effect for simple face recognition.

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Table 17.7 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Brunyé et al. [22]	Parallel 1. Study practice + F3/Fp2 2. Study practice + Fp2/F3 3. Study practice + S 4. retrieval practice + F3/Fp2 5. retrieval practice + Fp2/F3 6. retrieval practice + S	*lDLPFC*	Overall: 150 (81 f); 21.2 y. 1. 25 (N/S) 2. 25 (N/S) 3. 25 (N/S) 4. 25 (N/S) 5. 25 (N/S) 6. 26 (N/S)	A(F3): 5 × 5 cm/C(Fp2): 5 × 5 cm C(F3): 5 × 7 cm/A(Fp2): 5 × 7 cm	1.5 mA, 20 min, online, one session	Online: word list learning, starting 5 min after onset, followed by 3 min of arithmetic tasks Study practice groups: repetition of above-mentioned tasks 4 times. Retrieval practice groups: 2 min free recall, 3 min arithmetic task, verbal memory encoding, 3 min arithmetic task, 2 min free recall	FR: ↓ [F3/Fp2 compared to S and (marginally) to Fp2/F3]. ↑ (retrieval practice compared to study practice). No interaction between tDCS and practice condition. Number of intrusions: n.s.
Chen et al. [30]	Parallel and crossover 1. P3/*ext.* vs. M1/*ext.* vs. S 2. *Ext.*/P3 vs. M1/*ext.* vs. S	*lPPC, M1*	Overall: 36 (14 f); 21.2, 20–26 y 1. 18 (N/S) 2. 18 (N/S)	1. A(P3): 5 × 5 cm/C(*right cheek*): 5 × 7 cm A(*M1*): 5 × 5 cm/C(*left cheek*): 5 × 7 cm 2. C(P3): 5 × 7 cm/A(*right cheek*): 5 × 7 cm A(*M1*): 5 × 5 cm/C(*left cheek*): 5 × 7 cm	1.5 mA, 10 min, online (during retrieval)	Online: source memory test, 2 min after onset	Old/new recognition: n.s. Discrimination index: n.s. Response bias: n.s. RT: n.s Source memory performance: ↓ (*ext.*/P3 compared to *ext.*/M1 and S). No effect in anodal conditions.

Díez et al. [45]	Parallel FT9/*ext.* vs. *ext.*/ FT9 vs. S	*lATL*	Overall: 65 (48 f); 20 y, 17–29 y 1. 22 (N/S) 2. 21 (N/S) 22 (N/S)	A(FT9): 5 × 7 cm/C(*right shoulder*): 5 × 7 cm C(FT9): 5 × 7 cm/A(*right shoulder*): 5 × 7 cm	2 mA, 20 min, online and offline, one session	Online: learning (7 min visual search task, 8.5 min word lists encoding [DeeseeRoedigereMcDermott (DRM) paradigm, 2 min mathematical task] Offline: word recognition test	Correct recognition: n.s. (associative and categorical). Better recognition for categorical than associative lists across stimulation conditions. False recognition: ↓ (FT9/*ext.* compared to S in associative but not categorical lists).
Gaynor and Chua [65]	Parallel F3/*cSOA* vs. CP3/ CP4 vs. S	*lDLPFC, parietal cortex*	Overall: 72 (41 f); 20.8 ± 3.3 y 1. 24 (N/S) 2. 24 (N/S) 24 (N/S)	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm A(CP3): 5 × 7 cm/C(CP4): 5 × 7 cm	2 mA, 20 min, online, one session	Online: verbal paired associate encoding and judgements-of-learning task, 5 min after onset	Hits: ↓ (F3/*cSOA*). n.s. (CP3/CP4) False alarms: n.s. Judgement of learning: n.s.
Habich et al. [71]	Parallel F3/*cSOA* vs. S	*lDLPFC*	1. 21 (11 f); 25.14 ± 3.26 y 2. 22 (11 f); 24.55 ± 2.56 y	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 20 min, online (during encoding)	Online: word encoding and immediate recalls Offline: delayed recall, recognition	FR: n.s. (immediate retrievals, delayed recall) Recognition: n.s. Moderating effect with initially low performance predicting greater stimulation gains.
Habich et al. [72]	Crossover F3/*cSOA* vs. S	*lDLPFC*	33 (20 f); 24.5 ± 2.6, 20–30 y	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 20 min, online (during encoding)	Online: word encoding and immediate recalls Offline: delayed recall, recognition + MRS (pre-post)	FR: n.s. (immediate retrievals, delayed recalls) Recognition: n.s. Moderating effect of Glx/GABA ratio: Low excitatory tone at baseline predicting greater stimulation benefits in delayed recall.

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Table 17.7 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Hammer et al. [74]	Parallel and crossover 1. F3/*cSOA* vs. S 2. *cSOA*/F3 vs. S	*lDLPFC*	1. 18 (13 f); 23.3 ± 3.0 y 2. 18 (13 f); 23.0 ± 3.4 y	A(F3): 35 cm^2/C(*cSOA*): 35 cm^2 C(F3): 35 cm^2/A(*cSOA*): 35 cm^2	1 mA, 30 min, online (learning phase), two sessions	Online: errorful/errorless learning)	d': ↓ (*cSOA*/F3 compared to S in errorful learning only). n.s. (F3/*cSOA*). RT: n.s.
Jones et al. [93]	*Exp 1:* Crossover P3/*ext.* vs. S *Exp 2:* Crossover P3/*ext.* vs. S *Exp 3:* Crossover P4/*ext.* vs. S *Exp 4:* Crossover *ext.*/P4 vs. S	*Exp 1: lPPC* *Exp 2: lPPC* *Exp 3: rPPC* *Exp 4: rPPC*	*Exp 1:* 20 (15 f), 23.40 ± 3.33 y *Exp 2:* 20 (14 f), 22.20 ± 2.46 y *Exp 3:* 20 (14 f), 21.05 ± 1.61 y *Exp 4:* 20 (13 f), 21.40 ± 2.39 y 3.	*Exp 1:* A(P3): 5 × 7 cm/C(*right cheek*): 5 × 7 cm *Exp 2:* A(P3): 5 × 7 cm/C(*right cheek*): 5 × 7 cm *Exp 3:* A(P4): 5 × 7 cm/C(*left cheek*): 5 × 7 cm *Exp 4:* C(P4): 5 × 7 cm/A(*left cheek*): 5 × 7 cm	1.5 mA, 15 min, two sessions *Exp 1:* online (encoding) *Exp 2:* offline (prior to retrieval in delay period) *Exp 3:* online (encoding) *Exp 4:* online (encoding)	Online or offline: verbal memory task (CVLT)	*Exp 1:* Learning rate: ↑ (P3/*ext.* compared to S). Recalled words: ↑ (P3/*ext.* compared to S). Proportion correct: n.s. *Exp 2:* Learning rate: n.s. Recalled words: n.s. Proportion correct: n.s. *Exp 3:* Learning rate: n.s. Recalled words: n.s. Proportion correct: n.s. *Exp 4:* Learning rate: n.s. Recalled words: n.s. Proportion correct: n.s. WM (after long delayed recall): ↑ (*ext.*/CP4 compared to S).

Leshikar et al. [104]	Parallel F3/*ext.* vs. S	*lDLPFC*	Overall 42 (N/S). 1. N/S (15 f); 22.5 N/S (11 f); 20.6	A(F3): 3.3 × 3.3 cm/C(*right upper arm*): 3.3 × 3.3 cm	1.5 mA, 25 min, online (during encoding)	Online: associative memory: face-name Offline: retrieval	FR: ↑ (F3/*ext.* at day 1 and day 2). Correct recognition: n.s. No correlation with mood ratings.
Nikolin et al. [134]	Crossover HD-F3 vs. HD-CP5 vs. HD-P9 vs. S	*lDLPFC, PT, lMTL*	16 (8 f), 21.8 ± 2.4 y	HD A(F3)/4xC(AF3,F1,FC3,F5) A(CP5)/4x(C5,CP3,P5,TP7) A(P9)/3xC(Fp1,Fp2,FC4)	2 mA, 20 min, online (during encoding)	Online: verbal memory task (RAVLT)	Verbal learning score: ↑ (HD-F3 compared to S). n.s. (HD-CP5 and HD-P9)
Perceval et al. [145]	Parallel HD-CP5 vs. S	*TPC*	50 (34 f), 23.16 ± 3.79 y	HD A(CP5): diameter: 2.5 cm/C(CP5) diameter [inner]: 7.5, diameter [outer]: 9.8 cm	1 mA, 20 min, online (during training)	Online: word learning association with picture Offline: recognition	Accuracy: n.s. RT: ↓ (HD-CP5 all three recognition blocks)
Pergolizzi and Chua [146]	*Exp 1:* Parallel CP3/CP4 vs. S *Exp 2:* Parallel CP3/CP4 vs. CP4/CP3 vs. S	*Exp 1: lPPC/rPPC* *Exp 2: lPPC/rPPC, rPPC/lPPC*	*Exp 1:* Overall (pre-exclusions): 56 (30 f), 21.35 ± 0.52 y, 18–35 y Overall (post-exclusions): 52 (29 f); N/S. 1. 26 (N/S) 2. 26 (N/S) *Exp 2:* Overall (pre-exclusions):75 (47 f), 20.9 ± 3.4 y Overall (post-exclusions): 72 (N/S) 7. 24 (N/S) 8. 24 (N/S) *9.* 24 (N/S)	*Exp 1:* A(CP3): 5 × 7 cm/C(CP4): 5 × 7 cm *Exp 2:* A(CP3): 5 × 7 cm/C(CP4): 5 × 7 cm A(CP4): 5 × 7 cm/C(CP3): 5 × 7 cm	2 mA, one session *Exp 1:* 10 min, online (during retrieval)/ offline (20 min after online) *Exp 2:* 20 min, online (during retrieval)/ offline (20 min after online)	Online: false memory task Offline: false memory task	*Exp 1:* False alarm rate: ↑ (CP3/CP4 compared to S, for critical lures). Different confidence rating between groups: Higher confidence for correct rejection compared to false alarms in S. Higher confidence for false alarms compared to misses in CP3/CP4. *Exp 2:* False alarm rate: ↑ (CP3/CP4 and CP4/CP3 compared to S). Hits: ↑ (CP4/CP3). Confidence in correction rejection: ↑ (CP3/CP4 compared to S), n.s. (CP4/CP3 compared to S).

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Table 17.7 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Pergolizzi and Chua [147]	Parallel F3/F4 vs. CP3/CP4 vs. S	*lDLPFC/ rDLPFC, lPPC/ rPPC*	54 (31 f). 19.6 ± 3.06 y 1. 18 (N/S) 2. 18 (N/S) 18 (N/S)	A(F3): 35 cm^2/C(F4): 35 cm^2 A(CP3): 35 cm^2/C(CP4): 35 cm^2	2 mA, 20 min, online (during recognition)	Online: verbal source memory task, recognition	Hit rate: n.s. False alarms: ↓ (CP3/CP4 compared to S, particularly for false alarms 'bigger'). n.s. (F3/F4 compared to S and CP3/CP4)
Pergolizzi and Chua [148]	Parallel F3/F4 vs. CP3/CP4 vs. S	*lDLPFC/ rDLPFC, lPPC/ rPPC*	Overall (pre-exclusions): 81 (54 f), 21.4 ± 4.25 y Overall (post-exclusions): 72 (N/S) 3. 24 (N/S) 4. 24 (N/S) 24 (N/S)	A(F3): 35 cm^2/C(F4): 35 cm^2 A(CP3): 35 cm^2/C(CP4): 35 cm^2	2 mA, 20 min, online (during retrieval)	Online: shallow verbal encoding inexplicit memory cueing paradigm	Correct rejection: ↑ (F3/F4 compared to sham when cued with 'likely new' but not with 'neutral' or 'likely old' cues). n.s. (P3/P4) Cue utilisation scores: ↑ (F3/F4 compared to S for 'likely new' and 'likely old'). ↑ (F3/F4 compared to P3/P4 with 'likely old' but not 'likely new').
Schaal et al. [167]	*Exp 1:* Crossover CP3/*cSOA* vs. S *Exp 2:* Crossover CP4/*cSOA* vs. S	*Exp 1: lSMG Exp 2: rSMG*	*Exp 1:* 20 (15 f), 22.80 ± 4.16 y *Exp 2:* 22 (17 f), 22.59 ± 3.08 y	*Exp 1:* A(CP3): 5 × 5 cm/C(*cSOA*): 5 × 7 cm *Exp 2:* C(CP4): 5 × 5 cm/A(*cSOA*): 5 × 7 cm	2 mA, 15 min, offline, two sessions	Offline: pitch and rhythm span task, after offset	*Exp 1:* Pitch memory, mean memory span: ↑. Rhythm memory performance, mean memory span: n.s. *Exp 2:* Pitch memory performance, mean memory span: n.s. Rhythm memory performance, mean memory span: ↑.

Silas and Brandt [170]	Parallel F3/F4 vs. S	*lDLPFC/ rDLPFC*	30 (22 f); 18.8 ± 1 y 1. 15 (N/S) 2. 15 (N/S)	A(F3): 5 × 7 cm/C(F4): 5 × 7 cm	1 mA, 10 min, offline (prior to task)	Offline: word list learning (remember and forget instructions)	Directed forgetting: ↓ (F3/F4). First and second list in forget condition were equally well remembered.
Stramaccia et al. [179]	Parallel FC4/*cSOA* vs. *cSOA*/ FC4 vs. S	*rIFG*	*Exp 1:* 1. 17 (11 f), 23.65 ± 1.80 y 2. 16 (10 f), 23.25 ± 1.34 y 3. 20 (14 f), 23.05 ± 1.90 y *Exp 2:* 1. 24 (15 f), 23.96 ± 3.74 2. 24 (12 f), 23.33 ± 2.28 24 (17 f), 23.42 ± 2.43	A(FC4): 5 × 5 cm/C(*cSOA*): 5 × 5 cm C(FC4): 5 × 5 cm/A(*cSOA*): 5 × 5 cm	1.5 mA, 20 min, online, one session	*Exp 1:* Online: practice phase of retrieval practice paradigm *Exp 2:* Online: practice phase of retrieval practice paradigm, SST	*Exp 1:* Recall accuracy: n.s. Facilitation effect: n.s. Corr. between retrieval-induced forgetting and facilitation effect: n.s. *Exp 2:* Recall accuracy: n.s. Retrieval-induced forgetting only significant for sham group. Facilitation effect: n.s. SST: n.s.
Wang et al. [188]	Crossover P4/*ext.* vs. F3/*ext.* vs. S	*rPPC, lDLPFC*	20 (14 f), 22.9 ± 1.94 y	A(P4): 5 × 7 cm/C(*left cheek*): 5 × 7 cm A(F3): 5 × 7 cm/C(right cheek): 5 × 7 cm	2 mA, 15 min, offline, three sessions	Offline: sensory memory task, VSTM task	VSTM capacity: ↑ (P4/*ext.*, only at set size 6, that is, when the number of memory items exceeded capacity limit). VSTM capacity: n.s. (F3/*ext.*). VSTM precision: n.s. vs.TM normalised precision parameter: n.s. Sensory memory performance: n.s.

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Table 17.7 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Westphal et al. [194]	Parallel and crossover 1. Fp1–F7/C4 vs. S 2. C4/Fp1–F7 vs. S 3. S vs. S	*lRLPFC/rM1*, *rM1/lRLPFC*	1. 24 (13 f), 20 2. 24 (13 f), 20 3. 24 (13 f), 20	A(Fp1–F7): 5 × 7 cm/C(C4): 5 × 7 cm C(Fp1–F7): 5 × 7 cm/A(C4): 5 × 7 cm	1.5 mA, 30 min, online, two sessions	Online: memory task (episodic source memory retrieval), reasoning task (analogical reasoning), perception task (visuospatial perception)	Episodic memory retrieval was measured by the corrected recognition Pr score; the false alarm rate minus the hit rate. 1. Episodic memory source retrieval performance (memory source retrieval Pr score): ↑. Reasoning task: n.s. Perception task: n.s. 2. Episodic memory source retrieval performance: n.s. Reasoning task: n.s. Perception task: n.s. Group 1 vs. 2, episodic memory source retrieval performance: ↑.

Wong et al. [197]	*Exp 1:* Parallel F3/*cSOA* vs. S *Exp 2:* Parallel F3/*cSOA* vs. S *Exp 3:* Parallel 1. F3/*cSOA* 2. S, electrodes at F3/*cSOA* 3. F4/*cSOA* 4. S, electrodes at F4/*cSOA* *Exp 4:* Parallel 1. F3/*cSOA* 2. F3/*cSOA* 3. S 4. S	*Exp 1:* *lDLPFC* *Exp 2:* *lDLPFC* *Exp 3:* *lDLPFC, rDLPFC* *Exp 4:* *lDLPFC*	*Exp 1:* Overall: 48 (N/S); 20 y, 18–30 y 1. 24 (N/S) 2. 24 (N/S) *Exp 2:* Overall: 48 (N/S), 20 y, 18–30 y 1. 24 (N/S) 2. 24 (N/S) *Exp 3:* Overall: 120 (N/S), 19.6 y, 18–30 y 1. 40 (N/S) 2. 20 (N/S) 3. 40 (N/S) 4. 20 (N/S) *Exp 4:* Overall: 120 (N/S), 20.8 y, 18–31 y 1. 30 (N/S) 2. 30 (N/S) 3. 30 (N/S) 4. 30 (N/S)	*Exp 1:* A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm *Exp 2:* A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm *Exp 3:* A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm A(F4): 5 × 7 cm/C(*cSOA*): 5 × 7 cm *Exp 4:* A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	*Exp 1:* 2 mA, 20 min, offline, one session *Exp 2:* 2 mA, 20 min, offline, one session *Exp 3:* 2 mA, 20 min, offline, one session. All sessions between 8 and 12 AM *Exp 4:* 2 mA, 20 min, offline, one session starting at: 1. 9 AM 2. 1 PM 3. 9 AM 4. 1 PM	*Exp 1:* Offline: Red Word Test and Picture test, after encoding but prior to retrieval phase *Exp 2:* Offline: Red Word Test and a Green Word Test, after encoding but prior to retrieval phase *Exp 3:* Offline: Word Recollection Task, Face Recognition Task, after encoding but prior to retrieval phase *Exp 4:* Offline: Red Word Test, Picture Test, Exclusion Test, after encoding but prior to retrieval phase	*Exp 1:* Recollection accuracy (hits minus false alarms): n.s. *Exp 2:* Recollection accuracy: n.s. Effect on time of day on recollection accuracy in Exp 1 and 2: n.s. *Exp 3:* Recollection accuracy: n.s. Marginal effect of time-of-day (9 AM vs. 12 AM) on recollection accuracy in Word recollection task ($p = 0.07$): ↑. *Exp 4:* Recollection accuracy: ↑ (9 AM). n.s. (1 PM).

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Table 17.7 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Zwissler et al. [203]	Parallel 1. F3/*ext.* 2. *ext.*/F3 S	*lDLPFC*	Overall: 85 (51 f), 24.82 ± 2.95 y 1. 24 (14 f), 25.33 y 2. 22 (15 f), 24.41 y 3. 39 (22 f), 24.87 y	A(F3): 5 × 7 cm/C(*right deltoid*): 5 × 7 cm C(F3): 5 × 7 cm/A(*right deltoid*): 5 × 7 cm	1 mA, 15 min, online (during encoding)	Online: episodic memory	Correct recognition rate: n.s. False alarms: ↑ (F3/*ext.*, for pictures instructed to remember and forget), ↓ (*ext.*/F3, for pictures instructed to remember).

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham

[2]r = right. l = left. c = contralateral. i = ipsilateral. ATL = anterior temporal lobe. DLPFC = dorsolateral prefrontal cortex. IFG = inferior frontal gyrus. M1 = primary motor cortex. MTL = medial temporal lobe. PPC = posterior parietal cortex. PT = planum temporale. RLPFC = rostrolateral prefrontal cortex. SMG = supramarginal gyrus. SOA = supraorbital area. TPC = temporoparietal cortex

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]CVLT = California Verbal Learning Test. RAVLT = Rey Auditory Verbal Learning Test. VSTM = visual short-term memory. MRS = magnetic resonance spectroscopy

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. Corr = correlation. FR = free recall. GABA = γ-aminobutyric acid. Glx = glutamatergic metabolites. RT = reaction time. WM = working memory

processes. The involvement of the right PPC in short-term memory has been corroborated by Wang and colleagues [188], whose adequately powered crossover study on 20 participants demonstrated that visual short-term memory capacity, but not precision, can be increased with anodal tDCS. This effect only occurred with the highest set size, that is, when the number of items to be remembered exceeded the capacity limit.

Ferrucci and colleagues [52] applied anodal and cathodal tDCS to the cerebellum and found an impairment of practice-dependent improvements in reaction times in a modified numerical Sternberg task, while accuracy was not affected. Generally, problems with ceiling effects tend to be common with short-term memory tasks, as is often the case with simple cognitive paradigms. This might explain why most studies show effects on reaction time, but not accuracy.

The enhancement of learning and long-term memory processes with tDCS has been investigated in a number of studies, mostly attempting to modulate the learning phase. Based on the known underlying neurobiological mechanisms of the respective domain tested, some studies targeted left prefrontal areas, some frontal or parietal areas and a few targeted right prefrontal areas. Consequently, the use of different stimulation and testing paradigms makes it difficult to synthesise the findings from these studies. In previous studies, improvements in long-term memory have been reported when placing the anode over the DLPFC [91, 98] or other prefrontal areas [194]. We previously discussed a study by Nikolin and colleagues [133] wherein they attempted to modulate sustained attention using HD-tDCS (see Sect. 17.2). In the same study, they also assessed the effects of HD-tDCS over left DLPFC, PT and left MTL on declarative verbal learning and memory. HD-tDCS over the left DLFPC significantly improved the rate of declarative verbal learning. However, no effects on verbal learning, retention or retrieval were found tDCS applied over the PT and left MTL, with which the authors hoped to target the hippocampus. In line with this, Leshikar and colleagues [104] found that anodal tDCS applied to the left DLPFC enhanced the free recall performance in a face-name association task, both on the same day on which learning occurred and the day after. In contrast, impairments in different word-based learning paradigms were reported when the cathode was placed over the DLPFC [50, 73, 91] or the supramarginal gyrus [186]. Silas and Brandt [170] found that directed forgetting was reduced when bilateral tDCS with the anode over the left and the cathode over the right DLPFC was administered prior to a word list learning. Notably, some studies found no detrimental effect when placing the cathode over frontal areas [98, 165, 179] or improvement when placing the anode over frontal areas [73, 147, 165, 186]. It is, however, worth mentioning that in the absence of a beneficial group-level effect of anodal tDCS, stimulation-related gains may still emerge in subsets of study samples. For instance, Habich and colleagues demonstrated that stimulation gains in a word list learning task were restricted to initially low performers [71] and likewise, that the excitatory tone at baseline may be predictive of subsequent stimulation gains [72] (for further elaboration on inter-individual differences see Sect. 17.8). An extensive study by Wong and colleagues [197], comprising four experiments, contributed additional evidence that beneficial stimulation effects might be connected to suboptimal cognitive processing. While their first three experiments failed to replicate the beneficial impact of stimulation applied to the left or right DLPFC on various episodic memory paradigms, explorative analyses revealed a potential effect of time of day. The latter was confirmed by a fourth experiment, in which 120 participants were pseudorandomly allocated to morning (9 a.m.) or afternoon (1 p.m.) sessions. Stimulation reversed the typically observed diurnal performance pattern by significantly improving recollection accuracy in the morning session, while stimulation in the afternoon even exhibited a trend towards impairing recall performance. Accordingly, this study attests to the selectivity of tDCS effects, even within a relatively homogeneous population of young healthy adults that might even take on greater significance in more heterogeneous patient pop-

ulations in which even more stringent stimulation protocols, not least with regard to timing, may be required.

In a study by Zwissler and colleagues [203], anodal tDCS over the left DLPFC applied during the encoding of pictures, resulted in an increase of false alarms, whereas cathodal tDCS decreased false alarms during the recognition testing. The authors attribute the beneficial effect of cathodal stimulation to its potential noise filtering capacity. The poorer performance under anodal stimulation, on the other hand, was attributed to a deterioration of the signal-to-noise ratio due to the excitability enhancing impact of the stimulation. Two other studies confirmed the occasional detrimental influence of anodal tDCS applied to the left DLPFC in a verbal paired-associates task [65] as well as in a word list learning task [22]. An explanation for this seemingly counterintuitive effect may be found in the small margin for improvement in the tested task, especially when retrieval is assessed via a recognition test, which is often perceived as less demanding than free recall.

Numerous studies also focused on the involvement of parietal cortical areas in memory processes. Jones and colleagues [93] placed the anode either over the left or right PPC and found a significant improvement in learning and retrieval only when stimulation was administered over the left but not right parietal area, and only during encoding but not prior to retrieval. In a study by Bjekić and colleagues [12], applying anodal tDCS to both left and right PPC proved to be beneficial for face-word associative memory performance. It stands to reason that this discrepancy may have been caused by the different choices of cathode placements in the two studies, with one positioning it over the contralateral supraorbital area [93] and the other positioning it extracephalically on the contralateral cheek [12], thus creating different electric field distributions. Furthermore, Bjekić and colleagues [11] provided evidence to support the persistence of left parietal stimulation effects, with performance gains in free recalls lasting for up to 4 days following the stimulation. Analogous to findings in the DLPFC, cathodal tDCS over the left PPC, but not the primary motor cortex, which served as an active control region, decreased source memory performance, while old/new recognition performance remained unaffected [30]. In the same study, no significant effect emerged for anodal tDCS.

Jacobson and colleagues [90] found improved verbal memory when administering bilateral tDCS with the anode over the left and the cathode over the right parietal cortex, during verbal encoding, but not vice versa. Contrarily, a similar bilateral montage over the PPC as well as the reversed electrode arrangement led to higher false alarm rates [146]. Moreover, the study revealed that subjective aspects of memory were also altered with a higher confidence in false alarms relative to misses with a CP3/CP4 montage.

Boggio and colleagues [17] placed the anode over the left anterior temporal lobe and the cathode over the contralateral homologue area. The latter was either the same size as the anode or enlarged in order to mimic a unilateral stimulation. Irrespective of the size of the cathode, both active conditions significantly reduced false memories compared to sham. A more recent study [45] also demonstrated benefits of anodal tDCS over the left anterior temporal lobe, this time placing the cathode on the right shoulder, in decreasing false recognition for associative but not categorical lists. Perceval and colleagues [145] conducted a study on face-name associative memory. Anodal HD-tDCS over the temporoparietal cortex reduced reaction times but did not affect accuracy in the recognition task.

Finally, Schaal and colleagues [167] investigated the contribution of the left and right supramarginal gyrus to pitch and rhythm memory. Their study revealed a hemisphere-specific impact of anodal tDCS. Specifically, pitch memory was facilitated with left anodal stimulation, while rhythm memory was unaffected. The opposite pattern emerged for right anodal stimulation, which augmented memory span for rhythm without modulating pitch memory.

As evident from the literature reviewed in this section, tDCS has been shown to successfully modulate many aspects of learning and memory. It is, however, important to note that many of the

memory paradigms employed require components of executive functioning such as inhibitory control, decision-making and working memory, as well as attention, which are known to draw on frontal and frontoparietal networks. For instance, Pergolizzi and Chua [148] found that correct rejection rates during a recognition task were increased due to a more efficient use of cues, pinpointing that advantageous results in the memory domain might, at least partially, reflect indirect effects on executive functions (see Sects. 17.2, 17.3 and 17.4).

17.7 Inter-Individual Differences in Cognitive Benefits from tDCS

While benefits of tDCS have been demonstrated for a wide variety of cognitive functions, results from studies that examine similar questions also feature a persistent heterogeneity if not outright contradictions. It is widely acknowledged that the wide variety of stimulation protocols employed in the studies significantly affect the reproducibility of results [32, 122]. However, even if methodological parameters are held constant, inter-individual variability in response to tDCS can still confound results. Many studies on the electric current flow induced by tDCS suggested that inter-individual differences in micro- and macro-anatomical features (e.g., skull thickness, gyration and volume of cortical regions) impact the spread of the electric current and thus underlie different effect sizes of the stimulation. Leaving those universal determinants of tDCS effects aside, in the following section, we focus on studies that have provided insights into behavioural, genetic and neurophysiological characteristics of participants, which influence their responsiveness to tDCS in cognitive domains (Table 17.8).

A growing number of studies are reporting that individual differences in baseline cognitive ability modulate tDCS outcomes, even in the relatively homogenous group of healthy young adults [11, 71, 87, 97, 180, 184]. Habich and colleagues [71] showed that the application of anodal tDCS during the encoding phase of a verbal episodic memory task did not produce a beneficial group effect during the delayed recall of the word list. Instead, stimulation gains were restricted to initially low performers. Similarly, in a study by Katz and colleagues [97] the advantage of active compared to sham stimulation accompanying a visuospatial memory training declined with increasing baseline scores. Likewise, Tseng and colleagues [184] found that performance in a visual short-term memory task was enhanced with anodal tDCS to the right PPC only in participants who had initially exhibited poor performance. It did not improve for participants with initially high performance. Furthermore, concurrent EEG recordings revealed that the improvement in the visual short-term memory task performance with tDCS was accompanied by increased amplitude of ERPs related to attention deployment. On the other hand, those who did not further improve exhibited relatively large amplitude ERPs at baseline. Employing a very similar change detection task, Hsu and colleagues [87] demonstrated a similar interaction between stimulation gains and natural memory capacity with only low but not high performers benefitting from anodal tDCS. This dissociation was also reflected in changes in oscillatory activity in the alpha band. In low performers, relative to sham, anodal tDCS led to a decrease in pre-stimulus alpha power in parieto-occipital regions. By contrast, no such change in pre-stimulus alpha power was revealed in high performers, who possessed a low alpha power to begin with. Another of these three-way connections between initial performance level, tDCS-induced cognitive improvement and neural oscillatory power was revealed by Splittgerber and colleagues [176]. Corroborating previous results, their multi-channel stimulation of the left DLPFC mainly improved the working memory capacity of low performers, while high performers tended to show poorer tDCS-related performance. The importance of baseline performance was corroborated by the observation that task-related theta power increased more, the worse the baseline performance level. On the other hand, initial high performers showed increased alpha power after tDCS compared to the sham condition. Furthermore, Liang and colleagues [109] found

Table 17.8 Inter-individual differences in cognitive benefits from tDCS

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Bjekić et al. [11, 12]	Crossover P3/*ext.* vs. S	*lPPC*	40 (22 f), 21–35 y	A(P3): 5 × 5 cm/C(*contralateral cheek*): 5 × 5 cm	1.5 mA, 20 min, offline (computer game)	Offline: associative memory (face-word), verbal fluency	Greater gain in face-word associative memory task for low performers in sham condition.
Cheng and Lee [31]	Crossover F3/F4 vs. F4/F3 vs. S	*lDLPFC, rDLPFC*	16 (10 f), 20.9 ± 2.8 y	A(F3): 5 × 7 cm/C(F4): 5 × 7 cm C(F3): 5 × 7 cm/A(F4): 5 × 7 cm	2 mA, ~19 min, online	Online: risk-taking tasks (risky-gains task and BART)	High attentional impulsivity leads to greater tDCS-induced reduction in risk-taking (F4/F3).
Habich et al. [71]	Parallel F3/*cSOA* vs. S	*lDLPFC*	43 (22 f), 24.8 ± 2.9 y, 20–30 y	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 20 min, online	Online: encoding verbal episodic memory task	Initial low performers show greater benefit from tDCS.
Habich et al. [72]	Crossover F3/*cSOA* vs. S	*lDLPFC*	33 (20 f), 24.5 ± 2.6 y, 20–30 y	A(F3): 5 × 7 cm/C(*cSOA*): 5 × 7 cm	1 mA, 20 min, online (during encoding)	Online: word encoding and immediate recalls Offline: delayed recall, recognition + MRS (pre-post)	Moderating effect of Glx/GABA ratio: Low excitatory tone at baseline predicting greater stimulation benefits in delayed recall.
Hsu et al. [87]	Crossover P4/*ext.* vs. S	*rPPC*	20 (13 f), 22 y	A(P4): 4 × 4 cm/C(*left cheek*)	1.5 mA, 15 min, offline	Offline: prior to change detection task	Alpha power ↓ in low performers, n.s. in high performers (low alpha power to begin with).
Jones and Berryhill [92]	Crossover P4/*ext.* vs. *ext.*/P4 vs. S	*rPPC*	20 (12 f), 23.25 ± 3.46 y	A(P4): 5 × 7 cm/C(*left cheek*): 5 × 7 cm C(P4): 5 × 7 cm/A(*left cheek*): 5 × 7 cm	1.5 mA, 10 min, online	Online: change detection task	Performance: ↑ (with both P4/*ext.* and *ext.*/P4 in high performers while impairing low performers in high load condition).

Jongkees et al. [94]	Parallel 1. F3/F4 + placebo 2. F3/F4 + Tyr 3. F4/F3 + placebo 4. F4/F3 + Tyr	*lDLPFC, rDLPFC*	72 (61 f), 1. 20.8 ± 2.0 y 2. 19.7 ± 1.7 y 3. 20.7 ± 2.3 y 4. 20.9 ± 1.4 y	A(F3): 5 × 7 cm/C(F4): 5 × 7 cm C(F3): 5 × 7 cm/A(F4): 5 × 7 cm	1 mA, 15 min, offline	Offline: prior to n-back task	Modulation of tDCS effect on WM by Tyr: n.s. (placebo groups). d': ↑ (F4/F3 compared to F3/F4 condition (opposite to usually expected tDCS effects, hinting at causal role of dopamine levels). RT: same pattern as for sensitivity.
Kasahara et al. [96]	Crossover P3/P4 vs. P4/P3 vs. S	*lPPC, rPPC*	16 (5 f), 21.1 y, 20–23 y	A(P3): 35 cm^2/C(P4):35 cm^2 C(P3): 35 cm^2/A(P4):35 cm^2	2 mA, 10 min, online	Online: mental calculation task	RT: ↓ F3/F4 (compared to F4/F3 and S for subjects with left-hemispheric activation but not for bilateral activation assessed in fMRI).
Katz et al. [97]	Parallel F4/Fp1 vs. F3/Fp2 vs. S	*rDLPFC, lDLPFC*	67 (42 f), 18–35 y	A(F4/F3): 5 × 7 cm/C(Fp1/Fp2): 5 × 7 cm	2 mA, 25 min, online, six sessions	Online: visuospatial WM	Baseline performance: greater benefits in low performing individuals at baseline.
Learmonth et al. [101]	Crossover P3/*cSOA* vs. P4/*cSOA* vs. S	*lPPC, rPPC*	20 (11 f), 20.9 ± 1.97 y, 18–24 y	A(P3): 5 × 5 cm/C(*cSOA*): 5 × 7 cm A(P4): 5 × 5 cm/C(*cSOA*): 5 × 7 cm	1 mA, 15 min, online	Online: lateralised visual detection task	Sensitivity: ↓ [P3/*cSOA* (low performers)]. ↑ [P4/*cSOA* (high performers)].
Liang et al. [109]	Crossover Fz/*ext.* vs. S	*preSMA*	18 (8 f), 25.4 y	A(Fz): 4 × 4 cm/ C(*left cheek*): 4 × 4 cm	1.5 mA, 10 min, online	Online: SST	Low, compared to high performers, benefitted more from Fz/*ext.* as indexed by greater changes in multi-scale entropy.
London and Slagter [112]	Crossover F3/*cSOA* vs. *cSOA*/F3	*lDLPFC*	38 (22 f), 22.4 ± 2.8 y	A(F3): 5 × 7 cm/C(*cSOA*) C(F3): 5 × 7 cm/A(*cSOA*)	1 mA, 20 min, online	Online: attentional blink assessment	Attentional blink: ↓ (under P3/*cSOA* in participants with large attentional blink at baseline). Attentional blink: ↑ in participants with small attentional blink at baseline.

(continued)

Table 17.8 (continued)

Authors	Design[1]	Target(s)[2]	Participants *N* (*N* females), age[3]	Electrode montage[4]	Stimulation protocol (intensity, duration, online/offline, task)	Measure(s)[5]	Results[6]
Nieratschker et al. [131]	Crossover *cSOA*/F3 vs. S	*lDLPFC*	41 (32 f), 24.0 ± 4.2 y	C(F3): 35 cm^2/A(*cSOA*): 35cm^2	1 mA, 20 min, online	Online: GNGT	Response inhibition: ↓ (*cSOA*/F3 in COMT Val/Val homozygotes compared to Met carriers).
Plewnia et al. [152]	Crossover F3/*cSOA* vs. S	*lDLPFC*	46 (21 f), 25.87 ± 7.29 y	A(F3): 35 cm^2/C(*cSOA*): 35cm^2	1 mA, 20 min, online	Online: GNGT	Set-shifting ability: ↓ (F3/*cSOA* compared to S in COMT Met/Met homozygotes compared to Val carriers).
Splittgerber et al. [176]	Crossover F3/Fp2 vs. AF3 + AF7 + F3/Fp2 + T7 vs. S	*lDLPFC*	24 (13 f), 24.8 ± 2.7 y	A(F3): 25 cm^2/C(Fp2): 25 cm^2 3xA(AF3, AF7, F3): 3.14 cm^2/2xC (Fp2, T7): 3.14 cm^2	1 mA, 20 min, online/offline	Online: 2-back task Offline: 2-back and EEG	Initially low performers increased accuracy, while initially high performers decreased accuracy for multi-channel tDCS compared to S. The worse initial performance, the greater task-related theta power induction by either of the two stimulation conditions.
Strobach et al. [180]	*Exp 1:* Crossover F4–C4/ *cSOA* vs. S *Exp 2:* Crossover *cSOA*/ F4–C4 vs. S	*IFJ*	*Exp 1:* 30 (20 f), 24.8 ± 3.1 y *Exp 2:* 28 (17 f), 22.6 ± 3.0 y	*Exp 1:* A(F4–C4): 5 × 7 cm/C(*cSOA*): 10 × 10 cm *Exp 2:* C(F4–C4): 5 × 7 cm/A(*cSOA*): 10 × 10 cm	1 mA, 20 min, online, two sessions	Online: dual-tasks	*Exp 1:* Lower accuracy at baseline positively correlated with improvements after tDCS for tasks 1 and 2. *Exp 2:* Corr between baseline performance and tDCS effect on accuracy, task 1: n.s. (after removing outlier).

Tseng et al. [184]	Crossover P4/*ext.* vs. S	*rPPC*	30 (18 f), 21 y, 22 y	A(P4): 4 × 4 cm/C(*left cheek*): 4 × 4 cm	1.5 mA, 15 min, online	Online: visual change detection	Only initial low performers improve performance under tDCS.
Weidacker et al. [190]	Crossover F4/*ext.* vs. *ext.*/F4 vs. S	*rDLPFC*	18 (9 f), 22.06 ± 0.98 y, 18–32 y	A(F4): 5 × 5 cm/C(*left biceps*): 5 × 5 cm C (F4): 5 × 5 cm/A(*left biceps*): 5 × 5 cm	1.5, 20 min, offline	Offline: prior to parametric GNGT	Higher scores of coldheartedness predict relative better performance under *ext.*/F4 in high load condition.

[1]Conditions are defined in terms of EEG positions for anode/cathode montage. In case of high-definition (HD) montage, only anode position is listed. – between EEG positions signifies tDCS electrode was placed at mid-point between the listed EEG positions. + between EEG positions indicates that separate electrodes were used. If no EEG positions were mentioned in the article, targeted brain region is specified instead (for specifics of definition, see column 'electrode montage'). ext. = extracephalic electrode (for specifications, see column 'electrode montage'). S = sham. Tyr = tyrosine

[2]r = right. l = left. c = contralateral. i = ipsilateral. DLPFC = dorsolateral prefrontal cortex. IFJ = inferior frontal junction. PPC = posterior parietal cortex. preSMA = pre-supplementary motor area. SOA = supraorbital area

[3]Total number of participants (with number of females). Mean, SD and range of age are reported as available

[4]Electrode dimensions or surface area are reported as available. A = anode. C = cathode

[5]BART = balloon analogue risk task. GFI = general fluid intelligence. GNGT = go/no-go task. SST = stop-signal task. WM = working memory. EEG = electroencephalography. fMRI = functional magnetic resonance imaging. MRS = magnetic resonance spectroscopy

[6]Results refer to verum versus sham stimulation sessions or groups if not specified otherwise. ↑ = significant increase. ↓ = significant decrease. n.s. = non-significant. N/A = not available. N/S = not specified. Corr = correlation. GABA = γ-aminobutyric acid. Glx = glutamatergic metabolites. RT = reaction time

that a group difference in multi-scale entropy of the EEG signal interacted with improvements in a stop-signal task under anodal tDCS. Therein, anodal tDCS specifically increased the small and medium multi-scale entropy in frontal and parietal lobes of low performers, while the already high multi-scale entropy of high performers could not be enhanced further, hinting at a natural neurophysiological limit for tDCS-induced cognitive improvements.

Another set of studies provides evidence that the relationship between baseline performance and tDCS outcomes is not necessarily always unidirectional and/or linear. First, London and Slagter [112] tested the effects of anodal and cathodal tDCS on the attentional blink. In the absence of a stimulation effect of either of the two stimulation conditions on the group level, they found that individuals who exhibited a large attentional blink at baseline exhibited a less pronounced attentional blink under anodal tDCS, while participants with a small attentional blink at baseline showed an increased attentional blink. By contrast, Learmonth and colleagues [101] demonstrated that anodal tDCS to the left PPC of low performers decreased their sensitivity compared to baseline, while high performers retained their initial performance level under anodal tDCS to their right PPC. The authors suggest that these observations could be related to inter-hemispheric competition during visuospatial attention. Specifically, initial high performers might be more robust in the face of disrupting the balanced activity between left and right hemispheres, since they activated their right hemisphere more efficiently than low performers. Additionally, Jones and Berryhill [92] found that when cognitive demands of a working memory task were high, both anodal and cathodal tDCS over the right PPC improved change detection performance in high-performing participants, but impaired performance in low-performing individuals. The authors suggest that low performers may not efficiently recruit their right PPC during task performance and are, thus, precluded from experiencing stimulation benefits. The importance of a favourable interaction between engaged brain regions and stimulation has also been demonstrated in a study by Kasahara and colleagues [96]. Split according to the lateralisation of parietal activity during a mental calculation task, only participants with left-hemispheric, but not bilateral, activation responded faster under bilateral tDCS when the anode was placed over the left and the cathode over the right parietal cortex.

Apart from cognitive skills at baseline, differential tDCS effects have also been associated with personality traits. Gordon and colleagues [31] showed that tDCS applied bilaterally, with the cathode over the left and the anode over the right DLPFC, reduced risk-taking behaviour under the context of haste. This effect was even larger in individuals with high attentional impulsivity. In addition, a positive relationship between higher scores of cold-heartedness, and relative improvement in a GNGT task under anodal tDCS in the high load condition, was reported in a study by Weidacker and colleagues [190]. The authors put forth the notion that this personality trait appears in the context of a disrupted ratio between inhibitory and excitatory inputs to the DLPFC and that the observed improvement with cathodal tDCS results from a rebalancing of the system towards a more optimal range of excitation.

Moreover, a number of studies have highlighted the role of genetic polymorphisms in moderating the susceptibility to tDCS effects. For instance, Plewnia and colleagues [152] found that the application of anodal tDCS to the left DLPFC had a deleterious effect on performance in a GNGT task in COMT Met/Met homozygotes compared to carriers of the Val-allele. A subsequent study [131] from the same research group showed that cathodal tDCS over the left DLPFC impaired response inhibition in participants who were homozygous for the COMT Val-allele but had no effect on carriers of the Met-allele. The COMT gene is known to be an important regulator of dopaminergic transmission, particularly in the prefrontal lobes. Interestingly, Lachman and colleagues [100] established that Val/Val homozygotes possess the lowest levels of prefrontal dopamine, heterozygotes show intermediate levels and Met/Met homozygotes exhibit the highest levels. Further, it has been hypothesised that

cognitive performance is not linearly related to dopamine levels but that the relationship is better characterised as an inverted U shape [2, 35, 128]. Hence, these studies suggest that increasing neuronal excitability via anodal tDCS shifts the characteristically high dopaminergic activity of Met/Met homozygous participants to the extreme right and thus beyond the optimal range for cognitive performance. Vice versa, cathodal tDCS further decreases the already low baseline dopaminergic activity of Val/Val homozygotes to the extreme left of the inverted U shape, pushing them out of the optimal range for cognitive performance as well. This proposed role of dopamine levels on tDCS effects has been further corroborated by Jongkees and colleagues [94]. In their study, no difference between stimulation conditions emerged in the group that received a placebo preparation. However, the administration of the dopamine precursor L-tyrosine reversed the previously observed and usually predicted effects of tDCS on working memory performance. More specifically, left cathodal/right cathodal tDCS increased task performance compared to bilateral stimulation with the opposite polarity. Despite the coherence between these findings, it should also be noted that a highly powered study involving the same first author [95] could not replicate the distinctive influence of the COMT $Val^{158}Met$ genotype on tDCS effects. Whether this can be attributed to the slightly different electrode montage, the use of a different task or yet another parameter, remains to be tested. Generally, it should be noted that individual differences on different levels may interact with each other resulting in a multi-factorial influence on the induction of tDCS effects. Going forward, highly powered multi-modal studies that thoroughly characterise their participants might remedy the current perplexing heterogeneity in stimulation outcomes.

17.8 Conclusion

Research investigating the modulation of cognition using tDCS is one of the most rapidly growing fields in cognitive neuroscience today. The technique holds considerable promise as a tool for exploring novel theoretical hypotheses, as well as for improving cognitive function. Nevertheless, the field has become more measured in its enthusiasm regarding the neuroenhancing potential of tDCS, especially in young healthy populations, which has also been reflected in numerous meta-analyses [21, 63, 116, 124, 182].

The future success of harnessing the potential of tDCS is contingent on identifying the sources for inconsistent findings across studies. Beyond the current heterogeneity of tDCS protocols, an improved understanding of the sources of inter- as well as intra-individual differences in stimulation outcomes, as it has a significant impact on the nature, magnitude and direction of tDCS effects reported across studies is required to harness the potential of tDCS. Incorporating physiological measures, such as MRS, EEG, fMRI and genetic profiling, more routinely in tDCS studies will facilitate more informed interpretation of results. The increasing efforts to recruit sufficiently large sample sizes are already laudable. Increased sample sizes not only obviate the risk of underpowered studies, they also enable sub-group analyses to be carried out, which may elucidate the subject profiles that exhibit the optimal response to tDCS, and which in turn, could be of great importance for the real-world application of findings.

Furthermore, the vast majority of studies reviewed only reported short-term improvements in cognitive functioning following single sessions of tDCS, and rarely examined the extent to which the tDCS-induced effects generalised to related tasks that should rely on the same underlying neural processes. This currently constrains the translational potential of these findings, as cognitive enhancement regimes are only worthwhile if they can produce long-term changes in cognition that confer benefits to activities of daily living. Some studies have begun to investigate the impact of multiple tDCS sessions and yielded promising results. Yet, more work is required before we will have a reasonable understanding of the optimal tDCS protocols for maximising long-term benefits, while also minimising potential side effects.

References

1. Adelhöfer N, Gohil K, Passow S, Beste C, Li S-C. Lateral prefrontal anodal transcranial direct current stimulation augments resolution of auditory perceptual-attentional conflicts. NeuroImage. 2019;199:217–27.
2. Aguilera M, Barrantes-Vidal N, Arias B, Moya J, Villa H, Ibanez M, Ruiperez M, Ortet G, Fananas L. Putative role of the COMT gene polymorphism (Val158Met) on verbal working memory functioning in a healthy population. Am J Med Genet B Neuropsychiatr Genet. 2008;147:898–902.
3. Albein-Urios N, Chase H, Clark L, Kirkovski M, Davies C, Enticott PG. Increased perseverative errors following high-definition transcranial direct current stimulation over the ventrolateral cortex during probabilistic reversal learning. Brain Stimulat. 2019;12:959–66.
4. Artemenko C, Moeller K, Huber S, Klein E. Differential influences of unilateral tDCS over the intraparietal cortex on numerical cognition. Front Hum Neurosci. 2015;9
5. Au J, Katz B, Buschkuehl M, Bunarjo K, Senger T, Zabel C, Jaeggi SM, Jonides J. Enhancing working memory training with transcranial direct current stimulation. J Cogn Neurosci. 2016;1–14
6. Baddeley A. Working memory. London: Oxford University Press; 1986.
7. Barch DM, Sheline YI, Csernansky JG, Snyder AZ. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol Psychiatry. 2003;53:376–84.
8. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994;50:7–15.
9. Beddington J, Cooper CL, Field J, Goswami U, Huppert FA, Jenkins R, Jones HS, Kirkwood TB, Sahakian BJ, Thomas SM. The mental wealth of nations. Nature. 2008;455:1057–60.
10. Berryhill ME, Wencil EB, Branch Coslett H, Olson IR. A selective working memory impairment after transcranial direct current stimulation to the right parietal lobe. Neurosci Lett. 2010;479:312–6.
11. Bjekić J, Vulić K, Živanović M, Vujičić J, Ljubisavljević M, Filipović SR. The immediate and delayed effects of single tDCS session over posterior parietal cortex on face-word associative memory. Behav Brain Res. 2019a;366:88–95.
12. Bjekić J, Čolić MV, Živanović M, Milanović SD, Filipović SR. Transcranial direct current stimulation (tDCS) over parietal cortex improves associative memory. Neurobiol Learn Mem. 2019b;157:114–20.
13. Bliss T, Collingridge G. A synaptic model of memory - long-term potentiation in the Hippocampus. Nature. 1993;361:31–9.
14. Boehringer A, Macher K, Dukart J, Villringer A, Pleger B. Cerebellar transcranial direct current stimulation modulates verbal working memory. Brain Stimulat. 2013;6:649–53.
15. Bogdanov M, Schwabe L. Transcranial stimulation of the dorsolateral prefrontal cortex prevents stress-induced working memory deficits. J Neurosci. 2016;36:1429–37.
16. Bogdanov M, Ruff CC, Schwabe L. Transcranial stimulation over the dorsolateral prefrontal cortex increases the impact of past expenses on decision-making. Cereb Cortex. 2017;27:1094–102.
17. Boggio PS, Khoury LP, Martins DCS, Martins OEMS, de Macedo EC, Fregni F. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosurg Psychiatry. 2009;80:444–7.
18. Boudewyn M, Roberts BM, Mizrak E, Ranganath C, Carter CS. Prefrontal transcranial direct current stimulation (tDCS) enhances behavioral and EEG markers of proactive control. Cogn Neurosci. 2019;10:57–65.
19. Breitenstein C, Jansen A, Deppe M, Foerster A-F, Sommer J, Wolbers T, Knecht S. Hippocampus activity differentiates good from poor learners of a novel lexicon. NeuroImage. 2005;25:958–68.
20. Brückner S, Kammer T. Both anodal and cathodal transcranial direct current stimulation improves semantic processing. Neuroscience. 2017;343:269–75.
21. Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 2014;86:1–9.
22. Brunyé TT, Smith AM, Horner CB, Thomas AK. Verbal long-term memory is enhanced by retrieval practice but impaired by prefrontal direct current stimulation. Brain Cogn. 2018;128:80–8.
23. Burgess N, Maguire EA, O'Keefe J. The human Hippocampus and spatial and episodic memory. Neuron. 2002;35:625–41.
24. Butterworth B, Kovas Y. Understanding neurocognitive developmental disorders can improve education for all. Science. 2013;340:300–5.
25. Cabanac M. Pleasure: the common currency. J Theor Biol. 1992;155:173–200.
26. Campanella S, Schroder E, Monnart A, Vanderhasselt M-A, Duprat R, Rabijns M, Kornreich C, Verbanck P, Baeken C. Transcranial direct current stimulation over the right frontal inferior cortex decreases neural activity needed to achieve inhibition: a double-blind ERP study in a male population. Clin EEG Neurosci. 2017a;48:176–88.
27. Campanella S, Schroder E, Monnart A, Vanderhasselt M-A, Duprat R, Rabijns M, Kornreich C, Verbanck P, Baeken C. Transcranial direct current stimulation over the right frontal inferior cortex decreases neural activity needed to achieve inhibition: a double-blind ERP study in a male population. Clin EEG Neurosci. 2017b;48:176–88.
28. Campanella S, Schroder E, Vanderhasselt M-A, Baeken C, Kornreich C, Verbanck P, Burle B. Short-

term impact of tDCS over the right inferior frontal cortex on impulsive responses in a go/no-go task. Clin EEG Neurosci. 2018;49:398–406.
29. Chechlacz M, Hansen PC, Geng JJ, Cazzoli D. Polarity-dependent effects of Biparietal transcranial direct current stimulation on the interplay between target location and distractor saliency in visual attention. J Cogn Neurosci. 2018;30:851–66.
30. Chen N-F, Lo C-M, Liu T-L, Cheng S. Source memory performance is modulated by transcranial direct current stimulation over the left posterior parietal cortex. NeuroImage. 2016;139:462–9.
31. Cheng GLF, Lee TMC. Altering risky decision-making: influence of impulsivity on the neuromodulation of prefrontal cortex. Soc Neurosci. 2016;11:353–64.
32. Chew T, Ho K-A, Loo CK. Inter-and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. Brain Stimulat. 2015;8:1130–7.
33. Choi JY, Perrachione TK. Noninvasive neurostimulation of left temporal lobe disrupts rapid talker adaptation in speech processing. Brain Lang. 2019;196:104655.
34. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. NeuroImage. 2014;85:895–908.
35. Cools R, D'Esposito M. Inverted-U–shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011;69:e113–25.
36. Cowan N. What are the differences between long-term, short-term, and working memory? In: Sossin WS, Lacaille JC, Castellucci VF, Belleville S, editors. Essence of memory. Elsevier Science Bv: Amsterdam; 2008. p. 323–38.
37. Cummine J, Boliek CA, McKibben T, Jaswal A, Joanisse MF. Transcranial direct current stimulation (tDCS) selectively modulates semantic information during reading. Brain Lang. 2019;188:11–7.
38. Cunillera T, Fuentemilla L, Brignani D, Cucurell D, Miniussi C. A simultaneous modulation of reactive and proactive inhibition processes by anodal tDCS on the right inferior frontal cortex. PLoS One. 2014;9
39. Dambacher F, Schuhmann T, Lobbestael J, Arntz A, Brugman S, Sack AT. No effects of bilateral tDCS over inferior frontal gyrus on response inhibition and aggression. PLoS One. 2015;10:e0132170.
40. De Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Flöel A. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cogn Neurosci. 2010;22:2427–36.
41. D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature. 1995;378:279–81.
42. D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res. 2000;133:3–11.
43. Di Rosa E, Bardi L, Umiltà C, Masina F, Forgione M, Mapelli D. Transcranial direct current stimulation (tDCS) reveals a dissociation between SNARC and MARC effects: implication for the polarity correspondence account. Cortex. 2017a;93:68–78.
44. Di Rosa E, Bardi L, Umiltà C, Masina F, Forgione M, Mapelli D. Transcranial direct current stimulation (tDCS) reveals a dissociation between SNARC and MARC effects: implication for the polarity correspondence account. Cortex. 2017b;93:68–78.
45. Díez E, Gómez-Ariza CJ, Díez-Álamo AM, Alonso MA, Fernandez A. The processing of semantic relatedness in the brain: evidence from associative and categorical false recognition effects following transcranial direct current stimulation of the left anterior temporal lobe. Cortex. 2017;93:133–45.
46. D'Mello AM, Turkeltaub PE, Stoodley CJ. Cerebellar tDCS modulates neural circuits during semantic prediction: a combined tDCS-fMRI study. J Neurosci. 2017;37:1604–13.
47. Ebbinghaus H. Memory: a contribution to experimental psychology. New York, NY: Teachers College Press; 1913.
48. Edgcumbe DR, Thoma V, Rivolta D, Nitsche MA, Fu CHY. Anodal transcranial direct current stimulation over the right dorsolateral prefrontal cortex enhances reflective judgment and decision-making. Brain Stimulat. 2019;12:652–8.
49. Edwards W. The theory of decision making. Psychol Bull. 1954;51:380–417.
50. Elmer S, Burkard M, Renz B, Meyer M, Jancke L. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav Brain Funct BBF. 2009;5:29.
51. Fehring DJ, Illipparampil R, Acevedo N, Jaberzadeh S, Fitzgerald PB, Mansouri FA. Interaction of task-related learning and transcranial direct current stimulation of the prefrontal cortex in modulating executive functions. Neuropsychologia. 2019;131:148–59.
52. Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A. Cerebellar transcranial direct current stimulation impairs the practice-dependent proficiency increase in working memory. J Cogn Neurosci. 2008;20:1687–97.
53. Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res. 2010;208:311–8.
54. Filmer HL, Lyons M, Mattingley JB, Dux PE. Anodal tDCS applied during multitasking training leads to transferable performance gains. Sci Rep. 2017;7:12988.
55. Fiori V, Cipollari S, Caltagirone C, Marangolo P. "If two witches would watch two watches, which witch would watch which watch?" tDCS over the left fron-

tal region modulates tongue twister repetition in healthy subjects. Neuroscience. 2014;256:195–200.
56. Fiori V, Kunz L, Kuhnke P, Marangolo P, Hartwigsen G. Transcranial direct current stimulation (tDCS) facilitates verb learning by altering effective connectivity in the healthy brain. NeuroImage. 2018;181:550–9.
57. Flöel A, Rösser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci. 2008;20:1415–22.
58. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005a;166:23–30.
59. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MTA, Paulus W, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005b;166:23–30.
60. Friehs MA, Frings C. Cathodal tDCS increases stop-signal reaction time. Cogn Affect Behav Neurosci. 2019a;19:1129–42.
61. Friehs MA, Frings C. Offline beats online: transcranial direct current stimulation timing influences on working memory. Neuroreport. 2019b;30:795–9.
62. Fukai M, Bunai T, Hirosawa T, Kikuchi M, Ito S, Minabe Y, Ouchi Y. Endogenous dopamine release under transcranial direct-current stimulation governs enhanced attention: a study with positron emission tomography. Transl Psychiatry. 2019;9:1–10.
63. Galli G, Vadillo MA, Sirota M, Feurra M, Medvedeva A. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) on episodic memory. Brain Stimulat. 2019;12:231–41.
64. Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci. 1999;96:8301–6.
65. Gaynor AM, Chua EF. tDCS over the prefrontal cortex alters objective but not subjective encoding. Cogn Neurosci. 2017;8:156–61.
66. Gbadeyan O, McMahon K, Steinhauser M, Meinzer M. Stimulation of dorsolateral prefrontal cortex enhances adaptive cognitive control: a high-definition transcranial direct current stimulation study. J Neurosci. 2016;36:12530–6.
67. Giustolisi B, Vergallito A, Cecchetto C, Varoli E, Romero Lauro LJ. Anodal transcranial direct current stimulation over left inferior frontal gyrus enhances sentence comprehension. Brain Lang. 2018;176:36–41.
68. Gladwin TE, den Uyl TE, Fregni FF, Wiers RW. Enhancement of selective attention by tDCS: interaction with interference in a Sternberg task. Neurosci Lett. 2012;512:33–7.
69. Grant DA, Berg E. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol. 1948;38:404–11.
70. Guo H, Zhang Z, Da S, Sheng X, Zhang X. High-definition transcranial direct current stimulation (HD-tDCS) of left dorsolateral prefrontal cortex affects performance in balloon analogue risk task (BART). Brain Behav. 2018;8:e00884.
71. Habich A, Klöppel S, Abdulkadir A, Scheller E, Nissen C, Peter J. Anodal tDCS enhances verbal episodic memory in initially low performers. Front Hum Neurosci. 2017;11
72. Habich A, Slotboom J, Peter J, Wiest R, Klöppel S. No effect of anodal tDCS on verbal episodic memory performance and neurotransmitter levels in young and elderly participants, 2020.
73. Hammer A, Mohammadi B, Schmicker M, Saliger S, Münte TF. Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci. 2011a;12:72.
74. Hammer A, Mohammadi B, Schmicker M, Saliger S, Münte TF. Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci. 2011b;12:72.
75. Hämmerer D, Bonaiuto J, Klein-Flügge M, Bikson M, Bestmann S. Selective alteration of human value decisions with medial frontal tDCS is predicted by changes in attractor dynamics. Sci Rep. 2016;6
76. Hanenberg C, Getzmann S, Lewald J. Transcranial direct current stimulation of posterior temporal cortex modulates electrophysiological correlates of auditory selective spatial attention in posterior parietal cortex. Neuropsychologia. 2019;131:160–70.
77. Hannula DE, Tranel D, Cohen NJ. The long and the short of it: relational memory impairments in amnesia, even at short lags. J Neurosci. 2006;26:8352–9.
78. Hauser TU, Rotzer S, Grabner RH, Mérillat S, Jäncke L. Enhancing performance in numerical magnitude processing and mental arithmetic using transcranial direct current stimulation (tDCS). Front Hum Neurosci. 2013;7
79. Hauser TU, Rütsche B, Wurmitzer K, Brem S, Ruff CC, Grabner RH. Neurocognitive effects of transcranial direct current stimulation in arithmetic learning and performance: a simultaneous tDCS-fMRI study. Brain Stimulat. 2016;
80. Heimrath K, Sandmann P, Becke A, Muller NG, Zaehle T. Behavioral and electrophysiological effects of transcranial direct current stimulation of the parietal cortex in a visuo-spatial working memory task. Front Psych. 2012;3:56.
81. Heinen K, Sagliano L, Candini M, Husain M, Cappelletti M, Zokaei N. Cathodal transcranial direct current stimulation over posterior parietal cortex enhances distinct aspects of visual working memory. Neuropsychologia. 2016;87:35–42.
82. Herrmann MJ, Horst AK, Löble S, Möll MT, Katzorke A, Polak T. Relevance of dorsolateral and frontotemporal cortex on the phonemic verbal fluency – a fNIRS-study. Neuroscience. 2017;367:169–77.

83. Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimulat. 2015;
84. Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults. NeuroImage. 2017;152:142–57.
85. Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Effects of single versus dual-site high-definition transcranial direct current stimulation (HD-tDCS) on cortical reactivity and working memory performance in healthy subjects. Brain Stimulat. 2018;11:1033–43.
86. Hoy KE, Emonson MRL, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia. 2013;51:1777–84.
87. Hsu T-Y, Tseng P, Liang W-K, Cheng S-K, Juan C-H. Transcranial direct current stimulation over right posterior parietal cortex changes prestimulus alpha oscillation in visual short-term memory task. NeuroImage. 2014;98:306–13.
88. Iyer M, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann E. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology. 2005;64:872–5.
89. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res. 2012a;216:1–10.
90. Jacobson L, Goren N, Lavidor M, Levy DA. Oppositional transcranial direct current stimulation (tDCS) of parietal substrates of attention during encoding modulates episodic memory. Brain Res. 2012b;1439:66–72.
91. Javadi AH, Walsh V. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain Stimulat. 2012;5:231–41.
92. Jones KT, Berryhill ME. Parietal contributions to visual working memory depend on task difficulty. Front Psych. 2012;3:81.
93. Jones KT, Gözenman F, Berryhill ME. Enhanced long-term memory encoding after parietal neurostimulation. Exp Brain Res. 2014;232:4043–54.
94. Jongkees BJ, Sellaro R, Beste C, Nitsche MA, Kühn S, Colzato LS. l-Tyrosine administration modulates the effect of transcranial direct current stimulation on working memory in healthy humans. Cortex. 2017;90:103–14.
95. Jongkees BJ, Loseva AA, Yavari FB, Nitsche MA, Colzato LS. The COMT Val158Met polymorphism does not modulate the after-effect of tDCS on working memory. Eur J Neurosci. 2019;49:263–74.
96. Kasahara K, Tanaka S, Hanakawa T, Senoo A, Honda M. Lateralization of activity in the parietal cortex predicts the effectiveness of bilateral transcranial direct current stimulation on performance of a mental calculation task. Neurosci Lett. 2013;545:86–90.
97. Katz B, Au J, Buschkuehl M, Abagis T, Zabel C, Jaeggi SM, Jonides J. Individual differences and long-term consequences of tDCS-augmented cognitive training. J Cogn Neurosci. 2017;29
98. Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia. 2004;42:113–7.
99. Kinsbourne M. Hemi-inattention and hemispheric rivalry. Hemi-Inattention Hemispheric Spetextasciitilde Iulizttion. 1977;18
100. Lachman HM, Papolos DF, Saito T, Yu Y-M, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenet Genomics. 1996;6:243–50.
101. Learmonth G, Thut G, Benwell CSY, Harvey M. The implications of state-dependent tDCS effects in aging: Behavioural response is determined by baseline performance. Neuropsychologia. 2015;74:108–19.
102. Leite J, Gonçalves ÓF, Pereira P, Khadka N, Bikson M, Fregni F, Carvalho S. The differential effects of unihemispheric and bihemispheric tDCS over the inferior frontal gyrus on proactive control. Neurosci Res. 2018;130:39–46.
103. Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Strong DR, Brown RA. Evaluation of a behavioral measure of risk taking: the balloon analogue risk task (BART). J Exp Psychol Appl. 2002;8:75–84.
104. Leshikar ED, Leach RC, McCurdy MP, Trumbo MC, Sklenar AM, Frankenstein AN, Matzen LE. Transcranial direct current stimulation of dorsolateral prefrontal cortex during encoding improves recall but not recognition memory. Neuropsychologia. 2017;106:390–7.
105. Levasseur-Moreau J, Fecteau S. Translational application of neuromodulation of decision-making. Brain Stimulat. 2012;5:77–83.
106. Lewald J. Bihemispheric anodal transcranial direct-current stimulation over temporal cortex enhances auditory selective spatial attention. Exp Brain Res. 2019;237:1539–49.
107. Li B, Liu H, Pérez A, Xie N. Cathodal transcranial direct current stimulation over right dorsolateral prefrontal cortex improves language control during language switching. Behav Brain Res. 2018;351:34–41.
108. Li S, Cai Y, Liu J, Li D, Feng Z, Chen C, Xue G. Dissociated roles of the parietal and frontal cortices in the scope and control of attention during visual working memory. NeuroImage. 2017;149:210–9.
109. Liang W-K, Lo M-T, Yang AC, Peng C-K, Cheng S-K, Tseng P, Juan C-H. Revealing the brain's adaptability and the transcranial direct current stimulation

facilitating effect in inhibitory control by multiscale entropy. NeuroImage. 2014;90:218–34.
110. Lo O-Y, van Donkelaar P, Chou L-S. Effects of transcranial direct current stimulation over right posterior parietal cortex on attention function in healthy young adults. Eur J Neurosci. 2019;49:1623–31.
111. Logan GD, Cowan WB. On the ability to inhibit thought and action: a theory of an act of control. Psychol Rev. 1984;91:295–327.
112. London RE, Slagter HA. Effects of transcranial direct current stimulation over left dorsolateral pFC on the attentional blink depend on individual baseline performance. J Cogn Neurosci. 2015;27:2382–93.
113. Lum JAG, Clark GM, Rogers CM, Skalkos JD, Fuelscher I, Hyde C, Enticott PG. Effects of anodal transcranial direct current stimulation (atDCS) on sentence comprehension. J Int Neuropsychol Soc. 2019;25:331–5.
114. Luque-Casado A, Fogelson N, Iglesias-Soler E, Fernandez-Del-Olmo M. Exploring the effects of transcranial direct current stimulation over the prefrontal cortex on working memory: a cluster analysis approach. Behav Brain Res. 2019;375:112144.
115. Maldonado T, Goen JRM, Imburgio MJ, Eakin SM, Bernard JA. Single session high definition transcranial direct current stimulation to the cerebellum does not impact higher cognitive function. PLoS One. 2019;14:e0222995.
116. Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ. Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. J Cogn Neurosci. 2016;1–27
117. Mannarelli D, Pauletti C, De Lucia MC, Delle Chiaie R, Bersani FS, Spagnoli F, Minichino A, Curra A, Trompetto C, Fattapposta F. Effects of cerebellar transcranial direct current stimulation on attentional processing of the stimulus: evidence from an event-related potentials study. Neuropsychologia. 2016;84:127–35.
118. Mannarelli D, Pauletti C, Currà A, Marinelli L, Corrado A, Delle Chiaie R, Fattapposta F. The cerebellum modulates attention network functioning: evidence from a cerebellar transcranial direct current stimulation and attention network test study. Cerebellum Lond Engl. 2019;18:457–68.
119. Mansouri FA, Tanaka K, Buckley MJ. Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. Nat Rev Neurosci. 2009;10:141–52.
120. Mansouri FA, Fehring DJ, Feizpour A, Gaillard A, Rosa MGP, Rajan R, Jaberzadeh S. Direct current stimulation of prefrontal cortex modulates error-induced behavioral adjustments. Eur J Neurosci. 2016;44:1856–69.
121. Martin DM, Liu R, Alonzo A, Green M, Player MJ, Sachdev P, Loo CK. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. Int J Neuropsychopharmacol. 2013;16:1927–36.
122. Mathys C, Loui P, Zheng X, Schlaug G. Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. Front Psychol. 2010;1:193.
123. McDermott TJ, Wiesman AI, Mills MS, Spooner RK, Coolidge NM, Proskovec AL, Heinrichs-Graham E, Wilson TW. tDCS modulates behavioral performance and the neural oscillatory dynamics serving visual selective attention. Hum Brain Mapp. 2019;40:729–40.
124. Medina J, Cason S. No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations. Cortex. 2017;94:131–41.
125. Meinzer M, Yetim Ö, McMahon K, de Zubicaray G. Brain mechanisms of semantic interference in spoken word production: an anodal transcranial direct current stimulation (atDCS) study. Brain Lang. 2016;157–158:72–80.
126. Mengarelli F, Spoglianti S, Avenanti A, di Pellegrino G. Cathodal tDCS over the left prefrontal cortex diminishes choice-induced preference change. Cereb Cortex N Y N. 2015;1991(25):1219–27.
127. Miler JA, Meron D, Baldwin DS, Garner M. The effect of prefrontal transcranial direct current stimulation on attention network function in healthy volunteers. Neuromodulation Technol. Neural Interface. 2018;21:355–61.
128. Monte-Silva K, Kuo M-F, Thirugnanasambandam N, Liebetanz D, Paulus W, Nitsche MA. Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. J Neurosci. 2009;29:6124–31.
129. Nejati V, Salehinejad MA, Nitsche MA. Interaction of the left dorsolateral prefrontal cortex (l-DLPFC) and right orbitofrontal cortex (OFC) in hot and cold executive functions: evidence from transcranial direct current stimulation (tDCS). Neuroscience. 2018;369:109–23.
130. Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). NeuroImage. 2014;85:909–17.
131. Nieratschker V, Kiefer C, Giel K, Krüger R, Plewnia C. The COMT val/met polymorphism modulates effects of tDCS on response inhibition. Brain Stimulat. 2015a;8:283–8.
132. Nieratschker V, Kiefer C, Giel K, Krüger R, Plewnia C. The COMT val/met polymorphism modulates effects of tDCS on response inhibition. Brain Stimulat. 2015b;8:283–8.
133. Nikolin S, Loo CK, Bai S, Dokos S, Martin DM. Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. NeuroImage. 2015a;
134. Nikolin S, Loo CK, Bai S, Dokos S, Martin DM. Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. NeuroImage. 2015b;117:11–9.

135. Nikolin S, Martin D, Loo CK, Boonstra TW. Effects of TDCS dosage on working memory in healthy participants. Brain Stimulat. 2018;
136. Ohn SH, Park C-I, Yoo W-K, Ko M-H, Choi KP, Kim G-M, Lee YT, Kim Y-H. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport. 2008a;19:43–7.
137. Ohn SH, Park C-I, Yoo W-K, Ko M-H, Choi KP, Kim G-M, Lee YT, Kim Y-H. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport. 2008b;19:43–7.
138. Olson IR, Berryhill M. Some surprising findings on the involvement of the parietal lobe in human memory. Neurobiol Learn Mem. 2009;91:155–65.
139. Olson IR, Moore KS, Stark M, Chatterjee A. Visual working memory is impaired when the medial temporal lobe is damaged. J Cogn Neurosci. 2006a;18:1087–97.
140. Olson IR, Page K, Moore KS, Chatterjee A, Verfaellie M. Working memory for conjunctions relies on the medial temporal lobe. J Neurosci. 2006b;26:4596–601.
141. Ouellet J, McGirr A, Van den Eynde F, Jollant F, Lepage M, Berlim MT. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over the orbitofrontal cortex (OFC): a randomized and sham-controlled exploratory study. J Psychiatr Res. 2015;69:27–34.
142. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp. 2005;25:46–59.
143. Pachella RG, Pew RW. Speed-accuracy tradeoff in reaction time: effect of discrete criterion times. J Exp Psychol. 1968;76:19.
144. Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. NeuroImage. 2003;19:1439–48.
145. Perceval G, Martin AK, Copland DA, Laine M, Meinzer M. High-definition tDCS of the temporo-parietal cortex enhances access to newly learned words. Sci Rep. 2017;7:17023.
146. Pergolizzi D, Chua EF. Transcranial direct current stimulation (tDCS) of the parietal cortex leads to increased false recognition. Neuropsychologia. 2015;66:88–98.
147. Pergolizzi D, Chua EF. Transcranial direct current stimulation over the parietal cortex alters bias in item and source memory tasks. Brain Cogn. 2016;108:56–65.
148. Pergolizzi D, Chua EF. Increased contextual cue utilization with tDCS over the prefrontal cortex during a recognition task. Brain Res. 2017;1655:1–9.
149. Pesonen M, Hämäläinen H, Krause CM. Brain oscillatory 4–30 Hz responses during a visual n-back memory task with varying memory load. Brain Res. 2007;1138:171–7.
150. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. Annu Rev Neurosci. 2012;35:73–89.
151. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. Cereb Cortex N Y N. 2018;1991(28):1132–40.
152. Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT val/met polymorphism. Cortex. 2013;49:1801–7.
153. Posner MI, Petersen SE. The attention system of the human brain. Annu Rev Neurosci. 1990;13:25–42.
154. Price AR, Peelle JE, Bonner MF, Grossman M, Hamilton RH. Causal evidence for a mechanism of semantic integration in the angular gyrus as revealed by high-definition transcranial direct current stimulation. J Neurosci. 2016;36:3829–38.
155. Ranganath C, D'Esposito M. Medial temporal lobe activity associated with active maintenance of novel information. Neuron. 2001;31:865–73.
156. Raud L, Westerhausen R, Dooley N, Huster RJ. Differences in unity: the go/no-go and stop signal tasks rely on different mechanisms. NeuroImage. 2020;210:116582.
157. Reteig LC, Talsma LJ, van Schouwenburg MR, Slagter HA. Transcranial electrical stimulation as a tool to enhance attention. J Cogn Enhanc. 2017;1:10–25.
158. Richmond LL, Wolk D, Chein J, Olson IR. Transcranial direct current stimulation enhances verbal working memory training performance over time and near transfer outcomes. J Cogn Neurosci. 2014;26:2443–54.
159. Rodrigues de Almeida L, Pope PA, Hansen PC. Task load modulates tDCS effects on language performance. J Neurosci Res. 2019;97:1430–54.
160. Roe JM, Nesheim M, Mathiesen NC, Moberget T, Alnaes D, Sneve MH. The effects of tDCS upon sustained visual attention are dependent on cognitive load. Neuropsychologia. 2016;80:1–8.
161. Roy LB, Sparing R, Fink GR, Hesse MD. Modulation of attention functions by anodal tDCS on right PPC. Neuropsychologia. 2015;74:96–107.
162. Ruf SP, Fallgatter AJ, Plewnia C. Augmentation of working memory training by transcranial direct current stimulation (tDCS). Sci Rep. 2017;7
163. Sallard E, Mouthon M, Pretto MD, Spierer L. Modulation of inhibitory control by prefrontal anodal tDCS: a crossover double-blind sham-controlled fMRI study. PLoS One. 2018;13:e0194936.
164. Sandrini M, Xu B, Volochayev R, Awosika O, Wang W-T, Butman JA, Cohen LG. Transcranial direct current stimulation facilitates response inhibition through dynamic modulation of the fronto-basal ganglia network. Brain Stimulat. 2020;13:96–104.

165. Savic B, Müri R, Meier B. A single session of prefrontal cortex transcranial direct current stimulation does not modulate implicit task sequence learning and consolidation. Brain Stimulat. 2017a;10:567–75.
166. Savic B, Cazzoli D, Müri R, Meier B. No effects of transcranial DLPFC stimulation on implicit task sequence learning and consolidation. Sci Rep. 2017b;7
167. Schaal NK, Pollok B, Banissy MJ. Hemispheric differences between left and right supramarginal gyrus for pitch and rhythm memory. Sci Rep. 2017;7
168. Schroeder PA, Nuerk H-C, Plewnia C. Reduction of implicit cognitive bias with cathodal tDCS to the left prefrontal cortex. Cogn Affect Behav Neurosci. 2018;18:263–72.
169. Sdoia S, Zivi P, Ferlazzo F. Anodal tDCS over the right parietal but not frontal cortex enhances the ability to overcome task set inhibition during task switching. PLoS One. 2020;15:e0228541.
170. Silas J, Brandt KR. Frontal transcranial direct current stimulation (tDCS) abolishes list-method directed forgetting. Neurosci Lett. 2016;616:166–9.
171. Smith EE, Jonides J. Working memory: a view from neuroimaging. Cognit Psychol. 1997;33:5–42.
172. Soutschek A, Ugazio G, Crockett MJ, Ruff CC, Kalenscher T, Tobler PN. Binding oneself to the mast: stimulating frontopolar cortex enhances precommitment. Soc Cogn Affect Neurosci. 2017;12:635–42.
173. Soutschek A, Kang P, Ruff CC, Hare TA, Tobler PN. Brain stimulation over the frontopolar cortex enhances motivation to exert effort for reward. Biol Psychiatry. 2018;84:38–45.
174. Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR. Enhancing language performance with non-invasive brain stimulation—a transcranial direct current stimulation study in healthy humans. Neuropsychologia. 2008;46:261–8.
175. Spielmann K, van der Vliet R, van de Sandt-Koenderman WME, Frens MA, Ribbers GM, Selles RW, van Vugt S, van der Geest JN, Holland P. Cerebellar cathodal transcranial direct stimulation and performance on a verb generation task: a replication study. Neural Plast. 2017;2017
176. Splittgerber M, Salvador R, Brauer H, Breitling-Ziegler C, Prehn-Kristensen A, Krauel K, Nowak R, Ruffini G, Moliadze V, Siniatchkin M. Individual baseline performance and electrode montage impact on the effects of anodal tDCS over the left dorsolateral prefrontal cortex. Front Hum Neurosci. 2020;14
177. Stone DB, Tesche CD. Transcranial direct current stimulation modulates shifts in global/local attention. Neuroreport. 2009;20:1115–9.
178. Stramaccia DF, Penolazzi B, Sartori G, Braga M, Mondini S, Galfano G. Assessing the effects of tDCS over a delayed response inhibition task by targeting the right inferior frontal gyrus and right dorsolateral prefrontal cortex. Exp Brain Res. 2015;233:2283–90.
179. Stramaccia DF, Penolazzi B, Altoè G, Galfano G. TDCS over the right inferior frontal gyrus disrupts control of interference in memory: a retrieval-induced forgetting study. Neurobiol Learn Mem. 2017;144:114–30.
180. Strobach T, Antonenko D, Abbarin M, Escher M, Flöel A, Schubert T. Modulation of dual-task control with right prefrontal transcranial direct current stimulation (tDCS). Exp Brain Res. 2018;236:227–41.
181. Talsma LJ, Kroese HA, Slagter HA. Boosting cognition: effects of multiple-session transcranial direct current stimulation on working memory. J Cogn Neurosci. 2016;29:755–68.
182. Tremblay S, Lepage J-F, Latulipe-Loiselle A, Fregni F, Pascual-Leone A, Théoret H. The uncertain outcome of prefrontal tDCS. Brain Stimulat. 2014;7:773–83.
183. Trumbo MC, Matzen LE, Coffman BA, Hunter MA, Jones AP, Robinson CSH, Clark VP. Enhanced working memory performance via transcranial direct current stimulation: the possibility of near and far transfer. Neuropsychologia. 2016;93:85–96.
184. Tseng P, Hsu T-Y, Chang C-F, Tzeng OJL, Hung DL, Muggleton NG, Walsh V, Liang W-K, Cheng S, Juan C-H. Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. J Neurosci. 2012;32:10554–61.
185. Verbruggen F, Logan GD. Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. J Exp Psychol Gen. 2008;137:649–72.
186. Vines BW, Schnider NM, Schlaug G. Testing for causality with transcranial direct current stimulation: pitch memory and the left supramarginal gyrus. Neuroreport. 2006;17:1047–50.
187. de Vries MH, Barth ACR, Maiworm S, Knecht S, Zwitserlood P, Flöel A. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cogn Neurosci. 2009;22:2427–36.
188. Wang S, Itthipuripat S, Ku Y. Electrical stimulation over human posterior parietal cortex selectively enhances the capacity of visual short-term memory. J Neurosci. 2019;39:528–36.
189. Watanabe J, Sugiura M, Sato K, Sato Y, Maeda Y, Matsue Y, Fukuda H, Kawashima R. The human prefrontal and parietal association cortices are involved in NO-GO performances: an event-related fMRI study. NeuroImage. 2002;17:1207–16.
190. Weidacker K, Weidemann CT, Boy F, Johnston SJ. Cathodal tDCS improves task performance in participants high in Coldheartedness. Clin Neurophysiol. 2016;127:3102–9.
191. Weigl M, Mecklinger A, Rosburg T. Transcranial direct current stimulation over the left dorsolateral prefrontal cortex modulates auditory mismatch negativity. Clin Neurophysiol. 2016;127:2263–72.
192. Weintraub-Brevda RR, Chua EF. Transcranial direct current stimulation over the right and left VLPFC

leads to differential effects on working and episodic memory. Brain Cogn. 2019;132:98–107.
193. Wen Y, Turel O, Peng Y, Lv C, He Q. Cathodal stimulating the left DLPFC changes risk disposition toward common risky behaviors in daily-life. Neurosci Lett. 2019;709:134400.
194. Westphal AJ, Chow TE, Ngoy C, Zuo X, Liao V, Storozuk LA, Peters MAK, Wu AD, Rissman J. Anodal transcranial direct current stimulation to the left rostrolateral prefrontal cortex selectively improves source memory retrieval. J Cogn Neurosci. 2019;31:1380–91.
195. Westwood SJ, Olson A, Miall RC, Nappo R, Romani C. Limits to tDCS effects in language: failures to modulate word production in healthy participants with frontal or temporal tDCS. Cortex J Devoted Study Nerv Syst Behav. 2017;86:64–82.
196. Wirth M, Rahman RA, Kuenecke J, Koenig T, Horn H, Sommer W, Dierks T. Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia. 2011;49:3989–98.
197. Wong LYX, Gray SJ, Gallo DA. Does tDCS over prefrontal cortex improve episodic memory retrieval? Potential importance of time of day. Cogn Neurosci. 2018;9:167–80.
198. Wong MN, Chan Y, Ng ML, Zhu FF. Effects of transcranial direct current stimulation over the Broca's area on tongue twister production. Int J Speech Lang Pathol. 2019;21:182–8.
199. Wynn SC, Driessen JMA, Glennon JC, Brazil IA, Schutter DJLG. Cerebellar transcranial direct current stimulation improves reactive response inhibition in healthy volunteers. Cerebellum Lond Engl. 2019;18:983–8.
200. Ye H, Chen S, Huang D, Wang S, Jia Y, Luo J. Transcranial direct current stimulation over prefrontal cortex diminishes degree of risk aversion. Neurosci Lett. 2015;598:18–22.
201. Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci. 2011;12:2.
202. Zanto TP, Gazzaley A. Fronto-parietal network: flexible hub of cognitive control. Trends Cogn Sci. 2013;17
203. Zwissler B, Sperber C, Aigeldinger S, Schindler S, Kissler J, Plewnia C. Shaping memory accuracy by left prefrontal transcranial direct current stimulation. J Neurosci. 2014;34:4022–6.

18 tDCS in Exercise, Sport Performance, and Recovery Process

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18.1 Introduction

Regular exercise is being recognized as an essential practice for both physical and mental health [1–4]. Despite its benefits, most individuals do not exercise regularly, especially in developed countries [5, 6]. Although the lack of time is one of the top reasons for not exercising, other motives may be related to low exercise tolerance and high fatigability, which results in increased perceived exertion (RPE) and unpleasant sensations. These unpleasant and exacerbated effortful sensations may create an unpleasant experience that results in exercise withdrawal. In fact, systematic-review-level of evidence shows that affective responses (i.e., pleasure/displeasure) to exercise influence future exercise behavior [7, 8]. On the other hand, improved exercise performance is aimed at both individuals who train for health and fitness (i.e., nonathletes), and those seeking sport performance (i.e., athletes).

Ergogenic agents are defined as any means of enhancing physical performance in physical activities, sports, or occupational activities.

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Ergogenic aids are traditionally attributed to mechanical aids (e.g., especially shoes or clothing), psychological aids (e.g., hypnosis), physiological aids (e.g., injection of red blood cells), pharmacological aids (e.g., steroids), and nutritional aids (e.g., nutritional supplements) [9]. Many ergogenic aids are used aiming at improving exercise performance, especially nutritional ergogenic aids such as creatine, caffeine, bicarbonate, and proteins [9]. Some of these had their efficacy confirmed, such as caffeine and bicarbonate, while others not [10]. This is especially important in the elite-level sports performance where even seemingly trivial differences have an important sportive outcome. For instance, Christensen et al. [10] pointed out that Olympic endurance medal rankings would be different by only 1% change in average speed of events lasting ~45 s to 8 min, such as 100 m swimming, 400 m running, 1500 m running and 4000 m track cycling, and 2000 m rowing.

Exercise performance is determined by different physical, physiological, and psychological factors that influence pacing and fatigue. Muscle fatigue may be defined as any exercise-induced reduction in the ability to produce force or power with a muscle or muscle group [11]. It has been demonstrated that fatigue may occur not only due to processes at or distal to the neuromuscular junction, which is termed as "peripheral fatigue," but also due to process in the central nervous system (CNS) that limits its capacity to stimulate muscle fibers, which also contributes to decline in muscle activation and limits performance, this latter is termed as "central fatigue" [11]. Most importantly, despite the earlier assumption of a secondary or absent role of the brain in regulating exercise performance and fatigue, more recently, it has been recognized as a crucial factor in both exercise-induced fatigue and exercise-related perceptions (e.g., exertion and pleasure) [12–15]. In this regard, several approaches focusing on the central nervous system have been used to improve exercise performance which spans from mental rehearsal and motor imagery [16], meditation [17], psychological interventions [18], and biofeedback [19, 20].

Currently, there are different forms of neuromodulation with potential usefulness in the exercise context. Transcranial direct current stimulation (tDCS) is considered as one of the most promising due to its low cost, ease of use, and high portability [21]. tDCS consists of applying a weak electric current on the scalp using electric conductive electrodes over a brain area of interest. This electric current may change the neuronal excitability pattern, increasing it if a positive charge is applied (i.e., anodal tDCS, a-tDCS) or decreasing it if a negative charge is used (i.e., cathodal tDCS, c-tDCS) [22]. tDCS aftereffects may last tens of minutes after stimulation is finished [23], which presents an important window of opportunity to be used for both treatments in patients with clinical conditions or healthy individuals aiming to boost performance.

At present, several studies have tested the effects of tDCS on exercise-related measures and presented promising results on both sensations related to exercise and exercise performance. Curiously, some researchers have coined the term "neurodoping" to refer to the possible performance enhancement effect of tDCS [24]. In this chapter, we review the current evidence related to the use of tDCS application in the exercise science field aiming to summarize the results and guide future interventions in the research and practical field.

18.2 Target and Mechanisms of tDCS Use for Performance Enhancement

In recent years, several studies used neuroimaging techniques to assess how the brain controls exercise, and exercise affects the brain. In this regard, several brain regions are potentially involved in the processing of exercise-related cues, and the generation of exercise-related sensation as well as exercise performance. Studies investigated some brain areas with tDCS to evaluate its effects

on exercise-related measures. Here, we present a summary of these areas and the possible mechanisms through which tDCS may impact on exercise. Figure 18.1 presents an illustration of tDCS montages targeting brain regions related to exercise performance.

The *primary motor cortex* (M1) – M1 is the most obvious target for tDCS considering its direct role in the control of the muscles. During prolonged exercise, the excitability of the motor neuron pool decreases, which results in diminished stimulus to the muscle [11]. If exercise is to be continued, there should be an increase in

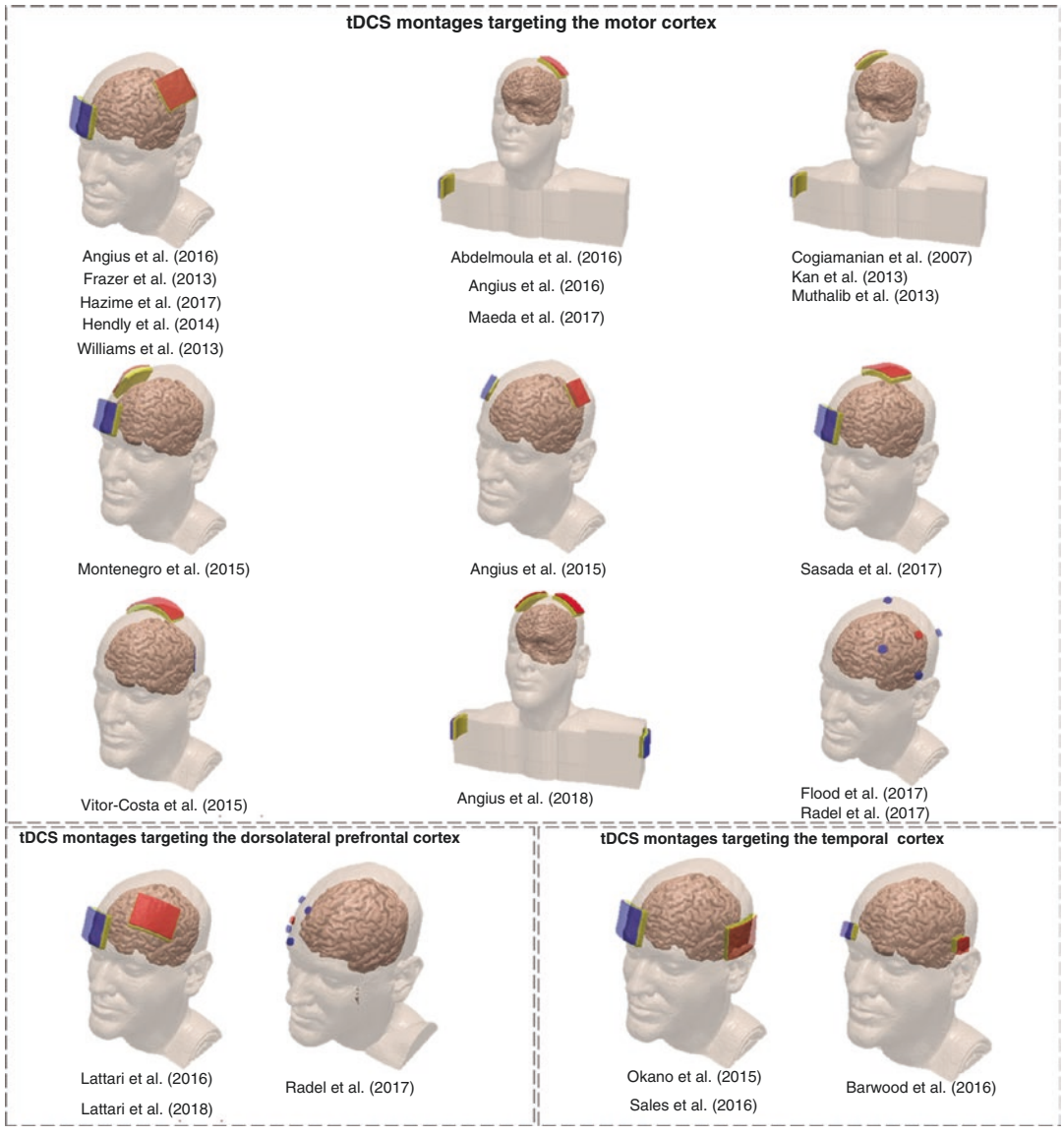

Fig. 18.1 Examples of transcranial direct current stimulation montages used in different studies in the exercise science field targeting the primary motor cortex, dorsolateral prefrontal cortex, and temporal cortex. The red color represents the anodal electrode (positive), the blue color represents the cathodal electrode (negative), and the yellow color represents the sponge that involves the electrodes

the descending neural drive from M1 and other supraspinal areas [11]. If this supraspinal neural drive is suboptimal, a decrease in muscle activation will occur, which ultimately will result in a decrease in pace or exercise termination. In this regard, increased excitability of M1 due to tDCS could heal to maintain an adequate neural drive to compensate for the decrease in the motor neuron pool in prolonged exercise and, thus, postpone fatigue.

Alternatively, exercise-induced pain has been suggested to play a key role in exercise tolerance and performance [25–27]. In this regard, M1 has connections to subcortical areas involved in pain processing [28, 29]. Moreover, it has been suggested that tDCS may modulate the corollary discharge from M1, which in turn influences sensory feedback and, ultimately, pain processing [30]. In fact, meta-analytical evidence has shown that tDCS over M1 may modulate pain perception and pain threshold in both healthy individual and clinical samples [29]. Therefore, tDCS over M1 may improve exercise perception and exercise performance via its impact on pain processing.

The *dorsolateral prefrontal cortex* (DLPFC) – the DLPFC is another region involved in exercise performance and perception due to its involvement in cognitive and emotional processing [31]. In addition, considering the voluntary nature of the exercise, its termination would be a conscious decision to disengage from the tasks [32]. Finally, studies have demonstrated that performing a cognitively demanding task previous to exercise may affect the physiological and psychological response to exercise as well as exercise performance [18, 33, 34]. tDCS over DLPFC would strengthen cognitive and emotional processing that would increase the conscious capacity to ignore or deal with the overwhelming negative interoceptive stimuli generated by prolonged or high-intensity exercise, hence improving exercise perception and performance. tDCS over DLPFC is also suggested to promote a corollary discharge stronger than M1 that could also affect the sensory feedback and pain processing [30], which could be an alternative mechanism.

The *insular cortex* (IC) – the IC is a subcortical region involved in several processes including the processing of the interoceptive signals, emotional response, and autonomic cardiovascular control. For instance, during an operative procedure, the electrical stimulation of the left IC resulted in an increase in blood pressure and heart rate, while stimulating the right IC resulted in opposite effects [35]. The involvement of the IC in cardiac autonomic control has also been confirmed in neuroimaging studies [36]. Also, the IC has been demonstrated to play a crucial role in interoception (i.e., sense of the physiological condition of the entire body) [37, 38], which influences the perceptions related to exercise (i.e., RPE and pleasure) and also influences pacing and exercise performance. Interoception also influences the emotional state [37, 38]. Therefore, tDCS targeting IC may improve exercise performance and exercise-related perceptions via alteration of the cardiac autonomic control, which may influence the cardiovascular responses to exercise (i.e., lower HR and blood pressure), modulation of interoception (i.e., perception of body signals), and emotional processing.

The *supplementary motor area* (SMA) – the SMA is involved in the generation of RPE, which is an important factor for exercise performance [14, 32] and also influences the affective response to exercise [39, 40]. Zénon et al. [41] performed an experiment in which participants were asked to perform a handgrip force exercise and to report their RPE. After each trial, participants were offered varying ammounts of reward (i.e., money) in order to repeat the effort, which they could or not accept. During the handgrip strength task, however, the activity of M1 or SMA was disrupted using theta-burst TMS. They found that disruption of SMA, but not M1, decreased RPE [41]. Thus, tDCS over SMA could reduce RPE which would result in improved exercise performance or exercise experience.

18.3 Effect of tDCS on Exercise Performance

Studies on the effect of tDCS on exercise performance have assessed different exercise types and physical fitness-related capacities. In the next subtopics, we summarized the current evidence describing the results of some of these studies individually, pointing out the type of exercise/

physical capacity assessed as well as the tDCS protocol used (electrode positions, current intensity, and duration). It is noteworthy that the systematic reviews with meta-analysis (SRMA) are considered as the highest level of evidence. Therefore, in addition to the description of some individual studies, we also present the results of the SRMA published in this field. One measure of effect in SRMA may be presented as the mean difference (MD) that represent the difference between the raw results of the experimental condition (e.g., a-tDCS) and a control condition (e.g., sham tDCS), which is interesting when the studies included in the SRMA use the same type of outcome (i.e., continuous data) and unit of measure (e.g., exercise time in seconds or minutes). The other type of measure of effect in SRMA is the standardized mean difference (SMD), which is used when the included studies use different outcome measures (e.g., average power in a time trial and time to reach exhaustion). Both MD and SMD are presented with the corresponding 95% confidence interval (95% CI) to represent the variation of the effect.

The MD interpretation is pretty much straightforward and the significance of the effect depends on the specific context, for instance, a reduction in the time trial by 10 s in sedentary or physically active individuals may seem of little significance, but for competitive athletes, it may represent the difference between winning or losing a competition. Regarding the SMD, the interpretation is similar to the effect size in an original study. Researchers, in general, use the classification proposed by Cohen: small (0.2), medium (0.5), and large (0.8). Although these limits and labels may also depend on the research field, in the exercise sciences they are used as described.

18.3.1 Muscle Strength Exercise

The first study assessing the effect of a-tDCS on exercise performance was performed by Cogiamanian et al. [42]. They applied a-tDCS over M1 (1.5 mA for 10 min) in healthy individuals before performing a second time to exhaustion (TTE) task of a sustained isometric contraction at 35% of maximum isometric contraction (MIVC). They found that the TTE decreased significantly after a-tDCS compared to c-tDCS and no stimulation. This result served as the basis for several posterior studies. Other studies using similar methods either confirmed [43, 44] or found null results [45, 46]. Interestingly, Williams et al. [47] applied a-tDCS online during a sustained submaximal contraction (at 20% of MIVC) of the elbow flexors until task failure and found no change when assessing the entire sample. However, a subgroup analysis showed a 31% long TTE in the group where task failure occurred prior to the termination of tDCS compared to the group where failure occurred after tDCS had finished [47]. Radel et al. [48] found no change in TTE of sustained isometric elbow flexion with a-tDCS over M1 or DPFC in 22 healthy individuals.

Some studies have also assessed the effects of a-tDCS on isometric muscle performance of the lower limbs. Angius et al. [49] found increased TTE in a sustained isometric knee extension (at 20% of MIVC) after a-tDCS (2 mA for 10 min) over M1. Interestingly, the improvement was found only when the return (cathodal) electrode was placed over the shoulder but not when it was placed on the contralateral supraorbital area [49]. Other studies using conventional a-tDCS (i.e., which used large electrodes pads) over M1 (1 mA or 2 mA for 10 minutes), anodal high-definition tDCS (HD-tDCS) over M1 [50], and left DLPFC [50, 51] have failed to replicate the positive results.

Few studies assessed the effect of tDCS on isokinetic muscle performance. Sales et al. [52] found an increased isokinetic performance (total work) of knee extension at $60°.s^{-1}$ and $180°.s^{-1}$ and a trend toward significance in both velocities for peak torque after a-tDCS over TC (2 mA for 20 min) in 19 trained men. On the other hand, a-tDCS over TC (2 mA for 30 min) did not change the average torque and fatigue index of isokinetic knee extension (50 maximum reps at $180°.s^{-1}$) in 20 healthy individuals [53]. Also, a-tDCS over M1 (2 mA for 20 min) did not improve total work and peak torque of knee flexors and extensors (3 sets of 10 reps at 60°.s-1) in 14 healthy individuals. An interesting study was performed by Washabaugh et al. [54] found that performing low-level intermittent quadriceps activity (5% of MIVC for 10 s with 20 s

resting interval) during a-tDCS over M1 (2 mA for 12 min) improved isokinetic knee extension torque compared to receiving tDCS while resting and sham. In this regard, Maeda et al. [55] applied a-tDCS over M1 (2 mA for 10 min) during eccentric strength training of the knee extensors and flexors of the nondominant side in seven sessions (over 3 weeks). The peak torques of knee extension and flexion improved in both groups that received a-tDCS and sham, with no difference between groups. It should be noted that a recent study found increased fatigability with a moderate-to-large effect size of the knee extensors isokinetic fatigue testing (40 maximal reps, $120°.s^{-1}$) with a-tDCS over M1 with 2 mA and 4 mA for 20 min in 16 healthy young adults [56].

Finally, regarding dynamic isotonic muscle strength performance, a series of studies by Lattari and colleagues [57–59] have found positive results on resistance exercise volume (number of repetitions) and RPE. In the first study with a model of exercise closer to the daily training routine, they found a-tDCS over DLPFC (2 mA for 20 min) increased the total number of repetitions for elbow flexion performed with a load of ten repetition maximum (10RM) and also found decreased RPE in ten men experienced with resistance training [58]. Similar results regarding the training volume were presented recently by the same authors using similar tDCS protocol for leg press exercise with 10RM load, but no change for RPE was found with a-tDCS, while c-tDCS increased RPE [59]. They also recently found that combining a-tDCS over DLPFC (2 mA for 20 min) with caffeine or a-tDCS alone increased the total number of repetitions and the former decreased RPE in bench press exercise with 10RM load in 15 young healthy men [57]. Alix-Fages et al. [60] found increased volume, reduced movement speed loss, and decreased RPE performing five sets of repetitions to momentary muscular failure with 75% of one maximum repetition (1RM) after a-tDCS over DLPFC (2 mA for 15 min). Finally, Kamali et al. [61] applied a-tDCS simultaneously over TC and M1 (2 mA for 13 min) and assessed the performance in maximal strength (1RM) and total volume (repetitions × load) in leg extension until momentary failure with 30% of 1RM in 12 experienced bodybuilders (≥2 years of consistent bodybuilding exercise). After real a-tDCS, they found an increased maximal muscle strength (1RM), total volume, decreased RPE, decreased HR, and decreased muscular electrical activity [61]. The results on dynamic isotonic strength seem, so far, to be the most consistent regarding the effects of tDCS on exercise performance.

A summary of the effect of a-tDCS on strength performance was presented in a recent meta-analysis by Lattari et al. [62]. The authors found a small but significant effect of a-tDCS on MIVC (SMD = 0.29; 95% CI = 0.05–0.54) and also a significant effect on muscular endurance with greater TTE in a sustained isometric contraction (MD = 43.66; 95% CI = 29.76–57.55). However, when considering muscular endurance based on the total work (i.e., repetition × sets × load) a non-significant small effect was found (SMD = 0.22; 95% CI = −0.11 to 0.54). It is important to note that while the results on MIVC was based on the inclusion of studies that applied a-tDCS over M1, the results of TTE and total work also included studies applying a-tDCS over DLPFC and TC in the same meta-analysis. Patel et al. [63] found an increased muscle strength (SMD = 0.10; 95% CI = 0.08–0.13) and a trend toward increased TTE (SMD = 0.04; 95% CI = −0.01 to 0.10). However, besides including studies with tDCS over different targets and at different timing (before vs. during), their meta-analyses present high heterogeneity (I^2 = 63.8), especially for the analysis of muscle strength (I^2 = 98.6% and 99.9%). Holgado et al. [64] found a small and significant effect of a-tDCS on objective measures of performance (SMD = 0.36; 95% CI = 0.16–0.56) but included both muscle strength and whole-body dynamic exercise, tDCS over different areas and timing. Finally, Machado et al. [65] analyzed the effect of a-tDCS on TTE in a sustained isometric contraction including in the meta-analysis only studies applying tDCS over M1 and also separated between upper and lower limbs as well as studies that applied tDCS before and during exercise. No significant effect was found for any comparison [65]. Taken together, a-tDCS seems to improve performance in muscle strengthening exercises with a small magnitude, but the level of evidence is still weak.

18.3.2 Whole-Body Endurance Exercise

Endurance performance is an important feature of several sports. To differentiate from localized muscular endurance (which involves low muscle mass and generally single joint), as described in the previous topic, we refer to whole-body endurance performance characterized by dynamic and cyclic exercise that involves multiple joints and large muscle mass. The whole-body endurance tests may be divided into two main groups named closed- and open-loop exercise tests. The former is characterized by a defined endpoint (e.g., 20 km time trial), while the later individuals do not know the exercise endpoint (e.g., time to exhaustion [TTE]). Due to the proximal relationship between whole-body endurance performance with performance in several sports, this physical capacity has been a target of tDCS studies.

Most studies assessing the effects of tDCS on whole-body endurance performance have used open-loop protocol. The first study of this nature was published by Okano et al. [66] who applied a-tDCS over TC (2 mA for 20 min), targeting the left IC, in 10 elite-level cyclists before a maximal incremental test. They found that a-tDCS improved peak power and TTE, as well as decreased RPE and HR in submaximal workloads. Other studies that followed targeted mostly M1. Vitor-Costa et al. [67] applied tDCS over M1 (2 mA for 13 min) in 11 physically active individuals (i.e., who performed physical activities ≥3 times a week for ≥6 months) before performing a TTE test with 80% of peak power. They found improved TTE after a-tDCS compared to c-tDCS and sham, with no effect of c-tDCS. The improvement in TTE in cycling (70% of peak power) has also been corroborated by Angius et al. [68] with bilateral a-tDCS (2 mA for 10 min) in 12 recreationally active participants. Park et al. [69] found improved running performance (80% of the VO2 max load) in 10 trained men after a-tDCS over M1 (1.98 mA for 20 min).

The PFC has also targeted whole-body endurance performance enhancement. Lattari et al. [70] applied a-tDCS over the left DLPFC (2 mA for 20 min) before a TTE test (100% of peak power) in 11 moderately active women (i.e., aerobically active during the last 6 months with a frequency of 3 days per week for 30–90 min) and found longer TTE compared to sham. Recently, Angius et al. [71] used a similar protocol, a-tDCS over the left DLPFC (2 mA) but with a longer duration (30 min) in 12 recreationally trained participants before a TTE test (70% of peak power). Participants were able to cycle for longer durations after a-tDCS, with lower HR and RPE compared to sham. Interestingly, cognitive performance also improved after the TTE test in the a-tDCS condition.

It is important to note that despite the positive results previously reported, some studies, however, have found null results using relatively similar protocols to the previous studies regarding electrode montage, current intensity, and duration with a-tDCS over M1 in cycling, running, and swimming [72–76], a-tDCS over TC in cycling [74], and a-tDCS over left DLPFC [75]. These studies presented samples ranging from 6 to 13 individuals, except for Holgado et al. [75] who assessed 36 trained male cyclists.

Recent meta-analyses have indicated a significant, despite weak, evidence that a-tDCS improves whole-body endurance exercise performance. Machado et al. found that a-tDCS over M1 improved TTE in cycling by 93.4 s (95% CI = 27.4–159.4 s), but a single study presented ~85% of the weight in the meta-analysis. Other meta-analyses have also indicated a positive effect of a-tDCS on whole-body endurance performance with a small effect size (Hedge's g = 0.34, 95% CI = 0.12–0.52) [64] and (SMD = 0.26; 95% CI = 0.07–0.45) [77]. However, these studies have included in the same meta-analysis studies that assessed whole-body and single-joint exercise, strength, and dynamic/cyclical exercise, measures of performance and RPE, and/or tDCS over different areas [64, 77]. Therefore, more studies may still change the current evidence status either showing a null or positive consistent effect. The current evidence indicates that a-tDCS may improve whole-body endurance performance.

18.3.3 Sprint Exercise

Two studies have assessed the effect of tDCS on sprint performance. Sasada et al. [78] compared the effect of tDCS (2 mA for 15 min) over the M1 representation of the lower limbs to another neuromodulatory technique called transcutaneous spinal direct current stimulation (tsDCS), which consists of applied direct current to the spine to modulate spinal neurons activity. The researcher used anodal, cathodal, and sham stimulation before performing a single maximal effort sprint cycling for 30 s under a constant load with a group of 23 athletes from different sports (track and field $n = 13$, basketball $n = 2$, baseball $n = 3$, triathlon $n = 1$, water polo $n = 1$, cycling $n = 1$, lacrosse $n = 1$, and soccer $n = 1$). The authors found that the mean power was greater after a-tDCS compared to c-tDCS, although a-tDCS was not statistically different from sham. Interestingly, cathodal tsDCS also resulted in greater mean power than anodal and sham tsDCS. Note that only 13 individuals received tDCS and 15 received tsDCS.

A recent study by Huang et al. [79] tested the effect of a-tDCS over M1 (2 mA for 20 min) on repeated sprint performance in nine physically active individuals. Participants performed five sprints of 6 s duration with a load of 10% of body weight, interspersed by a 24 s of unloaded cycling between sprints. Their results showed that a-tDCS improved mean power in all sprints, except for the first one. Interestingly, a-tDCS also improved the accuracy in incongruent trials of the Stroop task (inhibitory control) after the sprint task. Hence, despite only two studies that have been published so far, their results suggest that a-tDCS over M1 may improve sprint performance. These results have to be replicated by other studies, especially with larger sample sizes.

18.3.4 Flexibility

Few studies have investigated the effect of tDCS on flexibility. Mizuno and Aramaki [80] applied tDCS (2 mA for 10 min) over Cz (motor representation of the lower limbs) and assessed the wrist and ankle flexibility in 10 healthy men. Cathodal tDCS improved the range of motion of the ankle by 10.5%, but the effect of anodal or sham tDCS was not found [80]. More recently, Henriques et al. [81] assessed the effect of tDCS (2 mA for 20 min) with two montages: (a) cathodal electrode placed horizontally over M1 and anodal electrode over left DLPFC and (b) opposite polarity (anode over M1 and cathode over left DLPFC). c-tDCS over M1 (montage a) improved hip range of motion, while a-tDCS over M1 (montage b) decreased it. Moreover, only c-tDCS over M1 decreased pain perception compared to baseline and also compared to a-tDCS over M1 and sham at post-intervention [81]. This is still a field of study with the preliminary result and certainly warrants further investigation.

18.3.5 Balance

Few studies have assessed the effect of tDCS on measures of balance. Considering that the main focus of the present chapter is on healthy individuals, the results presented so far are found to be mixed. For instance, two studies applied tDCS over the cerebellum and found either unchanged (2.8 mA) [82] or impaired balance performance with c-tDCS (1 mA for 13 min) [83]. A recent systematic review and meta-analysis on the effect of tDCS on postural balance claimed that tDCS may improve balance with the most prominent effects in healthy individuals and individuals with cerebral palsy, and the M1 was the only target with comparable results that yielded a significant result [84]. However, this meta-analysis presents several aspects that warrant mention. First, most comparisons presented high heterogeneity, which limited the number of studies included in the analysis. Second, the general comparison showing positive results included not only young healthy individuals but also patients with cerebral palsy and older adults. Finally, the comparison including only studies with healthy participants was able to compare two studies. Hence, at present, it is difficult to draw any conclusion regarding the effects of tDCS on balance.

18.3.6 Sport-Specific Performance

Despite some of the aforementioned results that may translate into sport-specific performance (e.g., cycling exercise), the direct link with competitive performance is relatively weak. Few studies have tested individuals in conditions closer to their sportive context. Valenzuela et al. [76] found no improvement in 800-m swimming performance in eight elite triathletes after a-tDCS over M1 (2 mA for 20 min). Mesquita et al. [85] applied a-tDCS over M1 (1.5 mA for 15 min) in 19 taekwondo athletes and found a worsened taekwondo-related performance (i.e., reduced number of kicks). These are two recent studies, and testing of tDCS efficacy with more direct measures of sports outcome remain to be tested.

18.3.7 Cognitive Performance

An alternative perspective on the use of tDCS in the exercise/sporting context is the modulation of cognitive performance, which plays a key role in sports performance, especially in team sports. Several recent meta-analyses have shown a positive effect of a-tDCS on some measures of cognitive performance in healthy individuals and neuropsychiatric populations [86–89]. Specifically, a-tDCS over the DLPFC demonstrated to improve working memory (i.e., increased accuracy, faster response times, a lower percentage of error responses) [86, 87], as well as a decrease in response times and an increase in accuracy, in particular, for the executive functioning tasks [88, 89].

An interesting result was reported by Borducchi et al. [90] who tested the effects of 2 mA of a-tDCS over the DLPFC for 10 days on professional athletes (judo [$n = 4$ athletes], swimming [$n = 3$ athletes], and rhythmic gymnastics [$n = 3$ athletes]). They showed an improvement in cognitive performance including a significant improvement in alternated, sustained, and divided attention and in memory scores. More recently, Angius et al. [71] applied a-tDCS over the left DLPFC (2 mA for 30 min) and found increased TTE in cycling exercise at 70% of peak power output and also increased inhibitory control performance in recreationally trained healthy participants. Other studies have also reported improved both exercise and cognitive performance with a-tDCS in repeated sprint [79] and strength exercise [61].

Improved cognitive performance may increase top-down control over the exercise-related body signals and sensations, which could help to ameliorate exercise perception (exertion and pleasure), ultimately generating a better exercise psychological experience, which is related to exercise adherence. Additionally, improved cognitive performance may attenuate the effects of mental fatigue, either due to exhaustive training routine, prolonged exposure to smartphones/computer/tablets, or a hard day of work, also improving psychological responses to exercise and help to maintain performance. A recent study showed improved cognitive response during exercise without a change in performance in a sustained knee extensor isometric contraction at 30% of MVC, after HD-tDCS over the right DLPFC [51].

18.3.8 Recovery Strategy in Athletes

Participation in competitions can result in fatigue and perceptions of soreness while inducing decreased alertness and motivation to train during days postexercise [91]. Altered decision-making, mood disturbances, and motivation changes [92] suggest that a type of predominantly brain-related fatigue should be addressed. In this regard, it was demonstrated that applying tDCS with the anode electrode over the left DLPFC and the cathode over the right DLPFC (bilateral montage) induced beneficial and long-lasting effects on vigilance, reaction time, and aspects of mood which are negatively influenced by fatigue in active-duty military subjects [93]. Indeed, a-tDCS over the left DLPFC has been shown to improve cognitive abilities in healthy individuals and patients. These data, together with reports demonstrating that a-tDCS over the DLPFC results in large amounts

of electric current in the anterior insula [94] and to produce significant peaks of electric current in PFC [95], suggest that applying a bilateral tDCS montage (F3-F4) over the DLPFC might emerge as an alternative recovery strategy to be adopted in professional athletes as well. Among the few studies that have used the application of the tDCS as a recovery strategy in professional athletes [96], applied a bilateral DLPFC montage (+F3/-F4; 2 mA, 20 min) among a sample of professional male soccer athletes following official matches and reported improvements in perceived well-being and cardiac autonomic control with both a-tDCS and sham conditions. In another investigation [97], examined the effect of tDCS (2 mA for 20 minutes; +F3/-F4 montage) combined with a recovery training session on the well-being and self-perceived recovery of professional world-class female soccer players after official matches. The results of this study suggest that a-tDCS (+F3/-F4 montage) combined with a recovery training session may slightly improve perceived well-being beyond the level of changes after only the recovery training session. In conjunction, the results of these studies suggest the potential for adopting the tDCS as a recovery strategy in athletes. However, further study is still needed prior to its widely adoption in the sports setting.

If tDCS can improve the athletes' recovery from competitions, it could also be used during the training process as a whole not only aiming at improving short-term recovery but also to counteract the sports-related stress and non-sports environment in which athletes are submitted constantly during many years. The stress imposed on elite-level athletes may come from various sources, including uncontrollable conditions, which adds a higher complexity to the phenomena. Taking into account the definition suggested by McEwen [98], the "type" of the stress imposed on the individual is one that could be defined as the "toxic stress." McEwen [98] explains that this "toxic stress" would occur "when something bad happens," in addition to a feeling of a lack of personal resources or support systems to deal with that, and, as a consequence, the individual would have a sense that he/she does not have any control over it. If the situation is not interrupted (i.e., not resolved), mental and physical health problems might occur over time.

The concept of allostatic load appropriately describes this condition and its consequences. The allostatic load refers to the cumulative changes in the body and brain, as a result of dysregulation and overuse of the so-called "mediators" of allostasis. Allostasis is defined as a process aimed to maintain physiological stability by changing parameters (mediators) of its internal milieu in order to match them to environmental demands [99]. The mediators (i.e., cortisol, catecholamines, and cytokines) aid the organic adaptation, responding ("turned on") when facing a challenge, and in "normal" conditions, they are turned off due to the end of the challenge. While these mediators help us to adapt, a failure to habituate to a repetition of the same stressor, or in case of prolonged response due to a delayed shutdown [100], for example, could cause unhealthy changes in the brain and body.

A stressful and sustained experience leading to increases in allostatic load would therefore result in these unhealthy changes in brain and body, considering that the brain is the key organ of the stress response [100]. These changes could in turn impact on neurons in brain areas, such as the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens [98]. Due to these integrated and complex processes, it is imperative to seek strategies to minimize stress from participating in professional sports settings.

Indeed, possible changes in athletes' behavior due to stressful and sustained experiences might be attributed to changes in brain areas involved in the activity of the mesolimbic dopaminergic (DA) system. Felger and Treadway [101] proposed that deficits in motivation are associated with changes in corticostriatal neurocircuitry, consistent with abnormalities in mesolimbic and mesostriatal dopamine (DA). A primary function of the mesolimbic DA system is to determine motivational drive that can be understating as an interpretation from the brain of the value of investing effort in the rewarding pursuits [102].

The "reward system" of the brain and the dopamine neurotransmitters play a key role in

the motivation-related behavior and decision-making related to mental exertion and fatigue. The brain reward circuit consists of dopaminergic projections from the ventral tegmental area to the nucleus accumbens (NAc). The NAc has been implicated in several behavioral functions related to motivation [103]; indeed, dopaminergic projections have interactive connections with the basolateral amygdala and prefrontal cortex [104]. Boksem and Tops [102] suggested that dopaminergic pathways and the basal ganglia are major efferent targets of the anterior cingulate cortex, orbitofrontal cortex, basolateral amygdala, and insula and that the feeling of fatigue corresponds to a drive to abandon behavior when energetical costs continue to exceed perceived rewards of a given goal-directed behavior.

Regarding the activity of the DA system, a recent double-blind and sham-controlled study with 32 healthy individuals applied a-tDCS over the DLPFC while measuring brain activity with a positron emission tomography scan using [^{11}C]raclopride binding [105]. They found that a-tDCS caused a significant decrease in the [^{11}C] raclopride binding potential ratio in the striatum, suggesting an increase in extracellular dopamine in the striatum's reward–motivation network area [105]. Additionally, Mondino et al. [106] had previously shown that applying bilateral tDCS montage (F3–F4) induced beneficial emotional and attentional processing in healthy subjects. Moreover, clinical improvements in psychiatric conditions involving dopamine transmission abnormalities, such as major depressive disorder [107] and the cognitive alterations in Parkinson's disease were also demonstrated [108].

Alterations in the neuroplasticity of the brain regions such as the prefrontal cortex, amygdala, and hippocampus, for instance, can affect the emotional responses, recovery, and coping [100]. Due to the critical role of the brain structures associated with motivated behavior and decision-making, and their involvement with the issues related to exertion, fatigue, and cognitive features, it is reasonable to propose that neuromodulation, notably, tDCS, might be used as a strategy to ameliorate the athletes feeling of fatigue and recovery while increasing their motivation, and likely positively affecting the cognitive process, which could aid them in coping with the stress of the professional setting. This could possibly help reduce the risks of the accumulated allostatic load, related to the permanent stressful experience, that could generate unhealthy conditions in the long term. This hypothesis, however, remains to be tested.

18.3.9 Gaze Behavior

Another alternative tDCS could improve sport performance is by changing the ocular activity or gaze behavior. The gaze behavior/pattern has been investigated in sports for a long period and provided interesting results [109]. For instance, expert athletes differ from novice athletes regarding specific sports parameter [110]. In fact, there are several suggestions in the sport setting as how one could control his/her gaze behavior to increase the likelihood of a successful sportive action such as where to look at before/while kicking a ball toward the goal or shooting a ball to the basket, especially in sports that involves aiming to a target. With advanced technology, recent studies have addressed the issue of ocular behavior using eye-tracking devices. In fact, there is an intimate relationship between the ocular behavior and cognitive processes. The quiet eye is a phenomenon that describes the relationship between ocular behavior and attentional process, which frequently occurs in elite athletes. The quiet eye is defined as the final fixation or tracking gaze that is located on a specific location or object in the task environment within 3° or less of the visual angle for a minimum of 100 milliseconds [111]. Studies indicate that the quiet eye in elite performers occurs earlier and lasts longer compared to lower skilled individual [112, 113], which may represent a specific adaptation to long-term sports training or a feature of better performers. In this regard, the PFC is a source of top-down signals that bias selection in early visual areas favoring the attended features plays an important role in attention processing and skill [114]. Moreover, subregions of the PFC, namely, the DLPFC, interact with posterior visual areas

which also contribute to the modulation of attention [114, 115]. Hence, considering that a-tDCS over the DLPFC may improve cognitive performance in both clinical and healthy population, as discussed earlier (see Sect. 18.3.7), it could be speculated that applying tDCS over the DLPFC could improve attention, change the gaze behavior, and improve sportive performance, for instance, in tasks such as shootings in basketball. This is also a hypothesis that needs to be experimentally tested.

18.3.10 Perceptual Responses

The modulation of subjective perception by tDCS may have a promising impact on exercise experience and performance. One of the first studies to demonstrate the modulation of exercise-related perception was performed by Okano et al. [66] who found decreased RPE in submaximal intensities of a maximal incremental test in professional cyclists after a-tDCS (2 mA for 20 min) over the left TC, targeting the left IC. Decreased RPE in dynamic cycling whole-body exercise was also found in the TTE test [68, 70], dynamic resistance exercise [58, 60], isometric exercise [49] with tDCS targeting M1, and DLPFC. On the other hand, other studies did not find a positive effect of tDCS on RPE in cycling [72, 74, 75, 116], running [73], swimming [76] with tDCS targeting either M1, TC, or DLPFC. Interestingly, improved exercise performance has been reported even in the absence of changes in RPE [67, 69].

While RPE is a measure present in several studies, fewer studies have assessed the effect of tDCS on the affective response to exercise (pleasure/displeasure), and yet, there is no report on other behavioral measures that could be, for example, related to sensations associated with recovery from exercise. This approach could be tested in future studies to investigate the effect of tDCS on perceived fatigue and well-being in athletes. Considering that the affective responses to exercise influences future exercise behavior [7, 8], improving the affective response to exercise using tDCS could help improve exercise adherence, which is extremely important considering the role of physical activity and exercise in the public health as well as the fact that the majority of the population do not exercise regularly. So far, however, only two studies assessed the effect of tDCS on the affective response to exercise. The first study was performed by Okano et al. [116] who applied a-tDCS (2 mA for 20 min) over the left TC, targeting the left IC, before performing 30 min of exercise with constant load at a vigorous intensity (81.68 ± 6.37% of HR_{max}) in 13 sedentary men. There was no change in the affective responses, RPE, HR, or heart rate variability measured every 5 minutes [116]. The second study applied a-tDCS over M1 (2 mA for 20 min) before a maximal incremental test in 13 healthy recreational endurance runners and found no effect of tDCS on the affective response or RPE [73]. However, one study reported a reduction in negative affect at rest in young healthy individuals (1 mA for 20 min over left DLPFC) [117].

Interestingly, there were some reports of positive changes in mood, specifically vigor, in eight elite triathletes (2 mA for 20 min over M1) [76] and a decrease in depressive symptoms in 10 professional athletes (judo, swimming, rhythmic gymnastics) (2 mA for 20 min over left DLPFC) [90]. Also, no effect of a-tDCS (2 mA for 20 min over M1) on mood in 12 physically active individuals has been reported [67].

The reduction in RPE may be explained by the fact that a meta-analytical evidence level has shown that a-tDCS over M1 and the primary sensory cortex (S1) have a positive effect on pain threshold and sensory threshold in both clinical and healthy individuals [29]. Interestingly, c-tDCS over M1 and S1 has also resulted in an improvement in pain and sensory thresholds [118]. This mechanism could also apply for a possible improvement in the affective response, but the currently limited research found no change in affective response during exercise. In addition, a recent study reported that tDCS over the left DLPFC (2 mA for 20 min) did not enhance endurance exercise performance in a sustained isometric contraction of the leg extensors (25% of MVC) nor manipulate perceptions of pain intensity and affect (i.e., unpleasantness) [119].

18.4 Safety

tDCS has been demonstrated to be a safe technique [21, 120]. In fact, a recent update on tDCS safety showed that the use of conventional tDCS protocols in human trials (≤40 min, ≤4 milliamperes, ≤7.2 Coulombs) has not produced any reports of a serious adverse effect or irreversible injury across over 33,200 sessions and 1000 subjects with repeated sessions, which includes a wide variety of subjects, including persons from potentially vulnerable populations [21]. The contraindications for tDCS may vary from study to study, but most commonly includes metallic implants, epilepsy or history of epilepsy at family, seizure or history of seizure, neurologic disease, cognitive or consciousness disturbance, psychiatric disease, use of neuropsychoactive drugs, pacemaker, pregnancy, previous stroke, uncontrolled medical condition, skin or skull abnormalities, brain injury, surgery to the head, adverse reaction to TMS/tDCS [121, 122]. A safety screening questionnaire may be found in Villamar et al.'s study [121].

A study assessing 567 sessions of tDCS over motor and nonmotor areas in 102 healthy individuals (75.5%) and patients (24.5%) found that, during tDCS, a mild tingling sensation was the most common reported adverse effect (70.6%), followed by moderate fatigue (35.3%) and light itching sensation under the stimulation electrodes (30.4%) [123]. After tDCS, headache (11.8%), nausea (2.9%), and insomnia (0.98%) were reported fairly infrequently [123]. Examples of tools for assessing the sensations related to tDCS, side effects, adverse effects, and blinding of tDCS may be found in Villamar et al. [121] or Fertonani et al. [124]. The sensations related to tDCS (painfulness and unpleasantness of any scalp sensations) may also be assessed using numeric rating scales (e.g., 0 = no pain to 10 = worst pain imaginable) [125].

18.5 Limitations and Future Perspectives

At present, there is a huge variability in the tDCS technique. Several studies failed to present a clear and consistent rationale for using tDCS for a specific purpose, as well as the reason for using given tDCS parameters such as electrode montage (i.e., positioning), electrode type, electrode size, current intensity, and duration. This makes it difficult to compare studies as well to suggest specific parameters. For instance, Machado et al. [65] in a systematic review of the effects of tDCS on exercise performance found that the current density (i.e., current intensity × electrode area) ranged from 0.043 to 0.44 mA/cm^2 (mean ± SD = 0.104 ± 0.110 mA/cm^2); this represents a coefficient of variation of 105.8%. Furthermore, the role of the position and size of the return electrode has also been overlooked [126]. Especially considering that studies have demonstrated the position of the return electrode influenced the tDCS-induced performance enhancement effect [49].

Moreover, recent studies have shown that there is a large variability in response to tDCS. tDCS has long been assumed to cause a polarity-dependent effect on cortical excitability, especially due to the previous report on the effects of tDCS on corticospinal excitability [127, 128]. However, a more detailed investigation of individual responses to tDCS has shown that this polarity-dependent change does not always occur expectedly. For instance, López-Alonso et al. [129] assessed the effects of a-tDCS over the motor cortex (1 mA for 13 min) on corticospinal excitability and found that only 45% responded as expected to the stimulation (i.e., increased corticospinal excitability). Similarly, Wiethoff et al. [130] applied a-tDCS and c-tDCS over the motor cortex (2 mA for 10 min) and found that 50% of the individuals had poor or absent responses. In addition, from those who responded to tDCS, only 36% of the participants showed the "classical" polarity-dependent effect (anodal excites and cathodal inhibits), while 21% showed an inverted "classical" response (anodal inhibits and cathodal excites). For 38%, both polarities were facilitatory, and for 5%, both polarities were inhibitory [130]. The source of this high variability has also been studied [131]. Li et al. [131], in a literature review, showed that anatomical characteristics, functional organization of local circuits, the baseline level of function, individual

differences in task-related neurophysiological responses, psychological status, levels of neurotransmitters and receptor sensitivity, baseline neurophysiological state, genetics, development, and aging, would affect tDCS effectiveness while contributing to creating large interindividual variability in response to tDCS.

Considering the present limitations, future investigations are urged to include forms of predicting the effects of tDCS such as computational modeling, preferably individualized [132, 133]. Readers may refer to Chapter 4 on "Computer-Based Models of tDCS and tACS" and some interesting references on this topic [94, 134]. Also, the online correction of tDCS using neuroimaging techniques such as EEG is also desirable considering the data-driven approach [135, 136]. Moreover, considering the variables that may influence the effect of tDCS on exercise performance, an important advance in the field will be also measures of predictors of the effect of tDCS on exercise performance in order to identify potential "best" candidates for tDCS.

Moreover, there is a linear relationship between the current intensity and the rate of neuronal polarization as well as the current duration. However, studies with humans have failed to prove the linear relationship for both current intensity and duration [137, 138]. For this reason and safety concerns, most studies have tested the effects of tDCS with current intensity up to 2 mA and with durations up to 20 min. In fact, studies using tDCS for performance enhancement have tested current intensities of 1.5 or 2 mA and duration ranging from 10 to 20 min [65]. More recently, however, studies have expanded the current intensity and duration. For instance, the current intensity of up to 4 mA has been suggested and tested [56, 139].

Most studies available in the literature are based on single-session tDCS. Despite the positive results shown so far, it is likely that if tDCS-induced plasticity is to occur, it would be more probable to occur with repeated exposure to the stimulation (i.e., multiple sessions). For instance, it has been shown that five sessions of tDCS over the left DLPFC decreased alcoholic relapse 6 months later [140]. Although in a different context, this result demonstrates that multiple sessions of tDCS may induce long-lasting plasticity, which has to be tested in the context of exercise. Another important limitation is the low sample sizes which sometimes are as little as six or eight participants. A systematic review found that the mean and standard deviation of the sample size per study was 14.4 ± 5.7 (from 6 to 24 participants) with a median of 12 individuals [65]. Recently a study was published with 33 individuals, which is by far the largest sample size [75].

Recent studies have also suggested that the induction of long-term potentiation-like (LTP) plasticity is also dependent on a brain state so that the pairing of tDCS with a stimulus improves tDCS-induced plasticity [141–143]. In this regard, the use of tDCS paired with a physical training/task (i.e., online) may also be beneficial, but it is still poorly investigated. A previous study found that performing low-level intermittent quadriceps activity (5% of MIVC for 10 s with 20 s resting interval) during a-tDCS over M1 (2 mA for 12 min) improved isokinetic knee extension torque compared to receiving tDCS while resting and sham [54]. Another study applied tDCS online during a sustained submaximal contraction (at 20% of MVC) of the elbow flexors until task failure and found no change when assessing the entire sample [47]. However, a subgroup analysis showed a 31% long TTF in the group where task failure occurred prior to the termination of tDCS compared to the group where failure occurred after tDCS had finished [47]. More studies are needed to replicate these findings and expand on other exercise types.

It is noteworthy that a recognized feature of the so-called conventional tDCS, which uses large electrode pads with a high contact area with the scalp, induced a diffused electric field that results in stimulation of both target and nontarget areas (i.e., low focality), sometimes in a non-predicted fashion [23, 144]. This represents an important limitation that could explain the mixed findings in the previous studies. Recently, a new tDCS technique named high-definition tDCS (HD-tDCS) showed to improve focality with gyri precise stimulation [144] and provide modulation of corticospinal excitability of greater magnitude and longer duration of its aftereffects (>2 h and <6 h) [23]. However, no study has so far tested

whether this improved focality, greater modulation of corticospinal excitability, and prolonged duration would translate into improved motor performance. A practical tutorial on the use of HD-tDCS including a video may be found elsewhere [121].

Finally, there are other forms of transcranial electrical stimulation (tES) such as transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) that could also be used as stand-alone techniques or can be used to prime the effects of other movement training to improve motor/cognitive performance [145]. However, to the best of the authors' knowledge, there is no study performed so far evaluating the effects of these techniques on exercise performance.

18.6 Conclusion

tDCS is a promising tool for the exercise science field with a great beneficial potential for improving the exercise-related perception (perceived exertion and pleasure) which may impact on exercise adherence for a nonathletic sample and also with a potential to improve exercise performance in sporting setting. It is noteworthy that so far there is no solid evidence of its positive effect and systematic reviews and meta-analysis have shown only weak evidence of its effects on some measures of exercise performance and perception. Considering that tDCS in exercise science is a fast-growing field, it is possible that in the near future it could be elucidated whether tDCS works, as well as to whom, when, for what, and how tDCS works. Also, other forms of tES such as tACS and tRNS are still to be tested in the exercise field.

References

1. Liu R, Sui X, Laditka JN, Church TS, Colabianchi N, Hussey J, Blair SN. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. Med Sci Sports Exerc. 2012;44:253–9.
2. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens. 2012;30:1277–88.
3. Zhao G, Li C, Ford ES, Fulton JE, Carlson SA, Okoro CA, Wen XJ, Balluz LS. Leisure-time aerobic physical activity, muscle-strengthening activity and mortality risks among US adults: the NHANES linked mortality study. Br J Sports Med. 2014;48:244–9.
4. Herold F, Törpel A, Schega L, Müller NG. Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements – a systematic review. Eur Rev Aging Phys Act. 2019;16:10.
5. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, Lancet Physical Activity Series Working Group. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380:247–57.
6. Clarke J, Colley R, Janssen I, Tremblay MS. Accelerometer-measured moderate-to-vigorous physical activity of Canadian adults, 2007 to 2017. Health Rep. 2019;30:3–10.
7. Rhodes RE, Kates A. Can the affective response to exercise predict future motives and physical activity behavior? A systematic review of published evidence. Ann Behav Med. 2015;49:715–31.
8. Rhodes RE, Lubans DR, Karunamuni N, Kennedy S, Plotnikoff R. Factors associated with participation in resistance training: a systematic review. Br J Sports Med. 2017;51:1466–72.
9. Silver MD. Use of ergogenic aids by athletes. J Am Acad Orthop Surg. 2001;9:61–70.
10. Christensen PM, Shirai Y, Ritz C, Nordsborg NB. Caffeine and Bicarbonate for Speed. A Meta-Analysis of Legal Supplements Potential for Improving Intense Endurance Exercise Performance. Front Physiol. 2017;8:240.
11. Taylor JL, Amann M, Duchateau J, Meeusen R, Rice CL. Neural contributions to muscle fatigue: from the brain to the muscle and back again. Med Sci Sports Exerc. 2016;48:2294–306.
12. Marcora SM. Do we really need a central governor to explain brain regulation of exercise performance? Eur J Appl Physiol. 2008;104:929–31; author reply 933
13. Noakes TD. Time to move beyond a brainless exercise physiology: the evidence for complex regulation of human exercise performance. Appl Physiol Nutr Metab. 2011;36:23–35.
14. Noakes TD. Fatigue is a brain-derived emotion that regulates the exercise behavior to ensure the protection of whole body homeostasis. Front Physiol. 2012;3:82.
15. Noakes TD, St Clair Gibson A, Lambert EV. From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans: summary and conclusions. Br J Sports Med. 2005;39:120–4.
16. Holmes P, Calmels C. A neuroscientific review of imagery and observation use in sport. J Mot Behav. 2008;40:433–45.
17. Colzato LS, Kibele A. How different types of meditation can enhance athletic performance depending

on the specific sport skills. J Cogn Enhanc. 2017;1:122–6.
18. McCormick A, Meijen C, Marcora S. Psychological determinants of whole-body endurance performance. Sports Med. 2015;45:997–1015.
19. Galloway SM. The effect of biofeedback on tennis service accuracy. Int J Sport Exer Psychol. 2011;9:251–66.
20. Paul M, Garg K, Singh Sandhu J. Role of biofeedback in optimizing psychomotor performance in sports. Asian J Sports Med. 2012;3:29–40.
21. Bikson M, Grossman P, Thomas C, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimulat. 2016;9:641–61.
22. Dissanayaka T, Zoghi M, Farrell M, Egan GF, Jaberzadeh S. Does transcranial electrical stimulation enhance corticospinal excitability of the motor cortex in healthy individuals? A systematic review and meta-analysis. Eur J Neurosci. 2017;46:1968–90.
23. Kuo H-I, Bikson M, Datta A, Minhas P, Paulus W, Kuo M-F, Nitsche MA. Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimulat. 2013;6:644–8.
24. Davis NJ. Neurodoping: brain stimulation as a performance-enhancing measure. Sports Med. 2013;43:649–53.
25. Mauger AR. Fatigue is a pain-the use of novel neurophysiological techniques to understand the fatigue-pain relationship. Front Physiol. 2013;4:104.
26. Scheef L, Jankowski J, Daamen M, et al. An fMRI study on the acute effects of exercise on pain processing in trained athletes. Pain. 2012;153:1702–14.
27. Stevens CJ, Mauger AR, Hassmèn P, Taylor L. Endurance performance is influenced by perceptions of pain and temperature: theory, applications and safety considerations. Sports Med. 2018;48:525–37.
28. Stepniewska I, Preuss TM, Kaas JH. Thalamic connections of the dorsal and ventral premotor areas in New World owl monkeys. Neuroscience. 2007;147:727–45.
29. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clin Neurophysiol. 2014;125:1847–58.
30. Brasil-Neto JP. Motor cortex stimulation for pain relief: do corollary discharges play a role? Front Hum Neurosci. 2016;10:323.
31. Robertson CV, Marino FE. A role for the prefrontal cortex in exercise tolerance and termination. J Appl Physiol. 2016;120:464–6.
32. Pageaux B. The psychobiological model of endurance performance: an effort-based decision-making theory to explain self-paced endurance performance. Sports Med. 2014;44:1319–20.
33. Van Cutsem J, Marcora S, De Pauw K, Bailey S, Meeusen R, Roelands B. The effects of mental fatigue on physical performance: a systematic review. Sports Med. 2017;47:1569–88.
34. Brown DMY, Graham JD, Innes KI, Harris S, Flemington A, Bray SR. Effects of prior cognitive exertion on physical performance: a systematic review and meta-analysis. Sports Med. 2020;50:497–529.
35. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42:1727–32.
36. Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. NeuroImage. 2008;42:169–77.
37. Craig ADB. How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10:59–70.
38. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002;3:655–66.
39. Ramalho Oliveira BR, Viana BF, Pires FO, Júnior Oliveira M, Santos TM. Prediction of affective responses in aerobic exercise sessions. CNS Neurol Disord Drug Targets. 2015;14:1214–8.
40. Elsangedy HM, Nascimento PHD, Machado DGS, Krinski K, Hardcastle SJ, DaSilva SG. Poorer positive affect in response to self-paced exercise among the obese. Physiol Behav. 2018;189:32–9.
41. Zénon A, Sidibé M, Olivier E. Disrupting the supplementary motor area makes physical effort appear less effortful. J Neurosci. 2015;35:8737–44.
42. Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A. Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci. 2007;26:242–9.
43. Abdelmoula A, Baudry S, Duchateau J. Anodal transcranial direct current stimulation enhances time to task failure of a submaximal contraction of elbow flexors without changing corticospinal excitability. Neuroscience. 2016;322:94–103.
44. Hazime FA, da Cunha RA, Soliaman RR, Romancini ACB, Pochini A de C, Ejnisman B, Baptista AF. Anodal transcranial direct current stimulation (tDCS) increases isometric strength of shoulder rotators muscles in handball players. Int J Sports Phys Ther. 2017;12:402–7.
45. Kan B, Dundas JE, Nosaka K. Effect of transcranial direct current stimulation on elbow flexor maximal voluntary isometric strength and endurance. Appl Physiol Nutr Metab. 2013;38:734–9.
46. Muthalib M, Kan B, Nosaka K, Perrey S. Effects of transcranial direct current stimulation of the motor cortex on prefrontal cortex activation during a neuromuscular fatigue task: an fNIRS study. Adv Exp Med Biol. 2013;789:73–9.
47. Williams PS, Hoffman RL, Clark BC. Preliminary evidence that anodal transcranial direct current stimulation enhances time to task failure of a sustained submaximal contraction. PLoS One. 2013;8:e81418.
48. Radel R, Tempest G, Denis G, Besson P, Zory R. Extending the limits of force endurance:

stimulation of the motor or the frontal cortex? Cortex. 2017;97:96–108.
49. Angius L, Pageaux B, Hopker J, Marcora SM, Mauger AR. Transcranial direct current stimulation improves isometric time to exhaustion of the knee extensors. Neuroscience. 2016;339:363–75.
50. Flood A, Waddington G, Keegan RJ, Thompson KG, Cathcart S. The effects of elevated pain inhibition on endurance exercise performance. PeerJ. 2017;5:e3028.
51. Denis G, Zory R, Radel R. Testing the role of cognitive inhibition in physical endurance using high-definition transcranial direct current stimulation over the prefrontal cortex. Hum Mov Sci. 2019;67:102507.
52. Sales MM, De Sousa CV, Browne RAV, Fontes EB, Olher RRV, Ernesto C, Simões HG. Transcranial direct current stimulation improves muscle isokinetic performance of young trained individuals. Med Sport. 2016;69:1–10.
53. Ciccone AB, Deckert JA, Schlabs CR, Tilden MJ, Herda TJ, Gallagher PM, Weir JP. Transcranial direct current stimulation of the temporal lobe does not affect high-intensity work capacity. J Strength Cond Res. 2019;33:2074–86.
54. Washabaugh EP, Santos L, Claflin ES, Krishnan C. Low-level intermittent quadriceps activity during transcranial direct current stimulation facilitates knee extensor force-generating capacity. Neuroscience. 2016;329:93–7.
55. Maeda K, Yamaguchi T, Tatemoto T, Kondo K, Otaka Y, Tanaka S. Transcranial direct current stimulation does not affect lower extremity muscle strength training in healthy individuals: a triple-blind, sham-controlled study. Front Neurosci. 2017;11:179.
56. Workman CD, Kamholz J, Rudroff T. Increased leg muscle fatigability during 2 mA and 4 mA transcranial direct current stimulation over the left motor cortex. Exp Brain Res. 2020;238:333–43.
57. Lattari E, Vieira LAF, Oliveira BRR, Unal G, Bikson M, de Mello Pedreiro RC, Marques Neto SR, Machado S, Maranhão-Neto GA. Effects of transcranial direct current stimulation with caffeine intake on muscular strength and perceived exertion. J Strength Cond Res. 2019;33:1237–43.
58. Lattari E, Andrade ML, Filho AS, Moura AM, Neto GM, Silva JG, Rocha NB, Yuan T-F, Arias-Carrión O, Machado S. Can transcranial direct current stimulation improve the resistance strength and decrease the rating perceived scale in recreational weight-training experience? J Strength Cond Res. 2016;30:3381–7.
59. Lattari E, Rosa Filho BJ, Fonseca Junior SJ, Murillo-Rodriguez E, Rocha N, Machado S, Maranhão Neto GA. Effects on volume load and ratings of perceived exertion in individuals' advanced weight training after transcranial direct current stimulation. J Strength Cond Res. 2020;34:89–96.
60. Alix-Fages C, García-Ramos A, Calderón-Nadal G, Colomer-Poveda D, Romero-Arenas S, Fernández-Del-Olmo M, Márquez G. Anodal transcranial direct current stimulation enhances strength training volume but not the force-velocity profile. Eur J Appl Physiol. 2020; https://doi.org/10.1007/s00421-020-04417-2.
61. Kamali A-M, Saadi ZK, Yahyavi S-S, Zarifkar A, Aligholi H, Nami M. Transcranial direct current stimulation to enhance athletic performance outcome in experienced bodybuilders. PLoS One. 2019;14:e0220363.
62. Lattari E, Oliveira BRR, Monteiro Júnior RS, Marques Neto SR, Oliveira AJ, Maranhão Neto GA, Machado S, Budde H. Acute effects of single dose transcranial direct current stimulation on muscle strength: a systematic review and meta-analysis. PLoS One. 2018;13:e0209513.
63. Patel R, Ashcroft J, Patel A, Ashrafian H, Woods AJ, Singh H, Darzi A, Leff DR. The impact of transcranial direct current stimulation on upper-limb motor performance in healthy adults: a systematic review and meta-analysis. Front Neurosci. 2019;13:1213.
64. Holgado D, Vadillo MA, Sanabria D. The effects of transcranial direct current stimulation on objective and subjective indexes of exercise performance: a systematic review and meta-analysis. Brain Stimulat. 2019;12:242–50.
65. Machado DG da S, Unal G, Andrade SM, Moreira A, Altimari LR, Brunoni AR, Perrey S, Mauger AR, Bikson M, Okano AH. Effect of transcranial direct current stimulation on exercise performance: a systematic review and meta-analysis. Brain Stimulat. 2019;12:593–605.
66. Okano AH, Fontes EB, Montenegro RA, Farinatti P de TV, Cyrino ES, Li LM, Bikson M, Noakes TD. Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. Br J Sports Med. 2015;49:1213–8.
67. Vitor-Costa M, Okuno NM, Bortolotti H, Bertollo M, Boggio PS, Fregni F, Altimari LR. Improving cycling performance: transcranial direct current stimulation increases time to exhaustion in cycling. PLoS One. 2015;10:e0144916.
68. Angius L, Mauger AR, Hopker J, Pascual-Leone A, Santarnecchi E, Marcora SM. Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. Brain Stimulat. 2018;11:108–17.
69. Park S-B, Sung DJ, Kim B, Kim S, Han J-K. Transcranial direct current stimulation of motor cortex enhances running performance. PLoS One. 2019;14:e0211902.
70. Lattari E, de Oliveira BS, Oliveira BRR, de Mello Pedreiro RC, Machado S, Neto GAM. Effects of transcranial direct current stimulation on time limit and ratings of perceived exertion in physically active women. Neurosci Lett. 2018;662:12–6.
71. Angius L, Santarnecchi E, Pascual-Leone A, Marcora SM. Transcranial direct current stimulation over the left dorsolateral prefrontal cortex improves inhibitory control and endurance performance in healthy individuals. Neuroscience. 2019;419:34–45.

72. Angius L, Hopker JG, Marcora SM, Mauger AR. The effect of transcranial direct current stimulation of the motor cortex on exercise-induced pain. Eur J Appl Physiol. 2015;115:2311–9.
73. Baldari C, Buzzachera CF, Vitor-Costa M, Gabardo JM, Bernardes AG, Altimari LR, Guidetti L. Effects of transcranial direct current stimulation on psychophysiological responses to maximal incremental exercise test in recreational endurance runners. Front Psychol. 2018;9:1867.
74. Barwood MJ, Butterworth J, Goodall S, House JR, Laws R, Nowicky A, Corbett J. The effects of direct current stimulation on exercise performance, pacing and perception in temperate and hot environments. Brain Stimulat. 2016;9:842–9.
75. Holgado D, Zandonai T, Ciria LF, Zabala M, Hopker J, Sanabria D. Transcranial direct current stimulation (tDCS) over the left prefrontal cortex does not affect time-trial self-paced cycling performance: evidence from oscillatory brain activity and power output. PLoS One. 2019;14:e0210873.
76. Valenzuela PL, Amo C, Sánchez-Martínez G, Torrontegi E, Vázquez-Carrión J, Montalvo Z, Lucia A, de la Villa P. Enhancement of mood but not performance in elite athletes with transcranial direct-current stimulation. Int J Sports Physiol Perform. 2019;14:310–6.
77. Alix-Fages C, Romero-Arenas S, Castro-Alonso M, Colomer-Poveda D, Río-Rodriguez D, Jerez-Martínez A, Fernandez-Del-Olmo M, Márquez G. Short-term effects of anodal transcranial direct current stimulation on endurance and maximal force production. A systematic review and meta-analysis. J Clin Med. 2019; https://doi.org/10.3390/jcm8040536.
78. Sasada S, Endoh T, Ishii T, Komiyama T. Polarity-dependent improvement of maximal-effort sprint cycling performance by direct current stimulation of the central nervous system. Neurosci Lett. 2017;657:97–101.
79. Huang L, Deng Y, Zheng X, Liu Y. Transcranial direct current stimulation with halo sport enhances repeated sprint cycling and cognitive performance. Front Physiol. 2019;10:118.
80. Mizuno T, Aramaki Y. Cathodal transcranial direct current stimulation over the Cz increases joint flexibility. Neurosci Res. 2017;114:55–61.
81. Henriques IAD, Lattari E, Torres G, Rodrigues GM, Oliveira BRR, Neto GAM, Neto SRM, Machado S. Can transcranial direct current stimulation improve range of motion and modulate pain perception in healthy individuals? Neurosci Lett. 2019;707:134311.
82. Steiner KM, Thier W, Batsikadze G, Ludolph N, Ilg W, Timmann D. Lack of effects of a single session of cerebellar transcranial direct current stimulation (tDCS) in a dynamic balance task. J Neurol. 2020;267:1206–8.
83. Foerster Á, Melo L, Mello M, Castro R, Shirahige L, Rocha S, Monte-Silva K. Cerebellar transcranial direct current stimulation (ctDCS) impairs balance control in healthy individuals. Cerebellum. 2017;16:872–5.
84. de Moura MCDS, Hazime FA, Marotti Aparicio LV, Grecco LAC, Brunoni AR, Hasue RH. Effects of transcranial direct current stimulation (tDCS) on balance improvement: a systematic review and meta-analysis. Somatosens Mot Res. 2019;36:122–35.
85. Mesquita PHC, Lage GM, Franchini E, Romano-Silva MA, Albuquerque MR. Bi-hemispheric anodal transcranial direct current stimulation worsens taekwondo-related performance. Hum Mov Sci. 2019;66:578–86.
86. Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 2014;86:1–9.
87. Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimulat. 2016;9:197–208.
88. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimulat. 2016;9:501–17.
89. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt M-A. The effect of the interval-between-sessions on prefrontal transcranial direct current stimulation (tDCS) on cognitive outcomes: a systematic review and meta-analysis. J Neural Transm. 2016;123:1159–72.
90. Borducchi DMM, Gomes JS, Akiba H, Cordeiro Q, Borducchi JHM, Valentin LSS, Borducchi GM, Dias ÁM. Transcranial direct current stimulation effects on athletes' cognitive performance: an exploratory proof of concept trial. Front Psych. 2016;7:183.
91. Brownstein CG, Dent JP, Parker P, Hicks KM, Howatson G, Goodall S, Thomas K. Etiology and recovery of neuromuscular fatigue following competitive soccer match-play. Front Physiol. 2017;8:831.
92. Rattray B, Argus C, Martin K, Northey J, Driller M. Is it time to turn our attention toward central mechanisms for post-exertional recovery strategies and performance? Front Physiol. 2015;6:79.
93. McIntire LK, McKinley RA, Nelson JM, Goodyear C. Transcranial direct current stimulation versus caffeine as a fatigue countermeasure. Brain Stimulat. 2017;10:1070–8.
94. DaSilva AF, Truong DQ, DosSantos MF, Toback RL, Datta A, Bikson M. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. Front Neuroanat. 2015;9:89.
95. Tabibnia G, Creswell JD, Kraynak T, Westbrook C, Julson E, Tindle HA. Common prefrontal regions activate during self-control of craving, emotion,

and motor impulses in smokers. Clin Psychol Sci. 2014;2:611–9.
96. Moreira A, Machado DGDS, Moscaleski L, Bikson M, Unal G, Bradley PS, Baptista AF, Morya E, Cevada T, Marques L, Zanetti V, Okano AH. Effect of tDCS on well-being and autonomic function in professional male players after official soccer matches. Physiol Behav. 2021;1:233:113351. https://doi.org/10.1007.1016/j.physbeh.2021.113351. Epub 2021 Feb 6.
97. Moreira A, Machado DGDS, Bikson M, Unal G, Bradley PS, Moscaleski L, Costa T, Kalil GCSG, Chao LW, Baptista AF, Morya E, Okano AH. Effect of Transcranial Direct Current Stimulation on Professional Female Soccer Players' Recovery Following Official Matches. Percept Mot Skills. 2021;30:315125211021239. https://doi.org/10.1177/00315125211021239. Epub ahead of print.
98. McEwen BS. The untapped power of allostasis promoted by healthy lifestyles. World Psychiatry. 2020;19:57–8.
99. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. Handbook of life stress, cognition, and health. New York: John Wiley & Sons; 1988. p. 629.
100. McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. Annu Rev Med. 2011;62:431–45.
101. Felger JC, Treadway MT. Inflammation effects on motivation and motor activity: role of dopamine. Neuropsychopharmacology. 2017;42:216–41.
102. Boksem MAS, Tops M. Mental fatigue: costs and benefits. Brain Res Rev. 2008;59:125–39.
103. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012;76:470–85.
104. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10:397–409.
105. Fonteneau C, Redoute J, Haesebaert F, Le Bars D, Costes N, Suaud-Chagny M-F, Brunelin J. Frontal transcranial direct current stimulation induces dopamine release in the ventral striatum in human. Cereb Cortex. 2018;28:2636–46.
106. Mondino M, Thiffault F, Fecteau S. Does non-invasive brain stimulation applied over the dorsolateral prefrontal cortex non-specifically influence mood and emotional processing in healthy individuals? Front Cell Neurosci. 2015;9:399.
107. Brunoni AR, Moffa AH, Fregni F, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208:522–31.
108. Leite J, Gonçalves OF, Carvalho S. Facilitative effects of bi-hemispheric tDCS in cognitive deficits of Parkinson disease patients. Med Hypotheses. 2014;82:138–40.
109. Hüttermann S, Noël B, Memmert D. Eye tracking in high-performance sports: evaluation of its application in expert athletes. Int J Comput Sci Sport. 2018;17:182–203.
110. Piras A, Lobietti R, Squatrito S. Response time, visual search strategy, and anticipatory skills in volleyball players. J Ophthalmol. 2014;2014:189268.
111. Vickers JN, Causer J, Vanhooren D. The role of quiet eye timing and location in the basketball three-point shot: a new research paradigm. Front Psychol. 2019;10:2424.
112. Lebeau J-C, Liu S, Sáenz-Moncaleano C, Sanduvete-Chaves S, Chacón-Moscoso S, Becker BJ, Tenenbaum G. Quiet eye and performance in sport: a meta-analysis. J Sport Exerc Psychol. 2016;38:441–57.
113. Mann DTY, Williams AM, Ward P, Janelle CM. Perceptual-cognitive expertise in sport: a meta-analysis. J Sport Exerc Psychol. 2007;29:457–78.
114. Paneri S, Gregoriou GG. Top-Down Control of Visual Attention by the Prefrontal Cortex. Functional Specialization and Long-Range Interactions. Front Neurosci. 2017;11:545.
115. Opris I, Barborica A, Ferrera VP. Microstimulation of the dorsolateral prefrontal cortex biases saccade target selection. J Cogn Neurosci. 2005;17:893–904.
116. Okano AH, Machado DGS, Oliveira Neto L, et al. Can transcranial direct current stimulation modulate psychophysiological response in sedentary men during vigorous aerobic exercise? Int J Sports Med. 2017;38:493–500.
117. Peter J, Neumann-Dunayevska E, Geugelin F, Ninosu N, Plewnia C, Klöppel S. Reducing negative affect with anodal transcranial direct current stimulation increases memory performance in young- but not in elderly-individuals. Brain Struct Funct. 2019;224:2973–82.
118. Vaseghi B, Zoghi M, Jaberzadeh S. A meta-analysis of site-specific effects of cathodal transcranial direct current stimulation on sensory perception and pain. PLoS One. 2015;10:e0123873.
119. Byrne R, Flood A. The influence of transcranial direct current stimulation on pain affect and endurance exercise. Psychol Sport Exerc. 2019:101554.
120. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin Neurophysiol. 2003;114:2220–2; author reply 2222
121. Villamar MF, Volz MS, Bikson M, Datta A, Dasilva AF, Fregni F. Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (HD-tDCS). J Vis Exp. 2013:e50309.
122. Russo C, Souza Carneiro MI, Bolognini N, Fregni F. Safety review of transcranial direct current stimulation in stroke. Neuromodulation. 2017;20:215–22.
123. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation

concerning healthy subjects and patients. Brain Res Bull. 2007;72:208–14.
124. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol. 2015;126:2181–8.
125. Borckardt JJ, Bikson M, Frohman H, Reeves ST, Datta A, Bansal V, Madan A, Barth K, George MS. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain. 2012;13:112–20.
126. Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. Clin Neurophysiol. 2010;121:1976–8.
127. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol (Lond). 2000;527 Pt 3:633–9.
128. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57:1899–901.
129. López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-Del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. Brain Stimulat. 2014;7:372–80.
130. Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimulat. 2014;7:468–75.
131. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci. 2015;9:181.
132. Truong DQ, Magerowski G, Blackburn GL, Bikson M, Alonso-Alonso M. Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines. Neuroimage Clin. 2013;2:759–66.
133. Bikson M, Rahman A, Datta A. Computational models of transcranial direct current stimulation. Clin EEG Neurosci. 2012;43:176–83.
134. Russell MJ, Goodman TA, Visse JM, Beckett L, Saito N, Lyeth BG, Recanzone GH. Sex and electrode configuration in transcranial electrical stimulation. Front Psych. 2017;8:147.
135. Schestatsky P, Morales-Quezada L, Fregni F. Simultaneous EEG monitoring during transcranial direct current stimulation. J Vis Exp. 2013; https://doi.org/10.3791/50426.
136. Cancelli A, Cottone C, Tecchio F, Truong DQ, Dmochowski J, Bikson M. A simple method for EEG guided transcranial electrical stimulation without models. J Neural Eng. 2016;13:036022.
137. Esmaeilpour Z, Marangolo P, Hampstead BM, Bestmann S, Galletta E, Knotkova H, Bikson M. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. Brain Stimulat. 2018;11:310–21.
138. Jamil A, Batsikadze G, Kuo H-I, Labruna L, Hasan A, Paulus W, Nitsche MA. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol Lond. 2017;595:1273–88.
139. Nitsche MA, Bikson M. Extending the parameter range for tDCS: safety and tolerability of 4 mA stimulation. Brain Stimulat. 2017;10:541–2.
140. Klauss J, Penido Pinheiro LC, Silva Merlo BL, de Almeida Correia Santos G, Fregni F, Nitsche MA, Miyuki Nakamura-Palacios E. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol. 2014;17:1793–803.
141. Bergmann TO. Brain State-Dependent Brain Stimulation. Front Psychol. 2018;9:2108.
142. Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, Rothwell JC, Carmichael DW, Sharp DJ. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp. 2019;40:904–15.
143. Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts hebbian plasticity in vitro. Brain Stimulat. 2020;13:287–301.
144. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimulat. 2009;2:201–7, 207.e1.
145. Jaberzadeh S, Zoghi M. Non-invasive brain stimulation for enhancement of corticospinal excitability and motor performance. Basic Clin Neurosci. 2013;4:257–65.

19 Transcranial Direct Current Stimulation in Social and Emotion Research

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19.1 Introduction

Social and affective neurosciences are topics of increasing popularity and great urgency in contemporary brain research. The social and emotional aspects of cognition are inexorably linked, since the adaptive value of emotions is closely related to its social relevance and most social interactions seem to be related to some level of affective processing [1]. Social neuroscience is, therefore, an interdisciplinary field that combines methods and knowledge from cognitive and behavioral neuroscience, as well as social sciences, aiming to unveil how the human brain processes social information and how it can be modified by the complex social world that surrounds us [2]. Affective neuroscience is also an interdisciplinary field, combining cognitive and behavioral neuroscience for the understanding of emotion processing [3, 4].

Before the introduction of the main noninvasive brain stimulation methods used presently, most of the research on social and emotional processes relied on behavioral methods, brain lesions, and electrophysiological studies, all of them considered as correlational methods. As discussed before in the present book, the possibility to noninvasively and transiently interfere with the ongoing brain function using a site-specific technique as transcranial direct current stimulation (tDCS) allows us to understand brain-behavior relationships with another level of causality that cannot be achieved with imaging or behavioral methods alone.

In this chapter, we will review how tDCS has been used in social and emotional neuroscience studies. With this purpose, this chapter is organized in two main sessions: emotion studies (including those that might involve some relevant social phenomena) and social cognition studies (gathering the ones that are not mostly focused on emotional processes). We will focus on basic research, as there are specific chapters in this book addressing tDCS effects on social and emotional processes related to neurological and psychiatric disorders.

19.2 tDCS on Emotion Studies

Emotions are present in our daily life, influencing the way we perceive the world and our behavior. According to Fridja [5], emotion is defined as a physiological, behavioral, and subjective response to a given situation. It is very important for decision-making, helping us to predict and rapidly react to internal or external demands [4].

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Lippold and Redfearn [6], in one of the first studies investigating tDCS effects on emotion, reported that tDCS could affect participants' mood. In this study, tDCS was placed bilaterally over the frontal lobes with the reference placed on the leg. However, posterior attempts to replicate these results have failed so far [7, 8], probably due to participant selection: most of the participants recruited in the Lippold and Redfearn [6] study presented a history of psychiatric disorder. In addition, Lippold and Redfearn evaluated, mood subjectively, a procedure that could have biased the results. Furthermore, replication studies used only healthy subjects and double-blind designs.

Some studies have also tried to assess tDCS effects on healthy participants' mood [9–14], all of them stimulating the dorso-lateral prefrontal cortex (DLPFC) but finding no significant results. Nonetheless, two studies were successful in modulating mood by stimulating the DLPFC of healthy volunteers [14, 15]. In these studies, participants were exposed to negative stimuli [15] or performed a task aimed at inducing frustration feelings [14]. In both studies, active tDCS significantly suppressed negative feelings in comparison to sham. In these cases, tDCS appeared to affect mood indirectly, preventing changes evoked by external stimuli, probably by controlling emotion regulation processes [16] or other interference mechanisms on emotion processing, rather than directly modulating mood.

What do these conflicting results tell us about tDCS effects on emotional processing? Some of them suggest that tDCS does not influence mood directly, as first proposed by Lippold and Redfearn [6]. Instead, it might have indirect effects on mood; probably by interfering with other cognitive processes involved in emotion processing, such as encoding and retrieval of emotional memory, detection of emotional prosody, detection of emotional facial expressions, emotion regulation, and fear conditioning.

19.3 Emotional Memory Encoding and Retrieval

A well-known phenomenon is that emotional events and stimulus are usually better remembered than neutral ones. Two important phases in memory consolidation are the encoding and retrieval: the former is the process involving the mechanisms related to the storage and creation of a memory and the latter is the process related to retrieval of already consolidated memories. At least two studies have assessed emotional memory encoding and retrieval after tDCS [13, 17]. Penolazzi et al. [17] stimulated fronto-temporal areas bilaterally (left cathodal/right anodal and the opposite) during the encoding of emotional stimuli. They found that right cathodal and left anodal stimulation inhibited memory retrieval of pleasant stimuli, while the opposite montage inhibited retrieval of unpleasant stimuli. Using also a bilateral electrode montage, but this time over DLPFC, Morgan et al. [13] investigated whether stimulation of this area influenced memory retrieval of emotional stimuli; however, no significant effects were found.

These studies in tDCS and emotional memory addressed a promising topic, since they could help to clarify neural circuitries involved in emotional memory and could point to the possibility of using tDCS clinically, for example, in post-traumatic stress or depression. However, given their conflicting results, the limited number of investigations in the field and some limitations of the tDCS technique, it is not yet possible to circumscribe the role of DLPFC and fronto-temporal areas in emotional memory encoding and retrieval. The effects found by Penolazzi et al. [17] are intriguing, since anodal tDCS is typically related to facilitation or increased cortical activity and would most likely be associated with enhanced memory processing. In this case, a possible explanation could be that the anodal stimulation enhanced a competing neural population that disrupted the activity of emotional memory circuitry.

19.4 Emotional Prosody

Indeed, many cognitive and affective processes involve complex circuitries, recruiting various brain areas that may sometimes compete or share mutually inhibitory connections. This hypothesis may also explain the results found by Alexander et al. [18], who evaluated the effects of anodal and cathodal tDCS over the right inferior frontal gyrus (IFG) in emotional prosody stimuli presented on a dichotic listening paradigm. The authors have found that cathodal tDCS improved emotional prosody detection, probably inhibiting competing neural activations and acting as a noise filter. These results illustrate the complexity involved in using tDCS to address such intricate processes that rely on multiple interdependent neural populations.

19.5 Emotional Face Processing

Another relevant topic is how people process emotional faces, an ability that is on the core of our social skills. Most studies using tDCS to assess emotional face processing have focused on the role of temporal areas, DLPFC, and cerebellum in face processing [11, 19–21]. Boggio et al. [19] have applied bilateral tDCS with the anode over the left and cathode over right temporal cortex in subjects performing a go-no-go task with positive and negative-valence emotional face expressions as stimuli. They found different effects according to gender when seeing sad faces, with a disrupted performance in men and an enhanced performance in women. The authors suggested that this effect was due to possible different networks subserving the perception of sad faces in women and men. These results also suggested the specialization of the temporal cortex role only on sad face processing, as no significant effects were found for positive facial expressions.

The role of temporal cortex on negative valence stimulus is not only restricted to faces, as another tDCS study has suggested by investigating biological bodily motion from point-light displays [22]. In this study, Vonck et al. [22] showed that anodal tDCS over right temporal lobe and contralateral supra-orbital reference enhanced recognition of light points copying a biological body motion in a negative emotional state, both in male and female participants. This study further suggests the role of the left temporal areas in negative emotion recognition not only from facial stimulus. An interesting point not addressed by the authors is a possible gender interaction effect, what could endorse the findings by Boggio et al. [19].

The role of other brain areas besides the temporal cortex in emotional face processing was also investigated. Ferrucci et al. [20] assessed the role of the cerebellum in emotional face recognition, finding that anodal and cathodal tDCS over the cerebellum could enhance the recognition of sad and angry faces [20], which highlights the role of the cerebellum in negative emotional face recognition. Also, anodal tDCS over the left DLPFC improved recognition of positive emotional faces, supporting the hemispherical specialization hypothesis for specific emotion processing, named the valence theory (see [23]). However, right DLPFC tDCS did not alter the recognition of negative emotional faces as expected [20], since this area has been believed to be involved in emotional face processing [24], at least for negative valence stimulus [23]. In fact, right DLPFC tDCS has only enhanced the recognition of fear faces in men [21].

In sum, these findings showed the role of the investigated areas in emotional face processing, suggesting specific circuitries for specific emotions. One question still unsolved is the role of lateralized prefrontal areas in emotional face and other emotional processing. The tDCS studies have suggested that DLPFC does not appear to have a general lateralized functioning for emotional valence, but a lateralized functioning linked to specific emotions, probably through the employment of cognitive resources in emotional processing.

19.6 Emotion Regulation

Emotion regulation is defined as the process by which one attempts to regulate his or her emotional experience and/or resulting behavior by cognitive control (for example, by attention deployment or reappraisal of emotional stimuli), aiming to achieve a more adaptive emotional respons0065Transcranial direct current stimulation (tDCS):emotional face processing. The emotion regulation can be divided in two main techniques, those focusing to enhance (upregulation) or to diminish (downregulation) an emotional response. Almost all tDCS studies targeted the DLPFC, a critical brain area for executive functioning and emotional regulation [16]. Feeser et al. [25] investigated the role of right DLPFC in the emotional regulation of negative stimuli. The participants received anodal tDCS over the right DLPFC (reference on supraorbital contralateral area) while exposed to negative valence stimuli and were asked to upregulate or downregulate their emotions. Active tDCS altered skin conductance response (SCR) and arousal ratings of participants in comparison to sham tDCS, enhancing these responses in upregulation and decreasing in downregulation condition; findings that clarify the right DLPFC role in cognitive control and emotion regulation through reappraisal.

This assumption was supported by Pripfl and Lamm [26], in which anodal tDCS over the right DLPFC was related to higher levels of cognitive control during affective pictures appraisal, specifically of negative valence. This study also evaluated anodal stimulation over the left DLPFC, but without significant effects. These results are also in agreement with Rêgo et al. [15], in which right anodal DLPFC seemed to control the impact of negative valence stimulus on mood. However, in contrast to Pripfl and Lamm, Rêgo et al. [15] found the same effect in anodal stimulation of left DLPFC.

The effect of anodal stimulation over left DLPFC on mood control was also observed in the study by Plewnia et al. [14]. Likewise, PeñaGómez et al. [9] found decreased valence evaluation for negative valence pictures after tDCS of the left DLPFC. Moreover, previous studies found that anodal tDCS over the left DLPFC increased physical pain thresholds [27], and decreased unpleasantness and discomfort assessment during pain-related pictures observation [28, 29]. These contradictory results between those studies and Pripfl and Lamm could be due to adopted methods. Importantly, Pripfl and Lamm have used a high-definition tDCS. These devices are associated with a much higher focality than the standard tDCS procedures and this must be taken into account when analyzing these results [26].

tDCS might also have a substantial effect on peripheral physiological responses, suggesting an impact in autonomic processes. For instance, Brunoni et al. [30] showed that during anodal left/cathodal right DLPFC tDCS, participants presented increased heart rate variability and decreased salivary cortisol, especially during the visualization of negative valence pictures, supporting the role of right DLPFC on the top-down regulation of autonomic and neuroendocrine responses. Furthermore, as presented in a study conducted with patients with anxiety disorders by Heeren et al. [31], anodal tDCS over left DLPFC combined with attentional bias modification (ABM) strategy promoted shorter eye gaze fixations during the observation of visually threatening stimuli, suggesting a role of left DLPFC on the modulation of attentional control. Notwithstanding, we suggest that future tDCS studies should further investigate hemispheric and interhemispheric roles of DLPFC on emotion-related cognitive control, considering that the number of studies is still limited and that this could lead to new clinical applications in individuals with mood and anxiety disorders [32].

19.7 Social Pain

These studies illustrate the potential of neuromodulation techniques for the investigation of the neural mechanisms behind understanding other's emotions. In this same line, there are numerous works investigating pain perception and judgment of painful situations. More recently, social pain,

which can be characterized as the experience of suffering due to personal losses or rejection and ostracism [33] has been studied using tDCS. Riva et al. [34] showed that anodal tDCS over the right ventro-lateral prefrontal cortex (VLPFC) could reduce the discomfort and feelings of pain. More recently, the same group showed that, under the same protocol, participants who received active tDCS reported lower levels of aggressiveness after being ostracized in a Cyberball task [35]. Anodal tDCS stimulation over the right DLPFC also had a similar effect in aggressive behavior, leading to lower levels of self-reported aggressiveness in men [36]. Furthermore, when assessing the impact of DLPFC on the control of emotional suffering due to social pain, Kelley et al. [37] showed that when submitted to right DLPFC anodal tDCS, participants showed higher levels of rumination while being ostracized in the so-called Cyberball task (see [38] for review). Altogether, these studies provide causal evidence for the role of the DLPFC and VLPFC in emotional control processes and emotional reappraisal [16], highlighting the relevance of tDCS for the study of pain, empathy for pain (see [39] for a discussion of this issue), and social pain phenomena.

19.8 Fear Conditioning

Two studies have investigated the modulation of fear conditioning with tDCS, suggesting different roles for the left and right DLPFCs [40, 41]. In the study by Asthana et al. [40], cathodal tDCS over the left DLPFC (reference over the left mastoid) inhibited fear memory consolidation, while anodal stimulation did not show any significant effects. Mungee et al. [41] showed that anodal tDCS over the right DLPFC (reference over contralateral supraorbital area) led to enhanced fear memory consolidation. These results indicate different roles for left and right DLPFC, as suggested by the previous literature. However, it is important to remember that these different effects between Asthana et al. [40] and Mungee et al. [41] could be due to differences in the methods adopted (stimuli used or task demands could have directed participants to use distinct emotion regulation methods), or even in the reference electrode location, that could change current direction and effects.

In this topic, we have discussed some of the main tDCS studies in affective neuroscience. It is important to highlight some issues: first, tDCS is a suitable technique to modulate cortical areas, but its efficiency for modulating activity of subcortical areas appears to be only indirectly, probably through cortico-subcortical connections (e.g., [42–44]). Therefore, as affective processing is particularly dependent on many subcortical areas, many of these studies here presented aimed to indirectly interfere with emotional processes by top-down mechanisms or by targeting cortical areas that are known to indirectly modulate relevant subcortical structures. As we have mentioned before, the DLPFC is one of the main areas involved in top-down emotional regulation. Both left and right DLPFC appear to be involved in distinct aspects of emotion regulation by mechanisms that are not clear yet.

19.9 Social Neuroscience

As mentioned in the introduction section, it is not reasonable to disentangle the social from the affective aspects of the human experience. Therefore, the separation between emotional and social aspects in the current text is strictly didactical and does not reflect the complexity of the interaction between these two constructs. With that being said, we will highlight some of the most successful investigations that have used tDCS in the elucidation of the neural correlates of prejudice and the neural processes behind social interaction and social decision-making, which have been intensively investigated in contemporary literature.

19.10 Implicit Prejudice

Although this is a controversial topic, it could be argued that the frequency of explicit demonstrations of prejudice (racial, social, and gender)

might be declining in many cultures. Implicit prejudice— hidden biases that are not always explicit but may influence some behavioral responses—is a topic of great relevance in contemporary social neuroscience. It is important to note that there are substantial methodological challenges involved in investigating a behavioral bias of which subjects are frequently not aware of (see [45] for a review). The case of tDCS in implicit prejudice research is an example of how this technique may be elegantly integrated with classic behavioral paradigms in order to shed a new light on methodologically demanding research questions.

The implicit association test (IAT) is one of the most robust paradigms to investigate implicit prejudice. It allows for the investigation of interactions between different stimuli categories (e.g., faces of different ethnicities with words of different valences) in a fast forced choice task that unveils biases that are frequently not explicitly accessible [46]. More recently, some groups started to investigate prejudice and its implicit associations using neuromodulation techniques as transcranial magnetic stimulation (TMS) and tDCS. These investigations have showed that the inhibition of the left DLPFC function was able to increase participant's gender bias [47] and religious bias [48] during IAT. These findings suggest that the left DLPFC may play a central role in inhibiting these stereotyped responses.

In this same line but using nonsocial stimuli, a recent tDCS work has also modulated the left DLPFC and found some interesting results. Gladwin et al. [49] found that tDCS of the left DLPFC did not affect the implicit bias processes in the association of insect images and insect names when using an IAT. Taken together with the works of Cattaneo et al. [47] and Crescentini et al. [48], these results could be interpreted as suggesting that there is a left DLPFC specialization for the processing of social (in contrast to nonsocial) bias.

19.11 Social Decision-Making

Social decision-making may be defined as the process by which a person chooses between alternatives in the context of social interaction [50]. So far, most studies combining social decision-making and neuroscience have focused on neuroimaging methods, but some new relevant studies have used noninvasive brain stimulation techniques and found exciting results. We will start by presenting studies that have investigated the role of the perception of fairness and social norm compliance in social decision-making.

A seminal investigation of this issue was conducted by Knoch et al. [51] using TMS during the ultimatum game (UG). The UG is a resource-sharing task used to investigate reaction to unfairness, where a player (the responder) have to respond to money-sharing proposals from another player (the proposer) that might range from very fair to very unfair. If the responder accepts the offer, both players gain the amount, whereas if the responder rejects the offer, both players get nothing. Knoch et al. [51] inhibited the right DLPFC activity during the UG and found that participants playing as responders had increased acceptance rates of unfair proposals, suggesting that the right DLPFC may mediate unfairness evaluation. These exciting results were later replicated by the same group using cathodal tDCS [52], a finding that supports tDCS as a suitable tool for social neuroscience research and that tDCS and TMS results may be compatible in many cases.

A few other works have also paired tDCS with modified versions of the UG with exciting results, in contrast to the standard task that just assesses the effect of unfairness from the point of view of the responder. Recent experiments have started to investigate the effects of unfairness when the responder has to decide for himself ("myself condition") or on behalf of a third-party [53] and found that inequity aversion may be observed on

both "myself" and "third-party" conditions. Civai et al. [53] have also found that the medial prefrontal cortex (MPFC) is particularly active in the myself condition.

In a subsequent study, Civai, Miniussi, and Rumiati [54] have used tDCS in order to better understand the causal role of MPFC in inequity evaluation. They found that cathodal tDCS over left MPFC (midpoint between Fpz and Fp1) led to diminished rejection of unfair proposals in the "myself" but not on the "third party" condition, supporting the hypothesis derived from previous functional magnetic resonance imaging (fMRI) studies suggesting that the MPFC is particularly engaged in the judgment of fairness in more egocentric conditions. This adds new relevant information on the fact that there is a distinct and complex neural circuitry to deal with egocentric vs. allocentric conditions.

A more recent study introduced the variable punishment in the UG. Ruff, Ugazio, and Fehr [55] have used a task developed by Spitzer et al. [56] in which two players should divide an initial endowment. One player was a proposer and should suggest a division rate to a second player, the receiver. Two different conditions are available: a control and a punishment one. In the control condition, the receiver could only accept the proposal passively, similar to a dictator game, while in the punish condition the receiver could spend money to punish the proposer. The authors found, in this neuroimaging study, that the punishment condition led the proposers to comply with the social norms and share the endowment more fairly and that this behavioral adaptation was related to an enhanced activation of right DLPFC, left VLPFC, and bilateral orbitofrontal cortex. Ruff et al. [55] modulated the right DLPFC with anodal and cathodal stimulation to investigate the role of the right DLPFC on norm compliance. They found that, in the punishment condition, the anodal stimulation (compared to sham) led the proposer to transfer more money after punishment, enhancing norm compliance. Contrary to that, the cathodal stimulation turned the proposers more self-interested and less oriented by social norms of fairness, diminishing the quantity transferred to the receivers. In the control condition (where the receiver could only accept passively), the stimulation acted in the opposite way. These results help to support the role of the right DLPFC in a network linked to norm compliance, but as highlighted by Sanfey et al. [57], the fact the punishment and the control conditions were oppositely affected by tDCS suggest that this network may be more complex than previously expected.

As social norm compliance may be affected in many clinical conditions, studies showing a significant modulation of these processes by tDCS highlight its potential as a social cognition rehabilitation tool for clinical populations. Social interaction is another field of research in social neuroscience where tDCS might have a promising clinical relevance too. Below are some basic research examples that not only support this clinical potential, but also seem to have helped to overcome some methodological challenges in investigating higher-order cognitive processes such as this one.

19.12 Perspective Taking

Perspective taking is a critical skill for effective social interaction and closely related to empathy and consequently to the development and maintenance of positive social connections (for a review see [58]). As Conson et al. [21] demonstrated, although promoting faster negative emotion recognition in males, right anodal/left cathodal tDCS over DLPFC decreased participants' ability to assume the perspective of others during a visual perspective taking task. Another relevant study has investigated the neuromodulation of temporo-parietal junction (TPJ) in par-

ticipant's performance on three social cognition tasks: on a motor imitation task, a spatial perspective-taking task, and a self-referential task [59]. Although some neuroimaging studies have suggested the involvement of the TPJ in abilities related to the execution of these tasks, TPJ tDCS effects were not the same for all tasks. This study has showed that anodal TPJ tDCS improved the control of self-other discrimination related to the imitation and perspective-taking tasks, while did not have any effect on mental attribution ability, as evaluated by the self-referential task [59]. This study has helped to clarify the involvement of TPJ in empathy and its role in self-other discrimination.

Hogeveen et al. [60] have expanded these findings by testing the effects of anodal tDCS over the right TPJ or right inferior frontal cortex (IFC) on imitative control functions. Interestingly, anodal tDCS of the right IFC improved the ability to inhibit imitation in a task when it was required but, at the same time, increased the imitation behaviors during a social interaction task (which is related to better social interaction). Thus, it seems that IFC is somehow involved in imitation, but in a way that is dependent on the task performed. In addition to that, anodal tDCS over TPJ was associated with increased ability to inhibit imitation but had no effect on the imitation during the social interaction task. These findings suggest a direct role of the IFC in imitative behavior and an indirect one of the TPJ in a way that is dependent on the social demands.

19.13 Conclusions

We have presented an overview of some of the most relevant investigations of social and affective neuroscience involving tDCS. We would like to argue that two things are clear after this review. First, that tDCS is indeed a valuable tool for contemporary social and affective neuroscience research, bringing important new insight into classical research questions and complementing the current knowledge of the field with another level of causality in bridging brain and behavior. Second, that the technique is still not used as much as would be appropriate given its potential. In fact, if we consider the works that have been presented here, we may argue that tDCS is indeed a technique that has brought a number of new insights into technically challenging questions of classical psychological science. Assessing causality and not being time limited in the same way as other brain investigation techniques (e.g., event-related potentials and fMRI) may be highlighted as some of its major strengths. Given that, we hope to see more tDCS in social and affective neuroscience research in the future.

References

1. Mitchell J, Heatherton TF. Components of a social brain. In: Gazzaniga MS, editor. Cognitive neuroscience. 4th ed. Cambridge, MA: MIT Press; 2009. p. 951–8.
2. Ochsner KN, Lieberman MD. The emergence of social cognitive neuroscience. Am Psychol. 2001;56:717–34.
3. Davidson RJ, Sutton SK. Affective neuroscience: the emergence of a discipline. Curr Opin Neurobiol. 1995;5:217–24.
4. Panksepp J. Affective neuroscience: the foundations of human and animal emotions. 1st ed. New York: Oxford University Press; 2004.
5. Fridja NH. The psychologists' point of view. Handbook of emotions. 3rd ed. New York: The Guilford Press; 2010. p. 68–87.
6. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry. 1964;110:768–72. https://doi.org/10.1192/bjp.110.469.768.
7. Sheffield LJ, Mowbray RM. The effects of polarization on normal subjects. Br J Psychiatry. 1968;114:225–32.
8. Koenigs M, Ukueberuwa D, Campion P, Grafman J, Wassermann E. Bilateral frontal transcranial direct current stimulation: failure to replicate classic findings in healthy subjects. Clin Neurophysiol. 2009;120:80–4. https://doi.org/10.1016/j.clinph.2008.10.010.
9. Peña Gómez C, Vidal Piñeiro D, Clemente IC, Pascual Leone Á, Bartrés Faz D. Down regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One. 2011;6:e22812. https://doi.org/10.1371/journal.pone.0022812.
10. Plazier M, Joos K, Vanneste S, Ost J, De Ridder D. Bifrontal and bioccipital transcranial direct current stimulation (tDCS) does not induce mood changes in healthy volunteers: a placebo controlled study. Brain Stimul. 2012;5:454–61. https://doi.org/10.1016/j.brs.2011.07.005.

11. Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Front Psych. 2012;3:58. https://doi.org/10.3389/fpsyt.2012.00058.
12. Motohashi N, Yamaguchi M, Fujii T, Kitahara Y. Mood and cognitive function following repeated transcranial direct current stimulation in healthy volunteers: a preliminary report. Neurosci Res. 2013;77:64–9. https://doi.org/10.1016/j.neures.2013.06.001.
13. Morgan HM, Davis NJ, Bracewell RM. Does transcranial direct current stimulation to prefrontal cortex affect mood and emotional memory retrieval in healthy individuals? PLoS One. 2014;9:e92162. https://doi.org/10.1371/journal.pone.0092162.
14. Plewnia C, Schroeder PA, Kunze R, Faehling F, Wolkenstein L. Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). PLoS One. 2015;10:e0122578. https://doi.org/10.1371/journal.pone.0122578.
15. Rêgo GG, Lapenta OM, Marques LM, Costa TL, Leite J, Carvalho S, et al. Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. Neurosci Lett. 2015;594:12–6. https://doi.org/10.1016/j.neulet.2015.03.042.
16. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2014;1251:E1.
17. Penolazzi B, Di Domenico A, Marzoli D, Mammarella N, Fairfield B, Franciotti R, et al. Effects of transcranial direct current stimulation on episodic memory related to emotional visual stimuli. PLoS One. 2010;5:e10623. https://doi.org/10.1371/journal.pone.0010623.
18. Alexander T, Avirame K, Lavidor M. Improving emotional prosody detection in the attending ear by cathodal tDCS suppression of the competing channel. Neurosci Lett. 2012;508:52–5. https://doi.org/10.1016/j.neulet.2011.12.017.
19. Boggio PS, Rocha RR, da Silva MT, Fregni F. Differential modulatory effects of transcranial direct current stimulation on a facial expression go-no-go task in males and females. Neurosci Lett. 2008;447:101–5. https://doi.org/10.1016/j.neulet.2008.10.009.
20. Ferrucci R, Giannicola G, Rosa M, Fumagalli M, Boggio PS, Hallett M, et al. Cerebellum and processing of negative facial emotions: cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness. Cogn Emot. 2012;26:786–99. https://doi.org/10.1080/02699931.2011.619520.
21. Conson M, Errico D, Mazzarella E, Giordano M, Grossi D, Trojano L. Transcranial electrical stimulation over dorsolateral prefrontal cortex modulates processing of social cognitive and affective information. PLoS One. 2015;10:e0126448. https://doi.org/10.1371/journal.pone.0126448.
22. Vonck S, Swinnen SP, Wenderoth N, Alaerts K. Effects of transcranial direct current stimulation on the recognition of bodily emotions from point light displays. Front Hum Neurosci. 2015;9:438. https://doi.org/10.3389/fnhum.2015.00438.
23. Davidson RJ, Fox NA. Asymmetrical brain activity discriminates between positive and negative affective stimuli in human infants. Science. 1982;218:1235–7.
24. Nakamura K, Kawashima R, Ito K, Sugiura M, Kato T, Nakamura A, et al. Activation of the right inferior frontal cortex during assessment of facial emotion. J Neurophysiol. 1999;82:1610–4.
25. Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimul. 2014;7:105–12. https://doi.org/10.1016/j.brs.2013.08.006.
26. Pripfl J, Lamm C. Focused transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex modulates specific domains of self regulation. Neurosci Res. 2015;91:41–7. https://doi.org/10.1016/j.neures.2014.09.007.
27. Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol. 2008;15:1124–30. https://doi.org/10.1111/j.14681331.2008.02270.x.
28. Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia. 2009;47:212–7. https://doi.org/10.1016/j.neuropsychologia.2008.07.022.
29. Wang J, Wang Y, Hu Z, Li X. Transcranial direct current stimulation of the dorsolateral prefrontal cortex increased pain empathy. Neuroscience. 2014;281C:202–7. https://doi.org/10.1016/j.neuroscience.2014.09.044.
30. Brunoni AR, Vanderhasselt MA, Boggio PS, Fregni F, Dantas EM, Mill JG, et al. Polarity and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. Psychoneuroendocrinology. 2013;38:58–66. https://doi.org/10.1016/j.psyneuen.2012.04.020.
31. Heeren A, Baeken C, Vanderhasselt MA, Philippot P, de Raedt R. Impact of anodal and cathodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex during attention bias modification: an eyetracking study. PLoS One. 2015;10:e0124182. https://doi.org/10.1371/journal.pone.0124182.
32. Mondino M, Thiffault F, Fecteau S. Does noninvasive brain stimulation applied over the dorsolateral prefrontal cortex nonspecifically influence mood and emotional processing in healthy individuals? Front Cell Neurosci. 2015;9:399. https://doi.org/10.3389/fncel.2015.00399.
33. Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nat Rev Neurosci. 2012;13:421–34. https://doi.org/10.1038/nrn3231.
34. Riva P, Romero Lauro LJ, Dewall CN, Bushman BJ. Buffer the pain away: stimulating the right ventro-

lateral prefrontal cortex reduces pain following social exclusion. Psychol Sci. 2012;23:1473–5. https://doi.org/10.1177/0956797612450894.
35. Riva P, Romero Lauro LJ, DeWall CN, Chester DS, Bushman BJ. Reducing aggressive responses to social exclusion using transcranial direct current stimulation. Soc Cogn Affect Neurosci. 2015;10:352–6. https://doi.org/10.1093/scan/nsu053.
36. Dambacher F, Schuhmann T, Lobbestael J, Arntz A, Brugman S, Sack AT. Reducing proactive aggression through noninvasive brain stimulation. Soc Cogn Affect Neurosci. 2015;10:1303–9. https://doi.org/10.1093/scan/nsv018.
37. Kelley NJ, Hortensius R, Harmon Jones E. When anger leads to rumination: induction of relative right frontal cortical activity with transcranial direct current stimulation increases anger related rumination. Psychol Sci. 2013;24:475–81. https://doi.org/10.1177/0956797612457384.
38. Williams KD, Jarvis B. Cyberball: a program for use in research on interpersonal ostracism and acceptance. Behav Res Methods. 2006;38:174–80. https://doi.org/10.3758/BF03192765.
39. Hétu S, Taschereau Dumouchel V, Jackson PL. Stimulating the brain to study social interactions and empathy. Brain Stimul. 2012;5:95–102. https://doi.org/10.1016/j.brs.2012.03.005.
40. Asthana M, Nueckel K, Mühlberger A, Neueder D, Polak T, Domschke K, et al. Effects of transcranial direct current stimulation on consolidation of fear memory. Front Psych. 2013;4:107. https://doi.org/10.3389/fpsyt.2013.00107.
41. Mungee A, Kazzer P, Feeser M, Nitsche MA, Schiller D, Bajbouj M. Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. Neuroreport. 2014;25:480–4. https://doi.org/10.1097/WNR.0000000000000119.
42. Bolzoni F, Bączyk M, Jankowska E. Subcortical effects of transcranial direct current stimulation in the rat. J Physiol. 2013;591:4027–42. https://doi.org/10.1113/jphysiol.2013.257063.
43. Nonnekes J, Arrogi A, Munneke MAM, van Asseldonk EHF, Oude Nijhuis LB, Geurts AC, et al. Subcortical structures in humans can be facilitated by transcranial direct current stimulation. PLoS One. 2014;9:e107731. https://doi.org/10.1371/journal.pone.0107731.
44. Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. Front Hum Neurosci. 2013;7:628. https://doi.org/10.3389/fnhum.2013.00628.
45. Kubota JT, Banaji MR, Phelps EA. The neuroscience of race. Nat Neurosci. 2012;15:940–8. https://doi.org/10.1038/nn.3136.
46. Greenwald AG, McGhee DE, Schwartz JLK. Measuring individual differences in implicit cognition: the implicit association test. J Pers Soc Psychol. 1998;74(6):1464–80.
47. Cattaneo Z, Mattavelli G, Platania E, Papagno C. The role of the prefrontal cortex in controlling gender stereotypical associations: a TMS investigation. NeuroImage. 2011;56:1839–46. https://doi.org/10.1016/j.neuroimage.2011.02.037.
48. Crescentini C, Aglioti SM, Fabbro F, Urgesi C. Virtual lesions of the inferior parietal cortex induce fast changes of implicit religiousness/spirituality. Cortex. 2014;54:1–15. https://doi.org/10.1016/j.cortex.2014.01.023.
49. Gladwin TE, den Uyl TE, Wiers RW. Anodal tDCS of dorsolateral prefontal cortex during an implicit association test. Neurosci Lett. 2012;517:82–6. https://doi.org/10.1016/j.neulet.2012.04.025.
50. Sanfey AG. Social decision making: insights from game theory and neuroscience. Science. 2007;318:598–602. https://doi.org/10.1126/science.1142996.
51. Knoch D, Pascual Leone A, Meyer K, Treyer V, Fehr E. Diminishing reciprocal fairness by disrupting the right prefrontal cortex. Science. 2006;314:829–32. https://doi.org/10.1126/science.1129156.
52. Knoch D, Nitsche MA, Fischbacher U, Eisenegger C, Pascual Leone A, Fehr E. Studying the neurobiology of social interaction with transcranial direct current stimulation—the example of punishing unfairness. Cereb Cortex. 2008;18:1987–90. https://doi.org/10.1093/cercor/bhm237.
53. Civai C, Crescentini C, Rustichini A, Rumiati RI. Equality versus self interest in the brain: differential roles of anterior insula and medial prefrontal cortex. NeuroImage. 2012;62:102–12. https://doi.org/10.1016/j.neuroimage.2012.04.037.
54. Civai C, Miniussi C, Rumiati RI. Medial prefrontal cortex reacts to unfairness if this damages the self: a tDCS study. Soc Cogn Affect Neurosci. 2015;10:1054–60. https://doi.org/10.1093/scan/nsu154.
55. Ruff CC, Ugazio G, Fehr E. Changing social norm compliance with noninvasive brain stimulation. Science. 2013;342:482–4. https://doi.org/10.1126/science.1241399.
56. Spitzer M, Fischbacher U, Herrnberger B, Grön G, Fehr E. The neural signature of social norm compliance. Neuron. 2007;56:185–96. https://doi.org/10.1016/j.neuron.2007.09.011.
57. Sanfey AG, Stallen M, Chang LJ. Norms and expectations in social decision making. Trends Cogn Sci. 2014;18:172–4. https://doi.org/10.1016/j.tics.2014.01.011.
58. Seyfarth RM, Cheney DL. Affiliation, empathy, and the origins of theory of mind. Proc Natl Acad Sci U S A. 2013;110(Suppl):10349–56. https://doi.org/10.1073/pnas.1301223110.
59. Santiesteban I, Banissy MJ, Catmur C, Bird G. Enhancing social ability by stimulating right temporoparietal junction. Curr Biol. 2012;22:2274–7. https://doi.org/10.1016/j.cub.2012.10.018.
60. Hogeveen J, Obhi SS, Banissy MJ, Santiesteban I, Press C, Catmur C, et al. Task dependent and distinct roles of the temporoparietal junction and inferior frontal cortex in the control of imitation. Soc Cogn Affect Neurosci. 2015;10:1003–9. https://doi.org/10.1093/scan/nsu148.

Neurodegenerative Cognitive Disorders

20

Tarek K. Rajji

Neurodegenerative cognitive disorders, also referred to as dementias, affect more than 46 million people worldwide [1]. By 2050, this number is estimated to be more than 131 million. The current costs associated with dementia are estimated to be US $818 billion. To date, there are no interventions to prevent, cure, or even slow down the underlying disease even though some pharmacological treatments could slow down the symptoms or for some of these disorders the underlying risk factors could be modified. Alzheimer's dementia (AD) is the most common form of dementia. Other forms of dementia include vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease dementia, and others.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that can be safely administered to conscious outpatients (i.e., it does not require general anesthesia or surgical implantation of a device). It utilizes low intensity electrical current either to typically increase cortical excitability with an anodal electrode or suppress cortical excitability with a cathodal electrode [2]. Given its ease of use, portability, and high potential of scalability, several studies have tested the effect of tDCS in patients with dementia. Most studies have focused on patients with AD, and more recently studies have focused on mild cognitive impairment (MCI) or other forms of dementia and cognitive impairments. In this chapter, these studies are reviewed and classified based on the clinical condition they targeted. Specific details and summaries of the clinical and cognitive findings are also presented in Table 20.1.

20.1 Alzheimer's Dementia

In Ferruci et al. [3], 10 participants with Alzheimer's dementia (AD) received 3, 15-min tDCS sessions in a random order and 1 week apart: anodal transcranial direct current stimulation (tDCS), cathodal tDCS, and sham tDCS. Two stimulators were used. For each stimulator, one electrode was placed over the temporoparietal area (left or right) and the other over the right deltoid muscle. Current was 1.5 mA. Cognition was assessed before and 30 min after each session. Anodal tDCS improved word recognition and discrimination by 17% while cathodal tDCS impaired both.

In Boggio et al. [4], 10 participants with AD received 2, 30-min sessions of unilateral anodal tDCS – 1 session to the left dorsolateral prefrontal cortex (DLPFC), another to the left temporal cortex – and a third session of sham tDCS. Cathodal electrode was placed over the right supra-orbital area. Current was 2 mA. Cognition was assessed

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Table 20.1 tDCS studies in neurodegenerative cognitive disorders: basic characteristics and summary of clinical and cognitive effects

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Alzheimer's dementia: tDCS alone							
Ferruci et al. (2008)	Alzheimer's demented	10	75.2 (7.3)	1.5	1	Anode, cathode, or sham over left or right temporoparietal Reference over right deltoid	Anodal stimulation at both sites, improved word recognition, and discrimination Cathodal stimulation impaired both
Boggio et al. (2009)	Alzheimer's dementia	10	70–92	2	1	Anode or sham over left dorsolateral prefrontal cortex or left temporal cortex Cathode over right deltoid	Anodal stimulation at both sites, improved visual recognition memory
Boggio et al. (2012)	Alzheimer's dementia	15	78.9 (8.2)	2	5 consecutive	Anodes over bilateral temporal cortices Cathode over right deltoid	Compared to sham stimulation, active stimulation improved visual recognition memory and these improvements persisted for 4 weeks
Khedr et al. (2014)	Alzheimer's dementia	34	69.7 (4.8)	2	10 consecutive	Anode, cathode, or sham over left DLPFC Reference over supra-orbital region	Anodal and cathodal stimulation improved performance on MMSE immediately and the improvement persisted at 1 and 2 months
Suemoto et al. (2014)	Alzheimer's dementia – focus on apathy	40	80.5 (7.5)	2	6 every other day	Anode over left DLPFC Cathode over right supra-orbital region	tDCS had no impact on apathy
Bystad et al. (2016a)	Alzheimer's dementia	25	~73	2	5 consecutive	Anode over left temporal cortex Cathode over right frontal cortex	tDCS had no impact on verbal memory (primary outcome), global cognition, executive function, or processing speed

Bystad et al. (2016b)	Alzheimer's dementia	1	59	2	12 (twice a day for 6 days)	Anode over left temporal cortex Cathode over right frontal cortex	Participant experienced a clinically significant improvement on verbal memory at 2 months following the last tDCS session
Bystad et al. (2017)	Alzheimer's dementia	1	60	2	Daily over 8 months	Anode over left temporal cortex Cathode over right frontal cortex	39% improvement in verbal immediate recall, 23% improvement in verbal delayed recall, 16% improvement in vocabulary, 10% decline in visuospatial ability, and general stability in other domains
Roncero et al. (2017)	Alzheimer's dementia or frontotemporal dementia	10 (Alzheimer's dementia: 3; frontotemporal dementia: 7)	67.4 (6.3)	2	10 daily sessions followed by 10 sham daily sessions 2 months later (or vice versa)	Anode over left inferior parietal cortex Cathode over right fronto-orbital cortex	Participants improved by 40% on picture naming after active tDCS vs. 19% after sham tDCS
Cespon et al. (2019)	Alzheimer's dementia and healthy older controls	26 Alzheimer's: 12 Healthy: 14	76.0 (5.9)70.2 (5.1)	1.5	1 (anodal, cathodal, or sham, with cross-over design to receive all three types)	Anode or cathode over left DLPFC Reference electrode over right shoulder	Neither anodal nor cathodal stimulation was associated with better working memory performance compared to sham with Alzheimer's and healthy participants analyzed together
Im et al. (2019)	Alzheimer's dementia	20	~73	2	Daily over 6 months	Anode over left DLPFC Cathode over right DLPFC	Active tDCS resulted in better global cognition and language compared to sham tDCS and a trend toward better executive function

(continued)

Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Gangemi et al. (In Press)	Alzheimer's dementia	2618	~68 ~ 68	22	10 consecutive10 consecutive per month for 8 months	Anode over left frontotemporal cortex Cathode over right frontal lobe Anode over left frontotemporal cortex Cathode over right frontal lobe	Anodal stimulation was associated with global cognitive stability compared to the sham stimulation which was associated with cognitive decline immediately after the intervention Anodal stimulation was associated with global cognitive stability compared to the sham stimulation which was associated with cognitive decline immediately after the intervention
Liu et al. (In Press)	Alzheimer's dementia or mild cognitive impairment	17 Alzheimer' dementia: 9 mild cognitive impairment: 8	77 (5)	2	Random cross-over design between one session of bitemporal vs. one session of bifrontal (DLPFC), vs, 1 session of sham Sessions separated by 1 week	Bifrontal: Two anodes over left and right DLPFC; cathode over inion Bitemporal: Two anodes over the left and right temporal cortices; cathode over inion	Compared to the performance on the day before stimulation, change on working memory immediately following the one session of bitemporal stimulation (and not bifrontal stimulation) was higher than change following sham stimulation
Alzheimer's dementia: tDCS combined with cognitive enhancement intervention							
Cotelli et al. (2014)	Alzheimer's dementia	36	~77	2	10 (5 days a week for 2 weeks)	Anode or sham over left DLPFC Both combined with memory or motor training Reference over right deltoid	Memory training improved face-name association and the improvement persisted at 3 months Anodal tDCS did not improve performance beyond memory training

Penolazzi et al. (2015)	Alzheimer's dementia	1	60	2	10 consecutive	Anode over left DLPFC Cathode over right supra-orbital region Each tDCS session was followed by cognitive training Two months later, cognitive training without tDCS	tDCS combined with cognitive training improved global cognitive function that it persisted for 1 month. No improvement without tDCS
Inagawa et al. (2019)	Alzheimer's dementia or mild cognitive impairment (except for two participants with Lewy body disease)	20	~76	2	Two sessions per day for 5 consecutive days during cognitive training	Anode over left DLPFC Cathode over right supra-orbital area	There were no significant differences between active and sham tDCS on one cognition using the MMSE or the Alzheimer's disease assessment scale – cognition subscale
Mild cognitive impairment: tDCS alone							
Meinzer et al. (2015)	Mild cognitive impairment	18	67.4 (7.3)	1	1 during a semantic word-retrieval task	Anode or sham over left inferior frontal gyrus Cathode over right supra-orbital region	Anodal stimulation normalized performance compared to healthy participants
Yun et al. (2016)	Mild cognitive impairment	16	~74	2	3 sessions per week for 3 weeks	Anode over the left DLPFC Cathode over right DLPFC	Active stimulation resulted in improved subjective memory ability and contentment compared to sham stimulation. No change in objective measures of cognition
Fileccia et al. (2019)	Mild cognitive impairment	34	~71	2	Daily sessions, 5 days per week, for up to 20 sessions	Anode over left DLPFC Cathode over right deltoid	Active stimulation and not sham stimulation was associated with improvement in episodic memory, figure naming, and general cognition, immediately after stimulation

(continued)

Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Gomes et al. (2019)	Mild cognitive impairment	58	~72	2	10 sessions, twice a week, over 5 weeks	Anode over left DLPFC Cathode over right supra-orbital region	Active stimulation was associated with better executive function, verbal fluency, and memory recall, but with worse visuospatial construction, when compared to sham stimulation
Manenti et al. (In Press)	Mild cognitive impairment	18	75.3 (3.7)	1.5	1 session during re-activation phase of an episodic memory task	Anode over left lateral prefrontal cortex Cathode over right supra-orbital area	Active tDCS was associated with better recognition of words compared to sham tDCS following
Mild cognitive impairment: tDCS combined with cognitive enhancement intervention							
Gonzalez et al. (2018)	Mild cognitive impairment	5	67.0 (6.6)	2	Cognitive stimulation alone (3 daily sessions) followed by sham tDCS + cognitive stimulation (1–5 daily sessions), followed by active tDCS + cognitive stimulation (1–5 daily sessions), followed by cognitive stimulation alone	Anode over left DLPFC Cathode over right deltoid muscle	Active tDCS was associated with shorter completion times on processing speed task
Das et al. (2019)	Mild cognitive impairment	22	62.9 (7.8)	2	1 session prior while watching Planet Earth videos and right before starting a cognitive training session, for a total of 8 sessions over 4 weeks	Anode over left inferior gyrus Cathode over right shoulder	Sham stimulation was associated with better executive function, inhibition, innovation, and episodic memory compared to active stimulation, immediately after the course of stimulation but not 3 months later

Martin et al. (2019)	Mild cognitive impairment	68	~72	2 mA for 30 min then 0.016 mA for 15 to 30 more min during the remaining of cognitive training Sham: 0.016 mA for 45–60 min	15 sessions of tDCS with cognitive training (3 per week for 5 weeks)	Anode over left DLPFC Cathode over right frontal cortex	Active and not sham stimulation was associated with improvement in verbal memory immediately after the tDCS course. Both were associated with further improvements at 3-month post-treatment
de Souza et al. (2020)	Mild cognitive impairment	16 MCI32 healthy individuals	70 (6)69 (7)	1 mA	3-day visuospatial training combined with active or sham tDCS, followed, 3 months later, with 3-day visuospatial training combined with the opposite stimulation	Anode over right temporoparietal cortex Cathode over left supra-orbital area	Immediately after the training, anodal and not sham stimulation was associated with better training on the visuospatial task among MCI participants and not healthy individuals. The gains experienced by MCI participants under active – and not sham – stimulation were similar to the gains observed for the HC participant No benefits were experienced at 1-month follow-up
Frontotemporal dementia; Lewy body dementia; Parkinson's disease; primary progressive aphasia; vascular dementia							
Benussi et al. (In Press)	Frontotemporal dementia	15 Presymptomatic, 55 Symptomatic	52.5 (9.6)62.0 (7.2)	2	10 sessions (5 daily sessions per week for 2 weeks)	Anode over left DLPFC Cathode over right deltoid	Active stimulation was associated with better global cognition, verbal fluency, processing speed, executive function, emotions recognition, and behavioral symptoms

(continued)

Table 20.1 (continued)

Authors (Year)	Disease	N	Age (SD)	tDCS current (mA)	tDCS number of sessions	Electrode placement	Clinical and cognitive Results
Elder et al. (2015)	Lew body dementia	13 (including 8 with Parkinson's disease dementia)	64.8 (7.7)	2.8	1	Anode over left DLPFC Cathode over right deltoid	Stimulation improved attention
Boggio et al. (2006)	Parkinson's disease	18	61.1	2	1 or 2	Anode over left DLPFC or left motor cortex Cathode over right orbital region	2 mA anodal stimulation improved working memory
Pereira et al. (2013)	Parkinson's disease	16	61.5 (9.9)	2	1	Anode over left DLPFC or left temporoparietal cortex Cathode over right orbital region	Stimulation improved phonemic but not semantic fluency
Doruk et al. (2014)	Parkinson's disease	18	61 (8)	2	10 (5 days a week for 2 weeks)	Anode or sham over left or right DLPFC or left motor cortex Cathode over contralateral supra-orbital region	Both anodal stimulation improved executive function and it persisted for 1 month
Manenti et al. (2016)	Mild cognitive impairment due to Parkinson's disease	20	~69	2	10 sessions (5 sessions per week for 2 weeks) combined with physical therapy	Anode over right or left DLPFC, contralateral to the most affected side Cathode over contralateral supra-orbital region	Active tDCS resulted in better cognition at the end of treatment compared to sham tDCS and this improvement was stable 3 months later Cognitive benefits were observed despite no added benefits in terms of mood or motor symptoms
Elder et al. (2017)	Parkinson's disease dementia	38	66.6 (8.4)	2.8	1 (active or sham, followed by the alternate stimulation after 24 hours)	Anode over left DLPFC Cathode over right deltoid	No difference between active and sham stimulation on cognition

Lau et al. (2019)	Parkinson's disease	10	62.7 (6.6)	2	1 (active or sham, followed by the alternate stimulation after 2 weeks) during the performance of a working memory and an inhibition task	Anode over left prefrontal cortex Cathode over right supra-orbital area	No differences on working memory and inhibition tasks were detected between active and sham stimulation
de Aguiar et al. (2020)	Primary progressive aphasia	30	66.4 (6.7)	2	10–15 sessions of active or sham tDCS delivered during the first 20 min of 45 min naming/spelling therapy sessions After a 2-month washout period, participants received another course of therapy with the alternate tDCS	Anode over left inferior frontal gyrus Cathode over right cheek	Active stimulation was associated with better performance on trained words compared to sham stimulation at the 2-month follow-up and not the 2-week or immediately after therapy assessments
Andre et al. (2016)	Vascular dementia	21	~78	2	4 at-home sessions on 4 consecutive days	Anode over left DLPFC Cathode over right supra-orbital region	Active stimulation was associated with reduced reaction time on working memory and inhibition tasks and increased performance on a picture naming task, compared to sham stimulation, immediately after the tDCS course and not 2 weeks later

DLPFC dorsolateral prefrontal cortex, *MMSE* Mini Mental State Examination, *tDCS* transcranial direct current stimulation

during stimulation. Anodal tDCS at both sites improved performance on a visual recognition memory task by 18% for the DLPFC and 14% for the temporal cortex [4].

The above two studies were followed by others that assessed the impact of a course of tDCS on cognition. In Boggio et al. [5], 15 participants with mild-to-moderate AD received daily consecutively for 5 days, 30-min sessions of bilateral anodal or sham tDCS in a random order. Anodes were placed over the temporal lobes. Cathodal electrode was placed over the right deltoid muscle. Current was 2 mA. Cognition was assessed before the first tDCS session, at the end of treatment on day 5, 1 week later, and then 4 weeks later. Anodal tDCS resulted in improvements in visual recognition memory, and these improvements persisted for 4 weeks following the course of tDCS. The percent change from baseline was about 11%. tDCS was well tolerated by all participants.

In Khedr et al. [6], 34 participants with mild-to-moderate AD were randomized to receive anodal tDCS, cathodal tDCS, or sham tDCS. tDCS was applied to the left DLPFC for 25 min daily for 10 days. The reference electrode was placed over the contralateral supra-orbital region. Current was 2 mA. Follow-up assessments were conducted immediately, and 1 and 2 months following the tDCS course. Other than for a couple of participants experiencing transient itching, headache, and dizziness, tDCS was well tolerated. Both anodal and cathodal tDCS resulted in improvement on Mini-Mental State Examination (MMSE) [7] compared with sham tDCS. The two forms of active tDCS did not differ in efficacy. Improvement on MMSE was by about four points with an initial improvement immediately following tDCS, an additional improvement 1 month later, and persistence of this improvement one additional month later. Such is a change is considered clinically significant.

In Bystad et al. [8], 25 participants with mild-to-moderate AD were randomized to receive anodal tDCS applied to the let temporal cortex with the cathodal electrode over the right frontal cortex or sham tDCS. tDCS was applied for 30 min daily for 5 days. Current was 2 mA. Follow-up assessments were conducted immediately. Other than for itching, transient headaches, and skin irritation, tDCS was well tolerated. Unlike, previous studies to date, active tDCS did not result in better verbal memory (primary outcome), global cognition, executive function, or processing speed compared to sham tDCS.

In a case report by the same group [9], a single participant with mild AD underwent an accelerated tDCS course of 12 sessions, twice a day, over 6 consecutive days. Each session consisted of anodal tDCS applied to the let temporal cortex with the cathodal electrode over the right frontal cortex and lasted for 30 min. Current was 2 mA. This report indicated that the participant experienced a clinically significant improvement in verbal memory recall and tDCS was well tolerated.

In another case report by the same group [10]), another single participant with mild AD received anodal tDCS daily for 8 months. The anode was placed over the left temporal cortex and the cathode over the right frontal cortex. Current was also 2 mA. tDCS was well tolerated. The participant experienced at the 8-month assessment 39% improvement in verbal immediate recall, 23% improvement in verbal delayed recall, 16% improvement in vocabulary, 10% decline in visuospatial ability, and general stability in other domains.

In Roncero et al. [11], 10 participants with AD ($N = 3$) or frontotemporal dementia ($N = 7$) were randomized in a cross-over design to active followed by sham tDCS (2 months later or vice versa) for 10 daily sessions. Anode was placed over the left inferior parietal cortex and the cathode over the right fronto-orbital region. Current was 2 mA. Each session was for 30 min. The primary outcome was picture naming. Active tDCS significantly improved picture naming ability by 40% vs. an improvement of 19% following sham tDCS.

In Cespon et al. [12], 12 participants with AD and 14 healthy older participants were randomized to receive anodal, cathodal or sham tDCS for 1 session delivered to the left DLPFC and then crossed over to receive all three types of stimula-

tion with a 5-day interval between 2 consecutive sessions. The reference electrode was placed over the right shoulder. Current was 1.5 mA. Duration of stimulation was 13 min. Before and after each stimulation session, participants underwent a working memory task while undergoing an electroencephalogram (EEG). All participants were analyzed together. There were no differences detected in working memory performance among the three types of stimulation. However, anodal tDCS was associated with increased P200 and P300 amplitudes in healthy participants while cathodal tDCS was associated with increased P200 amplitude and frontal theta activity in AD participants. Further, only in healthy participants improvements in working memory after anodal tDCS were correlated with increased P300.

In Liu et al. [13], 17 participants with mild AD or mild cognitive impairment (MCI; mean age: 77, SD: 5) were randomized in a cross-over design to receive 1 session of bifrontal or bitemporal or sham tDCS, all separated by 1 week. During bifrontal stimulation, two anodes were placed over the left and right DLPFC and the cathode over the inion. During bitemporal stimulation, two anodes were placed over the left and right temporal cortices and the cathode over the inion. Current was 2 mA. Duration of stimulation was 20 min. On the day before each stimulation and immediately after, participants were assessed cognitively including an assessment of working memory which was the primary domain. The authors report that only following bitemporal stimulation the improvement in working memory was significantly higher than the improvement following sham.

A few studies reported on the impact of tDCS on maintaining cognitive stability among patients with AD rather than cognitive improvement.

In Im et al. [14], 20 participants with mild AD were randomized to receive anodal tDCS to the left DLPFC with the cathode over the right DLPFC, or sham tDCS, daily for 6 months, 30 min per day. The first 3 sessions were delivered by a nurse in a hospital setting and the remaining sessions were delivered at home by a caregiver. Current was 2 mA. Active tDCS resulted in better global cognition as measured using the MMSE and better naming compared to sham tDCS at 6 months. Those randomized to active tDCS also experienced a trend toward improvement in executive function while those randomized to sham tDCS experienced a trend toward a decline. Further, those randomized to active tDCS experienced stability on 18F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) over the left middle/inferior temporal gyrus compared to a significant decline among those randomized to sham tDCS.

In Gangemi et al. [15], two randomized trials were reported. In the first one, 26 participants with mild AD were randomized to active or sham tDCS, for 10 daily consecutive sessions. Each session lasted for 20 min. Current was 2 mA. Anode was placed over the left frontotemporal cortex and the cathode over the right frontal lobe. Global cognition and a composite measure of cognitive and function were assessed before and immediately after the 10-day course of tDCS. Active stimulation was associated with stability in cognition/function compared to a decline in cognition among those randomized to sham stimulation. In the second one, 18 participants with mild AD were randomized to a similar protocol except that they received the 10 sessions every month for 8 months. At the end of the 8 months, active stimulation was also associated with stability in cognition/function compared to a decline that was associated with sham intervention. The two studies support the beneficial impact of tDCS on maintaining cognition/function among patients with mild AD although it was not clear why there was a significant decline over 10 days among those who were randomized to sham tDCS. In both studies, resting EEG were collected before and after the interventions and there were changes reported within certain frequencies although it was not clear what the specific EEG analyzed variables were.

Patients with AD not only experience cognitive dysfunction, but also significant behavioral and psychological symptoms. One study focused on the effects of tDCS on apathy. In Suemoto et al. [16], 40 participants with moderate AD were randomized to receive anodal or sham tDCS delivered to the left DLPFC for 20 min, every

other day for 6 sessions over 2 weeks. Cathodal electrode was placed over the right orbit. Current was 2 mA. Assessments were conducted at baseline, 1 week into the tDCS course, at the end of the 2-week course, and then 1 week after completing the course. The primary outcome measure was the score on the Apathy Scale [17]. tDCS was well tolerated with minor side effects, mainly scalp burning sensation and tingling. The two groups did not differ on Apathy Scale at any of the time points of assessments, nor did they differ on other secondary measure, including cognitive, mood, and caregiver burden measures.

Thus, studies in AD have had mixed results when assessing for an acute improvement following a short course of tDCS effect. However, and notwithstanding that the number of studies is small, those that assessed for a cognitive stabilization effect seems to have been more positive. A parallel line of research is to investigate whether the pro-cognitive effects of tDCS can optimize performance in response to other cognitive enhancing interventions, or whether they can be augmented through these other interventions.

In Cotelli et al. [18], 36 participants with mild-to-moderate AD were randomized to receive anodal tDCS combined with memory training, sham tDCS combined with memory training, or anodal tDCS combined with motor training. tDCS was applied to left DLPFC for 25 min, 5 days a week, for 2 weeks. The reference electrode was placed on the right deltoid muscle. Current was 2 mA. tDCS was initiated at the beginning of each training session that occurred 5 days a week for 2 weeks. Memory training consisted of training on face-name association task. Assessments were conducted at baseline, after the 2 weeks of tDCS course, and then 3 and 6 months from the start of the tDCS course. Both groups who received memory training experienced improvement in face-name association talk compared with the group who received motor training. The improvement persisted at 3 month follow-up. However, there was no significant generalization to other cognitive tasks beyond what the participants trained on. More importantly, groups who received anodal or sham tDCS, combined with memory training, did not differ in performance.

In Penolazzi et al. [19], one patient with mild AD received one course of anodal tDCS, daily for 20 min for 10 days, over the left DLPFC. Reference electrode was placed over the right supra-orbital area. Current was 2 mA. Each tDCS was followed by 45 min of cognitive training. Two months later, the patient received the same course of cognitive training but with sham tDCS. Following the first course, the patient experienced improvement in global cognitive function and it persisted for 1 month. There was no such improvement following the second course.

In Inagawa et al. [20], 20 participants with AD or MCI except for 2 with Lewy body disease were randomized to receive active or sham tDCS delivered during cognitive training and over 20 min, twice a day, for 5 consecutive days. Current was 2 mA. Anode was placed over the left DLPFC and the cathode over the right supra-orbital region. While active tDCS was well tolerated, it did not improve cognition as measured using the MMSE or the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [21] over sham tDCS.

20.2 Mild Cognitive Impairment

Given the early preliminary positive evidence supporting a pro-cognitive effect of tDCS in patients with AD, it was logical to assess its effects in pre-AD stages of the illness for potentially more impact on the course of illness.

In Meinzer et al. [22], 18 participants with MCI due to AD (11 amnestic MCI and 7 multiple domain MCI) received, in a cross-over design, 1 session of anodal or sham tDCS to the left inferior frontal gyrus for 20 min. The sessions were separated by 1 week. The cathode was placed over the right supra-orbital region. Current was 1 mA. Participants received tDCS while performing a semantic word-retrieval task and undergoing functional magnetic resonance imaging (fMRI). tDCS was well tolerated. During sham tDCS, participants performed worse than healthy control participants. In contrast, during anodal tDCS, their performance normalized to become comparable to that of the healthy control partici-

pants. This normalization was accompanied by normalization of task-related and resting-state brain activity as measured with fMRI.

In Yun et al. [23], 16 participants with MCI were randomized to receive active or sham tDCS for 3 sessions per week for 3 weeks. Anode was placed over the right DLPFC and the cathode over the left DLPFC. Current was 2 mA. Objective and subjective measures of cognition were completed before and after the tDCS course, as well as FDG-PET. tDCS was well tolerated. While there was no impact of active tDCS on objective measures of cognition, it was associated with better subjective measures and with increased cerebral metabolism in several brain regions, including dorsolateral, ventrolateral, and medial prefrontal cortices, the dorsal anterior cingulate, the anterior and posterior insular regions, and the hippocampal and parahippocampal regions.

In Fileccia et al. [24], 34 participants with MCI were randomized to receive active or sham tDCS, 1 session per day, 5 days per week for up to 20 sessions. Each session was 20 min. Current was 2 mA. Cognitive assessment was completed before and after the 20 sessions. The anode was placed over the left DLPFC and the cathode over the right deltoid. Active stimulation and not sham stimulation was associated with improved episodic memory, figure naming, and general cognition.

In Gomes et al. [25], 58 participants with MCI were randomized to active or sham tDCS, 2 sessions per week, each for 30 min, for 5 weeks with cognitive assessments completed before, and immediately and 90 days after the intervention. The anode was placed over the left DLPFC with the cathode over the right supra-orbital area. Current was 2 mA. Active stimulation was associated with better executive function, verbal fluency, and memory recall, but with worse visuospatial construction, when compared to sham stimulation immediately after the 10-session course. No results were reported on 90-day performances.

In Manenti et al. [26], 18 participants with amnestic MCI were randomized to receive 1 session of active or sham tDCS during the reactivation phase of an episodic memory task. The participants were administered the task on the day before. Then, they were tested on free recall and recognition on the day after and 30 days later. Each session was for 15 min. Current was 1.5 mA. The anode was placed over the left lateral prefrontal cortex and the cathode over the right supra-orbital region. Anodal tDCS was found to be associated with better recognition than sham tDCS after the day of stimulation, though it was not clear whether this was on the day after stimulation or 30 days later.

Similar to studies in AD, a few studies in MCI assessed the impact of adding tDCS to another cognitive enhancement intervention.

In Gonzalez et al. [27], 5 participants with MCI were assigned to receive cognitive stimulation for 3 daily sessions, followed by sham tDCS during cognitive stimulation for 1–5 daily sessions, followed by active tDCS during cognitive stimulation also for 1–5 daily sessions, followed by cognitive stimulation alone again. Each session was for 30 min. The anode was placed over the left DLPFC and the cathode over the right deltoid. Current was 2 mA. Each phase of this study was separated from the previous one by 1 week. Compared to cognitive stimulation alone, active tDCS with cognitive stimulation was associated with faster processing speed, attention, and planning.

In Das et al. [28], 22 participants with MCI were randomized to receive active or sham tDCS for 20 min while watching Planet Earth videos and right before starting a cognitive training session for a total of 8 sessions over 4 weeks. The anode was placed over the left inferior frontal gyrus and the cathode over the right shoulder. Current was 2 mA. In this study, sham tDCS was associated with better executive function, inhibition, innovation, and episodic memory even though active tDCS was associated with improved resting state cerebral blood flow in the right middle frontal cortex. These findings suggested that anodal tDCS inhibited any potential gains from the cognitive training program. The authors speculated that tDCS could have activated inhibitory homeostatic response that "blocked" benefit from cognitive training. Alternatively, the repeated stimulation could have increased

"firing" of neuronal networks and, in turn, prevented consolidation of top-down learning strategies acquired during cognitive training. A third speculation the authors provided, suggested by the increase in cerebral blood flow on the right side, that is, the side opposite of stimulation, is that tDCS could have disrupted the allocation of cerebral blood flow, and, in turn, compromised the neuronal processes that support the learning strategies. Of note, tDCS was delivered before and not during the cognitive enhancement intervention, and while being cognitively engaged in watching a stimulating video, which also could have contributed to the "blocking" effect.

In Martin et al. [29], 68 participants with amnestic MCI were randomized to active or sham tDCS that was combined with cognitive training for 15 sessions administered 3 days per week over 5 weeks. Each cognitive training session lasted 45 to 60 min. During the first 30 min of each session, active tDCS at 2 mA was delivered followed by tDCS at 0.016 mA for the remaining of the session, or sham tDCS at 0.016 mA was delivered for the whole session, after ramping up and down for 1.5 min. The anode was placed over the left DLPFC and the cathode over the right frontal cortex. Cognitive assessments with verbal memory being the primary outcome domain were administered at baseline, end of treatment, and 30 days later. While there was no interaction between time and group, the study showed that only those who received active tDCS experienced improvement in verbal memory from baseline at the first follow-up and both groups experienced an improvement at the 30-day follow-up. Concerns regarding the potential active role of low intensity current was raised given the persistent improvement in verbal memory among those who received the sham intervention.

In de Sousa et al. [30], 18 participants with MCI and 32 healthy older control participants were randomized to receive first active or sham tDCS combined with a training session on a visuospatial task for 3 days followed by 3 months later, by the alternate stimulation combined with the 3-day training on the same task. Current was 1 mA. The anode was placed over the right temporoparietal cortex and the cathode over the left supra-orbital area. Stimulation was for 20 min. Cognitive assessment was completed immediately after the 3-day training and 1 month later. At the first follow-up, only the MCI participants experienced an enhanced training under active tDCS compared to sham tDCS. They also experienced a gain under active tDCS that is similar to what the healthy control participants gained from the training. However, these benefits did not persist at the 1-month follow-up.

Taken together, and notwithstanding that the studies to date need to be replicated in larger samples, there seems to be an advantage of using tDCS during the earlier stages of cognitive impairment including when it is being combined with a cognitive enhancement intervention.

20.3 Frontotemporal Dementia, Lewy Body Dementia, Parkinson's Disease, Primary Progressive Aphasia, and Vascular Dementia

20.3.1 Frontotemporal Dementia

Frontotemporal dementia represents a group of neurodegenerative cognitive disorders that are typically characterized by early impairments in behavior, executive function, and language. Frontotemporal dementia is considered the third most common form of dementia following AD and Lewy body dementia [31]. Patients with frontotemporal dementia are divided into two subtypes depending on their predominant symptoms: behavioral or language subtype. The onset of frontotemporal dementia tends to be at a younger age than AD or Lewy body dementia. In addition to having no current treatments for the cognitive symptoms of frontotemporal dementia, and, in contrast to AD, there is minimal evidence to support treatments for the behavioral and emotional symptoms of this disorder.

In Benussi et al. [32], 55 participants with frontotemporal dementia were randomized to receive active or sham tDCS, 5 days per week for 2 weeks. Each session was for 20 min. Current was 2 mA. The anode was placed over the left

DLPFC and the cathode over the right deltoid. Cognitive and neurophysiological assessments using transcranial magnetic stimulation (TMS) were completed at baseline, and then immediately and 3 and 6 months after the 2-week course of tDCS. TMS measures were also conducted at 1 month after the 2-week course. tDCS was well tolerated. Active stimulation was associated with better global cognition, verbal fluency, processing speed, executive function, emotions' recognition, and behavioral symptoms compared to sham stimulation. Active stimulation was also associated with enhanced intracortical facilitation and enhanced inhibition as indexed using TMS. There was also a correlation between change in intracortical facilitation and change in processing speed and executive function.

20.3.2 Lewy Body Dementia

Lewy body dementia accounts for 3–15% of all dementias [33, 34]. It is typically characterized by fluctuating cognitive impairments, visual hallucinations, and Parkinsonian motor symptoms. It is also considered an umbrella that includes dementia of Lewy body and Parkinson's disease dementia. The diagnosis of dementia with Lewy body is made when the motor symptoms develop within 1 year before or after the onset of cognitive deficits. In contrast, a Parkinson's disease dementia diagnosis is made when the motor symptoms had been present for more than 1 year prior to the cognitive deficits [35]. Cholinesterase inhibitors are recommended for the treatment of Lewy body dementia, though their clinical impact is modest [36, 37].

In contrast to patients with AD, patients with Lewy body disease experience significant impairments in attention, executive function, and visuospatial abilities early on during the illness. These impairments may even precede deficits in learning and memory [38–40].

tDCS has been tested for its effects on Lewy body dementia-associated cognitive deficits. It has also been tested for its effects on cognitive impairment associated with Parkinson's disease per se, that is, without a full manifestation of dementia.

In Boggio et al. [41], 18 participants with Parkinson's disease received 1 session of anodal tDCS delivered to the left DLPFC for 20 min. Reference electrode was placed over the right orbit. They also underwent a session of motor cortex stimulation and sham tDCS to the left DLPFC. Current was 1 mA in one set of experiments and 2 mA in another set. Before and during the last 5 min of each tDCS session, participants were administered a working memory task. All experiments were well tolerated. tDCS at 1 mA did not result in any working memory change, In contrast, at 2 mA, left DLPFC stimulation resulted in more correct responses than motor cortex or sham tDCS. No change in speed of response was found.

In Pereira et al. [42], 16 participants with Parkinson's disease were randomized to receive 1 session of anodal tDCS to the left DLPFC or left temporoparietal cortex in a counterbalanced order, for 20 min. The cathode was placed over the right supra-orbital area. Current was 2 mA. Anodal tDCS to the DLPFC resulted in improved phonemic but not semantic fluency. It also resulted in enhanced functional connectivity and task-related deactivation as measured with fMRI.

In Doruk et al. [43], 18 participants with Parkinson's disease were randomized to receive anodal tDCS delivered to the left or right DLPFC, or sham tDCS for 20 min, daily, 5 days a week, for 2 weeks. The cathode was placed over the contralateral supra-orbital region. Current was 2 mA. Assessments were conducted at baseline, at the end of tDCS course, and 1 month following baseline. Overall, tDCS was well tolerated with reports of tingling, sleepiness, mild headache, neck pain, skin redness, and trouble concentrating. Anodal tDCS, irrespective of laterality, resulted in improved performance on executive function at the end of the tDCS course and that persisted at 1 month of follow-up. Sham tDCS resulted in improvement at the end of tDCS course, but the improvement did not persist. No significant effects were observed on other cognitive functions.

In Elder et al. [44], 13 participants with Lewy body dementia, including 8 with Parkinson's dis-

ease dementia and 5 with dementia with Lewy bodies, received a single session of anodal tDCS delivered to the left DLPFC for 20 min. The cathode was placed over the right deltoid muscle. Current was 2.8 mA. Before and 10 min after the stimulation, attentional and visuospatial cognitive tasks that have been shown to detect Lewy body dementia-specific deficits were administered. Participants experienced improvements on some of the attentional but on none of the visuospatial tasks following tDCS. tDCS was well tolerated.

In Manenti et al. [45], 20 participants with MCI due to Parkinson's disease were randomized to receive active or sham tDCS combined with physical therapy for 25 min per day, 5 days a week for 2 weeks. The anode was placed over the right or left DLPFC, contralaterally to the side of the body with more motor symptoms, for each individual. Current was 2 mA. Motor, mood, and cognitive symptoms were assessed at baseline and immediately and 3 months following the intervention. Despite no improvement over placebo with respect to motor or mood symptoms, participants randomized to active tDCS experienced better improvement in cognition immediately following the intervention and this enhanced improvement was stable at the 3-month assessment.

In Elder et al. [46], 38 participants with Parkinson's disease dementia were randomized to receive a single session of active or sham tDCS for 20 min and then crossed over to receive the alternate stimulation after 24 hours. Current was 2.8 mA. The anode was placed over the left DLPFC and the cathode over the right deltoid. Cognitive assessment was completed following each session. The study did not demonstrate any significant difference in cognition between active and sham tDCS.

In Lau et al. (2019), 10 participants with Parkinson's disease were randomized to 1 session of active or sham tDCS during the performance of a visual working memory and an emotional inhibition task. They were then crossed over to receive the alternate stimulation 2 weeks later. Current was 2 mA. The anode was placed on the left DLPFC and the cathode over the right supraorbital area. No differences in performance on the two cognitive tasks were detected between active and sham stimulation.

Overall, the literature on Lewy body dementia is consistent with the literature in AD and MCI. While there is a mixture of positive and negative findings, the less severe the cognitive impairment, the more beneficial tDCS seems, especially when combined with a cognitive enhancement intervention.

20.3.3 Primary Progressive Aphasia

Primary progressive aphasia is a diagnosis used to identify a heterogeneous group of patients who experience localized degeneration of the language-related brain regions. Patients with primary progressive aphasia are typically classified into one of three variants: the no-fluent/agrammatic variant, when the early clinical presentation consists of slow, effortful, and distorted speech; the semantic variant, when the early clinical presentation consists of well-structured sentences but with poor content and significant loss of the vocabulary; and the logopenic variant, when the early clinical presentation consists of word-finding difficulty and lapses during conversations, as well as sound and spelling errors [47, 48]. Primary progressive aphasia is gradually progressive and during the later stages of the illness, the distinction between the different types of language deficits becomes blurred and cognitive domains other than language become affected. No treatments are available to date.

In de Aguiar et al. [49], 30 participants with primary progressive aphasia were randomized to receive active of sham tDCS for 20 min during the first part of 45-min therapy sessions that were delivered for 10–15 sessions in total. Two months later, participants were crossed over to receive another course of therapy with the alternate type of stimulation. Current was 2 mA. Anode was placed over the left inferior frontal gyrus and the cathode over the right cheek. Assessments were conducted at baseline and then immediately, 2 weeks, and 2 months after the end of therapy. Active stimulation was associated with better

performance on trained words at the 2-month and not the previous follow-ups, compared to sham stimulation.

20.3.4 Vascular Dementia

While often in late life, dementias are associated with mixed pathologies, including pathologies of AD, Lewy body disease, and cerebrovascular disease, vascular dementia is diagnosed when the core clinical features are ascertained to be best attributed to vascular changes identified by brain imaging and cerebrovascular risk factors. The brain parenchymal changes can be ischemic or hemorrhagic in origin. Cerebral amyloid angiopathy can also lead to vascular dementia [50].

In Andre et al. [51], 21 participants with mild vascular dementia (mean age ~74) were randomized to receive active or sham tDCS, at home, for 1 session per day consecutively for 4 days. Current was 2 mA. Anode was placed over the left DLPFC and the cathode over the right supraorbital region. A comprehensive cognitive battery was completed at baseline, immediately after the tDCS course and 2 weeks later. Compared to sham tDCS, active tDCS was associated with faster reaction times on a working memory task and an inhibition task. It was associated with better performance on a naming task. However, these measures were few among many other cognitive measures on which there were no differences were detected between active and sham tDCS.

20.4 Conclusions and Future Directions

Overall, the current literature suggests that tDCS is potentially a useful non-surgical neurostimulation modality to improve cognition in patients with neurodegenerative cognitive disorders, especially during the early clinical stages of these disorders and when combined with another intervention that enhances cognition synergistically. However, it is important to note all studies to date are limited by generally small sample sizes and multiple outcome measures that the studies are exploring. In turn, many of the positive studies have not found differences between active and sham stimulation but positive signal of improvement within the group receiving the active stimulation and not within the group receiving sham. Hence, confirmatory and adequately powered studies are urgently needed and some are underway in older healthy adults (e.g., Woods et al. [52]) and older adults with a neurocognitive disorder (e.g., Rajji et al. [53]).

The literature suggests that if tDCS is to be effective with a persistent impact, it needs to be delivered repetitively, similar to most other interventions for brain disorders. It also suggests that long-term delivery of tDCS, close to a daily frequency, could prevent cognitive decline among older adults with a neurodegenerative cognitive disorder. Studies assessing different durations of tDCS along with different frequencies per week will help characterize the dosing of tDCS. This is especially critical for patients with neurodegenerative disorders who may either need to commute to a center where tDCS is to be delivered or may depend on caregivers and their availabilities to administer it. There is a high need to study the feasibility, tolerability, and acceptability of different remotely delivered tDCS regimens, whether delivered alone or in combination with other cognitive enhancement interventions for patients across the severity spectrum of neurodegenerative disorders [54].

Electrodes placement and current intensity are two other variables that need further studying in various disorders. The current literature supports the use of anodal tDCS in general and 2 mA currents. Further personalization could be supported by modeling studies. Modeling studies predict the flow of current during tDCS [55] and help minimize the impact of morphological variation on tDCS effects. Again, this is highly salient to patients with neurodegenerative disorders who are likely to have experienced cortical shrinkage and tissue loss and using individualized tDCS dosing based on patient's specific morphological characteristics may be necessary in future trials [56].

Combining tDCS with other interventions will add also another level of complexity to be

systematically investigated. tDCS interferes with neuroplasticity mechanisms [57, 58] as do other interventions such as cognitive training [59]. Timing of tDCS in relationship with another intervention will need to consider the potential interference of one intervention with another at the level of neuroplasticity mechanisms.

Finally, multidomain studies that combine different biological assessments, for example, genetics structural and functional imaging, neurophysiology, within the context of well-powered clinical trials are needed to better understand moderators of tDCS impact on cognition or other symptoms of neurodegenerative disorders, as well as its mechanisms of action in vivo.

References

1. Alzheimer's-Association. Alzheimer's disease facts and figures. Alzheimer Dement. 2015;11(3)
2. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95.
3. Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology. 2008;71(7):493–8.
4. Boggio PS, Khoury LP, Martins DCS, Martins O, de Macedo EC, Fregni F. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosurg Psychiatry. 2009;80(4):444–7.
5. Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimul. 2012;5(3):223–30.
6. Khedr EM, El Gamal NF, El-Fetoh NA, Khalifa H, Ahmed EM, Ali AM, et al. A double-bling randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease. Front Aging Neurosci. 2014;6
7. Folstein MF, Folstein SE, McHugh PR. Mini-mental state - practical method for grading cognitive state of patients for clinician. J Psychiatr Res. 1975;12(3):189–98.
8. Bystad M, Gronli O, Rasmussen ID, Gundersen N, Nordvang L, Wang-Iversen H, et al. Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial. Alzheimers Res Ther. 2016;8
9. Bystad M, Rasmussen ID, Abeler K, Aslaksen PM. Accelerated Transcranial direct current stimulation in Alzheimer's disease: a case study. Brain Stimul. 2016;9(4):634–5.
10. Bystad M, Rasmussen ID, Gronli O, Aslaksen PM. Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. Neurocase. 2017;23(2):146–8.
11. Roncero C, Kniefel H, Serivce E, Thiel A, Probst S, Chertkow H. Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia. Alzheimers Dement. 2017;3:247–53.
12. Cespon J, Rodella C, Miniussi C, Pellicciari MC. Behavioural and electrophysiological modulations induced by Transcranial direct current stimulation in healthy elderly and Alzheimer's disease patients: a pilot study. Clin Neurophysiol. 2019;130(11):2038–52.
13. Liu CS, Herrmann N, Gallagher D, Rajji TK, Kiss A, Vieira D, et al. A pilot study comparing effects of bifrontal versus bitemporal transcranial direct current stimulation in mild cognitive impairment and mild Alzheimer disease. J ECT. 2020;36(3):211–5.
14. Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12(5):1222–8.
15. Gangemi A, Colombo B, Fabio RA. Effects of short- and long-term neurostimulation (tDCS) on Alzheimer's disease patients: two randomized studies. Aging Clin Exp Res. 2021;33(2):383–90.
16. Suemoto CK, Apolinario D, Nakamura-Palacios EM, Lopes L, Paraizo Leite RE, Sales MC, et al. Effects of a non-focal plasticity protocol on apathy in moderate Alzheimer's disease: a randomized, double-blind, Sham-controlled Trial. Brain Stimul. 2014;7(2):308–13.
17. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1992;4(2):134–9.
18. Cotelli M, Manenti R, Brambilla M, Petesi M, Rosini S, Ferrari C, et al. Anodal tDCS during face-name associations memory training in Alzheimer's patients. Front Aging Neurosci. 2014;6
19. Penolazzi B, Bergamaschi S, Pastore M, Villani D, Sartori G, Mondini S. Transcranial direct current stimulation and cognitive training in the rehabilitation of Alzheimer disease: a case study. Neuropsychol Rehabil. 2015;25(6):799–817.
20. Inagawa T, Yokoi Y, Narita Z, Maruo K, Okazaki M, Nakagome K. Safety and feasibility of transcranial direct current stimulation for cognitive rehabilitation in patients with mild or major neurocognitive disorders: a randomized sham-controlled pilot study. Front Hum Neurosci. 2019;13
21. Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. J Alzheimers Dis. 2008;15(3):461–4.

22. Meinzer M, Lindenberg R, Mai Thy P, Ulm L, Volk C, Floeel A. Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms. Alzheimers Dement. 2015;11(9):1032–40.
23. Yun K, Song IU, Chung YA. Changes in cerebral glucose metabolism after 3 weeks of noninvasive electrical stimulation of mild cognitive impairment patients. Alzheimers Res Ther. 2016;8
24. Fileccia E, Di Stasi V, Poda R, Rizzo G, Stanzani-Maserati M, Oppi F, et al. Effects on cognition of 20-day anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex in patients affected by mild cognitive impairment: a case-control study. Neurol Sci. 2019;40(9):1865–72.
25. Gomes MA, Akiba HT, Gomes JS, Trevizol AP, Tavaes de Lacerda AL, Dias AM. Transcranial direct current stimulation (tDCS) in elderly with mild cognitive impairment: a pilot study. Dement Neuropsychol. 2019;13(2):187–95.
26. Manenti R, Sandrini M, Gobbi E, Binetti G, Cotelli M. Effects of Transcranial direct current stimulation on episodic memory in amnestic mild cognitive impairment: a pilot study. J Gerontol B Psychol Sci Soc Sci. 2020;75(7):1403–13.
27. Gonzalez PC, Fong KNK, Brown T. The effects of transcranial direct current stimulation on the cognitive functions in older adults with mild cognitive impairment: a pilot study. Behav Neurol. 2018;2018
28. Das N, Spence JS, Aslan S, Vanneste S, Mudar R, Rackley A, et al. Cognitive training and transcranial direct current stimulation in mild cognitive impairment: a randomized pilot trial. Front Neurosci. 2019;13
29. Martin DM, Mohan A, Alonzo A, Gates N, Gbadeyan O, Meinzer M, et al. A pilot double-blind randomized controlled trial of cognitive training combined with transcranial direct current stimulation for amnestic mild cognitive impairment. J Alzheimers Dis. 2019;71(2):503–12.
30. de Sousa AVC, Grittner U, Rujescu D, Külzow N, Flöel A. Impact of 3-day combined anodal transcranial direct current stimulation-visuospatial training on object-location memory in healthy older adults and patients with mild cognitive impairment. J Alzheimers Dis. 2020;75(1):223–44.
31. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015;386(10004):1672–82.
32. Benussi A, Dell'Era V, Cosseddu M, Cantoni V, Cotelli MS, Cotelli M, et al. Transcranial stimulation in frontotemporal dementia: a randomized, double-blind, Sham-Controlled Trial. Alzheimers Dement. 6(1):e12033.
33. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113–24.
34. Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of Lewy body disease – progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree – a new disease. Clin Neuropathol. 1984;3(5):185–92.
35. Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, Deteresa R, et al. The Lewy body variant of Alzheimers-disease – a clinical and pathological entity. Neurology. 1990;40(1):1–8.
36. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet. 2000;356(9247):2031–6.
37. Stinton C, McKeith I, Taylor J-P, Lafortune L, Mioshi E, Mak E, et al. Pharmacological management of Lewy body dementia: a systematic review and meta-analysis. Am J Psychiat. 2015;172(8):731–42.
38. Collerton D, Burn D, McKeith I, O'Brien J. Systematic review and meta-analysis show that dementia with Lewy bodies is a visual-perceptual and attentional-executive dementia. Dement Geriatr Cogn Disord. 2003;16(4):229–37.
39. Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain. 2006;129:729–35.
40. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: clinical features, diagnosis, and management. Front Neurol. 2012;3:88.
41. Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006;249(1):31–8.
42. Pereira JB, Junque C, Bartres-Faz D, Marti MJ, Sala-Llonch R, Compta Y, et al. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. Brain Stimul. 2013;6(1):16–24.
43. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson's disease. Neurosci Lett. 2014;582:27–31.
44. Elder GJ, Firbank MJ, Kumar H, Chatterjee P, Chakraborty T, Dutt A, et al. Effects of transcranial direct current stimulation upon attention and visuoperceptual function in Lewy body dementia: a preliminary study. Int Psychogeriatr. 2015:1–7.
45. Manenti R, Brambilla M, Benussi A, Rosini S, Cobelli C, Ferrari C, et al. Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. Mov Disord. 2016;31(5):715–24.
46. Elder GJ, Ashcroft J, Morgan KD, Kulsum MU, Banerjee R, Chatterjee P, et al. Transcranial direct current stimulation in Parkinson's disease dementia: a randomised double-blind crossover trial. Brain Stimul. 2017;10(6):1150–1.
47. Marshall CR, Hardy CJD, Volkmer A, Russell LL, Bond RL, Fletcher PD, et al. Primary pro-

gressive aphasia: a clinical approach. J Neurol. 2018;265(6):1474–90.
48. Montembeault M, Brambati SM, Gorno-Tempini ML, Migliaccio R. Clinical, anatomical, and pathological features in the three variants of primary progressive aphasia: a review. Front Neurol. 2018;9
49. de Aguiar V, Zhao Y, Faria A, Ficek B, Webster KT, Wendt H, et al. Brain volumes as predictors of tDCS effects in primary progressive aphasia. Nrain Lang. 2020;200:104707.
50. Vinters HV, Zarow C, Borys E, Whitman JD, Tung S, Ellis WG, et al. Review: vascular dementia: clinicopathologic and genetic considerations. Neuropathol Appl Neurobiol. 2018;44(3):247–66.
51. Andre S, Heinrich S, Kayser F, Menzler K, Kesselring J, Khader PH, et al. At-home tDCS of the left dorsolateral prefrontal cortex improves visual short-term memory in mild vascular dementia. J Neurol Sci. 2016;369:185–90.
52. Woods AJ, Cohen R, Marsiske M, Alexander GE, Czaja SJ, Wu S. Augmenting cognitive training in older adults (the ACT study): design and methods of a phase III tDCS and cognitive training trial. Contemp Clin Trials. 2018;65:19–32.
53. Rajji TK, Bowie CR, Herrmann N, Pollock PB, Bikson M, Blumberger DM, et al. Design and rationale of the PACt-MD randomized clinical trial: prevention of Alzheimer's dementia with cognitive remediation plus Transcranial direct current stimulation in mild cognitive impairment and depression. J Alzheimers Dis. 2020;76(2):733–51.
54. Gough N, Brkan L, Subramaniam P, Chiuccariello L, De Petrillo A, Mulsant BH, et al. Feasibility of remotely supervised transcranial direct current stimulation and cognitive remediation: a systematic review. PLoS One. 2020;15(2)
55. Bikson M, Rahman A, Datta A, Fregni F, Merabet L. High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. Neuromodulation. 2012;15(4):306–15.
56. Mahdavi S, Yavari F, Gharibzadeh S, Towhidkhah F. Modeling studies for designing transcranial direct current stimulation protocol in Alzheimer's disease. Front Comput Neurosci. 2014;8
57. Ranieri F, Podda MV, Riccardi E, Frisullo G, Dileone M, Profice P, et al. Modulation of LTP at rat hippocampal CA3-CA1 synapses by direct current stimulation. J Neurophysiol. 2012;107(7):1868–80.
58. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji YY, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
59. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology. 2012;37(1):43–76.

Part IV

Applications of tDCS in Neuropsychiatric Disorders

Mood Disorders: Clinical Results

21

Adriano H. Moffa, André R. Brunoni, and Colleen K. Loo

21.1 Introduction

Major depressive disorder (MDD) is currently one of the most prevalent and debilitating diseases worldwide [1]. MDD is a serious condition, associated with significant morbidity and with substantial personal, social and economic impairment [2]. Also, patients with MDD have a higher prevalence of medical comorbidities and lower quality of life [3]. This mood disorder is associated with persistent feelings of sadness and/or anhedonia (loss of interest or pleasure in previously pleasurable activities) as well as impaired sleep and weight changes [4]. Commonly, there is also the presence of negative thoughts marked by pessimism, worthlessness and guilt and, in the most severe spectrum, depression can be associated with increased suicidal thoughts and behaviours [4].

Depression can be considered a recurrent chronic disorder since approximately 80% of patients relapse within 1 year of treating an episode [5]. Additionally, approximately one-third of patients fail to obtain a satisfactory improvement of symptoms despite adequate pharmacological treatment, characterising treatment-resistant depression (TRD) [6].

Besides the use of medications and psychotherapy, other treatment options approved worldwide include neuromodulatory strategies such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). In a recently updated review, high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) was classified with a level "A" of recommendation (definite efficacy) for the treatment of depression [7]. A network meta-analysis comparing the clinical efficacy of non-invasive brain stimulation (NIBS) techniques indicated that bitemporal ECT and high dose right unilateral ECT were associated with the highest response rates [8]. However, in addition to the potential negative impact of specific ECT protocols on cognition [9], those techniques are not always available, have a relatively high total treatment cost, and require specialised personnel and services for their administration [10]. These aspects reinforce the need to develop new, safe, well tolerated and affordable interventions for the treatment of MDD, as an alternative to patients who do not respond to or tolerate traditional antidepressant treatments or who do not have access to them.

The exact pathophysiology of depression remains unclear despite the advances in knowledge gathered over the past decades. The initial

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"monoamine hypothesis" focused on the repercussion of neurochemical deficits in the brain. It proposes that the concentrations of monoamines (e.g. serotonin, noradrenaline and dopamine) in the synaptic cleft are decreased in the depressive state [11]. It is based on this hypothesis that most antidepressant medications that commonly work on monoamine transporters or receptors were created and developed. However, factors such as the latency of therapeutic response of at least 2 weeks observed in most patients who use antidepressant drugs, together with the refractoriness of another portion suggest that the monoaminergic hypothesis may not be the most appropriate pathophysiological theory to explain MDD [12].

More recently, two complementary pathophysiological theories of depression related to heightened stress response were proposed. The "inflammatory hypothesis of depression" postulates that an increase in the concentration of various pro-inflammatory cytokines affecting both peripheral and central nervous systems would lead to an overactivation of the hypothalamic-pituitary-adrenal (HPA) axis [13]. The dysregulation of the HPA axis, with particular impacts in components like the hippocampus, amygdala and prefrontal cortex (PFC), would result in a drop in the expression of neurotrophic factors, impairing neurogenesis and neuroplasticity [14]. The "neurotrophic hypothesis" states that maladaptive neurogenesis, a decreased neuroplasticity and neuronal atrophy would underlie the disorder [15]. Evidence suggests a decreased expression and concentration of several neurotrophins associated with neuroplasticity, notably brain-derived neurotrophic factor (BDNF), that tends to increase after antidepressant treatment [16].

In recent years, researchers began to identify critical neuroanatomical substrates and test alternative models, suggesting that depression is unlikely to be a disease that can be explained by a single brain region or neurotransmitter system [17]. Depression is currently understood to be associated with dysfunctional information processing in particular neurocircuits. For example, hypoconnectivity within the frontoparietal network (FPN) and hyperconnectivity within the default mode network (DMN) is found in major depression [18]. These networks are involved in the coordination of several processes (e.g. decision-making, working memory and attention), and their dysregulation may contribute to the appearance of commonly found depressive behaviours like negative bias and rumination about depressive thoughts [19].

The rationale for using different brain stimulation therapies, including transcranial direct current stimulation (tDCS), is based on their mechanisms of inhibition or activation of specific "nodes" of these networks. An important site that is considered to contribute to specific depression-related behaviours and symptoms is the dorsolateral prefrontal cortex (DLPFC). Based on studies of functional neuroimaging and electroencephalography (EEG), it was observed that, in comparison with healthy individuals, patients with MDD present a relative hypoactivity of the left DLPFC, while the right DLPFC and the ventromedial prefrontal cortex (vmPFC) are hyperactive [20, 21]. The negative emotional judgment commonly seen in depressive patients may be attributable to the imbalance between the left and right prefrontal activity, with psychomotor retardation and impaired executive function being linked with the hypoactivity of the left DLPFC [22]. Neuroimaging studies also show imbalances between the activity in the prefrontal and ventromedial cortices and subcortical structures, such as the amygdala and hippocampus. A recent meta-analysis of magnetic resonance imaging (MRI) from MDD patients showed a robust reduction in hippocampal volume compared to healthy controls, although volumetric changes in other subcortical regions were less evident [23]. The feelings of guilt and hopelessness are considered as arising from dysfunction in the activity of the amygdala, whereas anhedonia is related to the nucleus accumbens [24, 25].

The set of these findings suggests that patients with MDD exhibit "differential activity" in specific brain regions that affects the associated neural networks and may explain some of the behaviours and symptoms typically found in depression.

21.2 Technical Aspects of the Use of tDCS in Major Depression

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that involves the application of a low-intensity direct current through electrodes positioned on the scalp [26]. The anode is often placed over the left DLPFC (F3, according to the 10–20 EEG system) to enhance the activity of this region. As seen before, the left DLPFC is considered an important brain region involved in the pathophysiology of major depression. Its stimulation has already been associated with the improvement of depressive symptoms with rTMS [27, 28]. It remains, until now, the leading target for most tDCS montages in depression (see Tables 21.1, 21.2 and 21.3). The position of the cathode, which has been shown to have an inhibitory effect when assessed in the motor cortex [24],

Table 21.1 Summary of controlled randomised clinical trials investigating the antidepressant effects of tDCS as monotherapy

Author (year)	Total sample (tDCS/sham)	Anode/ cathode	Intensity (mA) / electrode size (cm^2) = Density (mA/ cm^2)	Number of sessions (regime)	Session duration (minutes)	Clinical results
Fregni et al. (2006) [47]	10 (5/5)	F3/Fp2	1/ 35 = 0.03	5 (every other day)	20	Significantly greater mood improvement (HDRS) with active tDCS (60%) vs. sham (12%)
Fregni et al. (2006) [48]	18 (9/9)	F3/Fp2	1/ 35 = 0.03	5 (every other day)	20	Significantly greater mood improvement (HDRS) with active tDCS (58.5%) vs. sham (13.1%)
Boggio et al. (2008) [49]	40(21 DLPFC/9 Occ/10 sham)	F3/ Fp2Occ/ Fp2	2/ 35 = 0.06	10 (once a day)	20	DLPFC group a significantly greater mood improvement (HDRS) in DLPFC group (40%) vs. occipital (21%) vs. sham (10%) persisting for 30 days
Loo et al. (2010) [50]	40 (19/15)	F3/F8	1/ 35 = 0.03	5 (every other day)	20	No significant difference in mood improvement (HDRS) between active tDCS vs. sham
Blumberger et al. (2012) [52]	24 (13/11)	F3/F4	2/ 35 = 0.06	15 (once a day)	20	No significant difference in remission rates between active vs. sham
Palm et al. (2012) [51]	22 (11/11)	F3/Fp2	1;2/35 = 0.03; 0.06	10 (once a day)	20	No significant difference in mood improvement (HDRS) between active tDCS vs. sham
Loo et al. (2012) [53]	64 (33/31)	F3/F8	2/ 35 = 0.06	15 (once a day)	20	Significantly greater mood improvement (HDRS) with active tDCS (58.5%) vs. sham (13.1%) No difference in response rates (13% in both groups)

(continued)

Table 21.1 (continued)

Author (year)	Total sample (tDCS/sham)	Anode/ cathode	Intensity (mA) / electrode size (cm^2) = Density (mA/ cm^2)	Number of sessions (regime)	Session duration (minutes)	Clinical results
Bennabi et al. (2015) [54]	24 (12/12)	F3/Fp2	2/ 35 = 0.06	10 (twice a day)	30	No significant difference in mood improvement (HDRS) between active tDCS vs. sham
Salehinejad et al. (2015) [55]	30 (15/15)	F3/F4	2/ 35 = 0.06	10 (once a day)	20	Significantly greater mood improvement (HDRS) with active tDCS vs. sham
Salehinejad et al. (2017) [56]	24 (12/12)	F3/F4	2/ 35 = 0.06	10 (once a day)	20	Significantly greater mood improvement (HDRS) with active tDCS vs. sham
Loo et al. (2018) [57]	130(66/64)	F3/F8	2.5/35 = 0.07	20 (once a day)	30	No significant difference in mood improvement (MADRS) between active tDCS vs. sham (both improved mood)
Sampaio-Junior et al. (2018) [67]	59 (30/29)	F3/F4	2/25 = 0,08	12 (10/ once a day +2/ every other week)	30	Cumulative response rates were higher with active tDCS vs. sham (but not for remission rates)

F3 left DLPFC, *Fp2* right supraorbital, *HDRS* Hamilton Depression Rating Scale, *occ* occipital, *F8* right lateral orbitofrontal, *F4* right DLPFC, *TRD* treatment-resistant depression, *BP* bipolar, *MDD* major depressive disorder, *AD* antidepressant, *DLPFC* dorsolateral prefrontal cortex, *MADRS* Montgomery-Asberg Depression Rating Scale

Table 21.2 Summary of controlled randomised clinical trials investigating the antidepressant effects of tDCS and pharmacotherapy

Author (year)	Total sample (tDCS/ sham)	Anode/ cathode	Intensity (mA) / electrode size (cm^2) = Density (mA/ cm^2)	Number of sessions (regime)	Session duration(minutes)	Clinical results
Brunoni et al. (2013) [34]	120 (40 tDCS only/40 sertraline only/40 tDCS + sertraline/40 placebo)	F3/F4	2/25 = 0,08	12 (10 daily +2 weekly)	30	tDCS accelerated and enhanced sertraline response; this association was superior for the treatment of depression than sertraline or tDCS alone
Brunoni et al. (2017) [59]	245 (94 tDCS/60 double placebo/91 escitalopram)	F3/F4	2/25 = 0,08	22 (15 daily +7 weekly)	30	Active tDCS was superior to placebo, but not noninferior to escitalopram
Pavlova et al. (2018) [60]	69 (27/21/20) (30 min/20 min/sham tDCS) + Sertraline 50 mg/day	F3/ Fp2	0.5/anode 3.5x5cm/cathode 5x7cm = 0.03	10 (once a day)	20/30	30-minute group had significantly greater improvement than 20-minute group Both better than sham

F3 left DLPFC, *F4* right DLPFC, *Fp2* right supraorbital, *DLPFC* dorsolateral prefrontal cortex

Table 21.3 Summary of controlled randomised clinical trials investigating the antidepressant effects of tDCS combined with cognitive interventions

Author (year)	Total sample (tDCS/sham)	Anode/ Cathode	Intensity (mA) / electrode size (cm^2) = Density (mA/ cm^2)	Number of sessions (regime)	Session duration(minutes)	Clinical results
Brunoni et al. (2014) [62]	37 (20 tDCS + CCT/17 sham tDCS + CCT)	F3/F4	2/25 = 0,08	10 (once a day)	30	CCT did not enhance the effects of tDCS(both groups were associated with a reduction in depression severity (HDRDS)
Segrave et al. (2014) [61]	27 (9 tDCS + CCT/ 9 sham tDCS + CCT/ 9 tDCS + sham CCT)	F3/F8	2/ 35 = 0.06	5 (once a day)	24	CCT enhanced the effects of tDCS(only tDCS + CCT resulted in a sustained AD response for 3 weeks)
Welch et al. (2018) [63]	14 (9 tDCS + eCBT/ 5 sham tDCS + eCBT)	F3/F4	2/25 = 0,08	12 (3 days a week)	30	No significant differences in mood improvement (HDRS) between active tDCS and sham (study was underpowered)

CCT Cognitive Control Therapy, *F3* left DLPFC, *F4* right DLPFC, *HDRS* Hamilton Depression Rating Scale, *F8* right lateral orbitofrontal, *eCBT* electronic Cognitive Behavioural Therapy

varies in depression involved studies between the right DLPFC (F4), the right lateral orbitofrontal (F8) and the right supraorbital (Fp2) areas.

Computational modelling is increasingly being used to simulate the theoretical distribution of the electric field in the brain of each type of montage. Although the clinical effects of these variations still need to be clarified, it can be a useful tool to guide targeting and potentially quantify individualised "dosage" [29]. In addition to the electrode placement and polarity (montage), other parameters involved in a tDCS session can influence its antidepressant efficacy. The intensity of the electric current (usually between 1 and 2.5 mA) in combination with the size of the electrode (typically 25 or 35 cm^2) defines the current density (intensity divided by the square area of the electrodes, usually from 0.028 to 0.08 mA / cm^2). The duration of the stimulation (typically between 20 and 30 minutes) and the total number of sessions (5–24) are also important, although further evidence to define the best interval between sessions is still needed. Even though there is no standard definition of how to measure the dosage of tDCS delivered in a clinical study, it is possible to combine the parameters discussed above into a measure of total charge (in Coulombs) or total charge density (e.g. in Coulombs per centimetre square, if the size of the electrodes is also considered) to provide an estimation of the total amount of energy delivered throughout the treatment.

Finally, the antidepressant effects of tDCS appear to be influenced by other concomitant interventions, be it pharmacotherapy or cognitive therapies, as discussed below in this chapter.

21.3 Mechanism of Action of tDCS

The mechanisms of action of the antidepressant effects of tDCS are yet to be completely elucidated. It is considered that anodal tDCS acts to increase cortical excitability by approximating the resting membrane potential of the stimulated neurons to the trigger threshold for the propagation of action potentials [30]. At the macro scale, in addition to the specific cortical regions located immediately below the electrodes, each montage results in a different current distribution within the brain. Given the diffuse nature of tDCS,

it can stimulate other regions and potentially deeper structures that are in the path of the current between the electrodes [31].

As previously discussed, the pathophysiology of MDD has been linked to abnormal functional and structural communication among large-scale brain networks [18]. The DLPFC is a key hub of the frontoparietal network (FPN), and it is believed that by facilitating its endogenous activity, an increase in FPN and a concurrent downregulation in the default mode network (DMN) activity occurs leading to an improvement in depressive symptoms [32].

The antidepressant effects of tDCS also appear to be involved with different neurotransmitter systems. The impact of citalopram, a selective serotonin reuptake inhibitor (SSRI), in the neuromodulatory effects of tDCS was explored in a pharmacological proof-of-concept study by Nitsche et al. [33]. They showed that, in healthy volunteers, the effects of anodal tDCS on motor cortical excitability were increased and prolonged with the concomitant use of citalopram. In contrast, the typical net results of the cathode were reversed, leading, in fact, to an increase in excitability. This principle was later used in the design of the Sertraline vs. Electric Current Therapy for Treating Depression Clinical Study (SELECT-TDCS) study [34], which showed that the antidepressant effects of tDCS were enhanced by sertraline (see details of the SELECT-TDCS study in Sect. 4.1.2 tDCS and pharmacotherapy).

In addition to its influence on cortical excitability, the concomitant use of citalopram also impacted neuroplasticity. The long-term aftereffects of tDCS appear to be due to alterations in synaptic neuroplasticity: increases in postsynaptic potentials induce long-term potentiation (LTP) mechanisms while decreasing synaptic efficacy results in processes similar to long-term depression (LTD) [35]. Restoration of impaired neuroplasticity was demonstrated in a small study of 18 depressed patients who received a 4-week course of tDCS [36]. The addition of citalopram may enhance these changes [33] by activating serotonin-sensitive potassium channels that decrease the external potassium current, thereby extending the influx of calcium into the synaptic cleft and ultimately increasing LTP after anodal tDCS.

The dopaminergic system might also be involved in the antidepressant mechanisms of tDCS. It was shown that the administration of dopamine agonists and antagonists in healthy volunteers modified the excitability and neuroplasticity induced by tDCS [37]. Also in healthy volunteers, high dopaminergic prefrontal activity mediated by a genetic polymorphism of the catechol-O-methyltransferase (an enzyme that degrades dopamine) influenced negatively the effects of anodal tDCS on executive functioning [37] and the cathodal effects on inhibitory control [38].

Although the diminished BDNF levels found in depression increased after treatment with pharmacotherapy [16] and ECT [38], tDCS trials to date failed to identify changes in this biomarker, hindering the inclusion of this aspect as a potential mechanism of action of the technique.

Moreover, most brain tissues and cells are sensitive to electric fields, therefore, tDCS may also influence non-neuronal tissues in the brain, including glial cells [39] and astrocytes [40]. These non-neuronal effects, although not systematically explored so far, could be involved in the therapeutic action of tDCS as well.

21.4 Clinical Evidence

Systematic studies on the effects of low-intensity current stimulation as an antidepressant therapy began in the 1960s, still under its old name of "brain polarisation". In comparison with the currently used tDCS parameters, it applied lower current intensities (<0.5 mA), longer session durations (>3 hours) and montages with two anodes in the frontal region and an extracephalic cathode (for a review see Esmaeilpour et al. [41]). However, the lack of methodological rigour in some parameters such as target area, current intensity, electrode size, position of the cathode, number of sessions and duration of each session may explain some contradictory findings between studies.

Lippold and Redfearn [42] conducted a double-blind, uncontrolled study in which 32

depressed individuals were stimulated in the frontal region ("anodes") with the "cathode" just above the right knee. The authors reported increased mood, attention and motor activity after anodic polarisation, while cathodic polarisation induced silence and apathy. On the other hand, Arfai et al. [43] found no significant effects on depression in a randomised, double-blind, sham-controlled study, in which 0.25 mA of stimulation was applied to the frontal cortex ("anodes") with the "cathode" on the thigh.

This scenario only started to change in the early 2000s with the new tDCS protocols, in which the stimulation parameters were better defined and controlled. The seminal study by Priori et al. [44], followed by Nitsche and Paulus [45], started what is now known as the modern era of tDCS. In parallel, the emergence of other brain stimulation techniques, such as TMS, also allowed a better understanding of the effects of tDCS on cortical excitability. Initially, some open-label studies explored the impact of different montages and dose variations on the antidepressant effects of tDCS [46]. Since 2006, several randomised, sham-controlled clinical trials have been published assessing the antidepressant efficacy of tDCS as monotherapy (Table 21.1) and in combination with pharmacotherapy (Table 21.2) or cognitive interventions (Table 21.3).

21.4.1 Randomised Sham-Controlled Clinical Trials (RCTs)

tDCS as Monotherapy

The first two RCTs of the modern era [47, 48] included outpatients with mild-to-moderate depression (10 and 18 participants, respectively) applying 1 mA tDCS on alternate days for 20-minute for 5 sessions. Both studies found a significant improvement in mood from baseline in the active tDCS group compared to sham. Fregni et al. [47] found a significant decrease in the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) with an average reduction in depression scores of 60–70% for active tDCS versus 12% in the simulated group. Similar results were demonstrated in the second study, with 18 patients [48]. In 2008, Boggio et al. [49] recruited 40 patients with moderate-to-severe depression, used a higher current intensity (2 mA) and a daily stimulation regime for 10 sessions. In addition to the same bifrontal montage of previous studies, the researchers used stimulation of the occipital cortex as an active control condition. The results showed that only the prefrontal tDCS significantly reduced depressive symptoms evaluated after 10 sessions, with its effects sustained for at least 30 days after the end of treatment.

After these initial positive results, another three studies were conducted and reported negative findings. Although they used a larger sample (N = 40) and the same parameters as the initial study by Fregni et al. [47], Loo et al. [50] found no significant differences between active and sham tDCS. The next two RCTs enrolled only drug-resistant depressed patients. Palm et al. [51] recruited 22 patients and randomised them to receive 1 mA, 2 mA or sham tDCS for 2 weeks (10 sessions) in a cross-over study design. No significant difference in depression scores was observed after 2 weeks between active tDCS and sham. Blumberger et al. [52], using a sample of 24 patients, also found no significant differences between active versus sham tDCS in terms of remission rates. Nevertheless, these studies recognised methodological limitations, notably small samples, which could have hindered the correct estimation of the antidepressant efficacy of tDCS.

Using stimulation parameters more robust than previous RCTs and a larger sample, Loo et al. [53] randomised 64 patients to receive active or sham tDCS (2 mA, 15 sessions over 3 weeks), followed by an open-label 3-week active treatment phase. A significantly greater improvement in mood was observed after active stimulation compared to sham. Furthermore, there was no indication of a decline in participants' neuropsychological functioning at the end of the total 3 to 6 weeks of active tDCS.

Recruiting a sample of 24 depressed and drug-resistant patients, Bennabi et al. [54] did not observe at the end of treatment (two daily sessions with an interval of 2 hours for 5 days) sig-

nificant differences in the antidepressant efficacy of active tDCS compared to sham. Interestingly, response rates increased when the sample was evaluated 12 and 30 days after the end of the stimulation period, suggesting that the ideal clinical effects of tDCS may take some time to fully manifest (see Sect. 4.3 Meta-analyses for more details).

Salehinejad and colleagues conducted two other RCTs [55, 56] finding that the active tDCS group had a significantly greater reduction in depressive symptoms compared to sham.

In the first international multicentre RCT (one centre in Australia and five in the United States), Loo et al. [57] examined the efficacy of tDCS in patients with unipolar (N = 91) and bipolar (N = 39) depression. Participants were randomised to either active (2.5 mA) or sham tDCS over 20 sessions of 30-minute, administered over 4 weeks. Simultaneous use of mood stabilisers and antidepressant medications was allowed. In comparison with baseline, a significant elevation in mood was observed in both patients with unipolar and bipolar depression at the end of the treatment. However, both active and sham treatments led to similar improvement. According to the authors, some reasons that may explain these non-significant findings were the heterogeneity of the sample and the relatively high current intensity in the active arm (which may have harmed the efficacy of tDCS). Additionally, it was also considered that the "sham" condition, which involved a low level of stimulation (in the order of microamperes) may have had positive neuromodulatory effects. A proof-of-concept study carried out later on healthy volunteers, and using the same parameters of the sham condition, reported measurable neurobiological effects, supporting this interpretation [58].

tDCS and Pharmacotherapy

In contrast to the studies previously mentioned that accepted patients with concomitant use of antidepressant drugs in their samples, two studies, the Sertraline vs. Electric Current Therapy for Treating Depression Clinical Study (SELECT-TDCS) [34] and Escitalopram versus Electrical Current Therapy for Treating Depression Clinical Study (ELECT-TDCS) [59], incorporated pharmacotherapy as an independent variable in their designs.

Brunoni et al. [34] randomised 120 antidepressant-free patients with moderate and severe depression to one of four arms: sham tDCS and placebo pill (double placebo), sham tDCS and sertraline (sertraline only), active tDCS and placebo pill (tDCS only) or active tDCS plus sertraline (combined treatment). The tDCS parameters were 2 mA for 30 minutes/day, for 2 weeks and 2 extra sessions of tDCS every 2 weeks until week 6 (endpoint of the study); the sertraline dose was fixed (50 mg/day). The main findings were that active tDCS as monotherapy was more effective than the placebo group and that the efficacy of tDCS and sertraline did not differ. The results also showed that tDCS improved and accelerated the response to the medication and that the association of sertraline with active tDCS was superior in treating depression to each of these interventions alone. There were five cases of hypomanic/manic episodes in the combined treatment group versus one case in tDCS only, one case in sertraline only and no case in the double placebo arm (although this difference was not statistically significant). The treatment was well tolerated, with the presence of mild adverse effects at similar rates in both arms, except for skin redness that was more prevalent in active tDCS.

To overcome the limitations of the SELECT-TDCS study (the dose of sertraline was low, and the study was not designed for non-inferiority comparisons), Brunoni et al. [59] designed and performed the ELECT-TDCS study with the main objective of comparing the antidepressant efficacy of tDCS with the maximum dose of a commonly used antidepressant medication (escitalopram 20 mg/day). In the largest RCT of tDCS in depression to date, 245 patients with MDD were randomised to one of three groups: active tDCS and placebo pill (tDCS only); sham tDCS and escitalopram (escitalopram only) and sham tDCS and placebo pill (double placebo). This non-inferiority study was designed under the hypothesis that tDCS would have an antidepressant efficacy of at least 50% of that found when

comparing escitalopram with the double placebo group. Twenty-two tDCS sessions (2 mA, 30 min) were delivered for 3 weeks on 15 consecutive days (without weekends) and then once a week until week 10 (endpoint). Although the antidepressant effects of escitalopram and tDCS were shown to be superior to that of the placebo group, the primary outcome showed that tDCS was not non-inferior to the drug. Taken together, the SELECT-TDCS and ELECT-TDCS results suggest that: (a) tDCS can be used as an augmentation strategy for sertraline (and possibly for other SSRIs) and (b) tDCS, with the parameters used in both trials is not a substitute intervention for pharmacological treatment at an adequate dose, although it could be considered for specific populations that do not tolerate antidepressant drugs.

Finally, Pavlova et al. [60] randomised 69 mild to moderately depressed participants to receive either 30-minute tDCS, 20-minute tDCS or sham in combination with 50 mg/day of sertraline. All groups showed improvement in depression scores, with both active groups performing better than sham. Significantly greater improvement in symptoms was achieved in the 30-minute group compared to the 20-minute one.

tDCS Combined with Cognitive Therapies

Another area of interest is the combination of tDCS with cognitive interventions or computer behavioural tasks that aim to increase endogenous prefrontal cortical activity.

In 2014, 2 RCTs evaluated the effectiveness of tDCS combined with cognitive control therapy (CCT). In a pilot study, Segrave et al. [61] randomised 27 patients with MDD to receive 2 mA active tDCS and CCT, sham tDCS and CCT or 2 mA active tDCS and simulated CCT for 5 consecutive days. All three treatment arms led to a reduction in the severity of depression after the 5 sessions. Still, only the combined treatment of active tDCS and CCT resulted in sustained antidepressant response in a follow-up review at week 4. The study provided preliminary evidence that CCT could improve the antidepressant results of tDCS.

On the other hand, Brunoni et al. [62] randomised 37 participants to receive sham tDCS and CCT or 2 mA active tDCS and CCT for 10 sessions and found similar antidepressant improvement in both groups at the endpoint. However, subsequent analyses showed that older patients and those with higher performance improvement in tasks (possibly indicating greater involvement and activation of DLPFC) also had greater improvement in depressive symptoms in the group combining active tDCS and CCT.

Welch et al. [63] investigated the feasibility of combining tDCS with a computerised version of cognitive-behavioural therapy (eCBT). At endpoint, the results showed that both groups (active tDCS with eCBT and simulated tDCS with eCBT) significantly improved compared to baseline. Although the combination proved to be viable, the statistical power of the study was insufficient to detect a difference between the treatment arms.

Thus, the evidence to date is still insufficient to support that the combination of tDCS with cognitive therapies leads to an improvement in antidepressant effects significantly different from that related to each intervention separately.

21.4.2 Follow-Up Studies

Up to the time of writing this chapter, no controlled follow-up studies were found in the literature evaluating the effectiveness of tDCS to prevent relapse of depressive symptoms. Three follow-up open-label studies assessed the efficacy of tDCS in the maintenance phase of the depressive episode.

Valiengo et al. [64] recruited 42 patients who were tDCS responders in the SELECT-TDCS study [34] and performed tDCS sessions every 2 weeks for 3 months and then every month for another 3 months. The maximum number of maintenance sessions was 9, and the stimulations were interrupted earlier in case of relapse (characterising treatment failure). In this follow-up study, the average duration of sustained response was 11.7 weeks (82 days) and the overall relapse rate at 6 months was approximately 50%, with

most relapses occurring in the first 3 months. The presence of treatment-resistant depression was significantly associated with an increased relapse rate (over 80% in 6 months). On the other hand, more than 80% of non-refractory patients maintained a clinical response for at least 6 months.

Martin et al. [65] also followed 26 responders previously treated in a randomised clinical trial [53], performing weekly tDCS sessions for 3 months, followed by tDCS sessions every 2 weeks for the remaining 3 months. As in Valiengo et al. [64], a relapse rate of around 50% was observed in 6 months. However, most relapses occurred after the initial 3 months, when the tDCS sessions were spaced fortnightly.

Finally, Aparicio et al. [66] recruited 24 patients who responded to previous RCTs, 16 from [59] with unipolar depression and 8 from [67] with bipolar depression. In this open-label crossover phase, participants were followed up with 2 sessions per week for a maximum of 6 months or until a relapse was observed. The average duration of the sustained response was 17.5 weeks (122 days), with no difference in efficacy between unipolar and bipolar depressed people.

21.4.3 Meta-Analyses

Several meta-analyses of aggregated data and two of individual patient data from RCTs that explored the efficacy of tDCS in depression have been published to date. Their overall results were varied, depending on the number of studies available at the time, the characteristics of the included sample and the outcome measure chosen (categorical, such as rates of response and remission or continuous, such as improvement in depressive symptoms).

Aggregated Data Meta-Analyses (AD-MA)

The first two published meta-analyses for tDCS in depression showed mixed results. Although they evaluated the same RCTs, they used different outcome measures to estimate the effect size of the intervention. Kalu et al. [68] using a continuous measure (improvement in depression), found significant results, whereas Berlin et al. [69], using dichotomous measures (response and remission rates), did not find significant differences regarding the efficacy of active tDCS versus sham. With the publication of the SELECT-TDCS study [34], not included in the previous meta-analyses, a new MA was conducted, indicating that active tDCS was more effective than sham for both continuous and categorical outcomes, although with a small-to-moderate effect size [70]. In 2015, including ten studies in which tDCS was used as monotherapy or as augmentation therapy with medication or cognitive therapy, Meron et al. [71] found that active tDCS was superior to sham only for depressive symptoms' reduction, but not in terms of response and remission rates. To avoid potential interaction confounders introduced by the co-initiation of other treatments, Mutz et al. [8] explored the antidepressant effects of tDCS only when it was used as monotherapy. The results showed that tDCS was superior to sham for all outcomes.

In the most recent to date aggregated data meta-analyses (AD-MA), Razza et al. [72] analysed 23 RCTs for a total of 1092 participants (591 in active tDCS and 501 in sham). Participants with an acute depressive episode associated with the diagnosis of major depressive disorder, bipolar disorder (BD) or secondary depression (e.g. post-stroke depression) were included. In addition to studies in which tDCS was administered as monotherapy, this MA also included those in which stimulation was co-initiated with other therapies (e.g. medications and behavioural interventions). Active tDCS was significantly better than sham concerning improvement in depression (Hedges' $g = 0.46$, 95% CI = 0.22–0.70) scores and also in terms of response (33.3% vs. 16.56%, respectively; number needed to treat, NNT = 6) and remission rates (19.12% vs. 9.78%, respectively; NNT = 10.7). NNT provides a value that is relative to sham and represents the number of patients with depression that is necessary to treat with active tDCS for one additional patient to experience response or remission. The results of the cumulative meta-analysis showed that the effect sizes have been

unchanged for at least the past 5 years, with the additional studies essentially narrowing the confidence interval. This suggests that, under the parameters currently employed, the effectiveness of tDCS in depression is relatively established and is associated with modest effect sizes.

Individual Patient Data Meta-Analyses (IPD-MA)

Two individual patient data meta-analyses (IPD-MAs) have been conducted to date. This approach is more accurate in estimating the effects of an intervention and also superior to the aggregated data method to obtain predictors of the treatment outcome since the specific characteristics of each participant are evaluated instead of overall means and frequencies.

The first IPD-MA was carried out in 2016 [73] and included RCTs with at least 10 participants per arm (i.e. initial tDCS studies were not considered) in which tDCS was used as add-on or monotherapy. Patients with an acute depressive episode diagnosed with MDD or bipolar disorder (BD) were included, but not depressive symptoms associated with other psychiatric diagnoses and secondary depression. These data were extracted based on individual patients and gathered from 6 RCTs, with the participation of 289 patients. The efficacy of active tDCS was significantly higher than sham in terms of response (34% vs. 19%, respectively; NNT = 7), remission (23.1% vs. 12.7%, respectively; NNT = 9) and improvement in depressive symptoms (β coefficient = 0.35, 95% CI = 0.12–0.57). These effect sizes were considered small to moderate, but comparable to those reported for the use of AD drugs in primary care [74]. Treatment-resistant depression and higher "doses" of tDCS were respectively negative and positively associated with the effectiveness of tDCS.

At the end of 2019, considering the publication of 3 large RCTs [57, 59, 67], a new systematic search of the literature and IPD meta-analysis was carried out [75]. The same eligibility criteria as the previous one was used. With 9 RCTs included and individual data from 572 participants (307 in active tDCS and 265 in sham), this version almost doubled the size of the sample. Using the predefined primary endpoint (i.e. according to the respective original authors' definition), active tDCS was significantly higher than sham for response (30.9% vs. 18.9%, respectively; NNT = 9) remission (19.9% vs. 11.7%, NNT = 13) and depression improvement (β coefficient = 0.31, [0.15–0.47]). These results indicate a low-to-medium efficacy of tDCS, with NNTs ranging from 9 (response) to 13 (remission), values higher than NNTs observed in the previous IPD-MA [73] that were 7 and 9 respectively. These new values indicate that the effectiveness of tDCS is lower than the clinical effects of antidepressant drugs (NNT for response between 7 and 9) [74, 76] and in accordance with the ELECT-TDCS non-inferiority study [59] showing that escitalopram 20 mg/day was superior to tDCS. Another interesting finding of the present analysis was the marked difference between the effect sizes of tDCS measured immediately after the end of the "acute" treatment period (e.g. once a day) and the "postponed" period (the last mood assessment available in the sham-controlled blind phase). In fact, active tDCS was not significantly different to sham when assessed immediately after the end of the acute stimulation phase. Taken together, these findings suggest that the ideal clinical effects of tDCS for depression may take some time after acute treatment to fully manifest and/or a decline in placebo improvement (since the patient's interactions with the team no longer occurred daily). It was not possible to identify predictors of response to tDCS in this updated version, with only non-significant trends being observed in relation to TRD and number of sessions (associated with less and greater response, respectively). No serious adverse effects have been described, and the intervention was tolerable and safe.

In summary, the antidepressant effects of tDCS shown in the IPD-MAs have been modest and mixed. Predictors of response to tDCS were not identified with the largest sample of the updated version. These results should encourage the development of strategies to identify characteristics of treatment responders and optimal stimulation parameters that could increase the efficacy of the technique in the future.

21.5 Bipolar Disorder

The effectiveness of tDCS as a treatment for acute depressive episodes associated with bipolar disorder has not been sufficiently investigated. Although an initial open-label study [77] and RCTs [51, 53, 57] included participants with bipolar depression in their sample, there is only one RCT which was carried out exclusively with bipolar participants. The Bipolar Depression Electrical Treatment Trial – BETTER [67] included 59 adults with bipolar disorder (type I or II) in a major depressive episode. Compared to sham, active tDCS was associated with greater improvement in depressive symptoms and higher rates of cumulative response. On the other hand, remission rates and adverse events were similar in both groups (except for localised skin redness that was higher in the active group).

Although tDCS is a technique generally considered to be devoid of serious adverse events, some reports of treatment-emergent mania (TEM) or hypomania have been described in clinical trials of depression. Brunoni and colleagues [78] carried out a systematic review and meta-analysis to assess the risk of TEM in depressed patients during RCTs in which tDCS was used as monotherapy or augmentation therapy. These data of 416 participants (10 RCTs) were analysed with only three of the trials describing all nine emerging episodes of mania/hypomania. There were eight cases of TEM out of 226 participants in active tDCS (3.5%) and 1 out of 190 participants in sham (0.5%), which were not statistically different.

A more recent meta-analysis explored TEM exclusively in patients with the diagnosis of unipolar depression [79]. Active tDCS was associated with a small but significantly increased risk compared to sham (3.3% in active vs. 0.27% in sham).

In the BETTER study (not included in the cited MAs), there were nine TEM throughout the trial: five in the sham and four in the active group. These episodes did not meet the criteria for a major depressive episode with mixed features, hypomania or mania (per *DSM-5* guidelines) and required no hospitalisation, trial discontinuation or specific treatment. It is important to notice that in this trial, most participants were using some type of mood stabiliser.

It is still unclear whether patients with the diagnosis of bipolar disorder are subject to a greater risk of TEM with tDCS. Therefore, the same recommendations and precautions for pharmacological antidepressant treatment should also be applied when using tDCS. In addition, patients should be carefully assessed for a history of mania/hypomania switch with previous antidepressant treatments, as this could indicate an increased risk also with tDCS. For these patients, the concomitant use of mood-stabilising drugs should be considered during the course of a tDCS treatment.

Regarding efficacy in mania, the evidence is limited to a single case report that shows improvement in manic symptoms after applying tDCS with the anode on the right and the cathode on the left DLPFC for 5 sessions [80].

21.6 Conclusion

In this chapter, we have presented the clinical evidence for the use of tDCS in the treatment of depressed patients with unipolar or bipolar depression. With the number of participants in tDCS clinical trials for depressive episodes exceeding 1000, the efficacy of tDCS, under the parameters currently employed, is relatively established and associated with modest effect sizes [72]. In addition, the cumulative meta-analysis showed that the effect size of active tDCS versus sham has been stable for at least 5 years, with additional trials essentially narrowing the confidence interval. These findings suggest that replication RCTs of tDCS versus sham stimulation in depression are not a priority.

When we analysed the evidence from IPD meta-analyses that adopted more restrictive eligibility criteria (e.g. tDCS only as monotherapy or add-on therapy, exclusion of cases related to secondary depression, a minimum number of participants per arm), outcomes also favoured active tDCS, with slightly smaller but similar effect sizes [75]. Comparisons with other treatments suggest

tDCS is not superior to pharmacotherapy in non-pharmacotherapy resistant patients [59] and is less effective than ECT [8]. Its efficacy compared to rTMS remains to be definitively assessed. Nonetheless, the combination of tDCS with antidepressant drugs, particularly SSRIs, was associated with superior improvement, opening up the possibility of using tDCS to augment the effects of medications. On the other hand, the combination of tDCS with the cognitive interventions showed mixed results. This association should be evaluated in future studies with special attention to whether tDCS is administered prior ("offline") or concurrently to task performance ("online").

One factor that can help explain the limited antidepressant effects achieved by tDCS and the variability of results within and between studies is the fact that stimulation is provided with the use of fixed stimulation parameters for all individuals. The variation in individual characteristics such as head size and shape, skull thickness and neuroanatomy will affect the amount of current and the distribution of the electric field that effectively reaches the brain tissue [81]. Brain scans and specific software could be used to simulate which montage, and stimulation parameters should be used for a particular individual to achieve the desired electric field in the region of interest.

The main advantage of tDCS among other forms of NIBS is its low cost, portability, ease of use, absence of serious adverse effects and the possibility of its use at home. Initial evidence showed that home-based tDCS is feasible, safe and presented similar efficacy for the treatment of depression as the site-based trials [82]. This is appealing once meta-analytical findings suggested that the therapeutic effects of tDCS may take some time to fully manifest [75]. Therefore, home-administered tDCS would increase treatment accessibility (particularly in remote areas), and adherence even with more intensive and prolonged protocols [83].

Another key and unclear point is the ideal treatment protocol during the maintenance phase. Only three follow-up studies were carried out so far [64–66]. Although limited by the fact that they were all open-label trials, these studies suggest that a continued intensive treatment regimen of at least once a week during early follow-up may be recommended to support clinical improvement and prevent recurrence of symptoms.

The use of biological markers is an appealing strategy to help to predict subgroups of patients more likely to respond to treatment and, at the same time, clarify the mechanisms of action of tDCS in depression. A recent functional magnetic resonance imaging (fMRI) study found that the antidepressant response to rTMS was associated with specific neurophysiological subtypes [84]. On the other hand, an ancillary investigation of the ELECT-TDCS study [59] showed that no baseline peripheral biomarkers were associated with tDCS antidepressant effects [85]. Similarly, in the international multicentre trial, the Val66Met BDNF polymorphism was unrelated to the antidepressant response to tDCS [57].

Finally, despite the mixed antidepressant outcomes found between trials, the overall results showed that tDCS was a safe and effective intervention in reducing depressive symptoms in patients with unipolar or bipolar depression. Its clinical efficacy was modest, and future studies should focus on the development of strategies to identify characteristics of treatment responders and optimal stimulation parameters.

References

1. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; 2017. Contract No.: WHO/MSD/MER/2017.2.
2. McKenna SP, Doward LC. The translation and cultural adaptation of patient-reported outcome measures. Value Health. 2005;8(2):89–91.
3. Wittchen HU, Knauper B, Kessler RC. Lifetime risk of depression. Br J Psychiatry Suppl. 1994;26:16–22.
4. American Psychiatric Pub. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub; 2013.
5. Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68(8):17.
6. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. Am J Psychiatry. 2006;163(11):1905–17.

7. Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol. 2020;131(2):474–528.
8. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehav Rev. 2018;92:291–303.
9. Porter RJ, Baune BT, Morris G, Hamilton A, Bassett D, Boyce P, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. BJPsych Open. 2020;6(3):e40.
10. Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry. 2019;41(1):70–81.
11. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry. 2000;61 Suppl 6:4–6.
12. Boku S, Nakagawa S, Toda H, Hishimoto A. Neural basis of major depressive disorder: beyond monoamine hypothesis. Psychiatry Clin Neurosci. 2018;72(1):3–12.
13. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139(3):230–9.
14. Malykhin NV, Coupland NJ. Hippocampal neuroplasticity in major depressive disorder. Neuroscience. 2015;309:200–13.
15. Sharma AN, Soares JC, Carvalho AF, Quevedo J. Role of trophic factors GDNF, IGF-1 and VEGF in major depressive disorder: a comprehensive review of human studies. J Affect Disord. 2016;197:9–20.
16. Molendijk M, Spinhoven P, Polak M, Bus B, Penninx B, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N= 9484). Mol Psychiatry. 2014;19(7):791–800.
17. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651–60.
18. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiat. 2015;72(6):603–11.
19. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3(5):472–80.
20. Bench CJ, Frackowiak RSJ, Dolan RJ. Changes in regional cerebral blood flow on recovery from depression. Psychol Med. 1995;25(2):247–61.
21. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry. 2008;63(4):369–76.
22. Grimm S, Ernst J, Boesiger P, Schuepbach D, Hell D, Boeker H, et al. Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures. Hum Brain Mapp. 2009;30(8):2617–27.
23. Schmaal L, Veltman DJ, van Erp TGM, Sämann PG, Frodl T, Jahanshad N, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry. 2016;21(6):806–12.
24. Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res. 2009;201(2):239–43.
25. Maletic V, Robinson M, Oakes T, Iyengar S, Ball SG, Russell J. Neurobiology of depression: an integrated view of key findings. Int J Clin Pract. 2007;61(12):2030–40.
26. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;127(2):1031–48.
27. O'Reardon JP, Cristancho P, Pilania P, Bapatla KB, Chuai S, Peshek AD. Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. Depress Anxiety. 2007;24(8):537–44.
28. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010;67(5):507–16.
29. Borrione L, Bellini H, Razza LB, Avila AG, Baeken C, Brem A-K, et al. Precision non-implantable neuromodulation therapies: a perspective for the depressed brain. Braz J Psychiatry. 2020;
30. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899–901.
31. Polania R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. Nat Neurosci. 2018;21(2):174–87.
32. Baeken C, De Raedt R. Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuitry in unipolar depression. Dialogues Clin Neurosci. 2011;13(1):139–45.
33. Nitsche MA, Kuo MF, Karrasch R, Wachter B, Liebetanz D, Paulus W. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatry. 2009;66(5):503–8.
34. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical

study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91.
35. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul. 2017;10(1):51–8.
36. Player MJ, Taylor JL, Weickert CS, Alonzo A, Sachdev PS, Martin D, et al. Increase in PAS-induced neuroplasticity after a treatment course of transcranial direct current stimulation for depression. J Affect Disord. 2014;167:140–7.
37. Nitsche MA, Kuo M-F, Grosch J, Bergner C, Monte-Silva K, Paulus W. D_1-receptor impact on neuroplasticity in humans. J Neurosci. 2009;29(8):2648–53.
38. Brunoni AR, Baeken C, Machado-Vieira R, Gattaz WF, Vanderhasselt M-A, JTWJoBP. BDNF blood levels after electroconvulsive therapy in patients with mood disorders: a systematic review and meta-analysis. World J Biol Psychiatry. 2014;15(5):411–8.
39. Ruohonen J, Karhu J. tDCS possibly stimulates glial cells. Clin Neurophysiol. 2012;123(10):2006–9.
40. Monai H, Hirase H. Astrocytes as a target of transcranial direct current stimulation (tDCS) to treat depression. Neurosci Res. 2018;126:15–21.
41. Esmaeilpour Z, Schestatsky P, Bikson M, Brunoni AR, Pellegrinelli A, Piovesan FX, et al. Notes on human trials of transcranial direct current stimulation between 1960 and 1998. Front Hum Neurosci. 2017;11(71)
42. Lippold OCJ, Redfearn JWT. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry. 1964;110(469):768–72.
43. Arfai E, Theano G, Montagu JD, Robin AA. A controlled study of polarization in depression. Br J Psychiatry. 1970;116(533):433–4.
44. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9(10):2257–60.
45. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(3):633–9.
46. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 2009;219(1):14–9.
47. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006;8(2):203–4.
48. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006;23(8):482–4.
49. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008;11(2):249–54.
50. Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol. 2010;13(1):61–9.
51. Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul. 2012;5(3):242–51.
52. Blumberger DM, Tran LC, Fitzgerald PB, Hoy KE, Daskalakis ZJ. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front Psych. 2012;3:74.
53. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9.
54. Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, et al. Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin Neurophysiol. 2015;126(6):1185–9.
55. Salehinejad MA, Rostami R, Ghanavati E. Transcranial direct current stimulation of dorsolateral prefrontal cortex in major depression: improving visual working memory, reducing depressive symptoms. Neuroregulation. 2015;2(1):37–49.
56. Salehinejad MA, Ghanavai E, Rostami R, Nejati V. Cognitive control dysfunction in emotion dysregulation and psychopathology of major depression (MD): evidence from transcranial brain stimulation of the dorsolateral prefrontal cortex (DLPFC). J Affect Disord. 2017;210:241–8.
57. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain Stimul. 2018;11(1):125–33.
58. Nikolin S, Martin D, Loo CK, Boonstra TW. Effects of TDCS dosage on working memory in healthy participants. Brain Stimul. 2018;11(3):518–27.
59. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376(26):2523–33.
60. Pavlova EL, Menshikova AA, Semenov RV, Bocharnikova EN, Gotovtseva GN, Druzhkova TA, et al. Transcranial direct current stimulation of 20- and 30-minutes combined with sertraline for the treatment of depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;82:31–8.
61. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014;7(2):325–31.
62. Brunoni AR, Boggio PS, De Raedt R, Bensenor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depres-

sion: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–9.
63. Welch ES, Weigand A, Hooker JE, Philip NS, Tyrka AR, Press DZ, et al. Feasibility of computerized cognitive-behavioral therapy combined with bifrontal transcranial direct current stimulation for treatment of major depression. Neuromodulation. 2019;22(8):898–903.
64. Valiengo L, Bensenor IM, Goulart AC, de Oliveira JF, Zanao TA, Boggio PS, et al. The sertraline versus electrical current therapy for treating depression clinical study (select-TDCS): results of the crossover and follow-up phases. Depress Anxiety. 2013;30(7):646–53.
65. Martin DM, Alonzo A, Ho K-A, Player M, Mitchell PB, Sachdev P, et al. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J Affect Disord. 2013;144(3):274–8.
66. Aparicio LVM, Rosa V, Razza LM, Sampaio-Junior B, Borrione L, Valiengo L, et al. Transcranial direct current stimulation (tDCS) for preventing major depressive disorder relapse: results of a 6-month follow-up. Depress Anxiety. 2019;36(3):262–8.
67. Sampaio B Jr, Tortella G, Borrione L, Moffa AH, Machado-Vieira R, Cretaz E, et al. Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression: a randomized clinical trial. JAMA Psychiat. 2018;75(2):158–66.
68. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42(9):1791–800.
69. Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res. 2013;47(1):1–7.
70. Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol. 2014;17(9):1443–52.
71. Meron D, Hedger N, Garner M, Baldwin DS. Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. Neurosci Biobehav Rev. 2015;57:46–62.
72. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020;37(7):594–608.
73. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31.
74. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev. 2009;3
75. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Benseñor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;99:109836.
76. Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology. 2012;37(4):851–64.
77. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35(1):96–101.
78. Brunoni AR, Moffa AH, Sampaio-Junior B, Galvez V, Loo CK. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. Brain Stimul. 2017;10(2):260–2.
79. Berlow YA, Zandvakili A, Carpenter LL, Philip NS. Transcranial direct current stimulation for unipolar depression and risk of treatment emergent mania: an updated meta-analysis. Brain Stimul. 2019;12(4):1066–8.
80. Schestatsky P, Janovik N, Lobato MI, Belmonte-de-Abreu P, Schestatsky S, Shiozawa P, et al. Rapid therapeutic response to anodal tDCS of right dorsolateral prefrontal cortex in acute mania. Brain Stimul. 2013;6(4):701–3.
81. Lisanby SH. Noninvasive brain stimulation for depression—the devil is in the dosing. N Engl J Med. 2017;376(26):2593–4.
82. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–83.
83. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Wörsching J, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. Neuromodulation. 2018;21(4):323–33.
84. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23(1):28.
85. Brunoni AR, Padberg F, Vieira ELM, Teixeira AL, Carvalho AF, Lotufo PA, et al. Plasma biomarkers in a placebo-controlled trial comparing tDCS and escitalopram efficacy in major depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;86:211–7.

Mood Disorders: Predictors of tDCS Response

22

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22.1 Introduction – Why Treatment Prediction Research Is Needed

After two decades of renewed interest and subsequent research efforts into clinical applications of transcranial direct current stimulation (tDCS), its value as antidepressant intervention among non-invasive brain stimulation (NIBS) techniques is still under debate: Two recent meta-analyses concluded that tDCS is superior to sham stimulation in treating major depressive disorder (MDD), with overall moderate effect sizes [1, 2]. However, randomized controlled trials (RCT) included in the meta-analysis by Razza et al. (2020) showed high heterogeneity in efficacy [2]. Moreover, a recent RCT failed to show non-inferiority to escitalopram in treating MDD [3]. Consequently, researchers have shifted their focus beyond monotherapeutic applications of tDCS to investigate if simultaneous treatment with antidepressant pharmacotherapy [4, 5], cognitive behavioral psychotherapy [6], or neurocognitive interventions [7, 8] could further improve treatment efficiency. While these approaches constitute promising avenues, they should be accompanied by efforts to better understand variables that predict treatment response. Insight into such response patterns could help to address two main questions directly related to the heterogeneous results of previous clinical trials: First, tDCS application requires decisions on multiple treatment parameters like electrode placement, current intensity and duration, as well as timing, amount, and frequency of treatment sessions [9]. Clinical tDCS trials have either adopted these parameters (e.g., tDCS intensity of 2 mA) from previous treatment studies or chosen modifications based on clinical or neurophysiological hypotheses [10, 11]. This has likely contributed to heterogeneous results across studies. Explorative response prediction in multiple study cohorts could help narrow down the set of possible parameter combinations to the "most-promising" settings that could then be systematically evaluated in prospective studies. Second, even with fixed parameters, tDCS likely results in significant inter- and intraindividual variability in neural effects, as suggested by studies on motor cortex excitability [12, 13]. Such variability might be especially pronounced in patients with MDD, since its diagnosis is currently based on broad clinical criteria that encompass highly variable disease phenotypes [14] with diverse neurobiological substrates [15]. Since the inclusion criteria of clinical MDD studies are based on the same broad operational criteria, their samples are likely to include patients with low probability of response. Using more fine-grained clinical and biological patient char-

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acteristics, predictive analysis could potentially be used to identify subgroups or even individual patients who are more likely to benefit from tDCS treatment. Personalization and stratification could potentially increase therapeutic specificity and prevent unnecessary treatment. In this chapter, we provide an overview of positive and negative findings reported on potential predictors of tDCS response in mood disorders across multiple domains. Furthermore, we discuss their clinical utility and current methodological limitations. Finally, we propose a roadmap for future research efforts on tDCS response prediction, taking into account recent developments in the field of precision medicine.

22.2 Current Research State – What Do We Know So Far?

At present, mainly exploratory, group-based findings of associations between baseline variables and subsequent tDCS response in clinical trials are available [4, 16, 17]. Some have aggregated these findings across studies using meta-regression [18] or individual patient data [1]. Only one study to date has applied a data-driven, cross-validated predictive modeling approach to offer a validated estimate of predictive accuracy, meaningful at the single subject level [19]. Most studies have focused on treatment response, which is usually defined by a minimum of 50% improvement in depression rating scales, that is, the Hamilton Depression Rating Scale (HDRS) or the Montgomery-Asberg Depression Rating Scale (MADRS). Regarding bipolar depression, studies have either not reported similar analyses [20] or included bipolar depression as a potential predictor of response [1].

22.2.1 Sociodemographic Variables

Several authors have investigated whether age or gender distributions are associated with tDCS response, but have found no evidence in the respective trials [3, 4] or across multiple clinical studies [1, 21]. A secondary analysis of response trajectories for tDCS from the Escitalopram versus Electrical Direct Current Therapy for Depression study (ELECT-TDCS) suggested that older age (within the range 18–75 years) might predict a more rapid improvement [22], which is in contrast to the long-standing belief that elderly patients take longer to respond to antidepressant treatment than younger patients [23]. Kambeitz et al. included the sociodemographic variables, namely, gender, age, years in school, income, ethnicity, marital status, and employment status in a cross-validated predictive model of tDCS response [19], using data from a large clinical trial [3]. While their model reached significant accuracy in predicting tDCS response, its performance was mainly driven by clinical, not sociodemographic features. In sum, there is currently no evidence on specific sociodemographic variables as predictors of tDCS response available. Nonetheless, they might show predictive value for other treatment outcomes like quality-of-life measures or functional outcomes, although this has not been investigated to date.

22.2.2 Clinical History and Disease Status

With biological, objective biomarkers largely absent in psychiatry, detailed clinical assessment is the hallmark of daily psychiatric diagnosis and care. Predicting response based on clinical history and depressive symptomatology would enable a relatively inexpensive and easily interpretable approach to treatment stratification. While overall baseline severity of MDD could not be associated with tDCS response in single studies [4] or a recent IPT meta-analysis [1], some authors have investigated more fine-grained symptomatic patterns: D'Urso et al. used predefined HDRS scale factors in a sample of three independent tDCS trials (n = 171, unipolar and bipolar depression) in a linear mixed model analysis [21]. They found factors such as "cognitive disturbance," "retardation," and "anxiety/somatization" to be associated with tDCS response. In a similar analysis, however, Martin et al. could not detect an association between pretreatment MADRS scale factors

and tDCS response [17], highlighting the need to validate such findings, before suggesting clinical applicability. Loo et al. explored the predictive value of a clinical assessment scale for psychomotor disturbance in depression (CORE), but did not find an association to treatment response in an RCT [24].

Several clinical studies have investigated tDCS as a potential treatment for treatment resistant depression (TRD), usually defined as failed response to two or more adequate antidepressant drug trials [2], but did not observe significant effects [25–27]. While an earlier meta-analysis identified TRD as a potential predictor of tDCS response [28], this could not be replicated in recent meta-analyses using aggregated [2] and individual patient data [1]. Interestingly, in the aforementioned machine learning analysis by Kambeitz et al., the number of past depressive episodes, but not TRD, showed prediction capacity [19]. This finding suggests that future prediction studies might benefit from considering continuous indicators of previous treatment trajectories instead of predefined categorical definitions of TRD. The authors also identified high negative affect, as measured by the Positive and Negative Affect Schedule (PANAS), as predictive of treatment response, which could be related to the involvement of the prefrontal cortex (PFC), that is, the main target region for tDCS in MDD, in emotion regulation [29]. Since negative affect constitutes a broad symptomatic domain encountered in various psychiatric disorders beyond MDD [30, 31], future studies should investigate tDCS effects on this domain in a transdiagnostic framework. Regarding concomitant medication, MDD patients with benzodiazepines showed lower response rates in a previous RCT (Brunoni, Valiengo, et al., 2013) and were less likely to rapidly respond to tDCS according to a secondary analysis of the ELECT-TDCS study [22]. A similar pattern was reported for repetitive transcranial magnetic stimulation (rTMS) [32, 33] and may be explained by inhibitory effects of benzodiazepines on cortical excitability [34]. Other disease characteristics like age of onset of depression, type of depression (e.g., unipolar, bipolar, post-stroke, and peripartal depression), duration of the current episode, or comorbid anxiety have not been found to be associated with tDCS response [2]. While Martin et al. reported concurrent antidepressant medication as a predictor of response [17, 35], this was not confirmed by meta-analyses [18, 28]. Similarly, other hypothetical predictors observed on an explorative level, for example, positive smoking status [3] and higher response rates in patients with certain personality traits (self-directedness, cooperativeness) measured by the Temperament and Character Inventory (TCI) [3] have not been replicated to date.

22.2.3 tDCS Parameters

Stimulation protocols for antidepressant tDCS have been developed largely based on neurophysiological considerations and clinical reasoning [9]. Post-hoc meta-analytic exploration of associations between specific treatment parameters and response yielded no significant findings for (1) number of treatment sessions, current intensity, total charge (in Coulombs [C]) total charge density (in Coulombs per square meter [C/m^2]) and (2) cathode positioning. Due to the standardized protocols, however, there is practically very little variation of parameters in single randomized controlled trials (RCTSs). Thus, either specific RCT designs addressing parameter response relationships or novel proxy parameters, for example, strengths of electric fields (efields) as approximation toward tDCS intensity in a cortical target, are needed to further explore this important field (Padberg et al. 2021 submitted).

22.2.4 Pretreatment Neurocognitive Functioning

Functional magnetic resonance imaging (fMRI) findings have suggested an imbalanced activation of the left and right dorsolateral prefrontal cortex (dlPFC) in MDD patients [36]. Based on these findings, several authors have explored if pretreatment neurocognitive performance as a functional marker of dlPFC integrity could predict tDCS treatment response: Martin et al. analyzed

cognitive assessments of 57 participants of five previous tDCS trials (two RCTs, three open label studies) in MDD patients [35]. In a multivariate analysis, the Controlled Oral Word Association Test (COWAT), a test of verbal fluency, was significantly associated with true but not sham tDCS response. Therefore, the authors concluded that pretreatment verbal fluency could be a specific predictor of tDCS response. In a second study, the same authors explored pretreatment cognition of 120 participants in a multicenter RCT [17] using data from several neuropsychological tests. Only speeded performance on the Ruff 2 and 7, measuring selective and sustained attention and processing speed, was associated with active tDCS response. However, these findings were not entirely specific for active tDCS as the effects were driven by the distribution of high performers in active and sham treatment conditions. They could not replicate their previous finding of an potentially higher likelihood of response in patients with higher verbal fluency. In their meta-analysis, Moffa et al. explored if impaired global cognitive functioning, dichotomized according to the Mini Mental Status Examination (MMSE) or Montreal Cognitive Assessment (MoCA), could be associated with lower treatment response, but did not find significant associations [1].

22.2.5 Genetic Polymorphisms

Several authors have investigated if specific genetic variants in genes that are implicated in neuroplasticity and neurotransmitter homeostasis are associated with tDCS response [37–39]. Most prominently, the Val66Met single nucleotide polymorphism (SNP) in the gene coding for brain-derived neurotrophic factor (BDNF) has been investigated, since it is hypothesized to mediate tDCS-induced neuroplasticity [40] and has been associated with differential responses to antidepressant medication [41]. Such an association was not observed for tDCS response in three seminal RCTs [37–39]. While Brunoni et al. reported an association between long/long carrier status of the 5-HTTLPR polymorphism (coding for the presynaptic sertraline re-uptake transporter) and treatment response to active vs. sham tDCS [37], they could not replicate their finding in an independent sample [38]. Furthermore, no associations to tDCS response could be found for polymorphisms of the tryptophan hydroxylase 1 gene [38], 5-hydroxytryptamine receptor 2A gene [38], and catechol-O-methyltransferase (COMT) gene [38, 39], though a COMT val158met polymorphism has been found to be associated with tDCS effects on cognition [42–44]. An alternative approach, yet to be explored, would be to focus on neuroanatomical traits, for example, cortical thickness or cortical surface areas, and their genetic underpinnings which might influence tDCS effects on neurons [16, 45]. Recent genome-wide association studies (GWAS) have found a high genetic overlap for these traits [46, 47]. Since GWAS require large datasets, currently not available for NIBS, explorative studies may investigate how polymorphisms relate to tDCS-induced efield strengths according to computational models based on individual MRI data from large cohorts.

22.2.6 Neuroimaging

Current tDCS applications have been specifically designed to target brain areas and networks that have been hypothesized to underlie MDD pathophysiology, largely based on neuroimaging findings [15, 36]. Consequently, structural and functional MRI measurements seem a promising choice, when investigating potential biomarkers of antidepressant treatment response. Bulubas et al. utilized structural T1 weighted MRI data from 52 patients enrolled in the ELECT-TDCS study to investigate if gray matter volumes at baseline in the left and right prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) were associated with antidepressant tDCS response [16]. They found an association between larger volumes of PFC subregions and improvement of MDD after treatment. Remarkably, this was only observed in the active tDCS group, but neither in escitalopram nor sham tDCS groups. The importance of the left PFC is further emphasized by Nord et al. (2019) who reported that higher

activation of the dlPFC in a baseline working memory task was associated with increased treatment response in a clinical trial combining tDCS with cognitive behavioral therapy [48]. While these findings strengthen the treatment rationale of current tDCS applications, namely, targeting of the dlPFC, they are based on small samples, have not yet been replicated, and have not been shown to predict response on a single-patient level. Promising results for repetitive transcranial magnetic stimulation (rTMS), for example, the identification of fMRI-based biomarkers with predictive value for treatment response via multivariate pattern analysis of resting-state fMRI [49] and the data-driven characterization of symptom-specific neural targets based on prior treatment effects [50], provide a strong rationale for multimodal imaging acquisition in future NIBS trials to enable robust analyses on a large-scale circuit level.

22.3 Limitations – Association Versus Prediction

tDCS development has followed a trajectory that corresponds well to traditional medical research: After initial neurophysiological findings [51] and first promising clinical studies [10, 52], current clinical research can be situated in the so-called phase III of clinical trials, with first larger RCTs published [3, 4, 39] and results from further multicenter trials ahead [5, 6]. As described above, these trials have been accompanied by efforts to gain a mechanistic understanding of tDCS effects, for example, via ancillary analyses of single trials. However, single site exploratory research relies strongly on the expertise of the specific research group as well as other factors, for example, the local availability of diagnostic utilities (e.g., MRI scanners and genetic laboratory). This often results in limited reproducibility and generalizability. With a single exception [19], studies have not conducted cross-validated tests of internal validity to date, and attempts to externally validate results are completely missing in the field. To rely on associative studies without an attempt to externally validate the respective findings has been identified as one major reason for the so-called reproducibility crisis in medicine that impeded the clinical translation of research findings [53, 54], especially in psychiatry [55, 56]. Furthermore, data scientists have questioned if correlational statistics allow conclusions toward prediction per se [57, 58].

There are multiple reasons why findings from prior tDCS research could suffer from poor generalizability: Owing to its relative novelty, treatment parameters like stimulation site (i.e., electrode montages) or simulation dose (e.g., tDCS intensity and duration of the session) have largely varied between studies, resulting in low comparability between cohorts. Likewise, previous studies have differed regarding treatment duration and setting, concomitant medication and patient characteristics. Compared to studies in the fields of neuropsychopharmacology and psychotherapy, NIBS datasets have been relatively small with few attempts of multisite collaboration. These caveats clearly caution against the premature extrapolation from current findings of associations to causal assumptions and clinical recommendations. In the following chapter, we discuss how future research could achieve more reliable predictive estimates.

22.4 The Road Ahead – Modern Analytics for a Novel Treatment Approach

Following the "Precision Medicine Initiative" in the United States in 2015 [59], there has been a shift in medicine toward the increasing application of so-called data-driven research methods that aim at retrieving individual predictive information from large, high-dimensional datasets. Rooted in early computational approaches [60], these efforts have been largely fuelled by exponential increases in computational processing speed and advances in machine learning algorithms [61]. Promising results across various health-care applications like X-ray evaluation [62], skin cancer classification [63], or the development of new antibiotic drugs [64] have been recently published. In psychiatry, precision medi-

cine has been promoted as a roadmap to translate research into precise clinical applications to enable accurate prediction [65], biomarker detection, and diagnosis [66] and personalized treatment [67, 68]. After initial enthusiasm, there are more realistic views now: Except for some diagnostic applications that have been approved by the U.S. Food and Drug Administration [69], most efforts have so far not been translated into clinical practice [70]. Concerns regarding low data quality, small samples (where the benefits of machine learning are generally not well established), imprecise hypothesis formulation, missing clinical relevance, as well as ethical considerations have been raised [70, 71]. Furthermore, some authors have argued that a precondition for individualized treatment, heterogeneous patient-by-treatment effects, are often assumed, but rarely tested [72]. For NIBS in general, modest treatment effect variation was found across multiple diseases and stimulation methods, though results for specific modalities are still inconclusive [73]. Some of the variability of response to tDCS may be explained by the considerable phenotypic heterogeneity on the patient level. However, the majority of the above-mentioned studies have operated on the group-level and attempted to predict traditional units of RCT analysis. These units often create arbitrary dichotomies (e.g., response vs. non-response) [74] and differentiate poorly in terms of individual symptom trajectories (cross-sectional endpoints) [75] as well as presented symptoms (aggregate symptom measures) [76].

In direct reference to these issues, three main methodological approaches seem particularly promising: First, as discussed above, Kambeitz et al. recently published first evidence that single-patient prediction based on pretreatment variables could be achieved through cross-validated predictive modeling approaches (e.g., using supervised machine learning) [19]. These algorithms may further be used to inform future explanatory studies by use of interpretable machine learning (IML) methods and are particularly suited to be translated into the single patient setting (e.g., clinical decision support systems). Second, instead of focusing on dichotomous response outcomes, Goerigk et al. categorized patients according to their temporal patterns of symptom improvement to identify distinct treatment trajectories ("no/minimal", "slow," and "rapid" response) for tDCS in MDD. These trajectory classes could be used as prediction targets to identify likely tDCS benefiters in advance and suggest the possibility of developing individualized treatment protocols [22]. Third, as suggested by Chekroud et al. in a study on response to antidepressant pharmacotherapy [76], the identification of statistically reliable symptom clusters with differential responsiveness to specific treatments would enable clinically comprehensible treatment decisions, though this approach has not been tested for tDCS yet. Fourth, assuming populations that are homogenous beyond the diagnosis-level, may ignore distinct clusters within the patients (i.e., endophenotypes) and result in inefficient analyses. Data-driven methods (e.g., unsupervised machine learning) can identify previously unknown patterns of variation from multimodal data that cut across diagnostic categories (manifolds). These patient subgroups can be explored in terms of distinct treatment response and used for stratification in future trials. Since these prior analyses have relied on data from single clinical trials, external validation across multiple treatment contexts (e.g., study sites, geographic, and cultural entities), naturalistic patient samples are inevitable to test the generalizability and scope of the models. Furthermore, their incremental utility has to be demonstrated in direct comparison to the current gold-standard (i.e., clinicians' rating) and in the real-life work flow to establish the potential of such models to augment clinical care [77]. Furthermore, all four approaches could be extended beyond subjective clinical ratings to incorporate measurements related to tDCS parameters (e.g., efield strength in target regions), multimodal neuroimaging data, other biological markers, or neuropsychological characteristics.

A main prerequisite of data-driven research is the availability of large, high-quality datasets across diverse clinical settings. Since this can hardly be achieved by single research institutions, the field should find ways to encourage multisite collaboration and data sharing. Furthermore, a commitment to transparent, reproducible research, as proposed by the open science ini-

tiative, could significantly increase efforts to clinically validate findings and accelerate their incorporation into clinical care.

In conclusion, while first efforts applying data-based prediction of tDCS response in patients with MDD have yielded promising results, their capacity for translation toward clinical applications has yet to be established in prospective studies across diverse clinical settings. At the moment, clinicians should base their recommendations regarding tDCS treatment on average efficacy estimates from RCTs and consider the individual cost benefit ratio including contraindications and side-effect profiles (Fig. 22.1).

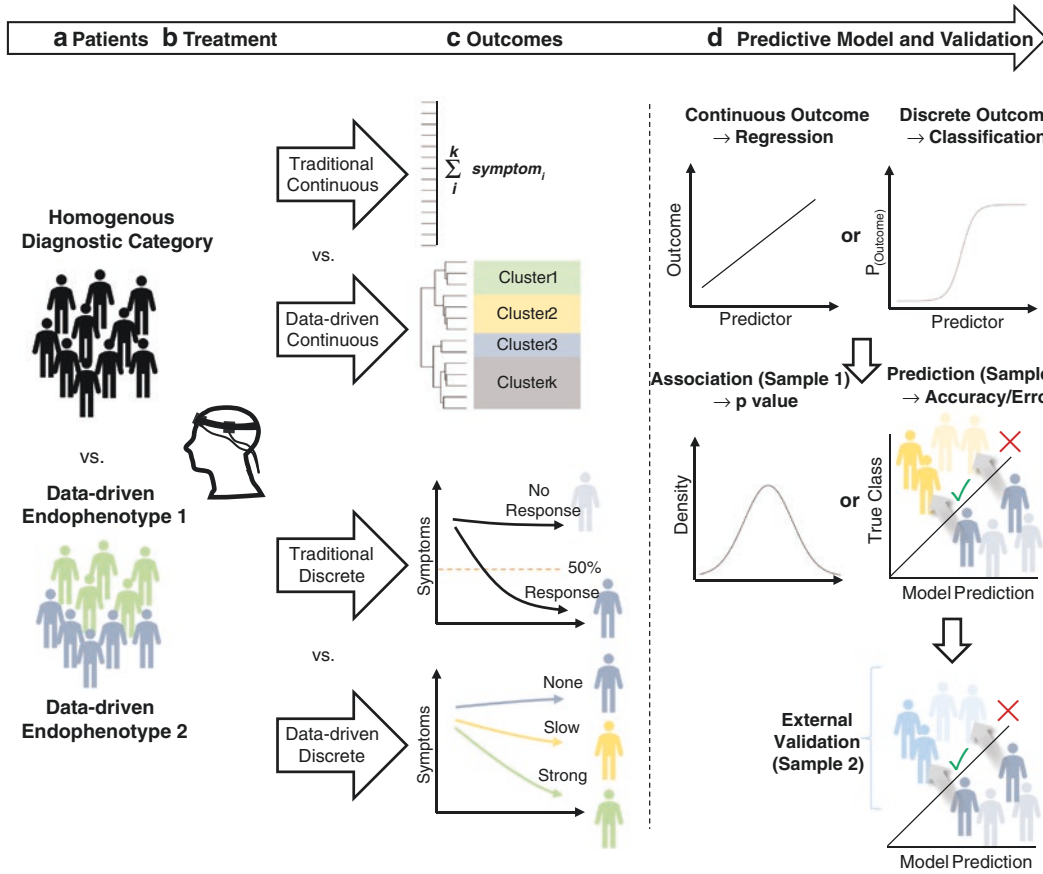

Fig. 22.1 (**a**) Patients can be treated according to their diagnostic category or receive stratified treatment according to distinct patterns of inter- and intra-disease variability. (**b**) Treatment with tDCS. (**c**) Potential units of analysis can be used to evaluate efficacy and can be targets for predictive modeling. Continuous measures for symptom severity traditionally use sum scores of depression rating scales that can mask response in certain symptom subgroups. Data-driven clustering allows more differentiated analysis within natural subgroups of symptoms. Discrete measures of treatment response traditionally uses cutoff values that create arbitrary dichotomies and that are not sensitive for the time course of symptomatic change. Data-driven categorization of patients by their individual trajectories of symptom improvement allows more differentiated analysis of response. (**d**) Continuous and discrete outcomes can be predicted using regression and classification models, respectively. For both objectives, models may have different degrees of complexity (e.g., ordinary least squares regression vs. supervised machine learning models). Models are traditionally evaluated using within-sample inference measures (e.g., p values) that are limited in terms of extrapolation beyond the sample. Predictive modeling allows judgment on the single-patient level. Predictive models can be formally evaluated on unseen instances within a given dataset (e.g., nested cross-validation). Generalizability of predictive models should be tested on external data (e.g., third-party datasets) or prospectively, by predicting future instances. All visualizations are hypothetical and not based on real data

References

1. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Benseñor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuro Psychopharmacol Biol Psychiatry [Internet]. 2020;99:109836. Available from: https://doi.org/10.1016/j.pnpbp.2019.109836.
2. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020;37(7):594–608.
3. Brunoni AR, Moffa AH, Sampaio B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376(26):2523–33.
4. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, De Oliveira JF, Goulart A, et al. The sertraline vs electrical current therapy for treating depression clinical study. JAMA Psychiat. 2013;70(4):383–91.
5. Padberg F, Kumpf U, Mansmann U, Palm U, Plewnia C, Langguth B, et al. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;
6. Bajbouj M, Aust S, Spies J, Herrera-Melendez AL, Mayer SV, Peters M, et al. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder—study design and methodology of a multicenter double-blind randomized placebo-controlled tria. Eur Arch Psychiatry Clin Neurosci. 2018;
7. Sathappan A V., Luber BM, Lisanby SH. The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. Prog Neuro Psychopharmacol Biol Psychiatry [Internet]. 2019;89:347–60. Available from: https://doi.org/10.1016/j.pnpbp.2018.10.006.
8. Weller S, Nitsche MA, Plewnia C. Enhancing cognitive control training with transcranial direct current stimulation: a systematic parameter study. Brain Stimul. 2020;
9. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol. 2016;
10. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol [Internet]. 2008 [cited 2020 Aug 6];11(2):249–54. Available from: https://pubmed.ncbi.nlm.nih.gov/17559710/
11. Jamil A, Batsikadze G, Kuo HI, Meesen RLJ, Dechent P, Paulus W, et al. Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: an fMRI study. Hum Brain Mapp. 2020;
12. Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. Brain Stimul [Internet] 2015;8(6):1130–7. Available from: https://doi.org/10.1016/j.brs.2015.07.031
13. Wiethoff S, Hamada M. Rothwell JC. Brain Stimul: Variability in response to transcranial direct current stimulation of the motor cortex; 2014.
14. Jablensky A. Psychiatric classifications: validity and utility. World Psychiatry. 2016;15(1):26–31.
15. Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety. 2017;
16. Bulubas L, Padberg F, Bueno PV, Duran F, Busatto G, Amaro E, et al. Antidepressant effects of tDCS are associated with prefrontal gray matter volumes at baseline: evidence from the ELECT-TDCS trial. Brain Stimul. 2019;12(5):1197–204.
17. Martin DM, McClintock SM, Aaronson ST, Alonzo A, Husain MM, Lisanby SH, et al. Pre-treatment attentional processing speed and antidepressant response to transcranial direct current stimulation: results from an international randomized controlled trial. Brain Stimul [Internet]. 2018;11(6):1282–90. Available from: https://doi.org/10.1016/j.brs.2018.08.011.
18. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012;42(9):1791–800.
19. Kambeitz J, Goerigk S, Gattaz W, Falkai P, Benseñor IM, Lotufo PA, et al. Clinical patterns differentially predict response to transcranial direct current stimulation (tDCS) and escitalopram in major depression: a machine learning analysis of the ELECT-TDCS study. J Affect Disord [Internet]. 2020;265(December 2019):460–7. Available from: https://doi.org/10.1016/j.jad.2020.01.118.
20. Sampaio B, Tortella G, Borrione L, Moffa AH, Machado-Vieira R, Cretaz E, et al. Efficacy and safety of transcranial direct current stimulation as an add-on treatment for bipolar depression: a randomized clinical trial. JAMA Psychiat. 2018;75(2):158–66.
21. D'Urso G, Dell'Osso B, Rossi R, Brunoni AR, Bortolomasi M, Ferrucci R, et al. Clinical predictors of acute response to transcranial direct current stimulation (tDCS) in major depression. J Affect Disord [Internet]. 2017;219(May):25–30. Available from: https://doi.org/10.1016/j.jad.2017.05.019
22. Goerigk SA, Padberg F, Bühner M, Sarubin N, Kaster TS, Daskalakis ZJ, et al. Distinct trajectories of response to prefrontal tDCS in major depression: results from a 3-arm randomized controlled trial. Neuropsychopharmacology. 2020;

23. Sackeim HA, Roose SP, Burt T. Optimal length of antidepressant trials in late-life depression. J Clin Psychopharmacol. 2005;
24. Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol. 2010;13(1):61–9.
25. Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, et al. Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin Neurophysiol [Internet]. 2015;126(6):1185–9. Available from: https://doi.org/10.1016/j.clinph.2014.09.026
26. Blumberger DM, Tran LC, Fitzgerald PB, Hoy KE, Daskalakis ZJ. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front Psych. 2012;3(August):1–8.
27. Palm U, Hasan A, Strube W, Padberg F. tDCS for the treatment of depression: a comprehensive review. Eur Arch Psychiatry Clin Neurosci. 2016;266(8):681–94.
28. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31.
29. Heller AS, Johnstone T, Peterson MJ, Kolden GG, Kalin NH, Davidson RJ. Increased prefrontal cortex activity during negative emotion regulation as a predictor of depression symptom severity trajectory over 6 months. JAMA Psychiat. 2013;70(11):1181–9.
30. Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. The nature, diagnosis, and treatment of neuroticism: Back to the future. Clin Psychol Sci. 2014;2(3):344–65.
31. Caspi A, Moffitt TE. All for one and one for all: mental disorders in one dimension. Am J Psychiatr. 2018;
32. Kaster TS, Downar J, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, et al. Trajectories of response to dorsolateral prefrontal rTMS in major depression: a three-D study. Am J Psychiatry. 2019;176(5):367–75.
33. Hunter AM, Minzenberg MJ, Cook IA, Krantz DE, Levitt JG, Rotstein NM, et al. Concomitant medication use and clinical outcome of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder. Brain Behav. 2019;
34. Turco CV, El-Sayes J, Locke MB, Chen R, Baker S, Nelson AJ. Effects of lorazepam and baclofen on short- and long-latency afferent inhibition. J Physiol. 2018;
35. Martin DM, Yeung K, Loo CK. Pre-treatment letter fluency performance predicts antidepressant response to transcranial direct current stimulation. J Affect Disord [Internet]. 2016;203:130–5. Available from: https://doi.org/10.1016/j.jad.2016.05.072
36. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry. 2008;63(4):369–76.
37. Brunoni AR, Kemp AH, Shiozawa P, Cordeiro Q, Valiengo LCL, Goulart AC, et al. Impact of 5-HTTLPR and BDNF polymorphisms on response to sertraline versus transcranial direct current stimulation: implications for the serotonergic system. Eur Neuropsychopharmacol [Internet]. 2013;23(11):1530–40. Available from: https://doi.org/10.1016/j.euroneuro.2013.03.009
38. Brunoni AR, Carracedo A, Amigo OM, Pellicer AL, Talib L, Carvalho AF, et al. Association of BDNF, HTR2A, TPH1, SLC6A4, and comt polymorphisms with tdcs and escitalopram efficacy: ancillary analysis of a double-blind, placebo-controlled trial. Brazilian J Psychiatry. 2020;42(2):128–35.
39. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial direct current stimulation in depression. Brain Stimul. 2018;11(1):125–33.
40. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity : potential implications for motor learning. Neuron [Internet]. 2011;66(2):198–204. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2864780&tool=pmcentrez&rendertype=abstract
41. Kishi T, Yoshimura R, Ikuta T, Iwata N. Brain-derived neurotrophic factor and major depressive disorder: Evidence from meta-analyses [Internet]. Vol. 8, Frontiers in Psychiatry. Frontiers Media S.A.; 2018 [cited 2020 Oct 27]. p. 17. Available from: /pmc/articles/PMC5776079/?report=abstract.
42. Nieratschker V, Kiefer C, Giel K, Krüger R, Plewnia C. The COMT Val/Met polymorphism modulates effects of tDCS on response inhibition. Brain Stimul. 2015;
43. Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/met polymorphism. Cortex. 2013;
44. Hayek D, Antonenko D, Witte AV, Lehnerer SM, Meinzer M, Külzow N, et al. Impact of COMT val158met on tDCS-induced cognitive enhancement in older adults. Behav Brain Res. 2021;
45. Filmer HL, Ehrhardt SE, Shaw TB, Mattingley JB, Dux PE. The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology. NeuroImage. 2019;196:41–8.
46. van der Meer D, Frei O, Kaufmann T, Chen C-H, Thompson WK, O'Connell KS, et al. Quantifying the polygenic architecture of the human cerebral cortex: extensive genetic overlap between cortical thickness and surface area. bioRxiv [Internet]. 2019;868307. Available from: http://biorxiv.org/content/early/2019/12/06/868307.abstract

47. Grasby KL, Jahanshad N, Painter JN, Colodro-Conde L, Bralten J, Hibar DP, et al. The genetic architecture of the human cerebral cortex. Science (80-). 2020;
48. Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, et al. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology. 2019;
49. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;
50. Siddiqi SH, Taylor SF, Cooke D, Pascual-Leone A, George MS, Fox MD. Distinct symptom-specific treatment targets for circuit-based neuromodulation. Am J Psychiatry. 2020;177(5):435–46.
51. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;
52. Fregni F, Boggio PS, Nitsche M, Marcolin MA, Rigonatti SP, Pascual-Leone A. Letters to the Editor Treatment of major depression with transcranial direct current stimulation Ephedrine-induced emergence of bipolar symptoms. Bipolar Disord. 2006;8:203–5.
53. Ioannidis JPA. Why Most Published Research Findings Are False. PLoS Med [Internet]. 2005 [cited 2020 Feb 28];2(8):e124. Available from: https://doi.org/10.1371/journal.pmed.0020124
54. Siontis GCM, Tzoulaki I, Castaldi PJ, Ioannidis JPA. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol [Internet]. 2015;68(1):25–34. Available from: https://doi.org/10.1016/j.jclinepi.2014.09.007
55. Hyman SE. Revolution stalled. Sci Transl Med. 2012;
56. Insel TR, Cuthbert BN. Brain disorders? Precisely. Science (80-). 2015;
57. Breiman L. Statistical modeling: the two cultures. Stat Sci. 2001;16(3):199–215.
58. Poldrack RA, Huckins G, Varoquaux G. Establishment of best practices for evidence for prediction: a review. JAMA Psychiat. 2020;77(5):534–40.
59. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;
60. Rosenblatt F. The perceptron: a probabilistic model for information storage and organization in the brain. Psychol Rev [Internet]. 1958 [cited 2020 Mar 26];65–386. Available from: https://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.588.3775
61. Kotsiantis SB. Supervised machine learning: a review of classification techniques. Inform. 2007;31(3):249–68.
62. Rajpurkar P, Irvin J, Zhu K, Yang B, Mehta H, Duan T, et al. CheXNet: Radiologist-Level Pneumonia Detection on Chest X-Rays with Deep Learning. 2017 [cited 2020 Feb 23]; Available from: http://arxiv.org/abs/1711.05225
63. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542(7639):115–8.
64. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, et al. A deep learning approach to antibiotic discovery. Cell. 2020;180(4):688–702.e13.
65. Koutsouleris N, Dwyer DB, Degenhardt F, Maj C, Urquijo-Castro MF, Sanfelici R, et al. Multimodal Machine Learning Workflows for Prediction of Psychosis in Patients With Clinical High-Risk Syndromes and Recent-Onset Depression. JAMA Psychiatry. 2020;
66. Dwyer DB, Kalman JL, Budde M, Kambeitz J, Ruef A, Antonucci LA, et al. An investigation of psychosis subgroups with prognostic validation and exploration of genetic underpinnings: The PsyCourse study. JAMA Psychiat. 2020:1–11.
67. Koutsouleris N, Kahn RS, Chekroud AM, Leucht S, Falkai P, Wobrock T, et al. Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: a machine learning approach. Lancet Psychiatry. 2016;3(10):935–46.
68. Chekroud AM, Zotti RJ, Shehzad Z, Gueorguieva R, Johnson MK, Trivedi MH, et al. Cross-trial prediction of treatment outcome in depression: a machine learning approach. Lancet Psychiatry [Internet] 2016;3(3):243–50. Available from: https://doi.org/10.1016/S2215-0366(15)00471-X
69. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med. 2018;1(1):1–8.
70. Wiens J, Saria S, Sendak M, Ghassemi M, Liu VX, Doshi-Velez F, et al. Do no harm: a roadmap for responsible machine learning for health care. Nat Med. 2019;25(9):1337–40.
71. Wilkinson J, Arnold KF, Murray EJ, Smeden M Van, Carr K, Sippy R, et al. Viewpoint Time to reality check the promises of machine learning-powered precision medicine. Lancet [Internet]. 2020;7500(20):1–4. Available from: https://doi.org/10.1016/S2589-7500(20)30200-4
72. Winkelbeiner S, Leucht S, Kane JM, Homan P. Evaluation of differences in individual treatment response in schizophrenia Spectrum disorders: a meta-analysis. JAMA Psychiat. 2019;
73. Winkelbeiner S, Muscat W, Joanlanne A, Marousis N, Vetter S, Seifritz E, et al. Treatment effect variation in brain stimulation across psychiatric disorders 2020;1–12.
74. Senn S. Statistical pitfalls of personalized medicine. Nature. 2018;
75. Uher R, Muthén B, Souery D, Mors O, Jaracz J, Placentino A, et al. Trajectories of change in depression severity during treatment with antidepressants. Psychol Med. 2010;
76. Chekroud AM, Gueorguieva R, Krumholz HM, Trivedi MH, Krystal JH, McCarthy G. Reevaluating the efficacy and predictability of antidepressant treatments: a symptom clustering approach. JAMA Psychiat. 2017;
77. Cearns M, Hahn T, Baune BT. Recommendations and future directions for supervised machine learning in psychiatry. Transl Psychiatry. 2019;

23 Effect of Transcranial Direct Current Stimulation on Hallucinations in Patients with Schizophrenia

Ondine Adam, Marine Mondino, and Jerome Brunelin

23.1 Introduction

Schizophrenia is a severe psychiatric disorder with a prevalence of approximately 0.7% [1], with severe repercussions: in addition to being one of the most debilitating diseases in the world [2], it significantly reduces life expectancy [3]. Clinical symptoms are heterogeneous, including disorganization (contradictory feelings, incoherent discourse), negative symptoms (emotional, speech impoverishment), and positive symptoms (hallucinations, megalomania, and delusions).

Auditory verbal hallucinations (AVHs) are a frequent and debilitating symptom of schizophrenia [4, 5], causing severe distress and being associated with suicidal tendencies [6]. They can be defined as hearing voices without appropriate external stimulus. Various mechanisms involving dopaminergic, glutamatergic, and serotoninergic transmission seem to underpin AVHs [7]. Hyperactivity of the language-related cortical areas (left pars opercularis or Brodmann's area 44) and the associative auditory cortex (left middle and superior temporal gyri or Brodmann's area 21 and 22) [8], as well as altered functional connectivity between frontal and temporal cortices have been strongly associated with this symptom [9].

Antipsychotics are used as a first line treatment but approximately 25–30% of patients with schizophrenia report medication-resistant AVHs. Hence, non-invasive brain stimulation techniques have emerged as new nonpharmacological approaches in refractory cases. In line with this, evidence suggested that low-frequency repetitive transcranial magnetic stimulation (TMS) targeting the left temporoparietal junction (TPJ) may improve AVHs in patients with schizophrenia.

In the 2010s, transcranial direct current stimulation (tDCS) has also been investigated as a safe well-tolerated treatment for AVH. Most of these studies were case reports or open-label trials, representing low quality of evidence. Randomized sham-controlled studies focusing on neurostimulation and its impact on hallucinations would provide more robust results.

Thus, we conducted a systematic review of randomized sham-controlled studies on the effect of tDCS on AVHs in patients with schizophrenia to provide an update of the current state of the art on this topic.

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23.2 Materials and Methods

Our systematic review followed the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

23.2.1 Literature Search Strategy

PubMed database were searched until February 2020 using the following search strategy: "hallu*" AND ("transcranial direct current stimulation" OR ("transcranial" AND "direct" AND "current" AND "stimulation) OR "tdcs") AND "schizophrenia." We also searched for articles in the reference lists of retrieved articles and in tDCS review articles.

23.2.2 Selection Criteria

We included articles selection criteria meeting the following criteria: (1) original articles written in the English language, (2) sham-controlled trials, and (3) studies that included patients with schizophrenia. We excluded (1) review articles, (2) meeting and conference abstracts, (3) case-reports, (4) open-label trials, (5) studies that did not provide a clear description of the tool used for the clinical measure of hallucinations severity, (6) articles addressing the effects of other brain stimulation techniques (e.g., transcranial random-noise stimulation), and (7) studies that did not use the assessment of AVHs as primary outcome.

23.2.3 Data Extraction

For each study, a standardized data sheet was used to extract the following variables: (1) demographic and clinical characteristics such as total sample size, diagnosis, sex (male/female), age (in years), handedness (right/left-handed), and antipsychotic medication dose, (2) tDCS parameters including type of device used, placement of the anode and the cathode [according to 10/20 international electroencephalogram (EEG) system], electrode size (cm^2), number and frequency of sessions, intensity (mA) and duration (min), as well as the sham-tDCS protocol used, and (3) outcomes and main results (scale used to measure hallucinations and its changes after tDCS regimen). The quality of each study was measured according to Jadad scale [10], on the online Oxford Quality Scoring System available on the Medical Online Calculators Library.

23.3 Results

Seventy-nine articles were selected from our literature search strategy on the PubMed database (Fig. 23.1). According to our selection criteria, nine randomized sham-controlled studies investigating the effect of tDCS on AVHs in patients with schizophrenia were included. Table 23.1 summarizes the data extracted from the selected articles.

The studies came from eight independent research groups. In total, 359 patients were included and 182 of them received active tDCS. All the studies included patients with schizophrenia diagnosis according to Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) or DSM-5 criteria. All the patients presented with disabling hallucinations. Some of the studies included mixed sample of patients with schizophrenia, schizoaffective disorders (in six studies [11–16]), psychotic disorder not otherwise specified (NOS), and affective or borderline personality disorders without provided results by categories of patients (in one study [14]). Patients with both sexes were included for a sex ratio of 1.65 (226 males, 137 females). The mean age of patients varied between 31.3 and 46.4 years. Among the seven studies that reported the handedness, three included only right-handed patients [15, 17, 18]. Most patients were on antipsychotic medication; the dose was reported in chlorpromazine or olanzapine equivalents. The medication dose varied from 493 to 1209 mg/d of chlorpromazine equivalents.

Regarding tDCS devices, the Eldith/Neuroconn DC stimulator was used in most stud-

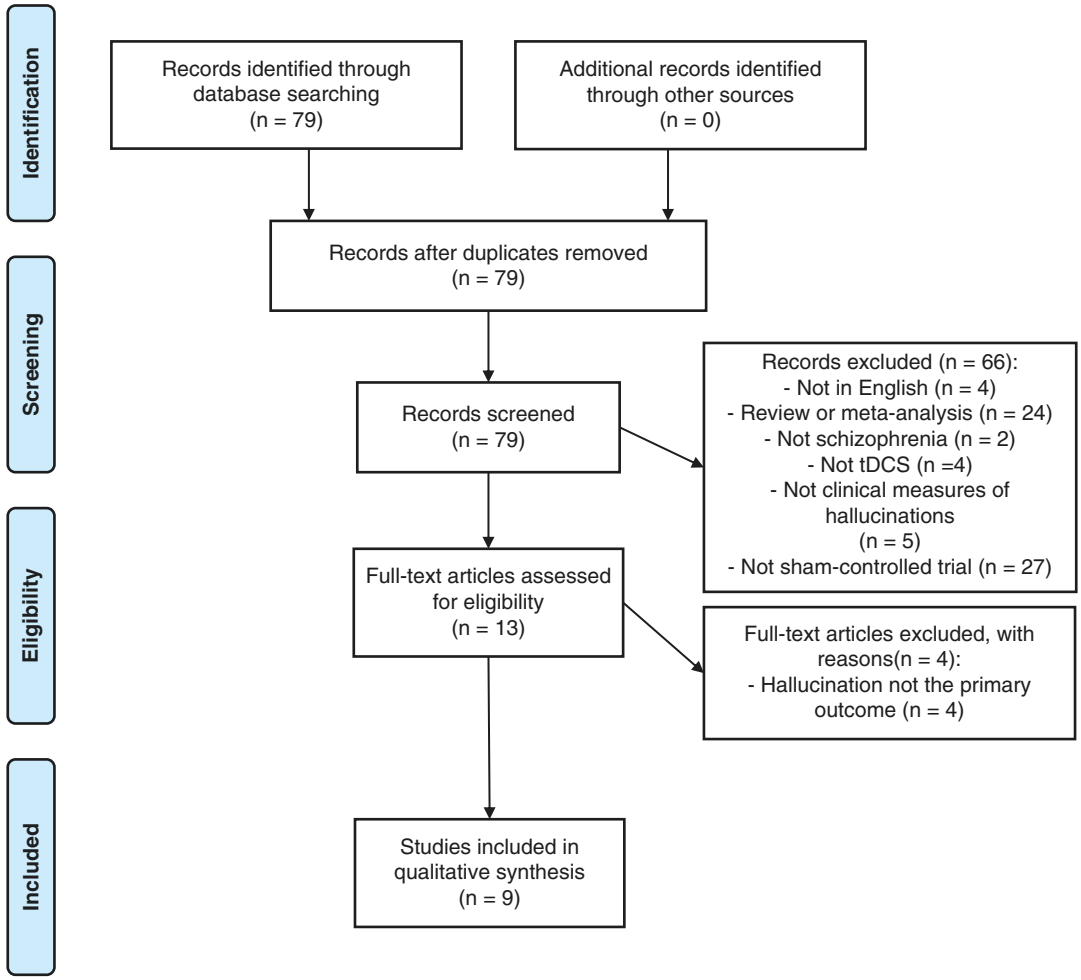

Fig. 23.1 PRISMA 2009 flow diagram describing the selection procedure of the studies investigating the effects of tDCS on auditory verbal hallucinations in patients with schizophrenia. PRISMA indicates preferred reporting items for systematic reviews and meta-analyses

ies; the two other devices that were used were the BrainStim SYS (Brainvision) [15] or the CHA-1335 stimulator (Chattanooga) [16]. In seven of the nine selected studies, the anode was placed over the left dorsolateral prefrontal cortex (between F3 and FP1 according to 10/20 international EEG system) and the cathode over the left temporoparietal junction (between T3 and P3), with two electrode-sponges of 35 cm^2. In all selected studies, tDCS was delivered with an intensity set at 2 mA during 20 min. The tDCS regimen used in most studies consisted of 10 sessions delivered twice a day over 5 consecutive weekdays. Consecutive stimulation sessions on the same day were separated by at least 3 hours [14–17] or between 2 and 3 hours [18, 19].

Concerning the sham protocol used, five studies used 40s of active 2 mA stimulation at the beginning of the stimulation session followed by brief pulses of 110 μA over 15 ms every 550 ms to check impedance for a total duration equal to the duration of the active stimulation [11, 12, 14, 18, 19]. Three other studies chose a short period of active stimulation (30s or 40s at 2 mA) at the beginning of the stimulation period followed by no stimulation through the remainder of the stimulation session [15–17]. One study chose 40s or ramp up to 2 mA immediately followed by 40s

Table 23.1 Characteristics of selected studies investigating tDCS for auditory verbal hallucinations

Author, date	Jadad score [a]	Diagnosis	Anode/ Cathode placement	Electrode size (cm^2)	*n* session	Time between 2 sessions	Intensity (mA)	Duration (min)	Group	*n*, sex	Age (years)	*n* laterality	Antipsychotic dose (mg/ day)[b]	AH scale	Main results	p
Brunelin et al., 2012	4	SZ	F3FP1/T3P3	35	10 (2×5 days)	>3 h	2	20	Active	15, 12 M/3F	40.4 ± 9.9	15R	994 ± 714	AHRS	−30.5%	<0.001
									Sham	15, 10 M/5F	35.1 ± 7.0	15R	1209 ± 998		−7.6%	
Fitzgerald et al., 2014	4	SZ / SZAff	F3F4/ TP3TP4	35	15 (1×5 days ×3 weeks)	1 day	2	20	Bilateral tDCS	11	39.3 ± 11.7			PANSS hallucination item (P3)	Active: −13%	0.3
															Sham: −3%	0.5
			F3/TP3						Unilateral tDCS	13					Active: −17%	0.9
															Sham: −6%	0.3
Fröhlich et al., 2016	4	SZ /SZAff	F3FP1/Cz/ T3P3	35	5 (1×5 days)	1 day	2	20	Active	13, 9 M/4F	43.4 ± 12.6	10R/3 L		AHRS	−24%	0.59
									Sham	13, 11 M/2F	40.0 ± 10.7	11R/2 L			−34%	
Mondino et al., 2016	4	SZ	F3FP1/T3P3	35	10 (2×5 days)	>2 h30	2	20	Active	11, 8 M/3F	36.7 ± 9.7	10R/1 L	23 ± 11 [b]	AHRS	−28%	<0.01
									Sham	12, 7 M/5F	37.3 ± 9.7	10R/2 L	25 ± 12 [b]		−10%	0.09
Bose et al., 2018	5	SZ	F3FP1/T3P3	35	10 (2×5 days)	2–3 h	2	20	Active	12, 9 M/3F	31.3 ± 8.3	12R	621 ± 378	AHRS	−30.2%	<0.001
									Sham	13, 5 M/8F	31.4 ± 7.6	13R	783 ± 337		−6.6%	
Chang et al., 2018	3	SZ / SZAff	F3FP1/T3P3	35	10 (2×5 days)	Not reported	2	20	Active	30, 14 M/16F	46.4 ± 10.3		494 ± 307	AHRS	−7.8%	0.15
									Sham	30, 13 M/17F	42.2 ± 10.3		493 ± 285		−3.9%	
Koops et al., 2018	4	SZ; SZAff; Aff; Bd; pNOS	F3FP1/T3P3	35	10 (2×5 days)	>3 h	2	20	Active	28, 14 M/14F	44 ± 11	25R/3 L		AHRS	−9.7%	0.27
									Sham	26, 11 M/15F	44 ± 12	24R/2 L			−9.3%	

Kantrowitz et al., 2019	4	SZ /SZAff	F3FP1/T3P3	38.81	10 (2×5 days)	>3 h	2	20	Active	47, 32 M/15F	38.2 ± 9.9	47R	806 ± 768	AHRS	−21.4%	0.036
									Sham	42, 35 M/7F	40.1 ± 8.6	42R	628 ± 466		−17.9%	
Lindenmayer et al., 2019	3	SZ /SZAff	F3FP1/T3P3	35	40 (2×5 days ×4 weeks)	>3 h	2	20	Active	15, 13 M/2F	40.2 ± 10.7		892	AHRS	−21.9%	0.025
									Sham	13, 11 M/2F					−12.6%	

Aff affective disorder, *AH* auditory hallucination, *AHRS* auditory hallucination rating scale, *Bd* borderline personality disorder, *L* left-handed, *PANSS* positive and negative syndrome scale, *pNOS* psychotic disorder not otherwise specified, *R* right-handed, *SZ* schizophrenia, *SZAff* schizoaffective disorder

[a]Jadad score from Oxford Quality Scoring system: score ≤2 for low range of quality score; score ≥3 for high range of quality score

[b]Antipsychotic dose is reported in chlorpromazine equivalents except for Mondino et al. [19], in which the dose was reported in olanzapine equivalents

of ramp down and no stimulation through the remainder of the stimulation session [13].

Most of selected studies used the Auditory Hallucination Rating Scale (AHRS) as standardized psychometric scales to measure AVH; one study used the hallucination item (P3) of the Positive and Negative Syndrome Scale (PANSS).

All studies showed a high range of quality score (score ≥3) on the Jadad scale.

Five studies reported a significant decrease in AVHs after active tDCS [15–19] (total mean decrease of 29.67%, varying from 21.4% to 46%), one found a trend toward a significant decrease in AVHs [13] ($p = 0.15$) and three found no significant effect of active tDCS on AVHs over sham [11, 12, 14].

23.4 Discussion

Nine studies fulfilled our selection criteria for this review, which aimed to provide an overview of the randomized sham-controlled studies regarding the effect of tDCS on AVHs in patients with schizophrenia. Five over the nine studies found a significant effect of active tDCS on AVHs compared to sham tDCS whereas three found no superiority of active tDCS over sham tDCS. Additionally, one study reported a trend toward significant difference. Demographic, clinical, and methodological differences must be highlighted and might explain the discrepancies observed between the selected studies.

First, methodological parameters (stimulation parameter and study design) differ between positive and negative studies. Regarding tDCS parameters, the majority of the positive studies delivered 10 twice-daily sessions over 5 consecutive days (except [16]), which delivered 40 twice-daily sessions whereas two of the three negative studies delivered once-daily sessions over either 5 [12] or 15 consecutive days [11]. The number of sessions per day and the total number of tDCS sessions seem to be an important parameter to take into account to explain the effectiveness of active tDCS in AVHs. Moreover, in all the positive studies, the duration between two consecutive sessions was of at least 2 hours. Only one study did not report these data [13]. This is in line with tDCS studies investigating the influence of these parameters when tDCS is applied over the motor cortex [20, 21] reporting that the duration between 2 consecutive sessions can modulate the direction of tDCS after-effect in terms of facilitation or inhibition. Regarding the montage of electrodes, all of them used an electrode montage with the anode placed over the left dorsolateral prefrontal cortex (DLPFC) (between F3 and FP1) and the cathode over the left TPJ (between T3 and P3), brain regions involved in the AVH pathophysiology [8], except two of the negative studies: Fröhlich et al. [12] used a three-electrode montage and a part of the Fitzgerald et al. [11] investigated the effects of four-electrode bilateral montage. Across all the studies, homogeneity was observed regarding the duration (20 min) and the intensity (2 mA) of the tDCS sessions.

Regarding the study design, Fitzgerald et al. [11] developed a cross-over study, whereas all positive studies used two-arm parallel study design. Since the duration of tDCS after-effect is still under debate, a cross-over design seems not to be the more appropriate study design to investigate tDCS effects because of the carry-over effect. Hence, further two-arm studies investigating the effects of twice-daily tDCS sessions for at least 5 consecutive days with the anode targeting the DLPFC and the cathode the left TPJ during 20 min with a current intensity of 2 mA are required.

Since the sham protocol has been described as a possible confounding factor [22], reporting this parameter should be systematic. In that regard, the selected studies are divided into two groups: those with active stimulation only during a short period at the beginning of the stimulation session [13, 15–17] and those with a small current in the form of a pulse for the rest of the session [11, 12, 14, 18, 19]. Positive and negative studies are homogeneously distributed in these two groups, thus not allowing conclusions to be drawn from this review. The detailed description of the sham condition design should therefore be the subject of future investigations.

Additionally, the sample size of most of the selected studies is small: only two of them have

a subject number greater than or equal to 30 subjects per group [13, 15], allowing for more robust statistical results compared to small sample size. One reported a significant decrease in AVHs following active tDCS protocol [15], the other showed a trend toward a decrease in AVHs [13].

Secondly, clinical characteristics of patients such as characteristics of AVH, diagnosis or medication intake also varied across studies. For instance, AVH frequency widely varied between studies: four out of the six positive studies included patients presented with continuous daily medication-resistant AVHs [13, 17–19], whereas negative studies included patients with three or five AVHs per weeks [12, 14]. It has been reported that the brain activity underlying continuous and intermittent AVHs is different, especially in language-related areas [23]. These different patterns of brain activity during the stimulation can have dissimilar influences on clinical outcome since brain state during the stimulation period is known to influence brain stimulation after-effects [24]. Regarding diagnosis of patients, all the studies that included only patients with schizophrenia reported a significant beneficial effect of tDCS on AVH. Conversely, two out of the three negative studies included a mixed sample with patients with schizophrenia and patients with schizoaffective disorder [11, 12], and the other one included a mixed sample ($n = 54$) composed by patients with schizophrenia ($n = 34$), schizoaffective disorder ($n = 2$), affective disorder ($n = 3$), borderline personality disorders ($n = 3$), and patients with psychosis NOS ($n = 12$) [14]. It would be interesting to investigate trajectories of response category by category of diagnosis. However, individual data were not provided and it was not possible to investigate whether the diagnosis influence tDCS outcome on AVH. One may hypothesize that tDCS has a better clinical effect on AVHs in patients with schizophrenia than in patients with other psychiatric disorders since studies with mixed sample are less convincing than studies including only patients with schizophrenia according to DSM criteria. Further studies are required to determine the interest of tDCS in the treatment of AVHs for other psychiatric conditions including borderline personality and affective disorders. Regarding medication, the three negative studies did not report subject's medication doses, including antipsychotic medication. However, it has been reported that patients receiving high dopamine D2 receptor-affinity antipsychotics were associated with significantly less improvement of AVHs after tDCS compared to patients receiving antipsychotics with low affinity for dopamine D2 receptors [25]. Moreover, studies in healthy participants highlighted that tDCS can induce dopamine release in the striatum [26] and that dopamine D2 receptor antagonists can abolish cathodal tDCS effects on neuronal plasticity [27]. Altogether, these studies suggested a close relationship between dopamine and response to tDCS in patients with AVHs. Other psychotropic treatments may also have an influence on tDCS outcome. In line with this, selective serotonin reuptake inhibitors such as sertraline are known to increase the clinical effect of tDCS in patients with depression [28] whereas serotonin–norepinephrine reuptake inhibitors such as venlafaxine did not increase response rate to repetitive TMS (rTMS) [29]. Thus, reporting medication of patients in studies investigating the effects of tDCS should be systematic.

Thirdly, some genetic functional polymorphisms have recently been involved in modification of the response to tDCS. Brain-derived neurotrophic factor (BDNF), which is known to influence in synaptic plasticity, presents functional polymorphisms that can influence tDCS-induced plasticity [30]: subjects with Val66Met polymorphism show a higher tDCS-induced plasticity compared to Val66Val carriers. Similarly, catechol-O-methyltransferase (COMT) polymorphisms, an enzyme that degrade dopamine mostly in frontal brain regions, interact with tDCS effects [31]. Patients who are Met carriers (Val158Met or Met158Met) showed less improvement of AVHs after active tDCS sessions than patients with Val158Val COMT polymorphism [32]. These findings suggest that different genetic functional polymorphisms could interact with the effect of tDCS and make subjects more or less responsive to this technique.

Finally, tobacco smoking may also have an influence on tDCS outcome. An open-study reported that non-smokers showed a significant improvement in AVHs after tDCS sessions (reduction of 46%) whereas smokers were qualified as non-responders to tDCS (non-significant reduction of 6%) [33]. None of selected studies did not report smoking status of participants. The evaluation of the interaction between smoking status, medication, and tDCS will need to be investigated in future studies.

Additionally, Jadad scale was used to assess the quality of reports of randomized controlled trials [10]. All the studies showed a high average of quality score (score ≥3).

To conclude, tDCS is a promising new tool for the treatment of medication-resistant AVHs in schizophrenia. However, some specific parameters seem to be needed to observe such effect. Ten twice-daily sessions over 5 consecutive days with an current intensity of 2 mA and a duration of the stimulation of 20 min, the anode placed between F3 and FP1, regarding the left DLPFC, and the cathode between T3 and P3, over the left TPJ, appear to be the most efficient design to induce with tDCS reduction in AVHs in patients with schizophrenia. Nonetheless, selected studies have mostly small effect sizes, and conflicting results still existing. Larger randomized controlled studies investigating the effect of tDCS on AVHs in patients with schizophrenia must be carried out in the future in order to clearly conclude on the effectiveness of this technique.

References

1. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67–76.
2. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1575–86.
3. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol. 2014;10:425–48.
4. McCarthy-Jones S, Smailes D, Corvin A, et al. Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. Psychiatry Res. 2017;252:154–60.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. American Psychiatric Association; 2013.
6. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. 2010;24:81–90.
7. Jardri R, Hugdahl K, Hughes M, et al. Are hallucinations due to an imbalance between excitatory and inhibitory influences on the brain? Schizophr Bull. 2016;42:1124–34.
8. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. AJP. 2011;168:73–81.
9. Ćurčić-Blake B, Ford JM, Hubl D, et al. Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. Prog Neurobiol. 2017;148:1–20.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12.
11. Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. Brain Stimul. 2014;7:813–6.
12. Fröhlich F, Burrello TN, Mellin JM, Cordle AL, Lustenberger CM, Gilmore JH, Jarskog LF. Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia. Eur Psychiatry. 2016;33:54–60.
13. Chang C-C, Tzeng N-S, Chao C-Y, Yeh C-B, Chang H-A. The effects of add-on Fronto-temporal transcranial direct current stimulation (tDCS) on auditory verbal hallucinations, other psychopathological symptoms, and insight in schizophrenia: a randomized, double-blind, sham-controlled trial. Int J Neuropsychopharmacol. 2018;21:979–87.
14. Koops S, Blom JD, Bouachmir O, Slot MI, Neggers B, Sommer IE. Treating auditory hallucinations with transcranial direct current stimulation in a double-blind, randomized trial. Schizophr Res. 2018;201:329–36.
15. Kantrowitz JT, Sehatpour P, Avissar M, et al. Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a replication/extension study. Brain Stimul. 2019;12:981–91.
16. Lindenmayer JP, Kulsa MKC, Sultana T, Kaur A, Yang R, Ljuri I, Parker B, Khan A. Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. Brain Stimul. 2019;12:54–61.
17. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny M-F, Saoud M, Mechri A,

Poulet E. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. AJP. 2012;169:719–24.
18. Bose A, Shivakumar V, Agarwal SM, Kalmady SV, Shenoy S, Sreeraj VS, Narayanaswamy JC, Venkatasubramanian G. Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: a randomized, double-blind, sham-controlled study. Schizophr Res. 2018;195:475–80.
19. Mondino M, Poulet E, Suaud-Chagny M-F, Brunelin J. Anodal tDCS targeting the left temporoparietal junction disrupts verbal reality-monitoring. Neuropsychologia. 2016;89:478–84.
20. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK. Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. Brain Stimul. 2012;5:208–13.
21. Monte-Silva K, Kuo M-F, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol. 2010;103:1735–40.
22. Fonteneau C, Mondino M, Arns M, et al. Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul. 2019;12:668–73.
23. Hoffman RE, Hampson M, Wu K, Anderson AW, Gore JC, Buchanan RJ, Constable RT, Hawkins KA, Sahay N, Krystal JH. Probing the pathophysiology of auditory/verbal hallucinations by combining functional magnetic resonance imaging and transcranial magnetic stimulation. Cereb Cortex. 2007;17:2733–43.
24. Bergmann TO. Brain state-dependent brain stimulation. Front Psychol. 2018; https://doi.org/10.3389/fpsyg.2018.02108.
25. Agarwal SM, Bose A, Shivakumar V, Narayanaswamy JC, Chhabra H, Kalmady SV, Varambally S, Nitsche MA, Venkatasubramanian G, Gangadhar BN. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatry Res. 2016;235:97–103.
26. Fonteneau C, Redoute J, Haesebaert F, Le Bars D, Costes N, Suaud-Chagny M-F, Brunelin J. Frontal transcranial direct current stimulation induces dopamine release in the ventral striatum in human. Cereb Cortex. 2018;28:2636–46.
27. Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex: dopamine in human neuroplasticity. Eur J Neurosci. 2006;23:1651–7.
28. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, Boggio PS, Lotufo PA, Benseñor IM, Fregni F. The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383.
29. Brunelin J, Jalenques I, Trojak B, et al. The efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression: the results from a large multicenter French RCT. Brain Stimul. 2014;7:855–63.
30. Antal A, Chaieb L, Moliadze V, Monte-Silva K, Poreisz C, Thirugnanasambandam N, Nitsche MA, Shoukier M, Ludwig H, Paulus W. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. Brain Stimul. 2010;3:230–7.
31. Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. Cortex. 2013;49:1801–7.
32. Chhabra H, Shivakumar V, Subbanna M, et al. Gene polymorphisms and response to transcranial direct current stimulation for auditory verbal hallucinations in schizophrenia. Acta Neuropsychiatr. 2018;30:218–25.
33. Brunelin J, Hasan A, Haesebaert F, Nitsche MA, Poulet E. Nicotine smoking prevents the effects of frontotemporal transcranial direct current stimulation (tDCS) in hallucinating patients with schizophrenia. Brain Stimul. 2015;8:1225–7.

Schizophrenia: Negative Symptoms

24

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24.1 Introduction

About 1–2% of the population suffers from schizophrenia, a disabling disorder with a variety of impairments in cognition, mood, impetus, interaction, and social functioning. Mortality of people with schizophrenia is increased with an average of 14.5 years of potential life lost [1]. Suicidality is increased 2–5-fold compared to general population. In fact, 10% of patients die by suicide [2]. Thus, schizophrenia is a disorder with high socioeconomic burden and a frequent chronic course [3].

Syndrome diversity of schizophrenia and related disorders include highly heterogeneous symptoms that have been classified into five dimensions that are represented in the most common clinical rating scale, the Positive and Negative Symptom Scale (PANSS) [4] and reflecting typical clinical symptoms, for example, delusions and hallucinations (positive symptoms), avolition and emotional withdrawal (negative symptoms), cognitive impairment and disorganization (cognition), depressed mood and fear (depression/anxiety), and impairment of social interaction (excitement/hostility). Negative symptoms occur in more than 50% of schizophrenia patients [5] and consist in affective flattening, alogia, avolition/apathy, anhedonia/asociality, and deficits in attention [6].

Although psychopharmacologic treatment of schizophrenia has advanced in recent years, even adequate drug regimen does not exert full remission in up to 30% of patients [7, 8]. Especially, auditory hallucinations and negative symptoms can be refractory to treatment [9]. However, epidemiological studies suggest that positive symptoms decrease over time [10, 11] while negative symptoms increase during disease course and count for chronicity and diminished psychosocial functioning [12–14]. Finally, treatment-resistant negative symptoms impair global functioning, recovery, occupational rehabilitation, and social integration, and are leading to passive and apathetic socioemotional withdrawal. Concomitant cognitive difficulties [12, 13, 15] have an additive effect on overall functioning, leading to a decline in global cognition [16] and to social impairment in two-thirds of patients. Negative symptoms are associated with obesity, dyslipidemia, hypertension, polypharmacy, and somatic comorbidity [5].

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Although new pharmacologic interventions exist, for example, the efficacy of cariprazine in negative symptoms [17], there is still a need for new interventions [18]. As a third track besides pharmacology and psychotherapy, noninvasive brain stimulation (NIBS) was investigated over more than two decades, showing promising results from repetitive transcranial magnetic stimulation (rTMS) applied over the left dorsolateral prefrontal cortex (DLPFC) [19], however, a conclusive recommendation is still pending after a more recent negative randomized controlled trial [20].

In contrast, transcranial direct current stimulation (tDCS) is investigated for one decade in the treatment of schizophrenia and there are several recent studies underlining the potential benefit of tDCS in the treatment of negative symptoms. Negative symptoms and related cognitive impairment are attributed to a dysfunction of fronto-thalamic-parietal or frontal-striatal networks [21–25]. tDCS modulates prefrontal function and changes large-scale networks assessed by functional connectivity magnetic resonance imaging (fcMRI) during resting state, that is, a reduced default mode network (DMN) in healthy volunteers [26] or leads to an activation in the medial-frontal cortex beneath the anode in schizophrenia patients [27]. Therefore, the rationale for a stimulation of prefrontal areas is deriving from pathophysiologic findings and from results in the treatment of depression, where bihemispheric prefrontal tDCS was shown to be effective [28]. Contrarily, studies on auditory verbal hallucinations [29, 30] reported improvement of negative symptoms after anodal stimulation of the left DLPFC and cathodal stimulation of the right temporo-parietal junction. It is likely that in both electrode montages, the anodal stimulation of the left prefrontal cortex is the driver of clinical improvement of negative symptoms. As the technique of tDCS is easy to handle, the intervention could be part of an integrated home care model for patients with severe loss of drive.

24.2 Schizophrenia and Negative Symptoms

24.2.1 Current Treatments for Schizophrenia

Standard treatment of schizophrenia includes a combination of psychopharmacologic, psychoeducational, psychosocial, and rehabilitation approaches.

Current guidelines suggest second-generation antipsychotics to treat psychotic episodes; however, first-generation antipsychotics are still used for otherwise treatment-resistant cases [9]. Electroconvulsive therapy is a treatment option to improve persistent positive symptoms and catatonia. rTMS has shown some efficacy in the treatment of auditory hallucinations and negative symptoms, however, results are inconsistent regarding negative symptoms [31] and cognitive symptoms [32].

24.2.2 Mechanisms of Action

The rationale of tDCS application in schizophrenia is based on neuroimaging findings and the results of clinical rTMS studies. Neuroimaging suggests a dysfunction of cortical areas with temporo-parietal hyperactivation during auditory hallucinations [33], frontal hypoactivation in negative symptoms and cognitive dysfunction [21], and a fronto-temporal dysconnectivity [34, 35]. Thus, tDCS can be used for neuromodulation of dysfunctional areas, that is, to decrease activity in temporo-parietal regions to reduce auditory hallucinations or to increase activity in frontal regions to enhance mood, impetus, and cognition. For this purpose, a monohemispheric electrode montage with the cathode over the left temporo-parietal junction and the anode over the left DLPFC has been successfully used to treat auditory hallucinations with a concomitant beneficial effect on negative symptoms [29, 36], and

a bihemispheric montage with the anode over the left DLPFC and the cathode contralaterally has been applied to improve negative symptoms with a focus of current distribution on frontal brain areas [37].

24.2.3 Clinical Evidence

More than 20 single case reports and several open-label studies and RCTs are available addressing various symptoms of schizophrenia, predominantly auditory hallucinations. Negative symptoms and improvement of cognition were investigated in either single case reports or some small open-label studies and RCTs. To provide only clinical evidence from RCTs and open-label studies, single case reports are not discussed here, however, can be found in a respective review article [36] (Table 24.1).

The first randomized placebo-controlled clinical trial using tDCS for treatment of schizophrenia was published in 2012 by Brunelin et al. [29]. Thirty patients with treatment-resistant auditory hallucinations were randomized to either receive twice-daily 20 min of 2 mA tDCS over 2 days with the anode over the left DLPFC and the cathode over the left temporo-parietal junction or sham tDCS. Although the primary outcome of this study was the effect of tDCS on *auditory verbal hallucinations*, shown by a significant reduction of 31% up to 3 months after stimulation, there was also a decrease of negative symptoms as a secondary outcome, opening the use of tDCS for research in negative symptoms as well.

Several subsequent studies investigated negative symptoms as a secondary outcome in addition to the primary outcome of auditory verbal hallucinations. Fitzgerald et al. [38] found no superiority of active tDCS over sham in an RCT with monohemispheric (F3-Tp3) and bihemispheric electrode montage (F3-Tp3, F4-Tp4, 2 tDCS devices) in 24 patients with persistent hallucinations and negative symptoms. Mondino et al. [36] used a partially overlapping sample and the same procedure as Brunelin et al. [29] and found a significant reduction of the subscale of negative symptoms of PANSS of 14.4% in active and no reductions in sham group. Fröhlich et al. [39] included 26 schizophrenia and schizoaffective patients in a randomized placebo-controlled trial with the anode over the left DLPFC (2 mA, 20 min, 5 sessions) and the cathode over the left temporo-parietal junction and did not find a significant difference in PANSS between groups, including negative symptoms. Chang et al. examined the effects of tDCS with 2-mA, twice-daily sessions for five consecutive days, with anodal stimulation over F3 and cathodal over TP3 [40]. They did not find significant changes in the positive or negative schizophrenia symptoms; however, the levels of insight into illness were largely promoted by 5 days of transcranial direct current stimulation relative to sham treatment.

Gomes et al. [37] investigated the effects of bifrontal tDCS (anode: left DLPFC, cathode: right DLPFC) in 15 patients with *negative symptoms as primary outcome* and reported a significant reduction of negative and general subscales after active tDCS, however, depression ratings (Calgary Depression Scale in Schizophrenia, CDSS) did not change after active tDCS compared to sham tDCS.

Kurimori et al. [41] conducted an open-label study with 9 patients with negative symptoms and found a significant reduction of the negative subscale of the PANSS but not in the other subscales after 5x anodal tDCS over the left DLPFC with the cathode over the right deltoid muscle. An RCT by Palm et al. [42] with 20 patients receiving either active or sham tDCS over the left DLPFC reported a significant reduction of negative symptoms in the Scale for the Assessment of Negative Symptoms (SANS) and PANSS after 10 sessions of active tDCS compared to sham stimulation.

Table 24.1 Summary of controlled tDCS trials in schizophrenia for negative symptoms

Author	Sample (n)	Anode	Cathode	Current (mA)/ electrode size (cm^2)	Number of sessions	Results
Brunelin et al. [29]	30	F3	Tp3	2 / 35	10	Positive[a]
(Brunelin et al.)						
Fitzgerald et al. [38]	24	F3 (F4)	Tp3 (Tp4)	2/35	15	Negative[a]
(Fitzgerald et al.)						
Gomes et al. [37]	15	F3	F4	2/35	10	Positive
(Gomes et al.)						
Mondino et al. [36]	28[a]	F3	Tp3	2/35	10	Positive[a]
(Mondino et al.)						
Fröhlich et al. [39]	26	F3	Tp3	2/35	5	Negative[a]
(Frohlich et al.)						
Palm et al. [42]	20	F3	Fp2	2/35	10	Positive
(Palm et al.)						
Chang et al. [40]	60	F3	TP3	2/35	10	Negative[a]
(Chang et al.)						
Kantrowitz et al. [44]	89	F3	TP3	2/35	20	Negative[a]
(Kantrowitz et al.)						
Valiengo et al. [43]	100	F3	TP3	2/35	20	Positive
(Valiengo et al.)						

[a]Negative symptoms as a secondary outcome R SO, right supraorbital, FCz, medial-frontal cortex; R cheek, right cheek between cheilion and condylion; Fp2, right fronto-polar; R UA, right upper arm

Two recent randomized sham-controlled clinical trials with very similar methodologies had a larger sample size [43, 44]. They used tDCS with anode over F3 and cathode over TP3, totalizing 10 sessions with 2 mA, twice a day, on 5 consecutive days. The first, Kantrowitz et al., measured the decrease of auditory hallucinations as primary outcome, and Valiengo et al. measured the negative symptoms. Both studies have the largest sample size using tDCS for schizophrenia so far (89 and 100, respectively). Kantrowitz et al. showed improvement in the auditory hallucinations but not in the negative symptoms. On the other hand, Valiengo et al. demonstrated the opposite, only efficacy in negative symptoms measured by the negative subscale of PANSS (Fig. 24.1). One possible explanation for these differences is the inclusion criteria. Kantrowitz et al. used the presence of moderate-to-severe auditory hallucinations symptomatology for eligibility, while Valiengo et al. did not (only 36% of patients had hallucinations). The opposite is true for negative symptoms: Valiengo et al. used a minimum of 20 points in negative subscale of PANSS for eligibility (mean 25.05 ± 3.7) and Kantrowitz (mean 17.3 ± 5) did not use the scale.

One recent meta-analysis addressed the effects of tDCS in schizophrenia [45]. Regarding negative symptoms, 9 studies with 313 patients showed that only studies using at least 10 sessions of tDCS (7 studies, 257 patients) had reduction of negative symptoms.

There are several studies without clinical improvement as primary outcome criterion although reporting on clinical efficacy as well. These studies primarily refer to an improvement of cognition, neurophysiological parameters, or cigarette craving in schizophrenia patients by tDCS. *Cognition* was investigated in a trial by Nienow et al. [46]. The authors found a significant improvement of cognitive functions in a word and picture 2-back test and the MATRICS Consensus Cognitive Battery (MCCB) after anodal compared to sham tDCS in 10 patients. Vercammen et al. [47] conducted a randomized placebo-controlled study in 20 schizophrenia patients who were treated with a single session of active and sham tDCS with the anode over the left DLPFC (F3) and the cathode contralateral supraorbital (Fp2) before undergoing a probabilistic learning test (cue and outcome reaction). They found no tDCS effect in the whole sample, however, patients with adequate performance at baseline showed a significant improvement of performance in the following tests. Hoy et al. [48] assessed changes of working memory after tDCS in a crossover trial in 18 schizophrenia patients. Prefrontal tDCS (anode F3, cathode Fp2) was delivered in two active (1 and 2 mA) and sham condition and led to improvement of working memory in the n-back task up to 40 min

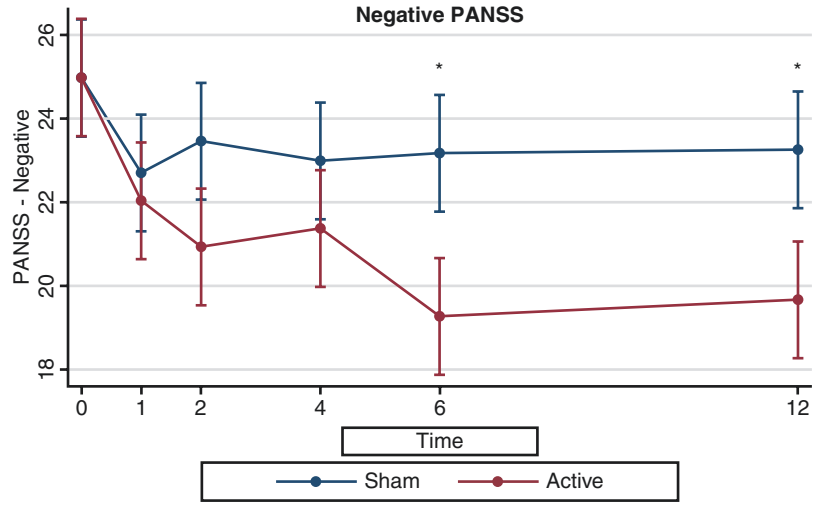

Fig. 24.1 Changes in mean PANSS negative over time by group from Valiengo et al. study. *$p < 0.05$

after 2 mA active tDCS compared to sham and 1 mA tDCS. Ribolsi et al. [49] investigated the effect of left and right hemisphere tDCS on spatial pseudoneglect in a sample of 15 schizophrenia patients and found that anodal stimulation of the right parietal cortex (P4) normalized the pseudoneglect bias in the line bisection task. Göder et al. [50] applied slow-oscillating tDCS (so-tDCS, 0.75 Hz, anodes F3/F4, cathodes mastoids) during sleep stage 2 in 14 schizophrenia patients and found a significant improvement of the Rey Auditory–Verbal Learning Test after active stimulation compared to sham. Rassovsky et al. [51] randomized 36 schizophrenia patients to either receive anodal, cathodal, or sham tDCS over both prefrontal cortices (F1/F2) with the reference at the right upper arm. They found no superiority of any condition after a single session of tDCS in four different cognitive tests except for an intragroup effect in facial recognition in the active tDCS group. Bose et al. [52] reported a reduction of auditory hallucinations by 32% and an increase in insight by 156% in an open-label study with 21 patients after 10 × 2 mA tDCS with the anode over left frontal areas and the cathode over the left temporo-parietal junction.

The impact of tDCS on *neurophysiological* changes in schizophrenia patients was assessed by Reinhardt et al. [53] with an investigation into the impact of tDCS on EEG-related error-related mismatch negativity (ERN) over frontal brain regions in a visual learning task as a predictor of error signaling in the brain of 19 schizophrenia patients and 18 healthy controls. They found a reduced ERN in patients compared to healthy controls indicating impaired prediction error calculation in patients and slower response and less accuracy in patients compared to healthy controls. Anodal tDCS over the mediofrontal cortex (FCz) boosted ERN amplitude in both schizophrenia patients and healthy controls, compared to sham stimulation. In schizophrenia patients, velocity and accuracy of the visual learning task after active stimulation was similar to the sham stimulation results of the healthy controls. Subramaniam et al. [54] conducted an open-label study in 13 patients with schizophrenia, treated with 10 sessions of 2 mA tDCS with the anode over F3 and the cathode over Tp3. They reported a significant reduction in antisaccade error percentage (eye-tracking antisaccade task) and severity of auditory verbal hallucinations. Jeon et al. [55] also assessed the effects of tDCS on cognition in a randomized sham-controlled clinical trial with 56 patients with schizophrenia. Each group received 30 min of active 2-mA tDCS or sham stimulation over the dorsolateral prefrontal cortex (anode F3, cathode F4) once per day for 10 consecutive weekdays. There was a significant improvement of working memory (using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery) and overall scores in the real-tDCS group compared to the sham-tDCS group. The authors also found improvement of depression scores but not differences in negative symptoms.

Lindenmayer et al. [56] examined the efficacy and safety of 20 sessions of tDCS (cathode over TP3 and anode between F3 and FP1) for 4 weeks for auditory hallucinations and cognition in hospitalized ultratreatment-resistant schizophrenia. Twenty-eight participants were enrolled (tDCS, $n = 15$; control, $n = 13$) and 21 participants completed all 4 weeks of the trial with a significant reduction for the auditory hallucination total score, but when assessing cognitive functioning, only Working Memory showed improvement for the tDCS group with no differences in other psychiatric measures like overall PANSS or negative symptoms.

Orlov et al. [27] performed a double-blind, sham-controlled study of 49 patients with schizophrenia, using real or sham tDCS stimulation groups. Subjects (24 in active and 25 in sham groups) participated in 4 days of cognitive training (days 1, 2, 14, 56) with tDCS applied at day-1 and day-14. The primary outcome measure was change in accuracy on working memory and implicit learning tasks from baseline. The working memory task demonstrated a significant mean difference in active group, while there were no significant effects of tDCS on implicit learning.

Cigarette craving, cognition, and clinical symptoms were assessed in a randomized placebo-controlled trial by Smith et al. [57] with 37 schizophrenia patients. They investigated the

effects of prefrontal tDCS on psychiatric symptoms (PANSS), hallucinations (PSYRATS), cigarette craving, and cognitive tasks (MCCB). Only cognitive improvement could be detected after five sessions of 2 mA prefrontal tDCS (anode F3, cathode, Fp2), whereas psychiatric symptoms (including negative symptoms) and cigarette craving did not change in the active group compared to sham.

Furthermore, two studies investigated the effects of *pharmacological interaction* and tDCS in schizophrenia patients. The impact of antipsychotic medication on the effects of tDCS was investigated by Agarwal et al. [58] in an open-label study in 36 patients individually treated with various antipsychotics. After 10 sessions of 2 mA tDCS, they found less improvement of auditory hallucinations in female patients treated with high D2-receptor affinity antipsychotics compared to low D2-receptor affinity antipsychotics.

The impact of tobacco smoking on tDCS effects on auditory hallucinations was investigated by Brunelin et al. [59] in an open-label study. They found a lower effect of tDCS on the improvement of auditory hallucinations in smokers than in nonsmokers.

Adverse Events

No specific treatment-emergent adverse effects of tDCS in schizophrenia trials have been reported so far.

24.3 Conclusions and Future Directions

This chapter provided an overview of the clinical evidence of tDCS efficacy in the treatment of negative symptoms in schizophrenia. In many studies, tDCS is investigated as an augmentative option to standard treatments in order to boost their response. Studies using tDCS as a standalone treatment or a replacement therapy for psychopharmacology are lacking. tDCS devices are affordable, portable, and easy to handle. Compared to other brain stimulation techniques like rTMS, these unique features provide the possibility of remotely supervised home treatment [60]. This could reduce the time spent in clinical setting, enhance patients' autonomy and adherence to the treatment, and reduce frequency of rehospitalization by continuously self-applied, but remotely supervised treatment. It is supposed that improvement of cognition and avolition leads to supporting effects in the occupational and psychosocial rehabilitation and delays the usually early onset of disability. Furthermore, tDCS could improve impaired illness awareness (IIA) in schizophrenia patients. IIA is referred to a disturbed interhemispheric connectivity between both posterior-parietal areas (PPA) and their DLPFC interconnections [61]. A recent tDCS study was able to modulate the PPA activity by anodal and cathodal stimulation albeit there was no improvement in IIA after a single tDCS session [62]. Anodal stimulation over the left DLPFC and cathodal stimulation over the left temporo-parietal junction (montage for the treatment of auditory verbal hallucinations) have shown some positive results in improving IIA [40, 52].

Generally, most trials presented good methodology, in terms of randomization, blinding, sham control, and definition of primary outcomes. However, several exploratory or proof of concept studies are lacking adequate control groups, rigor of protocols, and sufficient study duration including lack of follow-up phases. Except for one study [43], all clinical trials had very small sample sizes. Therefore, many non-significant findings might have occurred due to a type II error, that is, a false-negative finding, due to an underpowered trial.

Consensus papers recommend a 12-week treatment period in a clinically stable sample, that is, persistent negative symptoms for at least 6 months [3, 63]. This is a crucial problem in the design of a large tDCS trial as the patient must return daily to a clinical center. This obstacle could be alleviated by remotely supervised tDCS home administration. However, regarding the difficulties in adherence in this special population, domiciliary support by a member of the study group could be necessary. Furthermore, funding issues are an obstacle in trial design due to the lack of industrial funding. To date, tDCS is not used as

a substitution therapy for psychopharmacology. Add-on treatment could shadow tDCS effects during concomitant drug therapy. Moreover, it is still unknown which tDCS parameters (e.g., electrode placement, electrode size, dose, session duration, number of sessions, interval between sessions, and duration of maintenance treatment) are associated with sustained efficacy.

One issue is the efficacy at long term. There are not studies regarding maintenance and follow-up strategies. This would be very important in the future to decide the best use of tDCS in schizophrenia.

To conclude, in the past years, the amount of clinical trials investigating tDCS efficacy in schizophrenia has grown exponentially. Results have been particularly promising in improvement of negative symptoms, auditory verbal hallucinations, and cognitive functions. As the interactions between these main features of schizophrenia are complex and multidimensional, it is questionable to focus on a specific symptom or part of the disease. Therefore, tDCS studies in schizophrenia are likely to report an add-on benefit exceeding the primary study outcome.

References

1. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017;4(4):295–301.
2. Rössler W, Salize HJ, van Os J, Riecher-Rössler A. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol. 2005;15(4):399–409.
3. Kirkpatrick B, Fenton WS, Carpenter WT, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006;32(2):214–9.
4. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–76.
5. Sicras-Mainar A, Maurino J, Ruiz-Beato E, Navarro-Artieda R. Impact of negative symptoms on healthcare resource utilization and associated costs in adult outpatients with schizophrenia: a population-based study. BMC Psychiatry. 2014;14:225.
6. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry. 1982;39(7):784–8.
7. Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. Schizophr Res. 1998;32(3):137–50.
8. Murphy BP, Chung YC, Park TW, McGorry PD. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. Schizophr Res. 2006;88(1–3):5–25.
9. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2012;13(5):318–78.
10. Goghari VM, Harrow M, Grossman LS, Rosen C. A 20-year multi-follow-up of hallucinations in schizophrenia, other psychotic, and mood disorders. Psychol Med. 2013;43(6):1151–60.
11. Heilbronner U, Samara M, Leucht S, Falkai P, Schulze TG. The longitudinal course of schizophrenia across the lifespan: clinical, cognitive, and neurobiological aspects. Harv Rev Psychiatry. 2016;24(2):118–28.
12. Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. Schizophr Bull. 2007;33(4):1013–22.
13. Kirkpatrick B, Galderisi S. Deficit schizophrenia: an update. World Psychiatry. 2008;7(3):143–7.
14. Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry. 2005;162(3):495–506.
15. Fenton WS, McGlashan TH. Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. Am J Psychiatry. 1994;151(3):351–6.
16. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT. A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry. 2001;58(2):165–71.
17. Citrome L. Cariprazine for acute and maintenance treatment of adults with schizophrenia: an evidence-based review and place in therapy. Neuropsychiatr Dis Treat. 2018;14:2563–77.
18. Arango C, Garibaldi G, Marder SR. Pharmacological approaches to treating negative symptoms: a review of clinical trials. Schizophr Res. 2013;150(2–3):346–52.
19. Dougall N, Maayan N, Soares-Weiser K, McDermott LM, McIntosh A. Transcranial magnetic stimulation for schizophrenia. Schizophr Bull. 2015;41(6):1220–2.
20. Wobrock T, Guse B, Cordes J, Wölwer W, Winterer G, Gaebel W, et al. Left prefrontal high-frequency repetitive transcranial magnetic stimulation for the treatment of schizophrenia with predominant negative symptoms: a sham-controlled, randomized multicenter trial. Biol Psychiatry. 2015;77(11):979–88.
21. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, et al. Volumetric measure of

the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. Arch Gen Psychiatry. 2000;57(5):471–80.
22. Galderisi S, Merlotti E, Mucci A. Neurobiological background of negative symptoms. Eur Arch Psychiatry Clin Neurosci. 2015;265(7):543–58.
23. Benoit A, Bodnar M, Malla AK, Joober R, Lepage M. The structural neural substrates of persistent negative symptoms in first-episode of non-affective psychosis: a voxel-based morphometry study. Front Psych. 2012;3:42.
24. Hovington CL, Lepage M. Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. Expert Rev Neurother. 2012;12(1):53–69.
25. Sheffield JM, Repovs G, Harms MP, Carter CS, Gold JM, MacDonald AW, et al. Evidence for accelerated decline of functional brain network efficiency in schizophrenia. Schizophr Bull. 2016;42(3):753–61.
26. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, et al. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31(43):15284–93.
27. Orlov ND, Tracy DK, Joyce D, Patel S, Rodzinka-Pasko J, Dolan H, et al. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 2017;10(3):560–6.
28. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31.
29. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry. 2012;169(7):719–24.
30. Mondino M, Jardri R, Suaud-Chagny MF, Saoud M, Poulet E, Brunelin J. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. Schizophr Bull. 2016;42(2):318–26.
31. Wobrock T, Guse B, Cordes J, Wolwer W, Winterer G, Gaebel W, et al. Left prefrontal high-frequency repetitive transcranial magnetic stimulation for the treatment of schizophrenia with predominant negative symptoms: a sham-controlled, randomized multicenter trial. Biol Psychiatry. 2015;77(11):979–88.
32. Hasan A, Guse B, Cordes J, Wolwer W, Winterer G, Gaebel W, et al. Cognitive effects of high-frequency rTMS in schizophrenia patients with predominant negative symptoms: results from a multicenter randomized sham-controlled trial. Schizophr Bull. 2015;
33. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am J Psychiatry. 2011;168(1):73–81.
34. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. Biol Psychiatry. 2002;51(12):1008–11.
35. Schmitt A, Hasan A, Gruber O, Falkai P. Schizophrenia as a disorder of disconnectivity. Eur Arch Psychiatry Clin Neurosci. 2011;261(Suppl 2):S150–4.
36. Mondino M, Brunelin J, Palm U, Brunoni AR, Poulet E, Fecteau S. Transcranial direct current stimulation for the treatment of refractory symptoms of schizophrenia. Current evidence and future directions. Curr Pharm Des. 2015;21(23):3373–83.
37. Gomes JS, Shiozawa P, Dias AM, Valverde Ducos D, Akiba H, Trevizol AP, et al. Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in schizophrenia. Brain Stimul. 2015;8(5):989–91.
38. Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. Brain Stimul. 2014;7(6):813–6.
39. Frohlich F, Burrello TN, Mellin JM, Cordle AL, Lustenberger CM, Gilmore JH, et al. Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia. Eur Psychiatry. 2016;33:54–60.
40. Chang CC, Tzeng NS, Chao CY, Yeh CB, Chang HA. The effects of add-on fronto-temporal transcranial direct current stimulation (tDCS) on auditory verbal hallucinations, other psychopathological symptoms, and insight in schizophrenia: a randomized, double-blind, Sham-controlled trial. Int J Neuropsychopharmacol. 2018;21(11):979–87.
41. Kurimori M, Shiozawa P, Bikson M, Aboseria M, Cordeiro Q. Targeting negative symptoms in schizophrenia: results from a proof-of-concept trial assessing prefrontal anodic tDCS protocol. Schizophr Res. 2015;166(1–3):362–3.
42. Palm U, Hasan A, Kupka MJ, Blautzik J, Kaymakanova F, Unger I, et al. Prefrontal transcranial direct current stimulation (tDCS) for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. Schizophr Bull. 2016;
43. Valiengo LDCL, Goerigk S, Gordon PC, Padberg F, Serpa MH, Koebe S, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. JAMA Psychiat. 2019;
44. Kantrowitz JT, Sehatpour P, Avissar M, Horga G, Gwak A, Hoptman MJ, et al. Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a replication/extension study. Brain Stimul. 2019;12(4):981–91.

45. Kim J, Iwata Y, Plitman E, Caravaggio F, Chung JK, Shah P, et al. A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?". J Psychiatr Res. 2019;110:117–26.
46. Nienow TM, MacDonald AW 3rd, Lim KO. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. Schizophr Res. 2016;
47. Vercammen A, Rushby JA, Loo C, Short B, Weickert CS, Weickert TW. Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr Res. 2011;131(1–3):198–205.
48. Hoy KE, Arnold SL, Emonson MR, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res. 2014;155(1–3):96–100.
49. Ribolsi M, Lisi G, Di Lorenzo G, Koch G, Oliveri M, Magni V, et al. Perceptual pseudoneglect in schizophrenia: candidate endophenotype and the role of the right parietal cortex. Schizophr Bull. 2013;39(3):601–7.
50. Göder R, Baier PC, Beith B, Baecker C, Seeck-Hirschner M, Junghanns K, et al. Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. Schizophr Res. 2013;144(1–3):153–4.
51. Rassovsky Y, Dunn W, Wynn JK, Wu AD, Iacoboni M, Hellemann G, et al. Single transcranial direct current stimulation in schizophrenia: randomized, crossover study of neurocognition, social cognition, ERPs, and side effects. PLoS One. 2018;13(5):e0197023.
52. Bose A, Shivakumar V, Narayanaswamy JC, Nawani H, Subramaniam A, Agarwal SM, et al. Insight facilitation with add-on tDCS in schizophrenia. Schizophr Res. 2014;156(1):63–5.
53. Reinhart RM, Zhu J, Park S, Woodman GF. Synchronizing theta oscillations with direct-current stimulation strengthens adaptive control in the human brain. Proc Natl Acad Sci U S A. 2015;112(30):9448–53.
54. Subramaniam A, Agarwal SM, Kalmady S, Shivakumar V, Chhabra H, Bose A, et al. Effect of transcranial direct current stimulation on prefrontal inhibition in schizophrenia patients with persistent auditory hallucinations: a study on antisaccade task performance. Indian J Psychol Med. 2015;37(4):419–22.
55. Jeon DW, Jung DU, Kim SJ, Shim JC, Moon JJ, Seo YS, et al. Adjunct transcranial direct current stimulation improves cognitive function in patients with schizophrenia: a double-blind 12-week study. Schizophr Res. 2018;197:378–85.
56. Lindenmayer JP, Kulsa MKC, Sultana T, Kaur A, Yang R, Ljuri I, et al. Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. Brain Stimul. 2019;12(1):54–61.
57. Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res. 2015;168(1–2):260–6.
58. Agarwal SM, Bose A, Shivakumar V, Narayanaswamy JC, Chhabra H, Kalmady SV, et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatry Res. 2016;235:97–103.
59. Brunelin J, Hasan A, Haesebaert F, Nitsche MA, Poulet E. Nicotine smoking prevents the effects of frontotemporal transcranial direct current stimulation (tDCS) in hallucinating patients with schizophrenia. Brain Stimul. 2015;8(6):1225–7.
60. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Wörsching J, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. Neuromodulation. 2018;21(4):323–33.
61. Gerretsen P, Rajji TK, Shah P, Shahab S, Sanches M, Graff-Guerrero A, et al. Impaired illness awareness in schizophrenia and posterior corpus callosal white matter tract integrity. NPJ Schizophr. 2019;5(1):8.
62. Kim J, Plitman E, Nakajima S, Alshehri Y, Iwata Y, Chung JK, et al. Modulation of brain activity with transcranial direct current stimulation: targeting regions implicated in impaired illness awareness in schizophrenia. Eur Psychiatry. 2019;61:63–71.
63. Marder SR, Rabinowitz J, Kapur S. Clinical trials for negative symptoms–emerging directions and unresolved issues. Schizophr Res. 2013;150(2–3):327.

OCD, Anxiety Disorders, and PTSD

25

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25.1 Introduction

Obsessive-compulsive and related disorders, anxiety disorders, and trauma-related disorders are considered three different groups of psychiatric conditions and are described in three different chapters of the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]. However, these disorders share some important clinical features, including increased perception of thread, worry, harm avoidance, and neurovegetative hyperarousal. These similarities probably account for the shared response to treatments such as selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT). Taken together, they have a 12-month period prevalence of approximately 14% and a lifetime prevalence of approximately 21% in the general population, with extremely high costs for the community [2]. Moreover, these disorders can display high rates of partial or no response to first- and second-line treatments [3] and can lead to high levels of personal suffering, social dysfunction, and family burden, which are comparable to those found in schizophrenia [4]. In the last years, the greater availability of neuromodulation techniques in psychiatric settings [5] has facilitated the research on tDCS not only as a possible treatment of these disorders, but also for the elucidation of their mechanistic aspects [6]. In this chapter, we focus on the rationale of using tDCS for the treatment of obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and anxiety disorders and we review the available clinical data and published scientific literature.

25.2 OCD

It has been proposed that OCD symptoms results from aberrant functioning of cortico-striato-thalamo-cortical circuitry including the medial prefrontal cortex (MPFC), the supplementary motor area (SMA), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the basal ganglia [7, 8]. This model inspired the use of neuromodulation techniques for the treatment of patients with OCD. Indeed, deep transcranial magnetic stimulation, a variant of repetitive transcranial magnetic stimulation (rTMS), using a less focal coil to target midline regions (MPFC and ACC), has been approved by the US Federal Drug Administration (FDA) for the treatment of OCD, based on a randomized placebo-controlled

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multicenter trial [9, 10]. While rTMS has shown promising results, tDCS has been less investigated for the treatment of OCD. Therefore, questions about which area(s) should be targeted by tDCS and which parameters should be used still need to be addressed.

Several uncontrolled studies (case reports, case series and open-label studies) and three randomized clinical trials have evaluated tDCS as a treatment for OCD patients. The uncontrolled studies reported on adult patients, with a primary diagnosis of OCD and presenting comorbidities [11–14]. Most of them were on medication and had failed at least one first-line treatment. Concerning treatment parameters, in the different studies the number of sessions ranged from 10 to 20, once or twice a day. The anode was positioned over the neck, the pre-SMA, right occipital cortex, cerebellum, deltoid muscle, FP1 and F3 (according 10–20 EEG system), whereas the cathode was positioned over the F3, FP1, FP2, F4, pre-SMA, deltoid muscle, left OFC, and right supraorbital area [15]. Response to treatment ranged from no change in baseline YBOCS scores to 80% of improvement. It is important to evaluate the limitations of these studies, including sample size and bias publication of case reports.

Considering the controlled studies, the profile of the selected patients was similar to the one of the uncontrolled reports. D'Urso et al. [16] conducted a crossover trial evaluating cathodal versus anodal stimulation over the pre-SMA of adult patients with a primary diagnosis of OCD. The patients received 20 min of 2 mA tDCS sessions during 20 days of cathodal or anodal stimulation over the pre-SMA, and the other electrode placed over the right deltoid. If patients showed improvement or no change in OCD symptoms, the research on tDCS not only as a possible treatment of these disorders, but also for the after 10 sessions, they were maintained on the same current polarity for 10 additional sessions. In case of worsening after the first 10 sessions, subjects were switched to the other polarity for 10 additional sessions. The authors found that cathodal, but not anodal tDCS, over the pre-SMA, was associated with improvement of OCD symptoms. At the end of the study (4 weeks), the mean YBOCS scores of patients who underwent cathodal tDCS has decreased, while there was no difference between pre-post stimulation in the anodal tDCS.

The second published RCT was a randomized, double-blind, sham-controlled trial evaluating the efficacy of anodal tDCS over the pre-SMA and the cathode over the right supraorbital area [17]. Twenty-five adult patients who had not responded to at least one SSRI were randomized to receive sham stimulation or active tDCS. The sessions were conducted twice a day, on five consecutive days during 20 min. The authors found that active treatment was superior to sham based on an international expert consensus of response criteria (35% reduction in the baseline YBOCS total score with a CGI-I score of 1 (very much improved) or 2 (much improved)). After 10 days of follow-up (from baseline to primary outcome), the authors found that 4 out of 12 in the active tDCS group versus 0 out of 13 in the sham group had attained the response status.

While the two first RCTs targeted the pre-SMA (anodal and/or cathodal stimulation), the most recent study used a different target. This was a randomized shamcontrolled double-blind study on 21 patients with treatment-resistant OCD. TDCS protocol consisted in ten 20-min sessions (two sessions per day) of either active (2 mA) or sham tDCS over OFC (cathodal stimulation) and right cerebellum (anodal stimulation). Compared with the sham tDCS, active tDCS significantly decreased OCD symptoms immediately after the 10th tDCS session. However, no significant differences were observed between the groups in terms of changes in YBOCS score one and 3 months after tDCS [18].

Interestingly, even if electrode montages largely vary across published reports, computer modeling of electric fields (EFs) induced by tDCS showed that the used montages can be grouped into two main patterns [19]. One pattern can be identified as "focal montages," with EFs concentrating in the prefrontal cortex, and the other one as "diffuse montages," with wide-

spread EFs over several cortical areas. Although for both categories of montages, symptoms reduction has been reported, the results are mixed and sometimes conflicting, probably due to differences in other stimulation parameters (i.e., current intensity, number of sessions, session duration, and interval between sessions) so that it was not possible to conclude on which montage type may generate greater benefits for OCD patients [6]. Of note, in a case report, electroconvulsive therapy (i.e., the least focal brain stimulation technique) was shown to selectively revert OCD-related brain function abnormalities while inducing a dramatic clinical improvement [20] making it questionable the importance of targeting tDCS to the OCD regions. Hence, future trials are needed to determine the efficacy of tDCS in OCD and investigate the best electrode position, with larger samples and longer periods of follow-up. Regarding the methodology of such future tDCS trials, we suggest to include: (a) elderly patients, (b) subjects with less severe OCD, (c) treatment-naïve patients, (d) the assessment of the combined effect of tDCS and CBT.

25.3 PTSD

Brain regions involved in the anxiety network including the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), and the insular cortex somewhat overlap with the network involved in the acquisition of fear and its extinction, particularly relevant to PTSD [21]. PTSD patients seem to have deficits in extinction learning and/or recall [22], impairments that seem to be acquired after having developed PTSD [23]. It has been suggested that the deficit in recall extinction could explain the maintenance of PTSD symptoms and/or relapse following treatment [24]. In terms of neural correlates, this impaired ability for extinction memory has been linked with less activation in the vmPFC and the hippocampus and higher activation in the amygdala and the dACC [22].

If we understand the circuit and its maladaptive plastic changes, we can formulate and test hypotheses about the therapeutic efficacy of selective manipulation of these brain regions and networks. This can be achieved by using neuromodulation techniques attempting to reestablish homeostatic balance and healthy patterns of information processing. More specifically, if we can find ways of enhancing fear extinction memory in the laboratory within samples of healthy participants and replicate them in clinical population, we could consider these tools as potential adjuncts to augment the memory trace formed during exposure therapy, which could ultimately lead to a decrease in symptoms severity and a lesser likelihood of relapse.

The combination of tDCS and exposure therapy, as already shown for the combination of tDCS and CBT in depression [25], might have a synergistic effect in producing a clinical result in PTSD. The principle of the two interventions is the same: promoting the memory trace being formed during exposure therapy so that it becomes stronger. Because PTSD is well known for the deficit in recall extinction, enhancing extinction could benefit patients suffering from this disorder as well as from those anxiety disorders which share this cognitive feature. Clearly, this idea taps into the neural mechanisms of fear extinction that are relevant to some but certainly not all features and symptoms of PTSD.

Evidence for modulation of fear learning and extinction using tDCS remains scarce. In one study; cathodal stimulation of the left DLPFC led to an inhibitory effect on fear memory consolidation compared to anodal and sham stimulations, as indicated by decreased skin conductance response to the conditioning stimulus presentation during extinction training at day 2. Hence, this study suggests that left DLPFC cathodal stimulation interferes with processes of fear memory consolidation [26]. Furthermore, tDCS has been used in combination with a computerized working memory training in four patients suffering from both PTSD and poor working memory. This combined treatment led to the improvement of the cognitive and emotional disturbances as well

as to the change of the neurophysiological measures which are usually found altered in PTSD, such as the P3a component of event-related potentials (ERP) in response to novelty stimuli and the alpha peak frequency [27].

One randomized clinical trial evaluated 40 participants with PTSD who were assigned to receive either 10 tDCS sessions delivered at 2 mA to the right (cathode) and left (anode) dorsolateral prefrontal cortex (DLPFC) or 10 sham [28]. Active stimulation demonstrated a significant reduction in PTSD, depression, and anxiety symptoms compared to sham stimulation. However, there was no difference between active and sham tDCS on re-experiencing sub-symptom and avoidance behavior. Despite initial studies, we need a better understanding of how different tDCS parameters impact the PTSD circuitry to be able to design hypothesis-driven trials and confirm both safety and clinical efficacy.

25.4 Anxiety

Anxiety disorders include generalized anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition. Considering the wide range of symptoms and mechanisms involved, it is challenging to choose a target for neuromodulation treatments.

Anxious patients typically show negative biases in perception and memory, and such biases in emotional processing are believed to play a fundamental role in the maintenance of anxiety disorders. Coherently, the cognitive neuropsychological model of antidepressants action assumes that in anxiety disorders, such treatments work by reversing negative cognitive biases [29]. Following the administration of anxiolytic and antidepressant treatment, early changes in emotional processing have been observed in healthy subjects and clinical groups; specifically, the cognitive changes might be predictive of later therapeutic response in patients [30].

In addition, attentional control is highlighted in models of trait anxiety [31] and DLPFC activity has been negatively correlated with trait anxiety in neuroimaging studies examining attentional control over emotional and non-emotional stimuli [32]. This suggests that modulating DLPFC activity has the potential to causally modify attentional control, which has relevance to trait anxiety.

In fact, in a study by Heeren et al., tDCS to the DLPFC led to reduced vigilance to threatening stimuli in healthy subjects [33]. In this study, the attentional bias (faster reaction times) to fearful faces was present in the sham tDCS group, whereas in the active tDCS group, it was reversed, likewise with antidepressant and anxiolytic treatment [34]. Specifically, the bipolar-balanced montage (anode on the left DLPFC and cathode on the right DLPFC) significantly abolished the normal pattern of fear vigilance observed in the sham condition and suggests that intervening bilaterally, to change activity in both left and right DLPFC, may be critical for the observed anxiolytic-like effects. The above results in healthy volunteers reveal an anxiolytic-like effect of DLPFC tDCS on a cognitive biomarker relevant to clinical anxiety and indicate a potential neurocognitive mechanism (reduced fear vigilance) that may partially mediate the clinical efficacy of prefrontal tDCS in anxiety disorders [35].

One more evidence that subjects with anxiety disorders show an attentional bias for threat is that attention bias modification (ABM) procedures have been found to reduce this bias. Results indicate that combining ABM and anodal tDCS over the left DLPFC reduces the total duration that participants' gaze remains fixated on threat, as assessed using eye-tracking measurement. As the tendency to maintain attention to threat is known to play an important role in the maintenance of anxiety, these findings suggest that anodal tDCS over the left DLPFC may be considered as a promising tool to reduce the maintenance of gaze to threat [33].

The next logical step is to assess whether an enduring therapeutic effect can be found and if

early neurocognitive changes in patients can predict response to treatment of anxiety. In a case report on the effect of tDCS in GAD, Shiozawa et al. [36] performed 15 consecutive daily tDCS sessions in 3 weeks (except for weekends). The cathode was positioned over the right DLPFC and the anode was placed extracephalically over the contralateral deltoid. In each daily session, a direct current of 2.0 mA for 30 min was administered. Anxiety symptoms substantially improved during the 15-day treatment course. After 1 month of treatment, the patient was asymptomatic and reported significant clinical improvement. The use of cathodal stimulation over the right DLPFC was chosen based on recent neuroimaging and brain stimulation studies.

In the tDCS case study, cathodal stimulation over the right DLPFC might have diminished neuronal activity in this area, secondarily modulating other cortical and subcortical structures involved in GAD pathophysiology, such as the medial prefrontal cortex, the amygdala, and the insula [37]. It is also possible that the left DLPFC was secondarily modulated by the decrease in activity of the right DLPFC.

One recent systematic review of controlled and uncontrolled studies evaluating tDCS in anxiety symptoms and disorders found that most studies used anodal stimulation over the left DLPFC [38]. If bilateral stimulation was adopted, the cathodal electrode was placed over the right DLPFC. This study suggests that DLPFC has a major role in anxiety behaviors, and the imbalance between the right and left DLPFC may contribute to some anxiety symptoms.

25.5 Conclusion

Despite an intriguing rationale and some encouraging preliminary results, the use of tDCS in OCD, that is, obsessive-compulsive disorder, anxiety disorders, and PTSD is still in its infancy, and many mechanistic as well as clinical questions remain to be answered. In OCD, the positive results of the three randomized clinical trials published so far should be replicated using larger samples and longer follow-ups. Moreover, while the available trials mostly include treatment-resistant subjects, future studies should aim to assess the tDCS effect also in less severe conditions and look for potential response predictors, as was done for depressed patients [39]. Finally, considering the efficacy of CBT in OCD, and the well-known pro-cognitive effect of tDCS, the systematic exploration of the potential synergistic effect of the two interventions is paramount. Regarding tDCS in PTSD and anxiety disorders, the lack of randomized clinical trials involving patients with these disorders should be remedied as soon as possible, considering the great potential of tDCS in these conditions, as suggested by non-clinical studies and as reported by clinicians using tDCS in their clinical practice.

References

1. American Psychiatric Association, American Psychiatric Association. DSM-5 task force. Diagnostic and statistical manual of mental disorders: DSM-5. 2013.
2. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, Den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28:403–39. https://doi.org/10.1177/0269881114525674.
3. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry. 2006;11:622–32. https://doi.org/10.1038/sj.mp.4001823.
4. Bystritsky A, Liberman RP, Hwang S, Wallace CJ, Vapnik T, Maindment K, et al. Social functioning and quality of life comparisons between obsessive-compulsive and schizophrenic disorders. Depress Anxiety. 2001;14:214–8.
5. Sauvaget A, Poulet E, Mantovani A, Bulteau S, Damier P, Moutaud B, et al. The psychiatric neuromodulation unit. J ECT. 2018;34:211–9. https://doi.org/10.1097/YCT.0000000000000513.
6. D'Urso G, Mantovani A, Patti S, Toscano E, de Bartolomeis A. Transcranial direct current stimulation in obsessive-compulsive disorder, posttraumatic stress disorder, and anxiety disorders. J ECT. 2018;34:1. https://doi.org/10.1097/YCT.0000000000000538.

7. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res. 1990;85:119–46.
8. Milad MR, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci. 2012;16:43–51. https://doi.org/10.1016/j.tics.2011.11.003.
9. Voelker R. Brain stimulation approved for obsessive-compulsive disorder. JAMA. 2018;320:1098. https://doi.org/10.1001/jama.2018.13301.
10. Carmi L, Alyagon U, Barnea-Ygael N, Zohar J, Dar R, Zangen A. Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimul. 2018;11:158–65. https://doi.org/10.1016/j.brs.2017.09.004.
11. Volpato C, Piccione F, Cavinato M, Duzzi D, Schiff S, Foscolo L, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive–compulsive disorder. Neurocase. 2013;19:360–70. https://doi.org/10.1080/13554794.2012.667131.
12. Narayanaswamy JC, Jose D, Chhabra H, Agarwal SM, Shrinivasa B, Hegde A, et al. Successful application of add-on transcranial direct current stimulation (tDCS) for treatment of SSRI resistant OCD. Brain Stimul. 2015;8:655–7. https://doi.org/10.1016/J.BRS.2014.12.003.
13. Mondino M, Haesebaert F, Poulet E, Saoud M, Brunelin J. Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder. J ECT. 2015;31:271–2. https://doi.org/10.1097/YCT.0000000000000218.
14. D'Urso G, Brunoni AR, Anastasia A, Micillo M, de Bartolomeis A, Mantovani A. Polarity-dependent effects of transcranial direct current stimulation in obsessive-compulsive disorder. Neurocase. 2016;22:60–4. https://doi.org/10.1080/13554794.2015.1045522.
15. Da Silva RDMF, Brunoni AR, Miguel EC, Shavitt RG. Transcranial direct current stimulation for obsessive- compulsive disorder: patient selection and perspectives. Neuropsychiatr Dis Treat. 2019;15:2663–9. https://doi.org/10.2147/NDT.S184839.
16. D'Urso G, Brunoni AR, Mazzaferro MP, Anastasia A, de Bartolomeis A, Mantovani A. Transcranial direct current stimulation for obsessive–compulsive disorder: a randomized, controlled, partial crossover trial. Depress Anxiety. 2016;33:1132–40. https://doi.org/10.1002/da.22578.
17. Gowda SM, Narayanaswamy JC, Hazari N, Bose A, Chhabra H, Balachander S, et al. Efficacy of pre-supplementary motor area transcranial direct current stimulation for treatment resistant obsessive compulsive disorder: a randomized, double blinded, sham controlled trial. Brain Stimul. 2019;12(4):922–9. https://doi.org/10.1016/j.brs.2019.02.005.
18. Bation R, Mondino M, Le Camus F, Saoud M, Brunelin J. Transcranial direct current stimulation in patients with obsessive compulsive disorder: a randomized controlled trial. Eur Psychiatry. 2019;62:38–44. https://doi.org/10.1016/j.eurpsy.2019.08.011.
19. da Silva MF, Batistuzzo MC, Shavitt RG, Miguel EC, Stern E, Mezger E, et al. Transcranial direct current stimulation in obsessive-compulsive disorder: an update in electric field modeling and investigations for optimal electrode montage. Expert Rev Neurother. 2019;19(10):1025–35. https://doi.org/10.1080/14737175.2019.1637257.
20. D'Urso G, Mantovani A, Barbarulo AM, Labruna L, Muscettola G. Brain-behavior relationship in a case of successful ECT for drug refractory catatonic OCD. J ECT. 2012;28:190–3. https://doi.org/10.1097/YCT.0b013e3182542649.
21. Marin MF, Camprodon JA, Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: implications for ptsd treatment and beyond. Depress. Anxiety, vol. 31. Blackwell Publishing Ltd; 2014. p. 269–78. https://doi.org/10.1002/da.22252.
22. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66:1075–82. https://doi.org/10.1016/j.biopsych.2009.06.026.
23. Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman RK. Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. J Psychiatr Res. 2008;42:515–20. https://doi.org/10.1016/j.jpsychires.2008.01.017.
24. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research-past, present, and future. Biol Psychiatry. 2006;60:376–82. https://doi.org/10.1016/j.biopsych.2006.06.004.
25. D'Urso G, Mantovani A, Micillo M, Priori A, Muscettola G. Transcranial direct current stimulation and cognitive-behavioral therapy: evidence of a synergistic effect in treatment-resistant depression. Brain Stimul. 2013;6:465–7. https://doi.org/10.1016/j.brs.2012.09.003.
26. Asthana M, Nueckel K, Mühlberger A, Neueder D, Polak T, Domschke K, et al. Effects of transcranial direct current stimulation on consolidation of fear memory. Front Psych. 2013;4:107. https://doi.org/10.3389/fpsyt.2013.00107.
27. Saunders N, Downham R, Turman B, Kropotov J, Clark R, Yumash R, et al. Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. Neurocase. 2015;21:271–8. https://doi.org/10.1080/13554794.2014.890727.
28. Ahmadizadeh MJ, Rezaei M, Fitzgerald PB. Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): a randomized, double-blinded, controlled trial. Brain Res

Bull. 2019;153:273–8. https://doi.org/10.1016/j.brainresbull.2019.09.011.
29. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry. 2009;195:102–8. https://doi.org/10.1192/bjp.bp.108.051193.
30. Reinecke A, Waldenmaier L, Cooper MJ, Harmer CJ. Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. Biol Psychiatry. 2013;73:1064–70. https://doi.org/10.1016/j.biopsych.2013.02.005.
31. Bishop S, Duncan J, Brett M, Lawrence AD. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nat Neurosci. 2004;7:184–8. https://doi.org/10.1038/nn1173.
32. Bishop SJ. Trait anxiety and impoverished prefrontal control of attention. Nat Neurosci. 2009;12:92–8. https://doi.org/10.1038/nn.2242.
33. Heeren A, Billieux J, Philippot P, De Raedt R, Baeken C, de Timary P, et al. Impact of transcranial direct current stimulation on attentional bias for threat: a proof-of-concept study among individuals with social anxiety disorder. Soc Cogn Affect Neurosci. 2017;12:251–60. https://doi.org/10.1093/scan/nsw119.
34. Murphy SE, Yiend J, Lester KJ, Cowen PJ, Harmer CJ. Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers. Int J Neuropsychopharmacol. 2009;12:169–79. https://doi.org/10.1017/S1461145708009164.
35. Ironside M, O'Shea J, Cowen PJ, Harmer CJ. Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety. Biol Psychiatry. 2016;79:823–30. https://doi.org/10.1016/j.biopsych.2015.06.012.
36. Shiozawa P, Leiva APG, Castro CDC, Da Silva ME, Cordeiro Q, Fregni F, et al. Transcranial direct current stimulation for generalized anxiety disorder: a case study. Biol Psychiatry. 2014;75(11):e17–8. https://doi.org/10.1016/j.biopsych.2013.07.014.
37. Roy AK, Fudge JL, Kelly C, Perry JSA, Daniele T, Carlisi C, et al. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(3):290–9, e2. https://doi.org/10.1016/j.jaac.2012.12.010.
38. Stein DJ, Medeiros LF, Caumo W, Torres ILS. Transcranial direct current stimulation in patients with anxiety: current perspectives. Neuropsychiatr Dis Treat. 2020;16:161–9. https://doi.org/10.2147/NDT.S195840.
39. D'Urso G, Dell'Osso B, Rossi R, Brunoni AR, Bortolomasi M, Ferrucci R, et al. Clinical predictors of acute response to transcranial direct current stimulation (tDCS) in major depression. J Affect Disord. 2017;219:25–30. https://doi.org/10.1016/j.jad.2017.05.019.

26 Cognitive Functions in Substance-Related and Addictive Disorders

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26.1 Introduction

Substance-related and addictive disorders (SRADs), including alcohol, cannabis, gambling, and stimulant use disorders, are characterized by maladaptive behaviour or dysfunctional use of a substance that leads to clinically distressing consequences (e.g. craving, health issues, interference with work, school, or personal life) [1]. SRADs are difficult to treat, and relapse remains a big issue despite available pharmacological and behavioural treatments. Crucially, cognitive deficits (e.g. cognitive biases, deficits in executive functions) can predict relapse [2]. Hence, improving cognitive functions is a promising therapeutic option for dealing with craving and relapse [2]. Cognitive deficits can be present before the onset of SRADs and worsen with chronicity [3]. Yet, not all patients with SRADs present the same cognitive profile, as they can vary across diagnoses and as a function of comorbidities [2]. More specifically, a meta-analysis found that patients with alcohol and stimulant use disorders particularly present impaired cognitive flexibility; patients with cannabis and 3,4-methylenedioxy-methamphetamine (MDMA) use disorders predominantly display impairments in complex planning and processing speed; patients with opioid use disorder mostly demonstrate reasoning impairments, and patients with cannabis and methamphetamine use disorders mainly show memory deficits [4].

Within this context, transcranial current stimulation (tCS) over the dorsolateral prefrontal cortex (DLPFC) has been successfully used to strengthen cognitive functions [5–14] and help patients resist craving and avoid relapse. Given such evidence, an overview of which cognitive functions have been successfully improved in patients with SRADs can inform clinical practice and help develop new interventions. Hence, this chapter reviews studies that examined tCS-induced effects on cognitive

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functions relevant to SRADs, namely, cognitive bias and executive functions. The relationship between cognitive functions and craving, mood, and stress is also discussed. All included studies are sham-controlled, randomized, blinded, and used transcranial direct current stimulation, unless otherwise stated (Table 26.1).

26.2 tCS Effects in Cognitive Functions in SRADs

Several studies assessed the effects of tCS on cognitive functions in SRADs. These can be divided into two main categories: studies on implicit cognitive functions, for example, cognitive bias, and studies on explicit cognitive functions, for example, executive functions (see Fig. 26.1; Table 26.1).

26.2.1 tCS Effects on Cognitive Biases in SRADs

Some patients with SRADs are aware that their addictive behaviour is detrimental, yet they still carry it out despite the negative consequences. One way to explain this behaviour is by taking into account implicit cognitive functioning such as cognitive biases. Cognitive biases are automatic, implicit, and favourable processing of certain stimuli (e.g. external cues) over others [15]. Two major forms are approach bias and attentional bias. Approach bias happens when patients are quicker to approach rather than avoid cues [15]. Attentional bias occurs when patients display biased attention towards cues, which can increase craving [16]. Seven studies assessed the effects of tCS on cognitive biases [5, 6, 13, 14, 17–19] in alcohol and methamphetamine users. Four of these studies found significant reductions in cognitive biases when targeting the bilateral DLPFC [5, 6, 13, 14], as well as the DLPFC and shoulder [6]. In particular, two studies found reduced approach biases in alcohol users when placing the anode over the right and cathode over the left DLPFC [5] and vice versa [13]. Also, one of these studies combined tCS with a cognitive bias modification protocol [13]. In addition, one study found decreased attentional biases in tobacco smokers when patients received real transcranial alternating current stimulation (tACS) paired with attentional bias modification as compared to sham tACS with attentional bias modification training, as shown by decreased time observing smoking-related stimuli measured with an eye tracker [14]. Further, a single study reported decreased attentional bias towards drug cues in abstinent, treatment-seeking patients with methamphetamine use disorder [6]. Patients performed a probe detection task before and after they received two 13-min tCS sessions. Patients were randomly assigned to one of six groups with different electrode montages: (1) anode over the left DLPFC, cathode over the right shoulder; (2) anode over the right DLPFC, cathode over the left shoulder; (3) anode over the left DLPFC, cathode over the right supraorbital ridge; (4) anode over the right DLPFC, cathode over the left supraorbital ridge; and (5) anode over the left DLPFC, cathode over the right DLPFC. Sham condition consisted of electrodes over the right and left DLPFC. Of these, two groups displayed reduced attentional bias towards cues as measured by reaction times, that is, one group receiving anodal and cathodal transcranial direct current stimulation (tDCS) over the left and right DLPFC, respectively, and one group receiving anodal and cathodal tDCS over the left DLPFC and the shoulder, respectively.

26.2.2 tCS Effects on Executive Functions in SRADs

Higher order cognitive functions such as executive functions are believed to be impaired in SRADs [2, 3]. Some researchers purport that patients with SRADs have an imbalance between implicit and explicit processes, in which executive functions fail to control implicit urges. In line with this, a series of studies attempted to increase cognitive control to reduce addictive behaviour. Several studies have assessed the effects of tCS in SRADs on a wide range of executive functions, such as cognitive flexibility, decision-making, working memory, self-regulation, and selective attention (see Fig. 26.1; Table 26.1).

Table 26.1 Transcranial current stimulation can modulate several cognitive functions in substance-related and addictive disorders

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Cognitive bias							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10 Hz, 2 mA 30 min	N/A	N/A	Observation of smoking-related and neutral stimuli with eye tracking	↓ amount of time looking at smoking-related pictures
Vanderhasselt, 2020 [5]	Randomized Double-blind Sham-controlled Crossover (37)	Alcohol	1 session/condition 2 mA 20 min	R DLPFC	L DLPFC	Rewarded Go/No-Go	↓ reward-triggered approach bias
Claus, 2019 [18]	Randomized Double-blind Sham-controlled 2 × 2 factorial (79)	Alcohol	4 sessions (once a week for 4 consecutive weeks)[a] 2 mA 2 × 10 min	R IFG	L upper arm	Approach Avoidance-Task	No significant effect
Den Uyl, 2018 [17]	Randomized Double-blind Sham-controlled 2 × 2 factorial (83)	Alcohol	4 sessions over 1 week[a] 2 mA 20 min	L DLPFC	R DLPFC	Visual probe task Implicit Association Task	No significant effect
Shahbabaie, 2018 [6]	Randomized Double-blind Sham-controlled Parallel (90)	Methamphetamine	1 session 2 mA 2 × 13 min	L DLPFC	R shoulder or R DLPFC^ Other montages were used but were not associated with significant effects on attentional bias.	Probe detection task	↓ attentional bias towards drug cues

(continued)

Table 26.1 (continued)

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Den Uyl, 2017 [13]	Randomized Double-blind Sham-controlled Parallel (91)	Alcohol	4 sessions over 1 week[a] 2 mA 20 min	L DLPFC	R DLPFC	Approach avoidance task	↓ approach bias
Den Uyl, 2016 [19]	Randomized Double-blind Sham-controlled 2 × 2 factorial (78)	Alcohol	3 sessions over 3 or 4 days[a] 1 mA 15 min	L DLPFC	R supraorbital area	Approach avoidance task Implicit association task	No significant effect
Cognitive flexibility							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Wisconsin Card Sorting Task	↓ perseverative errors ↑ completed categories
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Wisconsin Card Sorting Task	↓ perseveration errors
Decision-making							
Mondino, 2020 [14]	Randomized Double-blind Sham-controlled Crossover (19)	Tobacco	1 session/condition[a] 10 Hz, 2 mA 30 min	N/A	N/A	Delay Discounting task	↓ percent of immediate choices
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Balloon Analog Risk Task	↓ adjusted value ↓ maximum pumping
Soyata, 2019 [8]	Randomized Triple-blind Sham-controlled Parallel (20)	Gambling	3 every other day sessions 2 mA 20 min	R DLPFC	L DLPFC	Iowa Gambling Task	↑ net score

Gorini, 2014 [9]	Randomized Single-blind Sham-controlled Crossover (18)	Cocaine	1 session/condition 1.5 mA 20 min	L/R DLPFC	L/R DLPFC	Game of Dice Task Balloon Analog Risk Task	↓ average of safe bets (anode over L DLPFC) ↑ average of safe bets (anode over R DLPFC) ↓ adjusted average pumps
Fecteau, 2014 [10]	Randomized Quadruple-blind Sham-controlled Crossover (12)	Tobacco	5 daily sessions/ condition 2 mA 30 min	R DLPFC	L DLPFC	Ultimatum Game	↑ rejected offers of cigarettes
Pripfl, 2013 [11]	Counterbalanced Sham-controlled Crossover (18)	Tobacco	1 session/condition .45 mA 15 min	L/R DLPFC	L/R DLPFC	Cold Columbia Card Task and Hot Columbia Card Task	↓ number of cards chosen in risky gamble (anode L DLPFC/cathode R DLPFC) ↓ number of cards chosen in risky gamble (anode R DLPFC/cathode L DLPFC)
Boggio, 2010 [25]	Randomized Double-blind Sham-controlled Parallel (25)	Cannabis	1 session 2 mA 15 min	L/R DLPFC	L/R DLPFC	Risk Task	↑ choice of more risky prospects
Self-regulation							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	Go/No-Go	↓ reaction time ↑ accuracy go trials ↑ accuracy no-go trials
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	Flanker Task	No significant effect
Witkiewitz, 2019 [31]	Randomized Double-blind Sham-controlled Parallel (84)	Alcohol	Variable number of sessions[a,b] 2 mA 30 min	R IFG	L upper arm	Stop signal reaction time task	No significant effect

(continued)

Table 26.1 (continued)

First author, year [ref#]	Design (*N*)	Addictive disorder	tDCS parameters	Anode placement	Cathode placement	Outcome measure (s)	Findings
Lee, 2018 [12]	Open-label Single-arm (15)	Internet gaming	3 sessions a week for 4 weeks 2 mA 30 min	L DLPFC	R DLPFC	Brief self control scale	↑ self-control
Selective attention							
Xu, 2013 [33]	Counterbalanced Single-blind Sham-controlled Crossover (24)	Tobacco	1 session/condition 2 mA 20 min	L DLPFC	R supraorbital area	Visual attention task	No significant effect
Working memory							
Alizadehgoradel, 2020 [7]	Randomized Double-blind Sham-controlled Parallel (39)	Methamphetamine	10 sessions over 5 weeks 2 mA 20 min	L DLPFC	R DLPFC	N-back	↓ response time ↑ accuracy
Aronson Fischell, 2020 [29]	Randomized Double-blind Sham-controlled Crossover (15)	Tobacco	1 session/condition 2 mA 25 min	L DLPFC R VMPFC	R VMPFC L DLPFC	N-back	No significant effect
Overall executive function							
da Silva, 2013 [34]	Randomized Sham-controlled Parallel (13)	Alcohol	One session per week for 5 weeks 2 mA 20 min	L DLPFC	R supradeltoid area	Frontal Assessment Battery	No significant effect
Klauss, 2014 [35]	Randomized Double-blind Sham-controlled Parallel (33)	Alcohol	2 daily sessions for 5 consecutive days 2 mA 13 min	R DLPFC	L DLPFC	Frontal Assessment Battery	No significant effect

Some articles appear more than once since they measured more than one cognitive function

DLPFC dorsolateral prefrontal cortex, *IFG* inferior frontal gyrus, *VMPFC* ventromedial prefrontal cortex, *L* left hemisphere, *R* right hemisphere, ↑ increase, ↓ decrease

[a]Some or all subjects received a behavioural intervention as well

[b]Subjects participated in a rolling group mindfulness-based relapse prevention while receiving either active or sham tDCS; those in the active and sham groups attended 4.32 and 3.78 sessions, respectively

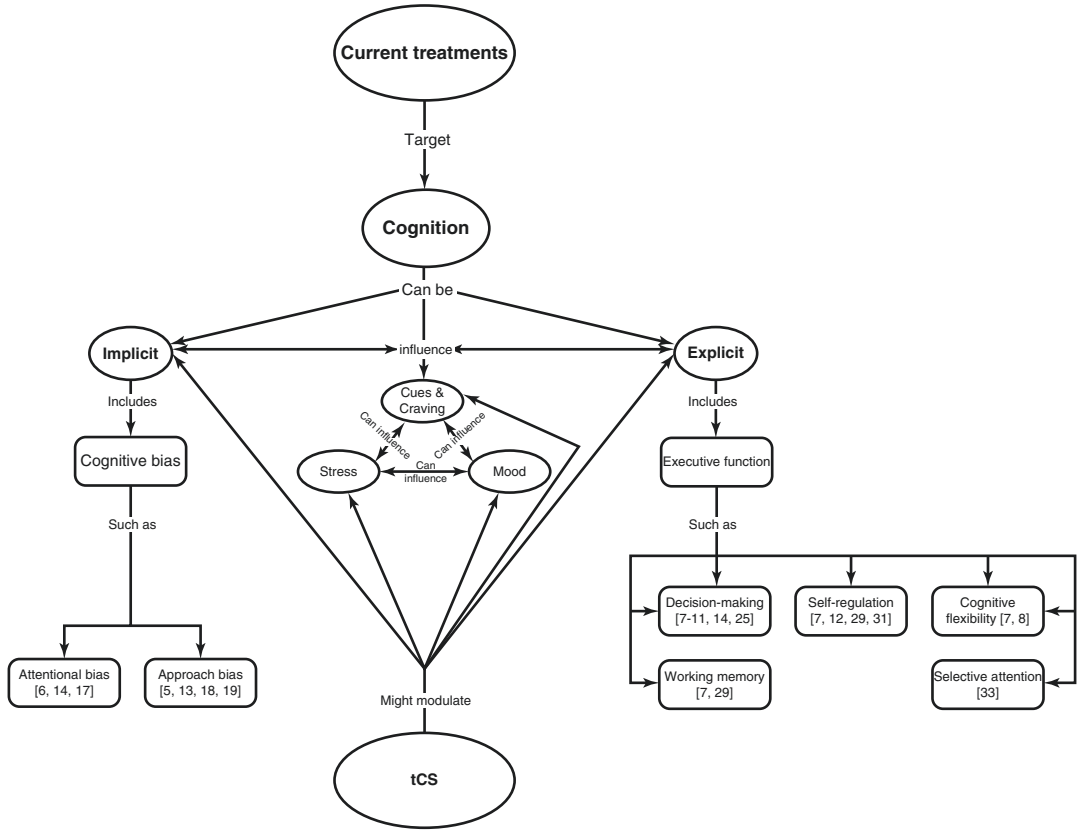

Fig. 26.1 Transcranial current stimulation and current treatments might be used to target implicit as well as explicit cognitive functions in substance-related and addictive disorders. Some other processes might be worth targeting as well, such as craving, mood, and stress, since they can influence cognitive functions and vice versa

Cognitive flexibility, also known as set-shifting, reflects the ability to adapt to different responses or situations [20]. Measuring cognitive flexibility can be a useful marker of cognitive control and possibly compulsivity [21]. Two studies reported improved cognitive flexibility following tCS over the DLPFC (anode over the left, cathode over the right DLPFC) in patients with methamphetamine use disorder [7] and gambling disorder (anode over the right, cathode over the left DLPFC) [8]. More specifically, patients showed decreased perseveration errors and/or completed categories on the Wisconsin Card Sorting Task [22].

Decision-making encompasses evaluating potential outcomes and selecting the most appropriate option [23]. This ability can be impaired in patients with SRADs, in that they show a tendency to choose immediate rewards (e.g. drug or monetary rewards) despite the possible detrimental consequences [24]. Up to now, six studies examined the effect on decision-making of tCS over the bilateral DLPFC across different SRADs, including cocaine [9], gambling [8], methamphetamine [7], tobacco [10, 11, 14], and cannabis [25] use disorders. Some studies applied the anode and cathode over the right and left DLPFC [8, 10], and vice versa [7], whereas some used both montages [9, 11, 25], and one used tACS to target both DLPFCs [14]. The first six studies reported improvements in various measures of decision-making (e.g. Balloon Analog Risk Task, Iowa Gambling Task, Game of Dice Task, Ultimatum Game, Columbia Card Task, Delay Discounting Task). The last study reported increased risky choices among patients with can-

nabis use disorder [25]. Nonetheless, this study demonstrated that these patients display different decision-making processes as compared to healthy individuals for the same task [26].

Working memory refers to the ability to store and use short-term information [3, 27] which can influence other processes, such as decision-making. For instance, working memory training decreases delay discounting in patients with stimulant use disorder [28]. Two studies evaluated the effects of tCS on working memory in patients with SRADs. The first one reported decreased response time and increased accuracy on the N-Back Task by applying tCS over the DLPFC (anode over the left and cathode over the right DLPFC) in methamphetamine use disorder [7]. The second study (which placed the electrodes over the ventromedial PFC and the DLPFC with reversed polarity) did not find significant effects on the N-Back Task [29].

Self-regulation reflects the ability to maintain ideal motivational, emotional, and cognitive arousal, including inhibition and self-control [27]. Inhibition is the ability to control actions, thoughts, behaviours, and/or emotions to overcome internal (e.g. craving) or external (e.g. cue-induced) desire [27]. Self-control reflects the ability to resist temptations and hastiness [27]. Low self-control is a hallmark of SRADs [1] as it may predispose individuals to the inability to control, reduce, or stop the addictive behaviour [30]. Four studies evaluated tCS-induced effects on response inhibition [7, 29, 31] and self-control [12]. Regarding response inhibition, one study applied tCS over the DLPFC (anode over the left DLPFC, cathode over the right DLPFC) and reported significantly increased accuracy of trials and decreased reaction time on the Go/No-Go task [7]. The other two studies were conducted in patients with tobacco use disorder [29] and heavy drinkers (98.9% of individuals displayed alcohol use disorder) [31] but they did not report significant tCS-induced effects. To note, one of these studies combined tCS with a mindfulness-based relapse prevention [31]. The effects of tCS on self-control were evaluated in a prospective study on patients with internet gaming disorder [12]. This was a single-arm, open-label study in which patients received 12 active tCS sessions (anode over the left and cathode over the right DLPFC) three times a week for 4 weeks. Patients displayed increased self-control, which correlated with decreased severity and time playing games as assessed by the Brief Self-Control Scale [12]. Interestingly, the tCS regimen was followed by a partial alleviation of the asymmetry of glucose metabolism between the two DLPFCs. Although speculative, this may reflect a better communication between the two DLPFCs, which could lead to increased self-control. Despite the promising results, randomized, sham-controlled studies are necessary to draw further conclusions.

Selective attention is demonstrated by the ability to maintain attentional focus on the environment [27]. This function is closely related to working memory and attentional biases, since both require holding attention for some time [15, 27]. In SRADs, selective attention predicts the motivation to engage in treatment [32]. Work by Xu and collaborators [33] found no effect of tCS on selective attention in patients with tobacco use disorder. The study used anodal and cathodal tCS over the left DLPFC and the right supraorbital area, respectively. The authors discussed that this may be due to spurious factors such as the fact that patients were abstinent overnight, which might influence tCS-induced effects on cortical excitability.

Two studies evaluated the effects of tCS on overall executive functions [34, 35], as assessed by the Frontal Assessment Battery, in patients with alcohol use disorder. Although the studies used different montages, neither of them found significant effects. Nevertheless, some limitations of the studies should be mentioned. For one, one study presented differences in the baseline amount of drinking between the active and sham groups [34]. Moreover, both studies had small sample sizes, which may reflect a lack of statistical power.

26.2.3 tCS Effects on Craving, Mood, and Stress in SRADs

Craving, mood, and stress also play a major role in SRADs. They can influence cognition and can be modulated by tCS [36] (see Fig. 26.1).

Craving is a complex process where individuals display a powerful urge or desire for a substance or an addictive behaviour (e.g. gambling, internet gaming) [1]. Craving can be triggered by external cues (e.g. a person, a place, or an object), as well as internal signals, such as mood or stress [37]. It is believed to play a central role in SRADs and constitutes one of the diagnostic criteria in the DSM-5 [1]. Several clinical studies confirmed that tCS over the bilateral DLPFC can decrease craving in SRADs (for reviews, see [36, 38]). Yet, it remains to be seen whether this effect is due to a direct impact of the stimulation on craving or to an indirect effect which is secondary to an improvement of cognitive control [2].

Mood can also influence SRADs, since it can reinforce addictive behaviour [39]. For instance, anxious or depressive moods can influence cognitive functions such as self-control or decision-making and trigger craving and relapse. Therefore, improving mood might be one way to improve cognitive control to resist substances. Some evidence points to the effectiveness of tCS in improving mood in patients with SRADs [33, 40]. Two studies on tobacco use disorder found reduced negative affect following (1) anodal stimulation over the right (but not the left) DLPFC and cathodal stimulation over the right DLPFC [40] and (2) anodal stimulation over the left DLPFC and cathodal stimulation over the right supraorbital area [33]. In both studies, there were differences neither in craving, nor in cigarette consumption. To note, patients were abstinent for at least 6 [40] or 10 [33] hours, possibly suggesting the pertinence of testing in sated patients. Further, a preliminary study reported that tCS increased the perception of the quality of life in patients with online gaming disorder [12] (the details of this study are described in Table 26.1 as well as in a previous section about self-control).

Stress is a psychological and phenomenological experience accompanied by a specific physiological response [41]. Stress is purported to play a role in different stages of SRADs, from the initiation of the addictive behaviour to its relapse [41]. Both stress and addictive disorders are thought to share a common neurophysiology, including a disrupted hypothalamic-pituitary-adrenal axis, as well as disrupted cognitive functions (e.g. selective attention, decision-making). In turn, both stress and addictive disorders may influence mood and cue reactivity, thereby increasing craving and probability of relapse. Furthermore, withdrawal symptoms themselves can cause stress for the individual. Thus, it is important to provide stress-coping strategies for patients with SRADs. Some evidence indicates that one session of active tCS over the DLPFC (anode over left DLPFC; cathode over right DLPFC), as compared to sham, can prevent a stress response (e.g. cortisol level) and decrease anxiety in healthy individuals that undergo psychosocial stress [42]. It remains to be seen whether tCS may be beneficial to stress reduction also in patients with SRADs.

26.3 Discussion

Taken together, there are some trends that allow us to observe a general picture. First, targeting the bilateral DLPFC appears to be the most effective tCS approach [5–10, 12–14], regardless of anode or cathode placement (see Table 26.1). This might suggest the importance of location and not laterality in SRADs [36], at least for cognitive functions. Second, decision-making was the most improved function across a variety of SRADs (tobacco, methamphetamine, gambling, cocaine use disorders, but not cannabis use disorder), which all targeted the bilateral DLPFC. Hence, there appears to be a link between targeting the

DLPFCs and ameliorated decision-making. One possible explanation is that tCS modulates the interhemispheric balance between the two DLPFCs that is needed for decision-making functions [43]. It might be interesting for future studies to examine any possible underlying mechanisms (e.g. using fMRI). Also, it might be worth examining whether tCS can modulate other cognitive functions that are impaired across different SRADs (e.g. cognitive flexibility in alcohol and stimulant use disorders, and reasoning in opioid use disorder [4]). Combining tCS with behavioural interventions such as cognitive bias modification, does not appear to lead to promising results for alcohol use disorder. This might be due to several factors, such as the motivation of the subjects (some were not treatment seeking, and therefore might not be motivated to reduce their drinking), or the study design (perhaps, there were too few sessions to induce changes). Interestingly, combining tACS with attentional bias modification decreased attentional biases, as well as improving decision-making and decreasing craving in patients with tobacco use disorder. Although this was a proof of concept study [14], it nevertheless demonstrated the potential pertinence of combining these two interventions in SRADs.

Furthermore, a series of limitations of the reviewed studies should be taken into account. First, patient characteristics such as age and sex knowingly influence tCS-induced effects [44–47] but were not always properly considered. In addition, the pattern of substance use disorders is different in men and women. For example, most studies included samples with a majority of men or even men only. It would be important to include more women in studies. Importantly, it would be imperative to determine whether there are differences between sexes in tCS responses. Second, the majority of studies included detoxified and abstinent patients, while other stages of SRADs (e.g. sated, non-treatment seekers) remain unexplored. A recent study in non-treatment-seeking tobacco smokers suggested that sated patients responded better to tCS as compared to deprived patients, as reflected by a greater deactivation of the default mode network [29]. To support, acute nicotine in sated, as compared to abstinent, patients may present greater neural plasticity [48], thus, presumably they may respond more to tCS. Third, most studies did not include patients with comorbid disorders other than tobacco use disorder. Considering that comorbidities (e.g. mood disorders) are common in SRADs [49], it might be worth examining different subgroups. Fourth, the motivation to change, which is associated with better response to tCS, remains unexplored [50]. Improving selective attention might be one way to improve motivation [32]. Also, greater motivation may relate to a better adherence to tCS regimens, which likely require several sessions in order to produce clinically meaningful improvements of symptoms [36]. Fifth, behavioural states before stimulation and individual differences in brain morphometry on the effect of tCS treatments should be considered [51]. For instance, we previously observed that behaviours and brain morphometry impacted tDCS changes on neural substrates in patients with gambling disorder. In one study, there were positive correlations between tCS-induced changes of neurotransmitter levels in prefrontal and striatal regions and gambling-related behaviours (i.e. craving, impulsivity, risk-taking) in patients with gambling disorder [52]. In another study, there were positive correlations between tDCS-induced elevations of prefrontal GABA levels and morphometry (volume and thickness) of the DLPFC in patients with gambling disorder [51]. In addition, the use of more objective and standardized outcome measures (e.g. a cue-provoked paradigm for craving) would allow more direct comparisons across studies. Finally, future work could assess whether tCS can modulate other cognitive functions that may be relevant to SRADs, such as memory bias [53] and mindfulness [54].

26.4 Conclusion

In conclusion, tCS holds a strong clinical potential to improve cognitive functions when targeting the DLPFC. Further work is needed to determine the most effective protocols. One interest-

ing therapeutic avenue might be individualized treatments based on patient characteristics such as brain morphometry, age, and sex. Future studies could aim to optimize outcomes by combining tCS with medications or behavioural interventions (e.g. cognitive behavioural therapy) in order to improve outcomes even more [36].

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References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596.
2. Verdejo-Garcia A, Garcia-Fernandez G, Dom G. Cognition and addiction. Dialogues Clin Neurosci. 2019;21(3):281–90. https://doi.org/10.31887/DCNS.2019.21.3/gdom.
3. Copersino ML. Cognitive mechanisms and therapeutic targets of addiction. Curr Opin Behav Sci. 2017;13:91–8. https://doi.org/10.1016/j.cobeha.2016.11.005.
4. Fernandez-Serrano MJ, Perez-Garcia M, Verdejo-Garcia A. What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? Neurosci Biobehav Rev. 2011;35(3):377–406. https://doi.org/10.1016/j.neubiorev.2010.04.008.
5. Vanderhasselt M-A, Allaert J, De Raedt R, Baeken C, Krebs RM, Herremans S. Bifrontal tDCS applied to the dorsolateral prefrontal cortex in heavy drinkers: influence on reward-triggered approach bias and alcohol consumption. Brain Cogn. 2020;138:105512. https://doi.org/10.1016/j.bandc.2019.105512.
6. Shahbabaie A, Hatami J, Farhoudian A, Ekhtiari H, Khatibi A, Nitsche MA. Optimizing electrode montages of transcranial direct current stimulation for attentional bias modification in early abstinent methamphetamine users. Front Pharmacol. 2018;9:907. https://doi.org/10.3389/fphar.2018.00907.
7. Alizadehgoradel J, Nejati V, Sadeghi Movahed F, Imani S, Taherifard M, Mosayebi-Samani M, et al. Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: a randomized, double-blind, parallel-group study. Brain Stimul. 2020;13(3):582–93. https://doi.org/10.1016/j.brs.2019.12.028.
8. Soyata AZ, Aksu S, Woods AJ, İşçen P, Saçar KT, Karamürsel S. Effect of transcranial direct current stimulation on decision making and cognitive flexibility in gambling disorder. Eur Arch Psychiatry Clin Neurosci. 2019;269(3):275–84. https://doi.org/10.1007/s00406-018-0948-5.
9. Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci. 2014;8:661. https://doi.org/10.3389/fnhum.2014.00661.
10. Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. Drug Alcohol Depend. 2014;140:78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036.
11. Pripfl J, Neumann R, Köhler U, Lamm C. Effects of transcranial direct current stimulation on risky decision making are mediated by "hot" and "cold" decisions, personality, and hemisphere. Eur J Neurosci. 2013;38(12):3778–85. https://doi.org/10.1111/ejn.12375.
12. Lee SH, Im JJ, Oh JK, Choi EK, Yoon S, Bikson M, et al. Transcranial direct current stimulation for online gamers: a prospective single-arm feasibility study. J Behav Addict. 2018;7(4):1166–70. https://doi.org/10.1556/2006.7.2018.107.
13. Den Uyl TE, Gladwin TE, Rinck M, Lindenmeyer J, Wiers RW. A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. Addict Biol. 2017;22(6):1632–40. https://doi.org/10.1111/adb.12463.
14. Mondino M, Lenglos C, Cinti A, Renauld E, Fecteau S. Eye tracking of smoking-related stimuli in tobacco use disorder: a proof-of-concept study combining attention bias modification with alpha-transcranial alternating current stimulation. Drug Alcohol Depend. 2020;214:108152.
15. Stacy AW, Wiers RW. Implicit cognition and addiction: a tool for explaining paradoxical behavior. Annu Rev Clin Psychol. 2010;6:551–75. https://doi.org/10.1146/annurev.clinpsy.121208.131444.
16. Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. Drug Alcohol Depend. 2008;97(1–2):1–20. https://doi.org/10.1016/j.drugalcdep.2008.03.030.
17. Den Uyl TE, Gladwin TE, Lindenmeyer J, Wiers RW. A clinical trial with combined transcranial direct current stimulation and attentional bias modification in alcohol-dependent patients. Alcohol Clin Exp Res. 2018;42(10):1961–9. https://doi.org/10.1111/acer.13841.
18. Claus ED, Klimaj SD, Chavez R, Martinez AD, Clark VP. A randomized trial of combined tDCS over right inferior frontal cortex and cognitive bias modification: null effects on drinking and alcohol approach bias. Alcohol Clin Exp Res. 2019;43(7):1591–9. https://doi.org/10.1111/acer.14111.
19. Den Uyl TE, Gladwin TE, Wiers RW. Electrophysiological and behavioral effects of combined transcranial direct current stimulation and alcohol approach bias retraining in hazardous drinkers. Alcohol Clin Exp Res. 2016;40(10):2124–33. https://doi.org/10.1111/acer.13171.

20. Jurado MB, Rosselli M. The elusive nature of executive functions: a review of our current understanding. Neuropsychol Rev. 2007;17(3):213–33. https://doi.org/10.1007/s11065-007-9040-z.
21. Morris LS, Voon V. Dimensionality of cognitions in behavioral addiction. Curr Behav Neurosci Rep. 2016;3:49–57. https://doi.org/10.1007/s40473-016-0068-3.
22. Berg EA. A simple objective technique for measuring flexibility in thinking. J Gen Psychol. 1948;39:15–22. https://doi.org/10.1080/00221309.1948.9918159.
23. Clark L, Robbins T. Decision-making deficits in drug addiction. Trends Cogn Sci. 2002;6(9):361. https://doi.org/10.1016/s1364-6613(02)01960-5.
24. Verdejo-Garcia A, Perez-Garcia M, Bechara A. Emotion, decision-making and substance dependence: a somatic-marker model of addiction. Curr Neuropharmacol. 2006;4(1):17–31. https://doi.org/10.2174/157015906775203057.
25. Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug Alcohol Depend. 2010;112(3):220–5. https://doi.org/10.1016/j.drugalcdep.2010.06.019.
26. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci. 2007;27(46):12500–5. https://doi.org/10.1523/JNEUROSCI.3283-07.2007.
27. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–68. https://doi.org/10.1146/annurev-psych-113011-143750.
28. Bickel WK, Yi R, Landes RD, Hill PF, Baxter C. Remember the future: working memory training decreases delay discounting among stimulant addicts. Biol Psychiatry. 2011;69(3):260–5. https://doi.org/10.1016/j.biopsych.2010.08.017.
29. Aronson Fischell S, Ross TJ, Deng Z-D, Salmeron BJ, Stein EA. Transcranial direct current stimulation applied to the dorsolateral and ventromedial prefrontal cortices in smokers modifies cognitive circuits implicated in the nicotine withdrawal syndrome. Biol Psychiatry. 2020;5(4):448–60. https://doi.org/10.1016/j.bpsc.2019.12.020.
30. Percy A. Moderate adolescent drug use and the development of substance use self-regulation. Int J Behav Dev. 2008;32(5):451–8. https://doi.org/10.1177/0165025408093664.
31. Witkiewitz K, Stein ER, Votaw VR, Wilson AD, Roos CR, Gallegos SJ, et al. Mindfulness-based relapse prevention and transcranial direct current stimulation to reduce heavy drinking: a double-blind sham-controlled randomized trial. Alcohol Clin Exp Res. 2019;43(6):1296–307. https://doi.org/10.1111/acer.14053.
32. Rubenis AJ, Fitzpatrick RE, Lubman DI, Verdejo-Garcia A. Sustained attention but not effort-based decision-making predicts treatment motivation change in people with methamphetamine dependence. J Subst Abus Treat. 2018;95:48–54. https://doi.org/10.1016/j.jsat.2018.09.007.
33. Xu J, Fregni F, Brody AL, Rahman AS. Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. Front Psych. 2013;4:112. https://doi.org/10.3389/fpsyt.2013.00112.
34. Da Silva MC, Conti CL, Klauss J, Alves LG, Do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J Physiol Paris. 2013;107(6):493–502. https://doi.org/10.1016/j.jphysparis.2013.07.003.
35. Klauss J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos GDA, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol. 2014;17(11):1793–803. https://doi.org/10.1017/s1461145714000984.
36. Ekhtiari H, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev. 2019;104:118–40. https://doi.org/10.1016/j.neubiorev.2019.06.007.
37. Sayette MA. The role of craving in substance use disorders: theoretical and methodological issues. Annu Rev Clin Psychol. 2016;12:407–33. https://doi.org/10.1146/annurev-clinpsy-021815-093351.
38. Hone-Blanchet A, Ciraulo DA, Pascual-Leone A, Fecteau S. Noninvasive brain stimulation to suppress craving in substance use disorders: review of human evidence and methodological considerations for future work. Neurosci Biobehav Rev. 2015;59:184–200. https://doi.org/10.1016/j.neubiorev.2015.10.001.
39. Koob GF. The dark side of emotion: the addiction perspective. Eur J Pharmacol. 2015;753:73–87. https://doi.org/10.1016/j.ejphar.2014.11.044.
40. Pripfl J, Lamm C. Focused transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex modulates specific domains of self-regulation. Neurosci Res. 2015;91:41–7. https://doi.org/10.1016/j.neures.2014.09.007.
41. Lemieux A, Al'Absi M. Stress psychobiology in the context of addiction medicine: from drugs of abuse to behavioral addictions. Prog Brain Res. 2016;223:43–62. https://doi.org/10.1016/bs.pbr.2015.08.001.
42. Carnevali L, Pattini E, Sgoifo A, Ottaviani C. Effects of prefrontal transcranial direct current stimulation on autonomic and neuroendocrine responses to psychosocial stress in healthy humans. Stress. 2020;23:26–36. https://doi.org/10.1080/10253890.2019.1625884.
43. Fecteau S, Fregni F, Boggio PS, Camprodon JA, Pascual-Leone A. Neuromodulation of decision-making in the addictive brain. Subst Use Misuse. 2010;45(11):1766–86. https://doi.org/10.3109/10826084.2010.482434.

44. Russell M, Goodman T, Wang Q, Groshong B, Lyeth BG. Gender differences in current received during transcranial electrical stimulation. Front Psych. 2014;5:104. https://doi.org/10.3389/fpsyt.2014.00104.
45. Thomas C, Datta A, Woods A. Effect of aging on cortical current flow due to transcranial direct current stimulation: considerations for safety. Conf Proc IEEE Eng Med Biol Soc. 2018;2018:3084–7. https://doi.org/10.1109/EMBC.2018.8513014.
46. Antonenko D, Nierhaus T, Meinzer M, Prehn K, Thielscher A, Ittermann B, et al. Age-dependent effects of brain stimulation on network centrality. NeuroImage. 2018;176:71–82. https://doi.org/10.1016/j.neuroimage.2018.04.038.
47. Lee S, Chung SW, Rogasch NC, Thomson CJ, Worsley RN, Kulkarni J, et al. The influence of endogenous estrogen on transcranial direct current stimulation: a preliminary study. Eur J Neurosci. 2018;48(4):2001–12. https://doi.org/10.1111/ejn.14085.
48. Grundey J, Thirugnanasambandam N, Kaminsky K, Drees A, Skwirba AC, Lang N, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J Neurosci. 2012;32(12):4156–62. https://doi.org/10.1523/JNEUROSCI.3660-11.2012.
49. NIDA. Common comorbidities with substance use disorders research report. 2020. Retrieved from https://www.drugabuse.gov/publications/research-reports/common-comorbidities-substance-use-disorders/.
50. Vitor de Souza Brangioni MC, Pereira DA, Thibaut A, Fregni F, Brasil-Neto JP, Boechat-Barros R. Effects of prefrontal transcranial direct current stimulation and motivation to quit in tobacco smokers: a randomized, sham controlled, double-blind trial. Front Pharmacol. 2018;9:14. https://doi.org/10.3389/fphar.2018.00014.
51. Bouchard AE, Dickler M, Renauld E, Lenglos C, Ferland F, Edden RA, et al. The impact of brain morphometry on tDCS effects on GABA levels. Brain Stimul. 2020;13(2):284–6. https://doi.org/10.1016/j.brs.2019.10.013.
52. Dickler M, Lenglos C, Renauld E, Ferland F, Edden RA, Leblond J, et al. Online effects of transcranial direct current stimulation on prefrontal metabolites in gambling disorder. Neuropharmacology. 2018;131:51–7. https://doi.org/10.1016/j.neuropharm.2017.12.002.
53. Goldfarb EV, Fogelman N, Sinha R. Memory biases in alcohol use disorder: enhanced memory for contexts associated with alcohol prospectively predicts alcohol use outcomes. Neuropsychopharmacology. 2020;45(8):1297–305. https://doi.org/10.1038/s41386-020-0650-y.
54. Cavicchioli M, Movalli M, Maffei C. The clinical efficacy of mindfulness-based treatments for alcohol and drugs use disorders: a meta-analytic review of randomized and nonrandomized controlled trials. Eur Addict Res. 2018;24(3):137–62. https://doi.org/10.1159/000490762.

27 Transcranial Direct Current Stimulation in Substance Use Disorders

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27.1 Introduction

27.1.1 Substance Use Disorder or Drug Addiction

The *substance use disorder* – SUD (or drug use disorder) – is a term adopted in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [1] to describe the wide range of the disorder, ranging from a mild form to a severe state of chronically relapsing, compulsive drug taking. It refers to a maladaptive pattern of substance use leading to clinically significant impairment or distress and essentially characterized by a cluster of cognitive, behavioral, and physiological changes inducing the individual to continue the use of the substance despite significant substance-related problems [1].

According to the *DSM-5*, *addiction* is a term in common usage to describe severe problems related to compulsive and habitual use of substances and may be clinically used to describe more extreme presentations of the SUDs. However, the term *drug addiction* may be interchangeably used with SUD in the scientific literature.

SUD is a serious health problem, constituting a significant burden for affected people and their families, with significant costs to society, including loss of productivity, security challenges, criminality and illegality, and increasing healthcare costs, yielding a myriad of negative social consequences [1–3].

It is a chronic mental disorder characterized as progressive, incurable, but treatable, at least relatively, despite the significant consequences for the addicted subject. It is a disease that has its own evolution and constitutes an important risk factor for the development of other diseases and physical, cognitive and mental disabilities [4–6], and it can result in legal consequences for being involved with crime and even death, if there is no treatment and an appropriate approach.

According to UNODC (United Nations Office on Drugs and Crime) in its world drug report from 2019, it has been estimated that 271 million people, or 5.5% of the global population aged 15–64 years, had used drugs at least once in 2017. This is 30% higher than it was in 2009. Also, in 2017, about 35 million people (almost 13%) were estimated to be suffering from drug

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use disorders, experiencing drug dependence and requiring treatment services [7]. It has been also estimated that, globally, in 2017, there were 585,000 deaths and 42 million "healthy" life lost as a result of the use of drugs [7].

For people with drug use disorders, the availability and access to treatment services remain limited at the global level, as only one in seven people with drug use disorders receive treatment [7]. In many countries, treatment is only available in large cities, but not in rural areas. Moreover, in many places the treatments available are often not effective, not supported by scientific evidence, and in some situations, are not even in line with human rights principles and are not voluntary. In highly developed countries, where there are evidence-based treatment programs, availability is often insufficient [7].

27.1.2 Why Is It So Difficult to Control the Use of an Addictive Drug?

An important characteristic of SUDs is an underlying change in brain circuits that may persist beyond detoxification, particularly in individuals with severe disorders [1]. The behavioral effects of these brain changes may be associated with the repeated *relapses* and intense drug *craving* when the individuals are exposed to drug-related stimuli [1].

After many years of scientific research, we now have a better understanding of drug addiction as a complex, multifactorial, biological, and behavioral disorder. Nowadays we understand that there are brain mechanisms that play a central role in the development and maintenance of behavioral signs and symptoms of drug use disorders [1].

This is a condition that is established in a small proportion (around 10–13%), but numerically significant considering the severity of the consequences mentioned earlier, of those who experience a drug abuse for the first time [7, 8]. In these susceptible individuals, the repeated consumption of the substance induces a pattern of compulsive use subsequent to the loss of use control and the uncontrollable and imperative craving for the use of the substance, establishing and maintaining an addictive, impulsive, and compulsive pattern of use, and therefore, a high risk for relapses to the consumption of the substance (Fig. 27.1), characterizing the use of excessive amounts and the loss of an excessive time in activities related to the drug.

At the same time, a series of changes occur in the organism under repeated exposure of the substance, promoting the development of tolerance and physiological dependence and the subsequent signs and symptoms, in general quite unpleasant, of the withdrawal (withdrawal syndrome) of the drug when it is discontinued [7, 9, 10] (Fig. 27.1).

The desire to use the drug can persist or be easily reactivated even after a long period of abstinence and lead to the resumption of regular use, despite a strong contrary intention to control or to stop using the substance. Over time, substance use becomes the highest priority in a person's life, overlapping all other activities and interests, including family, work, and social life. The use persists in spite of the recurring interpersonal and social problems, and even knowing that these situations are due to the use of the substance [7].

27.1.3 Is Drug Addiction an Executive Dysfunction?

For a long time, the understanding of the neurobiological processes underlying drug addiction was primarily focused on limbic subcortical structures referred to as central reward system (see Nakamura-Palacios [11]). The central reward system is mainly constituted by the mesocorticolimbic dopamine (DA) pathway [12–19] joining the ventral tegmental area (VTA) and the

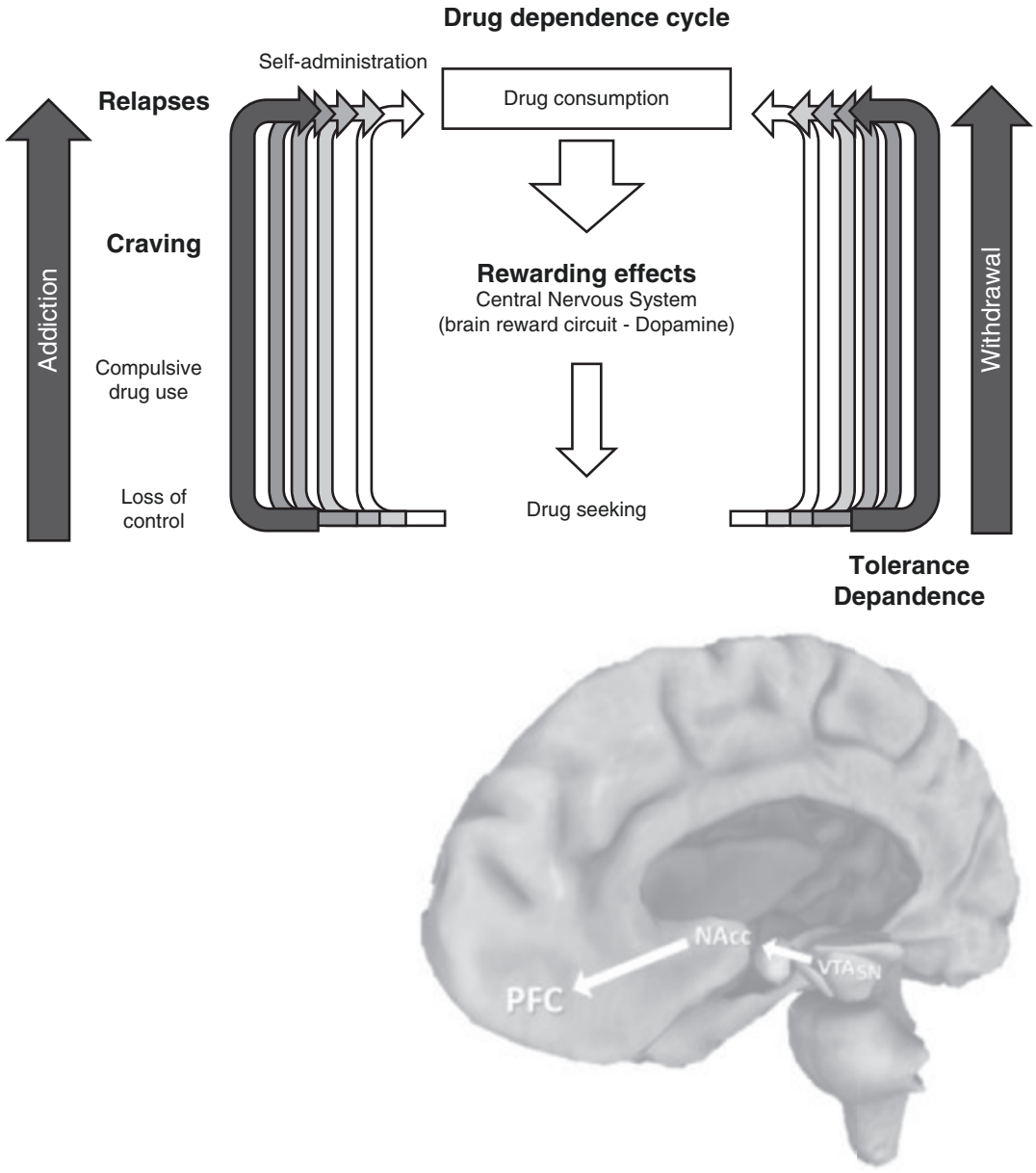

Fig. 27.1 Drug dependence cycle: the direct rewarding effects through the brain reward circuit (VTA: ventral tegmental area, SN: substantia nigra, NAcc; nucleus accumbens, PFC: prefrontal cortex) following drug consumption reinforces the search for additional drug intake. The seeking behavior is probably mediated by the mesocortical limbic system via a dopamine (DA) mechanism. This driving drug seeking behavior pursues to maintain the immediate central effects. The repetition of drug consumption may induce a more compulsive pattern of drug use, eventually leading to a loss of control and establishing the drug addiction with subsequent long-lasting risk for relapses

nucleus accumbens (NAcc) [18, 20, 21], but it also includes the prefrontal cortex (PFC) [16, 17, 22] (Fig. 27.1). This is a circuit that reinforces nonaddictive behaviors required for the survival of the individual (hunger and thirst) and the species (reproduction) [18, 23]. The frontal cortical brain area gets progressively larger across animal evolution [24, 25], gaining more complex control over several brain functions in primates, particularly in human beings. When this cortical function is compromised, the cognitive control is halted, and the behavior may exhibit in its primitive or in a stimulus-driven form [23].

The involvement of the frontal cortical structures in drug addiction started to gain more attention with the advance of neuroimaging evidence in human studies [23], identifying the key role of the PFC in the regulation of the limbic reward system and in its involvement in higher order executive function, such as self-control (emotion regulation and inhibitory control), salience attribution and maintenance of motivation arousal need to engage in goal-driven behaviors, and self-awareness [9].

Different regions of the PFC are involved in drug addiction. The dorsal PFC, including the dorsal anterior cingulate cortex (dACC), dorsolateral PFC (dlPFC), and inferior frontal gyrus (IFG), would be implicated in top-down control and metacognitive functions; the ventromedial PFC (vmPFC), including subgenual anterior cingulate cortex (sgACC) and medial orbitofrontal cortex (mOFC), in emotion regulation, including conditioning and assigning incentive salience to drugs and drug-related cues; and the ventrolateral PFC (vlPFC) and lateral OFC (lOFC) in automatic response tendencies and impulsivity [9].

Thus, the deficiency in directing behavior toward an objective, for planning future actions, to solve problems and make decisions, to inhibit inadequate responses, and to modify an ongoing behavior in face of new demands (behavioral flexibility), and finally in processing working memory, would characterize the frontal executive dysfunctions associated with SUDs and to the low resoluteness of drug dependence treatments [9, 26]. These executive dysfunctions in SUDs maintain and even aggravate the drug dependence condition (Fig. 27.2).

Fig. 27.2 Drug addiction disrupts executive function, which in turn maintains and aggravates the drug dependence

27.1.4 What Is Underneath the Drug-Induced Neuronal Changes?

During the early phase of drug experimentation, neurotransmission changes in the central nervous system may normalize as intoxication wears off and the substance leaves the brain. However, repeated drug consumption might lead to changes in neuronal structure and function that cause long-lasting or permanent neurotransmission abnormalities [10, 27]. These alterations underlie drug tolerance, withdrawal, and addiction.

All drugs of abuse bind initially to protein targets located at the synapse. Some of them act as ligands for G protein-coupled receptors such as opiates and cannabinoids, both as agonists

at selective receptors (opioid and cannabinoids, respectively). Other drugs act inhibiting the presynaptic transporters for dopamine and other monoamines such as cocaine and amphetamines, and others acting on ligand-gated ion channels, such as nicotine, an agonist of nicotinic acetylcholine receptors; phencyclidine, a noncompetitive inhibitor of *N*-methyl-D-aspartate (NMDA) glutamate receptors, and ethanol, an allosteric facilitator of gamma-aminobutyric acid (GABA) type A receptors and inhibitor of NMDA glutamate receptors [14].

Irrespective of their acute targets, these substances of abuse or other rewarding activities (games, social interaction) are known to activate the reward circuit in the brain, triggering DA neurons in the VTA of the midbrain to activate their projections in the limbic system such as NAcc, a crucial brain reward region; dorsal striatum, a region implicated in the encoding of habit and routines; amygdala, a region involved in emotions, stress, and desires; hippocampus, a region involved in memory; and PFC, a region involved in self-regulation and the attribution of salience [28, 29].

In this reward circuit, DA seems to signalize the appearance of novel salient stimuli or a cue predicting a familiar motivationally relevant event associated with environmental stimuli [19]. Once a salient stimulus has been associated with a drug effect, DA is no longer released during the drug action, but it does when a cue predicting the drug is perceived [12, 30].

In the NAcc, DA is required for the drug high and for the initiation of addiction, but when a drug is used repeatedly and rewarding effects take place, the glutamatergic projection from the PFC to the NAcc is the one most recruited [19]. According to Kalivas and Volkow [19], the glutamatergic projection emerging from the PFC (more precisely anterior cingulate and orbitofrontal cortex) to the core of the NAcc is the one associated to the drug-seeking behavior, and its dysfunction seems highly involved in the uncontrollable craving to the drug use that characterizes drug addiction [19].

The exposure to drug cues results in the activation of glutamatergic projections from the ventral PFC, the ventral hippocampus, and the amygdala (and presumably medial thalamus) to striatal projections that in turn increase DA signaling and release in the NAcc and dorsal striatum [27, 31]. The enhanced craving and desire for drug taking will eventually lead to drug consumption, and although the drug-induced DA increases are markedly attenuated in the NAcc, in particular of cocaine abusers and alcoholics, they are sufficient to enhance the craving and to sustain the drive to continue taking the drug [27].

The repeated exposure to a drug causes repeated activation of postsynaptic intracellular messenger pathways, which first initiates and then maintains the longer lasting and stable molecular and cellular adaptations underlying addiction [14]. One mechanism for these stable adaptations is associated with alterations of gene expression. Drug regulation of intracellular messenger pathways would cause changes on transcription factors that regulate gene transcription. These changes on transcription factors, in turn, would alter the expression of specific target genes in the brain changing the neural function and ultimately resulting in long-term changes in synapses, neural circuits, as well as consequent neuroadaptative and behavioral changes, promoting tolerance and increased drug-seeking behavior, which may underlie the development and maintenance of drug addiction [32–34].

Briefly, the direct or indirect activation of DA receptors by a drug exposition in the reward circuit increases the permeability of calcium channels and activates second messengers in the intracellular environment of these neurons (Fig. 27.3) [34, 35]. Besides the regulation of several intracellular processes, these second messengers reach the nucleus and activate the transcription of the binding protein in response to cAMP (CREB) in a short time of exposure to a drug, as it was seen with psychostimulants [34]. The increased CREB activation activates the transcription of other genes such as brain-derived neurotrophic factor (BDNF), dynorphins (endogenous opioids), and the Fos family, such as FosB [35]. Changes in the transcription levels of these genes initiate and develop the state of addiction.

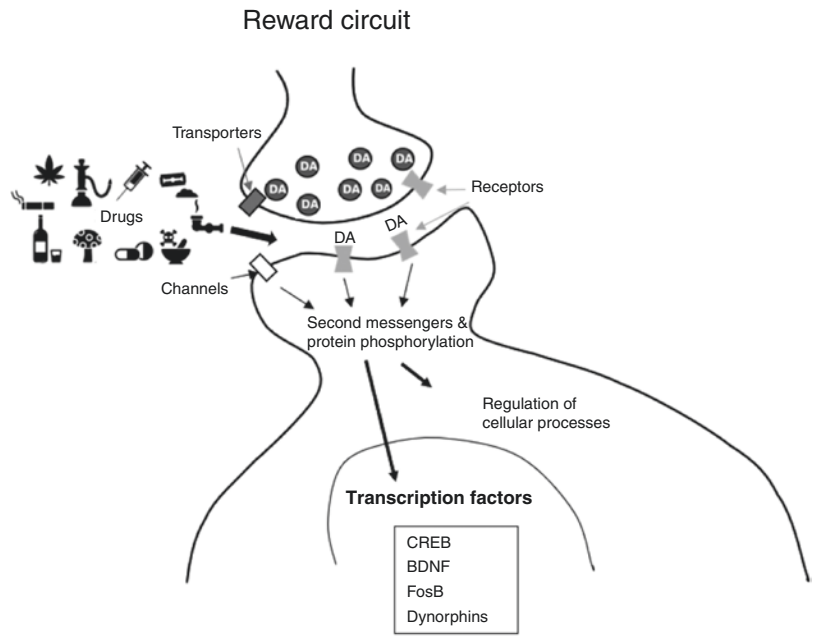

Fig. 27.3 Molecular changes in drug addiction. CREB: cAMP response element binding protein, FosB protein, BDNF: brain-derived neurotrophic factor (adapted from Nestler [35])

27.1.5 Are Changes in Neuroplasticity Long Lasting in Drug Addiction?

According to Volkow et al. [29], in the past two decades, neuroscience research has increasingly supported the view that addiction is a disease of the brain. The drug-induced release of dopamine triggers neuroplastic changes in the synaptic signaling, or communication, between neurons of the brain reward system. These neuroplastic changes are fundamental to the experience-dependent learning after repeated episodes of drug use, probably involving long-term potentiation and long-term depression, both well-known neuroplastic phenomena underlying learning and memory processes mediated by excitatory neurotransmitter glutamate acting through α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) and NMDA receptors [29].

According to Robinson and Kolb [36], "one of the most compelling examples of experience-dependent plasticity, whereby experience at one point in life changes behavior and psychological function for a lifetime, is addiction." The high risk to relapse, even months to many years after the discontinuation of drug use, and long after withdrawal symptoms have been treated provides strong evidence that drug use induces long-lasting plasticity.

Robinson and Kolb [36] had proved that repeated exposure to cocaine, amphetamine, morphine, or nicotine in adult rats, whether administered by an experimenter or self-administered, have long-lasting effects on the structure of dendrites and dendritic spines in brain regions involved in incentive motivation and reward (such as the NAcc) and in cognitive function (such as the PFC). This drug-induced structural plasticity was evident many months after drug discontinuation, suggesting that drugs of abuse produce a persistent reorganization of patterns of synaptic connectivity in these brain regions.

Furthermore, Freeman et al. [37] found long-lasting changes in gene expression in the medial PFC and identified cellular processes that could regulate the development and/or maintenance of incubation of drug seeking and drug taking.

Changes in the PFC could involve mostly distinct sets of genes indicating different metaplastic processes occurring in this brain region with the development and expression of abstinence-induced behaviors [37]. These changes may contribute to the persistent alteration of synap-

tic plasticity in this structure. As PFC mediates executive function and decision-making processes, Freeman et al. [37] suggested that it may constitute a key neuroanatomical region in addictive behaviors.

Despite the complexity of the mechanisms underlying drug addiction in humans, current evidence points toward the existence of a strong correlation between addictive drugs exposition and neuroadaptations involving the dopaminergic system [38]. These adaptive mechanisms are a result of the interference of psychostimulants in dopaminergic neurotransmission by means of increasing its synaptic availability. Therefore, the repeated drug abuse can promote permanent changes in the expression of DA and dopaminergic receptors, as well as transient or permanent changes in the expression of BDNF and FosB, leading to long-term neuronal drug-induced changes [39, 40].

Recently, Anders et al. [40] analyzed the gene expression of FosB in peripheral blood lymphocytes of crack cocaine and alcohol use disorder patients hospitalized for drug dependence treatment and found a reduced expression of this molecular target. Anders et al. also examined the gene expression of BDNF and D5 dopamine receptor genes in the same group of patients and found elevated mRNA levels of the former [41] and nonsignificant elevated mRNA levels of the latter (*unpublished data*). These results highlight the existence of altered molecular pathways in drug addicts, which could explain the long-term changes in reward circuits and executive function impairments observed in these patients [9, 40, 42].

27.1.6 Why Noninvasive Brain Stimulation (NIBS) in SUD?

As mentioned earlier, drug addiction is a chronic disease, mostly characterized by strong craving emergence and high relapse risk, coursing with important executive dysfunction that maintain and aggravate the addictive process, all because of long-lasting neuroplastic changes in brain reward regions induced by drug exposition, and consequently very difficult to be treated.

Because of the interference of different environmental factors, the complexity of the biological aspects, the involvement of different brain areas and diverse chemical substances in the central nervous system, even with fundamental biopsychosocial approaches, and the existence of different pharmacological treatments [43, 44], the management of drug addictions has been of modest effectiveness [4, 45–47].

Besides, treatments are mostly focused on the management of acute abstinence [43], and very rarely, or almost never, invest in the control of urgency, uncontrollable desire (craving), substance use [48, 49], and/or relapse [50, 51], conditions that appear more frequently in the late period of abstinence. Thus, appropriate treatments for various SUDs with more favorable outputs are yet to be found.

NIBS are classically represented by transcranial electrical (tES) and magnetic (TMS) stimulation. TES, usually applied in low intensity, includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS).

These techniques have emerged as nonpharmacological strategies providing a modulation of cortical excitability in several neuropsychiatric disorders [52–54], with the expectation of helping the treatment of SUDs [55–64].

27.1.7 Are There Prefrontal and Drug-Related Molecular Changes Under Direct Current Stimulation?

Throughout the last decades, NIBS techniques, including tDCS, have emerged as a promising tool for a variety of neuropsychiatric disorders, such as Parkinson and Alzheimer diseases, epilepsy, stroke, and addiction [65–67]. However, the underlying mechanisms on the potential cognitive and clinical beneficial effects of tDCS, especially at the molecular level, remain largely unknown [68]. In this sense, research using animals might allow rapid and risk-free screening of stimulation protocols in research and clinical

settings, and to address the mechanisms of tDCS with the ultimate goal of informing clinical efficiency and safety of tDCS [69]. Indeed, preclinical models have certainly disentangled some of the cellular and molecular mechanisms by which tDCS exert their neurophysiological effects, as well as effects of multiple stimulation sessions on drug-related behaviors [70].

In a healthy rat brain, several previous experiments have shown that tDCS can modulate neural plasticity by enhancing expression of NMDA and BDNF [71–73]. In 2017, Pedron et al. [74] reported the effects of tDCS on behavior and expression of mRNA in rats, showing a decrease in preference for cocaine after tDCS, besides a decrease in the expression of Zif268 mRNA, which is a transcription factor activated after the exposure to cocaine. These results corroborate the evidence that changes in the synaptic and behavioral plasticity of animals after tDCS might have their substrate in the molecular changes at the cellular level. Podda et al. [75], in 2016, had analyzed the expression of mRNA CREB and BDNF associated with behavioral tests 7 days before and after direct current stimulation in rats and found increased BDNF level and improved learning and memory, showing that behavioral changes observed after tDCS might be supported by underlying molecular mechanisms.

Rohan et al. [76], in 2015, studied anodal tDCS in vivo by evaluating synaptic effects ex vivo, showing enhanced long-term potentiation (LTP) dependent of NMDA receptor (NMDAR) activation after a single 30 min anodal tDCS session, remarkably persisting for at least 24 h. They also showed that anodal tDCS enhanced the paired pulse facilitation (PPF) ratio, but independent of NMDAR activation, and did not continue 24 h after tDCS completion. According to these authors, this was the first evidence of in vivo tDCS enhancing plasticity of neurons at both the presynaptic and postsynaptic sites of rat hippocampus.

A pivotal behavioral study published by de Souza Custódio et al. [77] in 2015 showed that animals receiving anodal epidural direct current stimulation (eDCS) at 400 mA intensity over a 5-mm round area of the dura mater above the left medial PFC (mPFC) for 11 min and were tested 5 min later on delayed tasks in the 8-arm radial maze had significantly fewer errors compared with sham-treated animals after 1-h, 4-h, and 10-h delays, suggesting a beneficial long-lasting effect on spatial working memory.

Later, de Souza Custódio et al. [78] explored, in a study published in 2018, the expression of BDNF – both precursor (proBDNF) and mature (mBDNF) isoforms – in rats' PFC at different time intervals after one single session of eDCS (400 μA for 11 min) or after its repetitive application (five consecutive sessions) applied over the left mPFC. They showed that levels of BDNF in the PFC, especially the proBDNF, were lower after a single and higher after repetitive anodal eDCS when compared to sham-eDCS. This was the first study showing that changes of prefrontal BDNF levels may disclose molecular changes underlying the plasticity induced by cortical anodal direct current stimulation, which may be opposite if applied in single or multiple sessions [78].

Interestingly, Wu et al. [79] had also shown that the repetitive anodal tDCS improved spatial working memory performance in streptozotocin-induced diabetic rats through augmentation of synaptic plasticity requiring BDNF secretion and transcription/translation of NMDARs in mPFC [79].

In a more recent study, now focusing in other glutamatergic receptors, Martins et al. [80] reported in a study published in 2019 that the improved long-term spatial working memory performance induced by the repetitive anodal eDCS (five consecutive sessions) over the left mPFC was largely dependent on AMPA receptors (AMPARs) activity, because it was abolished by perampanel (PRP), a selective noncompetitive AMPARs antagonist. They further showed that the expression of GAP-43 (growth-associated protein 43), an intrinsic determinant of neuronal development and plasticity [81], was increased after the repetitive eDCS in the PFC and was abolished by PRP. GAP-43 expression was increased in the hippocampus after repetitive eDCS when AMPARs were blocked by PRP, suggesting that GAP-43 expression could be influenced by AMPARs activity in both cortical regions. Therefore, the neuronal plasticity involv-

ing AMPARs may underlie, at least in part, the effects of the repetitive anodal prefrontal direct current stimulation on long-term spatial working memory and prefrontal and hippocampal GAP-43 expression [81].

Thus, as it can be seen in studies above, the understanding of direct current stimulation effects by using animal models has been especially important to explain the underlying molecular mechanisms of these techniques on learning and memory processes and to substantiate clinical studies in neuromodulation on neuropsychiatric conditions such as SUD.

Future preclinical research should invest on many other molecular targets and downstream cellular events, following the optimization efforts that have been suggested for clinical application considering stimulation targets and stimulation parameters such as electrodes/coil size and shape, duration, and number of stimulation sessions as suggested by Ekhtiari et al. [62].

27.2 tDCS in Different SUDs

27.2.1 Alcohol Use Disorder (AUD)

According to the global status report on alcohol and health [82], in 2016, about 2.3 billion people of the global population aged over 15 years were current drinkers. Alcohol had been consumed by more than half of the population in the United States, Europe, and Western Pacific.

In 2016, globally alcohol use disorders were the most prevalent of all substance use disorders, with 100.4 million estimated cases, with a prevalence of 1320.8 cases per 100.000 [83].

According to the American National Institute on Alcohol Abuse and Alcoholism [84], despite treatment developments, only about 14.6% of AUDs patients receive treatment. Thus, there is a large untreated population of patients in need for alcohol dependence treatment.

The first exploratory evidence of the effect of a single application of the transcranial direct current stimulation (tDCS) on bilateral dlPFC in 13 alcohol-dependent patients was published in 2008 by Boggio et al. [85]. In this study, the authors demonstrated that regardless of the polarity applied (anode on the left and cathode on the right or the reverse), the tDCS (2 mA, 35 cm^2, 20 min) decreased craving scores obtained by applying a visual analog scale (VAS) to 13 alcoholics.

A single exposure of anodal tDCS (1 mA, 35 cm^2, 15 min) over the left dlPFC (cathode over the contralateral supraorbital region) also reduced mild craving scores in 14 young heavy drinkers (AUDIT >8) when compared to 12 subjects from sham-tDCS condition, with no evidence for tDCS induced changes in alcohol biases as shown by den Uyl et al. [86].

An exploratory study published by Nakamura-Palacios et al. in 2012 [87] showed that 12 alcohol use disorder patients with severe dependence exposed to a single anodal tDCS (1 mA, 35 cm^2, 10 min) over the left dlPFC (cathode over the right supradeltoid region) had a mild, but statistically significant, improvement of frontal function measured by a brief frontal assessment battery (FAB) [88]. There was also an increase of the P300 amplitude, an event-related potential (ERP) component thought to index attention and memory processing during stimulus processing usually found decreased in AUD, when patients were hearing sounds related to the use of alcohol beverages [86].

However, 1 year later, in 2013, when da Silva et al. [66] applied the anodal tDCS (2 mA, 35 cm^2, 20 min) over the left dlPFC (cathode over the right supradeltoid region) repetitively (once a week for 5 consecutive weeks) to severe alcoholics in a double-blind, randomized study compared to sham-tDCS controls, six alcoholics from the tDCS group tended to have more frequent relapses when compared to seven patients from the sham-tDCS group, even though they had presented a significant reduction in craving scores, this time measured by the application of the five-item Obsessive Compulsive Drinking Scale (OCDS-5) [89].

Interestingly, in 2016, den Uyl et al. [90] also showed that three sessions (once a day) of anodal tDCS (1 mA, 35 cm^2, 15 min) over the left dlPFC (cathode over the contralateral supraorbital region) combined with an alcohol approach bias

retraining (a form of cognitive bias modification – CBM) reduced the cue-induced craving in 20 young hazardous drinkers (AUDIT >8) with no electrophysiological (P300) or behavioral effects.

In another study published in 2017, but now a double-blind, parallel study with AUD inpatients, den Uyl et al. [91] examined the effects of the anodal tDCS (2 mA, 35 cm^2, 20 min) applied over the left dlPFC with 100 cm^2 cathode electrode placed over the contralateral dlPFC combined with the CBM applied in four sessions and followed for their abstinence duration and relapses after 3 and 12 months, craving, and approach bias. They observed a trend of lower relapse rates in 30 patients receiving the active stimulation during the CBM after 1 year when compared to 30 patients receiving sham stimulation, but they did not find evidence for a specific enhancement effect of tDCS on CBM.

By changing the polarity to a cathodal stimulation (2 mA, 35 cm^2, double 13-min stimulation with 20-min interval – 13:20:13 schedule, current density 0.0571 mA/cm^2) over the left dlPFC and also, having the anode electrode placed over the right dlPFC, thus turning it a bilateral tDCS over the dlPFC, and applying it once a day for 5 consecutive days, Klauss et al. [92] demonstrated in 2014, in a randomized, double-blind, sham-controlled study that repetitive tDCS significantly reduced relapses to alcohol use over a 6-month posttreatment follow-up in AUD outpatients. At the end of this period, 11.8% of 17 AUD patients in the sham-tDCS group, while 50% of 16 patients in the real tDCS group were still abstinent. In addition, patients in the tDCS group reported a greater perception of better quality of life compared to AUD patients in the sham-tDCS group. There were, however, no differences between the groups regarding changes in craving scores, executive and cognitive functions, and the depressive and anxiety symptoms.

In a further randomized, double-blind, sham-controlled clinical trial with parallel arms published in 2018, Klauss et al. [93] extended the treatment to 10 sessions of bilateral tDCS (2 mA, 35 cm^2, 20 min) over the dlPFC (cathode left and anode right) and measured craving and relapses for alcohol use in AUD inpatients. They showed that 10 sessions of the bilateral tDCS treatment in 23 AUD patients enhanced the progressive reduction of craving scores, reaching an effect size threefold larger when compared to the initial scores and almost significantly larger effect size when compared to 22 AUD patients from the sham-tDCS group. They also showed a huge relapse rate (72.2%) in AUD patients from the sham-tDCS group, whereas 72.7% of the tDCS group were keeping abstinence in a 3-month follow-up period after intervention.

Using this same bilateral montage (cathode left and anode right) over the dlPFC, but at a lower current intensity (1 mA, 35 cm^2, 20 min), Wietschorke et al. [94] had reported in 2016 that a single session of the tDCS induced significantly increased startle amplitudes for alcohol-related cues, indicating a more negative processing of these cues in 15 AUD patients after brain stimulation, an effect not seen in 15 AUD patients from sham group, indicating that tDCS influenced the cognitive control of emotional processing in AUD patients.

Still employing the same bilateral tDCS montage over dlPFC (cathode left and anode right) and parameters (2 mA, 20 min, once a day), Biswal et al. [95] reported, in an abstract in 2018, results from functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) scanning under visual alcohol cues before and after 5 consecutive days in a small sample (total of 24) of AUD patients. They found a difference in relapse to the use of alcohol (80% of sham-tDCS vs. 33.3% in real tDCS) during 1-month follow-up period. They also found significant activation (post-pre) in bilateral dlPFC (left > right) in the real tDCS group [95].

Also reported as preliminary results in an abstract, Camchong et al. [96] showed in 2019 an increased functional connectivity between dlPFC and NAcc in six AUD patients after 10 cognitive training sessions combined with active-tDCS (anode over the left dlPFC), which was not seen in five AUD patients from a control group with sham-tDCS. Additionally, three of five AUD patients from sham-tDCS group relapsed and none of the six AUD patients

from real tDCS group relapsed to the alcohol use 1-month after magnetic resonance imaging (MRI) scan.

Interestingly, all studies investigating the effects of tDCS in AUD have aimed the dlPFC as the target brain region. Those studies that placed the anode over the left dlPFC, both with unilateral, having the cathode over contralateral supraorbital or supradeltoid regions, or bilateral, having the cathode over the right dlPFC, montages, with both single and with repetitive (three or four) sessions showed mild reduction on craving in heavy drinkers and AUD and tendency to reduce, but also a suggestive increased, in relapse rates in AUD. However, stronger evidence of relapse rates and craving scores reduction was seen with multiple sessions (5–10 sessions) with the bilateral tDCS montage having anode placed over the right dlPFC and cathode over the left dlPFC.

Thus, although tDCS has been shown to be favoring helping to control craving and relapses to the alcohol use, evidence is still limited to trials with small sample sizes and only few of them really aimed to investigate the potential effects of its repetitive application on the top of the regular biopsychosocial and pharmacological treatment of AUD. Therefore, the clinical indication for AUD treatment needs this favorable evidence to be confirmed in studies with much larger sample sizes and in variable AUD population.

27.2.2 Tobacco Use Disorder (TUD)

From the beginning of its use to the present day, tobacco has been consumed in several ways. When burned as a cigarette, pipe, cigar, and hookah or chewed and/or smelled in preparations that allow it to be absorbed by the oral and nasal mucosa, they share the nicotine release to the central nervous system [97].

Nicotine is mainly responsible for tolerance and dependence induced by tobacco use. Each cigarette has 800 mg of tobacco per unit, 9–17 mg of nicotine that is absorbed by the lung and in smaller quantities through the smoker's mouth and nasopharynx [98].

According to the Pan American Health Organization [99], the tobacco epidemic is responsible for the death of more than 8 million people a year, being one of the greatest threats to public health in the world. In addition, nonsmokers exposed to secondhand smoke account for 1.2 million deaths each year [99].

Adult smokers worldwide account for a total of 1.1 billion people, of which 367 million demonstrate a desire to quit. To this end, the WHO in its seventh report on the global tobacco epidemic [100] states that it is essential to help the user by offering a program that can meet this demand, offering access to the WHO-recommended cessation service since 2007.

The use of tDCS related to TUD has been done with multiple research purposes. The evolution of this research topic can be seen in reviews published by Lupi et al. in 2017 [101], Lapenta et al. in 2018 [102], and Kang et al. in 2019 [103].

Most studies had approached not only smoking intake and/or craving modulation by the tDCS, but also motivation to quit smoking; the resistance to smoke, attention bias, decision making, and cognitive processes have also been investigated. Studies aiming to investigate the nicotine effects on tDCS plasticity are briefly reported.

In 2013, Xu et al. [104] examined the modulation of craving, mood, and attention after an overnight abstinence, applying a single session of anodal tDCS (2 mA, 35 cm^2, 20 min) over the left dlPFC with cathode over the contralateral supraorbital area in 24 smokers. According to the Urge to Smoke Scale (UTS), used as a parameter for craving measurement, this tDCS montage had no significant effect on craving.

In 2014, Fecteau et al. [105] designed a study examining tDCS-induced changes on smoking intake and craving (Questionnaire of Smoking Urges using a cue-provoked paradigm) in TUD, but it was more focused on decision-making (ultimate game) and risk-taking behavior rewarded with not real money or cigarettes after brain stimulation. All the 12 subjects from this study received one real tDCS (2 mA, 35 cm^2, 30 min) and one sham-tDCS session in a counterbalanced order over the dlPFC (anode right and cathode left). They found a significant reduction of the

reported number of cigarettes smoked after active tDCS, even extending for 4 days after stimulation, but not after sham stimulation. Regarding craving, only the subscale *desire to smoke* from the Questionnaire of Smoking Urge was significantly reduced after real tDCS. They observed that some processes of reward-sensitive decision-making behaviors were modulated after tDCS in smokers, but no changes on risk-taking behavior was found [105].

Meng et al. [106] reported in 2014 the effects of inhibiting stimulation through cathodal tDCS (1 mA, diameter of 6.5 cm, 20 min) over the left frontoparietal-temporal association area (FPT, between T3, F3, C3, and F7) on attention bias to smoking-related cues and smoking behavior in subjects with TUD. They found that a single session of the bilateral cathodal stimulation of the left FPT area reduced the daily cigarette consumption in 10 subjects when compared to 10 subjects from sham-tDCS or 10 subjects from single cathodal tDCS, and attenuated, but at a nonsignificant level, the smoking cue-related attention.

In 2016, Falcone et al. [107] hypothesized that tDCS could increase the ability to resist smoking. In a within-subject, double-blind, randomized, and counterbalanced study in 25 smokers (at least 10 cigarettes per day for the past year), they investigated the effects of a single anodal tDCS session (1 mA, 25 cm^2, 20 min) over the left dlPFC (F3) with cathode over the right supraorbital area compared to sham stimulation conducted in the same subjects at least 2 weeks apart. The study outcomes proved that the active stimulation group consumed less cigarettes during the session and had also an increase in the latency to smoke the first cigarette.

In a study correlating craving modulation and heart rate variability during cue reactivity tasks, reported by Kroczek et al. [108] in 2016, also examined the connectivity between dlPFC and the orbitofrontal cortex (OFC) after tDCS in TUD. A single session of the anodal tDCS (2 mA, 35 cm^2, 15 min) over the left dlPFC with cathode over the orbitofrontal cortex in 13 subjects had not altered craving or heart rate variability during cue exposure when compared to 12 subjects from placebo group. However, they observed, through functional near-infrared spectroscopy, an increased functional connectivity between the dlPFC and the OFC produced by the tDCS in real stimulated smokers during smoking cue exposure [108].

One year later, in 2017, Yang et al. [109] showed, in a single-blind, sham-controlled within-subject study in 40 TUD patients, that a single session of bilateral tDCS (1 mA, 30 min) over the dlPFC (anode [35 cm^2] left and cathode [100 cm^2] right) significantly reduced craving (VAS). Through fMRI acquired simultaneously to the tDCS application, they showed that local smoking cue-elicited activation of the left dlPFC was altered by the tDCS, and that changes in craving scores was correlated with the coupling between the left dlPFC and the right parahippocampal gyrus.

In 2019, still investigating the effects of a single tDCS application, Fischell et al. [110] conducted a complex randomized, sham-controlled, double-blind, exploratory crossover study in 15 smokers and 28 matched nonsmokers to investigate the effects of the tDCS (2 mA, 25 min) applied to the dlPFC (anode left) and vmPFC (cathode right) on cognitive circuits implicated in the nicotine withdrawal syndrome. They found that tDCS promoted a deactivation of the default-mode network nodes during a working memory task and strengthened the anterior cingulate cortex activity (salience network) during an error monitoring task. In particular, the default-mode network suppression was more prominent when patients were sated compared to when they were in abstinence. They suggested that the cognitive circuit dysregulation (i.e., reduced suppression of default-mode network nodes) associated with nicotine withdrawal could be modified by tDCS.

In 2018, a parallel, double-blind, randomized controlled trial conducted by Brangioni et al. [111] investigated the effects of five sessions (once a day for 5 consecutive days) of anodal tDCS (1 mA, 35 cm^2, 20 min) over the left dlPFC with cathode over the right contralateral supraorbital region in 36 active smokers (at least 10 cigarettes per day) for at least 1 year. They found that

tDCS was associated with a significant reduction of cigarettes smoked per day and with the motivation to quit. They suggested that repetitive prefrontal tDCS coupled with high motivation reduce cigarette consumption up to 4 weeks postintervention.

Still in 2018, Mondino et al. [112] reported the effects of multiple tDCS sessions on smoking, craving, and brain reactivity to smoking cues in a double-blind, parallel-arms study in subjects with TUD. In this study, 29 smokers wishing to quit smoking were assigned to receive 10 sessions in 5 consecutive days (two sessions per day with 2-h interval in between) of anodal tDCS (2 mA, 20 min) applied over the right dlPFC (midway between F4 and Fp2, 35 cm^2) with a large cathode (100 cm^2) over the left occipital region (midway between O1 and T5) or sham-tDCS. They found a significant reduction of smoking craving (5-item Likert-type scale questionnaire of smoking urge) and increased brain reactivity to smoking cues within the right posterior cingulate (simultaneous fMRI) when compared to the control group, but they failed to find a between-group difference regarding the self-reported number of cigarettes smoked.

More recently, a study published in 2019 regarding tDCS-induced craving modulation in TUD was conducted by Hajloo et al. [113]. They had aimed to determine the effects of repetitive bilateral tDCS (2 mA, 20 min, electrode size not mentioned, 10 sessions, 2 times a week, with 72 h interval in between, over 5 weeks) of dlPFC (anode left and cathode right) on reduction of craving in 20 daily smokers (those who smoke within 1 h of waking up and smoke more than 10 cigarettes a day) and 20 social smokers (those smoking at intermittent times and no more than 20 cigarettes per week) randomly assigned into active and sham groups (10 subjects in each group). The active tDCS groups, from both daily and social smokers, presented greater reduction on craving (Desires for Drug Questionnaire Scale) when compared to their respective sham-tDCS, an effect that was maintained at least up to 1 month of follow-up. Therefore, they showed that multiple sessions of bilateral tDCS over the dlPFC reduced the nicotine craving not only in subjects with TUD, but also in social smokers, lasting for at least 1 month.

Finally, still in 2019, Behnam et al. [114] compared the effects of 20 sessions of the bilateral tDCS (2 mA, 20 min) over dlPFC (anode left, 35 cm^2; cathode right, 100 cm^2) for 4 weeks (five sessions per week) or 12 weeks (five sessions per week for 2 weeks, followed by one session per week), and respective sham groups, with standard bupropion (300 mg for 8 weeks) for the treatment of TUD in a large, randomized, sham-controlled trial starting with 210 subjects from which 170 completed the study. They found that the longer duration tDCS protocol (20 sessions over 12 weeks) done in 35 subjects resulted in the highest abstinence rate (measured by salivary cotinine) at 6 months follow-up and was significantly more effective than the short stimulation protocol (20 sessions over 4 weeks) realized in 35 subjects and both sham controls (33 and 32 subjects in each), but similar to bupropion treatment (35 subjects) in this outcome. However, the nicotine dependence measured by Fagerstrom test was lower in this group of longer tDCS treatment when compared to bupropion treatment. Authors concluded that 12-week tDCS was effective on smoking cessation and nicotine dependence and could substitute bupropion treatment.

Effects of nicotine over neuroplasticity induced by tDCS have been measured using motor-evoked potential (MEP). For this purpose usually the anode or cathode (35 cm^2) is placed over the motor cortex with reference electrode placed over the right supraorbital. Grundey et al. [115], in a study published in 2012, found that under nicotine withdrawal, facilitatory plasticity (measured by motor-evoked potentials elicited by a single-pulse transcranial magnetic stimulation) induced by anodal tDCS and paired associative stimulation procedures is absent in smokers, a compromise that has been reestablished with the nicotine exposition. According to these authors, the activity of the nicotinergic system might affect the efficacy of plasticity-inducing procedures and needs to be taken in consideration when studying the tDCS effects in TUD. Curiously, in a following study published by Lugon et al. in 2015 [116], they showed that in nonsmokers the nicotine abolishes

the anodal tDCS-induced facilitatory plasticity, which had been dose-dependently reestablished by NMDA-receptor blockage and subsequent reduction of calcium influx, indicating the existence of an interaction between nicotinergic receptors activation and glutamatergic plasticity.

In summary, there are a number of studies aiming to explore the effects of tDCS in TUD, but most of them investigated the effects of a single session of the tDCS on diverse clinical and cognitive measurements, with different tDCS montages and with small sample sizes. There are few studies investigating the effects of multiple sessions of the tDCS. Even with these limiting aspects, there are reasonable evidence that tDCS applied over the dlPFC with anode over the left side or bilaterally, with anode over the left and cathode over the right dlPFC, but also when the anode was placed over the right dlPFC, especially when applied in multiple sessions (5, 10, or 20), reduced craving or reduced smoke consumption, or favored smoking cessation and nicotine abstinence. However, more defined tDCS montage and parameters are required to reach an indication for its clinical use in the treatment of TUD.

27.2.3 Opioid Use Disorder (OUD)

Opioids are compounds derived from the opium poppy, used by the humankind for centuries. These substances are mentioned even in illustrious literature works such as The Odyssey and the consensus about its discovery is that it would have been made by the Sumerians at the end of the third millennium B C [117]. In the modern world, medicine uses opioids in pain management mostly.

Unfortunately, the biggest production worldwide of these substances is directed to the illegal consumption of opioids and its synthetics derivatives [7]. In 2017, the number of overdoses leading to death due to opioid consumption was 66% of the global total of deaths due to drug abuse. The same data also stated that the prevalence of usage around the world is increasing according to each region's profile [7]. The areas with higher prevalence are North America (use of fentanyl and its analogs), Europe (use of heroin), and Asia and Africa (use of tramadol) [7].

The burden caused by the opioid use disorder is significant because according to a study made by the Global Burden Disease (GBD) in 2017, 78% of the "healthy" years of life lost worldwide due to drug consumption refer to opioid usage [118]. When analyzing these "healthy" years lost, the Disability Adjusted Life years (DALYs) parameter shows that opioids do not cause so many premature deaths itself when compared to the life impairment rates [7, 118].

This substance class can be divided between opiates (e.g., morphine, heroin, and opium) and synthetics (e.g., fentanyl and its analogs). Among this division there is also the pharmaceutical opioids that includes substances from both previous groups (e.g., codeine, hydrocodone, oxycodone, tramadol, methadone, and fentanyl) and are commercialized for pain management under medical prescription [7]. It is important to mention that from 2008 up to 2010 the consumption of prescription controlled opioids more than doubled, according to the International Narcotic Control Board report [7].

If the abuse pattern of opioids is compared through decades, it is possible to see that the majority of patients enrolled in opioids abuse treatment programs shifted from heroin being the first drug of abuse used to that being pharmaceutical opioids [119]. This raises the question: how is the process of developing the opioid substance abuse disorder due to the use of prescribed medication? Studies show that patients start using pharmaceutical opioids due to pain causing conditions, being that chronic or acute, and if the usage is extended for more than 90 days, the patient is more prone to become a chronic opioid user [120].

The alarming increase of opioid usage has boosted the initial studies with tDCS, which was focused on preventing or reducing opioid use in pain conditions. Boggio et al. [121] showed in 2008 that, in 20 healthy volunteers, anodal tDCS over the primary motor cortex (M1) can increase perception of pain and pain threshold, while anodal tDCS over the dlPFC increases the pain threshold. These findings proved that M1 could

be modulated by tDCS, which could be a way to decrease the abnormal activity of the thalamus that occurs in chronic pain states, due to its reciprocal connection and pathway.

Still related to pain relief, tDCS studies were conducted in acute pain conditions, such as postoperative periods. When evaluating the amount of opioid usage after a tDCS session immediately after a surgery (total knee arthroplasty) compared to patients in the sham group, Borckardt et al. in 2013 [122] and in 2017 [123] showed in 40 and 58 subjects, respectively, that anodal stimulation of the dlPFC (with cathode over the right somatosensory cortex), but not the M1 stimulation, had the biggest potential to reduce the need of opioids use in this situation. Meanwhile, Khedr et al. [124] showed in 50 patients, also in 2017, that anodal tDCS applied over M1 for 4 consecutive days reduced the opioid consumption after arthroplasty, suggesting that tDCS is indeed a promising tool to help reduce the opioid use in postoperatives.

Irrespective of the brain region where the tDCS is applied, the principle and importance of these findings regarding SUD is that the less people starting the use of opioids, less people will be prone to become chronic users and potential opioid dependents.

At the moment, there are limited reported studies that aimed at treating the OUD itself with the employment of the tDCS. That was the proposal of Wang et al. in 2016 [125], hypothesizing that a single session of the stimulation over the frontal parietal temporal (FPT) area (1.5 mA, 35 cm^2, cathodal over bilateral FPT, anode on the occipital lobe, for 20 min) would reduce cue-induced craving scores in these patients. Although having interesting results in the 20 patients evaluated, more robust studies are necessary to reach a consensus about this hypothesis and, as mentioned by Gallucci et al. in a systematic review published in 2019 [126], this study had some design limitations in its execution, so it should be used as a reference for future studies and not as a final information.

Additional studies focusing on reducing craving scores in OUD are those reported as an abstract by Garg et al. in 2019 [127] with 20 patients, showing that anodal stimulation over the left dlPFC with cathode placed contralaterally (2 mA for 20 min, 2 sessions per day with at least 3-h interval, 20 sessions over 2 weeks) produced a greater craving (VAS) reduction (with the standardized mean difference effect size of 0.430), but at nonsignificant extent when compared to a group of subjects with regular treatment only (not a sham control).

Sharifi-Fardshad et al. reported in 2018 [128] a study comparing the dlPFC stimulation using anodal right with cathodal left montage versus anodal left with cathodal right montage in single sessions of tDCS (2 mA, 35 cm^2, 20 min) comparing to sham stimulation, separated with a time interval of 72 h, in drug cravings measured by Drug Desire Questionnaire in former crystalline heroin users enrolled in methadone maintenance treatment (MMT) programs in a double-blind, randomized, sham-controlled crossover study with pre/posttest design with 40 subjects. They found that applying anode right with cathode left tDCS on dlPFC significantly decreased craving among former crystalline heroin users in comparison to sham stimulation. Interestingly, the inverse tDCS montage on dlPFC, cathode right with anode left, was ineffective to reduce drug craving in this population.

Using the anodal right with cathodal left tDCS (1.5 mA, 25 cm^2, 20 min) on dlPFC Martinotti et al. [129] conducted a study published in 2019 with mixed substance use disorders, including cocaine, alcohol, heroine, cannabis use disorder, and also gambling disorder, to evaluate the efficacy of the tDCS for the short-term treatment of craving. They showed that tDCS applied once a day for 5 consecutive days in 34 subjects significantly reduced craving (VAS), and reduced depression and anxiety and trait impulsivity scores when compared to sham-tDCS. Unfortunately, they could not draw any specific conclusion for each substance use disorder included in their study.

A more robust, double-blinded, sham-controlled study was reported by Taremian et al. in 2019 [130] in a specific sample of 60 OUD patients showing that 20 of them constituting the active tDCS group with MMT submitted to mul-

tiple sessions (1 session per day for 10 consecutive days) of the bilateral tDCS (2 mA, 35 cm^2, 20 min) over the dlPFC (anode right and cathode left) had significantly greater reduction in Obsessive Compulsive Drug Use Scale and in Desire for Drug Questionnaire scores after treatment when compared with other 20 subjects from sham-tDCS (with MMT) and 20 subjects treated with MMT alone. They also showed favorable results of the active tDCS in depression and anxiety symptoms in these patients. Thus, they suggest that although methadone itself can be effective in reducing opiate craving, integration of the tDCS technique can lead to a more significant decrease in opium craving as well as depression and anxiety manifestations.

So far, these studies had shown favorable effects of the dlPFC (anode right and cathode left) tDCS on craving scores measured by a subjective scale (VAS) or more robust scales such as Desire for Drug Questionnaire or Obsessive Compulsive Drug Use Scale, but relapses to the drug use were not measured. A recent study published in 2020 by Bimorgh et al. [131] showed that 14 OUD patients under MMT receiving seven sessions of the tDCS (2 mA, 35 cm^2, 20 min) over the dlPFC (anode right and cathode left) showed relapse rate at similar extent to the sham group with 13 subjects. It must be noted that relapses were rated only during the treatment and subjects were not followed up for this outcome after treatment. However, they observed that depression, anxiety, and stress were significantly reduced after the seventh session of the tDCS. Authors suggested that tDCS could be an effective technique to relieve mental disorders among OUD receiving MMT. Indeed, the management of comorbid states may favor the SUD treatment.

Thus, up to now, there has been evidence for favorable effects of the tDCS applied over the dlPFC (anode right and cathode left) on craving, but not on relapse rate, to the opioid use in OUD on the top of MMT. This evidence resembles those mentioned for AUD, but also similarly, they were based on studies with small sample sizes, and also require to be confirmed in larger samples.

27.2.4 Stimulant Use Disorder

Cocaine Use Disorder (CUD)

According to the UNODC report, it was estimated that, in 2017, 18 million people worldwide – accounting for 0.4% of the global population aged between 15 and 64 years – reported having consumed cocaine in the previous year [7]. The astonishing prevalence of global cocaine use becomes even more impressive when we look at a more regional level, to account for the unequal predominance of drugs among different geographic regions: in the United States, in a 2017 survey, 5.9 million people (2.2% of the population aged 12 or older) had consumed cocaine in the previous year [7].

The substance derived from the leaves of the *Erythroxylum coca* plant blocks the reuptake of catecholamines and serotonin, causing numerous central nervous system and cardiovascular effects and, of foremost importance for this discussion, leading to addiction [132]. Cocaine is most consumed in two different presentations: a hydrochloride salt (known as "coke"), which can be snorted or diluted and injected, and a free base (known as "crack"), usually smoked. These two presentations allow cocaine to cross social barriers: while the "coke" use takes place among socially integrated individuals, particularly in recreational and nightlife settings; "crack" use is more common among socially marginalized persons, due to its lower cost [7, 132].

Following a growth in publications examining the effects of tES in other SUDs, the first exploratory studies presenting experimental evidence of its effects in CUD patients were published in 2014. Gorini et al. [133] examined the influence of bilateral dlPFC tDCS (1.5 mA, 32 cm^2, 20 min) in two tasks measuring risk-taking behavior, comparing 18 cocaine users to 18 nonaddicted controls, receiving three different interventions:

anode left and cathode right, anode right and cathode left, and a sham stimulation. The results demonstrated a reduction of risky behavior associated with the real interventions in both cocaine addicts and controls. However, in the more complex of the two tasks, only the anodal right tDCS stimulation led to a safer behavior. This study suggested that a dysfunction in neural networks comprising the dlPFC could be related to risk propensity in cocaine addicts and, moreover, that tDCS could lead to changes in such behavior.

In the same year, two studies published in 2014 by Conti et al. [67, 134] provided further evidence for the effects of tDCS in the neurophysiological processes underlying cocaine addiction. These studies evaluated the effects of bilateral dlPFC (anode right and cathode left) tDCS (2 mA, 35 cm^2, 20 min) in drug-cued ERPs components of crack cocaine addicts, using low-resolution brain electromagnetic tomography (LORETA) to estimate the three-dimensional current density distribution of these components. In the first study, evaluating 13 subjects, they demonstrated a decrease in the anterior cingulate cortex activity during the N200 component after a single session of the bilateral tDCS stimulation over the dlPFC, whereas an increase was observed after the sham stimulation [67]. The second study examined the effects of single and repetitive (five sessions, once a day every other day) bilateral dlPFC (anode right and cathode left) tDCS in the P300 component of 13 CUD patients. It was demonstrated that while a single session would decrease crack-related response in the left dlPFC, repetitive sessions would increase crack-related response in numerous prefrontal areas, further supporting that bilateral dlPFC tDCS could modulate prefrontal activity in crack cocaine addicts [134].

More compelling evidence was published in 2015 by Batista et al. [135], who performed a randomized, double-blind, and sham-controlled clinical trial evaluating the effects of five sessions (once a day every other day) of bilateral dlPFC (anode right and cathode left) tDCS (2 mA, 35 cm^2, 20 min) in 36 crack cocaine addicts. This study demonstrated a reduction in measured craving scores (brief scale with 5-item from Obsessive Compulsive Cocaine Use Scale – 5-item OCCS) in the 17 subjects from active tDCS group but not in 19 subjects from sham-tDCS group, providing evidence that a tES could impact on a clinical measurement of cocaine addicts. In this study, there were also significant changes in other measurements. Individual's overall perception of quality of life and health (WHOQOL-BREF) improved in crack cocaine users treated with tDCS after the end of the treatment and, specifically, the self-esteem of crack cocaine users from the real tDCS group improved in the psychological domain. They further showed that the decrease of depressive and anxiety scores, although mild, was significant in the real tDCS group [135].

Electrophysiologically, Moscon et al. [136] reported in 2016, in a study conduct on nine CUD patients and nine non-CUD controls, that crack cocaine users are more likely to show higher brain activity, notably in the frontal lobe region, when processing crack-related images, as compared to a nonuser health control group. In other study, also published in 2016 by Conti et al. [137], subsequently, showed that a single session of the bilateral dlPFC (anode right and cathode left) tDCS (2 mA, 35 cm^2, 20 min) was able to prevent the increasing activity in the dlPFC during the drug-cued P300 ERP component of 10 CUD patients, a phenomena observed to occur in the early days of abstinence.

Additional evidence was also presented in 2016 by Nakamura-Palacios et al. [138], who reported that five sessions of bilateral dlPFC (anode right and cathode left) tDCS (2 mA, 35 cm^2, 20 min) on nine CUD patients resulted in cue-reactivity changes in a discrete brain region, the ventromedial prefrontal cortex (vmPFC), during the drug-cued P300 ERP component of those patients that were able to keep abstinence during and after treatment. Furthermore, the authors demonstrated, by means of diffuse ten-

sor imaging, an increased connectivity between this region and the NAcc when comparing crack cocaine addicts that received active tDCS to those that received the sham intervention. The authors suggested that these changes in the vmPFC could underlie a reduction in craving, thus facilitating self-control to drug abuse.

A more recent clinical trial with the same montage (anode right and cathode left) examining the effects of the bilateral dlPFC tDCS (2 mA, 35 cm^2, 20 min) on 35 CUD subjects was published in 2018 by Klauss et al. [139], and this time evaluating the effects of 10 sessions (once a day every other day) and measuring not only craving (5-item OCCS), but also relapse rates at least for 30 days after hospital discharge as outcomes. The study showed that craving scores were progressively reduced in both groups over the treatment and there were no statistically significant differences between 19 subjects submitted to tDCS and 14 subjects submitted to the sham procedure. In addition, both groups showed high relapse rates in a similar manner. However, it must be noticed that differences in the sample characteristics might have influenced these results, divergent from those of Batista et al. [135], given a more severe addiction profile of these participants and the absence of any pharmacological maintenance treatment for psychiatric comorbidities because of the specific type of treatment applied in the public hospital from where these CUD patients were recruited.

There is an ongoing study with CUD inpatients that has been conducted in a rehabilitation facility (Psychiatry and Neuroscience Department, Icahn School of Medicine at Mount Sinai, NY) with the same montage (anode right and cathode left) over dlPFC of Batista et al. [135] and Klauss et al. [139], but extending tDCS (2 mA, 35 cm^2, 20 min) application to 15 sessions (once a day every other day). Their preliminary results, still in a very small sample, have shown no between-groups differences in changes on craving scores, but real-tDCS has presented less sleepiness, suggesting increased vigilance, and readiness to change after treatment when compared to sham-tDCS group [140]. According to the authors of this study, these results reinforce the hypothesis that real-tDCS over the dlPFC facilitates cognitive functions, which could reflect more flexibility to learn alternative strategies.

In summary, tDCS applied bilaterally over the dlPFC (anode right and cathode left) showed to reduce the risk-taking behavior and craving in CUD when applied repetitively (five sessions), but failed to replicate these favorable effects in a more severe and nonpharmacologically treated CUD patients, even with 10 sessions of the tDCS. Although there is evidence for changes promoted by tDCS in prefrontal cortex networks of cocaine addicts, further studies are needed in order to ascertain the optimal configurations and the clinical effects of this intervention.

Methamphetamine Use Disorder (MUD)

In 2017, the prevalence of past-year use of methamphetamine in the United States was estimated in 1.6 million people (0.6% of the population aged 12 years and older). In Europe, the estimates reach the mark of 2.9 million people (0.5% of the population aged between 15 and 64 years) [7]. This synthetic drug is thought to act primarily as a synaptic releaser of catecholamines and serotonin, although its mechanisms are now recognized to deleteriously comprise numerous pathways [141].

Studies examining the effects of tES in MUD are scarce. Shahbabaie et al. [142] conducted a study published in 2014 in which a single session of anodal tDCS (2 mA, 35 cm^2, 20 min) over the right dlPFC (cathode over the contralateral supraorbital area) was shown to reduce immediate self-assessed craving (VAS) in 32 MUD patients after the stimulation, when the patients were at rest, while increasing craving scores when the patients were submitted to drug-related cues during the stimulation. The authors suggest that this transient increase could be a result of an increased processing of drug cue saliency under anodal stimulation.

In 2018, Shahbabaie et al. [143] further demonstrated that tDCS modified functional connectivity of large-scale brain networks in 15 abstinent methamphetamine users. They showed that a single session of tDCS (2 mA, 35 cm^2, 20 min) over the dlPFC (anode right and cathode left) reduced

subjective immediate methamphetamine craving scores compared to sham stimulation and significantly modulated the default mode, executive control, and salience network. Additionally they observed that the modified activation of these three networks was correlated to the subjective craving scores.

Another study published by Shabbabaie et al. in 2018 [144] examined the effects of different tDCS (2 mA, 35 cm^2, double 13 min with 20-min interval in between) electrode montages targeting the right or left dlPFC (anode right with cathode over the left shoulder or left supraorbital ridge, anode left with cathode over the right shoulder, right supraorbital ridge or contralateral dlPFC) applied in a single session in a task designed to measure attentional bias of MUD patients. They showed that anodal stimulation over the left dlPFC (both with right shoulder and right dlPFC montages) decreased the engagement bias toward drug cues in 32 abstinent methamphetamine users compared to 16 subjects submitted to sham stimulation, suggesting that tDCS could be a rehabilitation tool for attentional bias modification [144].

More comprehensive evidence was published in 2020 by Alizadehgoradel et al. [145] who examined, in a double-blind, randomized, parallel group study, the effects of 10 sessions of tDCS (2 mA, 35 cm^2, 20 min) over bilateral dlPFC (anode left and cathode right), spaced over the course of 5 weeks (two sessions weekly with 72 h interval in between), on executive function tasks (N-back, go/no-go, Wisconsin Card Sorting Task, and Balloon Analogue Risk Task) and craving (measured with Desires for Drug Questionnaire) immediately after and 1 month following the treatment in 19 MUD patients and of 20 other MUD patients undergoing sham treatment. They demonstrated significant improvements of cognitive control functions involved in addictive behavior, including working memory, response inhibition, cognitive control/flexibility, and risk-taking behavior, all effects that were associated with significantly reduced craving in the real tDCS group. These improvements on executive performance and reduction of craving scores lasted for up to at least 1 month following the intervention.

In summary, evidence points toward promising beneficial effects of the anodal tDCS over the left dlPFC, probably combined with the contralateral cathode placement, on attentional bias and executive dysfunction, which may be associated with craving reduction in MUD. Although very important, most of these studies were focused on the effects of a single session on changes in functional connectivity of brain networks, attentional bias, and executive function and only one recent study was aimed to study the effects of multiple tDCS sessions not only on diverse executive functions, but also on craving, showing favorable effects of the bilateral dlPFC tDCS. Therefore, further studies are required to ascertain the optimal configuration and to incorporate more evidence of its effects on this SUD.

27.2.5 Other Substance Use Disorders

Marijuana refers to the dried leaves, flowers, stems, and seeds from the hemp plant, *Cannabis sativa*. The plant contains the mind-altering chemical delta-9-tetrahydrocannabinol (THC) and other related compounds [146]. Cannabis continues to be the most widely used drug worldwide. It is estimated that roughly 3.8% of the global population aged 15–64 years used cannabis at least once in 2017, the equivalent of some 188 million people [7]. The average global prevalence of cannabis use increased over the period 1998–2007 from 3.4% to 3.9% before remaining basically stable during the subsequent decade. However, the overall number of annual cannabis users is estimated to have increased by roughly 30% during the period 1998–2017 [7].

Although cannabis use is widespread around the world, there is only one study published in 2010 by Boggio et al. [147] that investigated the effects of tDCS in cannabis use disorder. These authors investigated the effect of a single session of tDCS (2 mA, 35 cm^2, 10 min) on risk taking and craving in chronic marijuana users. Eight chronic marijuana users demonstrated more conservative (i.e., less risky) decision making during sham stimulation. While right anodal

stimulation of the dlPFC (cathode over the left dlPFC) enhanced conservative decision making in 12 healthy volunteers, both right anodal (cathode over the left dlPFC) and left anodal (cathode over the right dlPFC) dlPFC stimulation increased the propensity for risk taking in nine and eight marijuana users, respectively. These findings reveal alterations in the decision-making neural networks among chronic marijuana users. The authors also reported that the bilateral tDCS over dlPFC (anode right and cathode left) was associated with reductions in marijuana cravings [147].

As already mentioned in the OUD section earlier, in 2019 Martinotti et al. [129] showed that bilateral tDCS (1.5 mA, 25 cm^2, 20 min) applied once a day for 5 consecutive days over dlPFC (anode right and cathode left) in individuals with different substance use disorders, including cannabis use disorder, reduced craving (VAS), depression, anxiety, and impulsiveness scores compared to sham group. An important limitation of this study, as also mentioned earlier, was the impossibility to draw conclusions about specific drugs.

Benzodiazepine misuse is a growing public health problem, with increases in benzodiazepine-related overdose deaths and emergency room visits in recent years. However, relatively little attention has been paid to this emergent problem. A recent systematic review showed that, in 2017, benzodiazepines and other tranquilizers were the third most misused prescription drug in the United States (approximately 2.2% of the population). Worldwide rates of misuse appear to be similar to those reported in the United States [148].

Unfortunately, although benzodiazepines and tranquilizers misuse seem to be an important public health problem, no studies have been conducted to investigate the effects of tDCS on these specific drug use disorders.

Finally, there are also no studies addressing the effects of tDCS on hallucinogen use disorder so far.

Studies aiming to investigate the effects of tDCS to help the clinical, cognitive, and behavioral management of other SUDs, including cannabis, benzodiazepines, and other sedatives and hypnotics, need to be developed.

27.3 vmPFC and Drug Addiction

Drug addiction has been associated with biases in cognitive processing with increasing cue reactivity to substance-related stimuli [149], in a way that these stimuli would be perceived as particularly salient and reinforcing, and attention would be preferentially allocated to them (see Littel et al. [149]).

Attentional processing of substance-related stimuli is consistently associated with late positive potentials (LPPs) when examining ERPs components under the drug cue reactivity paradigm. These LPPs components include the P3 (or P300), emerging between 300 and 800 ms after stimulus presentation, and sustained positive potentials, namely slow potential (SP), emerging above 800 ms (see Littel et al. [149]).

The P300, typically maximal at medial central and parietal electrodes sites, is suggestively a transient component and has been related to mental processes directing attentional resources to task-relevant stimuli, whereas the SP, in which activity shifts from parietal to more frontocentral sites, seems to be sustained for several seconds after the presentation of motivationally relevant stimuli, appearing to be related to memory encoding and storage (see Littel et al. [149] and Franken et al. [150]).

In general, substance users, irrespectively of the substance, show enhanced electrophysiological processing of substance-related stimuli when compared to neutral stimuli, in both P300 and SP time frame of the ERPs [149]. The increased late ERP reactivity has been related to an enhanced cognitive processing of substance cues or "processing bias," which would be consistent with results from behavioral studies demonstrating attentional bias for substance-related material [149]. In this case, substance-related stimuli become especially salient and receive more attention than other cues [22], that is, substance users

would allocate attention and memory resources to stimuli related to their motivational states toward drug use.

When analyzing drug-related brain activation, Nakamura-Palacios et al. [138] reported in 2016 that the region referred as vmPFC had the biggest change in the P300 cue reactivity in AUD and CUD patients after bilateral dlPFC (anode right and cathode left) repetitive (five sessions) tDCS (2 mA, 35 cm^2, 13:20:13 min schedule in AUD and 20 min in CUD) when current source densities (CSD) were extracted from ERPs data using the low-resolution electromagnetic tomography (LORETA) analysis (Fig. 27.4).

The designation of vmPFC does not refer to a specific or defined brain structure, instead, it refers to a large brain region centered at the ventral and medial surfaces of the prefrontal lobe [151, 152], which can also be considered the jointing of the medial and lateral orbitofrontal cortex [153], and can be named as anterior medial orbitofrontal cortex or subgenual cingulate cortex in human functional imaging studies [154].

Lesion and imaging studies have collected evidence indicating this prefrontal region as of a crucial role in a multitude of complex psychological functions underlying adaptive human behavior such as value-based decision making, emotion-related psychophysiology, and social cognition [152].

Individuals with significant losses of vmPFC have difficulties in generating viable options in making assertive decisions in the face of social dilemmas and tasks that involve reward. In tasks that involve decision making in conditions of uncertainty, related to the consequences,

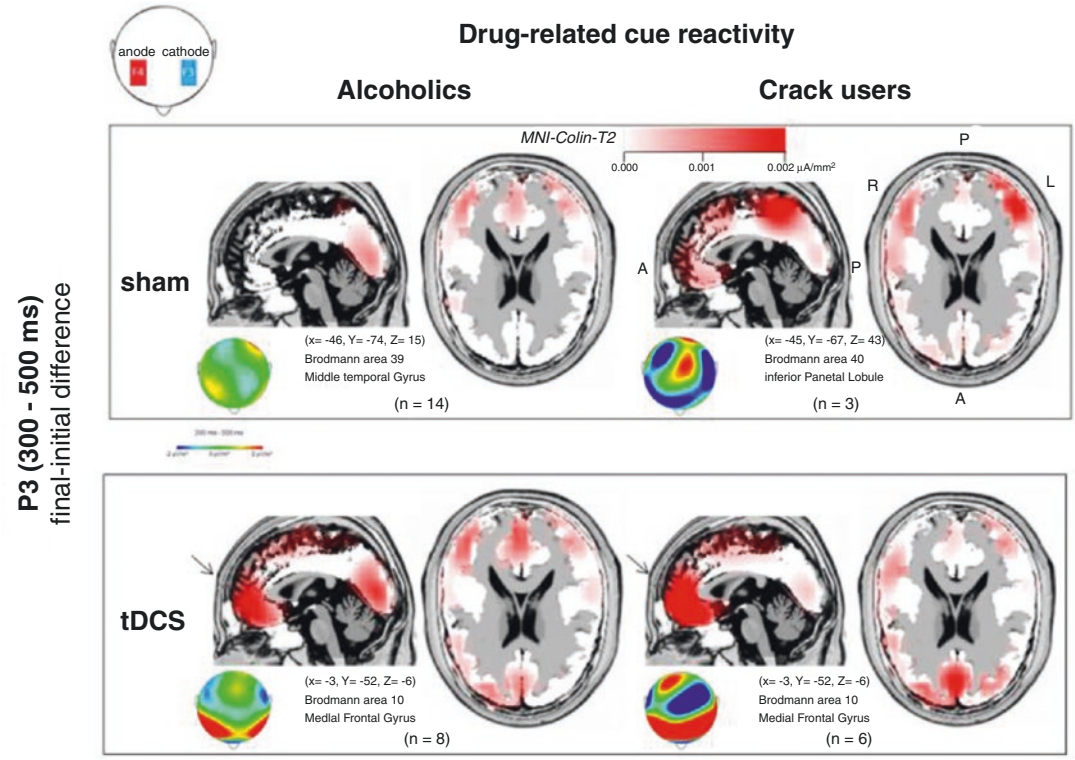

Fig. 27.4 LORETA analysis considering the differences of current densities (mA/mm^2) in the P3 segment (300–500 ms) in AUD and CUD patients after bilateral dlPFC tDCS compared to sham-tDCS. Coordinates and brain area depicted represent the highest activated brain region. Topographical distributions of the difference (final minus initial) of the current source density (mV/m^2) over the P3 segment are also shown in small top views. Arrows are pointed to the ventral medial prefrontal cortex (vmPFC) (extracted from Nakamura-Palacios et al. [138])

patients with injuries in the vmPFC make the least indicated choices, as they have a reduced ability to anticipate future consequences after a decision, producing events that are closer chronologically [152].

Despite the intact performance on conventional measures of intelligence, subjects with vmPFC injuries exhibit deficits in decision making based on values in a wide variety of situations [154]. With this pattern of functioning, the subject is not able to predict the consequences of his or her present actions. Their responses are based on the reflections on gains and losses that such actions can generate, often opting for risky behaviors that involve much more losses than gains, with reduced feelings of regret [152].

A hypofunction of the vmPFC has been reported in drug addiction and pathological gambling as mentioned by George and Koob in 2013 [31]. In 2002, Bonson. [155], in a positron emission tomography study on neural correlates of cue-induced cocaine craving, found an unexpected deactivation in the left ventral pole and left medial PFC when cocaine abusers were exposed to cocaine-related cues, to what, in that time, they had no explanation.

About 10 years later, in 2013, Seo et al. [156], in an fMRI study, also found that alcohol-dependent patients displayed decreased activation in the vmPFC and anterior cingulate cortex (ACC) during stress and alcohol cue trials when compared to matched nonalcoholic controls. These healthy controls, in its turn, showed robust vmPFC/ACC activation under this condition, Seo et al. [156] then suggested that disrupted vmPFC/ACC function in alcoholics could represent the functional neural state that drives high alcohol craving and relapse risk in recovering alcohol-dependent patients.

Subjects with pathological gambling, which may be considered an addictive condition sharing core features with drug dependence, also show relatively diminished blood-oxygen-level-dependent (BOLD) signal change induced by gambling stimuli in the vmPFC when compared to subjects without this condition [157].

The vmPFC connects anatomically with many brain structures, which connectivity had characterized this region as "visceral motor cortex" probably because of reciprocal projections to and from the amygdala and a unilateral projection to dorso- and ventromedial striatum [158], including the NAcc. In fact, according to Peters et al. [159], the primary efferent projection from vmPFC is the NAcc shell. Ghazizadeh et al. [160] showed evidence suggesting that the vmPFC and the NAcc shell are critical elements of brain circuits relevant to suppression of inappropriate actions, probably by promoting and sustaining the extinction of unreinforced actions.

According to the Bzdok et al. [161], besides the strong connections with NAcc, the vmPFC is also connected to hippocampus, posterior cingulate cortex, and retrosplenial cortex, that is, preferentially connected with limbic and reward-related medial brain areas associated with reward-related tasks. Therefore, the vmPFC would subserve predominantly nonambiguous subjective-value-related evaluative processes involved in bottom-up driven, approach/avoidance modulation, and evaluation related processing [161].

Furthermore, the vmPFC serves to couple two systems that are crucial to the decision-making ability, one in which the dlPFC is the key as neural substrate for working memory and its executive processes, and the other system that is critical for processing emotions, having insular cortex and posterior cingulate as key structures [162]. The integrity of these systems is essential for the vmPFC to mediate efficient decision making, thus, any impairment in one of them may compromise its functionality [162]. The disrupted ability to make decisions in SUD is one of the common features seen in patients with vmPFC lesions [162], which reinforce the hypothesis of dysfunction decision making mediated by vmPFC as an important mechanism involved in drug addiction.

According to Rudorf and Hare [163], the functional interaction between dlPFC and vmPFC is a key aspect of context-dependent valuation, which has a specific application when choices between competing outcomes preferences require adequate self-control to make a decision. SUD patients exhibit poor self-control, if any, with a deficiency in the valuation of drug context as

consequence, which may be associated with the compulsive drug seeking for immediate rewarding effects, or relief of abstinence symptoms, opposing any postponed reward that the drug abstinence could provide.

In more recent years, subregion scheme of this region has distinguished a more anterior/perigenual region of the vmPFC from a more posterior/subgenual region based on emotional valence [154, 164, 165], with the anterior region associated with positive valence (e.g., reward, value) and the posterior region associated with negative valence (e.g., threat, fear) [154].

A more nuanced scheme was proposed by Roy et al. [164], with a relatively rostral and dorsal subregion (primarily anterior to genu of the corpus callosum) associated with emotion, autonomic, and reward functions, and a relatively caudal and ventral subregion (primarily inferior to the genu of the corpus callosum) associated with memory functions.

Thus, irrespectively of the scheme proposed, the anterior vmPFC seems to be associated with rewarding properties and valence attribution of stimuli, which would be drug-related stimuli in drug addiction [154].

Therefore, there is reasonable evidence that the vmPFC is highly associated with drug addiction. This brain region seems to exhibit a low reactivity to drug-cued stimuli in SUD condition, which was changed by multiple sessions of the tDCS applied over dlPFC bilaterally. However, studies with larger samples and perhaps with more focused montages to reach this brain region are required to strengthen the vmPFC hypothesis in SUDs.

27.4 Final Considerations

Taken all together, most studies investigating the potential effects of the tDCS on SUDs conducted up to this moment has targeted the dlPFC (only one study have target other brain structure such as frontoparietotemporal region), with anode or cathode placed over the right or left hemisphere, with the return electrode placed over the contralateral supraorbital, occipital, or supradeltoid region when unilateral, or over the contralateral dlPFC region when the montage was bilateral.

Regarding the polarity, the anode placed over the right dlPFC, especially with the cathode placed over the left dlPFC, and mostly when applied in multiple sessions, showed to reduce craving and relapse rates in AUD, reduced craving in OUD, but not relapse rates in this SUD, and reduced craving in CUD, when patients were maintained under pharmacotherapy, but failed in more severely crack cocaine dependents with no underneath pharmacological treatment. On the other hand, the anode placed over the left dlPFC, in unilateral or bilateral montages and with multiple sessions, showed to reduce craving and smoke consumption and favored smoking cessation and the nicotine abstinence in TUD and mildly reduced craving and attention bias in MUD. However, investigations aiming to examine the effects of the tDCS in clinical management of these last SUDs, as well as in other SUDs, such as cannabis, hallucinogens, sedatives, hypnotics, are still missing.

It should be highlighted that although substances of abuse share common features in respect of drug addiction development, the type of the substance, whether primarily inhibitory or excitatory in its underlying mechanism of action and subsequent molecular biology modifications, may determine different effects of the tDCS, considering the brain region, polarity, and many other parameters such as electrode size, position and angulation, current intensity, duration, amount of sessions, whether single or double, and consecutive or intercalated. Therefore, it might not be possible to have only one tDCS protocol applicable to all SUDs. It may be necessary to find the best set of tDCS parameters for each SUD or possibly for a class of substances, such as depressants, stimulants, and hallucinogens.

Lefaucheur et al. published in 2017 [166] an evidence-based guideline on the therapeutic use of tDCS in which the potential clinical use of tDCS was critically indicated by experts according to the classification of selected publications, following a criteria classifying studies from I to IV according to decreasing value of evidence. Briefly, Class I considered a very well-conducted

placebo-controlled clinical trial with a representative population (above 25 patients receiving active treatment), Class II a well-conducted placebo-controlled clinical trial with small samples (equal or above 10, but less than 25), Class III other controlled trials with small samples (less than 10) or with methodological limitations, and Class IV uncontrolled studies, case series, or case report (see Lefaucheur et al. for more details). Then, this classification was applied to indicate the levels of evidence A to C, in which Level A would be "definitely effective or ineffective"; Level B, "probably effective or ineffective"; Level C, "possibly effective or ineffective"; or finally, no recommendation should be considered on isolated or no evidence. Especially, for drug addiction/craving, including alcohol, drugs, and smoking, these authors classified evidence as Level B ("probably effective"), requiring one Class I or at least two convincing Class II studies, or one convincing Class II study and at least two convincing Class III studies, for bihemispheric tDCS of the dlPFC (anode right and cathode left) and no recommendation for anodal tDCS of the left dlPFC with supraorbital cathode.

It has to be noted, however, that the authors above had made a general indication for tDCS therapeutic use in drug addiction considering all studies they found in SUDs up to that time. However, with studies published after their review, SUDs should be individualized, as it was also considered by Fregni et al. [167] in a more recent evidence-based guideline, and only studies with multiple sessions (five sessions and above) should be included for therapeutic purposes. Thus, the Lefaucheur et al. classification for clinical use of tDCS over dlPFC (anode right and cathode left) as probably effective (Level B) to decrease craving or relapses should be restricted for AUD. Similar bihemispheric montage seems to decrease craving in OUD, but in only one Class II study so far, therefore, it may be classified as possibly effective (Level C). The opposite polarity, that is, the anodal tDCS over the left dlPFC, in unilateral or bilateral montage, could be considered as probably effective (Level B) to decrease smoke craving, smoke cessation, and nicotine dependence in TUD. Similar montage was found to reduce craving in MUD in one Class II study, giving a possible effective level (Level C) for this SUD. For CUD, there was one Class II study showing that tDCS over bilateral dlPFC (anode right and cathode left) reduced craving, but it has not been replicated in following studies, thus, it should not be recommended yet.

No other SUDs reached sufficient evidence to receive any classification for therapeutic indication. This may be because the vast majority of the studies mentioned here are still initial studies (pilots), still exploratory in character, with single sessions, with many limitations to be considered, mainly the size of the samples involved, which are, in general, still very small. But it is also necessary to remember that we are referring here to a complex disease whose participation of the experimental subjects requires a great team work effort given the great risk of dropouts, relapses, and its high recurrence as an inevitable characteristic of the disease due to several factors, but particularly the craving to the drug use.

Furthermore, for the potential benefits of the tDCS gain undoubtedly clinical applicability in the treatment of SUDs, the results obtained so far must be reproduced in larger and more diversified samples, such as in multicentric studies, which would require a large investment from international research community such as the new framework assembling an international collaborative group of investigators with expertise in neuromodulation and addiction research named as INTAM (international network of transcranial electrical stimulation/transcranial magnetic stimulation trials for addiction medicine) for future jointing research [62].

Finally, clinical assessment methods and surrogate measurements in clinical trials investigating the effects of the tDCS in SUDs need to be extensively improved and aligned among research centers, and the involvement of particular prefrontal cortex regions, such as the vmPFC,

in drug addiction needs to be more carefully addressed to strengthen the potential use of the noninvasive brain stimulation in SUD, and hopefully helping SUDs patients to overcome this disease.

Glossary

ACC	Anterior cingulate cortex
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AUD	Alcohol use disorder
AUDIT	Alcohol use disorder identification questionnaire
BDNF	Brain-derived neurotrophic factor
BOLD	Blood-oxygen-level-dependent
CBM	Cognitive bias modification
CREB binding protein	cAMP response element
CSD	Current source densities
CUD	Cocaine use disorder
DA	Dopamine
dACC cortex	Dorsal anterior cingulate
DALYs years	Disability adjusted life
dlPFC cortex	Dorsolateral prefrontal
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*
eDCS stimulation	Epidural direct current
ERP	Event-related potential
FAB	Frontal assessment battery
fMRI	Functional magnetic resonance imaging
FPT	Frontoparietal-temporal
GABA	Gamma-aminobutyric acid
GAP-43	Growth-associated protein 43
GBD	Global burden of disease
IFG	Inferior frontal gyrus
INTAM	International network of transcranial electrical stimulation/transcranial magnetic stimulation trials for addiction medicine
lOFC	Lateral orbitofrontal cortex
LORETA	Low-resolution brain electromagnetic tomography
LPPs	Late positive potentials
LTP	Long-term potentiation
M1	Primary motor cortex
mBDNF	Mature brain-derived neurotrophic factor
MEP	Motor-evoked potential
MMT	Methadone maintenance treatment
mOFC	medial orbitofrontal cortex
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MUD	Methamphetamine use disorder
NAcc	Nucleus accumbens
NIBS	Noninvasive brain stimulation
NMDA	*N*-Methyl-D-aspartate
NMDAR	*N*-Methyl-D-aspartate receptor
OCCS	Obsessive Compulsive Cocaine Use Scale
OCDS-5	5-Item Obsessive Compulsive Drinking Scale
OUD	Opioid use disorder
PFC	Prefrontal cortex
PPF	Paired pulse facilitation
proBDNF	Precursor brain-derived neurotrophic factor
PRP	Perampanel
sgACC	Subgenual anterior cingulate cortex
SP	Slow potential
SUD	Substance use disorder
tACS	Transcranial alternating current stimulation

tDCS	Transcranial direct current stimulation
tES	Transcranial electrical stimulation
THC	Delta-9-tetrahydrocannabinol
tRNS	Transcranial random noise stimulation
TSM	Transcranial magnetic stimulation
TUD	Tobacco use disorder
UNODC	United Nations Office on Drugs and Crime
UTS	Urge to smoke scale
VAS	Visual analog scale
vlPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
VTA	Ventral tegmental area
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life – BREF

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013. 991 p.
2. Daley DC. Family and social aspects of substance use disorders and treatment. J Food Drug Anal. 2013;21(4):S73–6.
3. Healey A, Knapp M, Astin J, Gossop M, Marsden J, Stewart D, et al. Economic burden of drug dependency. Br J Psychiatry. 1998;173(2):160–5.
4. Fischer B, Blanken P, Da Silveira D, Gallassi A, Goldner EM, Rehm J, et al. Effectiveness of secondary prevention and treatment interventions for crack-cocaine abuse: a comprehensive narrative overview of English-language studies. Int J Drug Policy. 2015;26(4):352–63.
5. Navarro HJ, Doran CM, Shakeshaft AP. Measuring costs of alcohol harm to others: a review of the literature. Drug Alcohol Depend. 2011;114(2–3):87–99.
6. Proescholdt M, Walter M, Wiesbeck G. Alkohol und gewalt: eine aktuelle übersicht. Fortschr Neurol Psychiatr. 2012;80(8):441–9.
7. World Health Organization. World drug report 2019. United Nations Publication, Sales No. E.19.XI.8; 2019.
8. Sanchis-Segura C, Spanagel R. Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. Addict Biol. 2006;11(1):2–38.
9. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011;12(11):652–69.
10. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217–38.
11. Nakamura-Palacios EM. Working memory and prefrontal cortex and their relation with the brain reward system and drug addiction. In: Levin ES, editor. Working memory: capacity, developments and improvement techniques. New York: Nova Science Publishers; 2011. p. 454.
12. Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Mol Psychiatry. 2004;9(6):557–69.
13. Nestler EJ. Molecular mechanisms of drug addiction. Neuropharmacology. 2004;47:24–32.
14. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci. 2001;2(2):119–28.
15. Koob GF. The role of the striatopallidal and extended amygdala systems in drug addiction. Ann N Y Acad Sci. 1999;877(1 ADVANCING FRO):445–60.
16. Tzschentke TM. The medial prefrontal cortex as a part of the brain reward system. Amino Acids. 2000;19(1):211–9.
17. Steketee J. Neurotransmitter systems of the medial prefrontal cortex: potential role in sensitization to psychostimulants. Brain Res Rev. 2003;41(2–3):203–28.
18. Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci. 2005;8(11):1445–9.
19. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005;162(8):1403–13.
20. Koob G, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001;24(2):97–129.
21. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci. 1992;13:177–84.
22. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry. 2002;159(10):1642–52.
23. Bowirrat A, Oscar-Berman M. Relationship between dopaminergic neurotransmission, alcoholism, and reward deficiency syndrome. Am J Med Genet Part B Neuropsychiatr Genet. 2005;132B(1):29–37.
24. Fuster J. The prefrontal cortex. 4th ed. Amsterdam/London: Academic Press; 2008. 424 p.
25. McBride T, Arnold SE, Gur RC. A comparative volumetric analysis of the prefrontal cortex in human and baboon MRI. Brain Behav Evol. 1999;54(3):159–66.
26. Moselhy HF. Frontal lobe changes in alcoholism: a review of the literature. Alcohol Alcohol. 2001;36(5):357–68.
27. Volkow ND, Morales M. The brain on drugs: from reward to addiction. Cell. 2015;162(4):712–25.

28. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. Nat Rev Neurosci. 2011;12(11):623–37.
29. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. Longo DL, editor. N Engl J Med. 2016;374(4):363–71.
30. Hyman SE. Addiction: a disease of learning and memory. Am J Psychiatry. 2005;162(8):1414–22.
31. George O, Koob GF. Control of craving by the prefrontal cortex. Proc Natl Acad Sci. 2013;110(11):4165–6.
32. Gajewski PA, Turecki G, Robison AJ. Differential expression of FosB proteins and potential target genes in select brain regions of addiction and depression patients. Bachtell RK, editor. PLoS One. 2016;11(8):e0160355.
33. Schmidt HD, McGinty JF, West AE, Sadri-Vakili G. Epigenetics and psychostimulant addiction. Cold Spring Harb Perspect Med. 2013;3(3):a012047.
34. Nestler EJ. Transcriptional mechanisms of addiction: role of ΔFosB. Philos Trans R Soc Lond B Biol Sci. 2008;363(1507):3245–55.
35. Nestler EJ. Transcriptional mechanisms of drug addiction. Clin Psychopharmacol Neurosci. 2012;10(3):136–43.
36. Robinson TE, Kolb B. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology. 2004;47:33–46.
37. Freeman WM, Lull ME, Patel KM, Brucklacher RM, Morgan D, Roberts DC, et al. Gene expression changes in the medial prefrontal cortex and nucleus accumbens following abstinence from cocaine self-administration. BMC Neurosci. 2010;11(1):29.
38. Most D, Workman E, Harris RA. Synaptic adaptations by alcohol and drugs of abuse: changes in microRNA expression and mRNA regulation. Front Mol Neurosci. 2014;7:85.
39. McCarthy DM, Brown AN, Bhide PG. Regulation of BDNF expression by cocaine. Yale J Biol Med. 2012;85(4):437–46.
40. Anders QS, Klauss J, de Melo Rodrigues LC, Nakamura-Palacios EM. FosB mRNA expression in peripheral blood lymphocytes in drug addicted patients. Front Pharmacol. 2018;9:1205.
41. Anders QS, Ferreira LVB, de Melo Rodrigues LC, Nakamura-Palacios EM. BDNF mRNA expression in leukocytes and frontal cortex function in drug use disorder. Front Psychiatry. 2020;11:469.
42. Zago-Gomes MP, Nakamura-Palacios EM. Cognitive components of frontal lobe function in alcoholics classified according to Lesch's typology. Alcohol Alcohol. 2009;44(5):449–57.
43. Siegal HA, Li L, Rapp RC. Abstinence trajectories among treated crack cocaine users. Addict Behav. 2002;27(3):437–49.
44. McKay JR, Foltz C, Stephens RC, Leahy PJ, Crowley EM, Kissin W. Predictors of alcohol and crack cocaine use outcomes over a 3-year follow-up in treatment seekers. J Subst Abus Treat. 2005;28(2):S73–82.
45. Assanangkornchai S, Srisurapanont M. The treatment of alcohol dependence. Curr Opin Psychiatry. 2007;20(3):222–7.
46. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med. 2011;42(3):227–66.
47. Ekhtiari H, Bashir S. Brain stimulation technology in addiction medicine main problems waiting for solutions. Basic Clin Neurosci. 2010;1(4):3–4.
48. Robinson T, Berridge K. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev. 1993;18(3):247–91.
49. Hormes JM, Coffey SF, Drobes DJ, Saladin ME. The Obsessive Compulsive Cocaine Use Scale: development and initial validation of a self-rated instrument for the quantification of thoughts about cocaine use. Drug Alcohol Depend. 2012;120(1–3):250–4.
50. Wesson D, Havassy B, Smith D. Theories of relapse and recovery and their implications for drug abuse treatment. NIDA Res Monogr. 1986;72:5–19.
51. Iruzubieta P, Crespo J, Fábrega E. Long-term survival after liver transplantation for alcoholic liver disease. World J Gastroenterol. 2013;19(48):9198.
52. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125(11):2150–206.
53. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9):1774–809.
54. Lefaucheur J-P. A comprehensive database of published tDCS clinical trials (2005–2016). Neurophysiol Clin. 2016;46(6):319–98.
55. Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev. 2010;34(4):559–74.
56. Jansen JM, Daams JG, Koeter MWJ, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013;37(10):2472–80.
57. Hone-Blanchet A, Fecteau S. The use of non-invasive brain stimulation in drug addictions. In: The stimulated brain. Cognitive Enhancement Using Non-Invasive Brain Stimulation (Kadosh RC, ed.), Academic Press, London, UK; 2014;425–52.
58. Hone-Blanchet A, Ciraulo DA, Pascual-Leone A, Fecteau S. Noninvasive brain stimulation to suppress craving in substance use disorders: review of human evidence and methodological considerations for future work. Neurosci Biobehav Rev. 2015;59:184–200.
59. Yavari F, Shahbabaie A, Leite J, Carvalho S, Ekhtiari H, Fregni F. Noninvasive brain stimulation for addiction medicine. Prog Brain Res. 2016;224:371–99.

60. Trojak B, Sauvaget A, Fecteau S, Lalanne L, Chauvet-Gelinier J-C, Koch S, et al. Outcome of non-invasive brain stimulation in substance use disorders: a review of randomized sham-controlled clinical trials. J Neuropsychiatry Clin Neurosci. 2017;29(2):105–18.
61. Luigjes J, Segrave R, de Joode N, Figee M, Denys D. Efficacy of invasive and non-invasive brain modulation interventions for addiction. Neuropsychol Rev. 2019;29(1):116–38.
62. Ekhtiari H, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev. 2019;104:118–40.
63. Coles AS, Kozak K, George TP. A review of brain stimulation methods to treat substance use disorders. Am J Addict. 2018;27(2):71–91.
64. Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry. 2019;41(1):70–81.
65. Fregni F. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiatry. 2005;76(12):1614–23.
66. da Silva MC, Conti CL, Klauss J, Alves LG, Do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J Physiol. 2013;107(6):493–502.
67. Conti CL, Nakamura-Palacios EM. Bilateral transcranial direct current stimulation over dorsolateral prefrontal cortex changes the drug-cued reactivity in the anterior cingulate cortex of crack-cocaine addicts. Brain Stimul. 2014;7(1):130–2.
68. Yu T-H, Wu Y-J, Chien M-E, Hsu K-S. Transcranial direct current stimulation induces hippocampal metaplasticity mediated by brain-derived neurotrophic factor. Neuropharmacology. 2019;144:358–67.
69. Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, et al. Animal models of transcranial direct current stimulation: methods and mechanisms. Clin Neurophysiol. 2016;127(11):3425–54.
70. Levy D, Shabat-Simon M, Shalev U, Barnea-Ygael N, Cooper A, Zangen A. Repeated electrical stimulation of reward-related brain regions affects cocaine but not "natural" reinforcement. J Neurosci. 2007;27(51):14179–89.
71. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
72. Islam N, Moriwaki A, Hattori Y, Hayashi Y, Lu Y-F, Hori Y. C-Fos expression mediated by N-methyl-D-aspartate receptors following anodal polarization in the rat brain. Exp Neurol. 1995;133(1):25–31.
73. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(10):2238–47.
74. Pedron S, Beverley J, Haffen E, Andrieu P, Steiner H, Van Waes V. Transcranial direct current stimulation produces long-lasting attenuation of cocaine-induced behavioral responses and gene regulation in cortico-striatal circuits. Addict Biol. 2017;22(5):1267–78.
75. Podda MV, Cocco S, Mastrodonato A, Fusco S, Leone L, Barbati SA, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of BDNF expression. Sci Rep. 2016;6(1):22180.
76. Rohan JG, Carhuatanta KA, McInturf SM, Miklasevich MK, Jankord R. Modulating hippocampal plasticity with in vivo brain stimulation. J Neurosci. 2015;35(37):12824–32.
77. de Souza Custódio JC, Martins CW, Lugon MDMV, Fregni F, Nakamura-Palacios EM. Epidural direct current stimulation over the left medial prefrontal cortex facilitates spatial working memory performance in rats. Brain Stimul. 2013;6(3):261–9.
78. de Souza Custódio JC, Martins CW, Lugon MDMV, de Melo Rodrigues LC, de Figueiredo SG, Nakamura-Palacios EM. Prefrontal BDNF levels after anodal epidural direct current stimulation in rats. Front Pharmacol. 2018;9:755.
79. Wu Y-J, Lin C-C, Yeh C-M, Chien M-E, Tsao M-C, Tseng P, et al. Repeated transcranial direct current stimulation improves cognitive dysfunction and synaptic plasticity deficit in the prefrontal cortex of streptozotocin-induced diabetic rats. Brain Stimul. 2017;10(6):1079–87.
80. Martins CW, de Melo Rodrigues LC, Nitsche MA, Nakamura-Palacios EM. AMPA receptors are involved in prefrontal direct current stimulation effects on long-term working memory and GAP-43 expression. Behav Brain Res. 2019;362:208–12.
81. Benowitz LI, Routtenberg A. GAP-43: an intrinsic determinant of neuronal development and plasticity. Trends Neurosci. 1997;20(2):84–91.
82. World Health Organization. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018. 472 p.
83. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987–1012.
84. NIAAA. Alcohol Alert Number 81: Exploring treatment options for alcohol use disorders [Internet]. Available from: https://pubs.niaaa.nih.gov/publications/aa81/aa81.htm.

85. Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, Pascual-Leone A, et al. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: a double-blind, sham-controlled study. Drug Alcohol Depend. 2008;92(1–3):55–60.
86. den Uyl TE, Gladwin TE, Wiers RW. Transcranial direct current stimulation, implicit alcohol associations and craving. Biol Psychol. 2015;105:37–42.
87. Nakamura-Palacios EM, de Almeida Benevides MC, da Penha Zago-Gomes M, de Oliveira RWD, de Vasconcellos VF, de Castro LNP, et al. Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. Int J Neuropsychopharmacol. 2012;15(05):601–16.
88. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. Neurology. 2000;55(11):1621–6.
89. de Wildt WAJM, Lehert P, Schippers GM, Nakovics H, Mann K, van den Brink W. Investigating the structure of craving using structural equation modeling in analysis of the Obsessive-Compulsive Drinking Scale: a multinational study. Alcohol Clin Exp Res. 2005;29(4):509–16.
90. den Uyl TE, Gladwin TE, Wiers RW. Electrophysiological and behavioral effects of combined transcranial direct current stimulation and alcohol approach bias retraining in hazardous drinkers. Alcohol Clin Exp Res. 2016;40(10):2124–33.
91. den Uyl TE, Gladwin TE, Rinck M, Lindenmeyer J, Wiers RW. A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. Addict Biol. 2017;22(6):1632–40.
92. Klauss J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos GA, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol. 2014;17(11):1793–803.
93. Klauss J, Anders QS, Felippe LV, Nitsche MA, Nakamura-Palacios EM. Multiple sessions of transcranial direct current stimulation (tDCS) reduced craving and relapses for alcohol use: a randomized placebo-controlled trial in alcohol use disorder. Front Pharmacol. 2018;9:716.
94. Wietschorke K, Lippold J, Jacob C, Polak T, Herrmann MJ. Transcranial direct current stimulation of the prefrontal cortex reduces cue-reactivity in alcohol-dependent patients. J Neural Transm. 2016;123(10):1173–8.
95. Biswal J, Chand PK, Murthy P, Venkatsubramanian G, Benegal V, Bharath RD. Effect of transcranial direct current stimulation on relapse of alcohol dependence syndrome and associated changes in functional brain imaging. J Psychiatry. 2018;21:64.
96. Camchong Y, Roy A, Gilmore C, Thao M, Kazynski M, Fiecas M, et al. Using brain stimulation to modify a brain network and support abstinence during alcohol use disorder recovery. Brain Stimul. 2019;12:385–592.
97. Viegas CAA. Formas não habituais de uso do tabaco. J Bras Pneumol. 2008;34(12):1069–73.
98. Da Silva MTB, De Araújo FLO, Félix FHC, Simão AFL, Lobato R d FG, De Sousa FCF, et al. Álcool e nicotina. Rev Neurociências. 2010;18(4):531–7.
99. Pan American Health Organization. Folha informativa – tabaco [Internet]. Available from: https://www.paho.org/bra/index.php?option=com_content&view=article&id=5641:folha-informativa-tabaco&Itemid=1097.
100. World Health Organization. WHO report on the global tobacco epidemic. Geneva: World Health Organization; 2019.
101. Lupi M, Martinotti G, Santacroce R, Cinosi E, Carlucci M, Marini S, et al. Transcranial direct current stimulation in substance use disorders. J ECT. 2017;33(3):203–9.
102. Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. J ECT. 2018;34(3):182–92.
103. Kang N, Kim RK, Kim HJ. Effects of transcranial direct current stimulation on symptoms of nicotine dependence: a systematic review and meta-analysis. Addict Behav. 2019;96:133–9.
104. Xu J, Fregni F, Brody AL, Rahman AS. Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. Front Psychiatry. 2013;4:112.
105. Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. Drug Alcohol Depend. 2014;140:78–84.
106. Meng Z, Liu C, Yu C, Ma Y. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. J Psychiatr Res. 2014;54:19–25.
107. Falcone M, Bernardo L, Ashare RL, Hamilton R, Faseyitan O, McKee SA, et al. Transcranial direct current brain stimulation increases ability to resist smoking. Brain Stimul. 2016;9(2):191–6.
108. Kroczek AM, Häußinger FB, Rohe T, Schneider S, Plewnia C, Batra A, et al. Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure. Drug Alcohol Depend. 2016;168:123–7.
109. Yang L-Z, Shi B, Li H, Zhang W, Liu Y, Wang H, et al. Electrical stimulation reduces smokers' craving by modulating the coupling between dorsal lateral prefrontal cortex and parahippocampal gyrus. Soc Cogn Affect Neurosci. 2017;12(8):1296–302.
110. Aronson Fischell S, Ross TJ, Deng Z-D, Salmeron BJ, Stein EA. Transcranial direct current stimulation applied to the dorsolateral and ventromedial prefrontal cortices in smokers modifies cognitive circuits

implicated in the nicotine withdrawal syndrome. Biol Psychiatry. 2020;5(4):448–60.
111. Vitor de Souza Brangioni MC, Pereira DA, Thibaut A, Fregni F, Brasil-Neto JP, Boechat-Barros R. Effects of prefrontal transcranial direct current stimulation and motivation to quit in tobacco smokers: a randomized, sham controlled, double-blind trial. Front Pharmacol. 2018;9:14.
112. Mondino M, Luck D, Grot S, Januel D, Suaud-Chagny M-F, Poulet E, et al. Effects of repeated transcranial direct current stimulation on smoking, craving and brain reactivity to smoking cues. Sci Rep. 2018;8(1):8724.
113. Hajloo N, Pouresmali A, Alizadeh Goradel J, Mowlaie M. The effects of transcranial direct current stimulation of dorsolateral prefrontal cortex on reduction of craving in daily and social smokers. Iran J Psychiatry. 2019;14(4):291–6.
114. Ghorbani Behnam S, Mousavi SA, Emamian MH. The effects of transcranial direct current stimulation compared to standard bupropion for the treatment of tobacco dependence: a randomized sham-controlled trial. Eur Psychiatry. 2019;60:41–8.
115. Grundey J, Thirugnanasambandam N, Kaminsky K, Drees A, Skwirba AC, Lang N, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J Neurosci. 2012;32(12):4156–62.
116. Lugon MDMV, Batsikadze G, Fresnoza S, Grundey J, Kuo M-F, Paulus W, et al. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. Cereb Cortex. 2017;27(1):544–53.
117. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci. 1993;90(12):5391–3.
118. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2018;392(10159):1789–858.
119. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States. JAMA Psychiatry. 2014;71(7):821.
120. Martin BC, Fan M-Y, Edlund MJ, DeVries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med. 2011;26(12):1450–7.
121. Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol. 2008;15(10):1124–30.
122. Borckardt JJ, Reeves ST, Robinson SM, May JT, Epperson TI, Gunselman RJ, et al. Transcranial direct current stimulation (tDCS) reduces postsurgical opioid consumption in total knee arthroplasty (TKA). Clin J Pain. 2013;29(11):925–8.
123. Borckardt JJ, Reeves ST, Milliken C, Carter B, Epperson TI, Gunselman RJ, et al. Prefrontal versus motor cortex transcranial direct current stimulation (tDCS) effects on post-surgical opioid use. Brain Stimul. 2017;10(6):1096–101.
124. Khedr EM, Sharkawy ESA, Attia AMA, Ibrahim Osman NM, Sayed ZM. Role of transcranial direct current stimulation on reduction of postsurgical opioid consumption and pain in total knee arthroplasty: double randomized clinical trial. Eur J Pain. 2017;21(8):1355–65.
125. Wang Y, Shen Y, Cao X, Shan C, Pan J, He H, et al. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates cue-induced craving for heroin. J Psychiatr Res. 2016;79:1–3.
126. Gallucci A, Lucena PH, Martens G, Thibaut A, Fregni F. Transcranial direct current stimulation to prevent and treat surgery-induced opioid dependence: a systematic review. Pain Manag. 2019;9(1):93–106.
127. Garg H, Verma R, Balhara Y, Sarkar S, Kumar S, Kumar N, et al. Effect of targeted prefrontal cortex modulation with bilateral transcranial direct current stimulation (tDCS) in reducing craving in patients with opioid dependence: a case controlled trial. Brain Stimul. 2019;12(2):408.
128. Sharifi-Fardshad M, Mehraban-Eshtehardi M, Shams-Esfandabad H, Shariatirad S, Molavi N, Hassani-Abharian P. Modulation of drug craving in crystalline-heroin users by transcranial direct current stimulation of dorsolateral prefrontal cortex. Addict Health. 2018;10(3):173–9.
129. Martinotti G, Lupi M, Montemitro C, Miuli A, Di Natale C, Spano MC, et al. Transcranial direct current stimulation reduces craving in substance use disorders. J ECT. 2019;35(3):207–11.
130. Taremian F, Nazari S, Moradveisi L, Moloodi R. Transcranial direct current stimulation on opium craving, depression, and anxiety. J ECT. 2019;35(3):201–6.
131. Sadeghi Bimorgh M, Omidi A, Ghoreishi FS, Rezaei Ardani A, Ghaderi A, Banafshe HR. The effect of transcranial direct current stimulation on relapse, anxiety, and depression in patients with opioid dependence under methadone maintenance treatment: a pilot study. Front Pharmacol. 2020;11:401.
132. Goldstein RA, DesLauriers C, Burda A, Johnson-Arbor K. Cocaine: history, social implications, and toxicity: a review. Semin Diagn Pathol. 2009;26(1):10–7.
133. Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci. 2014;8:661.
134. Conti CL, Moscon JA, Fregni F, Nitsche MA, Nakamura-Palacios EM. Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. Int J Neuropsychopharmacol. 2014;17(9):1465–75.
135. Batista EK, Klauss J, Fregni F, Nitsche MA, Nakamura-Palacios EM. A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-

cocaine dependence. Int J Neuropsychopharmacol. 2015;18(12):pyv066.
136. Moscon JA, Conti CL, Nakamura-Palacios EM. Increased electroencephalographic activity in crack-cocaine users visualizing crack cues. J Psychiatr Res. 2016;83:137–9.
137. Contia CL, Moscona JA. Dorsolateral prefrontal cortex activity and neuromodulation in crack-cocaine dependents during early abstinence. J Neurol Neurophysiol. 2016;7(3):374.
138. Nakamura-Palacios EM, Lopes IBC, Souza RA, Klauss J, Batista EK, Conti CL, et al. Ventral medial prefrontal cortex (vmPFC) as a target of the dorsolateral prefrontal modulation by transcranial direct current stimulation (tDCS) in drug addiction. J Neural Transm. 2016;123(10):1179–94.
139. Klauss J, Anders QS, Felippe LV, Ferreira LVB, Cruz MA, Nitsche MA, et al. Lack of effects of extended sessions of transcranial direct current stimulation (tDCS) over dorsolateral prefrontal cortex on craving and relapses in crack-cocaine users. Front Pharmacol. 2018;9:1198.
140. Gaudreault P-O, Sharma A, Datta A, Nakamura-Palacios EM, King S, Malaker P, Wagner A, Vasa D, Parvaz MA, Parra LC, Alia-Klein N, Goldstein RZ. A double-blind shamcontrolled phase 1 clinical trial of tDCS of the dorsolateral prefrontal cortex in cocaine inpatients: Craving, sleepiness, and contemplation to change. Eur J Neurosci. 2021;53(9):3212–30. https://doi.org/10.1111/ejn.15172.
141. Paulus MP, Stewart JL. Neurobiology, clinical presentation, and treatment of methamphetamine use disorder: a review. JAMA Psychiatry. 2020;77(9):959–66.
142. Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimpoor M, Keshvari F, Nejati V, et al. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int J Neuropsychopharmacol. 2014;17(10):1591–8.
143. Shahbabaie A, Ebrahimpoor M, Hariri A, Nitsche MA, Hatami J, Fatemizadeh E, et al. Transcranial DC stimulation modifies functional connectivity of large-scale brain networks in abstinent methamphetamine users. Brain Behav. 2018;8(3):e00922.
144. Shahbabaie A, Hatami J, Farhoudian A, Ekhtiari H, Khatibi A, Nitsche MA. Optimizing electrode montages of transcranial direct current stimulation for attentional bias modification in early abstinent methamphetamine users. Front Pharmacol. 2018;9:907.
145. Alizadehgoradel J, Nejati V, Sadeghi Movahed F, Imani S, Taherifard M, Mosayebi-Samani M, et al. Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: a randomized, double-blind, parallel-group study. Brain Stimul. 2020;13(3):582–93.
146. National Institute on Drug Abuse. Marijuana [Internet]. Available from: https://www.drugabuse.gov/publications/drugfacts/marijuana.
147. Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug Alcohol Depend. 2010;112(3):220–5.
148. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: a systematic review. Drug Alcohol Depend. 2019;200:95–114.
149. Littel M, Euser AS, Munafò MR, Franken IHA. Electrophysiological indices of biased cognitive processing of substance-related cues: a meta-analysis. Neurosci Biobehav Rev. 2012;36(8):1803–16.
150. Franken IHA, Dietvorst RC, Hesselmans M, Franzek EJ, van de Wetering BJM, Van Strien JW. Cocaine craving is associated with electrophysiological brain responses to cocaine-related stimuli. Addict Biol. 2008;13(3–4):386–92.
151. Boes AD, Grafft AH, Joshi C, Chuang NA, Nopoulos P, Anderson SW. Behavioral effects of congenital ventromedial prefrontal cortex malformation. BMC Neurol. 2011;11(1):151.
152. Schneider B, Koenigs M. Human lesion studies of ventromedial prefrontal cortex. Neuropsychologia. 2017;107:84–93.
153. Nopoulos P, Boes AD, Jabines A, Conrad AL, Canady J, Richman L, et al. Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. J Neurodev Disord. 2010;2(4):235–42.
154. Hiser J, Koenigs M. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biol Psychiatry. 2018;83(8):638–47.
155. Bonson K. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology. 2002;26(3):376–86.
156. Seo D, Lacadie CM, Tuit K, Hong K-I, Constable RT, Sinha R. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. JAMA Psychiatry. 2013;70(7):727.
157. Potenza MN. The neurobiology of pathological gambling and drug addiction: an overview and new findings. Philos Trans R Soc Lond B Biol Sci. 2008;363(1507):3181–9.
158. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. Neuron. 2012;76(6):1057–70.
159. Peters J, LaLumiere RT, Kalivas PW. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. J Neurosci. 2008;28(23):6046–53.
160. Ghazizadeh A, Ambroggi F, Odean N, Fields HL. Prefrontal cortex mediates extinction of responding by two distinct neural mechanisms in accumbens shell. J Neurosci. 2012;32(2):726–37.

161. Bzdok D, Langner R, Schilbach L, Engemann DA, Laird AR, Fox PT, et al. Segregation of the human medial prefrontal cortex in social cognition. Front Hum Neurosci. 2013;7:232.
162. Verdejo-García A, Bechara A. A somatic marker theory of addiction. Neuropharmacology. 2009;56:48–62.
163. Rudorf S, Hare TA. Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. J Neurosci. 2014;34(48):15988–96.
164. Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. Trends Cogn Sci. 2012;16(3):147–56.
165. Myers-Schulz B, Koenigs M. Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. Mol Psychiatry. 2012;17(2):132–41.
166. Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.
167. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int J Neuropsychopharmacol. 2021;24(4):256–313.

28 Attention-Deficit/Hyperactivity Disorder

Douglas Teixeira Leffa and Luis Augusto Rohde

28.1 Epidemiology, Genetics, and Risk Factors of ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate and impairing symptoms of inattention, hyperactivity/impulsivity, or both. For diagnosing ADHD, symptoms should be present in different settings (e.g., home, school, work), and be associated with significant impairment in quality of social, academic, or occupational functioning [2]. In addition, several symptoms should be present before the age of 12 years and should not be better explained by other disorder [2]. The prevalence of ADHD is about 5.3% [99] in children, and longitudinal studies indicate that 50–80% of adults with childhood ADHD still retain the full diagnostic criteria [20]. In this sense, the prevalence of ADHD in adulthood is best estimated as 2.5% [112]. A meta-analysis performed with 154 studies with individuals from all continents showed that, over the last three decades, there is no evidence suggesting an increase in the ADHD prevalence rates in non-referred samples worldwide when standardized diagnostic procedures are followed [100]. Therefore, increasing rates of ADHD diagnosis over the last years [107, 130] likely reflect changes in administrative and clinical practice.

ADHD aggregates in families and has a heritability ranging around 60–90% [26]. Genome-wide studies have identified a polygenic cause for most cases of ADHD, with many genetic risk variants with small effects combining to increase the risk for the disorder [39]. In this sense, epidemiological and genetic studies have consistently demonstrated that the disorder lies at the extreme of a continuously distributed trait present in the population (for a review, see Posner et al. [101]). Moreover, a recent genome-wide association meta-analysis has found the first 12 significant risk loci for ADHD, mostly related to neurodevelopmental processes [39]. The polygenic architecture of ADHD is associated with a general genetic liability toward childhood psychopathology in the population [15], and also characterized by substantial pleiotropy with several neuropsychiatric disorders [67].

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A variety of environmental factors have been associated with ADHD. Among them are exposure to potentially toxic substances like lead [11, 48, 93], artificial food dyes [92, 110], and organophosphate pesticides [10]; prenatal exposure to maternal smoking [41, 57, 93]; maternal use of acetaminophen [25, 131] or the anti-epileptic drug valproate during pregnancy [32]; and nutrient deficiencies like iron [122, 128], omega-3 polyunsaturated fatty acids [9, 51], and maternal vitamin D [118]. Potentially harmful events during pregnancy are also associated with ADHD in the children, including hypertensive disorders [79] and preeclampsia [78], and exposure to trauma or stress [72]. Furthermore, ADHD is associated with low-birth weight [46, 86], prematurity [46, 76, 119], and lower levels of family income [31, 66]. Even though a causal association between environmental factors and ADHD is hard to define due to the observational nature of the studies, it seems that the combined effect of several genetic and environmental risks is responsible for most cases of ADHD.

28.2 Impact on Patients

ADHD is associated with several negative outcomes in social, academic, and occupational contexts across life cycle. Epidemiological studies have demonstrated that ADHD is associated with higher levels of emotional and conduct problems [117], emotional dysregulation [6], and impaired social skills [105]. Individuals with ADHD have a higher risk of accidental physical injuries [106], reported concussions during sports practice [90], and vehicular crashes [36, 123]. Patients with ADHD also present higher rates of suicide attempts [28, 43, 111]. In general, ADHD is associated with a higher risk for premature death, mostly due to accidents and suicide [38, 120]. ADHD patients are also more likely to be convicted of criminal offenses, including violent crimes [83, 84], less likely to graduate from school on time [14], and more likely to be unemployed [44, 45]. ADHD is a risk factor for substance use disorder [49, 68, 121], teen pregnancy [95, 113], and problem gambling [7]. It comes with no surprise that patients with ADHD experience lower quality of life when compared to typically developing peers [69]. Moreover, the quality of life of parents whose children were diagnosed with ADHD is also reduced [40].

28.3 ADHD and Associated Neuropsychological Deficits

Studies evaluating neurocognitive functions in subjects with ADHD have shown moderate impairments in several domains when compared to healthy subjects [98]. A worse performance in ADHD subjects was observed in decision-making, fluency, memory, planning/organization, reaction time, reaction time variability, response inhibition, selective attention, set-shifting, vigilance, and working memory [98]. Differences appear to be larger in children and adults when compared to adolescents [98]. The largest difference between ADHD subjects and healthy controls was observed in reaction time variability [98]. Meta-analyses have also found moderate tendency to favor small immediate rewards over large delayed rewards in ADHD patients [58, 81].

28.4 Neuroimaging Findings and the Catecholaminergic Theory

ADHD patients present anatomical and functional brain differences when compared to individuals without the disorder, which are likely to involve, among others, catecholaminergic neurotransmission. A recent study performed with structural magnetic resonance imaging (MRI) data from 2246 patients and 1934 controls found reduced cortical surface area, mainly in frontal, cingulate, and temporal regions, in children with ADHD [55]. Family analyses showed that unaffected siblings of ADHD patients presented similar surface area differences when compared to controls [55]. Moreover, cortical alterations were associated with attention problems in the general population, suggesting that ADHD lies at the extreme end of a continuous trait [55]. Another

study with a similar sample size measured subcortical differences between ADHD patients and controls using MRI data, and found smaller volumes in the accumbens, amygdala, caudate, putamen, and hippocampus in patients with the disorder [54]. These findings were not found to be correlated with ADHD symptoms. Both studies were only able to find statistically significant differences in children. One important message brought by both studies is that ADHD is clearly associated with widespread brain alterations, especially in childhood.

Besides the anatomical differences previously mentioned, several functional studies have evidenced distinct patterns of brain activation in ADHD, especially in fronto-striatal and fronto-cortical circuits. A meta-analysis performed with functional MRI data collected during inhibition tasks demonstrated decreased activation in the right inferior frontal gyrus (IFG), left caudate, right thalamus, left and right supplementary motor area, and anterior cingulate in ADHD patients when compared to healthy controls [50]. For attention tasks, ADHD patients presented decreased activation in the right dorsolateral prefrontal cortex (DLPFC), left putamen, left globus pallidus, right inferior parietal lobe, precuneus, and superior temporal lobe [50]. In a meta-analysis including 958 children and 414 adults with ADHD, Cortese et al. [34] reported decreased activation in ADHD in several frontal regions bilaterally, and in the right superior temporal gyrus, left inferior occipital gyrus, right thalamus, and midbrain during tasks requiring inhibitory behavior, and decreased activation in the left IFG/anterior insula and right middle frontal gyrus in ADHD during working memory tasks. A similar study was performed by McCarthy et al. [82], who conducted a meta-analysis including functional MRI data from 334 ADHD patients and 371 healthy controls. ADHD patients presented decreased activation in the bilateral superior frontal gyri and left medial frontal gyrus while performing the N-back task, decreased activation in the bilateral IFG, right superior frontal gyrus, and right middle frontal gyri while performing the stop task, and decreased activation in the left medial frontal gyrus and right caudate while performing the go/no-go task [82]. A fourth meta-analysis found decreased activation in bilateral ventrolateral prefrontal cortex, insula and putamen, right caudate, and supplementary motor area during inhibition tasks in ADHD patients when compared to healthy controls [94]. Summing up, functional MRI findings in ADHD patients suggest underactivation in several brain circuits typically associated with inhibitory behavior and attention, supporting that the disorder is characterized by deficits in distinct fronto-striatal and fronto-cortical circuits.

One of the hypotheses trying to explain the clinical, functional, and anatomical findings in ADHD states that the disorder is characterized by a catecholaminergic dysfunction, especially dopaminergic, in prefrontal areas. The dopaminergic hypothesis is supported by improvement in symptoms observed after the use of stimulants, which are known to increase central dopamine and norepinephrine activities [42]. Moreover, studies have shown lower dopamine receptors and dopamine transporter availability in the accumbens and in midbrain regions of patients with ADHD [126], and also lower dopamine receptors availability in the left caudate of patients with ADHD [127]. However, although there is evidence indicating a dysfunctional catecholaminergic system in ADHD, it is important to stress that the broad availability of clinical, genetic, and imaging data has shifted the understanding of ADHD from a single-cause model to a multifactorial model that understands ADHD as an heterogeneous disorder resulting from several genetic and environmental risk factors [91].

28.5 Treatment of ADHD

Treatment of ADHD involves the use of pharmacological and non-pharmacological interventions, and it is guided by the severity of symptoms, presence of comorbidities, and the period in which symptomatic relief is necessary [21]. Pharmacological treatment consists of stimulant (methylphenidate and amphetamine) and non-stimulant (atomoxetine, guanfacine, and clonidine) medications, and meta-analyses

of randomized clinical trials have demonstrated that both are effective in reducing symptoms in children and adults [33]. Stimulants, like amphetamine and methylphenidate, are the most commonly used and appear to have higher effect sizes when compared to non-stimulants [21]. Therefore, they are considered first-line therapy for ADHD in all ages. Besides symptoms reduction, treatment with ADHD medication appears to be related to better grades at school [60, 61, 77], reduction of criminality [75, 84], decreased rates of injuries [29, 37, 47, 74], less sexually transmitted infections [24], decrease in teenage pregnancy [56], and less risk of depression and suicide attempts [22, 27, 73].

Although effective, pharmacological treatment still has important limitations. Studies conducted in community samples observed that a consistent use of the medication was present for only 2–5 months in a majority of patients [80, 97]. After 2 years, only 50% of patients are adherent to treatment, and after 5 years, only 36% [23]. Low adherence appears to be partially related to adverse reactions commonly observed like insomnia, loss of appetite, abdominal pain, dysphoria, and irritability [19, 53, 85].

Regarding non-pharmacological treatments, behavioral therapies are likely the ones with the highest evidence of efficacy. Training parents of preschool children with ADHD seems to reduce parent-reported ADHD symptoms [104]. Cognitive behavioral therapy was shown to improve symptoms in adults with ADHD [63]. Organizational skills interventions improved inattention symptoms in adolescents with ADHD [8]. Meditation-based therapy was associated with moderate reductions in ADHD symptoms, but methodological issues in the clinical trials still do not support the recommendation of meditation-based therapy for this population [132]. Neurofeedback is another non-pharmacological intervention that has been studied for ADHD, and a recent meta-analysis found a small reduction in hyperactivity/impulsivity symptoms, but with no effects in inattention symptoms [124]. Cognitive training, on the other hand, has not shown significant effects in the treatment of ADHD [103].

28.6 tDCS Rationale and Current Evidence

The modulation of cortical activity with transcranial direct current stimulation (tDCS) has been proposed as a promising alternative treatment for ADHD symptoms. The underactivation of distinct fronto-striatal and fronto-cortical circuits in patients with ADHD, which seems to be associated with the behavioral phenotype of the disorder, could theoretically be alleviated with the modulation of frontal cortex activity. Thus, this intervention would have, as a final result, improvement of the attention and/or hyperactive/impulsive behaviors. There has been substantial evidence on the effects of tDCS on neuropsychological tasks in both patients with different psychiatric conditions and healthy subjects (more information can be found in previous chapters), including measures of behavioral inhibition, attention, and working memory. As previously discussed, a worse neuropsychological performance is observed in ADHD patients in several domains, including reaction time, reaction time variability, response inhibition, selective attention, vigilance, and working memory [98]. Therefore, it can be hypothesized that tDCS would be an effective treatment in this population.

Studies using animal models are also indicative of the efficacy of tDCS in ADHD. Studies performed in the most commonly used animal model of ADHD, the spontaneously hypertensive rats, have shown that daily bicephalic tDCS stimulations over 8 consecutive days were able to improve short- and long-term memory when compared to sham stimulations [70, 71]. Moreover, animals treated with tDCS presented increased dopamine levels in the hippocampus and striatum, suggesting a possible mechanism of action for tDCS in this animal model [71].

To date, a total of 14 phase II clinical trials have been performed evaluating tDCS or transcranial slow-oscillating direct current stimulation (toDCS) in patients with ADHD. Methodological aspects and main findings of these studies can be found in Table 28.1. Of the 14, two trials have used toDCS. Most studies present heterogeneous methodologies and distinct outcomes. Ten

Table 28.1 Methodological aspects and main results of pilot studies evaluating transcranial direct current stimulation or transcranial slow-oscillating direct current stimulation in attention-deficit/hyperactivity disorder

Reference	Sample size	ADHD diagnosis	Medication status	Study design	tDCS montage	Stimulation parameters	Outcomes	Main results
[102]	12 children with ADHD, 12 healthy controls	*DSM-IV*	Washout of 48 h	Crossover, randomized, double blinded, sham controlled	Anodal F3 and F4, cathodal M1 and M2	toDCS (0–250 μA, 0.75 Hz), single session, 5 × 5 min	Declarative memory, digit span	Increased memory consolidation. No stimulation effect in the digit span
[87]	14 children with ADHD	*DSM-IV*	Washout of 48 h	Crossover, randomized, double blinded, sham controlled	Anodal F3 and F4, cathodal M1 and M2	toDCS (0–250 μA, 0.75 Hz), single session, 5 × 5 min	Go/no-go task, motor memory task, intrinsic alertness task	Decreased RT after active stimulation in go/no-go task. No stimulation effect in motor memory task or intrinsic alertness task
[35]	60 adults with ADHD	*DSM-IV*	Could be on stimulants	Parallel, randomized, double blinded, sham controlled	Anodal F3 and cathodal F4	1 mA, single session, 20 min	Go/no-go task	No difference in behavioral performance
[115]	20 children with ADHD	Conner's Adult ADHD Rating Scale; Wender Utah Rating Scale	No stimulant treatment	Crossover, randomized, single blinded, sham controlled	Anodal F3, cathodal Fp2 (montage 1); cathodal F3, anodal Fp2 (montage 2)	1.5 mA, single session, 15 min	Go/no-go task, Stroop task	Increased inhibition accuracy with both montages in the go/no-go task. No effect in the Stroop task
[12]	21 children with ADHD, 21 healthy controls	*DSM-IV*	Washout of 24 h	Crossover, randomized, single blinded, sham controlled	Anodal F8 and reference electrode over M1 (montage 1); cathodal F8 and reference electrode over M1 (montage 2)	1 mA, single session, 20 min	Flanker task	No effects overall. Decreased commission error rates and reaction time variability after the first session only

(continued)

Table 28.1 (continued)

Reference	Sample size	ADHD diagnosis	Medication status	Study design	tDCS montage	Stimulation parameters	Outcomes	Main results
[4]	9 children with ADHD	*DSM-V*	Washout of 7 days	Open label, non-controlled	Anodal F3, cathodal Fp2	2 mA, five sessions, 30 min	Visual attention test (TAVIS-3), digit span, Corsi cubes, NEPSY-II (inhibitory control battery)	Decreased errors by omission in visual attention test (TAVIS-3), decreased uncorrected and total errors in the inhibitory control battery of NEPSY-II, no effect in digit span or Corsi cubes
[18]	17 adults with ADHD	*DSM-V*	No stimulant treatment for the last month	Parallel, randomized, double blinded, sham controlled	Anodal F4, cathodal F3	2 mA, five sessions, 20 min	ASRS, SDS	Decreased ASRS inattention scores and SDS scores after active stimulation
[88]	25 children with ADHD (15 in experiment 1 and 10 in experiment 2)	*DSM-V*	No stimulant during the experiment (no information on washout period)	Crossover, randomized, double blinded, sham controlled	Experiment 1: Anodal F3, cathodal F4 Experiment 2: Anodal F3, cathodal Fp2 (montage 1); and cathodal F3, anodal Fp2 (montage 2)	1 mA, single session, 15 min	Go/no-go task, Stroop task, N-back task, WCST	Experiment 1: improved response inhibition in Stroop task and reduced reaction time in N-back test. No effects in the go/no-go task or WCST Experiment 2: improved response inhibition in go/no-go task with montage 2, improved WCST performance with both montages, and improved N-back task performance with montage 1
[116]	13 children with ADHD	*DSM-IV*	Washout 96 h	Crossover, randomized, double blinded, sham controlled	Anodal F3, cathodal Cz	1 mA, single session, 20 min	Combination of the N-back task with the go/no-go component	Decreased reaction time and reaction time variability, and also more errors and less accuracy with active stimulation

[114]	15 children with ADHD	*DSM-IV*	Washout 96 h	Crossover, randomized, double blinded, sham controlled	Anodal F3, cathodal Cz	1 mA, 5 sessions, 20 min each	Changes of the parents' version of FBB-ADHD, working memory component of QbTest	Reduction in inattention symptoms evaluated with the FBB-ADHD. Reduction in inattention and hyperactivity measured with the working memory component of QbTest
[59]	21 adults with ADHD, 16 healthy controls	Diagnosis by outside psychiatrist or neurologist	No medications on the day of the experiments	Crossover, not randomized, single blinded, sham controlled	Anodal F3 and F4, cathodal cerebellar cortex	1.8 mA, single session, 20 min	MOXO-CPT	Improvement in hyperactivity. No change in attention, timing, or impulsivity
[1]	37 adults with ADHD	*DSM-V*	On stimulant	Crossover, randomized, double blinded, sham controlled	Anodal F3, cathodal Fp2	2 mA, 3 sessions, 20 min	CPT, SST	Decreased false positive errors in CPT, no effect in SST
[13]	14 children with ADHD, 14 healthy controls	*DSM-IV*	Washout of 24 h	Crossover, randomized, double blinded, sham controlled	Anodal F8, cathodal Fp1 (montage 1); HD-tDCS with 4x1 montage with the anode placed centrally in F8 (montage 2)	1 mA (conventional), single session, 20 min; 0.5 mA (HD-tDCS), single session, 20 min	N-back task	No difference in behavioral performance
[89]	20 children with ADHD	*DSM-V*	No stimulant treatment for the last month	Crossover, randomized, single blinded, sham controlled	Anodal Fp2, cathodal F3 (montage 1); anodal F3, cathodal Fp2 (montage 2)	1 mA, single session, 15 min	CDDT, BART	Increased tendency to choose a large but delayed reward in the CDDT and decreased risk-taking behavior in the BART with montage 1

ADHD attention-deficit/hyperactivity disorder, *tDCS* transcranial direct current stimulation, *toDCS* transcranial slow-oscillating direct current stimulation, *HD-tDCS* high-definition transcranial direct current stimulation, *F3* left dorsolateral prefrontal cortex, *F4* right dorsolateral prefrontal cortex, *M1* left mastoid, *M2* right mastoid, *Fp2* right supraorbital area, *Fp1* left supraorbital area, *F8* right inferior frontal gyrus, *WCST* Wisconsin Card Sorting Task, *ASRS* Adult ADHD Self-Report Scale Symptom Checklist-v1.1, *SDS* Sheehan Disability Scale, *FBB-ADHD* German adaptive ADHD Diagnostic Checklist, *CPT* continuous performance test, *SST* stop signal task, *CDDT* chocolate delay discounting task, *BART* balloon analogue risk-taking task

were performed in children or adolescents [4, 12, 13, 87–89, 102, 114–116], while four were performed in adult patients [1, 18, 35, 59]. The majority opted for a crossover, randomized, double-blinded, and sham-controlled design. Four studies were single blinded [12, 59, 89, 115], two had a parallel design [18, 35], and one study opted for an open-label, non-controlled trial [4]. ADHD diagnosis was determined according to *DSM-IV* or *DSM-V* in most studies. In the study published by Soltaninejad et al. [115], subjects were selected based on their scores on the Conner's Adult ADHD Rating Scale, together with the Wender Utah Rating Scale to evaluate symptoms during childhood. Jacoby and Lavidor [59] included subjects with a formal clinical diagnosis of ADHD by a psychiatrist or neurologist performed outside a research center. Only two studies included subjects concomitantly treated with stimulants [1, 35], while most performed a washout ranging from 1 to 7 days, and two studies included subjects without stimulant treatment for a minimum of 30 days [18, 89]. A bias assessment of the clinical trials presented in Table 28.1, based on the Cochrane risk of bias tool, was recently performed by Salehinejad et al. [108] in a systematic review. Generally speaking, the authors reported a low risk of bias. Most concerning aspects are the possibilities of detection bias and performance bias, both related to adequate blinding [108].

There was moderate variability regarding the site of stimulation. Eight studies placed the anodal electrode over the left DLPFC (EEG position F3) [1, 4, 35, 88, 89, 114–116], three studies performed tDCS or toDCS stimulation with anodal electrodes over both left and right DLPFC (EEG positions F3 and F4, respectively) [59, 87, 102], two studies placed the anode over the right IFG (EEG position F8) [12, 13], and one placed the anode over the right DLPFC [18]. As discussed previously, the DLPFC seems to be a key region in fronto-striatal and fronto-cortical circuits that are underactivated in ADHD patients during tasks requiring attention [50]. The right IFG, on the other hand, appears to be activated mainly during tasks requiring inhibitory behavior [50]. Primary outcomes include neurophysiological tests evaluating inhibitory control, attention, and working memory, as well as clinical outcomes measuring inattention and/or hyperactivity/impulsivity symptoms. Evidence regarding the use of tDCS and ADHD has been summarized below.

28.7 Neuropsychological Outcomes – Inhibitory Control

Ten studies evaluated the effects of tDCS in inhibitory control [1, 4, 12, 35, 59, 87–89, 115, 116]. The following neuropsychological tasks were conducted to assess this domain: continuous performance test (CPT), MOXO-CPT, stop signal task (SST), flanker task, Stroop task, go/no-go task, the inhibitory control battery subtest of the Neuropsychological Development Assessment Battery (NEPSY-II), chocolate delay discounting task (CDDT), and balloon analogue risk-taking task (BART). An improvement in inhibitory control was reported by seven studies in at least one task [1, 4, 12, 87–89, 115]. A meta-analysis performed with eight of those ten studies reported a small but statistically significant effect size of 0.197 (*p-value* = 0.006), indicating that tDCS is able to ameliorate inhibitory control in ADHD patients [109]. The same meta-analysis reported that a significant improvement was achieved with anodal stimulation over the DLPFC, while no effects were observed after IFG stimulation [109]. These results should be viewed in light of some limitations, especially since only two studies performed anodal stimulation over the IFG, dampening the statistical power of the analyses.

Among the studies with positive results, Breitling et al. [12] was the one with the largest sample size. Authors applied a single session of tDCS in 21 children with ADHD and 21 healthy controls in a crossover approach. There was no difference in the flanker test after a primary analysis. However, in an exploratory analysis using only data after the first stimulation (without considering the crossed over phase), the authors reported decreased commission error rates and reaction time variability, suggesting improved inhibitory

control after the active stimulation. Allenby et al. [1] performed three sessions of tDCS stimulation in 37 adult patients with ADHD with the anodal electrode over F3 and cathodal over right supraorbital area (EEG position Fp2). Stimulation was applied combined with a visual working memory training task. Inhibitory control was evaluated with the CPF and the SST. There was a decrease in false positive errors in CPT between active tDCS and sham at the end of the three sessions. However, the effect was not observed in a follow-up performed 3 days after the last stimulation. The authors found no effect in the SST. Bandeira et al. [4] performed five tDCS sessions in an open label, non-controlled trial in nine children with ADHD. Authors reported decreased uncorrected and total errors in the inhibitory control battery subtest of NEPSY-II, suggesting improved inhibitory control.

Soltaninejad et al. [115] reported increased inhibitory accuracy using two distinct montages: anodal F3, cathodal Fp2 (montage 1) and cathodal F3, anodal Fp2 (montage 2). Authors conducted a single tDCS session in 20 children with an ADHD diagnosis. With montage 1, authors observed increased accuracy in go responses, and with montage 2 they observed increased accuracy in no-go responses. There was no effect in the Stroop task. Improved performance in the go/no-go task was also observed by Munz et al. [87], who applied toDCS in five intervals for 5 min each during non-REM sleep in 14 ADHD children. Authors observed decreased reaction times in the go/no-go task. Nejati et al. [88] observed improved response inhibition in Stroop task and no effects in the go/no-go task after a single stimulation session (anodal F3, cathodal F4) in 15 children with ADHD. In a second experiment, authors described improved response inhibition in go/no-go task by applying the anodal electrode over F3 and the cathodal over Fp2. In a second study, Nejati et al. [89] performed a single session of tDCS in 20 children with ADHD. Patients were subjected to anodal Fp2, cathodal F3 (montage 1) and anodal F3, cathodal Fp2 (montage 2). Authors observed increased tendency to choose a large but delayed reward in the CDDT, as well as decreased risk-taking behavior in the BART after montage 1 stimulation. Both findings indicate improved reward processing after treatment with tDCS.

Negative results were obtained in three studies. After a single session of tDCS applied in 60 adults with ADHD, Cosmo et al. [35] did not find any difference in the go/no-go task. Jacoby and Lavidor [59] performed one stimulation session (anodal F3 and F4, cathodal over cerebellar cortex) in 21 adult ADHD patients and 16 healthy controls. Authors reported no effects in the impulsivity component of the MOXO-CPT. Finally, in the study of Sotnikova et al. [116], tDCS stimulation in 13 children with ADHD was associated with decreased accuracy in the go/no-go component of the test, suggesting deterioration of the behavioral performance.

Treatment with tDCS has shown promising results in improving inhibitory control in patients with ADHD. Nevertheless, future studies are required in order to better define the optimal montage and dosage for the stimulation. Moreover, better powered studies using clinical outcomes will be necessary for accessing the use of tDCS in clinical practice.

28.8 Neuropsychological Outcomes – Attention and Working Memory

Eight studies evaluated the effects of tDCS in attention or working memory in ADHD patients [1, 4, 13, 59, 88, 102, 114, 116]. The following tasks were performed: visual attention test from TAVIS-3, digit span, Corsi cubes, N-back task, working memory component of QbTest (combination of the n-back task with the no-go component), CPT, and MOXO-CPT. Five studies reported an improvement in attention or working memory in at least one task [1, 4, 88, 114, 116]. A meta-analysis that included five of the eight studies described in Table 28.1 reported no significant effects of tDCS in working memory when evaluating outcomes of the following tasks: digit span, N-back task, and working memory component of QbTest [109].

The N-back task was the most commonly performed. Sotnikova et al. [116] performed a

single stimulation section placing the anode over F3 and cathode over the vertex (Cz) in 13 children with ADHD. Authors described decreased reaction time and reaction time variability in the N-back task after active stimulation, indicating improved working memory performance. The N-back task was also selected as outcome by Nejati et al. [88]. In the first experiment performed (anodal F3 and cathodal F4), Nejati et al. [88] observed reduced reaction time in the N-back task. Moreover, in the second experiment (anodal F3, cathodal Fp2 stimulation), N-back task performance was also improved when compared to the sham stimulation. In the same study, authors described improved performance in the Wisconsin card sorting task (WCST), a task that measures cognitive flexibility, with two different electrode montages (anodal F3, cathodal Fp2, and cathodal F3, anodal Fp2). Breitling et al. [13], on the other hand, did not find any differences in N-back task performance after a conventional or high-definition tDCS stimulation in 14 ADHD children and 14 healthy controls.

While using the CPT as an outcome, Allenby et al. [1] observed decreased false positive errors, indicating improved attentional performance. Jacoby and Lavidor [59], on the other hand, found no changes in the attentional aspect of the MOXO-CPT after a single stimulation session in 21 adult ADHD patients and 16 healthy controls. An improvement in attentional performance was described by Bandeira et al. [4], who found decreased errors by omission in visual attention test (TAVIS-3) after active stimulation, but with no effect in the digit span or Corsi cubes. Soff et al. [114] also observed a reduction in inattention measured with the working memory component of the QbTest. This effect was observed 7 days after stimulation. Finally, Prehn-Kristensen et al. [102] found no effect of toDCS performed in 12 ADHD children and 12 healthy controls in the digit span, although he described improved memory consolidation after active stimulation.

The role of tDCS in improving attention in patients with ADHD is still being investigated. Although promising results have been demonstrated, there are several methodological issues that need to be overcome before the true potential of tDCS in clinical practice can be recognized.

28.9 Clinical Outcomes

Only two studies evaluated the effects of tDCS in ADHD with the use of clinical scales [18, 114]. In the study of Cachoeira et al. [18], 17 adult ADHD patients were randomized for an active or sham stimulation (anodal F4, cathodal F3). Clinical symptoms were measured with the use of the Adult ADHD Self-Report Scale Symptom Checklist-v1.1 (ASRS), and functional impairment was measured with the Sheehan Disability Scale (SDS). Authors reported decreased inattention symptoms after active stimulation, together with decreased functional impairment evaluated with the SDS. Soff et al. [114] explored the effects of five stimulation sessions with tDCS in 15 ADHD children. The parents' version of a German adaptive ADHD Diagnostic Checklist (FBB-ADHD) was used as main outcome. Authors observed a decrease in inattention symptoms after active stimulation.

28.10 Ongoing Studies

According to a search conducted in eight clinical trials database on May 2020, there were seven clinical trials of tDCS actively randomizing patients with ADHD at the time, and one clinical trial that has completed recruitment but was still not finished. The first search was conducted in ClinicalTrials.gov, and four studies testing the effects of tDCS exclusively in patients with ADHD were identified. The first study, "The Efficacy of Cathodal Transcranial Direct Current Stimulation in Children and Adolescents with Attention-deficit Hyperactivity Disorder" (NCT03955692), was a crossover, randomized, double-blinded, sham-controlled clinical trial with an estimated enrollment of 10 children with ADHD. In this study, authors aimed at evaluating the effects of five sessions of tDCS (cathodal F3 and anodal Fp2) in inhibitory control while measuring EEG event-related potentials. In the study

"Transcranial Direct Current Stimulation for the Treatment of Inattention Symptoms in Attention-deficit/Hyperactivity Disorder: a Randomized, Double-blind, Parallel, Controlled Clinical Trial (*TUNED* Trial)" (NCT04003740), 64 adult patients with ADHD were randomized to a parallel, double-blinded, sham-controlled clinical trial, testing the efficacy of a home-based tDCS device (anodal F4 and cathodal F3) in improving inattention symptoms. Subjects received a daily stimulation during the first 4 weeks, two weekly stimulations for the next 4 weeks, and one weekly stimulation over the last 4 weeks. A functional MRI was performed in a subsample of subjects before and after treatment. In the study "A Dose-Response Study of the Cognitive and Physiological Effects of tDCS to the DLPFC" (NCT04175041), 104 adult subjects (including patients with ADHD and healthy controls) were randomized to a crossover, double-blind study, testing the effects of tDCS (anodal F3) in the Eriksen flanker test while measuring the amplitude of EEG event-related potentials. In the study "Neuromodulation of Executive Function in the ADHD Brain" (NCT04175028), 120 subjects (including patients with ADHD and healthy controls) were randomized to a crossover, double-blind study, testing the effects of tDCS on executive functions and inhibitory control. The amplitude of EEG event-related potentials was also measured.

The second search was performed in the ISRCTN registry, and one ongoing study that was no longer recruiting subjects was found. In the study, "A novel brain-based therapy for attention deficit hyperactivity disorder children using transcranial direct current stimulation combined with cognitive training" (ISRCTN48265228), 50 male children with ADHD were randomized to a double-blind, sham-controlled trial testing the effects of tDCS (anodal F8, cathodal over the left eyebrow) combined with cognitive training in ADHD symptoms. EEG measurements were also performed. The third search was conducted in the German Clinical Trials Register, where two studies were identified. The first study, "Effects of transcranial electrical stimulation on the working memory and related neuronal networks in children with ADHD" (DRKS00010091), was a parallel, double-blinded, sham-controlled clinical trial with an estimated enrollment of 60 children with ADHD. In this study, authors evaluated the effects of tDCS on working memory, while also evaluating distinct effects of tDCS stimulation in the morning versus in the evening. Predictors of tDCS effects including genetic predisposition and patterns of neuronal connectivity in EEG were explored. The second study, "Improving neuropsychological functions and clinical course in children and adolescents with ADHD with anodal transcranial direct current stimulation (tDCS) of the prefrontal cortex: a randomized, double-blind, sham-controlled, parallel group trial using an uncertified class IIa device" (DRKS00012659), was a parallel, double-blinded, sham-controlled study investigating the effect of 10 sessions of anodal stimulation over F3 or F8 in improving working memory or inhibitory control, respectively. Target sample is of 200 children with ADHD, and authors also performed resting state EEG and resting state functional MRI. No studies were found in the European Union Clinical Trial Register, the Australian New Zealand Clinical Trials Registry, the Brazilian Registry of Clinical Trials, the Chinese Clinical Trial Registry, and the Netherlands Trial Register.

28.11 Challenges for Future Research

There are several challenges to be overcome in order to better understand the potential of tDCS treatment for patients with ADHD. A detailed analysis of the published literature allows us to identify the exploratory nature of most studies. Although exploratory studies are essential for providing hypothesis to be tested in future clinical trials, the results should be viewed in light of their intrinsic limitations. In this sense, future studies should use the available information as a backbone for the implementation of well-designed clinical trials that are necessary for a more precise judgment of the real potential of tDCS as a treatment for patients with ADHD. We have highlighted the following five main points

that we believe should be taken into consideration in the design of future clinical trials:

1. Sample size

The majority of studies published so far are characterized by small sample sizes. The use of a crossover design was the choice of 11 of the 14 studies, and it is a good alternative to increase the power to observe significant effects [129]. Nevertheless, the use of a crossover design will also require adequate washout periods, which could be a delicate decision since there is still not enough information to judge the full influence of carryover effects in tDCS research. Larger sample sizes with well-defined sample size calculations will be required in future studies in order to judge whether the clinical trial had enough power to detect differences between treatment arms. Although effect sizes reported by exploratory trials might be used in this calculation, researchers should be aware that effect sizes are usually overestimated in exploratory pilot studies [64].

2. Primary outcomes

Most studies published so far did not report a protocol submission prior to data acquisition. Protocol submission is a key step in the evaluation of a clinical trial results, since it presents which hypothesis were defined a priori, and whether a main outcome was defined prior to data acquisition. Most clinical trials of tDCS in ADHD have used more than one behavioral task, and some tasks even present two or more variables as outcomes. The performance of multiple analysis is known to increase the false-positive rate, and should be taken into consideration when analyzing the results. Only seven studies described in this chapter presented any kind of statistical correction for multiple comparisons. Although it could be argued that this absence is associated to the exploratory nature of the studies, it should definitely alert to the possibility of false positive results. Future studies should define primary outcome a priori and publish the protocol in appropriate databases prior to start data collection. Moreover, statistical tools to correct for multiple comparisons should be adequately used in order to decrease the chance of false positive findings.

3. Target population considering ADHD heterogeneity

The design of future studies should be adapted to specific aspects of the target population that includes, among others, the age of subjects (children/adolescents or adults), ADHD presentation (inattentive, hyperactive/impulsive or combined), comorbidities, and the use of concomitant pharmacological therapy. Ten of the 14 studies discussed in this chapter were performed in children with ADHD, while four studies were performed in adult patients. The higher number of studies in children and adolescents is in accordance to the epidemiology of the disorder, whose prevalence in childhood is about two times the prevalence in adulthood [30, 65, 99, 125]. In the design of future trials, the selection between children and adults would likely involve a careful consideration of safety and methodological aspects, including the more plastic nature of children's developing brain, anatomical differences between children and adults (smaller head size, smaller skull thickness, and lower corticospinal fluid volumes [96]), and differences in gray and white matter differentiation [5]. Identical electrical currents generated by tDCS appear to induce different cortical electrical fields in children and adults. Computational models have suggested that the same current intensity generated by tDCS stimulation will induce higher electrical currents at the cortical surface of children when compared to adults [62]. Due to that, most researchers advocate that children should be given an electrical current that is half the intensity of the one adults are given [62]. Finally, the substantial heterogeneity in the clinical presentation of ADHD across development should be considered before selecting which symptomatologic domain is the target of the intervention.

The ADHD presentation is another aspect to be considered in the design of future clinical trials. If a researcher aims at testing tDCS for improving attention or working memory, for instance, the target sample should ideally com-

prise subjects with the inattentive or combined presentations, or patients with significant working memory deficits, in order to avoid any floor effect. Researchers should also be aware that ADHD is characterized by substantial psychiatric comorbidity that can cause or intensify symptoms of ADHD. It is usually recommended that the treatment of comorbid conditions should be prioritized [21]. Therefore, researchers should include a broad assessment of psychiatric comorbidities in patients with ADHD before randomization, especially comorbid mood disorders. Randomization should be ideally performed in patients with ADHD without comorbid psychiatric disorders. However, since the exclusion of subjects with psychiatric comorbidities would likely decrease recruitment rates, comorbidities should be optimally treated before starting a clinical trial with tDCS.

Finally, future studies should consider whether tDCS could be used as an alternative to pharmacological treatment, or as an additive to these medications. The combination of tDCS and pharmacological treatment has been shown to produce synergic effects in depression [17], and thus the potentiation of pharmacological effects is a promising strategy. On the other hand, pharmacological therapy for ADHD, especially with stimulant medication, has been shown to present relevant effect sizes [33], and synergic effects with tDCS have not been investigated. Studies aiming to propose tDCS as an alternative treatment to medication should either include subjects without a history of pharmacological treatment, or submit subjects to an adequate washout period.

4. Electrode placement

Studies published so far have chosen the site of stimulation based on neuroimaging studies on ADHD, and on prior evidence of tDCS effects in other psychiatric disorders. The data collected until now indicates that anodal stimulation over the DLPFC is more effective than anodal stimulation over IFG, mainly for improving behavioral inhibition [109]. However, any conclusions derived from the current evidence regarding the optimal tDCS montage for ADHD would likely be biased due to the small number of studies. Therefore, further studies are required before an optimal stimulatory region can be proposed.

5. TDCS dosage

Even though there is still debate in the literature regarding the best approach to measure tDCS dosage, the following parameters are commonly considered: (1) intensity of stimulation, (2) session duration, (3) electrode size, and (4) number of sessions. Research is still needed on order to better understand the relation between tDCS dosage and clinical response in patients with ADHD. In depression, for instance, higher dosages were shown to induce better clinical responses [16]. Nevertheless, whether there is a linear relationship between tDCS dosage and clinical response is still not known.

In the studies reviewed, most have chosen a stimulatory intensity of 1 mA, in which the induced field density is approximately half of the one induced by a 2 mA stimulation [108]. The fact that most trials were conducted in children should be highlighted, since modeling studies have suggested that the field density induced by a 1 mA stimulation in children is similar to the one induced by a 2 mA stimulation in adults [62]. Even though there is still not a consensus on the relationship between electrical field density and the neuromodulatory effects of tDCS, a higher field strength appears to be associated with increased neuronal plasticity in healthy subjects [3].

The duration of tDCS sessions was of 20 min in eight studies, 15 min in three studies, 30 min in one study, and five sections of 5 min each in the two studies using toDCS. In a meta-analysis summarizing tDCS effects in depression using individual patient data, longer stimulation sessions were shown to be associated with better clinical responses [16]. In ADHD, however, we cannot summarize the influence of session duration due to the low number of studies. The electrode size is another aspect to be emphasized. Studies modeling the effects of tDCS have shown that the electrode size, together with the electrode distance, can alter the density of the electrical current in

brain tissue. In healthy subjects, for instance, stimulation with electrodes measuring 35 cm^2 resulted in increased cortical excitability when compared to electrodes measuring 16 cm^2 [52]. Finally, most studies reviewed here performed a single stimulation session. There are still questions regarding the number of sessions necessary to obtain clinically significant improvements.

28.12 Conclusions

To sum up, ADHD is a prevalent condition across the life cycle and is associated with several negative outcomes. Although the pathophysiology of ADHD is still not fully understood, meta-analyses of neuroimaging studies indicate reduced activation of fronto-striatal and fronto-cortical circuits during tasks requiring attention or behavioral inhibition. The efficacy of tDCS in ADHD has been evaluated in pilot studies. Promising findings have been reported, especially after anodal stimulation over the DLPFC. However, there are several methodological issues that still need to be better explored in order to judge the efficacy of tDCS treatment in patients with ADHD. The current literature should serve as a backbone for the design of future trials.

References

1. Allenby C, Falcone M, Bernardo L, Wileyto P, Rostain A, Ramsay JR, Lerman C, Loughead J. Transcranial direct current brain stimulation decreases impulsivity in ADHD. Brain Stimul. 2018;11(5):974–81.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013.
3. Antonenko D, Thielscher A, Saturnino GB, Aydin S, Ittermann B, Grittner U, Flöel A. Towards precise brain stimulation: is electric field simulation related to neuromodulation? Brain Stimul. 2019;12:1159–68.
4. Bandeira ID, Guimarães RS, Jagersbacher JG, Barretto TL, De Jesus-Silva JR, Santos SN, Argollo N, Lucena R. Transcranial direct current stimulation in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): a pilot study. J Child Neurol. 2016;31:918–24.
5. Beauchamp MS, Beurlot MR, Fava E, Nath AR, Parikh NA, Saad ZS, Bortfeld H, Oghalai JS. The developmental trajectory of brain-scalp distance from birth through childhood: implications for functional neuroimaging. PLoS One. 2011;6:e24981.
6. Beheshti A, Chavanon ML, Christiansen H. Emotion dysregulation in adults with attention deficit hyperactivity disorder: a meta-analysis. BMC Psychiatry. 2020;20:120.
7. Bernardi S, Faraone SV, Cortese S, Kerridge BT, Pallanti S, Wang S, Blanco C. The lifetime impact of attention deficit hyperactivity disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Psychol Med. 2012;42:875–87.
8. Bikic A, Reichow B, Mccauley SA, Ibrahim K, Sukhodolsky DG. Meta-analysis of organizational skills interventions for children and adolescents with attention-deficit/hyperactivity disorder. Clin Psychol Rev. 2017;52:108–23.
9. Bonvicini C, Faraone SV, Scassellati C. Attention-deficit hyperactivity disorder in adults: a systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. Mol Psychiatry. 2016;21:872–84.
10. Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics. 2010;125:e1270–7.
11. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect. 2006;114:1904–9.
12. Breitling C, Zaehle T, Dannhauer M, Bonath B, Tegelbeckers J, Flechtner HH, Krauel K. Improving interference control in ADHD patients with transcranial direct current stimulation (tDCS). Front Cell Neurosci. 2016;10:72.
13. Breitling C, Zaehle T, Dannhauer M, Tegelbeckers J, Flechtner HH, Krauel K. Comparison between conventional and HD-tDCS of the right inferior frontal gyrus in children and adolescents with ADHD. Clin Neurophysiol. 2020;131:1146–54.
14. Breslau J, Miller E, Joanie Chung WJ, Schweitzer JB. Childhood and adolescent onset psychiatric disorders, substance use, and failure to graduate high school on time. J Psychiatr Res. 2011;45:295–301.
15. Brikell I, Larsson H, Lu Y, Pettersson E, Chen Q, Kuja-Halkola R, Karlsson R, Lahey BB, Lichtenstein P, Martin J. The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. Mol Psychiatry. 2018;25(8):1809–21.
16. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, Daskalakis ZJ, Bennabi D, Haffen E, Alonzo A, Loo CK. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208:522–31.

17. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, De Oliveira JF, Goulart A, Boggio PS, Lotufo PA, Benseñor IM, Fregni F. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383–91.
18. Cachoeira CT, Leffa DT, Mittelstadt SD, Mendes LST, Brunoni AR, Pinto JV, Blazius V, Machado V, Bau CHD, Rohde LA, Grevet EH, Schestatsky P. Positive effects of transcranial direct current stimulation in adult patients with attention-deficit/hyperactivity disorder – a pilot randomized controlled study. Psychiatry Res. 2017;247:28–32.
19. Castells X, Cunill R, Capella D. Treatment discontinuation with methylphenidate in adults with attention deficit hyperactivity disorder: a meta-analysis of randomized clinical trials. Eur J Clin Pharmacol. 2013;69:347–56.
20. Caye A, Spadini AV, Karam RG, Grevet EH, Rovaris DL, Bau CH, Rohde LA, Kieling C. Predictors of persistence of ADHD into adulthood: a systematic review of the literature and meta-analysis. Eur Child Adolesc Psychiatry. 2016;25:1151–9.
21. Caye A, Swanson JM, Coghill D, Rohde LA. Treatment strategies for ADHD: an evidence-based guide to select optimal treatment. Mol Psychiatry. 2019;24:390–408.
22. Chang Z, D'onofrio BM, Quinn PD, Lichtenstein P, Larsson H. Medication for attention-deficit/hyperactivity disorder and risk for depression: a nationwide longitudinal cohort study. Biol Psychiatry. 2016;80:916–22.
23. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years: adherence, effectiveness, and adverse effects. J Am Acad Child Adolesc Psychiatry. 2004;43:559–67.
24. Chen MH, Hsu JW, Huang KL, Bai YM, Ko NY, Su TP, Li CT, Lin WC, Tsai SJ, Pan TL, Chang WH, Chen TJ. Sexually transmitted infection among adolescents and young adults with attention-deficit/hyperactivity disorder: a nationwide longitudinal study. J Am Acad Child Adolesc Psychiatry. 2018;57:48–53.
25. Chen MH, Pan TL, Wang PW, Hsu JW, Huang KL, Su TP, Li CT, Lin WC, Tsai SJ, Chen TJ, Bai YM. Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: a nationwide study in Taiwan. J Clin Psychiatry. 2019a;80(5):18m12612.
26. Chen Q, Brikell I, Lichtenstein P, Serlachius E, Kuja-Halkola R, Sandin S, Larsson H. Familial aggregation of attention-deficit/hyperactivity disorder. J Child Psychol Psychiatry. 2017a;58:231–9.
27. Chen Q, Sjölander A, Runeson B, D'onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ. 2014;348:g3769.
28. Chen VC, Chan HL, Wu SI, Lee M, Lu ML, Liang HY, Dewey ME, Stewart R, Lee CT. Attention-deficit/hyperactivity disorder and mortality risk in Taiwan. JAMA Netw Open. 2019b;2:e198714.
29. Chen VC, Yang YH, Liao YT, Kuo TY, Liang HY, Huang KY, Huang YC, Lee Y, Mcintyre RS, Lin TC. The association between methylphenidate treatment and the risk for fracture among young ADHD patients: a nationwide population-based study in Taiwan. PLoS One. 2017b;12:e0173762.
30. Cheung CH, Rijdijk F, Mcloughlin G, Faraone SV, Asherson P, Kuntsi J. Childhood predictors of adolescent and young adult outcome in ADHD. J Psychiatr Res. 2015;62:92–100.
31. Choi Y, Shin J, Cho KH, Park EC. Change in household income and risk for attention deficit hyperactivity disorder during childhood: a nationwide population-based cohort study. J Epidemiol. 2017;27:56–62.
32. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring. JAMA Netw Open. 2019;2:e186606.
33. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, Atkinson LZ, Tessari L, Banaschewski T, Coghill D, Hollis C, Simonoff E, Zuddas A, Barbui C, Purgato M, Steinhausen HC, Shokraneh F, Xia J, Cipriani A. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5:727–38.
34. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169:1038–55.
35. Cosmo C, Baptista AF, De Araujo AN, Do Rosario RS, Miranda JG, Montoya P, De Sena EP. A randomized, double-blind, sham-controlled trial of transcranial direct current stimulation in attention-deficit/hyperactivity disorder. PLoS One. 2015;10:e0135371.
36. Curry AE, Metzger KB, Pfeiffer MR, Elliott MR, Winston FK, Power TJ. Motor vehicle crash risk among adolescents and young adults with attention-deficit/hyperactivity disorder. JAMA Pediatr. 2017;171:756–63.
37. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry. 2015a;2:702–9.
38. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet. 2015b;385:2190–6.
39. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, Baldursson G, Belliveau R, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Churchhouse C, Dumont A, Eriksson

N, Gandal M, Goldstein JI, Grasby KL, Grove J, Gudmundsson OO, Hansen CS, Hauberg ME, Hollegaard MV, Howrigan DP, Huang H, Maller JB, Martin AR, Martin NG, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Ripke S, Robinson EB, Satterstrom FK, Stefansson H, Stevens C, Turley P, Walters GB, Won H, Wright MJ, Andreassen OA, Asherson P, Burton CL, Boomsma DI, Cormand B, Dalsgaard S, Franke B, Gelernter J, Geschwind D, Hakonarson H, Haavik J, Kranzler HR, Kuntsi J, Langley K, Lesch KP, Middeldorp C, Reif A, Rohde LA, Roussos P, Schachar R, Sklar P, Sonuga-Barke EJS, Sullivan PF, Thapar A, Tung JY, Waldman ID, Medland SE, Stefansson K, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Daly MJ, Faraone SV, Børglum AD, Neale BM. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51:63–75.

40. Dey M, Paz Castro R, Haug S, Schaub MP. Quality of life of parents of mentally-ill children: a systematic review and meta-analysis. Epidemiol Psychiatr Sci. 2019;28:563–77.
41. Dong T, Hu W, Zhou X, Lin H, Lan L, Hang B, Lv W, Geng Q, Xia Y. Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Reprod Toxicol. 2018;76:63–70.
42. Faraone SV. The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev. 2018;87:255–70.
43. Fitzgerald C, Dalsgaard S, Nordentoft M, Erlangsen A. Suicidal behaviour among persons with attention-deficit hyperactivity disorder. Br J Psychiatry. 2019;215(4):615–20.
44. Fleming M, Fitton CA, Steiner MFC, Mclay JS, Clark D, King A, Mackay DF, Pell JP. Educational and health outcomes of children treated for attention-deficit/hyperactivity disorder. JAMA Pediatr. 2017;171:e170691.
45. Fletcher JM. The effects of childhood ADHD on adult labor market outcomes. Health Econ. 2014;23:159–81.
46. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC, Procianoy RS, Rohde LA, Moreira-Maia CR. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics. 2018;141(1):e20171645.
47. Ghirardi L, Chen Q, Chang Z, Kuja-Halkola R, Skoglund C, Quinn PD, D'onofrio BM, Larsson H. Use of medication for attention-deficit/hyperactivity disorder and risk of unintentional injuries in children and adolescents with co-occurring neurodevelopmental disorders. J Child Psychol Psychiatry. 2020;61:140–7.
48. Goodlad JK, Marcus DK, Fulton JJ. Lead and attention-deficit/hyperactivity disorder (ADHD) symptoms: a meta-analysis. Clin Psychol Rev. 2013;33:417–25.
49. Groenman AP, Oosterlaan J, Rommelse N, Franke B, Roeyers H, Oades RD, Sergeant JA, Buitelaar JK, Faraone SV. Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. Addiction. 2013;108:1503–11.
50. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiat. 2013;70:185–98.
51. Hawkey E, Nigg JT. Omega-3 fatty acid and ADHD: blood level analysis and meta-analytic extension of supplementation trials. Clin Psychol Rev. 2014;34:496–505.
52. Ho KA, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, Dokos S, Loo CK. The effect of transcranial direct current stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. Brain Stimul. 2016;9:1–7.
53. Holmskov M, Storebo OJ, Moreira-Maia CR, Ramstad E, Magnusson FL, Krogh HB, Groth C, Gillies D, Zwi M, Skoog M, Gluud C, Simonsen E. Gastrointestinal adverse events during methylphenidate treatment of children and adolescents with attention deficit hyperactivity disorder: a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. PLoS One. 2017;12:e0178187.
54. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, Van Hulzen KJE, Medland SE, Shumskaya E, Jahanshad N, Zeeuw P, Szekely E, Sudre G, Wolfers T, Onnink AMH, Dammers JT, Mostert JC, Vives-Gilabert Y, Kohls G, Oberwelland E, Seitz J, Schulte-Ruther M, Ambrosino S, Doyle AE, Hovik MF, Dramsdahl M, Tamm L, Van Erp TGM, Dale A, Schork A, Conzelmann A, Zierhut K, Baur R, Mccarthy H, Yoncheva YN, Cubillo A, Chantiluke K, Mehta MA, Paloyelis Y, Hohmann S, Baumeister S, Bramati I, Mattos P, Tovar-Moll F, Douglas P, Banaschewski T, Brandeis D, Kuntsi J, Asherson P, Rubia K, Kelly C, Martino AD, Milham MP, Castellanos FX, Frodl T, Zentis M, Lesch KP, Reif A, Pauli P, Jernigan TL, Haavik J, Plessen KJ, Lundervold AJ, Hugdahl K, Seidman LJ, Biederman J, Rommelse N, Heslenfeld DJ, Hartman CA, Hoekstra PJ, Oosterlaan J, Polier GV, Konrad K, Vilarroya O, Ramos-Quiroga JA, Soliva JC, Durston S, Buitelaar JK, Faraone SV, Shaw P, Thompson PM, Franke B. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017;4:310–9.

55. Hoogman M, Muetzel R, Guimaraes JP, Shumskaya E, Mennes M, Zwiers MP, Jahanshad N, Sudre G, Wolfers T, Earl EA, Soliva Vila JC, Vives-Gilabert Y, Khadka S, Novotny SE, Hartman CA, Heslenfeld DJ, Schweren LJS, Ambrosino S, Oranje B, De Zeeuw P, Chaim-Avancini TM, Rosa PGP, Zanetti MV, Malpas CB, Kohls G, Von Polier GG, Seitz J, Biederman J, Doyle AE, Dale AM, Van Erp TGM, Epstein JN, Jernigan TL, Baur-Streubel R, Ziegler GC, Zierhut KC, Schrantee A, Hovik MF, Lundervold AJ, Kelly C, Mccarthy H, Skokauskas N, O'gorman Tuura RL, Calvo A, Lera-Miguel S, Nicolau R, Chantiluke KC, Christakou A, Vance A, Cercignani M, Gabel MC, Asherson P, Baumeister S, Brandeis D, Hohmann S, Bramati IE, Tovar-Moll F, Fallgatter AJ, Kardatzki B, Schwarz L, Anikin A, Baranov A, Gogberashvili T, Kapilushniy D, Solovieva A, El Marroun H, White T, Karkashadze G, Namazova-Baranova L, Ethofer T, Mattos P, Banaschewski T, Coghill D, Plessen KJ, Kuntsi J, Mehta MA, Paloyelis Y, Harrison NA, Bellgrove MA, Silk TJ, Cubillo AI, Rubia K, Lazaro L, Brem S, Walitza S, Frodl T, Zentis M, Castellanos FX, Yoncheva YN, Haavik J, Reneman L, Conzelmann A, Lesch KP, Pauli P, Reif A, Tamm L, Konrad K, Oberwelland Weiss E, Busatto GF, Louza MR, et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. Am J Psychiatry. 2019;176:531–42.
56. Hua MH, Huang KL, Hsu JW, Bai YM, Su TP, Tsai SJ, Li CT, Lin WC, Chen TJ, Chen MH. Early pregnancy risk among adolescents with ADHD: a nationwide longitudinal study. J Atten Disord. 2020; https://doi.org/10.1177/1087054719900232.
57. Huang L, Wang Y, Zhang L, Zheng Z, Zhu T, Qu Y, Mu D. Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. Pediatrics. 2018;141(1):e20172465.
58. Jackson JN, Mackillop J. Attention-deficit/hyperactivity disorder and monetary delay discounting: a meta-analysis of case-control studies. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1:316–25.
59. Jacoby N, Lavidor M. Null tDCS effects in a sustained attention task: the modulating role of learning. Front Psychol. 2018;9:476.
60. Jangmo A, Stålhandske A, Chang Z, Chen Q, Almqvist C, Feldman I, Bulik CM, Lichtenstein P, D'onofrio B, Kuja-Halkola R, Larsson H. Attention-deficit/hyperactivity disorder, school performance, and effect of medication. J Am Acad Child Adolesc Psychiatry. 2019;58:423–32.
61. Keilow M, Holm A, Fallesen P. Medical treatment of attention deficit/hyperactivity disorder (ADHD) and children's academic performance. PLoS One. 2018;13:e0207905.
62. Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8:e76112.
63. Knouse LE, Teller J, Brooks MA. Meta-analysis of cognitive-behavioral treatments for adult ADHD. J Consult Clin Psychol. 2017;85:737–50.
64. Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch Gen Psychiatry. 2006;63:484–9.
65. Lara C, Fayyad J, De Graaf R, Kessler RC, Aguilar-Gaxiola S, Angermeyer M, Demytteneare K, De Girolamo G, Haro JM, Jin R, Karam EG, Lepine JP, Mora ME, Ormel J, Posada-Villa J, Sampson N. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biol Psychiatry. 2009;65:46–54.
66. Larsson H, Sariaslan A, Långström N, D'onofrio B, Lichtenstein P. Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. J Child Psychol Psychiatry. 2014;55:428–35.
67. Lee PH, Anttila V, Won H, Feng Y-CA, Rosenthal J, Zhu Z, Tucker-Drob EM, Nivard MG, Grotzinger AD, Posthuma D, Wang MMJ, Yu D, Stahl EA, Walters RK, Anney RJL, Duncan LE, Ge T, Adolfsson R, Banaschewski T, Belangero S, Cook EH, Coppola G, Derks EM, Hoekstra PJ, Kaprio J, Keski-Rahkonen A, Kirov G, Kranzler HR, Luykx JJ, Rohde LA, Zai CC, Agerbo E, Arranz MJ, Asherson P, Bækvad-Hansen M, Baldursson G, Bellgrove M, Belliveau RA, Buitelaar J, Burton CL, Bybjerg-Grauholm J, Casas M, Cerrato F, Chambert K, Churchhouse C, Cormand B, Crosbie J, Dalsgaard S, Demontis D, Doyle AE, Dumont A, Elia J, Grove J, Gudmundsson OO, Haavik J, Hakonarson H, Hansen CS, Hartman CA, Hawi Z, Hervás A, Hougaard DM, Howrigan DP, Huang H, Kuntsi J, Langley K, Lesch K-P, Leung PWL, Loo SK, Martin J, Martin AR, Mcgough JJ, Medland SE, Moran JL, Mors O, Mortensen PB, Oades RD, Palmer DS, Pedersen CB, Pedersen MG, Peters T, Poterba T, Poulsen JB, Ramos-Quiroga JA, Reif A, Ribasés M, Rothenberger A, Rovira P, Sánchez-Mora C, Satterstrom FK, Schachar R, Artigas MS, Steinberg S, Stefansson H, Turley P, Walters GB, Werge T, Zayats T, Arking DE, Bettella F, Buxbaum JD, et al. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell. 2019;179:1469–82, e11.
68. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev. 2011;31:328–41.
69. Lee YC, Yang HJ, Chen VC, Lee WT, Teng MJ, Lin CH, Gossop M. Meta-analysis of quality of life in children and adolescents with ADHD: by both parent proxy-report and child self-report using PedsQL™. Res Dev Disabil. 2016;51-52:160–72.
70. Leffa DT, Bellaver B, Salvi AA, De Oliveira C, Caumo W, Grevet EH, Fregni F, Quincozes-Santos A, Rohde LA, Torres ILS. Transcranial direct cur-

rent stimulation improves long-term memory deficits in an animal model of attention-deficit/hyperactivity disorder and modulates oxidative and inflammatory parameters. Brain Stimul. 2018;11(4):743–51.
71. Leffa DT, De Souza A, Scarabelot VL, Medeiros LF, De Oliveira C, Grevet EH, Caumo W, De Souza DO, Rohde LAP, Torres ILS. Transcranial direct current stimulation improves short-term memory in an animal model of attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2016;26:368–77.
72. Li J, Olsen J, Vestergaard M, Obel C. Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. Eur Child Adolesc Psychiatry. 2010;19:747–53.
73. Liang SH, Yang YH, Kuo TY, Liao YT, Lin TC, Lee Y, Mcintyre RS, Kelsen BA, Wang TN, Chen VC. Suicide risk reduction in youths with attention-deficit/hyperactivity disorder prescribed methylphenidate: a Taiwan nationwide population-based cohort study. Res Dev Disabil. 2018;72:96–105.
74. Liao YT, Yang YH, Kuo TY, Liang HY, Huang KY, Wang TN, Lee Y, Mcintyre RS, Chen VC. Dosage of methylphenidate and traumatic brain injury in ADHD: a population-based study in Taiwan. Eur Child Adolesc Psychiatry. 2018;27:279–88.
75. Lichtenstein P, Halldner L, Zetterqvist J, Sjölander A, Serlachius E, Fazel S, Långström N, Larsson H. Medication for attention deficit-hyperactivity disorder and criminality. N Engl J Med. 2012;367:2006–14.
76. Lindström K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatrics. 2011;127:858–65.
77. Lu Y, Sjölander A, Cederlöf M, D'onofrio BM, Almqvist C, Larsson H, Lichtenstein P. Association between medication use and performance on higher education entrance tests in individuals with attention-deficit/hyperactivity disorder. JAMA Psychiat. 2017;74:815–22.
78. Maher GM, Dalman C, O'keeffe GW, Kearney PM, Mccarthy FP, Kenny LC, Khashan AS. Association between preeclampsia and attention-deficit hyperactivity disorder: a population-based and sibling-matched cohort study. Acta Psychiatr Scand. 2020;142(4):275–83.
79. Maher GM, O'keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, Khashan AS. Association of hypertensive disorders of pregnancy with risk of neurodevelopmental disorders in offspring: a systematic review and meta-analysis. JAMA Psychiat. 2018;75:809–19.
80. Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med. 2005;159:572–8.
81. Marx I, Hacker T, Yu X, Cortese S, Sonuga-Barke E. ADHD and the choice of small immediate over larger delayed rewards: a comparative meta-analysis of performance on simple choice-delay and temporal discounting paradigms. J Atten Disord. 2018;25(2):171–87. https://doi.org/10.1177/1087054718772138.
82. Mccarthy H, Skokauskas N, Frodl T. Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. Psychol Med. 2014;44:869–80.
83. Mccauley HL, Breslau JA, Saito N, Miller E. Psychiatric disorders prior to dating initiation and physical dating violence before age 21: findings from the National Comorbidity Survey Replication (NCS-R). Soc Psychiatry Psychiatr Epidemiol. 2015;50:1357–65.
84. Mohr-Jensen C, Müller Bisgaard C, Boldsen SK, Steinhausen HC. Attention-deficit/hyperactivity disorder in childhood and adolescence and the risk of crime in young adulthood in a Danish nationwide study. J Am Acad Child Adolesc Psychiatry. 2019;58:443–52.
85. Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry. 2009;48:484–500.
86. Momany AM, Kamradt JM, Nikolas MA. A meta-analysis of the association between birth weight and attention deficit hyperactivity disorder. J Abnorm Child Psychol. 2018;46:1409–26.
87. Munz MT, Prehn-Kristensen A, Thielking F, Mölle M, Göder R, Baving L. Slow oscillating transcranial direct current stimulation during non-rapid eye movement sleep improves behavioral inhibition in attention-deficit/hyperactivity disorder. Front Cell Neurosci. 2015;9:307.
88. Nejati V, Salehinejad MA, Nitsche MA, Najian A, Javadi AH. Transcranial direct current stimulation improves executive dysfunctions in ADHD: implications for inhibitory control, interference control, working memory, and cognitive flexibility. J Atten Disord. 2017;24(13):1928–43. https://doi.org/10.1177/1087054717730611.
89. Nejati V, Sarraj Khorrami A, Nitsche MA. Transcranial direct current stimulation improves reward processing in children with ADHD. J Atten Disord. 2020; https://doi.org/10.1177/1087054720923094.
90. Nelson LD, Guskiewicz KM, Marshall SW, Hammeke T, Barr W, Randolph C, Mccrea MA. Multiple self-reported concussions are more prevalent in athletes with ADHD and learning disability. Clin J Sport Med. 2016;26:120–7.
91. Nigg JT, Karalunas SL, Feczko E, Fair DA. Toward a revised nosology for attention-deficit/hyperactivity disorder heterogeneity. Biol Psychiatry Cogn Neurosci Neuroimaging. 2020;5(8):726–37.
92. Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or

attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. J Am Acad Child Adolesc Psychiatry. 2012;51:86–97, e8.
93. Nilsen FM, Tulve NS. A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. Environ Res. 2020;180:108884.
94. Norman LJ, Carlisi C, Lukito S, Hart H, Mataix-Cols D, Radua J, Rubia K. Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. JAMA Psychiat. 2016;73:815–25.
95. Østergaard SD, Dalsgaard S, Faraone SV, Munk-Olsen T, Laursen TM. Teenage parenthood and birth rates for individuals with and without attention-deficit/hyperactivity disorder: a nationwide cohort study. J Am Acad Child Adolesc Psychiatry. 2017;56:578–84, e3.
96. Palm U, Segmiller FM, Epple AN, Freisleder FJ, Koutsouleris N, Schulte-Körne G, Padberg F. Transcranial direct current stimulation in children and adolescents: a comprehensive review. J Neural Transm (Vienna). 2016;123:1219–34.
97. Perwien A, Hall J, Swensen A, Swindle R. Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder. J Manag Care Pharm. 2004;10:122–9.
98. Pievsky MA, Mcgrath RE. The neurocognitive profile of attention-deficit/hyperactivity disorder: a review of meta-analyses. Arch Clin Neuropsychol. 2018;33:143–57.
99. Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164:942–8.
100. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014;43:434–42.
101. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020;395:450–62.
102. Prehn-Kristensen A, Munz M, Göder R, Wilhelm I, Korr K, Vahl W, Wiesner CD, Baving L. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimul. 2014;7:793–9.
103. Rapport MD, Orban SA, Kofler MJ, Friedman LM. Do programs designed to train working memory, other executive functions, and attention benefit children with ADHD? A meta-analytic review of cognitive, academic, and behavioral outcomes. Clin Psychol Rev. 2013;33:1237–52.
104. Rimestad ML, Lambek R, Zacher Christiansen H, Hougaard E. Short- and long-term effects of parent training for preschool children with or at risk of ADHD: a systematic review and meta-analysis. J Atten Disord. 2019;23:423–34.
105. Ros R, Graziano PA. Social functioning in children with or at risk for attention deficit/hyperactivity disorder: a meta-analytic review. J Clin Child Adolesc Psychol. 2018;47:213–35.
106. Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, Magallón S, Alvarez Zallo N, Luis EO, De Castro-Manglano P, Soutullo C, Arrondo G. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2018;84:63–71.
107. Rydell M, Lundström S, Gillberg C, Lichtenstein P, Larsson H. Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample. J Child Psychol Psychiatry. 2018;59:863–71.
108. Salehinejad MA, Nejati V, Mosayebi-Samani M, Mohammadi A, Wischnewski M, Kuo M-F, Avenanti A, Vicario CM, Nitsche MA. Transcranial direct current stimulation in ADHD: a systematic review of efficacy, safety, and protocol-induced electrical field modeling results. Neurosci Bull. 2020;36(10):1191–212.
109. Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. PLoS One. 2019;14:e0215095.
110. Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. J Dev Behav Pediatr. 2004;25:423–34.
111. Septier M, Stordeur C, Zhang J, Delorme R, Cortese S. Association between suicidal spectrum behaviors and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2019;103:109–18.
112. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry. 2009;194:204–11.
113. Skoglund C, Kopp Kallner H, Skalkidou A, Wikström AK, Lundin C, Hesselman S, Wikman A, Sundström Poromaa I. Association of attention-deficit/hyperactivity disorder with teenage birth among women and girls in Sweden. JAMA Netw Open. 2019;2:e1912463.
114. Soff C, Sotnikova A, Christiansen H, Becker K, Siniatchkin M. Transcranial direct current stimulation improves clinical symptoms in adolescents with attention deficit hyperactivity disorder. J Neural Transm (Vienna). 2017;124:133–44.
115. Soltaninejad Z, Nejati V, Ekhtiari H. Effect of anodal and cathodal transcranial direct current stimulation

on DLPFC on modulation of inhibitory control in ADHD. J Atten Disord. 2015;23(4):325–32.
116. Sotnikova A, Soff C, Tagliazucchi E, Becker K, Siniatchkin M. Transcranial direct current stimulation modulates neuronal networks in attention deficit hyperactivity disorder. Brain Topogr. 2017;30:656–72.
117. Strine TW, Lesesne CA, Okoro CA, Mcguire LC, Chapman DP, Balluz LS, Mokdad AH. Emotional and behavioral difficulties and impairments in everyday functioning among children with a history of attention-deficit/hyperactivity disorder. Prev Chronic Dis. 2006;3:A52.
118. Sucksdorff M, Brown AS, Chudal R, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Gyllenberg D, Sourander A. Maternal vitamin D levels and the risk of offspring attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2019;60(1):142–51, e2.
119. Sucksdorff M, Lehtonen L, Chudal R, Suominen A, Joelsson P, Gissler M, Sourander A. Preterm birth and poor fetal growth as risk factors of attention-deficit/ hyperactivity disorder. Pediatrics. 2015;136:e599–608.
120. Sun S, Kuja-Halkola R, Faraone SV, D'onofrio BM, Dalsgaard S, Chang Z, Larsson H. Association of psychiatric comorbidity with the risk of premature death among children and adults with attention-deficit/hyperactivity disorder. JAMA Psychiat. 2019;76:1141–9.
121. Sundquist J, Ohlsson H, Sundquist K, Kendler KS. Attention-deficit/hyperactivity disorder and risk for drug use disorder: a population-based follow-up and co-relative study. Psychol Med. 2015;45:977–83.
122. Tseng PT, Cheng YS, Yen CF, Chen YW, Stubbs B, Whiteley P, Carvalho AF, Li DJ, Chen TY, Yang WC, Tang CH, Chu CS, Yang WC, Liang HY, Wu CK, Lin PY. Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis. Sci Rep. 2018;8:788.
123. Vaa T. ADHD and relative risk of accidents in road traffic: a meta-analysis. Accid Anal Prev. 2014;62:415–25.
124. Van Doren J, Arns M, Heinrich H, Vollebregt MA, Strehl U, S, K. L. Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2019;28:293–305.
125. Van Lieshout M, Luman M, Twisk JW, Van Ewijk H, Groenman AP, Thissen AJ, Faraone SV, Heslenfeld DJ, Hartman CA, Hoekstra PJ, Franke B, Buitelaar JK, Rommelse NN, Oosterlaan J. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. Eur Child Adolesc Psychiatry. 2016;25:1007–17.
126. Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM. Evaluating dopamine reward pathway in ADHD: clinical implications. JAMA. 2009;302:1084–91.
127. Volkow ND, Wang GJ, Newcorn J, Telang F, Solanto MV, Fowler JS, Logan J, Ma Y, Schulz K, Pradhan K, Wong C, Swanson JM. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2007;64:932–40.
128. Wang Y, Huang L, Zhang L, Qu Y, Mu D. Iron status in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. PLoS One. 2017;12:e0169145.
129. Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2012;109:276–81.
130. Xu G, Strathearn L, Liu B, Yang B, Bao W. Twenty-year trends in diagnosed attention-deficit/hyperactivity disorder among US children and adolescents, 1997–2016. JAMA Netw Open. 2018;1:e181471.
131. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, Davey Smith G, Stoltenberg C, Surén P, Håberg SE, Hornig M, Lipkin WI, Nordeng H, Reichborn-Kjennerud T. Prenatal exposure to acetaminophen and risk of ADHD. Pediatrics. 2017;140(5):e20163840.
132. Zhang J, Díaz-Román A, Cortese S. Meditation-based therapies for attention-deficit/hyperactivity disorder in children, adolescents and adults: a systematic review and meta-analysis. Evid Based Ment Health. 2018;21:87–94.

29 Cognitive Effects of Transcranial Direct Current Stimulation in Clinical Trials

Donel M. Martin and Adriano H. Moffa

29.1 Introduction

Neurocognitive dysfunction is a common comorbidity for many neuropsychiatric disorders for which there is still no effective treatment. These impairments are clinically significant due to their strong association with reduced patient functioning. To date, in clinical trials of transcranial direct current stimulation (tDCS), the investigation of neurocognitive effects has been common, primarily to establish the safety of the technique. This has also provided a valuable opportunity to evaluate the potential efficacy of tDCS for producing cognitive-enhancing effects. Such cognitive repercussions may not only contribute to therapeutic effects but are also of interest for clarifying the therapeutic mechanisms of this type of brain stimulation.

In the mid-1960s and early 1970s, initial open-label studies and randomised sham-controlled clinical trials (RCTs) were conducted examining the efficacy of "brain polarisation", the original term denoting the non-invasive administration of direct electrical currents to the brain. Although similar to tDCS, this technique typically used lower current intensities (i.e. <0.5 mA), longer session durations (e.g. >3 h) and a montage with two anodes in the frontal region and an extracephalic cathode, usually over the leg. Interestingly, the first report of neurocognitive effects from this form of tDCS emerged in a double-blind uncontrolled trial. In 32 patients with mild depression, a single prolonged session (1–4 h) of anodal polarisation was reported to increase alertness, motor activity and elevate mood, while cathodal polarisation, instead, induced silence and apathy [1]. These observations were made from blinded observers but without the use of any standardised instruments. By the late 1990s, a new stage in the development of the technique emerged in the context of advancements in the understanding of the pathophysiology of neuropsychiatric disorders and increased awareness of the limitations of pharmacological treatment. The modern tDCS clinical trials started using higher current intensities (between 1 and 2.5 mA), shorter session durations (typically from 20 to 30 min), a single anode and a cathode commonly placed over the cephalic region.

Since then, the efficacy of tDCS for treating many different neuropsychiatric and neurological conditions, ranging from schizophrenia, addiction, traumatic brain injury and stroke, has been explored in controlled trials. These studies further utilised enhanced clinical trial methodologies, including better characterisation of study participants, improved standardisation of treatment parameters, blinding with sham treatment and administration of standardised outcome mea-

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sures including neurocognitive tests. In this chapter, we describe the effects of tDCS on cognition as reported in modern clinical trials and provide an overview and discussion of its acute and potential lasting neurocognitive effects. Finally, we also include recent studies which have aimed to further enhance tDCS' neurocognitive effects with concurrent cognitive training.

29.2 Acute Cognitive Effects in Depression Clinical Trials

Acute cognitive effects refer to those measured either during or immediately after a single stimulation session. The first modern studies investigating these effects were conducted in the mid-2000s with healthy subjects and examined performance outcomes on executive functions, including probabilistic learning [2] and working memory [3]. Stimulation was administered concurrently "online" during task performance, with the anode placed over the left prefrontal cortex, consistent with the most commonly used montage for treating major depression. The initial promising results from these studies provided the rationale for investigating acute cognitive effects in patients with depression, to date, the most studied clinical disorder in the field of electrical stimulation.

In patients with major depression, reductions in neurocognitive function are common and can persist even in the remitted state [4]. A small proportion of patients additionally show significant deficits which are unrelated to the severity of other depressive symptomology, including mood [5]. Importantly, it is these neurocognitive symptoms which are most strongly associated with poorer functional outcomes [6]. For tDCS for depression, the anode is typically placed over the left dorsolateral prefrontal cortex (L-DLPFC), a key node within the neural circuitry that subserves cognitive functioning as well as mood regulation [7, 8].

In 2006 the first two modern sham-controlled clinical trials in depression were conducted involving 10 and 18 antidepressant medication-free participants, respectively [9, 10]. It was in Fregni and colleagues [10] that standardised neurocognitive measures to examine both acute and potentially cumulative cognitive effects from repeated treatments were included for the first time.

In another early tDCS RCT in depression, Boggio and colleagues [11] reported acute cognitive-enhancing effects after a single stimulation session. In that study, 26 patients with major depression were randomised to receive a single session of "offline" active tDCS with the anode placed either over the L-DLPFC or the occipital cortex, or sham tDCS. Cognitive effects were examined using an affective go/no go task that previously had been found sensitive to the effects of transcranial magnetic stimulation (TMS) [12]. Significant performance improvements only occurred in the active L-DLPFC tDCS condition and were just in relation to improved correct responses to stimuli with positive emotional valence (e.g. a couple holding hands). The participants then continued to receive the same stimulation condition over the next 10 consecutive weekdays, after which those in the active L-DLPFC condition showed superior antidepressant effects relative to the other experimental arms [11]. These results provided an important foundation for further study of cognitive and mood effects of tDCS in later larger clinical trials.

Correspondingly, other larger clinical trials followed, which similarly incorporated standardised neurocognitive testing to investigate the acute cognitive effects of tDCS. In a double-blind sham-controlled clinical trial of 64 patients with depression, Loo and colleagues [13] administered the Symbol Digit Modalities Test (SDMT) as well as a simple and choice reaction-time test immediately prior to and following the first active or sham tDCS session. Consistent with prior modern tDCS trials in depression, the anode was placed over the L-DLPFC, although the cathode was instead placed over F8 [International 10–20 electroencephalogram (EEG) system]. Only participants who received active tDCS significantly improved performance on the SDMT

after stimulation, suggesting enhanced attention and processing speed. No effect was found on the reaction-time measures. These cognitive gains were consistent with participants' subjective reports of improved concentration with active tDCS assessed after each treatment in the same trial (unpublished data).

Acute cognitive effects from a single tDCS session were then explored in subsequent trials. Interestingly, these effects have been most apparent on tests assessing "cognitive control" and complex attentional processing (see Table 29.1). Tests assessing "cognitive control" include those that evaluate functions which involve emotion regulation. For example, Brunoni and colleagues [14] found that "online" active tDCS significantly improved reaction times for negative compared to neutral words on the emotional Stroop task, a task which assesses response inhibition in the context of emotional stimuli. Other trials have alternatively found improvements in neurocognitive measures which assess complex attentional processing, including working memory [15] and visual attention [16]. Critically, reduced cognitive functioning in both domains is characteristic of the dysfunctional neural circuitry commonly identified in people with depression, suggesting "normalising" effects from stimulation. The potential clinical significance of these effects (e.g. for mood improvement), though, has yet to be determined. Additionally, whether similar or different, acute effects occur in other neuropsychiatric conditions is another area requiring further investigation.

Table 29.1 Summary of results from controlled clinical studies investigating the cognitive effects of a single tDCS session in patients with depression

Study	On/ offline	Electrode montage (anode/ cathode)	Current density(mA/ cm^2)	Sham setting	Task	Performance effect
Boggio et al., 2007 [11]	Offline	F3/RSO	0.057	On for 20 sec (max 2 mA), then off	Affective go/no go	Improved correct responses
Loo et al., 2012 [13]	Offline	F3/F8	0.057	On for 30 sec (max 1 mA), then left on	SDMT, SRT, CRT	Improved correct responses SDMT
Brunoni et al. 2013 [40]	Online	F3/F4	0.080	On for 60 sec (max 2 mA), then off	PCL	Absence of practice effect
Oliveira et al. 2013 [15]	Online	F3/F4	0.080	On for 60 sec (max 2 mA), then off	2-back	Improved correct responses
Brunoni et al., 2014 [29]	Online	F3/F4	0.080	On for 60 sec (max 2 mA), then off	WEST	Faster reaction times
Moreno et al., 2015 [41]	Offline	OLE	0.080	On for 30 sec (max 2 mA), then unknown	2-back, IST	Improved residual score change on 2 back Faster switch cost on emotion IST
Gogler et al., 2016 [16]	Offline	F3/RSO	0.057	On for 45 sec (max 2 mA), then sham setting	TVA	Increased elements processed/sec

Anode (A) and cathode (C) sites using the 10–20 system for EEG. EX refers to extracephalic (right deltoid muscle). *CRT* Choice Reaction Time, *DST* Digit Span Test, *ERT* Emotion Recognition Test, *IST* Internal Shift Task, *PCL* Probabilistic Classification Learning Task, *SDMT* Symbol Digit Modalities Test, *SRT* Simple Reaction Time, *TMT* Trail Making Test, *TT* Tapping Test, *TVA* Theory of Visual Attention, *WEST* Word Emotional Stroop Task

29.3 Cognitive Effects from Repeated tDCS Sessions in Clinical Trials

In modern trials, a typical treatment course has involved patients attending daily tDCS sessions over a period ranging from 1 to 4 weeks. In the majority of these trials, tDCS has been given while the patients are sitting at rest. Neurocognitive outcomes have often been assessed at pre and post completion of the treatment course primarily to establish the safety from repeated sessions. The question of whether repeated stimulation protocols may conversely cause enhancements in cognitive functioning however is additionally of clinical interest, as this has potentially significant implications for disorders where neurocognitive dysfunction is common.

The first modern double-blind controlled tDCS clinical trial in depression provided preliminary evidence for neurocognitive benefits from repeated tDCS sessions [10]. This small study included 18 participants who were randomised to receive five sessions of active or sham tDCS given over alternate days. A battery of neuropsychological tests was administered before the first session and immediately after the last treatment day. While there was no difference in outcomes for the majority of cognitive tasks, a significant difference between conditions was found for the Digit Span Forward and Digit Span Backward tasks, indicating greater improvement with active compared to sham stimulation. This suggested that active tDCS had positive effects on attention and working memory. Interestingly, cognitive improvement was unrelated to antidepressant effects. This study provided encouraging preliminary evidence supporting further investigation of the potential neurocognitive benefits from repeated tDCS sessions.

Subsequent larger trials, however, were unable to replicate that early finding. Loo and colleagues [13, 17] similarly administered neuropsychological batteries before and after repeated treatments, in 40 and 64 patients with depression, respectively. While the earlier of these [17] replicated the stimulation parameters used in Fregni and colleagues [9, 10], the latter study [13] employed further enhanced stimulation parameters, including daily treatment, stronger stimulus intensity and an increased number of treatment sessions. Nevertheless, both studies showed no differences in cognitive performance between the active and sham tDCS conditions. Unlike in the study by Fregni and colleagues [10], the majority of participants were taking concomitant antidepressant medications during treatment, which potentially may have interacted with stimulation effects [18].

These negative findings were confirmed in an individual patient data meta-analysis that included data from seven double-blind sham-controlled studies [19]. Data from 478 patients (260 who received active tDCS and 218 who received sham) were included, and analyses examined effects across common neurocognitive domains (i.e. global cognition, verbal learning and delayed recall). No benefit with active tDCS was found compared to sham after controlling for mood effects. Instead, active tDCS was found to be associated with less cognitive improvement on a measure of processing speed and attention, though this analysis included data from only two studies [20, 21]. This meta-analysis provided strong evidence for no neurocognitive benefit from repeated active tDCS sessions in patients with depression. A potential caveat to this finding, however, is that effects were only examined immediately following the treatment course. Given recent evidence for increased antidepressant effects after the acute treatment course [22], the potential for delayed neurocognitive benefits in patients with depression then cannot be ruled out.

Evidence of neurocognitive effects from repeated tDCS treatment in other neuropsychiatric conditions is still emerging (see Table 29.2). Although these studies have so far been small, potentially promising results have been found in patients with schizophrenia [23, 24] which require replication in larger trials.

Table 29.2 Summary of results from controlled clinical studies investigating the cognitive effects of repeated tDCS sessions

Study	Disorder	Sample size (active/sham)	Sessions	Electrode montage (anode/cathode)	Current density(mA/cm^2)	Tasks	Performance effect
Fregni et al., 2006 [10]	Dep	9/9	5	F3/RSO	0.028	MMSE, SDMT, DSp, Stroop, FPT	Improved DSp Forward and Back
Loo et al., 2010 [17]	Dep	20/20	5	F3/F8	0.028	RAVLT, TMT A and B, DSp, COWAT letter and category	No effect
Loo et al., 2012 [13]	Dep	33/31	15	F3/F8	0.057	RAVLT, DSp, Stroop, COWAT letter	No effect
Brunoni et al., 2013 [42]	Dep	30/30	12	F3/F4	0.080	MoCA, DSp, Stroop, TMT A and B	No effect
Bennabi et al., 2015 [43]	Dep	12/12	10	F3/RSO	0.057	MMSE, TMT A and B, COT, IST, PNT	No effect
Salehinejad et al., 2015 [44]	Dep	15/15	10	F3/F4	0.057	DMS, PRM	Improved visual recognition
Brunoni et al., 2017 [20]	Dep	94/60	22	OLE	0.080	MoCA, DSp, DSST, COWAT letter and category, TMT A and B	No effect
Loo et al., 2017 [21]	Dep/BP	61/59	20	F3/F8	0.071	MoCA, CVLT-II, DSp, SDMT, Ruff 2&7, DKEFS verbal fluency	No effect
Salehinejad et al., 2017 [45] Valiengo et al., 2017 [46]	DepPost-stroke Dep	12/1224/24	1012	F3/F4F3/F4	0.0570.080	PAL, SRM, RVP, CRTFAB, MMSE, MoCA, DSp, Stroop, TMT A and B, SDMT	Improved visual memory, visual spatial recognition and attention No effect
Bersani et al., 2017 [47]	BP	21/21	15	F3/RCerebellar	0.057	TMT A and B, WCST, RCFT	Improved TMT B

(continued)

Table 29.2 (continued)

Study	Disorder	Sample size (active/sham)	Sessions	Electrode montage (anode/cathode)	Current density(mA/cm^2)	Tasks	Performance effect
Tortella et al., 2020 [48]	BP	30/29	12	OLE	0.080	TMS A and B, BD, DSp, Stroop, DSST, RAVLT, LM, COWAT	No effect
Smith et al., 2015 [23]	Sz	19/18	5	F3/Fp2	0.080	MATRICS battery	Improved global composite, working memory, attention
Palm et al., 2016 [49]	Sz	10/10	10	F3/Fp2	0.057	SOPT, TMT A and B	No effect
Jeon et al., 2018 (24)Khedr et al., 2019 [50]	SzAD	28/2823/23	1010	F3/F4T3/P4 and T4/P4/left deltoid	0.0800.028	MATRICS battery, WCSTMMMSE, Clock drawing, MoCA	Improved global composite and working memory Improved global cognitive functioning

AD Alzheimer's disease, *BD* block design, *BP* bipolar disorder, *COT* Crossing Off Test, *COWAT* Controlled Oral Word Association Test, *CRT* Choice Reaction Time, *CVLT-II* California Verbal Learning Test Second Edition, *Dep* depression, *DKEFS* Delis-Kaplan Executive Function System, *DMS* delayed matching to sample, *DSST* Digit Symbol Substitution Test, *DSp* Digit Span, *FAB* Frontal Assessment Battery, *FPT* Five Point Test, *IST* Isaacs Set Test, *LM* logical memory, *MATRICS* Measurement and Treatment Research to Improve Cognition in Schizophrenia, *MMMSE* Modified Mini Mental State Examination, *MMSE* Mini Mental State Examination, *MoCA* Montreal Cognitive Assessment, *PAL* Paired Associates Learning, *PNT* Picture Naming Test, *RAVLT* Rey Auditory Verbal Learning Test, *Ruff 2&7* Ruff 2 & 7 Selective Attention Test, *SDMT* Symbol Digit Modalities Test, *SRM* Spatial Recognition Memory, *RCFT* Rey Complex Figure Test, *RVP* Rapid Visual Information Processing, *SOPT* Self Ordered Pointing Task, *Sz* schizophrenia, *TMT* Trail Making Test, *PRM* pattern recognition memory, *WCST* Wisconsin Card Sorting Test

29.4 Cognitive Effects of Repeated tDCS Sessions Combined with Cognitive Training in Clinical Trials

In the clinical trials discussed in the previous section, multiple sessions of tDCS were administered while the participants were seated at rest, without performing any concomitant task or activity (i.e. "offline" treatment). Pre-clinical studies of tDCS have since established that neural activity taking place during stimulation is an important aspect for the production of neuroplastic changes [25, 26]. Thus, the lack of control or standardisation of brain activity in these "offline" trials may have potentially caused increased interindividual variability in response to tDCS and/or limited treatment efficacy [27]. With that in mind, several more recent trials combined the administration of multiple sessions of tDCS with the simultaneous execution of tasks that involved the activation of the target regions being stimulated (i.e. "online" treatment), in search of increased therapeutic effects [28–30]. Many of these trials have combined tDCS with cognitive training (CT), a psychological intervention involving the repeated practice of targeted exercises, which alone has been shown to produce generalised cognitive improvement in various clinical populations [31, 32]. In such combined trials, for example, a participant with depression would simultaneously perform a working memory task to activate the L-DLPFC while being treated with tDCS applied over the same region. In the next section, we review preliminary clinical trials which have investigated neurocognitive effects from the combination of repeated tDCS sessions with "online" cognitive training in a variety of clinical disorders (See Table 29.3).

29.4.1 Depression

In a pilot study with depressed patients, Segrave and colleagues [28] investigated the effects on mood and cognition of the combination of tDCS with cognitive training (CT). CT involved two tasks requiring complex attentional processing, functions known to recruit the DLPFC. A sham CT condition requiring simple attention was additionally included as an active control. No differences between groups were found on a non-trained affective working memory task (positive and negative stimuli) administered following completion of the five combined treatment sessions. However, when re-evaluated during a follow-up visit after 3 weeks, only the group that received active tDCS together with "online" active CT showed better accuracy for negative stimuli.

29.4.2 Schizophrenia

In schizophrenia, cognitive impairment is more common, and hence an important target for novel interventions. In a pilot study with 49 patients with schizophrenia, Orlov and colleagues [33] examined the cognitive effects of combining active tDCS or sham with tasks requiring working memory and implicit language learning. Cognitive training took place twice a day (on days 1, 2, 14, 56), with "online" tDCS applied in the second session on days 1 and 14 (endpoint of cognitive assessment). No significant differences were found between the two experimental arms in terms of executive functioning (set-shifting task) or attention/vigilance (identification task) following the intervention. A limitation of this trial was that tDCS was only applied with CT in two of the eight sessions.

In a recent study, Weickert and colleagues [34] also assessed the effects of the combination of tDCS with CT in a small trial involving 12 outpatients with schizophrenia. Participants were randomised to receive active or sham tDCS administered during performance on a spatial working memory training task. The group receiving CT combined with active tDCS showed significantly greater improvement in working memory after 2 weeks and category fluency after 2 and 4 weeks compared to the sham tDCS condition. These promising results from this intensive study provided preliminary support for future larger trials of this combined technique in this clinical population.

Table 29.3 Summary of results from controlled clinical studies investigating the cognitive effects of repeated tDCS sessions combined with cognitive training

Study	Disorder	Sample size per arm	Number of tDCS sessions (total/combined with training)	Electrode montage (anode/cathode)	Current density(mA/cm^2)/tDCS duration	Cognitive training task(s)	Performance effect on non-trained tasks
Segrave et al., 2014 [28]	Dep	9 CT+tDCS/9 sham CT+tDCS/9 CT+sham tDCS	5/all	F3/F8	0.057/24 min	CT: modified WAT and adaptative PSAT; Sham CT: PVT	Improved accuracy with active tDCS+active CT at 3-week follow-up
Orlov et al., 2017 [33]	Sz	24 tDCS/25 sham	2/all	F3/Fp2	0.057/30 min	Working memory (n-back), implicit learning (language) and probabilistic learning	No effect
Weickert et al., 2019 [34]	Sz	6 tDCS/6 sham	20/all	F4/T3-P3	0.057/20 min	Spatial working memory (2-back)	Improved working memory after 2 weeks and category fluency after 2 and 4 weeks
Park et al., 2013 [51]	Stroke	6 tDCS/5 sham	mean of 18.5 days for tDCS; 17.8 days for sham/all	F3 or F4/non-dominant arm	0.08/30 min	Training programs for attention and memory	Improved auditory and visual attention
Martin et al., 2019 [35]	MCI	33 CT+tDCS/35 CT+sham	15/all	F3/F8	0.057/30 min	Exercises for working memory, processing speed and attention	No effect
Roncero et al., 2019 [36]	Anomia in AD or frontotemporal dementia	27 (crossover: I. tDCS at F3; II. tDCS at TP9; III. sham)	10+10+10/9+9+9	F3/right deltoid;TP9/Fp2	0.057/30 min	Protocol to improve naming accuracy of pictures	Improvement in naming untrained items

Tsapkini et al., 2018 [37]	Aphasia in neurodegenerative dementia	36 (crossover:I. active tDCS; II. sham)	15+15/all	F7 /right cheek	0.08/20 min	Language/spelling therapy	Improved spelling of non-trained words
Meinzer et al., 2016 [37]	Post-stroke aphasia	13 tDCS/13 sham	16 (twice a day for 8 days)/all	C3/Fp2	0.028 anode-0.01 cathode/20 min	Computer-assisted naming treatment for pictures	Improved naming of untrained items
den Uyl et al., 2018 [52]	Addiction (alcohol)	25 ABM+tDCS/26 ABM+sham/23 control ABM+ tDCS/ 24 control ABM+ sham	4/all	F3/F4	0.057 anode-0.02 cathode/ 20 min	Attentional bias modification task	No effect

CT cognitive training, *Dep* depression, *F3* left dorsolateral prefrontal cortex, *F8* right lateral orbitofrontal, *WAT* Wells Attentional Training, *PSAT* Paced Serial Addition Task, *PVT* peripheral vision training, *Sz* schizophrenia, *Fp2* right supraorbital, *T3-P3* left temporoparietal junction, *F4* right dorsolateral prefrontal cortex, *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *TP9* left temporoparietal, *C3* left primary motor cortex, *F7* left frontal lobe

29.4.3 Neurodegenerative and Neurological Conditions

Research attention has particularly focussed on investigating potential cognitive-enhancing effects in people with neurodegenerative and neurological disorders, due to the urgent need for novel interventions to alter or ameliorate disease progression and improve patient functioning. Martin and colleagues [35] investigated whether the adjuvant use of tDCS combined with CT could improve memory in people diagnosed with amnesic mild cognitive impairment (aMCI). Participants were randomised to receive CT combined with active or sham tDCS for 15 sessions conducted over 5 weeks (two or three sessions per week). CT included exercises to train abilities important for new learning and memory skills (e.g. complex attention, processing speed). Although the intention-to-treat analysis showed that the group that combined active tDCS with CT significantly improved memory after treatment compared to baseline (and that the group combined with sham did not), no statistically significant differences between conditions were found across a battery of non-trained tasks.

Several trials have now additionally examined for potential effects in patients with aphasia due to various conditions. Using a double-blind crossover design, Roncero et al. [36] analysed 12 participants (from the initial 27) with Alzheimer's disease or frontotemporal dementia who were trained in image naming in three series of 10 simultaneous sessions with active tDCS or sham stimulation. At the end of the experimental sessions, significantly greater improvements were observed in the naming of untrained images in the two groups that combined active tDCS with CT when compared to the group that received sham stimulation with CT. No differences, however, were found between conditions on a battery of other non-trained cognitive tasks. Similarly using a crossover design, Tsapkini and colleagues [37] randomly assigned 36 participants with primary progressive aphasia (PPA) to 15 daily sessions of active tDCS (2 mA for 20 minutes) or sham together with language training. Written naming/spelling training was simultaneously started with stimulation in both conditions. Spelling accuracy for the treated and untreated words was assessed at baseline (before training/stimulation), immediately after the end of the treatment course and at 2-week and 4-month follow-up. Overall, active tDCS combined with CT was more effective than its combination with sham for both word sets, suggesting generalisation of treatment effects. Finally, in an RCT in patients with chronic post-stroke aphasia, active tDCS or sham was administered at the beginning of each of the two daily language training sessions in an intensive 2-week intervention [38]. Training consisted of a computerised protocol to improve the naming accuracy of pictures lasting 1.5 h. All outcome measures were evaluated immediately before and after the end of the intervention, in addition to a 6-month follow-up evaluation. In the assessment immediately after the end of the treatment course and in the 6-month follow-up, the transfer of performance gains to untrained items was significantly greater in the group that received active tDCS combined with CT. Importantly, functional communication capacity was also significantly improved in both time points in the arm that received the active tDCS, suggesting generalised benefits.

29.4.4 Summary of Trials of tDCS Combined with CT in Clinical Conditions

The combination of tDCS given together with CT for producing cognitive enhancement is a rational development of the technique which capitalises on the neurophysiological and acute cognitive effects from stimulation [39]. Although trials to date have tended to be small and variable in terms of patient populations and treatment protocols, preliminary findings suggest additional generalised cognitive benefits relative to CT given alone. These benefits appear to be greater in clinical populations associated with more severe neurocognitive dysfunction. Future larger trials may benefit from including longer intervention periods and follow-ups that include functional assessments, to further assist with elucidating treatment efficacy.

29.5 Overall Conclusions and Future Directions

The last two decades have seen a proliferation of modern clinical trials which have systematically investigated tDCS neurocognitive effects in clinical populations. In this chapter, we reviewed studies which investigated both acute effects following a single stimulation session and effects from repeated sessions given both alone and together with adjunctive cognitive training. In terms of acute effects, trials in depression have tended to provide evidence that tDCS has some cognitive benefits, particularly in relation to "cognitive control" and complex attention functions. The significance of these effects in terms of their relation to other therapeutic effects, for example, mood, has yet to be determined. Further, the reliability of reported effects on specific cognitive functions remains unclear, suggesting that future replication studies are required. Although not reviewed in this chapter, the question of whether these effects generalise to other clinical conditions remains unclear, as this evidence is more limited.

In contrast, multiple clinical trials have now examined the potential for cognitive-enhancing effects from repeated tDCS sessions, primarily in people with depression. Unfortunately, this research has failed to provide compelling evidence for any benefit from tDCS treatment independent from mood effects, yet several outstanding issues remain unresolved. These include whether cognitive benefits from active tDCS may be more pronounced after the intervention period, similar to what has been found with mood effects. Also, the potential additional therapeutic benefit of combining repeated tDCS with adjunctive "online" tasks to standardise and potentially increase neurophysiological changes from stimulation has yet to be fully determined. Preliminary clinical trials of this technique reviewed in this chapter suggest that this combined approach has greater potential for producing cognitive benefit than what has been so far seen with repeated tDCS given alone. The emerging translation of tDCS as a clinical treatment in the domiciliary setting could provide the next frontier for future trials to more systematically evaluate neurocognitive benefits from the combination of tDCS with CT and other adjunctive concurrent cognitive behavioural therapies.

References

1. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. Br J Psychiatry. 1964;110:768–72.
2. Kincses TZ, Antal A, Nitsche MA, Bártfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia. 2004;42(1):113–7.
3. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005;166(1):23–30.
4. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. Lancet Psychiatry. 2019;6(10):851–61.
5. Martin DM, Wollny-Huttarsch D, Nikolin S, McClintock SM, Alonzo A, Lisanby SH, et al. Neurocognitive subgroups in major depressive disorder. Neuropsychology. 2020;34(6):726–34.
6. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res. 2006;145(1):39–48.
7. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci. 1997;9(3):471–81.
8. Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety. 2017;34(1):9–24.
9. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006;8(2):203–4.
10. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006;23(8):482–4.
11. Boggio PS, Bermpohl F, Vergara AO, Muniz AL, Nahas FH, Leme PB, et al. Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. J Affect Disord. 2007;101(1–3):91–8.
12. Bermpohl F, Fregni F, Boggio PS, Thut G, Northoff G, Otachi PT, et al. Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go

task in patients with major depression: role of stimulation site and depression severity. Psychiatry Res. 2006;141(1):1–13.
13. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9.
14. Brunoni AR, Zanao TA, Vanderhasselt MA, Valiengo L, De Oliveira JF, Boggio PS, et al. Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression. Neuromodulation. 2014;17(2):138–41.
15. Oliveira JF, Zanao TA, Valiengo L, Lotufo PA, Bensenor IM, Fregni F, et al. Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci Lett. 2013;537:60–4.
16. Gogler N, Willacker L, Funk J, Strube W, Langgartner S, Napiorkowski N, et al. Single-session transcranial direct current stimulation induces enduring enhancement of visual processing speed in patients with major depression. Eur Arch Psychiatry Clin Neurosci. 2017;267(7):671–86.
17. Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol. 2010;13(1):61–9.
18. McLaren ME, Nissim NR, Woods AJ. The effects of medication use in transcranial direct current stimulation: a brief review. Brain Stimul. 2018;11(1):52–8.
19. Martin DM, Moffa A, Nikolin S, Bennabi D, Brunoni AR, Flannery W, et al. Cognitive effects of transcranial direct current stimulation treatment in patients with major depressive disorder: an individual patient data meta-analysis of randomised, sham-controlled trials. Neurosci Biobehav Rev. 2018;90:137–45.
20. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376(26):2523–33.
21. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain Stimul. 2018;11(1):125–33.
22. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Benseñor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;99:109836.
23. Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res. 2015;168(1–2):260–6.
24. Jeon DW, Jung DU, Kim SJ, Shim JC, Moon JJ, Seo YS, et al. Adjunct transcranial direct current stimulation improves cognitive function in patients with schizophrenia: a double-blind 12-week study. Schizophr Res. 2018;197:378–85.
25. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
26. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: activity dependence and dendritic effects. Brain Stimul. 2017;10(1):51–8.
27. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. Cereb Cortex. 2018;28(4):1132–40.
28. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014;7(2):325–31.
29. Brunoni AR, Boggio PS, De Raedt R, Bensenor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–9.
30. Martin DM, Teng JZ, Lo TY, Alonzo A, Goh T, Iacoviello BM, et al. Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. J Affect Disord. 2018;232:89–95.
31. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology. 2012;37(1):43–76.
32. Hill NT, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment: a systematic review and meta-analysis. Am J Psychiatry. 2017;174(4):329–40.
33. Orlov ND, Tracy DK, Joyce D, Patel S, Rodzinka-Pasko J, Dolan H, et al. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 2017;10(3):560–6.
34. Weickert T, Salimuddin H, Lenroot R, Bruggemann J, Loo C, Vercammen A, et al. Preliminary findings of four-week, task-based anodal prefrontal cortex transcranial direct current stimulation transferring to other cognitive improvements in schizophrenia. Psychiatry Res. 2019;280:112487.
35. Martin DM, Mohan A, Alonzo A, Gates N, Gbadeyan O, Meinzer M, et al. A pilot double-blind randomized controlled trial of cognitive training combined with transcranial direct current stimulation for amnestic mild cognitive impairment. J Alzheimers Dis. 2019;71(2):503–12.
36. Roncero C, Service E, De Caro M, Popov A, Thiel A, Probst S, et al. Maximizing the treatment benefit of tDCS in neurodegenerative anomia. Front Neurosci. 2019;13:1231.

37. Tsapkini K, Webster KT, Ficek BN, Desmond JE, Onyike CU, Rapp B, et al. Electrical brain stimulation in different variants of primary progressive aphasia: a randomized clinical trial. Alzheimers Dement (N Y). 2018;4:461–72.
38. Meinzer M, Darkow R, Lindenberg R, AJB F. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. Brain. 2016;139(4):1152–63.
39. Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. Restor Neurol Neurosci. 2015;33(3):263–78.
40. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio P, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: findings from a naturalistic study. Eur Psychiatry. 2013;28(6):356–61.
41. Moreno ML, Vanderhasselt MA, Carvalho AF, Moffa AH, Lotufo PA, Bensenor IM, et al. Effects of acute transcranial direct current stimulation in hot and cold working memory tasks in healthy and depressed subjects. Neurosci Lett. 2015;591:126–31.
42. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91.
43. Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, et al. Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin Neurophysiol. 2015;126(6):1185–9.
44. Salehinejad MA, Rostami R, Ghanavati E. Transcranial direct current stimulation of dorsolateral prefrontal cortex in major depression: improving visual working memory, reducing depressive symptoms. NeuroRegulation. 2015;2(1):37–49.
45. Salehinejad MA, Ghanavai E, Rostami R, Nejati V. Cognitive control dysfunction in emotion dysregulation and psychopathology of major depression (MD): evidence from transcranial brain stimulation of the dorsolateral prefrontal cortex (DLPFC). J Affect Disord. 2017;210:241–8.
46. Valiengo LC, Goulart AC, de Oliveira JF, Bensenor IM, Lotufo PA, Brunoni AR. Transcranial direct current stimulation for the treatment of post-stroke depression: results from a randomised, sham-controlled, double-blinded trial. J Neurol Neurosurg Psychiatry. 2017;88(2):170–5.
47. Bersani FS, Minichino A, Bernabei L, Spagnoli F, Corrado A, Vergnani L, et al. Prefronto-cerebellar tDCS enhances neurocognition in euthymic bipolar patients. Findings from a placebo-controlled neuropsychological and psychophysiological investigation. J Affect Disord. 2017;209:262–9.
48. Tortella G, Sampaio-Junior B, Moreno ML, Moffa AH, da Silva AF, Lafer B, et al. Cognitive outcomes of the bipolar depression electrical treatment trial (BETTER): a randomized, double-blind, sham-controlled study. Eur Arch Psychiatry Clin Neurosci. 2021;271(1):93–100.
49. Palm U, Keeser D, Hasan A, Kupka MJ, Blautzik J, Sarubin N, et al. Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. Schizophr Bull. 2016;42(5):1253–61.
50. Khedr EM, Salama RH, Abdel Hameed M, Abo Elfetoh N, Seif P. Therapeutic role of transcranial direct current stimulation in Alzheimer disease patients: double-blind, placebo-controlled clinical trial. Neurorehabil Neural Repair. 2019;33(5):384–94.
51. Park SH, Koh EJ, Choi HY, Ko MH. A double-blind, sham-controlled, pilot study to assess the effects of the concomitant use of transcranial direct current stimulation with the computer assisted cognitive rehabilitation to the prefrontal cortex on cognitive functions in patients with stroke. J Korean Neurosurg Soc. 2013;54(6):484–8.
52. den Uyl TE, Gladwin TE, Lindenmeyer J, Wiers RW. A clinical trial with combined transcranial direct current stimulation and attentional Bias modification in alcohol-dependent patients. Alcohol Clin Exp Res. 2018;42(10):1961–9.

Epilepsy

30

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30.1 Introduction

The rise of interest in neuromodulation is particularly relevant in epilepsy, in which seizures are resistant to pharmacotherapy in approximately one-third of cases, a rate that has not changed despite the introduction of more than 20 new antiepileptic drugs in the late twentieth and early twenty-first centuries [1]. Accordingly, neurostimulation protocols are emerging as potentially valuable tools for seizure control.

Stimulating the nervous system with electricity to treat neuropsychiatric symptoms, seizures included, is not new. In the first century AD, the Roman physician, Scribonius Largus, documented treating headaches by applying electric torpedo fish to the head, and another Roman physician, Pedanius Dioscorides, in 76 AD applied the torpedo fish to a patient with epilepsy [2]. As brain stimulation in general, neuromodulation for epilepsy has advanced considerably in recent years. Neurostimulation protocols can be coarsely divided into either invasive or noninvasive. Invasive options include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Noninvasive protocols include trigeminal nerve stimulation (TNS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS).

30.2 tDCS in Epilepsy

Applied to the mammalian cerebral cortex, tDCS induces both acute and sustained changes in cortical excitability. After a short exposure time to a single session (e.g., 20–30 min), cathodal tDCS typically leads to a reduction in cortical excitability, while anodal tDCS usually increases cortical excitability. Beyond the neocortex, experimental in vitro DC stimulation (DCS) indicates a potential for similar modulation of excitability in the hippocampus [3–5]. In epilepsy, the capacity of cathodal tDCS to reduce cortical excitability has prompted research into this technique's potential in controlling clinical seizures [6, 7].

The relatively low intracranial currents and the absence of directly triggered neuronal action potentials associated with tDCS likely account

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for its favorable safety profile. In contrast to other noninvasive neurostimulation techniques like rTMS, seizures have not been directly associated with tDCS in humans. Currently, five cases of seizures arising during active tDCS have been reported in epilepsy clinical trials, all of which occurred in drug-resistant patients that had events with typical duration and intensity, pointing to a probable coincidental association [8, 9]. The remaining side effects are usually mild and largely limited to skin discomfort and irritation at the electrode sites [10, 11].

30.3 Clinical Studies

Objective changes in cortical excitability as detected by various methods both in humans and animal models have led investigators to implement tDCS interventions for the management of epilepsy with several trials that were undertaken in the past 15 years. In a review of published clinical data in epilepsy through 2020, Sudbrack-Oliveira and colleagues (unpublished data) identified interventions performed in 328 individual patients where 259 were participants in randomized clinical trials (RCTs) and 69 were divided between uncontrolled studies and case series/reports.

tDCS clinical trial results, while still inconclusive, are overall encouraging. In the first human RCT, adults ($N = 19$; average age 24 years) with medically refractory epilepsy secondary to malformations of cortical development were subjected to 1 mA cathodal tDCS delivered in a single session for 20 min using surface sponge electrodes (35 cm^2) arranged with the cathode over the seizure focus and the anode over the region with either normal EEG or the least frequent epileptiform abnormalities in case of multifocal epilepsy. In the sham control condition, the device was turned off after 5 s to generate the similar initial itching sensation without any current delivery for the remainder of the stimulation period. Clinical seizures were monitored by seizure diaries. Electrographic abnormalities were measured by 20-min EEGs obtained at baseline, as well as immediately after, 15 days, and 30 days after stimulation. EEG readers were blinded to the treatment condition. The results indicate that cathodal tDCS was safe and well tolerated in this population. The frequency of interictal epileptiform discharges was reduced by 64% immediately after tDCS. A favorable trend toward seizure reduction (44% in the treatment group vs. 11% in the control group) was detected, but significant differences in clinical seizure frequency (SF) between treatment and control groups were not identified. Notably, the electrographic response and the trend toward seizure reduction lasted as long as 1 month in some patients [12].

In a study of pediatric patients with refractory focal epilepsy ($N = 36$), children (6–15 years old) received a single session of sham tDCS or verum cathodal 1 mA tDCS for 20 min. tDCS in this study was also administered via a 35 cm^2 sponge cathodal electrode placed over the 10–20 EEG defined epileptogenic irritative zone and the reference anode placed on the contralateral shoulder. While the treatment group received the current for 20 min, in sham stimulation, the current was discontinued just after 30 s in a blinded setting. Epileptiform discharges (spikes and sharp waves) per 30 min of EEG recording at baseline and at different endpoints (15 min, 24 h, 48 h, and 4 weeks) were compared. EEG readers in this study as well were blinded to the treatment condition. The results indicate that tDCS was well tolerated and associated with a significant 50% decrease in EEG epileptiform abnormalities at 24 h and 58% at 48 h after active stimulation. Moreover, a statistically significant, but small decrease of 5% in the clinical seizure frequency was observed in the verum tDCS group with no difference in sham-treated group [11].

Following initial studies that delivered single continuous cathodal tDCS sessions, Zoghi and colleagues undertook a parallel RCT in a sample of patients with temporal lobe epilepsy ($N = 29$, average age 38 years) with a protocol that consisted of two bouts of a 9-min-long stimulation spaced by an interval also during 9 min. This intervention was delivered in a single day, with the cathode positioned in the scalp above the affected temporal lobe and anode positioned at the contra-

lateral supra-orbital area (current = 1 mA, electrode area = 12 cm^2). The investigators observed that active stimulation was associated with a greater reduction in seizure frequency at 1-month follow-up (42.14% SF reduction in active tDCS and 16.98% reduction in sham group). However, this study has some issues: baseline seizure frequency assessment was based on participant's recollection and six patients did not return their seizure diaries following the intervention, which might have influenced the results. Interestingly, authors used short interval intracortical inhibition (SICI) as detected by paired-pulse transcranial magnetic stimulation (pp-TMS) as a surrogate measure of cortical excitability. They observed that inhibitory activity in the primary motor cortex was increased in the experimental group as compared to the sham arm [13].

Two other RCTs have investigated the effects of tDCS interventions in patients with temporal lobe epilepsy, in this case secondary to hippocampal sclerosis, both delivering repeated stimulation sessions. In the first study, which had a crossover design ($N = 12$, average age 35 years), Tekturk and colleagues delivered three 30-min sessions of either active or sham tDCS over consecutive days. The second bout of three sessions was separated from the first by a washout period of 60 days. The intervention, as done by prior investigators, had a montage with cathode placed in the scalp region overlying the affected temporal lobe and the anode at the contralateral supraorbital area (current = 2 mA peak to peak, electrode area = 35 cm^2). However, instead of delivering stimulation at a fixed intensity, the intervention consisted on what authors called modulated tDCS, characterized by a sinusoidal fluctuating current. The chosen frequency for the stimulation was 12 Hz, in the upper alpha range, aimed to restore abnormal brain activity with this physiologic rhythm based on results from neurofeedback studies. Results showed a 84% decrease in SF at 1-month follow-up after active tDCS as compared to no change following the sham treatment [14]. In the second study, San-Juan and colleagues randomized 28 participants also with a diagnosis of hippocampal sclerosis (average age 38 years) to one of three treatment arms: active tDCS consisting of either three or five 30-min sessions (current = 2 mA, electrode area = 35 cm^2) delivered once in consecutive days or sham/placebo. As usual, the cathode was positioned over the affected temporal lobe and anode at the contralateral supraorbital area. Active stimulation was associated with a significant decrease in seizure frequency at 2-month follow-up (43.4% and 54.6% SF reduction for 3 and 5 sessions, respectively). EEG epileptiform activity was also quantified, but it was similarly reduced in active and sham groups [8].

In the largest RCT so far, Yang and coworkers investigated the effectiveness of an intensified tDCS protocol on seizure frequency in a sample of patients with drug-resistant focal epilepsy of varied etiologies ($N = 70$, average age 31 years). Participants were randomized to one of two active tDCS protocols or sham stimulation. The intervention consisted of 14 consecutive days of stimulations (current = 2 mA, electrode area = 11.9 cm^2) delivered once a day during 20 min in one active arm and twice a day (totalizing 40-min session daily) in the second active group. The cathode was as well positioned in the scalp area with most abnormal EEG findings and the anode at a contralateral "silent" area. Both active groups presented a significant decrease in SF when compared to the sham group, a decline that was more pronounced with the more intense protocol (50.73–21.91% and 63.19–49.79% weekly SF reduction for 20-min and 40-min stimulation, respectively). Furthermore, the intensified protocol was associated with a longer duration of the effects (5 weeks as compared to 4 weeks for 20-min stimulation) [9].

The single RCT that performed tDCS interventions in a sample not solely composed by participants with focal epilepsy was undertaken by Auvichayapat and colleagues. In that study, 22 children (average age 6.5 years) diagnosed with Lennox-Gastaut Syndrome (LGS), a condition characterized as combined focal and generalized epilepsy, were randomized to either sham or active stimulation. Sessions lasted 20 min and were delivered once through 5 consecutive days. This study was also unique in relation to electrode montage, with the cathode positioned at

C3 (close to the left primary motor area) in all patients and the anode at the right shoulder (current = 2 mA, electrode area = 35 cm^2). Results showed a 89.75% reduction in daily SF in the active group at 1 week with a gradual loss of the effects observed up to 1-month follow-up (55.96% reduction) [15].

In addition to seizure suppression, tDCS may have a role in mitigating behavioral symptoms that are commonly comorbid with epilepsy. In a recent pilot study of 33 adults with controlled temporal lobe epilepsy, Liu and colleagues explored the tDCS effects on depression and memory dysfunction [16]. Two mA, 20-min tDCS was delivered for 5 days with anode over the left dorsolateral prefrontal cortex and cathode over the right supraorbital area. While the active treatment group received current for 20 min, the current during sham control stimulation was ramped up only for 30 s and thereafter ramped down. The 5-day tDCS course corresponded to a modest improvement in depressive symptoms immediately after active treatment. Notably, investigators did not find an increase in interictal discharge frequency thus indicating tDCS safety for applications other than seizure suppression in patients with epilepsy.

30.4 Preclinical Studies

The mixed outcomes of human tDCS trials in epilepsy underscore the need for preclinical studies that may inform future clinical tDCS study design. Notably, as the term "transcranial" is not relevant for in vitro brain stimulation, "DCS" rather than "tDCS" is often used to describe the stimulation condition in preclinical studies.

Preclinical DCS research can provide insight is the mechanism by which DCS may produce a sustained antiepileptic effect. This was recently addressed by Chang and colleagues who studied the cathodal DCS effect on acute chemoconvulsant in isolated mouse thalamocingulate brain slices, an in vitro model of frontal lobe epilepsy. In their experiment, brain slices were stimulated by two parallel Ag/Ag-Cl electrodes connected to an isolated stimulator placed external to the slice in a recording chamber to generate a uniform electric field (4 mV/mm). Spontaneous excitatory postsynaptic currents (EPSCs) were recorded, as were epileptic EPSCs induced by bath application of either the potassium channel blocker 4-aminopyridine or the $GABA_A$ receptor antagonist bicuculline. Consistent with the past studies, cathodal DCS suppressed evoked synaptic transmission and spontaneous EPSCs, a finding that the authors attributed to real-time neuronal membrane hyperpolarization. However, the antiepileptic effect persisted in this model, and was shown to be dependent on activation of the n-methyl-d-aspartate (NMDA) type glutamate receptor, thus behaving in ways like the well-described phenomenon of NMDA-dependent long-term depression (LTD) of excitatory synaptic strength [17]. The value of such data is an identification of a molecular pathway by which DCS may suppress seizures. This not only satisfies a scientific curiosity but also offers an opportunity to test whether pharmacotherapy that facilitates a component of this pathway may also facilitate the antiepileptic efficacy of tDCS, which, as above, is incomplete in clinical practice. However, systematic in vitro studies that investigate the molecular substrate of the DCS antiepileptic effect are rare. More commonly, in vitro DCS data provide insight into the electrophysiologic basis of seizure suppression by tDCS. For instance, early in vitro studies in a low-calcium hippocampal slice model identified that epileptiform discharges may be suppressed by field strengths in the 1–5 mV/mm range and that such suppression is polarity dependent [18, 19].

Among the more specialized applications that can be tested in animal epilepsy models is the capacity for cathodal tDCS, applied as a pretreatment to prophylax against seizures. This was first tested by Liebetanz and colleagues in a modified cortical ramp-stimulation focal seizure model in rats. In these experiments, tDCS was delivered with unilateral epicranial conductive electrodes to rat sensorimotor cortex, and threshold for localized seizure activity was determined by trains of pulsatile stimulation (50 Hz; 2 ms; 2 mA) delivered through the same epicranial

contact. One group of animals received cathodal tDCS (100 μA) for 30 and 60 min or anodal tDCS for 60 min. In another group, the current intensity was doubled (200 μA) and stimulation durations were halved in all three conditions. The main finding of the work was that cathodal tDCS caused an elevation of localized seizure threshold lasting for ≥2 h. In contrast, anodal tDCS had no significant effect on seizure threshold, confirming in vivo a polarity-dependent anticonvulsant tDCS effect, and the absence of seizure exacerbation by anodal stimulation, as suggested also by clinical tDCS trials [20].

In complement to the preclinical study of tDCS in focal seizures [20], the antiepileptic potential of cathodal tDCS was also demonstrated in a rat amygdala-kindling temporal lobe epilepsy model. Here, Kamida and colleagues demonstrated that cathodal tDCS reduced clinical seizure severity and EEG after discharge duration, while elevating the after discharge threshold, and these effects lasted at least 1 day after the last tDCS session (30-min daily treatment at 200 μA for 1 week). This treatment regimen also corresponded to improved cognitive performance on the Morris water maze [21]. The same group also investigated the effects of cathodal tDCS on convulsions in a rat pup lithium-pilocarpine status epilepticus model. In this study, rats were treated for 2 weeks with 200 μA cathodal tDCS delivered for 30 min per session using epicranial electrodes. Monitored over 2 weeks post stimulation, the authors found a significant 21% reduction in the frequency of convulsions between sham and cathodal tDCS treated rats suggesting an antiepileptic effect. Among other findings, long-term treatment with cathodal tDCS also had neuroprotective effects on the rat hippocampus and led to improvements in performance of the water maze spatial memory task [22].

The above data indicate an intriguing prospect for tDCS as a means to interfere with epileptogenesis, rather than just seizures. The search for an effective and safe antiepileptogenic treatment is an active field in experimental epilepsy. The unmet need for such treatment is underscored by complete absence of clinical antiepileptogenic interventions: For instance, none of the approximately 40 drugs that are prescribed to treat seizures are antiepileptogenic. Thus, further studies of tDCS in its capacity to prevent the onset of epilepsy after an epileptogenic brain injury such as trauma, stroke, or status epilepticus are necessary.

In contrast to in vivo experiments that tested a delayed antiepileptic tDCS effect, in a study by Dhamne and colleagues, cathodal tDCS was tested in the acute seizure setting that approximates status epilepticus to assess an immediate anticonvulsant effect. In this experiment, investigators modeled the realistic scenario that seizures will have already started by the time tDCS is deployed in the clinical arena. Moreover, a patient with status epilepticus will be likely to have received an anticonvulsant before the start of tDCS. Cathodal tDCS in this experiment was delivered via a scalp electrode for 20 min at either 1 mA, 0.1 mA, or, in the control condition, 0 mA. And to simulate a likely clinical combination, tDCS was also tested in combination with lorazepam, a first-line anticonvulsant benzodiazepine that is routinely administered to human patients with status epilepticus. The results identify electrographic seizure suppression within minutes of 1 mA cathodal stimulation. Moreover, a combination of tDCS and a subeffective lorazepam dose suppressed seizures better than either intervention alone, suggesting that cathodal tDCS may act synergistically with lorazepam [23]. Of translational relevance for future clinical application, these data indicate an important direction for neuromodulation research toward systematic testing of combination drug-device therapy in epilepsy.

30.5 Conclusions

Given that the rate of drug-resistant epilepsy has not changed much in recent years, tDCS offers a plausible noninvasive and nonpharmacologic option to improve seizure control in patients with intractable seizures, particularly when surgical intervention has either failed or is not an option. Most RCTs so far indicate that tDCS is an effective intervention regarding seizure control, with

measurable effects being detected up to 2 months after the end of the stimulation sessions. However, tDCS antiseizure effects as well as its influence on surrogate markers of cortical excitability have yet to be substantiated and replicated in larger clinical trials. Additionally, further work should address samples other than patients with drug-resistant focal epilepsies (e.g., generalized epilepsy, status epilepticus). Nonetheless, tDCS's promising clinical effects in addition to a benign side-effect profile suggest a favorable risk: benefit ratio and high likelihood of near-future implementation in clinical epilepsy. The inconsistent findings with respect to seizure suppression in some trials underscore the need for improved patient-specific protocols that enable superior targeting of the epileptogenic foci/networks [24–26]. Last, novel neuroprotective and antiepileptogenic tDCS applications are suggested by preclinical research, and also may lead to disease-modifying treatment strategies in future clinical embodiments of this technology.

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References

1. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
2. Kellaway P. The part played by electric fish in the early history of bioelectricity and electrotherapy. Bull Hist Med. 1946;20:112–37.
3. Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172:369–82.
4. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
5. Kabakov AY, Muller PA, Pascual-Leone A, Jensen FE, Rotenberg A. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. J Neurophysiol. 2012;107:1881–9.
6. Nitsche MA, Paulus W. Noninvasive brain stimulation protocols in the treatment of epilepsy: current state and perspectives. Neurotherapeutics. 2009;6:244–50.
7. San-Juan D, Morales-Quezada L, Orozco Garduño AJ, Alonso-Vanegas M, González-Aragón MF, Espinoza López DA, Vázquez Gregorio R, Anschel DJ, Fregni F. Transcranial direct current stimulation in epilepsy. Brain Stimul. 2015;8:455–64.
8. San-Juan D, López DAE, Gregorio RV, et al. Transcranial direct current stimulation in mesial temporal lobe epilepsy and hippocampal sclerosis. Brain Stimul. 2017;10:28–35.
9. Yang D, Wang Q, Xu C, et al. Transcranial direct current stimulation reduces seizure frequency in patients with refractory focal epilepsy: a randomized, double-blind, sham-controlled, and three-arm parallel multicenter study. Brain Stimul. 2020;13:109–16.
10. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14:1133–45.
11. Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, Auvichayapat P. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul. 2013;6:696–700.
12. Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia. 2006;47:335–42.
13. Zoghi M, O'Brien TJ, Kwan P, Cook MJ, Galea M, Jaberzadeh S. Cathodal transcranial direct-current stimulation for treatment of drug-resistant temporal lobe epilepsy: a pilot randomized controlled trial. Epilepsia Open. 2016;1:130–5.
14. Tekturk P, Erdogan ET, Kurt A, et al. The effect of transcranial direct current stimulation on seizure frequency of patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Clin Neurol Neurosurg. 2016;149:27–32.
15. Auvichayapat N, et al. Transcranial direct current stimulation for treatment of childhood pharmacoresistant Lennox-Gastaut syndrome: a pilot study. Front Neurol. 2016;7:66.
16. Liu A, Bryant A, Jefferson A, et al. Exploring the efficacy of a 5-day course of transcranial direct current stimulation (TDCS) on depression and memory function in patients with well-controlled temporal lobe epilepsy. Epilepsy Behav. 2016;55:11–20.
17. Chang W-P, Lu H-C, Shyu B-C. Treatment with direct-current stimulation against cingulate seizure-like activity induced by 4-aminopyridine and bicuculline in an in vitro mouse model. Exp Neurol. 2015;265:180–92.
18. Ghai RS, Bikson M, Durand DM. Effects of applied electric fields on low-calcium epileptiform activity in the CA1 region of rat hippocampal slices. J Neurophysiol. 2000;84:274–80.

19. Bikson M, Ghai RS, Baraban SC, Durand DM. Modulation of burst frequency, duration, and amplitude in the zero-Ca(2+) model of epileptiform activity. J Neurophysiol. 1999;82:2262–70.
20. Liebetanz D, Klinker F, Hering D, Koch R, Nitsche MA, Potschka H, Löscher W, Paulus W, Tergau F. Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. Epilepsia. 2006;47:1216–24.
21. Kamida T, Kong S, Eshima N, Fujiki M. Cathodal transcranial direct current stimulation affects seizures and cognition in fully amygdala-kindled rats. Neurol Res. 2013;35:602–7.
22. Kamida T, Kong S, Eshima N, Abe T, Fujiki M, Kobayashi H. Transcranial direct current stimulation decreases convulsions and spatial memory deficits following pilocarpine-induced status epilepticus in immature rats. Behav Brain Res. 2011;217:99–103.
23. Dhamne SC, Ekstein D, Zhuo Z, Gersner R, Zurakowski D, Loddenkemper T, Pascual-Leone A, Jensen FE, Rotenberg A. Acute seizure suppression by transcranial direct current stimulation in rats. Ann Clin Transl Neurol. 2015;2:843–56.
24. Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimul. 2011;4:169–74.
25. Sunderam S, Gluckman B, Reato D, Bikson M. Toward rational design of electrical stimulation strategies for epilepsy control. Epilepsy Behav. 2010;17:6–22.
26. Bikson M, Datta A. Guidelines for precise and accurate computational models of tDCS. Brain Stimul. 2012;5:430–1.

Pain Syndromes

31

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31.1 Introduction

Pain is a phenomenon that has been identified and explored since the beginning of time, in distinct cultures and civilizations. Pain is a disabling symptom common to several pathologies and it is considered the primary reason that leads individuals to seek medical care [1]. Nevertheless, its concepts and definitions have been modified considerably throughout the centuries and especially during the second half of the twentieth century, when it evolved from a notion of a purely sensory event to a model of a complex and multifaceted experience. Indeed, since the outstanding work of Melzack and Casey (1968), it has been accepted that pain is not restricted to a sensory-discriminative dimension, which is unquestionably important to the full characterization of a given noxious stimulus (e.g., nature, location, intensity, and duration). Instead, pain is considerably more complex than that, since it includes not only nociception but also encompasses motivational-affective properties, intrinsically connected to the reticular formation and limbic system and a cognitive-evaluative dimension, processed by higher order cortical areas, and that exerts control over the other two dimensions (e.g., sensory-discriminative and cognitive evaluative) [2]. Such concept led clinicians and researchers that take part in the field to define pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" a concept that goes beyond nociception [3].

Pain is classically differentiated into two basic categories: acute or chronic. Although overly simplistic, this classification can be extremely useful in the clinical setting, since acute and chronic pain have distinct clinical presentations. Furthermore, chronic pain is usually incapacitating and associated with greater psychological and social impairment [4–7]. The adequate management of chronic pain is still considered a challenge for clinicians worldwide and its prevalence as well as the impact it produces in healthcare systems have been hugely studied and debated in the last years [8]. Therefore, other than distinguishing acute and chronic pain based only on arbitrarily chronological markers (classically 3 or 6 months), it is important to understand the pathophysiological events underlying both conditions.

The struggle to treat chronic pain derives mostly from the difficulty to understand its complex mechanisms, which leads researchers in the field to focus their attention on the biological

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mechanisms related to this. In fact, the intricate machinery that triggers and maintains chronic pain has been partially unveiled. It has been established that a maladaptive plasticity affecting both the peripheral and the central nervous systems and associated with central and peripheral sensitization plays a major role [9].

Also, chronic pain does not represent a single nosological entity, since it comprises a variety of conditions of somatic, neuropathic, or even psychological origins, each one with particular characteristics [10]. For instance, different symptom profiles (e.g., pain quality and its spatial properties) can distinguish patients with neuropathic pains (e.g., postherpetic neuralgia painful diabetic, painful idiopathic sensory polyneuropathy, peripheral neuropathy) from those subjects with nociceptive pain (e.g., non-neuropathic low back pain and osteoarthritis) [11, 12]. Such findings very likely reflect the presence of specific events, concurring to the mechanisms of each chronic pain syndrome. For instance, a reduction in the intracortical inhibition has been shown in peripheral neuropathic pain, but not in osteoarthritis, which might suggest the presence of specific mechanisms related to neuropathic and nociceptive pain [13]. Moreover, a huge variability occurs during chronic, especially neuropathic, pain among the individuals affected. This variability depends on the body region affected and is believed to be the result of interactions between etiological, and environmental factors as well as genetic polymorphisms. In the future, the precise identification of dysfunctional mechanisms, representative of each chronic pain syndrome will permit the development of more individualized treatments, which will probably result in a significant improvement of efficacy and decrease of side effects [14].

Due to the enormous challenge of treating chronic pains with the pharmacological therapies and surgical interventions currently available, clinicians and researchers have devoted to developing and enhancing clinical strategies to provide relief for chronic pain patients, especially those suffering from refractory conditions. In this context, despite the long history in the use of electrical brain stimulation to provide pain relief [15], the use of neuromodulatory techniques to this purpose has only received considerable attention in the last three decades, especially after the studies of Tsubokawa et al. in the early 1990s [16, 17] that successfully applied motor cortex stimulation (MCS) to treat chronic neuropathic pain syndromes. As a matter of fact, the choice of the motor cortex as a target for pain treatment occurred after the unexpected discovery that thalamic hyperactivity could be decreased by MCS, while sensory cortical stimulation failed to produce comparable results [16–18].

In reality, a possible connection between the motor cortex and pain had emerged years before, with the report of successful facial pain relief after cortical removals of both postcentral (sensory) and precentral (motor) cortex facial representations, in two patients [19], while cortical removals limited to the postcentral gyrus did not result in lasting pain relief for central pain sufferers [20]. In the following years after Tsubokawa's work, clinical studies investigated the efficacy of MCS as well as noninvasive neuromodulatory techniques, to treat chronic pain disorders [21–25]. Furthermore, the ability of those methods to modulate the activity of faulty neural networks was also demonstrated [26].

Among the noninvasive neuromodulatory therapies applied for pain control, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are the most investigated. One of the main advantages of adopting protocols restricted to noninvasive methods of neuromodulation is the lower incidence of side effects. Although rare cases of TMS-related seizures have been documented [27, 28], typically only minor and transient side effects, such as tingling, transient headaches, skin irritation, itching, burning sensation, and nausea, occur with noninvasive procedures [29, 30] as long as the safety criteria are followed [31, 32].

With respect to tDCS, it is considered an effective method to modulate brain activity. Moreover, it permits a reliable sham condition, and its technical operation is relatively simple [24, 25, 33, 34]. All these features make this procedure particularly suitable for pain studies. Not surprisingly, since its reintroduction in

neurophysiological and clinical research, during the late 1990s and early 2000s [35, 36], several studies have reported that it is an effective method to treat distinct chronic pain syndromes, including fibromyalgia [25, 37–40], pain due to traumatic spinal cord injury [24, 41–43], chronic pelvic pain [44], refractory orofacial pain [45], postherpetic neuralgia [46], painful diabetic polyneuropathy [47], chronic neuropathic pain following burn injury [48], neurogenic pain [49], trigeminal neuralgia [50], low back pain [51], migraine [52–54], and chronic temporomandibular disorders (TMD) [55].

However, the effectiveness of tDCS for pain control is still a matter of debate in the literature. Although the results of a recent meta-analysis suggest that tDCS provides a significant reduction of pain levels [56]; according to the results of another study, there is insufficient evidence that this method is effective to treat chronic pain in all patients [29]. Nevertheless, it is important to emphasize the elevated heterogeneity of the samples evaluated in those studies, which included subjects affected by chronic pains associated with a great variety of diseases (e.g., fibromyalgia, spinal cord syndrome, multiple sclerosis, and migraine), the majority presenting completely unrelated pathophysiological mechanisms, which in turn may have impacted the findings.

Another important aspect is the presence of adequate subject blinding during active and sham stimulation. Incomplete blinding may exaggerate the clinical outcome by up to 25% [57]. This aspect is especially prominent with TMS, since auditory clues along with the sensation of stimulation occur with active but not sham stimulation [58, 59]. Thus, some novel TMS strategies have been elaborated to address this concern [60]. Regarding tDCS, the feasibility of conducting double-blind sham-controlled clinical trials has been reported at current intensities of 1 mA in tDCS-naive participants [61, 62]. However, active tDCS stimulation could be distinguished from sham at a current intensity of 1.5 mA [30], and both subject and operator blinding would be compromised at intensities of 2 mA since active and sham stimulations could be markedly differentiated [63].

One crucial feature, specifically related to tDCS, is the type of montage chosen. *M1-SO* is the montage classically adopted for pain studies. In this setup, the anode (positive pole) is placed over the region corresponding to primary motor cortex (M1) and the cathode (negative pole) over the contralateral supra-orbital (SO) area [64, 65]. Nevertheless, along the recent years, other montages have been successfully built and tested, including *DLPFC*, that used both electrodes (anode and cathode) positioned over the dorsolateral prefrontal cortex (DLPFC) and *Cz-Oz*, with the anode over the vertex and the cathode over the occipital cortex. *M1-SO, DLPFC,* and *Cz-Oz* have been referred as conventional montages, since they use the same large electrodes (5 × 7 cm) positioned in different locations [53, 54, 66] and some of those methods have been compared. It has been reported that fewer subjects can distinguish sham, anodal, and cathodal stimulation when Cz-Oz is the montage applied. On the other hand, more subjects would recognize the type of stimulation when M1-SO is applied [67]. However, future studies must confirm such findings.

More recently, high-definition-tDCS (HD-tDCS) montages using smaller ring electrodes have been developed, with the goal of increasing the focality of the electrical current. HD-tDCS montages include *HD-tDCS 4x1*, with the anode centered on the EEG 10–20 location C3, surrounded by four cathodes, over Cz, F3, T7, and P3 and HOPE *HD-tDCS 2x2,* with two anodes and two cathodes positioned across the face/head region of M1. In the case of 2 × 2 HD-tDCS, it was especially tailored based on MCS parameters [55, 64, 68–70]. On chronic temporomandibular disorder (TMD) patients, five daily sessions with this montage provided significant improvements on clinical pain and motor measurements compared to the placebo group, with pain relief above 50% at 4-week follow-up and increase pain-free mouth opening at 1-week follow-up. There was also decrease on pain area, intensity and their sum measures contralateral to the M1 stimulation, not the ipsilateral side, during the treatment week. In addition, no changes in emotional values were shown between active and placebo TMD groups.

Interestingly, recent studies, using computational models, have demonstrated that the strength of the regional current flow generated by tDCS differs significantly among distinct conventional and HD-tDCS montages [68] (Figs. 31.1 and 31.2) and even changes in the intracortical functional connectivity generated by conventional tDCS depend on the montage chosen [71]. Therefore, it is possible to postulate that each tDCS montage could be utilized to target specific dysfunctional areas in chronic pain patients, or extrapolating this concept, different montages could be chosen to treat distinct pain disorders.

Furthermore, HD-tDCS montages should be preferable when increased focality is a goal. Another important feature that should be considered is the possible reduction of undesirable effects with more focused stimulation techniques, though the safety profile is considered very good particularly in the case of tDCS [29].

Despite the vast number of studies investigating the clinical effects of tDCS and the mounting evidence suggesting its analgesic effects, many of its mechanism's aspects remain practically unexplored and it is still not possible to fully comprehend how it modulates brain activity. Nevertheless, some of the underpinnings related to tDCS mechanisms have been elucidated by recent studies. Past studies reported the occurrence of immediate as well as long-lasting changes in the cortical excitability [31, 36, 72]. In addition, studies with computational models, which can predict the patterns of the current distribution throughout the central nervous system (CNS), have indicated that not only outer brain areas but also deeper and even more remote brain regions, such as insula, cingulate, thalamus, and brainstem, can be reached by tDCS [52, 68]. Considering that the presence of neuroplasticity, occurring at the structural [73–80], functional [81–86], and even molecular level [87–91], has been consistently reported in patients with a variety of chronic pain conditions, it is possible to speculate that, acting at cortical and subcortical structures, tDCS could contribute to reverse the ingrained neuroplastic changes developed by chronic pain patients. Remarkably, the effects of anodal and cathodal tDCS on cortical excitability can be suppressed by the N-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan (DMO) [92]. Such results support the hypothesis that synaptic plasticity can be driven by tDCS and that the analgesic effects of this neuromodulatory technique can be related to neuroplasticity changes involving brain areas related to pain and pain-related neural networks, which are dysfunctional in chronic pain patients.

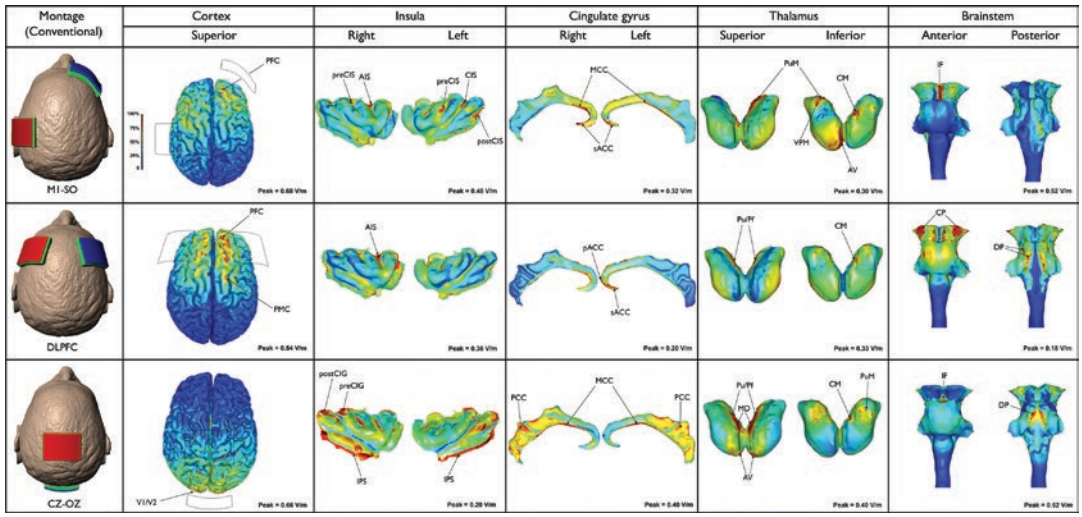

Fig. 31.1 Electrical current distribution through cortical and subcortical brain structures in three distinct conventional tDCS montages [68]

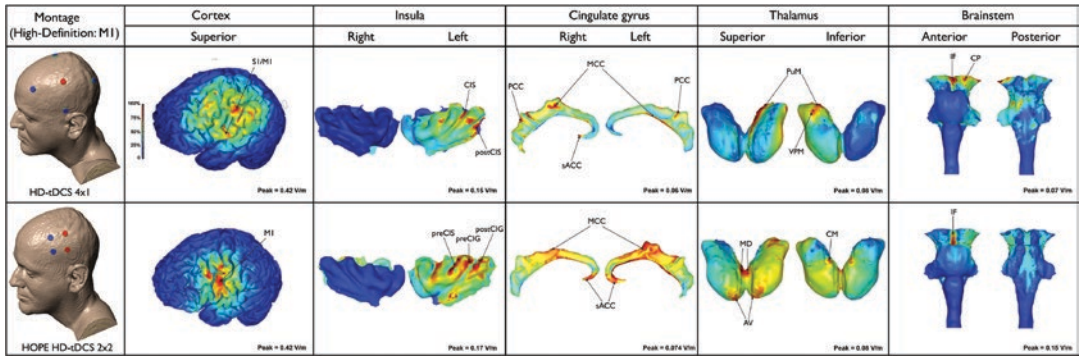

Fig. 31.2 Electrical current flow delivered through the brain in two HD-tDCS montages [68]

Supporting this hypothesis, tDCS-induced changes in the levels of Glx, a combined marker of glutamine and glutamate, and N-acetylaspartate (NAA) and that provides information regarding neuronal integrity, have been recently demonstrated in the anterior cingulate cortex [93]. Such findings confirm previous findings that had reported changes in the levels of Glx with tDCS. However, in that case, the changes were detected in the parietal area beneath the anode [94]. Another interesting result is the trend of increase in the levels of GABA, a major inhibitory neurotransmitter, in the anterior insula, produced by tDCS [93].

Furthermore, changes in the mu-opioid neurotransmission induced by M1 tDCS have been documented in both healthy subjects [46] and in a case report of a chronic pain patient [95]. Interestingly, the activation of the endogenous mu-opioid system occurred with both active and sham stimulation. However, the pattern of regional opioidergic activation permitted the differentiation between sham and active tDCS (Fig. 31.3). While changes in the mu-opioid receptor availability in the periaqueductal gray matter (PAG) and precuneus occurred during both sham and active stimulation, changes in the thalamus were specific for sham tDCS, corroborating the thalamic mu-opioid activation reported in previous placebo studies [96, 97]. On the other hand, Changes in the prefrontal cortex (PFC) were only observed during active tDCS. These findings possibly indicate that a placebo effect contributes to the beneficial effects obtained with tDCS, when applied to produce analgesia. Supporting this hypothesis, changes in the levels of NAA were found in the posterior insula after M1 tDCS [93]. Although still very preliminary, these findings also suggest that mutual as well as specific mechanisms can be associated with placebo and active tDCS [95].

Nevertheless, there are several aspects related to the neuromechanisms elicited by tDCS that still must be answered. At the current stage, it is important to establish a complete characterization of the clinical effects as well as the putative mechanisms associated with tDCS in each chronic pain syndrome. The following sections will discuss the main findings of studies investigating the effects and mechanisms of tDCS in some major chronic pain syndromes (e.g., migraine, fibromyalgia) and also in neuropathic pains.

31.2 Effects and Putative Mechanisms of tDCS in Different Chronic Pain Syndromes

31.2.1 Fibromyalgia

Fibromyalgia is a condition that affects 2–8% of the general population [98–100]. This syndrome was originally defined by the presence of tenderness and chronic spontaneous widespread pain [101]. Since women have much more tender points than men, fibromyalgia was

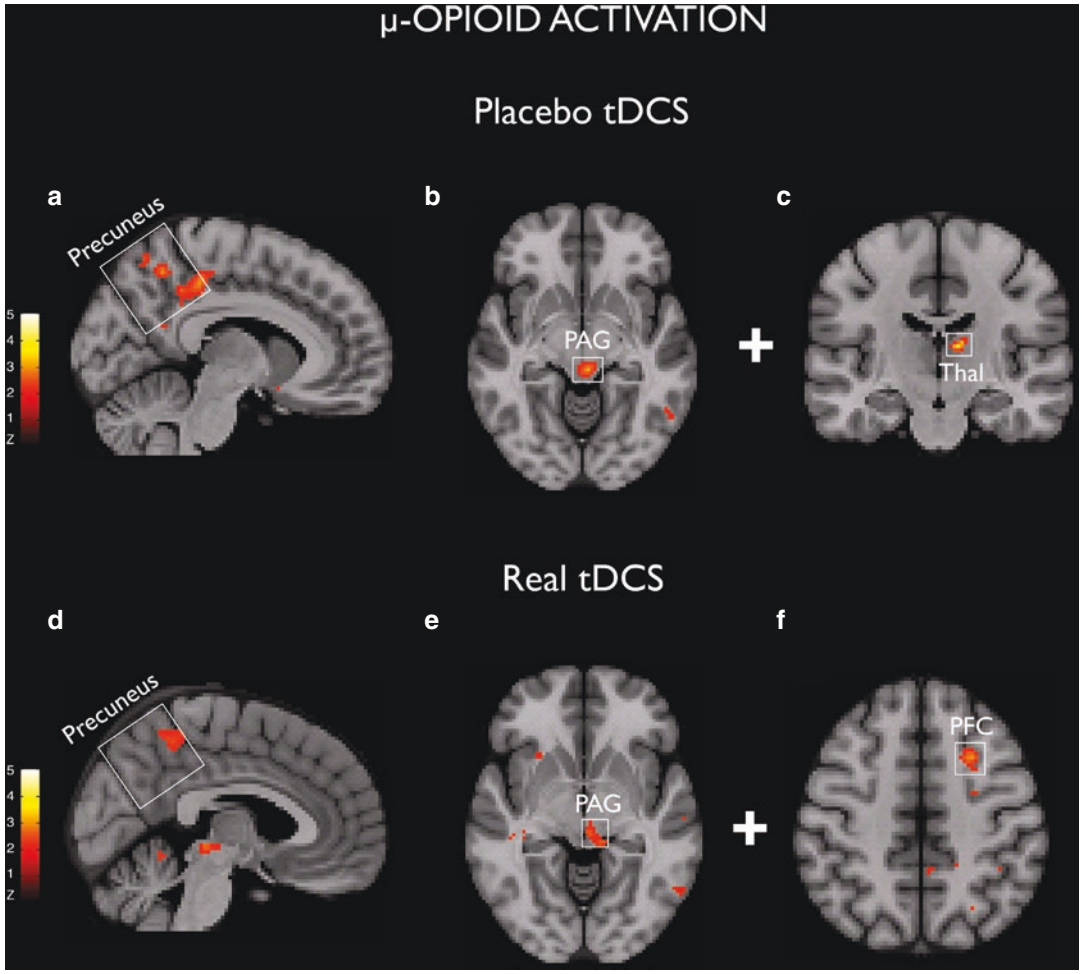

Fig. 31.3 μ-opioid receptor (MOR) activation induced by placebo (**a**–c) and active (**d**–**e**) tDCS. (**a** and **d**) Precuneus MOR activation in the sagittal plane. (**b** and **e**) PAG MOR activation in the axial plane. (**c**) Left thalamus (Thal) MOR activation in the coronal plane. (**f**) Left prefrontal cortex (PFC) MOR activation in the axial plane [95]

almost exclusively found in women, when using that characterization [102]. Nonetheless, recent diagnostic criteria do not require counting the number of tender points. Instead, it is entirely based on patient's symptoms [103]. With this diagnostic criteria, the female: male ratio is 2:1 [100]. Multiple symptoms occur in fibromyalgia, including widespread pain, cognitive and physical fatigue, mood disturbance, pain catastrophizing, autonomic dysfunction, sleep and memory disturbances [102]. A history of regional musculoskeletal pain, irritable bowel syndrome, headache, and TMD, among other conditions, are also usually observed in fibromyalgia patients [104].

Fibromyalgia has been referred as a centralized pain state [102]. In fact, there is mounting evidence, deriving mainly from neuroimaging studies, that confirms the occurrence of functional changes in the CNS activity of fibromyalgia patients. Those changes involve not only the cerebral blood flow [105] but also regional changes in the γ-aminobutyric acid (GABA) concentrations [106], dopaminergic [107], and opioidergic systems [87] as well as altered brain connectivity [84, 86, 108]. Linking those findings with the lack of effectiveness of drugs commonly applied to treat peripheral pains and higher effectiveness of centrally acting drugs in the treatment

of fibromyalgia patients [102], it is very likely that neuromodulatory methods can provide some degree of pain relief for individuals affected by this syndrome.

As a matter of fact, one of the pioneer studies exploring the possible use of tDCS for pain treatment was performed in fibromyalgia patients [25]. In that study, positive results that lasted for 3 weeks after the end of the treatment period were obtained with five sessions (2 mA/20 min of stimulation) of M1-SO tDCS but not with DLPFC tDCS or sham. The outcomes of that proof-of-concept research were also important to confirm the safety of the procedure, especially when applied in chronic pain patients, since only few and mild adverse effects, with a frequency similar in the verum and sham groups, were found. Furthermore, the absence of antidepressant effects could suggest that DLPFC-tDCS might not be the most suitable montage in fibromyalgia patients. Nonetheless, a subsequent study demonstrated significant improvements of pain and quality of life with both M1-SO and DLPFC montages, when applying protocols consisting of 10 sessions (2 mA/20 min) of stimulation [40]. Interestingly, M1-SO montage resulted in long-lasting outcomes, as assessed at 30 and 60 days after the end of the period of stimulation, stressing the importance of the treatment duration to the long-term effects of tDCS, at least in fibromyalgia patients. The analgesic and long-term effects of tDCS in samples that included fibromyalgia patients have been confirmed in other studies, even when applying lower currents [109], unusual montages (e.g., cathodal-SO) [38], or the combination of tDCS and rehabilitation programs [37].

More recently, significant pain decreases have been reported with only a single session of anodal or cathodal 4 × 1 HD-tDCS, when compared to sham [39]. These findings endorse the use of HD-tDCS montages in future fibromyalgia trials. As previously discussed, HD-tDCS techniques enhance the current focality, which remains practically restricted to M1. Considering that the most pronounced analgesic effects are achieved with M1 stimulation, it is reasonable to advocate that HD-tDCS montages specifically targeting M1 should be preferred to treat chronic pain syndromes, including fibromyalgia. In fact, the question whether the use of somatotopically oriented stimulation through smaller electrodes optimizes the analgesic effects induced by tDCS has been proposed since the first study of tDCS in chronic pain [24]. However, the clinical relevance of increasing focality must be confirmed, since modeling studies have proved that conventional montages modulate several deeper structures related to pain. Although also affected by the electrical current, those areas are not reached at the same intensity with HD-tDCS montages [52, 68].

Despite the increasing number of studies investigating the clinical aspects of tDCS in fibromyalgia, the specific mechanisms by which tDCS modulates pain pathways in this disorder have not been explored in depth. The results of one of the few studies in the topic suggest that M1-SO tDCS could possibly act by altering the levels of GABA, glutamate and glutamine (Glx), and NAA in pain-related brain areas, such as the anterior cingulate, the anterior insula, and the thalamus (Fig. 31.4). In addition, the baseline levels of Glx in the anterior cingulate can predict the clinical responses to tDCS [93]. Interestingly, significant increases in the levels of NAA in the posterior insula were found after sham tDCS, which suggests the presence of a placebo effect underlying the tDCS-induced analgesia. Nevertheless, more studies are needed to confirm those findings and to expand the current understanding regarding the mechanisms by which tDCS acts in fibromyalgia.

31.2.2 Migraine Headache

Migraine is characterized by recurrent attacks of unilateral pulsating headache, associated with nausea and/or photophobia and phonophobia [110]. Its lifetime prevalence is around 14% [111]. Two subtypes are encountered: migraine without aura and migraine with aura. Migraine without aura is characterized by headache with some specific aspects and symptoms associated. Migraine with aura is characterized by the presence of transient focal neurological symptoms

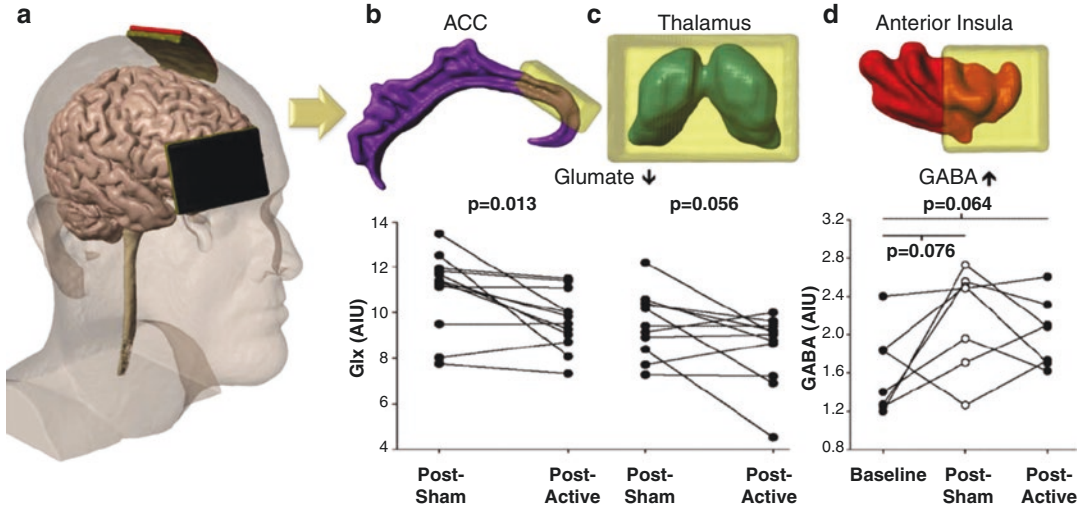

Fig. 31.4 tDCS and 1H-MRS protocol. Top left image (**a**): M1-SO tDCS montage. This is followed on the right by the segmentation of the regions of interest (ROIs): cingulate cortex (**b**), thalamus (**c**), and anterior insula (**d**). Bottom images: Longitudinal changes in glutamate + glutamine (Glx) as well as GABA following five daily active tDCS in patients with fibromyalgia (FM). Left bottom graph. Individual data points show Glx concentrations in ACC in patients with FM, in whom post-sham and post-active tDCS samples were obtained. Glx decreases in ACC ($p = 0.013$) following active tDCS treatment; center bottom graph: same for thalamus ($p = 0.056$). Right bottom graph: Individual data points show a trend on increasing GABA concentrations (AIU) in the anterior insula ($p = 0.064$) following active tDCS treatment [93]

(e.g., visual or sensory symptoms) that precede or accompany the headache [110]. In some patients, migraine evolves from an episodic form to a chronic condition, referred as chronic migraine (CM). CM is defined as a headache that occurs on 15 or more days per month for more than 3 months, and that features the aspects of migraine headache on at least 8 days per month [110]. Besides, medication overuse has been considered the main cause of symptoms suggestive of chronic migraine [110]. As in other painful syndromes, where the progression from an episodic to a chronic form is marked not simply by an increase in the number of episodes but also by the occurrence of other phenomena, such as allodynia (pain due to a stimulus that usually does not provoke pain) as well hyperalgesia (increased response to a normally painful stimulus). In fact, allodynia affects a large proportion of migraine sufferers [112–115] and is more common in migraine than in other primary headaches [116].

Along with the largely documented neural and neurovascular mechanisms, it has been proposed that central sensitization, which may lead to cutaneous allodynia, plays a role in the migraine pathophysiology [117, 118]. Interestingly, our group has recently demonstrated the presence of altered mu-opioid receptor functioning in the periaqueductal gray and red nucleus associated with ictal trigeminal allodynia, developed during a thermal challenge, in migraine patients [91]. Furthermore, neuroimaging studies have confirmed the presence of neuroplastic changes associated with migraine headache [74, 75, 77, 82, 83, 90]. When analyzed together, these findings corroborate the development of research protocols to investigate the use of noninvasive neuromodulatory tools, such as tDCS, to modulate the activity of pain-related structures and perhaps reverse faulty mechanisms that constitute the basis of the migraine pathophysiology.

Regarding the clinical use of tDCS in migraine patients, there are still few studies in the literature, and they differ with respect to the montage chosen as well as the patient selection. The most used montages are M1-SO [52] and Cz-Oz [53, 54, 66]. Positive effects, such as pain reduction, decrease in the duration of

attacks and in the number of migraine-related days post-treatment were reported in a study that applied Cz-Oz tDCS [53]. On the other hand, the frequency of migraine attacks was not affected, which might be explained by the relatively low intensity (1 mA), short duration (15 min), and frequency of the stimulation applied (three sessions per week for 3 weeks). Increasing those parameters might have produced stronger effects in that study, but it might have also impacted the sham arm of the study and the placebo condition, which was considered optimal, based on the side effects reported. Nonetheless, another limitation of that preliminary study that must be considered when interpreting the results is the heterogeneity of the experimental group analyzed, consisting of patients diagnosed with migraine with aura, without aura, and chronic migraine. Interestingly, persistent analgesic effects induced by tDCS were found in a sample consisting only of patients diagnosed with episodic migraine without aura [54]. In that study, each subject received preventive treatment with anodal tDCS applied to the visual cortex (1 mA/15 min) twice a day, for 8 weeks. Active stimulation reduced the frequency and duration of the migraine attacks as well as migraine days and the acute medication intake for a period of 4.8 weeks [54]. The same study showed that tDCS can induce a transient increase in the habituation in migraineurs, which could be one of the mechanisms underlying tDCS-induced analgesia in migraine patients.

In another tDCS study, significant decreases in the pain intensity, length of episodes, and clinical impression have been reported in chronic migraine patients treated with M1-SO tDCS [52]. Unexpectedly, only long-term effects (4 months after the period of treatment) were detected in that study, while immediate effects could not be demonstrated. Such findings could also be related to the protocol chosen, consisting of every other day stimulation, instead of daily sessions. Nevertheless, the most important contribution of that study was the detection of peaks of current flow in deeper pain-related structures (e.g., cingulate, thalamus, insula, and brainstem), demonstrated through a finite element model analysis, which has been confirmed afterwards [68].

tDCS can also provide insights into the pathophysiology of migraine headache, as demonstrated by a study that revealed, through a combination of tDCS and TMS, different patterns of changes in the cortical excitability induced by tDCS [119]. Anodal tDCS stimulation produced an increase in the visual cortex excitability in both healthy subjects and migraine patients, with larger variations observed in the group of migraine patients with migraine with aura. Conversely, cathodal tDCS (Cz-Oz) resulted in a decrease in the cortical excitability of healthy volunteers, but did not alter the cortical excitability in migraine patients, suggesting the presence of deficient inhibitory process in the cortex of migraine patients and indicating that a more prominent inhibitory dysfunction occurs in migraine with aura, when compared to migraine without aura [119]. In a following study that also combined TMS and tDCS, cathodal tDCS, but not anodal tDCS, restored the abnormal facilitatory response to HF-rTMS in migraine patients [120]. The presence of interictal visual cortical hyperexcitability has also been found in another study applying a similar methodology [121]. The same study reported significant reductions in duration and number of migraine attacks as well as painkillers intake when cathodal visual cortex stimulation was applied as a prophylactic therapy. Nevertheless, such effects were not higher than in a group of migraine patients that received sham stimulation [121]. Intriguingly, the beneficial effects obtained in the active group were not correlated to changes in cortical excitability, indicating that the analgesic effects induced by tDCS in migraineurs may occur independently of cortical excitability normalization.

Although still scarce, the data currently available suggest that tDCS can be a useful tool to treat migraine headache. However, it is still necessary to define the specific montage that offers more beneficial effects as well as the ideal parameters (e.g., current intensity, duration, and frequency) that should be used in migraine patients. To accomplish those objectives, further studies with larger sample sizes and individualizing different forms of migraine headache will be necessary.

31.2.3 Neuropathic Pains

The IASP taxonomy (Merskey et al., 1994), revised in 2012 (https://www.iasp-pain.org/terminology?navItemNumber=576), defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." However, neuropathic pain is considered an umbrella term, that encompasses distinct disorders, such as trigeminal and postherpetic neuralgias, painful diabetic polyneuropathy, painful nerve lesions, radiculopathies, and postamputation pain. Moreover, several CNS disorders (e.g., spinal cord injury, multiple sclerosis, and stroke) can be associated with neuropathic pain [122, 123]. The prevalence of neuropathic pain on the general population ranges from 2% to 3% [124, 125], but this number can be even higher. It has been estimated that the prevalence of pain with neuropathic characteristics can be around 6.9–10% [126]. Neuropathic pain is considered challenging to manage [127]. Furthermore, it often produces significant negative impact on quality of life [128]. The mechanisms that trigger and maintain neuropathic pain symptoms have not been totally unveiled. Nonetheless, peripheral as well as central mediation, which involve complex physiological events, are certainly important [9, 129, 130]. Considering the satisfactory results produced by MCS in neuropathic pain patients [17, 23, 131], it is reasonable to consider the use of tDCS to reduce the negative impact provoked by such disorders on the patients affected, or even as a predictive method for invasive therapies.

In fact, the first study investigating the efficacy and safety of tDCS in chronic pain was performed in patients with refractory neuropathic central pain due to traumatic spinal cord injury. The results indicated the presence of significant positive results on pain, without significant effects on anxiety and depression associated with five consecutive sessions of M1-SO tDCS but not with sham [24]. Remarkably, the magnitude of the results obtained in that study was impressively high, with a mean pain response of 58%. Besides, the lack of changes in cognitive and motor performed associated with tDCS verified in that study, corroborated the safety of the procedure, and supported the development of further tDCS studies in chronic pain patients. A recent study confirmed the safety and efficacy of anodal M1 stimulation in patients with neuropathic pain associated with spinal cord injury. Strikingly, a significant association was found between the decrease of pain intensity and increase in the peak theta–alpha frequency at the site of stimulation, with only a single session of tDCS [132].

A further study, evaluating patients with painful diabetic polyneuropathy, showed significant higher analgesic effects of M1-SO tDCS, when compared to DLPFC tDCS and sham, indicating that M1-SO tDCS might be optimal montage for neuropathic pain studies [47]. In other studies, M1-SO tDCS produced more significant and in some cases longer lasting results in neuropathic pain patients when combined with another therapy, such as transcutaneous electrical nerve stimulation [49] or visual illusion [41]. Nonetheless, in both examples, tDCS alone also granted beneficial effects to the patients evaluated.

Little is known regarding the mechanisms of M1-SO tDCS in chronic neuropathic pain syndromes. In a previous study, our group demonstrated for the first time significant changes in the availability of mu-opioid receptor in pain-related structures (insula, cingulate, nucleus accumbens, and thalamus) during a single session of M1-SO tDCS in a postherpetic neuralgia patient [46]. Such findings are very similar to those obtained with MCS in refractory neuropathic pain patients [133, 134] and suggest the contribution of the mu-opioidergic system to the tDCS-driven analgesia in neuropathic pain patients.

Negative results have also been reported with tDCS in neuropathic pain conditions. For example, in one study, five sessions of anodal M1 tDCS stimulation failed to produce analgesia in patients with neuropathic pain due to spinal cord injury, contrasting the findings of previous studies. Noteworthy, the duration of the injury in the patients of that study was longer than in other studies, suggesting that the pain decreases related to tDCS also depend on the pain duration [43]. Negative results of M1-SO tDCS in neuropathic pain have been documented in other studies. Nonetheless, those results should be interpreted

cautiously, since in those cases, the protocol consisted of single sessions of stimulation [42, 48], which in some cases could not be enough to produce significant analgesia and especially in refractory neuropathic pain patients.

31.3 Concluding Remarks

The current scientific literature indicates that tDCS is safety and well-tolerated procedure that can be effectively used as a prophylactic or even acute therapy in different chronic pain syndromes. Nevertheless, there are still many questions that must be answered before it can be clinically applied in a large scale. Future studies should not only focus on establishing the ideal montages and protocols for each pain syndrome but also on determining to what extension a placebo effect contributes to its analgesic effects and more important, the pain-related neural mechanisms that can be targeted and potentially modulated by tDCS.

References

1. Fishman S, Ballantyne J, Rathmell JP, Bonica JJ. Bonica's management of pain. Lippincott: Williams & Wilkins; 2010.
2. Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain: a new conceptual model. In: Kenshalo D, editor. The skin senses. Springfield, IL: Charles C Thomas; 1968. p. 423–39.
3. Merskey H, Bogduk N. International Association for the Study of P. classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994. p. xvi, 222 p.
4. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain. 1998;77(3):231–9.
5. Elliott AM, Smith BH, Hannaford PC, Smith WC, Chambers WA. The course of chronic pain in the community: results of a 4-year follow-up study. Pain. 2002;99(1–2):299–307.
6. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet. 1999;354(9186):1248–52.
7. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287–333.
8. Patel AS, Farquharson R, Carroll D, Moore A, Phillips CJ, Taylor RS, et al. The impact and burden of chronic pain in the workplace: a qualitative systematic review. Pain Pract. 2012;12(7):578–89.
9. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267–84.
10. McMahon SB. Wall and Melzack's textbook of pain. 6th ed. Philadelphia: Elsevier/Saunders; 2013. p. xxix, 1153 p.
11. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. J Pain. 2007;8(2):118–26.
12. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS. Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. J Pain. 2005;6(2):98–106.
13. Schwenkreis P, Scherens A, Rönnau AK, Höffken O, Tegenthoff M, Maier C. Cortical disinhibition occurs in chronic neuropathic, but not in chronic nociceptive pain. BMC Neurosci. 2010;11:73.
14. von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73(4):638–52.
15. Largus S. De compositionibus medicamentorum. Minerva Med. 1529;53:2398–402.
16. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol. 1991;14(1):131–4.
17. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien). 1991;52:137–9.
18. Nguyen JP, Nizard J, Keravel Y, Lefaucheur JP. Invasive brain stimulation for the treatment of neuropathic pain. Nat Rev Neurol. 2011;7(12):699–709.
19. Lende RA, Kirsch WM, Druckman R. Relief of facial pain after combined removal of precentral and postcentral cortex. J Neurosurg. 1971;34(4):537–43.
20. White JC, Sweet WH. Pain and the neurosurgeon; a forty-year experience. Springfield: C. C. Thomas; 1969. p. xxxi, 1000 p.
21. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport. 2001;12(13):2963–5.
22. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P. Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl (Wien). 1993;58:150–3.
23. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, et al. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain. 1999;82(3):245–51.

24. Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1–2):197–209.
25. Fregni F, Gimenes R, Valle A, Ferreira M, Rocha R, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum. 2006;54(12):3988–98.
26. Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology. 2006;67(9):1568–74.
27. Lee SJ, Kim DY, Chun MH, Kim YG. The effect of repetitive transcranial magnetic stimulation on fibromyalgia: a randomized sham-controlled trial with 1-mo follow-up. Am J Phys Med Rehabil. 2012;91(12):1077–85.
28. Picarelli H, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, et al. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. J Pain. 2010;11(11):1203–10.
29. O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev. 2014;4:CD008208.
30. Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul. 2012;5(2):155–62.
31. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Suppl Clin Neurophysiol. 2003;56:255–76.
32. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Group SoTC. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008–39.
33. Fregni F, Boggio P, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005;166(1):23–30.
34. Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol. 2002;113(1):101–7.
35. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;9(10):2257–60.
36. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
37. Riberto M, Marcon Alfieri F, et al. Efficacy of transcranial direct current stimulation coupled with a multidisciplinary rehabilitation program for the treatment of fibromyalgia. Open Rheumatol J. 2011;5:45–50.
38. Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, et al. Transcranial DC stimulation in fibromyalgia: optimized cortical target supported by high-resolution computational models. J Pain. 2011;12(5):610–7.
39. Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, et al. Focal modulation of the primary motor cortex in fibromyalgia using 4 × 1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J Pain. 2013;14(4):371–83.
40. Valle A, Roizenblatt S, Botte S, Zaghi S, Riberto M, Tufik S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. J Pain Manage. 2009;2(3):353–61.
41. Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain. 2010;133(9):2565–77.
42. Jensen MP, Sherlin LH, Askew RL, Fregni F, Witkop G, Gianas A, et al. Effects of non-pharmacological pain treatments on brain states. Clin Neurophysiol. 2013;124(10):2016–24.
43. Wrigley PJ, Gustin SM, McIndoe LN, Chakiath RJ, Henderson LA, Siddall PJ. Longstanding neuropathic pain after spinal cord injury is refractory to transcranial direct current stimulation: a randomized controlled trial. Pain. 2013;154(10):2178–84.
44. Fenton BW, Palmieri PA, Boggio P, Fanning J, Fregni F. A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. Brain Stimul. 2009;2(2):103–7.
45. Antal A, Paulus W. A case of refractory orofacial pain treated by transcranial direct current stimulation applied over hand motor area in combination with NMDA agonist drug intake. Brain Stimul. 2011;4(2):117–21.
46. DosSantos MF, Love TM, Martikainen IK, Nascimento TD, Fregni F, Cummiford C, et al. Immediate effects of tDCS on the μ-opioid system of a chronic pain patient. Front Psych. 2012;3:93.
47. Kim YJ, Ku J, Kim HJ, Im DJ, Lee HS, Han KA, et al. Randomized, sham controlled trial of transcranial direct current stimulation for painful diabetic polyneuropathy. Ann Rehabil Med. 2013;37(6):766–76.
48. Portilla AS, Bravo GL, Miraval FK, Villamar MF, Schneider JC, Ryan CM, et al. A feasibility study assessing cortical plasticity in chronic neuropathic pain following burn injury. J Burn Care Res. 2013;34(1):e48–52.

49. Boggio PS, Amancio EJ, Correa CF, Cecilio S, Valasek C, Bajwa Z, et al. Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. Clin J Pain. 2009;25(8):691–5.
50. Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener HC, et al. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J Headache Pain. 2014;15:78.
51. Schabrun SM, Jones E, Elgueta Cancino EL, Hodges PW. Targeting chronic recurrent low back pain from the top-down and the bottom-up: a combined transcranial direct current stimulation and peripheral electrical stimulation intervention. Brain Stimul. 2014;7(3):451–9.
52. Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache. 2012;52(8):1283–95.
53. Antal A, Kriener N, Lang N, Boros K, Paulus W. Cathodal transcranial direct current stimulation of the visual cortex in the prophylactic treatment of migraine. Cephalalgia. 2011;31(7):820–8.
54. Viganò A, D'Elia TS, Sava SL, Auvé M, De Pasqua V, Colosimo A, et al. Transcranial Direct Current Stimulation (tDCS) of the visual cortex: a proof-of-concept study based on interictal electrophysiological abnormalities in migraine. J Headache Pain. 2013;14(1):23.
55. Donnell A, D Nascimento T, Lawrence M, Gupta V, Zieba T, Truong DQ, et al. High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD. Brain Stimul. 2015;8(6):1085–92.
56. Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clin Neurophysiol. 2014;125(9):1847–58.
57. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ. 2008;336(7644):601–5.
58. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry. 2001;49(5):460–3.
59. Loo CK, Taylor JL, Gandevia SC, McDarmont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biol Psychiatry. 2000;47(4):325–31.
60. Sommer J, Jansen A, Dräger B, Steinsträter O, Breitenstein C, Deppe M, et al. Transcranial magnetic stimulation–a sandwich coil design for a better sham. Clin Neurophysiol. 2006;117(2):440–6.
61. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in–short stimulation–fade out approach to sham tDCS–reliable at 1 mA for naïve and experienced subjects, but not investigators. Brain Stimul. 2012;5(4):499–504.
62. Gandiga P, Hummel F, Cohen L. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol. 2006;117(4):845–50.
63. O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, Moseley GL, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. PLoS One. 2012;7(10):e47514.
64. DaSilva AF, Volz MS, Bikson M, Fregni F. Electrode positioning and montage in transcranial direct current stimulation. J Vis Exp. 2011;51:2744.
65. Mylius V, Borckardt JJ, Lefaucheur JP. Noninvasive cortical modulation of experimental pain. Pain. 2012;153(7):1350–63.
66. Siniatchkin M, Sendacki M, Moeller F, Wolff S, Jansen O, Siebner H, et al. Abnormal changes of synaptic excitability in migraine with aura. Cereb Cortex. 2012;22(10):2207–16.
67. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 2007;72(4–6):208–14.
68. DaSilva AF, Truong DQ, DosSantos MF, Toback RL, Datta A, Bikson M. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. Front Neuroanat. 2015;9:89.
69. Villamar MF, Volz MS, Bikson M, Datta A, Dasilva AF, Fregni F. Technique and considerations in the use of 4 × 1 ring high-definition transcranial direct current stimulation (HD-tDCS). J Vis Exp. 2013;77:e50309.
70. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2(4):201–7, 7.e1.
71. Sehm B, Kipping J, Schäfer A, Villringer A, Ragert P. A comparison between uni- and bilateral tDCS effects on functional connectivity of the human motor cortex. Front Hum Neurosci. 2013;7:183.
72. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57(10):1899–901.
73. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004;24(46):10410–5.
74. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med. 2006;3(10):e402.

75. DaSilva AF, Granziera C, Snyder J, Hadjikhani N. Thickening in the somatosensory cortex of patients with migraine. Neurology. 2007;69(21):1990–5.
76. DaSilva AF, Becerra L, Pendse G, Chizh B, Tully S, Borsook D. Colocalized structural and functional changes in the cortex of patients with trigeminal neuropathic pain. PLoS One. 2008;3(10):e3396.
77. Kim J, Suh S, Seol H, Oh K, Seo W, Yu S, et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia. 2008;28(6):598–604.
78. Schmidt-Wilcke T, Luerding R, Weigand T, Jürgens T, Schuierer G, Leinisch E, et al. Striatal grey matter increase in patients suffering from fibromyalgia–a voxel-based morphometry study. Pain. 2007;132(Suppl 1):S109–16.
79. Lutz J, Jäger L, de Quervain D, Krauseneck T, Padberg F, Wichnalek M, et al. White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study. Arthritis Rheum. 2008;58(12):3960–9.
80. Gustin SM, Peck CC, Wilcox SL, Nash PG, Murray GM, Henderson LA. Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. J Neurosci. 2011;31(16):5956–64.
81. Youssef AM, Gustin SM, Nash PJ, Reeves JM, Petersen ET, Peck CC, et al. Differential brain activity in subjects with painful trigeminal neuropathy and painful temporomandibular disorder. Pain. 2013;155(3):467–75.
82. Mainero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. Ann Neurol. 2011;70(5):838–45.
83. Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A. 2001;98(8):4687–92.
84. Kim J, Loggia ML, Cahalan CM, Harris RE, Beissner F, Garcia RG, et al. The somatosensory link in fibromyalgia: functional connectivity of the primary somatosensory cortex is altered by sustained pain and is associated with clinical/autonomic dysfunction. Arthritis Rheumatol. 2015;67(5):1395–405.
85. Napadow V, Harris RE. What has functional connectivity and chemical neuroimaging in fibromyalgia taught us about the mechanisms and management of 'centralized' pain? Arthritis Res Ther. 2014;16(5):425.
86. Ichesco E, Schmidt-Wilcke T, Bhavsar R, Clauw DJ, Peltier SJ, Kim J, et al. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. J Pain. 2014;15(8):815–26, e1.
87. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. J Neurosci. 2007;27(37):10000–6.
88. Dossantos MF, Martikainen IK, Nascimento TD, Love TM, Deboer MD, Maslowski EC, et al. Reduced basal ganglia mu-opioid receptor availability in trigeminal neuropathic pain: a pilot study. Mol Pain. 2012;8(1):74.
89. Martikainen IK, Nuechterlein EB, Peciña M, Love TM, Cummiford CM, Green CR, et al. Chronic back pain is associated with alterations in dopamine neurotransmission in the ventral striatum. J Neurosci. 2015;35(27):9957–65.
90. DaSilva AF, Nascimento TD, DosSantos MF, Lucas S, van HolsbeecK H, DeBoer M, et al. Association of μ-opioid activation in the prefrontal cortex with spontaneous migraine attacks – brief report I. Ann Clin Transl Neurol. 2014;1(6):439–44.
91. Nascimento TD, DosSantos MF, Lucas S, van Holsbeeck H, DeBoer M, Maslowski E, et al. μ-Opioid activation in the midbrain during migraine allodynia – brief report II. Ann Clin Transl Neurol. 2014;1(6):445–50.
92. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(Pt 10):2238–47.
93. Foerster BR, Nascimento TD, DeBoer M, Bender MA, Rice IC, Truong DQ, et al. Excitatory and inhibitory brain metabolites as targets of motor cortex transcranial direct current stimulation therapy and predictors of its efficacy in fibromyalgia. Arthritis Rheumatol. 2015;67(2):576–81.
94. Clark VP, Coffman BA, Trumbo MC, Gasparovic C. Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a ^{1}H magnetic resonance spectroscopy study. Neurosci Lett. 2011;500(1):67–71.
95. DosSantos MF, Martikainen IK, Nascimento TD, Love TM, DeBoer MD, Schambra HM, et al. Building up analgesia in humans via the endogenous μ-opioid system by combining placebo and active tDCS: a preliminary report. PLoS One. 2014;9(7):e102350.
96. Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci U S A. 2007;104(26):11056–61.
97. Zubieta JK, Stohler CS. Neurobiological mechanisms of placebo responses. Ann N Y Acad Sci. 2009;1156:198–210.
98. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995;38(1):19–28.
99. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol. 2007;21(3):403–25.
100. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing

the Rochester Epidemiology Project. Arthritis Care Res (Hoboken). 2013;65(5):786–92.
101. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum. 1990;33(2):160–72.
102. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311(15):1547–55.
103. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113–22.
104. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. J Pain. 2009;10(8):777–91.
105. Foerster BR, Petrou M, Harris RE, Barker PB, Hoeffner EG, Clauw DJ, et al. Cerebral blood flow alterations in pain-processing regions of patients with fibromyalgia using perfusion MR imaging. AJNR Am J Neuroradiol. 2011;32(10):1873–8.
106. Foerster BR, Petrou M, Edden RA, Sundgren PC, Schmidt-Wilcke T, Lowe SE, et al. Reduced insular γ-aminobutyric acid in fibromyalgia. Arthritis Rheum. 2012;64(2):579–83.
107. Albrecht DS, MacKie PJ, Kareken DA, Hutchins GD, Chumin EJ, Christian BT, et al. Differential dopamine function in fibromyalgia. Brain Imaging Behav. 2015;10(3):829–39.
108. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum. 2012;64(7):2398–403.
109. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag. 2010;39(5):890–903.
110. (IHS) HCCotIHS. The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808.
111. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27(3):193–210.
112. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. Brain. 2000;123(Pt 8):1703–9.
113. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol. 2000;47(5):614–24.
114. Lovati C, D'Amico D, Bertora P. Allodynia in migraine: frequent random association or unavoidable consequence? Expert Rev Neurother. 2009;9(3):395–408.
115. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. Ann Neurol. 2008;63(2):148–58.
116. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: a population study. Neurology. 2008;70(17):1525–33.
117. Burstein R. Deconstructing migraine headache into peripheral and central sensitization. Pain. 2001;89(2–3):107–10.
118. Dodick D, Silberstein S. Central sensitization theory of migraine: clinical implications. Headache. 2006;46(Suppl 4):S182–91.
119. Chadaide Z, Arlt S, Antal A, Nitsche MA, Lang N, Paulus W. Transcranial direct current stimulation reveals inhibitory deficiency in migraine. Cephalalgia. 2007;27(7):833–9.
120. Cosentino G, Brighina F, Talamanca S, Paladino P, Vigneri S, Baschi R, et al. Reduced threshold for inhibitory homeostatic responses in migraine motor cortex? A tDCS/TMS study. Headache. 2014;54(4):663–74.
121. Rocha S, Melo L, Boudoux C, Foerster Á, Araújo D, Monte-Silva K. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. J Neurol Sci. 2015;349(1–2):33–9.
122. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol. 2014;13(9):924–35.
123. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain. 2011;152(10):2204–5.
124. Hall G, Carroll D, Parry D, McQuay H. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain. 2006;122(1–2):156–62.
125. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008;136(3):380–7.
126. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. Clin J Pain. 2002;18(6):355–65.
127. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3 Suppl):S3–14.
128. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology. 2007;68(15):1178–82.

129. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron. 2006;52(1):77–92.
130. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32:1–32.
131. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg. 1993;78(3):393–401.
132. Ngernyam N, Jensen MP, Arayawichanon P, Auvichayapat N, Tiamkao S, Janjarasjitt S, et al. The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. Clin Neurophysiol. 2015;126(2):382–90.
133. Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, et al. Brain opioid receptor density predicts motor cortex stimulation efficacy for chronic pain. Pain. 2013;154(11):2563–8.
134. Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, et al. Motor cortex stimulation for pain control induces changes in the endogenous opioid system. Neurology. 2007;69(9):827–34.

32 Transcranial Direct Current Stimulation for the Treatment of Tinnitus

Sook Ling Leong and Sven Vanneste

32.1 Introduction

Tinnitus, as characterized by the perception of sound in the absence of an external acoustic source [1], has been estimated to have a worldwide prevalence of 12–30% in the general public, rising to 30% in those above 50 years of age [2]. Population studies have reported higher tinnitus presence among males and those with hearing loss, lower socioeconomic status or education, besides a wide range of diseases such as hypothyroidism, hyperlipidemia, and osteoarthritis [3, 4]. Although symptoms can be sufficiently managed in most patients with tinnitus, severe tinnitus has a prevalence of approximately 20% of all cases [5]. This disorder has a significant negative impact on patients' quality of life, ranging from debilitating physical pain to mental and emotional effects [5].

The experience of tinnitus is remarkably heterogenous. It can be intermittent or constant, varying in perceived intensity and observed in one or both ears. The perceived sensations of tinnitus are far ranging, described as being ringing, hissing, or sizzling to more complex depictions of musical hallucinations. Broadly, tinnitus is subjective when noises are audible only to the individual, and objective when the ringing can be witnessed by an outside observer. Objective tinnitus often has an identifiable origin associated with disorders of the vascular or muscular systems whereas subjective tinnitus is idiopathic and is more common. Onwards, discussion in this chapter is centered around subjective tinnitus.

Despite the marked increase in tinnitus research, particularly in the past decade, the pathophysiology of this phantom sound remains to be clarified. Yet, neuroimaging studies have allowed for some plausible clarifications regarding the neural correlates and changes in the brain that trigger the clinical manifestation of tinnitus. The pathophysiology of tinnitus has been linked to changes in the auditory system and several non-auditory brain areas. Damages to the cochlea and subsequent hearing loss have been shown to cause an abnormal increased rate of spontaneous firing (i.e., hyperactivity) in the central auditory circuit [6]. The reorganization of tonotopic maps and downregulation of inhibition (i.e., disinhibition) in the auditory system are well-received mechanisms responsible for tinnitus [6].

As for non-auditory areas, great emphasis has been placed on regions of the limbic structures

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(i.e., amygdala, anterior cingulate cortex, hippocampus, orbitofrontal cortex, and anterior insular cortex) that are involved with the evaluation and upkeep of emotional and sensory (e.g., auditory) salience, motivation, and memory [6]. The underlying mechanisms regarding the interactions between the auditory system and the limbic structures, and how they contribute to the generation and maintenance of tinnitus distress, are debatable. Nonetheless, in the process of unraveling this interconnected relationship, intense research efforts have identified potential new tinnitus treatment strategies centered around modulating the plasticity of the "distress network" through connected areas such as the dorsal lateral prefrontal cortex, auditory cortex, and temporoparietal junction.

On such basis, the capability of noninvasive brain stimulation methods in performing effective modulation has raised clinical and scientific interest. The potential therapeutic role of transcranial electrical stimulation, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS), is appealing and relevant considering the limited success of current pharmacological and nonpharmacological approaches [1, 7]. In the following sections, a review regarding evidence on tDCS, tACS, tRNS treatments for tinnitus is presented, elucidating perspective for future directions and developments.

32.2 tDCS

32.2.1 tDCS Targeting the Left Temporoparietal Area (LTA) and Auditory Cortex (AC)

Alike the utilization of tDCS in other neuropsychiatric disorders, the main supposition of tDCS in tinnitus recognizes that anodal tDCS increases neural excitability through depolarization, while cathodal tDCS achieves the opposite effect by inducing neuronal hyperpolarization. Thus, to attain therapeutic outcomes, anodal tDCS is applied to areas with decreased activity and cathodal tDCS to regions that are hyperactive. The ultimate goal would be to revert activity and function of the impaired brain areas toward normal states. In tinnitus, the main goal of tDCS is to regulate the tinnitus perception or its affective aspects by disrupting the impaired pathological neural activity.

Initial studies have investigated the effects of tDCS over the left temporoparietal area (LTA). Targeting the LTA could mean modulating a neural network that has a significant impact on the primary auditory cortex, the auditory association areas, and parts of the limbic system, especially the amygdala and hippocampus [8, 9]. It was hypothesized that anodal stimulation could depolarize neurons that are associated with the abovementioned cortical and subcortical structures [10], and subsequently, via inhibition networks, promote suppression of ongoing states of abnormal hyperactivity in the auditory cortex (AC).

The first tDCS tinnitus study assessed the effects of cathodal tDCS, anodal tDCS, and 10-Hz repetitive transcranial magnetic stimulation (rTMS) (i.e., excitatory stimulation) versus a sham stimulation protocol in modulating the LTA [10]. Anodal tDCS of the LTA with cathode placed contralaterally at the supraorbital area resulted in a transient suppression of tinnitus, which was akin to rTMS results. These promising findings were replicated by Garin and colleagues [11], with therapeutic effects lasting for several days in some of their participants [11]. Accordingly, it was concluded that cathodal tDCS of the LTA with anode over the contralateral supraorbital area does not improve tinnitus symptoms.

A subsequent study applying anodal tDCS on the LTA in a dose-response design showed that tinnitus suppression was greatest after 20 minutes of 2 mA stimulation compared to lower stimulation intensities [12] as utilized by previous studies [10, 11]. This could however be a result of the cumulative impact of sessions as the wash-out period was 10 minutes between stimulation sessions. This inclination was reinforced by later sham-controlled studies with similar stimulation parameters, reporting no significant tinnitus reduction when comparing LTA anodal stimulation to sham [13–15].

Collectively, positive tinnitus suppression in LTA interventions might be driven by placebo effects. This could bring into question whether previous negative findings for cathodal LTA stimulation by Fregni et al. [10] and Garin et al. [11] were a result of weak stimulation parameters (<10 minutes, <2 mA). Stronger and longer stimulation may settle ongoing cortical hyperactivity, delivering significant tinnitus suppression [16]. Hereof, theoretically, higher cathodal stimulation intensity coupled with repeated sessions may induce beneficial effects on tinnitus severity—a consideration that was adapted in following research.

Subsequent studies investigating the effects of tDCS over the AC produced mixed results [17–23]. For example, in one of the first studies using bilateral tDCS, Joos and colleagues [18] demonstrated that suppression of tinnitus loudness and annoyance were independent of stimulation polarity. Yet, further studies utilizing cathodal tDCS on the AC showed no effect on tinnitus intensity [17, 19–22]. It is noteworthy that protocols for tDCS-AC stimulation were heterogenous. While all studies included a cathodal stimulation, some compared this to anodal [18, 19] while others to sham stimulation [17, 20, 21]. Interestingly, a recent study showed that anodal stimulation was more effective than cathodal in reducing tinnitus intensity [23]. However, it was questionable whether the control protocol of the study was indeed a sham procedure or an electrical stimulation was admitted [23].

32.2.2 tDCS Targeting the Prefrontal Cortex (PFC)

Several studies have targeted the prefrontal cortex (PC), specifically the dorsal lateral prefrontal cortex (DLPFC). The DLPFC has been shown to contain auditory memory cells and functions as a bilateral facilitator of auditory memory storage [24]. Furthermore, in humans, the DLPFC exerts early inhibitory modulation of input to the primary auditory cortex [25] and is associated with auditory attention [26], causing a top-down modulation of auditory processing [27]. Also, studies have suggested that the PFC plays an important role in the integration of sensory and emotional aspects of tinnitus [28]. Particularly, the DLPFC could be the regulatory hub of brain structures (i.e., anterior cingulate cortex, amygdala, and insula) that are involved in the emotional perception of tinnitus [28].

Most studies administered bifrontal stimulation with 1.5 mA or 2.0 mA for 20 minutes, with the anode over the right DLPFC and the cathode over the left DLPFC. The first study using this bifrontal tDCS design reported that a single session of anodal right and cathodal left resulted in a transient improvement in tinnitus severity but with no significant effect after anodal left and cathodal right (i.e., when the polarity was reversed) [29]. In addition, an interaction between the amount of distress reduction and tinnitus laterality was noted. This, however, was not observed for tinnitus intensity [29].

Concurrently, neuroimaging literature suggested that the DLPFC plays an important role in anxiety, depression [30], and unpleasantness related to pain [31]. Fregni and colleagues [32] demonstrated that anodal tDCS of the left DLPFC improved depressive symptoms after five sessions. Given that tinnitus is usually accompanied by depression, a subsequent study examining electrode placement of repetitive (five sessions) bifrontal tDCS was carried out in a double-blind, placebo-controlled, cross-over manner. Results indicated that both montages (anodal right/cathodal left and cathodal right/anodal left) decreased tinnitus annoyance but not tinnitus intensity. However, as hypothesized, left DLPFC anodal stimulation modulated depression. In addition, study findings revealed that right DLPFC anodal stimulation resulted in improved anxiety symptoms.

These results were consistent with the theory of a unified tinnitus percept whereby a tinnitus network consists of multiple dynamically adaptive overlapping subnetworks [33]. Each of these subnetworks represents a clinical aspect of tinnitus, such as distress, lateralization, or sound characteristics [33]. In an effort to improve tDCS protocols, an EEG-driven tDCS study was carried out, using source localized resting-state

electrical activity to determine the placement of anodal and cathodal electrodes [34]. Findings of the study showed suppression of tinnitus when the parahippocampal area, pregenual anterior cingulate cortex, and the primary AC were modulated. However, there was no difference in tinnitus severity when compared to bifrontal tDCS with anode over the right DLPFC and cathode over the left DLPFC [34].

One possible explanation of these negative findings could be the use of gamma band functional connectivity as an index of the tinnitus network instead of the theta band [34]. This reasoning is based on the thalamocortical dysrhythmia model [35] where the emerging property of tinnitus, a consequence of deafferentation can lead to decrease neural firing in corresponding thalamocortical columns. This results in the "edge effect" or hyperactivity in adjacent regions [36] and the distinctive 40 Hz (gamma) oscillation as the marker of tinnitus.

Although gamma band activity is important in tinnitus perception [37], gamma oscillations are confined to small neural spaces and are responsible for encoding tinnitus intensity [38]. On the other hand, theta oscillations synchronize large networks and may be carrier waves with gamma (and the encoding of tinnitus intensity) nested onto them [39]. It has been shown that theta connectivity increases when patients perceive tinnitus compared to when they do not [40], thus, suggesting that theta waves are required for coactivation of the tinnitus network.

Consistent with the need to improve DLPFC tinnitus treatment tDCS protocols, Shekhawat and Vanneste [41] conducted a tDCS dose-response trial to optimize current intensity (1.5 mA or 2.0 mA), stimulation duration (20 minutes or 30 minutes), and number of sessions (2, 4, 6, 8, 10, etc.) with a 3- to 4-day washout period between each session. Study findings showed a significant decrease in tinnitus loudness with optimal setting of six sessions, 20 minutes at 1.5 mA over a 3-week period with washout of 3–4 days.

32.2.3 New Target Sites

Most tDCS tinnitus treatment trials have focused on modulating either the LTA, AC, or DLPFC. But this does not mean that tinnitus loudness is only associated with auditory cortex hyperactivity or that tinnitus distress is solely related the DLPFC activity. There is evidence indicating that observed therapeutic tDCS effects on tinnitus symptoms could be induced through a complex large interconnected neural network [42].

Properties of tinnitus have been shown to be associated with both structural and function changes in the prefrontal, parietal, and cingulate cortices as well as the amygdala, hippocampus, nucleus accumbens, insula, thalamus, and the cerebellum [42]. Damages in the cochlea could potentially instigate activation of areas regulating auditory memory, salience, and emotion [43]. In accordance with this theoretical framework, a mismatch between expected auditory input from memory and true auditory input, a result of activation of the auditory cortex, becomes attention seeking and distressful when the resting states of the salience and emotional networks are triggered, respectively [43]. This theory has been supported by EEG, MEG, and resting-state fMRI studies [44–46] demonstrating increased functional connectivity between the auditory cortex and the frontoparietal attention network and distress network.

Specifically, using source localized EEG, it has been shown that tinnitus distress is associated with increased beta activity in the dorsal region of the anterior cingulate cortex (ACC), while the amount of distress correlated with an alpha network that included the amygdala, ACC, insula-parahippocampus, and DLPFC [28]. Tinnitus distress has also been associated with an increased bidirectional connection of gamma bands between the DLPFC, orbitofrontal cortex, and the parieto-occipital region [45].

In short, the conscious perception of tinnitus is the consequence of a dynamic interaction

between partially overlapping brain networks. At present, there is a lack of consistency regarding the best target location for tDCS tinnitus treatment. Exploring networks, hubs and regions association with tinnitus using available neuroscience research tools such as fMRI, MEG, and source localized EEG in conjunction with network theory could impart new knowledge of alternative targets for tinnitus tDCS stimulation.

32.3 Alternative Approaches in Synergy with tDCS

32.3.1 High-Definition (HD) tDCS

Besides the use of conventional tDCS, studies have investigated the potential positive effects of HD-tDCS in the treatment of tinnitus, with the main goal of improving the focality of stimulation. In these studies, the most commonly adopted configuration was a 4×1 ring, with one central anode surrounded by four cathodes.

One of the first studies using HD-tDCS reported a suppression of tinnitus loudness and annoyance by a minimum of one point in 78% of the 27 tinnitus participants after two sessions of stimulation targeting the LTA and DLPFC. Results of the study also documented that the protocol implementing a higher intensity of 2 mA compared to 1 mA and longer duration of 20 versus 10 minutes was superior in reducing tinnitus symptoms [47]. The optimal HD-tDCS stimulation parameter was further established by Shekhawat and Vanneste (2017) when they confirmed a significant reduction in tinnitus loudness after 15 minutes of stimulation of the DLPFC compared to a sham session [48]. Contrary to these findings, one study, which utilized a 2×2 electrode montage with two anodal electrodes placed over the targeted primary AC and two cathodal electrodes over the lateral prefrontal cortex, with a combined stimulation of 2 mA for 4 sessions, each lasting 20 minutes, reported a nonsignificant reduction in tinnitus [17]. However, the splitting of delivered stimulation current across two sets of electrodes and a short washout time could have shrouded some of its therapeutic effects [17].

It is noteworthy that a study comparing HD to the classical tDCS targeting the DLPFC reported no significant difference between techniques with observed clinical improvement scores on the Tinnitus Functional Index (TFI) for both approaches [49]. Moreover, analysis of follow-up data from end of treatment showed no differences in outcome on the TFI between HD and convention tDCS over time [49]. Yet, results of this study should be interpreted with caution given the lack of a sham group to rule out the possibility of any observed placebo effects.

Although there is a lack of significant enhanced tinnitus suppression when comparing HD-tDCS to conventional tDCS, HD-tDCS has advantages in terms of administration and focality of stimulation. In terms of safety, tingling, sleepiness, and scalp pain were the only common transient sensations experienced during HD-tDCS to date [48]. Results from HD-tDCS studies, albeit limited at the moment, for the treatment of tinnitus are encouraging and the benefits resulting from this treatment approach merit further exploration.

32.3.2 tACS, tRNS, and TI

Alternatively, more recent novel noninvasive neuromodulation techniques that have been investigated in tinnitus are the use of transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). Instead of a direct and constant current as in tDCS, tACS delivers a rhythmic oscillating current at a prespecified frequency and is independent of direction of current flow [50]. A strength of tACS is its potential capability of modulating functions that are akin to brain oscillations at specific frequencies [51].

In tRNS, the alternating current is delivered to cortical regions with a constantly changing

frequency ranging from 0.1 to 600 Hz [52]. It has been reported that excitability increases induced by tRNS can last for up to 60 minutes after stimulation [52]. Postulated principles of tRNS underlying mechanisms include long-term potentiation [53], and repeated subthreshold stimulations that prevent the system from building up homeostasis and potentiating task-related neural activity [54]. Another hypothesized tRNS mechanism is the occurrence of "stochastic resonance," where neuronal signals of nonlinear systems such as the brain can be modulated by noise stimulations [55].

In tinnitus, the first comparison of tACS with tDCS and its effects on the suppression of annoyance and loudness was carried out in a sham-controlled designed study [56]. Results confirmed that a single session of bifrontal tDCS, with anodal over the right DLPFC and cathodal over the left DLPFC, can reduce suppression of both annoyance and loudness, while alpha frequency tACS of the DLPFC had no effect on these measures compared to sham stimulation [56]. The authors stipulated that although alpha frequency in the frontal brain region has been previously indicated tinnitus distress, a different frequency setting or possibly a different target area may yield better clinical outcomes [56].

A subsequent study assessing the effects of single or repeated sessions of alpha-modulated tACS and tRNS of the auditory cortex reported that a single session of tRNS can deliver suppressive effects on tinnitus loudness and annoyance [57]. Moreover, repetitive tRNS sessions seem to strengthen the therapeutic effects on loudness [57]. Similar to the previously described study, alpha tACS modulation of the auditory cortex did not appear to exhibit beneficial effects [57].

In an attempt to reveal the different clinical effects of tDCS, tACS, and tRNS in tinnitus, Vanneste and colleagues [22] compared single sessions of these stimulation modalities on the AC bilaterally in 111 tinnitus patients. Study results demonstrated that compared to tDCS and tACS, tRNS induced a larger transient suppressive effect on tinnitus loudness and distress [22]. tDCS and tACS, however, induced small nonsignificant effects on tinnitus symptoms [22].

Although studies of tACS and tRNS in tinnitus are at a preliminary stage, results point toward the superiority of tRNS over tDCS and tACS. Also, there seems to be a lack of indication that tACS can deliver positive outcomes in tinnitus. Results also stipulate that DLPFC stimulation using tDCS can improve tinnitus loudness and distress while tRNS of the AC yields the best therapeutic outcomes. This led to a proof-of-concept study, in which To and colleagues [58] compared prefrontal anodal tDCS followed by auditory tRNS to effects of only prefrontal tDCS. Results demonstrated the added beneficial value of auditory tRNS over absolute tDCS prefrontal stimulation [58].

On the basis of tRNS superiority, Joos and colleagues [59] assessed the effects of low-frequency tRNS (lf-tRNS) and high-frequency tRNS (hf-tRNS) in 154 chronic tinnitus patients. Results showed significant reductions in loudness and distress in both groups [59]. While the authors were not able to provide a clear mechanistic explanation for differences in hf- and lf- tRNS, hf-tRNS eventuated in a more pronounced suppression of loudness and distress [59]. Following these results, the capability of hf-tRNS over the bilateral temporal cortex was examined in a one-arm feasibility study of 30 patients who had previously received rTMS [60]. It was reported that the daily 2-week long treatment was effective in 31% of patients as measured by the Tinnitus Questionnaire (TQ), comparable to rTMS results [60]. Nonetheless, a carry-over effect from rTMS cannot be ruled out [60].

Based on previously discussed results, a natural inclination would be to investigate the use of hf-tRNS in a multisite stimulation study. As anticipated, a recent study set out to examine the feasibility and effectiveness of 2 weeks of daily lf-tRNS over the AC preceded by hf-tRNS over the DLPFC compared to AC-lf-tRNS [61]. Results demonstrated that the multisite group had significant larger reduction in tinnitus loudness and distress compared to sham and the AC-lf-tRNS groups [61].

Taken together, tRNS or more specifically, hf-tRNS when applied in a multisite modality is a promising treatment option for tinnitus patients. It is worth noting that results of the aforemen-

tioned studies are preliminary. Protocols from these studies need to be replicated and alternative protocols have to be explored to achieve optimal stimulation conditions for tRNS before any firm conclusions can be made on the subject matter.

Another novel noninvasive neuromodulation method in development that has pronounced potential in the treatment of tinnitus is temporal interference (TI) [62]. TI may have a focality comparable of deep brain stimulation, with results indicating that TI stimulation can discriminately activate the hippocampus in an animal model [63]. Using two electrode pairs to deliver a one-point focal stimulation site, TI injects current that are higher than the normal neuronal frequencies through the scalp. The envelope of the meeting point or interference current from the two electrode sets causes low-frequency activation of neurons in the selected brain region [62, 63]. Although TI research is still in its infancy, TI offers a very promising alternative to traditional deep brain stimulation approaches given the advantage of a greater safety profile and ease of application.

32.3.3 Multidisciplinary Approaches

A division of research on tDCS in tinnitus has focused on combining other treatment modalities with tDCS aiming to achieve potential synergistic beneficial outcomes. For instance, Shekhawat and colleagues explored the combination of tDCS and hearing aids in facilitating tinnitus suppression [64]. It was rationalized that tDCS could potentially enable priming of the brain, and subsequently boost the therapeutic properties of sound therapy from hearing aids. Although results indicated that significant improvements in tinnitus were dominated by effects from hearing aids independent of anodal tDCS stimulation of the LTA, theirs was the first study at attempting to prime the auditory central nervous system for hearing aid-based tinnitus suppression [64].

The use of priming to achieve augmented clinical results is established in rehabilitation stroke therapy, where noninvasive or invasive stimulation is applied as an underlying stimulant to prompt ipsilesional excitability of the motor cortex prior to physical therapy sessions [65]. In tinnitus, the central gain theory postulates that hyperactivity in the central auditory system resulting from damages to the cochlea is an adaptation process to maintain default neural coding and firing efficiency [66]. Reduced auditory input accompanied by amplification of neural activity due to increased gain (sensitivity) and reduced inhibition precedes the generation of tinnitus [66]. Thus, theoretically, suppressive tDCS could reduce central gain of tinnitus signals and by restoring some balance in the central auditory system, the effects of sound therapy from hearing aids could be amplified [66].

In another study, the effectiveness of tDCS combined with tailor-made notched music training (TMNMT) in tinnitus suppression was investigated [21]. Study protocol consisted of TMNMT for 10 days where auditory cortex tDCS was concurrently applied during the initial 30 minutes in the first 5 days [21]. Similar to Shekhawat and colleagues [64], results indicated that while there were significant improvement in tinnitus severity as measured by the Tinnitus Handicap Questionnaire (THI) after 5 days of treatment and during follow-up, tDCS did not significantly modulate the efficacy of treatment with no different between anodal, cathodal, or sham auditory cortex tDCS [21].

While the use of tDCS as an add-on treatment has yielded poor therapeutic outcomes, a multidisciplinary approach to tinnitus treatment as described above is still in its infancy. Different research parameters such as target sites, stimulation protocols, and treatment durations need to be examined. A resolved understanding of the neuropathophysiological underpinnings of tinnitus would also further draw insight of the interaction of tDCS and other treatment approaches.

32.3.4 Biomarkers

Tinnitus is a well-known heterogenous disorder with diagnosis and outcomes of therapeutic success measured subjectively in a self-reported manner. Given that not all patients respond to

tDCS or neuromodulation in general, the identification of tinnitus-specific biomarkers or a parameter that reflects the neural mechanisms of tinnitus could predict and strengthen existing diagnostic methods and help contribute to more successful development of neuromodulation approaches.

It has been reported that compared to nonresponders, responders of bifrontal tDCS had higher gamma band activity in the right primary and secondary auditory cortices as well as the right parahippocampus prior to tDCS stimulation [67]. Furthermore, bifrontal tDCS responders demonstrated an increased functional gamma band connectivity between the right DLPFC and parahippocampus in addition to the right DLPFC and pregenual ACC [67]. As previously discussed, there is evidence that gamma band activity in the auditory cortex is related to tinnitus loudness [39] while tinnitus distress requires the activation of brain regions associated with salience, attention, and emotion [28]. Moreover, bifrontal tDCS responders seem to experience a larger tinnitus suppression during TMS of the right auditory cortex in contrast to nonresponders [67].

Although findings are preliminary, these results are encouraging given that tDCS stimulation protocols can potentially be enhanced by providing more tailored closed-loop neuromodulation designs, where stimulation parameters are defined based on electrophysiological neural features of each patient and adjusted in real time according to brain activity recordings [68].

Another important research avenue is the study of potential associations between brain-derived neurotrophic factor (BDNF) gene polymorphisms and tinnitus. BDNF is important in the regulation of neural plasticity. It has been demonstrated that the Vall66Met polymorphism has adverse effects on the anatomy and functions of the prefrontal cortex and hippocampus [69]; non-auditory brain regions that are implicated in the development and maintenance of tinnitus [28]. Indeed, in tinnitus patients, results from MRI scans revealed significant gray matter decreases in the right inferior colliculus and left hippocampus [70].

In addition, among Met-allele carriers, there appears to be decreased functional connectivity between hippocampal and parahippocampal with areas of the default mode, executive and paralimbic networks at resting state [71], particularly in situations involving behavioral adaptation [32]. In a complementary fashion, one could speculate that given the influence of BDNF polymorphism on functional connectivity between large-scale networks, Vall66Met polymorphism carriers and noncarriers would respond differently to tinnitus treatments such as tDCS [16].

The documentation of electrophysiological and neurobiological parameters as discussed in this section has the potential of linking tinnitus-related subtypes to certain brain regions and their functions. These specifications could in the future permit the refinement of tinnitus therapies beyond what current electrical stimulation applications can achieve, paving a path for the advancement of personalized and targeted tinnitus therapies.

32.4 Discussion

In summary, to date, results from tDCS studies demonstrate that bifrontal tDCS of the DLPFC with anodal over the right and cathodal over the left represents the most investigated stimulation protocol that can to a certain extent consistently induce significant transient beneficial effects on tinnitus measures. Less reliable support is available for the efficacy of tDCS stimulation protocols targeting the AC or the LTA. One likely reason for more favorable outcomes when targeting the DLPFC is the probable stimulation of a large connected underlying tinnitus network involving both auditory and non-auditory-related brain regions [25, 26], resulting in reduction in not only annoyance [48] but also loudness [15].

The uncertainty around the impact of stimulation polarities in yielding therapeutic outcomes demonstrates the obscurity regarding our understanding of the pathophysiological mechanisms underlying the effects of tDCS in tinnitus treatment. At present, cathodal stimulation is sug-

gested to result in inhibition of tinnitus-related hyperactivity producing a transient relief of tinnitus symptoms. Yet, results from certain studies suggest that anodal stimulation may perhaps be more effective compared to cathodal stimulation [18, 20]. Evidence suggests that tDCS modulation is brain state dependent [16]. For example, it has been reported that theta tDCS during non-rapid eye movement (REM) generates a global decrease in slow oscillatory activity and a local reduction of frontal slow EEG spindle power (8–12 Hz). Conversely, during REM sleep, theta tDCS increases global gamma activity [16, 72].

By far, the quality of evidence is hindered by inconsistencies in study design and methodology. Small sample sizes, the lack of a control sham group, and the heterogeneity in stimulation protocols, including current amplitude, number of sessions, and total electrical dosage, contribute to the inconclusive effects of tDCS in the treatment of tinnitus. In addition, there is a need to explore the beneficial effects of tDCS over time. Criticism aside, tDCS is safe, well tolerated, user-friendly, and has the potential of being a home-based treatment. Advances in tDCS technology such as the invention of HD-tDCS which allows more focal stimulation patterns must be further examined. Adequately powered, well-designed randomized trials with prospective follow-ups assessing clinically relevant effect sizes and cost-effectiveness are needed to establish tDCS as a treatment tool in routine clinical practice.

There is an urgency for researchers to implement the above-mentioned paths of action to ascertain the efficacy of tDCS for the treatment of tinnitus. At present, there is a dearth of effective and reliable pharmacological as well as non-pharmacological treatment for tinnitus. Briefly, none of the investigated pharmacological drugs to date have shown long-term suppressive tinnitus impact when compared to placebo [7]. Studies of passive auditory amplification with hearing aid or active auditory amplification through sound therapy produced weak evidence of their efficacy in tinnitus management [73, 74]. Psychological approaches, such as cognitive behavioral therapy, improve quality of life among tinnitus sufferers but do not influence tinnitus loudness [75]. Thus, the emergence of noninvasive stimulation devices such as tDCS and their potential therapeutic effects for tinnitus is well received.

32.5 Conclusion

The aim of this chapter was to provide a general overview of the use of tDCS in the treatment of tinnitus. We discussed the therapeutic efficacy of different stimulation protocols and montages, the possible mechanisms of action as well as the advances and future directions. Although much challenging research remains to be done to establish the true clinical efficacy of tDCS for the treatment of tinnitus, this can be attained through appropriately designed studies and more homogenous protocols with longer follow-ups. Undeniably, tDCS has the potential of being an effective, inexpensive, and easy to apply approach for the treatment of tinnitus patients.

References

1. Baguley D, McFerran D, Hall D. Tinnitus. Lancet. 2013;382(9904):1600–7.
2. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med. 2010;123(8):711–8.
3. Kim H-J, Lee H-J, An S-Y, Sim S, Park B, Kim SW, et al. Analysis of the prevalence and associated risk factors of tinnitus in adults. PloS One. 2015;10(5):e0127578.
4. Nondahl DM, Cruickshanks KJ, Huang G-H, Klein BE, Klein R, Tweed TS, et al. Generational differences in the reporting of tinnitus. Ear Hear. 2012;33(5):640.
5. McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. Hear Res. 2016;337:70–9.
6. Galazyuk AV, Wenstrup JJ, Hamid MA. Tinnitus and underlying brain mechanisms. Curr Opin Otolaryngol Head Neck Surg. 2012;20(5):409–15.
7. Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic approaches to the treatment of tinnitus. Annu Rev Pharmacol Toxicol. 2019;59:291–313.
8. Mirz F. Cortical networks subserving the perception of tinnitus-a PET study. Acta Otolaryngol. 2000;120(543):241–3.

9. Mühlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci. 1998;95(17):10340–3.
10. Fregni F, Marcondes R, Boggio P, Marcolin M, Rigonatti S, Sanchez TG, et al. Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Eur J Neurol. 2006;13(9):996–1001.
11. Garin P, Gilain C, Van Damme J-P, De Fays K, Jamart J, Ossemann M, et al. Short-and long-lasting tinnitus relief induced by transcranial direct current stimulation. J Neurol. 2011;258(11):1940–8.
12. Shekhawat GS, Stinear CM, Searchfield GD. Transcranial direct current stimulation intensity and duration effects on tinnitus suppression. Neurorehabil Neural Repair. 2013;27(2):164–72.
13. Forogh B, Mirshaki Z, Raissi GR, Shirazi A, Mansoori K, Ahadi T. Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial. Neurol Sci. 2016;37(2):253–9.
14. Hyvärinen P, Mäkitie A, Aarnisalo AA. Self-administered domiciliary tDCS treatment for tinnitus: a double-blind sham-controlled study. PLoS One. 2016;11(4):e0154286.
15. Shekhawat GS, Kobayashi K, Searchfield GD. Methodology for studying the transient effects of transcranial direct current stimulation combined with auditory residual inhibition on tinnitus. J Neurosci Methods. 2015;239:28–33.
16. Vanneste S, De Ridder D. Noninvasive and invasive neuromodulation for the treatment of tinnitus: an overview. Neuromodulation: Technol Neural Interface. 2012;15(4):350–60.
17. Henin S, Fein D, Smouha E, Parra LC. The effects of compensatory auditory stimulation and high-definition transcranial direct current stimulation (HD-tDCS) on tinnitus perception–a randomized pilot study. PloS One. 2016;11(11):e0166208.
18. Joos K, De Ridder D, Van de Heyning P, Vanneste S. Polarity specific suppression effects of transcranial direct current stimulation for tinnitus. Neural Plast. 2014;2014:1–8.
19. Minami SB, Oishi N, Watabe T, Uno K, Kaga K, Ogawa K. Auditory resting-state functional connectivity in tinnitus and modulation with transcranial direct current stimulation. Acta Otolaryngol. 2015;135(12):1286–92.
20. Pal N, Maire R, Stephan MA, Herrmann FR, Benninger DH. Transcranial direct current stimulation for the treatment of chronic tinnitus: a randomized controlled study. Brain Stimul. 2015;8(6):1101–7.
21. Teismann H, Wollbrink A, Okamoto H, Schlaug G, Rudack C, Pantev C. Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress–a pilot study. PloS One. 2014;9(2):e89904.
22. Plazier M, Dekelver I, Vanneste S, Stassijns G, Menovsky T, Thimineur M, et al. Occipital nerve stimulation in fibromyalgia: a double-blind placebo-controlled pilot study with a six-month follow-up. Neuromodulation. 2014:17(3):256–64.
23. Abtahi H, Okhovvat A, Heidari S, Gharagazarloo A, Mirdamadi M, Nilforoush MH, et al. Effect of transcranial direct current stimulation on short-term and long-term treatment of chronic tinnitus. Am J Otolaryngol. 2018;39(2):94–6.
24. Bodner M, Kroger J, Fuster JM. Auditory memory cells in dorsolateral prefrontal cortex. Neuroreport: Int J Rapid Commun Res Neurosci. 1996;7:1905–8.
25. Knight RT, Scabini D, Woods DL. Prefrontal cortex gating of auditory transmission in humans. Brain Res. 1989;504(2):338–42.
26. Voisin J, Bidet-Caulet A, Bertrand O, Fonlupt P. Listening in silence activates auditory areas: a functional magnetic resonance imaging study. J Neurosci. 2006;26(1):273–8.
27. Mitchell TV, Morey RA, Inan S, Belger A. Functional magnetic resonance imaging measure of automatic and controlled auditory processing. Neuroreport. 2005;16(5):457.
28. Vanneste S, Plazier M, Van Der Loo E, Van de Heyning P, Congedo M, De Ridder D. The neural correlates of tinnitus-related distress. NeuroImage. 2010;52(2):470–80.
29. Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D. Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Exp Brain Res. 2010;202(4):779–85.
30. Avery DH, Holtzheimer PE III, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. J Nerv Ment Dis. 2007;195(5):378–81.
31. Freund W, Stuber G, Wunderlich AP, Schmitz B. Cortical correlates of perception and suppression of electrically induced pain. Somatosens Mot Res. 2007;24(6):203–12.
32. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006;23(8):482–4.
33. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci. 2011;108(20):8075–80.
34. De Ridder D, Vanneste S. EEG driven tDCS versus bifrontal tDCS for tinnitus. Front Psych. 2012;3:84.
35. Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci. 1999;96(26):15222–7.
36. Llinás R, Urbano FJ, Leznik E, Ramírez RR, Van Marle HJ. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 2005;28(6):325–33.
37. Ashton H, Reid K, Marsh R, Johnson I, Alter K, Griffiths T. High frequency localised “hot spots” in

temporal lobes of patients with intractable tinnitus: a quantitative electroencephalographic (QEEG) study. Neurosci Lett. 2007;426(1):23–8.
38. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R. Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. Science. 2005;309(5736):951–4.
39. Varela F, Lachaux J-P, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci. 2001;2(4):229–39.
40. De Ridder D, van der Loo E, Vanneste S, Gais S, Plazier M, Kovacs S, et al. Theta-gamma dysrhythmia and auditory phantom perception: case report. J Neurosurg. 2011;114(4):912–21.
41. Shekhawat GS, Vanneste S. Optimization of transcranial direct current stimulation of dorsolateral prefrontal cortex for tinnitus: a non-linear dose-response effect. Sci Rep. 2018;8(1):1–8.
42. Vanneste S, Figueiredo R, De Ridder D. Treatment of tinnitus with cyclobenzaprine: an open-label study. Int J Clin Pharmacol Ther. 2012;50(5):338–44.
43. Elgoyhen AB, Langguth B, De Ridder D, Vanneste S. Tinnitus: perspectives from human neuroimaging. Nat Rev Neurosci. 2015;16(10):632–42.
44. Maudoux A, Lefebvre P, Cabay J-E, Demertzi A, Vanhaudenhuyse A, Laureys S, et al. Auditory resting-state network connectivity in tinnitus: a functional MRI study. PloS One. 2012;7(5):e36222.
45. Schlee W, Hartmann T, Langguth B, Weisz N. Abnormal resting-state cortical coupling in chronic tinnitus. BMC Neurosci. 2009;10(1):11.
46. Vanneste S, van Dongen M, De Vree B, Hiseni S, van der Velden E, Strydis C, et al. Does enriched acoustic environment in humans abolish chronic tinnitus clinically and electrophysiologically? A double blind placebo controlled study. Hear Res. 2013;296:141–8.
47. Shekhawat GS, Sundram F, Bikson M, Truong D, De Ridder D, Stinear CM, et al. Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief. Neurorehabil Neural Repair. 2016;30(4):349–59.
48. Shekhawat GS, Vanneste S. High-definition transcranial direct current stimulation of the dorsolateral prefrontal cortex for tinnitus modulation: a preliminary trial. J Neural Transm. 2018;125(2):163–71.
49. Jacquemin L, Shekhawat GS, Van de Heyning P, Mertens G, Fransen E, Van Rompaey V, et al. Effects of electrical stimulation in tinnitus patients: conventional versus high-definition tDCS. Neurorehabil Neural Repair. 2018;32(8):714–23.
50. Zaghi S, de Freitas Rezende L, de Oliveira LM, El-Nazer R, Menning S, Tadini L, et al. Inhibition of motor cortex excitability with 15 Hz transcranial alternating current stimulation (tACS). Neurosci Lett. 2010;479(3):211–4.
51. Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PloS One. 2010;5(11):e13766.
52. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28(52):14147–55.
53. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol. 2009;219(1):14–9.
54. Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. J Neurosci. 2011;31(43):15416–23.
55. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol. 2004;115(2):267–81.
56. Vanneste S, Walsh V, Van De Heyning P, De Ridder D. Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. Exp Brain Res. 2013;226(1):25–31.
57. Claes L, Stamberger H, Van de Heyning P, De Ridder D, Vanneste S. Auditory cortex tACS and tRNS for tinnitus: single versus multiple sessions. Neural Plast. 2014;2014:436713.
58. To WT, Ost J, Hart J, De Ridder D, Vanneste S. The added value of auditory cortex transcranial random noise stimulation (tRNS) after bifrontal transcranial direct current stimulation (tDCS) for tinnitus. J Neural Transm. 2017;124(1):79–88.
59. Joos K, De Ridder D, Vanneste S. The differential effect of low-versus high-frequency random noise stimulation in the treatment of tinnitus. Exp Brain Res. 2015;233(5):1433–40.
60. Kreuzer PM, Poeppl TB, Rupprecht R, Vielsmeier V, Lehner A, Langguth B, et al. Daily high-frequency transcranial random noise stimulation of bilateral temporal cortex in chronic tinnitus–a pilot study. Sci Rep. 2019;9(1):1–6.
61. Mohsen S, Mahmoudian S, Talebian S, Pourbakht A. Prefrontal and auditory tRNS in sequence for treating chronic tinnitus: a modified multisite protocol. Brain Stimul. 2018;11(5):1177–9.
62. Grossman N. Modulation without surgical intervention. Science. 2018;361(6401):461–2.
63. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169(6):1029–41.e16.
64. Shekhawat GS, Searchfield GD, Stinear CM. Randomized trial of transcranial direct current stimulation and hearing aids for tinnitus management. Neurorehabil Neural Repair. 2014;28(5):410–9.
65. Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain. 2008;131(5):1381–90.
66. Norena AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neurosci Biobehav Rev. 2011;35(5):1089–109.

67. De Ridder D, Vanneste S, Kovacs S, Sunaert S, Menovsky T, van de Heyning P, et al. Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression. J Neurosurg. 2011;114(4):903–11.
68. Zrenner C, Belardinelli P, Müller-Dahlhaus F, Ziemann U. Closed-loop neuroscience and non-invasive brain stimulation: a tale of two loops. Front Cell Neurosci. 2016;10:92.
69. Bhang S, Ahn J-H, Choi S-W. Brain-derived neurotrophic factor and serotonin transporter gene-linked promoter region genes alter serum levels of brain-derived neurotrophic factor in humans. J Affect Disord. 2011;128(3):299–304.
70. Landgrebe M, Langguth B, Rosengarth K, Braun S, Koch A, Kleinjung T, et al. Structural brain changes in tinnitus: grey matter decrease in auditory and non-auditory brain areas. NeuroImage. 2009;46(1):213–8.
71. Thomason ME, Yoo DJ, Glover GH, Gotlib IH. BDNF genotype modulates resting functional connectivity in children. Front Hum Neurosci. 2009;3:55.
72. Marshall L, Kirov R, Brade J, Mölle M, Born J. Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PloS One. 2011;6(2):e16905.
73. Hobson AR, Sarkar S, Furlong PL, Thompson DG, Aziz Q. A cortical evoked potential study of afferents mediating human esophageal sensation. Am J Physiol Gastrointest Liver Physiol. 2000;279(1):G139–G47.
74. Moffat G, Adjout K, Gallego S, Thai-Van H, Collet L, Norena A. Effects of hearing aid fitting on the perceptual characteristics of tinnitus. Hear Res. 2009;254(1–2):82–91.
75. Martinez-Devesa P, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev. 2010;(9):CD005233.

33 Transcranial Direct Current Stimulation in Disorders of Consciousness

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33.1 Introduction

33.1.1 Definition of Disorders of Consciousness (DOC)

Various definitions of consciousness have been so far proposed by scientists, neuroscientists, and philosophers. Nevertheless, a universally accepted definition has not been agreed upon yet. As such, it is widely accepted that consciousness is a comprehensive term involving series of cognitive processes such as attention and memory [1, 2]. At the bedside, mainly for scientific purposes, consciousness has been simplified into two main components: arousal and awareness. Arousal (also referred to as wakefulness) is necessary to experience awareness and has been considered as the level of consciousness. Anatomically, it is related to structures in the brainstem and it is clinically evidenced by opening of the eyes both spontaneous and/or induced by stimulation [3]. Awareness refers to the ability to live experiences of any kind and is thought to represent the content of consciousness [4]. Awareness itself has been subclassified into internal awareness (i.e., awareness of self) and external awareness (i.e., awareness of the environment). At present, there is no singular marker of awareness, but its presence can be clinically deduced from a range of behaviors and motor outputs (e.g., responses to command, visual pursuit) which indicate that an individual can perceive self and surroundings [5]. From an anatomical point of view, internal awareness is related to midline fronto-parietal regions such as the mesio-prefrontal cortex (MPFC)/anterior cingulate cortex (ACC) and precuneus/posterior cingulate cortex (PCC) while external awareness seems to depend on lateral fronto-parietal regions [6, 7]. Functional connectivity within and between these networks and the thalamus has proved to be important for sustained consciousness [8].

Patients in coma are neither awake nor aware [9]. This condition is self-limited and usually cannot last longer than 4 weeks, after which patients either evolve to brain death (i.e., permanent loss of brainstem functions), recover consciousness, or evolve to unresponsive wakefulness syn-

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drome (UWS), the current term for patients once called in a "vegetative state" [10]. Patients in UWS recover sleep wake cycles, but they do not show any sign of awareness of themselves and their surroundings, hence, exhibit only reflexive behaviors [11]. When patients regain minimal and fluctuating signs of awareness (e.g., answer to simple commands, visual pursuit, object localization), not encompassing the ability to communicate consistently, they are considered to be in a minimally conscious state (MCS) [12, 13]. Patients who recover a level of consciousness sufficient for functional communication and/or object use are referred to as emerged from minimally conscious state (EMCS). The boundaries between these different states of consciousness are ill-defined but rather progressive even if there are no step-by-step recovery transitions. These conditions can however be categorized according to the length of time since injury; if the state persists for more than 28 days, it is possible to describe it as prolonged [14]. The gradual transitional steps from coma to recovery are illustrated in Fig. 33.1.

33.1.2 Diagnosis

The DOC population is highly susceptible to misdiagnosis [15, 16]. The gold standard for the diagnosis of these patients is the behavioral evaluation through the use of standardized and sensitive scales such as the Coma Recovery Scale-Revised (CRS-R) [17]. Through behavioral assessment, responsiveness can be evaluated and consciousness level indirectly deduced. However, lack of motor responsiveness does not necessarily imply lack of consciousness, as patients can suffer from different disabilities impairing their responsiveness, such as paralysis, aphasia, and fluctuation of arousal level [15, 18, 19].

Advances in neurophysiology and neuroimaging techniques witnessed in the last decade, can now further offer the possibility to overcome the limits of the behavioral assessment in the detection of possible retained consciousness in unresponsive patients. However, no technique has led to a clear-cut diagnosis. Gathering information from different sources helps to determine if the behavioral, the neurophysiological, and neuro-

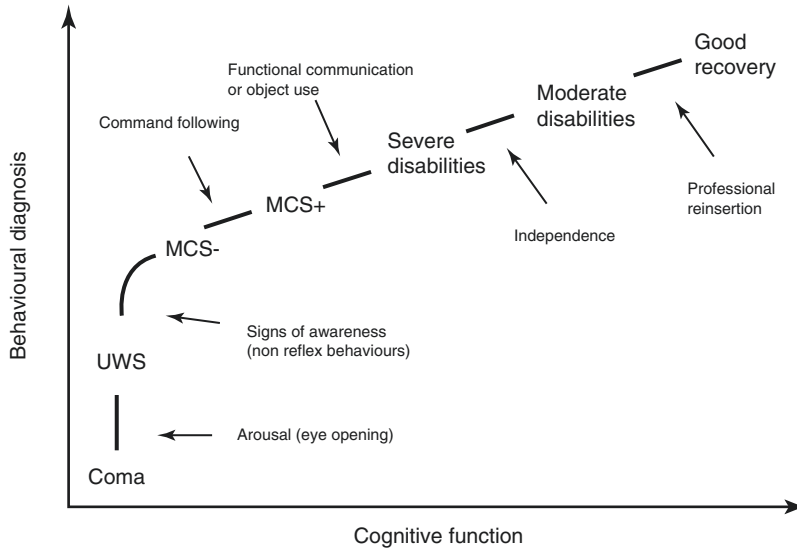

Fig. 33.1 Different clinical entities encountered on the gradual recovery from coma, illustrated as a function of cognitive and motor capacity. Restoration of spontaneous or elicited eye-opening, in the absence of voluntary motor activity, marks the transition from coma to unresponsive wakefulness syndrome (UWS). The transition from the UWS to the minimally consciousness state minus (MCS−) is marked by reproducible evidence of "voluntary behavior". Simple command following characterizes the MCS plus (MCS+). Emergence from MCS is signaled by the return of functional communication or object use. (Adapted from Ref. [15])

imaging results align and describe a coherent pattern that fits with UWS or MCS diagnosis or an incoherent one that requires more medical investigations.

A proper diagnosis in this patient population is imperative, especially when considering that a misdiagnosis may contribute to withdrawal of life-sustaining care and lead to inappropriate medical management such as neglecting pain treatment [20]. Indeed, an accurate diagnosis would have a strong impact on the quality of life and rehabilitation of the patient. For example, failure to detect signs of consciousness may limit access to specialized neuro-rehabilitation centers and, therefore, somehow decrease patients' possibilities to recover.

33.1.3 Therapeutic Interventions in Patients with Disorders of Consciousness (DOC) and Their Limitations

While several studies have focused on improving the diagnosis of these patients, only a few studies have investigated treatment options in order to improve their rehabilitation and their quality of life. At present, there are no evidence-based guidelines regarding the treatment of patients with DOC [20] as opposed to diagnosis and prognosis [14]. Until recently, the medical community has viewed patients in UWS and MCS with great pessimism regarding both prognosis and effective treatments. Unfortunately, this pessimism may contribute in some cases to a disregard of this population, especially in the prolonged stage, as no improvement is expected. Nevertheless, in the past 10 years, a number of studies have reported that some patients in MCS could improve even several years after the insult [21] and several treatments can enhance signs of consciousness [22–24].

Up to date, there is no universally accepted drug option to treat these patients. Some studies have shown that amantadine [25], apomorphine [26], intrathecal baclofen [27], and zolpidem [28] can sometimes improve behavioral signs of consciousness in patients with DOC (see Table 33.1). So far, only amantadine has been shown to increase signs of consciousness in a large cohort of acute and subacute patients with DOC in a placebo-controlled trial [25]. Despite no convulsions have been reported in the amantadine clinical trial experimental group when com-

Table 33.1 Main studies using amantadine, apomorphine, baclofen, or zolpidem treatment in patients with disorders of consciousness

Authors	Drug	Design	N (etiology)	Time since injury	Results
Estraneo et al. [29]	Amantadine (NMDA antagonist and indirect dopamine agonist) (100 mg BID)	Case report	1 MCS	16 months	Dose-dependent response to amantadine and emergence of MCS. Myoclonus as side effect was reported
Giacino et al. [25]	Amantadine (progressive increase from 100 mg BID to 200 mg BID)	Prospective, multicentric, randomized, double-blind, placebo-controlled	184 (all TBI)	1–3 months	Amantadine group: faster recovery; decrease of DRS scores and increase of behavioral bench markers on the CRS-R
Schnakers et al. [32]	Amantadine (200 mg daily)	Case report	1 anoxic MCS	2 years	Increase in fronto-parietal metabolism led to new sign of consciousness but remained in MCS

(continued)

Table 33.1 (continued)

Authors	Drug	Design	N (etiology)	Time since injury	Results
Fridman et al. [26]	Apomorphine (dopamine agonist) (2–8 mg/h)	Prospective case series	8 (all TBI)	1–4 months	Functional recovery with decrease of the CNC and DRS and increase of GOS scores
Margetis et al. [33]	Baclofen (GABA agonist) (intrathecal)	Open label observational and prospective	8 (6 TBI)	5–108 months	Three patients showed at least one new sign of consciousness
Sara et al. [27]	Baclofen (intrathecal)	Case report	5 (2 TBI)	6–10 months	Clinical improvement in all patients after 2 weeks (increase in CRS-R scores)
Carboncini et al. [34]	Midazolam (benzodiazepine non-selective GABA A agonist) (5 mg)	Case report	1 MCS (TBI)	>1 year	Patient emerged from MCS for 2 h and could be replied
Lanzillo et al. [35]	Ziconotide (selective blockers of N-type calcium channels) (intrathecal)	Case report	1 MCS	7 months	Patient emerged from MCS
Calabro et al. [36]	Zolpidem (nonbenzodiazepine $GABA_A$ receptor agonist) (from 10 to 30 mg)	Case report	1 anoxic UWS	>3 years	Consciousness improvement started at 20 mg and increased with dosage up to 30 mg
Machado et al. [37]	Zolpidem (10 mg)	Randomized controlled trial	8 UWS (1 TBI)	1–114 months	Led to the observation of yawning and hiccups
Thonnard et al. [28]	Zolpidem (10 mg)	2 phases: Open-label study and placebo-controlled trial	60 (31 TBI)	1 months to 24 years	12 patients (20%) showed improvement in CRS-R scores, 11 were in MCS.
Whyte and Myers [22]	Zolpidem (10 mg)	Multicentric, double-blind, randomized study	15 (8 TBI)	3 months to 23 years	One responder (UWS to MCS+); increase in CRS-R score, visual pursuit, response to command
Whyte et al. [38]	Zolpidem (10 mg)	Double-blind, crossover randomized controlled trial	84	>4 months	Response-rate of 4.8% (four responders, one UWS, and three MCS); improvement of at least five points in the CRS-R score for at least 2 h.

DRS disability rating scale, *CRS-R* Coma Recovery Scale, *CNC* Coma/Near-Coma Scale, *GOS* Glasgow Coma Scale, *NMDA* N-methyl-D-aspartate, *GABA* γ-Aminobutyric acid, *TBI* traumatic brain injury, *UWS* Unresponsive wakefulness Syndrome, *MCS* Minimally Conscious State, *EMCS* emergence from MCS

pared to placebo [25], an association between amantadine medication and the occurrence of seizures has been reported [29]. Patients with DOC are vulnerable to convulsions and epilepsy, which can significantly affect their cognitive state [30]. Moreover, the mechanisms underlying the recovery of behavioral signs of consciousness observed in some patients with DOC following the administration of these drugs are still poorly understood.

Zolpidem, a selective $GABA_A$ receptor agonist, has shown to be impressively effective, inducing the recovery of communication or functional use of objects in patients in MCS (i.e., emergence

from MCS) in single cases studies. Nevertheless, an extremely low percentage of patients benefit from this drug and so far its mechanism of action and the reason why only a few subjects respond to it needs still to be elucidated [22, 31].

With regard to neurophysiological treatment, deep brain stimulation (stimulation of the intralaminar nuclei of the thalamus) [39–41] as well as invasive vagus nerve stimulation [42] and spinal cord stimulation [43] have shown to improve signs of consciousness in patients in MCS. However, these techniques are invasive and expensive, limiting their accessibility for a large number of patients. Moreover, device implantation did not guarantee positive results and consciousness recovery [24, 44].

Relatively new in the DOC therapeutic arsenal, transcutaneous auricular vagal nerve stimulation is a promising non-invasive device that promotes a bottom-up stimulation. By stimulating a cutaneous (peripheral) branch of the vagus nerve, two studies (one case report and two open-label studies) have shown emergence of new signs of consciousness after multiple stimulation sessions in a population with prolonged DOC [45–47].

As opposed to bottom-up stimulations, transcranial direct current stimulation (tDCS) is a form of cortical stimulation that could be categorized as a top-down stimulation which also includes repetitive transcranial magnetic stimulation (rTMS). Both devices have shown to improve recovery in several disabling neurological pathologies, such as Parkinson's, Alzheimer's disease, stroke and traumatic brain injury patients [48–51] as well as in DOC [52, 53]. The next section will be dedicated to studies using tDCS in the DOC population to deepen knowledge in relation to this technique.

33.2 tDCS in Disorders of Consciousness (DOC)

Several studies have shown that a single anodal stimulation of a damaged cortical area in post stroke or TBI patients can improve the function of the stimulated area. An anodal session of tDCS over C3 or C4, corresponding to the primary motor cortex (M1) according to the 10–20 electroencephalogram (EEG) international system [54], can enhance motor function [55, 56]. Likewise, stimulation of the prefrontal cortex (F3 or F4) has shown positive effects on memory [57, 58] and attention [59]. Given the above-mentioned encouraging results showing enhancement of motor and cognitive functions following tDCS, its efficacy has also been tested on behavioral recovery in patients suffering from DOC, and respective results will be presented in this section.

33.2.1 Single Stimulation Studies

Thibaut et al. [60] used a crossover study design to compare active tDCS stimulation to sham on both UWS (6 traumatic, 9 vascular, and 10 anoxic) and MCS patients (19 traumatic, 6 vascular, and 5 anoxic), in acute-subacute (>7 days, <3 months) and prolonged states. They demonstrated that MCS patients had significantly improved signs of consciousness when compared to UWS after a single 20-minute (min) session of tDCS over the left DLPFC with a 2 milliamperes (mA) current. When evaluated by the CRS-R, the gold standard behavioral scale in DOC, 13 of 30 MCS patients (43%) showed new signs of consciousness during or directly after the stimulation compared to 2 of 25 UWS patients (8%). Both responding UWS patients had their injury less than 3 months before the stimulation starting time. No side effects were reported.

In 2019, Martens and colleagues [61] studied tDCS effects when applied over the motor cortex of the most injured hemisphere in a single 20-min stimulation at 2 mA. Of four prolonged UWS patients (one traumatic, two vascular, and one anoxic) and six prolonged MCS patients (four traumatic and two anoxic), only one UWS patient changed diagnosis because he presented a new sign of consciousness (visual pursuit). Another patient in MCS showed a new sign of consciousness (localization of object) but did not change diagnosis according to CRS-R. However, at the group level, no treatment effect was reported and there were no side effects.

The same year, this research team [62] used tDCS in a unique protocol that positioned two anodes over the left and right DLPFC and two cathodes over the left and right M1 cortices, to measure if tDCS could have effects on spasticity. They tested their montage on a cohort with prolonged DOC of five UWS patients (three traumatic and two anoxic), seven MCS patients (three traumatic, three vascular, and one anoxic), one vascular EMCS patient, and one locked-in syndrome patient with vascular etiology. After two 1 mA 20-min sessions (one sham and one active stimulation, in a randomized order, separated by at least 48 h of washout), four patients (one anoxic UWS, two MCS – one traumatic, one vascular – and the EMCS patient) improved upper limbs spasticity according to the modified Ashworth scale (MAS). However, no treatment effect on spasticity was observed at the group level, and no new sign of consciousness was reported.

To summarize, a single session of tDCS with the anode positioned over the left DLPFC seems to be more effective to reveal new signs of consciousness when compared to the anode positioned over the most injured primary motor cortex. However, larger cohorts and protocols that compare different brain stimulation sites are needed before reaching conclusions. Nonetheless, tDCS seems to be a promising treatment for DOC patients as it has potential to transiently enhance consciousness in a safe manner.

33.2.2 Multiple Repeated Stimulation Studies

Single tDCS stimulation studies were essential to assess feasibility and safety of different parameters with the DOC population as these patients are at risk to develop seizures [30]. Nonetheless, multiple tDCS sessions were the next natural step to assess if the effects of tDCS could be prolonged and magnified [63, 64]. An overview of the related publications follows.

Angelakis et al. [65] performed five 20-min sham tDCS sessions followed by 10 tDCS sessions (once a day, 20 min each, 5 days a week, 1 mA for the first week, and 2 mA for the second week). The anode was located alternatively over either the left primary sensorimotor cortex or the left DLPFC with the cathode over the right eyebrow, except if there was a severe cortical lesion at the stimulation site. All prolonged MCS patients (two traumatic, one vascular) but no prolonged UWS patients (three traumatic, four anoxic) showed clinical improvement, measured with CRS-R, immediately after the tDCS sessions for two of them and 1 week post-stimulation for the other one. One of three MCS patients received tDCS over the left DLPFC, as well as four of seven UWS patients. They re-evaluated the cohort after 12 months; one UWS patient progressed to MCS; one MCS patient maintained the new sign of consciousness; and the two other recovered consciousness. No side effects were reported.

Dimitri et al. [66] published the case of a 20-year-old woman who had been in MCS for over 5 years due to brain anoxia post-cardiac resuscitation. They used two anodes: one over the left DLPFC and one over the cerebellar midline and the cathode was placed over the right sensorimotor cortex**.** tDCS was given in parallel with psychosensory cognitive-behavioral rehabilitation. They used the DOCS-scale [67] as behavioral evaluation to measure consciousness recovery after 20-min sessions at 1.5 mA, three times a week for 12 weeks. They obtained an increase in alertness after 45 and 90 days and in responsiveness after 45 days which was maintained at 90 days of combined stimulation. Interestingly, they also noted a decrease in upper limbs spasticity.

In 2017, Estraneo et al. [68] proposed a double-blind sham-controlled crossover design with five sessions of tDCS stimulation over the left DLPFC. Once a day, for five consecutive days, seven prolonged UWS patients (one traumatic, two vascular, and four anoxic) and six prolonged MCS patients (four vascular and two anoxic) went through 20-min tDCS at 2 mA or through sham and then switched conditions after 1 week of washout. CRS-R scores improved in

both groups during the 3-week protocol period but also in the 12 weeks following the end of it. Five of 13 patients (38% – two UWS and three MCS) regained signs of consciousness. Changes were observed during the second and fourth week following active stimulation and were maintained in the eight subsequent weeks.

Thibaut et al. [69] used a similar protocol (five consecutive days of 20-min tDCS at 2 mA with anode positioned over the left DLPFC and sham separated by 1-week washout period) with 16 prolonged MCS patients (11 traumatic, two vascular, and three anoxic). Nine of 16 patients (56%) demonstrated at least one new sign of consciousness and were considered responders. Behavioral positive effects were measured at days 5 and 12 after the end of the active stimulation. No side effects were reported.

The same year, Huang et al. [70] recruited 37 patients with prolonged MCS; however, only 33 completed the protocol (20 traumatic, 11 vascular, and 2 anoxic). Patients received both five 20-min tDCS sessions at 2 mA and five sham session for five consecutive days separated by 5 days of washout. The anode was located over the posterior parietal cortex. Improvement of clinical signs of consciousness was observed 5 days after the last stimulation but was not maintained at 10 days. The reported response rate was 27.3% (9/33 who completed the study). No severe side effects were observed by the authors, but four patients did not complete the protocol related to medical complications not associated with tDCS or moved to another facility.

In 2018, Martens et al. [71] suggested a home-based 4-week protocol study to evaluate tDCS effects and recruited 27 prolonged MCS patients (12 traumatic, 5 vascular, and 10 anoxic) from which 22 received at least 80% of the 20 tDCS sessions. One patient withdrew because of a seizure that occurred during the sham period. The response rate observed in this study was 22% (6/27). This low responsiveness might be explained by the long time since injury ranging from 10 to 401 months (mean: 97 months (8 years), standard deviation: 83 months (±7 years)).

Recently, Cavinato et al. [72] proposed a crossover design of 2 weeks (5 days a week) of sham or active tDCS before switching groups after a 10-day washout period. They positioned the anode over the left DLPFC for 20 min at 2 mA on a cohort of 12 prolonged UWS patients (two traumatic, five vascular, and five anoxic) and 12 prolonged MCS patients (seven traumatic, two vascular, and three anoxic). No improvement was observed in the CRS-R score, but the Western Neurosensory Stimulation Profile (WNSSP) increased in the MCS patient group only. The response rate differed from other cited studies as no change was observed for any of the 24 enrolled patients when measured with the CRS-R. The major difference between this study and others was the position of the cathode: they located it over the contralateral deltoid instead of over the right supraorbital region. This protocol characteristic might be an explanation for their divergent results.

Finally, Straudi et al. [73] proposed an open label multiple tDCS session protocol with the anode positioned over the primary motor cortex (M1) bilaterally. They enrolled 10 prolonged MCS patients (10 traumatic) and applied tDCS 5 days a week for two consecutive weeks for 40 min at 2 mA. Reported response rate was 80%, as eight of 10 patients showed new signs of consciousness, and improvement was maintained 3 months after the last stimulation. No side effect other than skin redness was reported.

To summarize all eight studies, multiple tDCS sessions for at least five consecutive days seemed to help consciousness recovery, that is, the expression of at least one new sign of consciousness. The best cerebral areas to stimulate have not been determined yet; however, targeting the left DLPFC shows consistent clinical effects in MCS patients in randomized controlled studies [73].

33.2.3 Long-Term Effects

To achieve long-term effects of tDCS is the ultimate goal which would be necessary to allow a

permanent DOC recovery. In this context, several sessions of tDCS may be required in order to achieve the desired effect. A study of repeated tDCS over the primary motor cortex in healthy volunteers highlighted a consolidation mechanism which lasted up to 3 months after five tDCS sessions [74]. Results on the maintenance of new signs of consciousness have been encouraging in studies with multiple tDCS sessions when follow-up was reported. In one of the first multiple session studies, Angelakis et al. [65] reported that one MCS patient who received primary sensorimotor stimulation emerged from MCS at the 12-month follow-up. This behavioral improvement could be either natural evolution or improvement post-stimulation with a delay. No other time point evaluation was done in between. Dimitri et al. [66], in their case report, observed that responsiveness was maintained at least 3 months post-stimulation. Others reported that benefits were maintained at 12 days [69], 8 weeks [68], and 12 weeks [73]. However, results were not homogeneous as one study observed that the behavioral improvement was not preserved 10 days following the end of stimulation [70]. One parameter of the latter study which specifically differed from the others was that this was the only study where the anode was placed over the parietal cortex.

Overall, multiple tDCS session approaches seem to lead to new signs of consciousness that could persist as long as 3 months. Studies with the anode positioned over the left DLPFC and possibly over the M1 were suggestive of a better effect when compared to the study that located the anode over the parietal cortex.

33.2.4 Neuronal Correlates of tDCS in DOC

Mechanisms of action of tDCS remain only partly understood. It has already been hypothesized that tDCS could be involved in the re-establishment of the cortico-striato-thalamo-cortical loop by the stimulation of the frontal cortex as proposed in the mesocircuit model [75] shown in Fig. 33.2.

However, some studies reported physiological effects of tDCS recorded by EEG that could suggest some underlying answers. Naro et al. [77] combined oscillating and direct currents to stimulate the cerebellum and positioned the anode over its median line in a cohort with prolonged DOC. They delivered five blocks of 2 min at 2 mA with 30 s of inter-train intervals and compared it to sham stimulation in a DOC cohort of 10 patients with prolonged UWS (seven traumatic, three non-traumatic) and 10 patients with prolonged MCS (six traumatic and four non-traumatic). They measured effects on power and coherence with EEG and showed a significant increase of gamma power at the frontal areas and of the theta power at the central areas after stimulation (not sham) for the MSC patients only. When they analyzed the coherence, only MCS patient's theta coherence significantly increased within fronto-central areas immediately after the end of stimulation followed by a decrease at 30-min post-stimulation. Gamma coherence significantly increased within the central area and partially in fronto-central areas for up to 30 min. No side effect, other than tingling at the beginning of the stimulation, was observed.

Bai et al. [78] stimulated once 20 min at 2 mA over the left DLPFC of nine prolonged UWS patients and eight prolonged MCS patients of mixed etiologies (seven traumatic, five vascular, and five anoxic). They measured a significant increase in the theta band fronto-parietal coherence and a significant decrease in the gamma band fronto-parietal coherence in the MCS patient group only. Both changes were, respectively, positively and negatively correlated to the baseline CRS-R score.

Cavinato et al. [72], cited above, analyzed EEG data in addition to behavioral data and noticed that the MCS group showed an increase in frontal and posterior beta band as well as a decrease in delta band activity in the same areas (only after active stimulation). The authors also observed a stronger connectivity in the alpha frequency band over the posterior areas and a higher coherence in the beta frequency band between the fronto-parietal and the posterior areas. In the

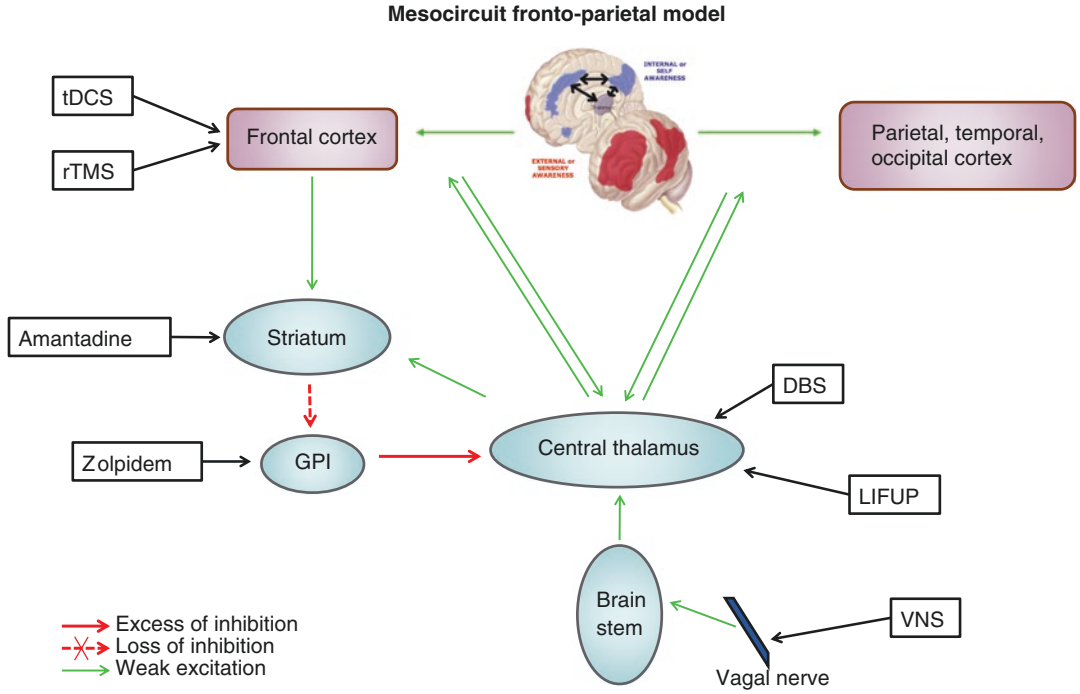

Fig. 33.2 The mesocircuit model [75]. Reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons from the central thalamus withdraws important afferent drive to the medium spiny neurons of the striatum, which may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity. Loss of active inhibition from the striatum allows neurons of the globus pallidus internus (GPi) to tonically fire and provide active inhibition to their synaptic targets, including relay neurons of the already strongly disfacilitated central thalamus, and possibly also the projection neurons of the pedunculopontine nucleus. Several treatments that have shown promising results in the recovery of signs of consciousness in severely brain-injured patients are related to the mesocircuit model [24]. About tDCS, a partial preservation of the prefrontal cortex (i.e., stimulated area) seems to be necessary to induce a clinical response [76]

UWS group, they described higher frontal coherence in the delta frequencies as the only change.

Another study also analyzed EEG in addition to behavioral data [73] and performed an ANOVA using bandwidth frequency, time (relative to stimulation), side (left or right), and site (frontal, central, or parietal) as factors after they applied tDCS over M1 bilaterally. They revealed that upper alpha band (11–13 Hz) activity increased after the first five tDCS sessions over the parietal area when they compared to baseline. They also observed that the increase in alpha frequency activity correlated to CRS-R total score increase.

In 2019, Thibaut et al. [62] proposed a protocol including placement of the anodes over bilateral DLPFC and the cathodes over bilateral M1 cortices to test the relevance of tDCS in the treatment of spasticity. They analyzed spasticity, CRS-R, and EEG of 14 DOC patients (five UWS, seven MCS, one EMCS, and one locked-in syndrome) before and after a single 20-min session of tDCS. Despite the lack of significant results at level group for spasticity and CRS-R improvement, at the individual level, four individuals were identified as responders. They showed a significant decrease in spasticity in at least two articulations after the active session only. The group level EEG analysis from eight participants (the four responders and four non-responders) showed a significant increase weighted phase lag index values in beta band higher frequencies (18–30 Hz) between motor and frontal areas when they compared active to sham stimulation for the whole group. No difference was shown in the relative band power. However, responders increased their weighted phase lag index values

between the frontal and motor brain areas, but in lower beta frequencies (12–18 Hz). Relative band power analyses showed an increase in beta band for the frontal and fronto-central areas. These results suggested an increase in beta connectivity and synchronization which have been associated with a higher degree of motor adaptation in healthy subjects [79] and in stroke patients [80].

To sum up, tDCS obviously has an influence over electrical brain activity. Many analyses are possible with EEG data and most of the studies focused on coherence and connectivity analyses. However, they all used different statistical methods and stimulation protocols, which most likely resulted in different observations. Despite methodological disparity, it seemed that the common findings in these studies are an increase in coherence (theta, alpha, and beta) in the fronto-parietal/fronto-central region. In DOC, alpha band dominance has been associated with higher level of consciousness and emergence [81, 82]. Nonetheless, further research involving neuroimaging and neurophysiology is needed to better understand the involvement of tDCS in the recovery of consciousness and the role of the lateral fronto-parietal cortex in it.

33.2.5 Responders' Versus Non-responders' Characteristics

Several clinical trials have shown that the proportion of tDCS responders may vary from 40% to 80% in other populations than DOC [83–85]. Regarding patients with DOC, the first published study on the subject reported that left DLPFC tDCS could improve signs of consciousness in 43% of patients in MCS [60]. If these findings suggest the potential relevance of tDCS as a treatment for DOC, they also highlight the lack of a clinical improvement following tDCS in more than half of the patient population. The natural step was, therefore, to define the structural and functional brain features of the patients that are likely to respond to tDCS [86].

Therefore, after publishing the first study testing the safety and efficacy of tDCS in patients with DOC, Thibaut et al. [60] retrospectively used multi-modal neuroimaging analyses to identify some common characteristics of tDCS responders that differentiated them from the remaining cohort. Fluorodeoxyglucose positron emission tomography (FDG-PET), structural and functional magnetic resonance imaging (MRI) from eight patients with prolonged MCS patients (four traumatic, two vascular, and two anoxic) were analyzed and it seemed that a preserved gray matter associated with a residual metabolic activity in cortical and subcortical brain areas was the key to a measurable behavioral improvement. The transient improvement of signs of consciousness following tDCS seemed to require gray matter integrity and/or residual metabolic activity in three brain regions: (i) the presumed stimulated area (i.e., left DLPFC), (ii) long-distance cortical areas such as the precuneus, and (iii) subcortical brain areas known to be involved in conscious processes (i.e., thalamus), see Fig. 33.3.

In 2016, the same team of authors looked further into the MRI data of six responders (three traumatic, one vascular, and two anoxic) and performed a seed-based analysis to evaluate functional connectivity during resting state. They demonstrated that, after a single tDCS session over the left DLPFC, responders had higher connectivity between the DLPFC and the inferior frontal gyrus and an increased coactivation of the left lateral fronto-parietal cortices which have been associated with the external awareness brain network [87]. On the other hand, non-responders showed a more diffuse and bilateral activation of median structures as the anterior cingulate cortex and the precuneus. As previously mentioned, these structures are associated with the default mode network responsible for internal awareness [88, 89].

Clinically, some parameters might be suggestive of a better response to tDCS, first of all being diagnosed MCS rather than UWS. In the cited studies, when put together, 6 of 58 UWS (10.3%) versus 53 of 155 MCS (34.2%) patients have

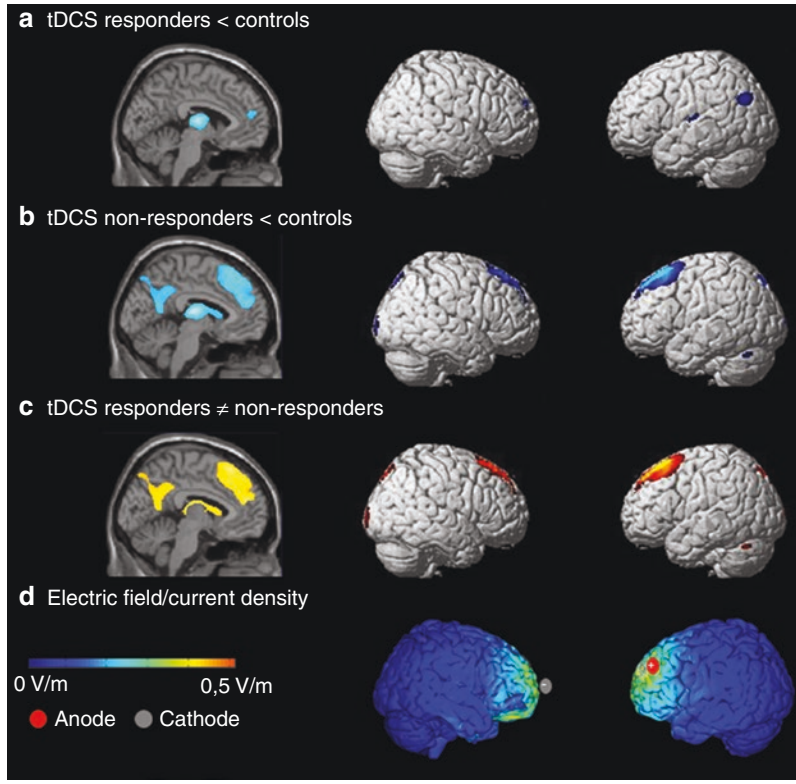

Fig. 33.3 Positron emission tomography (PET): Brain areas showing hypometabolism (in blue), as compared to controls, in patients in a minimally conscious state (FWE corrected): (**a**) eight tDCS responders and (**b**) 13 non-responders. (**c**) Regions with less hypometabolism in responders as compared to non-responders (in red). (**d**) Model-based tDCS induced electric fields. Note that behavioral responsiveness to left dorsolateral prefrontal cortex (DLPFC) tDCS correlates with less impaired metabolism in the areas presumed to be stimulated by tDCS (left DLPFC and mesiofrontal cortices) but also of distant cortical (precuneus) and subcortical (thalamus) regions. (From Ref. [76])

shown at least one new sign of consciousness after tDCS. When response rates were statistically compared, it seemed highly suggestive that MCS patients were better responders than UWS patients. Having a shorter time-to-injury seemed also likely to lead to a better response [60, 68] despite also contradictory results [61]. These two subject characteristics could be associated with better preserved brain metabolism [6] and higher network connectivity [90] as well as a greater plasticity [91]. Even if it is possible to reveal new sign(s) of consciousness after a long time since injury, it could be possible that a shorter time is in favor of a positive response.

33.2.6 tDCS as a Diagnostic Tool

tDCS has been studied as a diagnostic tool to differentiate MCS from UWS patients. According to the patient's brain excitability when measured by TMS, studies showed encouraging results to suggest that tDCS could be useful in the evaluation of level of consciousness.

Naro et al. [92] assessed cortical connectivity and excitability by means of a dual-site TMS approach in a cohort of 12 prolonged UWS patients (five traumatic and seven anoxic) and 10 prolonged MCS patients (five traumatic and five anoxic). More specifically, the authors recorded

resting motor threshold, motor evoked potential amplitude and latency, central conduction time, intracortical facilitation and short-interval inhibition, as well as interregional interactions between left primary motor cortex and right dorsal premotor cortex and pre-supplementary motor area. After the first testing, tDCS (active or sham) was applied over the orbitofrontal cortex (anode between Fp1 and Fp2 and cathode over Cz, according to the 10–20 international system). TMS was performed 60 and 120 min after tDCS. Results showed an increase in motor evoked potential (MEP) amplitudes, intracortical facilitation, and a reduction of premotor-motor inhibition for all MCS patients. Concerning UWS patients, tDCS had no effects on three of seven anoxic participants, whereas it induced a reduction of premotor-motor inhibition and a partial increase of primary motor cortex excitability in the remaining four. None of the five traumatic patients had tDCS effects. The authors suggested that the four patients who were diagnosed as being in UWS but showed an increase in cortical connectivity and excitability had actually covert consciousness not detected by the clinical exam, as previously reported in the literature [93–95]. Behaviorally, no patients showed any CRS-R scoring changes after tDCS, but a correlation between CRS-R total score, premotor-motor connectivity, and primary motor cortex excitability modulation was observed. No side effects were reported.

Bai et al. [96] also combined tDCS with TMS and EEG to measure cortical excitability/inhibition in a DOC sample of nine patients with prolonged UWS (two traumatic, three vascular, and four anoxic), and seven patients with prolonged MCS (two traumatic, two vascular, and three anoxic). As in their other study (single stimulation section), they stimulated 20 min at 2 mA over the left DLPFC and applied TMS over the left DLPFC before and after the active or sham stimulation. They reported a significant increase in global mean field amplitude of MCS patients within 200 ms after the TMS pulse. Local excitability analyses showed a significant increase in frontal and central areas and in the left hemisphere (as compared to the right) in the 0–100 ms interval after TMS pulse and in frontal and right hemisphere in the 100–200 ms interval. For the UWS patients, the global mean field amplitude increased in the 0–100 ms period and decreased in the 300–400 ms period. Local excitability analyses showed a significant increase in the left hemisphere during the 0–100 ms time window and a significant decreased excitability in frontal and left hemisphere during 300–400 ms of TMS pulse. This difference between both levels of consciousness has been proposed as marker to help make a diagnosis between UWS and MCS. However, a larger cohort needs to be tested to confirm this hypothesis.

In 2018, Thibaut et al. [97] described the case of one patient diagnosed as UWS for almost 4 years that responded to a command after one 20-min session of 2 mA tDCS over the left DLFPC. Neuroimaging studies revealed a mismatch between cerebral activity and bedside signs of consciousness, also called cognitive-motor dissociation [98].

These three studies are examples that tDCS could be a useful tool to reveal signs of consciousness either clinically by facilitating motor responses when cognitive functions are preserved or physiologically by showing brain reactivity when combined to TMS and EEG. Future studies should be conducted to determine whether tDCS could be reliably used as a diagnostic and prognostic tool.

33.2.7 tDCS Safety

It is worth to say that tDCS seems to be a safe tool. Indeed, out of a total of 284 DOC patients included in the cited studies, no severe side effects were observed, even considering that many of these patients had severe brain injuries with widespread lesions possibly involving the stimulated areas. The only reported side effects were tingling sensations and skin redness that disappeared within 30 min [71, 73]. Moreover, it is well known that brain-injured patients are more vulnerable to epileptic seizures; thus, some of them were probably under antiepileptic treatment due to previous seizures or as pre-

vention. Nonetheless, in all cited studies above, no seizures have been reported during or after tDCS. One study withdrew a patient that experienced a seizure, but this occurred in the sham group and an association between tDCS and the seizure was excluded [71]. With the limitation of a relatively small population included so far, the above-mentioned findings suggest that tDCS can be safely used in the treatment of patients with severe brain injury and adult DOC patients, with no severe side effects [99].

33.3 Conclusions and Future Directions

In this chapter, the potential therapeutic effects of tDCS on patients with DOC has been described. It has been shown that MCS patients have more potential to respond to tDCS when compared to UWS patients and that new signs of consciousness can be revealed after either a single or multiple tDCS sessions. It has also been demonstrated that behavioral improvement can be maintained for up to 3 months. It has been highlighted that a response to tDCS defined as an increase of signs of consciousness in patients with DOC requires residual metabolic activity and gray matter preservation in cortical and subcortical brain areas important for consciousness recovery (i.e., left DLPFC, precuneus, and thalamus). Moreover, tDCS, coupled with TMS, seemed to have the potential to differentiate MCS from UWS patients. Most importantly, tDCS has shown to be a handy and safe device with minimal side effects for DOC patients; even when tDCS was applied by family members or caregivers. Even though these first findings seem encouraging, further studies are required in order to investigate the long-term effects of tDCS in this population of patients and its value in clinical practice.

So far, different areas of stimulation have been tested, but it is difficult to draw a conclusion and stipulate the best localization to stimulate the brain. As DOC patients seemed to need at least a partial preservation of the stimulated area to respond to tDCS, in the future, it might be advantageous to personalize electrode placements according to a patients' cortical damage. Here, stimulation over a preserved area (at least partially) should be more effective than stimulation over an injured brain region. To help to target the proper area to stimulate, neuroimaging acquisition (MRI, PET, and HD-EEG) before and after tDCS sessions should be carried out. This might give the opportunity to (i) investigate the effect of tDCS on the brain of each patient to better understand the mechanisms of action, (ii) differentiate between responders and non-responders, and (iii) better identify the patients who could benefit from left DLPFC tDCS or M1 tDCS or other areas. The final aim is to develop a patient-tailored stimulation to maximize chances of recovery.

References

1. Baars BJ, Ramsoy TZ, Laureys S. Brain, conscious experience and the observing self. Trends Neurosci. 2003;26(12):671–5.
2. Zeman A. The boundaries of consciousness: neurobiology and neuropathology. Prog Brain Res. Elsevier. 2005:1–10.
3. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci. 2005;9(12):556–9.
4. Posner J, Saper C, Schiff N, Plum F. Plum and Psoner's diagnosis of stupor and coma. New York: Oxford University Press; 2007.
5. Boly M, Massimini M, Garrido MI, Gosseries O, Noirhomme Q, Laureys S, et al. Brain connectivity in disorders of consciousness. Brain Connect. 2012;2(1):1–10.
6. Thibaut A, Bruno MA, Chatelle C, Gosseries O, Vanhaudenhuyse A, Demertzi A, et al. Metabolic activity in external and internal awareness networks in severely brain-damaged patients. J Rehabil Med. 2012;44(6):487–94.
7. Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. J Cogn Neurosci. 2010;23(3):570–8.
8. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 2000;355(9217):1790–1.
9. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol. 2004;3(9):537–46.
10. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, et al. Unresponsive wakeful-

ness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68.
11. Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med. 2003;3(3):249–54.
12. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
13. Bruno MA, Majerus S, Boly M, Vanhaudenhuyse A, Schnakers C, Gosseries O, et al. Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. J Neurol. 2012;259(6):1087–98.
14. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Practice guideline update recommendations summary : disorders of consciousness. Neurology. 2018:1–12.
15. Chatelle C, Laureys S. Understanding disorders of consciousness. In: Illes J, Sahakian B, editors. The Oxford handbook of neuroethics. New York: Oxford University Press; 2011. p. 119–33.
16. Stender J, Gosseries O, Bruno M, Charland-verville V, Vanhaudenhuyse A, Demertzi A, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet. 2014;384:514–22.
17. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9.
18. Majerus S, Bruno MA, Schnakers C, Giacino JT, Laureys S. The problem of aphasia in the assessment of consciousness in brain-damaged patients. Prog Brain Res. 2009;177:49–61.
19. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
20. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol. 2014;10(2):99–114.
21. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology. 2010;75(3):239–45.
22. Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil. 2009;88(5):410–8.
23. Schnakers C, Monti MM. Disorders of consciousness after severe brain injury: therapeutic options. Curr Opin Neurol. 2017;30(6):573–9.
24. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol. 2019;18(6):600–14.
25. Giacino J, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med [Internet]. 2012;366(9):819–26. Available from: https://doi.org/10.1056/NEJMoa1102609.
26. Fridman EA, Calvar J, Bonetto M, Gamzu E, Krimchansky BZ, Meli F, et al. Fast awakening from minimally conscious state with apomorphine. Brain Inj. 2009;23(2):172–7.
27. Sara M, Sacco S, Cipolla F, Onorati P, Scoppetta C, Albertini G, et al. An unexpected recovery from permanent vegetative state. Brain Inj. 2007;21(1):101–3.
28. Thonnard M, Gosseries O, Demertzi A, Lugo Z, Vanhaudenhuyse A, Marie-Aurelie B, et al. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. Funct Neurol. 2014:1–6.
29. Estraneo A, Pascarella A, Moretta P, Loreto V, Trojano L. Clinical and electroencephalographic on–off effect of amantadine in chronic non-traumatic minimally conscious state. J Neurol. Springer Berlin Heidelberg. 2015;262:1584–6.
30. Bagnato S, Boccagni C, Galardi G. Structural epilepsy occurrence in vegetative and minimally conscious states. Epilepsy Res. 2013;103(1):106–9.
31. Chatelle C, Thibaut A, Gosseries O, Bruno MA, Demertzi A, Bernard C, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. Front Hum Neurosci. 2014;8:917.
32. Schnakers C, Hustinx R, Vandewalle G, Majerus S, Moonen G, Boly M, et al. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 2008;79:225–7.
33. Margetis K, Korfias SI, Gatzonis S, Boutos N, Stranjalis G, Boviatsis E, et al. Intrathecal baclofen associated with improvement of consciousness disorders in spasticity patients. Neuromodulation Technol Neural Interface. 2014;17(7):699–704.
34. Carboncini MC, Piarulli A, Virgillito A, Arrighi P, Andre P, Tomaiuolo F, et al. A case of post-traumatic minimally conscious state reversed by midazolam: clinical aspects and neurophysiological correlates. Restor Neurol Neurosci. 2014;32(6):767–87.
35. Lanzillo B, Loreto V, Calabrese C, Estraneo A, Moretta P, Trojano L. Does pain relief influence recovery of consciousness? A case report of a patient treated with ziconotide. Eur J Phys Rehabil Med. 2016;52:263–6.
36. Calabrò RS, Aricò I, De Salvo S, Conti-Nibalie V, Bramanti P. Transient awakening from vegetative state: is high-dose zolpidem more effective? Psychiatry Clin Neurosci. 2015;69:122–3.
37. Machado C, Estevez M, Rodriguez R, Perez-Nellar J, Chinchilla M, DeFina P, et al. Zolpidem arousing effect in persistent vegetative state patients: autonomic, Eeg and behavioral assessment. Curr Pharm Des. 2014;20(26):4185–202.
38. Whyte J, Rajan R, Rosenbaum A, Katz D, Kalmar K, Seel R, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil. 2014;93(2):101–13.
39. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with tha-

lamic stimulation after severe traumatic brain injury. Nature. 2007;448:600–3.
40. Lemaire J, Sontheimer A, Nezzar H, Pontier B, Luauté J, Roche B, et al. Electrical modulation of neuronal networks in brain-injured patients with disorders of consciousness : a systematic review. Ann Françaises d'Anesthésie Réanimation [Internet]. 2014;33(2):88–97. Available from: www.sciencedirect.com/science/article/pii/S0750765813012185.
41. Chudy D, Deletis V, Almahariq F, Marčinković P, Škrlin J, Paradžik V, et al. Deep brain stimulation for the early treatment of the minimally conscious state and vegetative state: experience in 14 patients. J Neurosurg. 2018;128:1189–98.
42. Corazzol M, Lio G, Lefevre A, Deiana G, Tell L, André-Obadia N, et al. Restoring consciousness with vagus nerve stimulation. Curr Biol [Internet]. Elsevier; 2017;27(18):R994–6. Available from: https://doi.org/10.1016/j.cub.2017.07.060.
43. Bai Y, Xia X, Liang Z, Wang Y, Yang Y, He J, et al. Frontal connectivity in EEG gamma (30–45Hz) respond to spinal cord stimulation in minimally conscious state patients. Front Cell Neurosci. 2017;11:177.
44. Magrassi L, Maggioni G, Pistarini C, Di Perri C, Bastianello S, Zippo A, et al. Results of the prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. J Neurosurg. 2016;125(4):972–81.
45. Noé E, Ferri J, Colomer C, Moliner B, O'Valle M, Ugart P, et al. Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness. Brain Stimul. 2020;13(2):427–9.
46. Yu Y, Yang Y, Wang L, Fang J, Chen Y, He J, et al. Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: the first case report. Brain Stimul [Internet]. Elsevier Inc.; 2017;10(2):328–30. Available from: https://doi.org/10.1016/j.brs.2016.12.004.
47. Hakon J, Moghiseh M, Poulsen I, Øland CML, Hansen CP, Sabers A. Transcutaneous vagus nerve stimulation in patients with severe traumatic brain injury: a feasibility trial. Neuromodulation [Internet]. 2020; E-pub ahead of print. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ner.13148.
48. Thibaut A, Chatelle C, Gosseries O, Laureys S, Bruno MA. Transcranial direct current stimulation: a new tool for neurostimulation. Rev Neurol. 2013;169(2):108–20.
49. Wagle Shukla A, Shuster JJ, Chung JW, Vaillancourt DE, Patten C, Ostrem J, et al. Repetitive transcranial magnetic stimulation (rTMS) therapy in Parkinson disease: a meta-analysis. PM&R [Internet]. 2016;8(4):356–66. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1016/j.pmrj.2015.08.009.
50. Chen J, Zhao L, Liu Y, Fan S, Xie P. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: a systematic review and multiple-treatments meta-analysis. Behav Brain Res [Internet]. 2017;320:30–6. Available from: http://www.sciencedirect.com/science/article/pii/S0166432816308051.
51. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128:56–92.
52. Xia X, Bai Y, Zhou Y, Yang Y, Xu R, Gao X, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness. Front Neurol. 2017;8:1–8.
53. Naro A, Russo M, Leo A, Bramanti P, Quartarone A, Calabrò RS. A single session of repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in patients with unresponsive wakefulness syndrome: preliminary results. Neurorehabil Neural Repair. 2015;29(7):603–13.
54. Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr. 2003;16(2):95–9.
55. Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, et al. Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett. 2006;404(1–2):232–6.
56. Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag. 2010;39(5):890–903.
57. Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH. Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil. 2009;88(5):404–9.
58. Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: A pilot study. J Rehabil Med. 2012;44(4):346–50.
59. Kang EK, Baek MJ, Kim S, Paik NJ. Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci. 2009;27(6):645–50.
60. Thibaut A, Bruno M, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness. Neurology. 2014;1–7.
61. Martens G, Fregni F, Carrière M, Barra A, Laureys S, Thibaut A. Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study. Brain Inj [Internet]. Taylor & Francis; 2019;33(13–14):1679–83. Available from: https://doi.org/10.1080/02699052.2019.1667537.
62. Thibaut A, Piarulli A, Martens G, Chatelle C, Laureys S. Effect of multichannel transcranial direct current stimulation to reduce hypertonia in individuals with prolonged disorders of consciousness: a randomized controlled pilot study. Ann Phys Rehabil Med [Internet]. 2019;62(6):418–25. Available from: http://www.sciencedirect.com/science/article/pii/S1877065719300934.

63. Orrù G, Baroni M, Cesari V, Conversano C, Hitchcott PK, Gemignani A. The effect of single and repeated tDCS sessions on motor symptoms in Parkinson's disease: a systematic review. Arch Ital Biol. Italy. 2019;157(2–3):89–101.
64. Narita Z, Stickley A, DeVylder J, Yokoi Y, Inagawa T, Yamada Y, et al. Effect of multisession prefrontal transcranial direct current stimulation on cognition in schizophrenia: A systematic review and meta-analysis. Schizophr Res [Internet]. 2020;216:367–73. Available from: http://www.sciencedirect.com/science/article/pii/S0920996419305092.
65. Angelakis E, Liouta E, Andreadis N, Korfias S, Ktonas P, Stranjalis G, et al. Transcranial direct current stimulation effects in disorders of consciousness. Arch Phys Med Rehabil. 2014;95(2):283–9.
66. Dimitri D, De Filippis D, Galetto V, Zettin M. Evaluation of the effectiveness of transcranial direct current stimulation (tDCS) and psychosensory stimulation through DOCS scale in a minimally conscious subject. Neurocase [Internet]. Routledge; 2017;23(2):96–104. Available from: https://doi.org/10.1080/13554794.2017.1305112.
67. Pape TLB, Heinemann AW, Kelly JP, Hurder AG, Lundgren S. A measure of neurobehavioral functioning after coma. Part I: theory, reliability, and validity of the disorders of consciousness scale. J Rehabil Res Dev. 2005;42(1):1–18.
68. Estraneo A, Pascarella A, Moretta P, Masotta O, Fiorenza S, Chirico G, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: a double-blind cross-over study. J Neurol Sci. Elsevier B.V. 2017;375:464–70.
69. Thibaut A, Wannez S, Donneau AF, Chatelle C, Gosseries O, Bruno MA, et al. Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. Brain Inj [Internet]. Taylor & Francis; 2017;31(4):466–74. Available from: https://doi.org/10.1080/02699052.2016.1274776.
70. Huang W, Wannez S, Fregni F, Hu X, Jing S, Martens G, et al. Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: a sham-controlled randomized clinical trial. Brain Stimul [Internet]. 2017;10(3):718–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1935861X17306083.
71. Martens G, Lejeune N, O'Brien AT, Fregni F, Martial C, Wannez S, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. Brain Stimul. 2018;11(5):982–90.
72. Cavinato M, Genna C, Formaggio E, Gregorio C, Storti SF, Manganotti P, et al. Behavioural and electrophysiological effects of tDCS to prefrontal cortex in patients with disorders of consciousness. Clin Neurophysiol [Internet]. International Federation of Clinical Neurophysiology; 2019;130(2):231–8. Available from: https://doi.org/10.1016/j.clinph.2018.10.018.
73. Straudi S, Bonsangue V, Mele S, Craighero L, Montis A, Fregni F, et al. Bilateral M1 anodal transcranial direct current stimulation in post traumatic chronic minimally conscious state: a pilot EEG-tDCS study. Brain Inj [Internet]. Taylor & Francis; 2019;33(4):490–5. Available from: https://doi.org/10.1080/02699052.2019.1565894.
74. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A. 2009;106(5):1590–5.
75. Schiff ND. Recovery of consciousness after brain injury : a mesocircuit hypothesis. Cell Press. 2009;33(1):1–9.
76. Thibaut A, Di Perri C, Chatelle C, Bruno MA, Bahri MA, Wannez S, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul [Internet]. Elsevier Inc.; 2015;8(6):1116–23. Available from: https://doi.org/10.1016/j.brs.2015.07.024.
77. Naro A, Russo M, Leo A, Cannavò A, Manuli A, Bramanti A, et al. Cortical connectivity modulation induced by cerebellar oscillatory transcranial direct current stimulation in patients with chronic disorders of consciousness: a marker of covert cognition? Clin Neurophysiol [Internet]. Int Fed Clin Neurophysiol; 2016;127(3):1845–54. Available from: https://doi.org/10.1016/j.clinph.2015.12.010.
78. Bai Y, Xia X, Wang Y, Guo Y, Yang Y, He J, et al. Fronto-parietal coherence response to tDCS modulation in patients with disorders of consciousness. Int J Neurosci [Internet]. Taylor & Francis; 2018;128(7):587–94. Available from: https://doi.org/10.1080/00207454.2017.1403440.
79. Faiman I, Pizzamiglio S, Turner DL. Resting-state functional connectivity predicts the ability to adapt arm reaching in a robot-mediated force field. Neuroimage [Internet]. Elsevier Ltd; 2018;174:494–503. Available from: https://doi.org/10.1016/j.neuroimage.2018.03.054.
80. Simis M, Doruk D, Imamura M, Anghinah R, Morales-Quezada L, Fregni F, et al. Neurophysiologic predictors of motor function in stroke. Restor Neurol Neurosci. 2016;34:45–54.
81. Lehembre R, Bruno MA, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, et al. Resting-state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct Neurol. 2012;27(1):41–7.
82. Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Mazzilli R, Galardi G. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. Clin Neurophysiol [Internet]. Int Fed Clin Neurophysiol; 2015;126(5):959–66. Available from: https://doi.org/10.1016/j.clinph.2014.08.005.

83. Song JJ, Vanneste S, Van de Heyning P, De Ridder D. Transcranial direct current stimulation in tinnitus patients: a systemic review and meta-analysis. ScientificWorldJournal. 2012;2012:427941.
84. Ferrucci R, Vergari M, Cogiamanian F, Bocci T, Ciocca M, Tomasini E, et al. Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. NeuroRehabilitation. 2014;34(1):121–7.
85. Goncalves GS, Borges IC, Goes BT, de Mendonca ME, Goncalves RG, Garcia LB, et al. Effects of tDCS induced motor cortex modulation on pain in HTLV-1: a blind randomized clinical trial. Clin J Pain. 2013;30(9):809–15.
86. Whyte J. Disorders of consciousness: the changing landscape of treatment. Neurology. 2014;82(13):1106–7.
87. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci [Internet]. 2002;3(3):201–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11994752.
88. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci. 2001;98(2):676–82.
89. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJF, Bruno MA, Boveroux P, Schnakers C, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 2010;133(1):161–71.
90. Di Perri C, Bahri MA, Amico E, Thibaut A, Heine L, Antonopoulos G, et al. Neural correlates of consciousness in patients who have emerged from a minimally conscious state: a cross-sectional multimodal imaging study. Lancet Neurol [Internet]. Elsevier Ltd. 2016;15(8):830–42. Available from: https://doi.org/10.1016/S1474-4422(16)00111-3.
91. Chen H, Epstein J, Stern E. Neural plasticity after acquired brain injury: evidence from functional neuroimaging. PM&R [Internet]. 2010;2(12S):S306–12. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1016/j.pmrj.2010.10.006.
92. Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol. 2000;523(Pt 2):503–13.
93. Bekinschtein TA, Coleman MR, Niklison 3rd J, Pickard JD, Manes FF. Can electromyography objectively detect voluntary movement in disorders of consciousness? J Neurol Neurosurg Psychiatry. 2008;79(7):826–8.
94. Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernandez-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet. 2011;378(9809):2088–94.
95. Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med. 2010;362(7):579–89.
96. Bai Y, Xia X, Kang J, Yang Y, He J, Li X. TDCS modulates cortical excitability in patients with disorders of consciousness. NeuroImage Clin [Internet]. The Authors. 2017;15:702–9. Available from: https://doi.org/10.1016/j.nicl.2017.01.025.
97. Thibaut A, Chatelle C, Vanhaudenhuyse A, Martens G, Cassol H, Martial C, et al. Transcranial direct current stimulation unveils covert consciousness. Brain Stimul. 2018;11(3):642–4.
98. Schiff ND. Cognitive motor dissociation following severe brain injuries. JAMA Neurol [Internet]. 2015;72(12):1413–5. Available from: https://doi.org/10.1001/jamaneurol.2015.2899.
99. Zhao H, Qiao L, Fan D, Zhang S, Turel O, Li Y, et al. Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): clinical applications and safety concerns. Front Psychol. 2017;8:685.

tDCS in the Context of Rehabilitation

34

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34.1 Overview

Rehabilitation is a widely used term, with many definitions. According to the World Health Organization, "*Rehabilitation is a set of interventions needed when a person is experiencing or is likely to experience limitations in everyday functioning due to aging or a health condition, including chronic diseases or disorders, injuries or traumas.*" In the context of tDCS, it is commonly used to improve/maintain function (motor, sensorial, autonomic, and cognitive), decrease the impact of symptoms (such as pain), with the ultimate goal of improving the quality of life of the patient and the caregiver. tDCS is being studied in the context of rehabilitation for several applications. This investigation has been associated with exponential growth. The growing understanding of the biological mechanisms of the effects of tDCS applied in rehabilitation is contributing to this growth. It is currently understood that tDCS can alter and strengthen spontaneous synaptic activity and inflect plasticity interceded by neurotransmitters on a structural level. Thus, tDCS's ability to promote broad neuroplasticity emphasizes its promise in the framework of rehabilitation [1].

The development of tDCS has been concomitant with the search of new technologies to enhance rehabilitation therapies' effectiveness, including robotic-assisted training, virtual reality, brain-computer interface, and new assistive technology. Therefore, the studies with tDCS commonly associated it with conventional and new therapies to potentialize the benefits. However, as we discuss below, recent evidence suggested that the interaction between tDCS and other therapies is not always synergic [2].

Moreover, for the rehabilitation of neurological diseases (neurorehabilitation), the use of tDCS must be based on the biological mechanisms of the specific diseases, which differs depending on etiology (neoplastic, traumatic, hereditary, degenerative, vascular, infectious, and inflammatory/autoimmune), affected structures, time since the injury (acute and chronic), age, and other individual characteristics of the patient [3].

The parameters and location of application also vary, but in general, the electrodes are placed over the lesioned area of the brain or in an area with functional connectivity with the affected region (for instance, anode stimulation can be applied over the primary motor cortex (M1) of a patient with spinal cord injury, or in a stroke, the cathode is usually applied in the uninjured hemisphere, on the area homologous to the injury) [3].

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One of the main topics of tDCS is motor rehabilitation, especially post-stroke due to its high prevalence. Motor function is a complex system, and its improvement can be related to different aspects, such as dexterity, speed, strength, muscle tone, spasticity, and the influence of sensitivity, alteration of mood, and cognition. Furthermore, the improvement is not necessarily related to the restoration of function, but it can be associated with movement compensation or adaptation (such as using orthoses). Thus, all these characteristics are associated with motor learning and may be modulated by tDCS [4].

Below we discuss the application of tDCS in the most studied conditions within the pediatric and adult rehabilitation fields. We emphasize the level of evidence of effectiveness, with a high level of evidence being considered when randomized clinical trials exist. Moreover, the existence of a placebo control group is considered essential to evaluate the effects of tDCS since it is known to induce a placebo effect. Besides, patients may show improvement due to the disease's natural course (e.g., patients with stroke in the acute phase tend to improve regardless of the treatment).

34.2 Pediatric Rehabilitation and tDCS

It is captivating to watch a young healthy child learn how to meaningfully manipulate a toy, while professing natural curiosity to discover what the toy represents. Children learn through trial and error demonstrating a remarkably learning curve, favored by the opportunities and resources children must have to acquired new cognitive and motor skills. Therefore, one can conclude that experience-dependent neuronal activity regulates the development of function in a child's brain. Opposite to normal learning, spontaneous recovery of function after a disabling injury or illness has been observed in pediatric populations. Early reports documented cases of infants and young children exposed to destruction of the cortical speech area that did not result in lasting aphasia [1]. Moreover, the notion of age-dependent decline in plasticity was described in adolescents who underwent left hemispherectomies and showed remarkable recovery in the understanding and expression of speech, while adult patients displayed profound affectation in their language skills post-hemispherectomy [2]. Perhaps, the most extraordinary and well-documented case of developmental plasticity is observed in children with sensorineural hearing loss, it is widely recognized that auditory stimulation should be provided as soon as possible after hearing loss is identified to best ensure that a child can maximize residual hearing and reach auditory language and learning potential [3].

tDCS has the potential to reduce or alleviate a variety of symptoms associated with neurological and psychiatric pediatric conditions, including stroke, cerebral palsy, autism, depression, and neurodevelopmental syndromes [4]. Additionally, tDCS modulates learning processes in a polarity-dependent manner (facilitation vs. inhibition), making tDCS a suitable technique for neurological rehabilitation. Transcranial electrical brain stimulation is under active investigation in child neurology and psychiatry, particularly in disorders where focal cortical hypo- or hyperactivation is believed to be part of the neural pathophysiology [5]. Current tDCS research in children is driven in part by a favorable safety profile [6], the low cost of tDCS stimulators, and by fairly reproducible effects on the cortex, where exposure to cathodal stimulation leads to cortical inhibition and exposure to anodal current leads to cortical activation [7]. Despite the growing number of tDCS studies in the adult population, studies in pediatrics remain an unmet needed, particularly in pediatric rehabilitation, where traditional therapeutic options still far to be comprehensive, when considering principles of brain damage and repair.

Considering tDCS applications in pediatric rehabilitation is important to understand the underlying mechanisms of developmental neurophysiology. Neuronal activity is critical for normal neural development in utero, and thus, neuronal circuits are hyperexcitable early in life [8]. Yet, the hyperexcitable state is not compatible with mature brain function, and the excitation/inhibition (E/I) balance shifts toward progres-

sively lower excitability with age [9], thus, favoring cognitive and motor function maturation as a result of glutamatergic/GABAergic synaptic balance. Neurons and circuits coordinate their excitatory and inhibitory inputs to establish and maintain a constant E/I ratio that is thought to be essential for circuit function and stability. Theoretical modeling demonstrated that when inhibition tightly matches excitation and tracks it on milliseconds timescale in the neural network, it provides great advantage to the precision and efficiency of neuronal coding mechanisms [10]. To equate tDCS clinical effects obtained in adults studies and expect similar results in children, is misguided, especially because the unique anatomy and the developmental changes that take place throughout childhood, suggesting that tDCS effects will vary and differ from adults [11]. Evidence from computational current modeling demonstrates that local electric field strength may be twofold greater in children compared to adults [12], especially when considering the developmental trajectories from white and gray matter and its relation to scalp distance, all these factors may affect peak current densities over the brain surface and subcortical regions [13].

Available evidence suggests that tDCS is safe to use in children, yet a clear deficit of pediatric studies prevents the generalization of these results. A review of tDCS studies to date found that <2% of nearly 7000 subjects were under 18 years of age [6]. As expected, this limitation makes difficult the objective analysis of current available data; therefore, the following discussion focuses on those conditions where reliable data suggest a tDCS beneficial effect.

34.2.1 Motor Rehabilitation

Promising studies in pediatric neurological rehabilitation have focused on detecting and examining the therapeutic effectiveness of tDCS in pediatric motor disorders following brain Injury, such as cerebral palsy (CP), traumatic brain injury, or pediatric stroke. A recent systematic review and meta-analysis [14, 15] assessed the evidence of tDCS effectiveness, for the rehabilitation of pediatric motor disorders, while most of the reviewed studies used anodal stimulation over M1 (lesional motor cortex), the return electrode was placed either at the contralateral M1 or contralateral orbitofrontal area. Using gait as functional assessment, most studies evaluated the effects of a single or 10-day sessions of stimulation mainly in diplegic CP patients. The level of evidence of these studies was 1b (moderate evidence), with tDCS showing significant changes in velocity, cadence, and stride length. Overall, there was a positive effect on balance after tDCS in most center of pressure (COP) variables [14]. When considering functional abilities, there was no significant change in the gross motor function measure (GMFM) for standing, walking, mobility, self-care, or in the pediatric balance (PBS) scores immediately after stimulation; however, at 1-month follow-up, significant improvements were observed in standing and balance, indicating that a synergistic effect with other therapies can be expressed overtime. In relation to muscle tone, it was noted that the efficacy of tDCS on spasticity is uncertain. Based on these reviews, tDCS can be considered a safe technique in pediatric motor disorders, with the potential to improve some gait measures, especially when combined with other forms of therapies. Few studies have explored the neurophysiological effects of tDCS. Unfortunately, inconclusive results in measures of cortical excitability/neurophysiology (TMS, EEG, fMRI) after tDCS have been reported in children with motor disorders [16–18]. It has been demonstrated the role of abnormal plasticity in the cortico-spinal tracts (CST) and their connectivity between M1 and S1, particularly in hemiplegic conditions where MEPs can be elicited following ipsilateral single-pulse TMS [19, 20], although small, these studies offered the possibility to explore the use of physiological markers and its relation to physiological and clinical improvements after tDCS.

Further research is required to integrate tDCS as a valuable technique for the rehabilitation of motor disorders in children, particular attention deserve investigations exploring the effects of age-related differences in therapeutic responses and the safety of tDCS in the pediatric brain.

34.2.2 Cognitive and Behavioral Rehabilitation

tDCS has been used in healthy adults to modulate cognitive, behavioral, social, and emotional processes. As well, tDCS is often used to boost neuropsychological or psychiatric rehabilitation, by applying principles of neuroplasticity and polarity-dependent cortical modifications. Studies in children have focused on autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), dyslexia, Tourette syndrome, and tic disorders. Prior to consider tDCS as an alternative in cognitive/behavioral rehabilitation, a deep understanding of neural development is required. Cognitive development is more difficult to appreciate than development in other domains, such as gross motor, fine motor, and language. This is because in the early period of development, clues to a child's cognitive development are more indirectly expressed through the child's interactions with the environment [21]. Concerns about lack of interaction with the environment or delay in the achievement of early cognitive (because of disease, neglect, poverty/violence to mention some) milestones should trigger an immediate response and intervention, to minimize the effects of factors disturbing cognitive development. While the economic burden of neurodevelopmental disorders is well known, current standards of cognitive interventions and pharmacological therapy still limited. Therefore, it is imperative to consider alternatives such as tDCS, particularly because of its safety profile and applicability in the rehabilitation environment.

In cognitive/behavioral rehabilitation, especially in neurodevelopmental disorders, it is important to identify the neural substrates involved in the physiopathology of each condition. For instance, developmental apraxia of speech is characterized by difficulty in speech motor planning, and it has been reported to result following damage to the anterior insula in the language-dominant hemisphere as well the left posterior inferior frontal gyrus [22, 23]. By understanding the involvement of these structures, clinical research aiming to explore the effects of tDCS should target the left frontal gyrus [24]. The rationale for such approach will follow the principle that increased activation by anodal stimulation (ideally with concomitant speech therapy) may facilitate left hemisphere reorganization and plasticity-based functional improvements. Consequently, clinical research involving tDCS and neurodevelopmental conditions must always consider issues associated with developmental plasticity, circuit reorganization, and E/I balance. The ideal approach to address these issues would be the "mapping" of the changes associated with functional recovery. Imaging studies (fMRI, fNIRS), neurophysiology (EEG, ERPs) evaluations, and clinical outcomes should always guide tDCS interventions in the young developing brain, as to avoid the occurrence of "aberrant" learning and "faulty plasticity."

34.2.3 ASD and tDCS

ASD consists of several complex neurodevelopmental disorders, featured by the presence of persistent impairments in social communication and interaction, restricted and repetitive patterns of behaviors or interests; onset is in the early developmental period, and the symptoms cause clinically significant impairment in social, occupational, or other areas of functioning [25]. Few studies have investigated the effects of tDCS in children and adolescents with ASD, a recent systematic review identified four studies, from those only two were randomized control trials [26]. All of these studies targeted the left dorsolateral prefrontal cortex (DLPFC) based on the evidence of a hypo-activation of the left hemisphere toward a rightward lateralization in ASD [27]. Overall, no adverse effects were reported in these studies and all participants tolerated the stimulation. The results from these studies highlight the feasibility to use DLPFC tDCS to improve autistic behaviors and some features of language abilities; however, further randomized and controlled studies with larger and more representative and homogeneous ASD children are needed [26].

34.2.4 ADHD and tDCS

The core symptoms of ADHD are inattention, hyperactivity, and impulsivity. ADHD is one of the most common and most extensively studied behavioral disorders in school-aged children, with a worldwide prevalence of 7%, that can persist into adolescence and adulthood in 60–80% of individuals diagnosed with ADHD during childhood. Structural and functional imaging studies suggest that dysfunction in the fronto-subcortical pathways as well as imbalances in the dopaminergic and noradrenergic systems contribute to the pathophysiology of ADHD [25, 28]. Standard treatment for ADHD includes pharmacological management based on the use of stimulants (methylphenidate) as the first-line therapy and non-stimulants such as norepinephrine reuptake inhibitors (atomoxetine). Common adverse effects include appetite suppression, weight loss, headaches, mood effects, and sleep disorders, which however, can be problematic for children whose comorbid conditions can be worsened by the stimulant treatment [29]. It has been proposed that behavioral deficits in ADHD can be associated with faulty inhibitory processes, resulting in a failure in executive control, impulsive behavior, and hyperactivity (inhibition-based model), or to impaired motivational and reward processing (motivational-dysfunction model) [30, 31]. By following the rationale behind these models, we can assume that the DLPFC and the orbitofrontal cortex (OFC) are the main structures to be targeted by tDCS applications.

Current evidence for the use of tDCS in ADHD is limited by the few number of randomized, double-blinded, sham-controlled trials, yet positive results have been obtained in memory consolidation, working memory, and inhibitory control by targeting the DLPFC with different tDCS protocols [26]. Slow oscillating tDCS (toDCS) during sleep using bilateral prefrontal montage (F3, F4) showed improvements in declarative memory [32] and behavioral inhibition. Overall, findings from these studies suggested that toDCS may be considered as a useful tool to increase slow oscillatory power during sleep in DLPFC, thus improving declarative memory and executive functions in ADHD [26]. Stimulation targeting the left DLPFC with cathodal return over the right supraorbital area showed improvements in visual attention, inhibitory control, overall inattention, and hyperactivity after tDCS [33, 34]. Studies exploring other electrode montage (prefrontal or bilateral prefrontal) have failed to show any significant effect in ADHD symptoms, probably due to underpower or methodological issues. Given the available evidence, tDCS may be useful for improving cognitive functions in ADHD; however, better powered studies are required to replicate the initial findings presented here.

34.2.5 Dyslexia and tDCS

Learning disabilities are frequently diagnosed in children. Specific learning disorder (SLD) is the umbrella term for mathematics, reading, and written expression disorder [25]. Dyslexia is the term used to refer to a pattern of learning difficulties characterized by problems with fluent word recognition, poor decoding, and poor spelling abilities [21]. Neuroimaging studies have demonstrated alterations in the left temporoparietal-occipital region among children with dyslexia, with specific asymmetries located in the angular gyrus and inferior frontal hyperactivation [35]. A possible progress in the treatment of this disorder could be achieved by the integration of cognitive trainings with tDCS, to promote the activation of the areas that are involved in compensatory processes in dyslexia [36]. Left anodal parietotemporal stimulation has shown improvements in text reading accuracy [37]. When combined with cognitive reading training, children exposed to left anodal parietotemporal stimulation exhibited long-lasting improvements in reading efficiency [38]. Although these studies demonstrated positive outcomes, stronger evidence is needed, particularly the replication of these results in larger samples.

34.2.6 Conclusion

Transcranial direct current stimulation offers the possibility to become an integral treatment option in pediatric rehabilitation, especially because its mechanisms of action may promote plasticity in a manner closer to developmental processes. The portability and costs facilitate their use in combination with other rehabilitation methodologies and techniques (e.g., physical, occupational, and speech therapies, robotic therapy, VR, cognitive training), which in turn, may potentiate the effects of such techniques in a bidirectional way. More important, in all the reported studies, tDCS achieved an excellent safety profile with few serious adverse effects reported. Unfortunately, as in the case of drug-based clinical trials, research of tDCS applications in pediatric populations still underrepresented, and this is driving the crisis in the generation of evidence supporting noninvasive neuromodulation for conditions whose treatments are far to be comprehensive in children and adolescents. Considerations, based on stimulation parameters such as current flow modeling, should guide treatment options for appropriate dosing and target localization. Moreover, close clinical supervision accounting for in-depth investigations of cognitive or behavioral side effects and the use of supporting neurophysiology (EEG/ERPs) and imaging studies (MRI/CT scans) must be required in tDCS research, especially because the young brain represents a dynamic entity capable to change and adapt faster than the adult or aging brain.

34.3 Adult Rehabilitation and tDCS

34.3.1 Stroke

For most of the studies, the rationale behind the use of tDCS in stroke is based on the theory of interhemispheric imbalance. This model proposes that after a unilateral stroke, the injured hemisphere reduces the inhibition it exerted in the uninjured hemisphere, resulting in hyperexcitability in the uninjured hemisphere, which in turn further inhibits the injured hemisphere. There is evidence that this imbalance in interhemispheric activity is a maladaptive plastic change since the increase in activity in the uninjured hemisphere is related to a worse motor function of the post-stroke deficit [3].

Thus, most of the tDCS studies in stroke rehabilitation aimed to improve function by improving the interhemispheric imbalance. The first studies with tDCS in 2005 demonstrated an improvement in motor function with cathodic (inhibitory) stimulation over the M1 of the hemisphere. The hypothesis is that the balance of brain activity, and the improvement of the maladaptive plastic alteration, unmasks perilesional areas inhibited, allowing to replace the function of the neurons injured by the stroke. Currently, there are several randomized clinical trials with similar approaches, performing excitatory stimulation in the injured hemisphere, with anodic stimulation, or using both approaches (excitatory and inhibitory) in the same patient.

There is evidence that tDCS has a synergistic effect with other therapies such as conventional kinesiotherapy and constraint-induced movement therapy (CIMT), among others. Neuroplasticity is the mechanism that allows the recovery of functional deficits in stroke, which is influenced by environmental pressures, physiological changes, and experiences. So, it is likely that rehabilitation therapies induce brain modification that will be enhanced and better consolidated with tDCS. Since tDCS modifies spontaneous neuronal activity (facilitating or inhibiting) and therapies generate this activity, the combination is likely synergistic [2].

On the other hand, a recent review and meta-analysis concluded that anodal tDCS of ipsilesional M1 to enhance robotic therapy is definitely *not* effective (Level A) for motor rehabilitation in subacute stroke. A possible explanation is that the robotic training, an intensive therapy, can induce a ceiling effect. But another possibility is that the concomitant training/treatments may change or even reverse expected tDCS effects. In this same review, the anode, cathode, and bilateral stimulation were considered level B (probably effective) to improve

motor function, when combined with other therapies rather than robotics [2].

Furthermore, a possible temporal relationship is suggested between the use of tDCS and post-stroke motor function recovery. This indicates that tDCS in acute/subacute stroke compared to chronic stroke might yield different results. For instance, the use of tDCS for upper limb function recovery has been shown to convey moderate chronic stroke results, but not in acute/subacute stroke. It is also suggested that early overactivation of the ipsilesional cortex in acute and subacute stroke stages might be related to a good recovery. However, this relationship's nature has yet to be better elucidated in the context of post-stroke rehabilitation [5, 6].

TDCS has been studied, based on the theory of interhemispheric imbalance, for other post-stroke deficits, such as hemianopsia and hemineglegence, in which case stimulation is performed in the occipital and parietal cortex, respectively. In the case of aphasia, the most studied approach is the inhibitory stimulation of the area homologous to the Broca area and the Wernicke area of the right hemisphere.

Recent studies suggest enhancing tDCS-mediated post-stroke rehabilitation through its association with neuroimaging procedures, such as magnetic resonance imaging (MRI). The association of tDCS with functional MRI for the treatment of post-stroke aphasia has already been used and conveys promising results for the impact on motor function recovery. Moreover, this association strengthens the identification of non-responders and responders for tDCS treatment and identifies the locations of electrode placement that yield the most effective results. In addition, the use of fMRI might also produce better insights into the neurophysiological role of tDCS in stroke rehabilitation [2, 7, 8].

In post-stroke dysphagia, there are positive studies with the cathode stimulation of the uninjured hemisphere and with anode stimulation of the injured hemisphere. Besides, some studies applied bilateral anode stimulation, which may seem contradictory; however, they are based on the fact that the corticobulbar pathways for the swallowing muscles are predominantly bilateral. Thus, stimulation of the uninjured hemisphere aims to enhance the recovery of function by optimizing the ipsilateral corticobulbar pathway, which in this case, is not based on the interhemispheric imbalance theory [9].

34.3.2 Spinal Cord Injury

Among the suggested mechanisms for functional recovery after SCI, there are neuronal plasticity processes that can contribute to the reorganization of neuronal circuits at the medullary level. Thus, the reorganization of the cerebral cortex allows the functional optimization of the ascending and descending pathways that remained complete after the injury.

Anodal tDCS on patients with spinal cord injury conveys promising results when used concomitantly with rehabilitative training. The function of the cerebral cortex in the neuroplasticity of injured spinal cord neurons can be explained by the relationship of uninjured neurons excitability's influence on the plasticity and reformation of neuronal circuits of injured spinal cord neurons. Moreover, recent MRI studies have conveyed the role of tDCS in regulating spinal excitability. Brainstem activation of uninjured corticospinal axons intercedes the rehabilitation of reticulospinal pathways. Thus, the increase in corticospinal excitability of anodal-tDCS conveys potentially promising results for SCI rehabilitation [10, 11].

A few studies use tDCS anode over the primary motor cortex to enhance the functional recovery process, but the results are heterogeneous. A recent study showed that the group of patients with incomplete spinal cord injury who received bilateral anode stimulation has higher chances of gait improvement than a sham. In this protocol, tDCS was applied before the robotic-assisted gait training, and the statistical difference between active and sham group occurred after 30 sessions, but not after 15 sessions. These results suggested that tDCS is dose dependent, and in the case of SCI, robotic treatment has a synergistic effect, which needs to be confirmed in future studies. In addition to being dose

dependent, several studies have also depicted a better effect of tDCS in SCI motor recovery is intensity dependent. Motor rehabilitation of patients with SCI is more effective when higher intensities (i.e., 2 mA) of anodal-tDCS are applied [9, 11].

Furthermore, single-session clinical trials have shown an intensity-dependent impact on the voluntary motor function of quadriplegic patients with incomplete SCI. A recent, single-session pilot study conveyed positive, intensity-dependent results in the improvement of grasp and other hand motor functions when 2 mA anodal-tDCS was applied in patients with chronic SCI. It is further suggested that the improvement in hand motor function by a single-session anodal tDCS implies greater enhancement if multiple sessions are to be applied, supporting the dose-dependent nature of tDCS. Nonetheless, further, larger studies need to be performed to confirm the positive impact on motor rehabilitation that the relationship between tDCS intensity and dose has on SCI patients [11].

Additionally, studies in SCI patients have conveyed that the use of tDCS within a shorter period since the SCI has demonstrated better motor function, suggesting a temporal relationship between tDCS and SCI rehabilitation [11].

In the context of SCI, tDCS electrode placement in the M1 cortex may have other roles that are not related to motor function improvement. Patients with SCI often end up with a down-regulated autonomic nervous system (ANS) due to damage to afferent pathways that connect cortical and subcortical regions to the spinal cord. The activation of afferent subcortical and cortical regions has been suggested to upregulate and restore ANS function in SCI patients [12].

34.3.3 Traumatic Brain Injury

TBI's deleterious effects are due to primary traumatic injury to the brain, in addition to secondary biochemical and physiological changes, resulting in neuronal loss and diffuse axonal injury. In the long term, such changes may predispose to Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease.

As in stroke, secondary biochemical changes are specific to each TBI phase, so that in the acute phase, an increase in glutamatergic activity and hyperactivity of n-methyl-D-aspartate (NMDA) receptors is described. Still, in this phase, the process of reorganizing brain connections begins, with the possibility of forming functionally abnormal circuits resulting in long-term changes such as pain, spasticity, seizures, and memory deficit. After the acute phase, there is an increase in GABAergic inhibitory activity, causing excess inhibition and preventing brain connectivity recovery, which results in long-lasting functional deficits. Thus, the use of tDCS in patients with TBI is based on the premise of cathodal-tDCS application to reduce the excitotoxicity mediated by NMDA receptors in the acute phase and anodal-tDCS use in the subacute stage to compensate for the overbearing GABAergic inhibitory activity [1].

The rehabilitation aspect of tDCS-mediated neuroplasticity in patients with TBI depends largely on alterations of NMDA receptor activation. Therefore, multisession tDCS might imply longer lasting effects as the after effect of cathodal inhibition of NMDA hyperexcitability lasts longer when more tDCS sessions are applied [1].

Given the broad spectrum of affective, somatic, cognitive, and functional impairments caused by TBI, tDCS can target a myriad of domains for the recovery of these patients. Anodal-tDCS application on the injured primary motor cortex or the precentral gyrus's premotor cortex may improve hand motor dysfunction following a TBI. The same effect can be extracted by cathodal-tDCS application in the uninjured motor or premotor cortices. Bilateral frontal tDCS stimulation has also conveyed considerable antidepressant effects, an important use of tDCS in patients with TBI as 77% of them might experience affective impairments such as depression or depressive symptoms. The combination of left frontotemporal cathodal-tDCS with speech therapy might also contribute to post-traumatic expressive (nonfluent) aphasia recovery in TBI patients. Moreover, the bilateral neuromodulation

of the dorsolateral prefrontal cortex (DLPFC) might limit and reduce decision-making impairments provoked by TBI [1, 13].

TDCS has also been thought to reduce inflammatory and oxidative stress manifestations present in traumatic brain injuries. Neuroimaging studies have conveyed the effect of tDCS on changing oxygen metabolism within the context of TBI. It has been shown to reverse biomarkers related to TBI's secondary damages, enhancing and speeding up recovery [1].

Although these are all promising therapeutic targets for tDCS in TBI patients, they are solely based on theoretical information about TBI's biological mechanisms. Thus, more clinical trials need to be conducted to prove the benefits of this therapy within the realm of TBI recovery [1].

Thus, tDCS can be used to decrease or increase neuronal excitability to minimize specific changes in the acute and chronic phase of TBI. However, to date, few studies use tDCS for the functional improvement of patients with TBI. Most of the trials aim to improve cognitive impairment and to recover consciousness of patients in a coma, especially in the minimally conscious post-TBI state (better explained in the Chap. 33).

34.3.4 Cognitive Rehabilitation

TDCS has been used in neuroscience in healthy subjects to understand the mechanisms of neuronal factors of cognition. In addition, tDCS has been studied in the elderly's cognitive decline, mild cognitive impairment (MCI), and dementia syndromes, to minimize cognitive deficits and to disable symptoms and ultimately delay their progression of deficits [14].

The mechanism of probable action of tDCS is related to the ability to induce changes in cortical excitability and to modulate the activity in neural networks related to a certain cognitive activity. Long-term effects are probably related to changes in synaptic (long-term potentiation (LTP)-like and long-term depression (LTD)-like). Other models proposed include the modulation of glial activity, modification of the brain-derived neurotrophic factor (BDNF, from the brain-derived neurotrophic factor), and the reduction of inflammatory activity. These other mechanisms could, in theory, alter the course of the disease; however, there is no experimental data to support this hypothesis.

In patients with Alzheimer's disease, there are positive studies with tDCS showing augmentation of memory, attention, and word recall. The aspect of cognitive improvement is related to the area of stimulation, for instance, the enhancement in the performance of the word recognition task after a single session of anode tDCS over the bilateral temporoparietal cortex. Besides, improved visual recognition memory with anodic stimulation applied to the left dorsolateral prefrontal cortex and left temporal cortex. Furthermore, tDCS has shown divergent results in the rehabilitation of MCI compared to major cognitive impairment. The rehabilitation aspect of tDCS requires some neuronal function to be spared as to promote neuroplasticity, which might not be possible in patients with advanced Alzheimer's dementia (AD) and other major cognitive impairment conditions. Moreover, early dementia stages may convey reversible and treatable MCI, which is shown to improve when combining tDCS and cognitive training techniques [15].

Nonetheless, current systematic reviews have not yet established a significant, guideline-modifying effect between tDCS therapy and improvement in AD and other MCI scores. This may be a result of a limited number of clinical trials as well as underpowered studies, implying the need for further studies to be conducted to convey tDCS' supposedly positive benefits in cognitive recovery [15, 16].

It is important to note that some studies convey the improvement of MCI through the use of tDCS as a trade-off in respective cognitive abilities, meaning that the improvement of a functional aspect of MCI (e.g., memory, attention) might come in detriment of another. Additionally, the site-specific character of tDCS limits its ability to transfer its effects to other brain regions on its own, preventing the use of tDCS on its own for

global cognition improvement. This further emphasizes the positive results of tDCS when combined with cognitive training [15].

Within the context of dementia-related disorders, tDCS has shown promising results in the improvement of memory recall and long-term memory. The effects on tDCS memory in patients with dementia-related disorders have shown to be beneficial in patients with mild to moderate cognitive impairment in contrast to the improvement of other cognitive domains which are limited to patients with MCI [15–17].

With similar rationality as describe for stroke, researchers have explored the effect of tDCS combined with cognitive training with promising results. Some studies also suggest that the combination of tDCS and the use of cholinesterase inhibitors for the treatment of AD cognitive impairment might also yield positive results [16]. However, for neurodegenerative diseases, the illness's evolutionary character is one of the main challenges for cognitive rehabilitation since the functional gains may not be long-lasting due to its progressive aspect. On the other hand, the technique's safety and the possibility of home use increase the potential of the technique to be used frequently, which can improve the symptoms, quality of life, and survival of patients with progressive diseases.

34.3.5 Conclusion

Functional improvement in CNS injuries, especially when they are not neurodegenerative, is one of the most promising indications for tDCS. The functional gains can be long term, especially when incorporated into daily living activities since the frequent use of a certain function contributes to the consolidation of the networks of recruited neuronal connections. Furthermore, the association of tDCS with some additional standardized therapies in the domains of stroke, SCI, TBI, and cognitive rehabilitation may create a synergistic effect, which depicts better results than tDCS own.

The main challenges for tDCS in clinical practice are the determination of the best stimulation parameters, such as frequency, intensity, and duration (in hours per day). Besides, the ideal parameters probably vary between the subjects, due to genetic differences, lesion characteristics, environmental factors, phase of injury (acute, subacute, or chronic phase), among others. The parameters will probably be better determined with the development of biomarkers that make it possible to individualize the therapies.

References

1. Demirtas-Tatlidede A, et al. Noninvasive brain stimulation in traumatic brain injury. J Head Trauma Rehabil. 2012;27(4):274–92. https://doi.org/10.1097/HTR.0b013e318217df55.
2. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders [published online ahead of print, 2020 Jul 26]. Int J Neuropsychopharmacol. 2020:pyaa051. https://doi.org/10.1093/ijnp/pyaa051.
3. Adeyemo BO, Simis M, Macea DD, Fregni F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. Front Psych. 2012;3:88. https://doi.org/10.3389/fpsyt.2012.00088.
4. Ammann C, Spampinato D, Márquez-Ruiz J. Modulating motor learning through transcranial direct-current stimulation: an integrative view. Front Psychol. 2016;7:1981. https://doi.org/10.3389/fpsyg.2016.01981.
5. Elsner B, Kugler J, Mehrholz J. Transcranial direct current stimulation (tDCS) for upper limb rehabilitation after stroke: future directions. J Neuroeng Rehabil. 2018;15:106. https://doi.org/10.1186/s12984-018-0459-7.
6. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. Arch Neurol. 2008;65:1571–6. https://doi.org/10.1001/archneur.65.12.1571.
7. Stagg C, Johansen-Berg H. Studying the effects of transcranial direct-current stimulation in stroke recovery using magnetic resonance imaging. Front Human Neuroscienc. 2013;7(1):1–8. https://doi.org/10.3389/fnhum.2013.00857.
8. Shaker HA, Sawan S, Fahmy EM, Ismail RS, Elrahman S. Effect of transcranial direct current stimulation on cognitive function in stroke patients. Egypt J Neurol Psychiatry Neurosurg. 2018;54(1):32. https://doi.org/10.1186/s41983-018-0037-8.
9. Simons A, Hamdy S. The use of brain stimulation in dysphagia management. Dysphagia. 2017;32(2):209–15. https://doi.org/10.1007/s00455-017-9789-z.
10. Hofer AS, Schwab ME. Enhancing rehabilitation and functional recovery after brain and spinal cord

trauma with electrical neuromodulation. Curr Opin Neurol. 2019;32(6):828–35. https://doi.org/10.1097/WCO.0000000000000750.
11. Cortes M, Medeiros AH, Gandhi A, et al. Improved grasp function with transcranial direct current stimulation in chronic spinal cord injury. NeuroRehabilitation. 2017;41(1):51–9. https://doi.org/10.3233/nre-171456.
12. Da Silva FTG, Browne RAV, Pinto CB, Saleh Velez FG, do Egito EST, do Rêgo JTP, et al. Transcranial direct current stimulation in individuals with spinal cord injury: assessment of autonomic nervous system activity. Restor Neurol Neurosci. 2017;35(2):159–69. https://doi.org/10.3233/rnn-160685.
13. Dhaliwal SK, Meek BP, Modirrousta MM. Non-invasive brain stimulation for the treatment of symptoms following traumatic brain injury. Front Psych. 2015;6:119. https://doi.org/10.3389/fpsyt.2015.00119.
14. Martins AR, Fregni F, Simis M, Almeida J. Neuromodulation as a cognitive enhancement strategy in healthy older adults: promises and pitfalls. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2017;24(2):158–85. https://doi.org/10.1080/13825585.2016.1176986.
15. Inagawa T, Yokoi Y, Narita Z, Maruo K, Okazaki M, Nakagome K. Safety and feasibility of transcranial direct current stimulation for cognitive rehabilitation in patients with mild or major neurocognitive disorders: a randomized sham-controlled pilot study. Front Hum Neurosci. 2019;13:273. https://doi.org/10.3389/fnhum.2019.00273.
16. Inagawa T, et al. A meta-analysis of the effect of multisession transcranial direct current stimulation on cognition in dementia and mild cognitive impairment. Clin EEG Neurosci. 2018:1–10. https://doi.org/10.1177/1550059418800889.
17. Gomes MA, Akiba HT, Gomes JS, Trevizol AP, Lacerda AL, Dias ÁM. Transcranial direct current stimulation (tDCS) in elderly with mild cognitive impairment: a pilot study. Dement Neuropsychol. 2019;13(2):187–95. Epub June 18, 2019. https://doi.org/10.1590/1980-57642018dn13-020007.
18. Cotard J. Etude sur l'atrophie cerebrale. 1868.
19. Hillier WF. Total left cerebral hemispherectomy for malignant glioma. Neurology. 1954;4(9):718.
20. Langman AW, Quigley SM, Souliere CR Jr. Cochlear implants in children. Pediatr Clin N Am. 1996;43(6):1217–31.
21. Krishnan C, et al. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 2015;8(1):76–87.
22. Frye RE, et al. Transcranial magnetic stimulation in child neurology: current and future directions. J Child Neurol. 2008;23(1):79–96.
23. Bikson M, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9(5):641–61.
24. Rehmann R, et al. Polarity-specific cortical effects of transcranial direct current stimulation in primary somatosensory cortex of healthy humans. Front Hum Neurosci. 2016;10:208.
25. Sanchez RM, Jensen FE. Maturational aspects of epilepsy mechanisms and consequences for the immature brain. Epilepsia. 2001;42(5):577–85.
26. Hameed MQ, et al. Transcranial magnetic and direct current stimulation in children. Curr Neurol Neurosci Rep. 2017;17(2):11.
27. Denève S, Machens CK. Efficient codes and balanced networks. Nat Neurosci. 2016;19(3):375–82.
28. Zewdie E, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: prospective single center evidence from 3.5 million stimulations. Brain Stimul. 2020;13(3):565–75.
29. Kessler SK, et al. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112.
30. Beauchamp MS, et al. The developmental trajectory of brain-scalp distance from birth through childhood: implications for functional neuroimaging. PLoS One. 2011;6(9):e24981.
31. Elbanna ST, Elshennawy S, Ayad MN. Noninvasive brain stimulation for rehabilitation of pediatric motor disorders following brain injury: systematic review of randomized controlled trials. Arch Phys Med Rehabil. 2019;100(10):1945–63.
32. Saleem GT, et al. Transcranial direct current stimulation in pediatric motor disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2019;100(4):724–38.
33. Nemanich ST, et al. Influence of combined transcranial direct current stimulation and motor training on corticospinal excitability in children with unilateral cerebral palsy. Front Hum Neurosci. 2019;13:137.
34. Morales-Quezada L, et al. Abstract# 111: transcranial direct current stimulation (tDCS) in cerebral palsy: open-label safety and feasibility study. Brain Stimul. 2019;12(2):e38.
35. Simon-Martinez C, et al. Influence of the corticospinal tract wiring pattern on sensorimotor functional connectivity and clinical correlates of upper limb function in unilateral cerebral palsy. Sci Rep. 2019;9(1):8230.
36. Rich TL, et al. Ipsilateral corticospinal tract excitability contributes to the severity of mirror movements in unilateral cerebral palsy: a case series. Clin EEG Neurosci. 2020;51(3):185–90.
37. Zewdie E, et al. Contralesional corticomotor neurophysiology in hemiparetic children with perinatal stroke. Neurorehabil Neural Repair. 2017;31(3):261–71.
38. Voigt RG, et al. Developmental and behavioral pediatrics. American Academy of Pediatrics; 2011.

Part V

The Clinical Use of tDCS

Safety and Tolerability

35

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35.1 Introduction

Transcranial direct current stimulation (tDCS) has been applied increasingly in recent years to alter brain function in healthy humans and patients suffering from neurological and psychiatric diseases. Although in many publications, the presence or absence of side effects has been mentioned, overall suggesting a favorable profile, only a few studies applied a systematic method for evaluation of safety outcomes. Moreover, studies primarily aimed to explore safety of the technique are rare. It is also important to distinguish between tolerability and safety in a strict sense. The former describes the presence of uncomfortable and unintended effects, which do not however induce structural or functional damage (e.g., tingling or itching sensations under the electrodes), whereas the latter refers to damaging effects per se. However, both are often reported as adverse events. For clinical trial reporting, the Food and Drug Administration (FDA) defines an adverse event as any undesirable experience associated with the use of a medical product in a patient – this can be further divided into common and serious, the latter referring to patient outcome of death, life-threatening condition, hospitalization, disability or permanent damage, congenital anomaly, need of an intervention to prevent permanent impairment or damage, or other serious, important medical events (notably seizures or convulsions). We here discuss the main issues regarding safety and tolerability of tDCS.

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35.2 Tolerability

35.2.1 Common Adverse Effects

Poreisz et al. [1] collected data from 567 tDCS sessions delivered over different cortical areas from previous studies of their group. They observed that a mild tingling sensation (70.6%) was the most common side effect, followed by fatigue (35.3%), itching

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(30.4%), and, less frequently, headache (11.8%), nausea (2.9%), and insomnia (0.8%). All side effects were mild, short lived, and well tolerated, and for most symptoms, the rate was not different between active and sham stimulation. Brunoni et al., in a systematic review and meta-analysis, collected data from all tDCS clinical studies performed from 1998 to August 2010 [2]. Of 209 studies (172 articles, encompassing almost 4000 subjects), 56% monitored adverse effects and, of those, 63% reported at least one adverse effect. According to the retrieved studies, similar rates of the most commonly reported adverse effects were observed in both active versus sham arms, namely headache, itching, burning sensation, discomfort, and tingling (Table 35.1).

This systematic review also showed, however, that only eight studies systematically addressed the frequency and intensity of adverse effects. In other words, almost all studies failed to systematically report the frequency and intensity of adverse effects. Although this could indicate that these effects might be benign and well tolerated, this also indicates that the prevalence of tDCS-related adverse effects is probably underestimated in literature. Therefore, the authors recommended that all tDCS clinical studies should provide estimates of the frequency and intensity of adverse effects observed.

After this study, Kessler et al. [3] evaluated side effects in 131 subjects undergoing 277 tDCS sessions, finding that sensory side effects were common, of low severity, more common in the active compared to sham tDCS, and included tingling (76%), itching (68%), burning sensation (54%), and pain (25%). In this context, Russo et al. [4] assessed adverse effects and the level of comfort experienced by 149 subjects who received a total of 195 tDCS sessions in a double-blind fashion. The authors reported no serious adverse effects, overall low rate of common adverse effects and also that levels of comfort increased over time, which were distinctly higher (i.e., more comfortable) for sham stimulation. Finally, Fertonani et al. [5] analyzed data from 531 subjects – 693 different sessions – receiving transcranial electrical stimulation (tES; mostly tDCS, but also other forms of stimulation). Similar to other studies, they observed that the most common side effects were itchiness, pain, burning sensation, fatigue, and discomfort, which were mild, well tolerated, and short lived. Since 2015, when the report of Fertonani et al. was published, two more recent evidence-based updates [6] and guidelines [7] on tolerability and safety aspects of tDCS have been published. Typical common side effects observed in these reports include itching, burning sensations under the electrode, or transient mild headaches (Table 35.2).

Table 35.1 Adverse effects of transcranial direct current stimulation

Sensation	Active group	Sham group
Itching	46 (39.3%)	27 (32.9%)
Tingling	26 (22.2%)	15 (18.3%)
Headache	17 (14.8%)	13 (16.2%)
Burning sensation	10 (8.7%)	8 (10%)
Discomfort	12 (10.4%)	11 (13.4%)
Total	117 studies	82 studies

Rate of adverse effects in clinical transcranial direct current stimulation studies. Adapted from Brunoni et al., International Journal of Neuropsychopharmacology, 2011 [2]

Skin Reddening

Another common side effect is tDCS-induced erythema, that is, the reddening of the skin that occurs after tDCS. The intensity of this adverse effect varies in patients; most of them experience only mild redness whereas a few others might have more intense skin reddening. Erythema is due to direct effects of the current on the skin, but may also arise from the physical pressure of the electrode pad, which must be strapped firmly against the skin to ensure good contact. For this reason, redness is also occasionally observed after sham tDCS due to electrode pressure over the skin. Although not particularly uncomfortable for the majority of patients, skin reddening may be a threat to adequate blinding if it occurs more frequently or persistently in the active stimulation condition. The mechanisms involved in erythema induced by tDCS are only partially understood, but this phenomenon seems to be caused by increased blood flow in the dermal vessels that occurs as a direct result of the current application. It may also be due to the release of multiple neuropeptides by primary afferent nerves following noxious and non-noxious stimulation, with secondary release of vasoactive substances, including histamine and prostaglandins [9]. In a study investigating this issue, Guarienti et al. [10] evaluated the effects of 2 mA, 30-min anodal/cathodal tDCS on skin reddening. They observed that the erythema was more promi-

Table 35.2 Summary of studies evaluating common adverse effects

Author	Study design	*N*	Main adverse effects	Comments
Poreisz et al. [1]	Individual patient data	567	Tingling (71%), fatigue (35%), itching (30%), headache (12%)	Most rates were similar in active versus sham tDCS
Brunoni et al. [2]	Meta-analysis	3836	Itching (39%), tingling (22%), headache (15%), burning sensation (9%), discomfort (10%)	Rates were non-statistically higher in active tDCS (vs. sham)
Kessler et al. [3]	Individual patient data	277	Tingling (76%), itching (68%), burning (54%), pain (25%)	Rates were higher in active tDCS (vs. sham)
Fertonani et al. [5]	Individual patient data	693	Itchiness, pain, burning sensation, heat, pinching, iron taste, fatigue, discomfort	Frequency not described, adverse effects' intensity was associated with higher current and larger electrodes
Nikolin et al. [8]	Meta-analysis	4130	Discomfort, dizziness, erythema, fatigue, headache, paresthesia (tingling, itching, and burning sensations)	Frequency not described. Only erythema and paresthesia were significantly more likely to occur in active compared to sham tDCS

nent over the anode than the cathode, although it was mild in both conditions. The erythema was also short lived, lasting less than 18–24 min. Moreover, erythema was less intense in subjects with darker skin color and was not influenced by gender, age, and smoking habits. Finally, the authors observed that erythema intensity was decreased by previous application of topical ketoprofen.

35.2.2 Parameters Associated with Adverse Effects

Several factors influence the perception and intensity of adverse effects. For instance, higher current intensities are usually associated with more adverse effects. In a systematic investigation of the threshold for perception of stimulation, Ambrus et al. [11] observed that, at 0.4 mA, half of subjects perceived the stimulation sensation, whereas at 1 mA, all subjects were able to perceive the stimulation. In addition, composition of electrolyte solution seems to play a role: electrolyte solutions with lower NaCl concentrations (15 mM) seem to be more comfortable during tDCS than solutions with higher NaCl concentrations (220 mM) [12]. Dundas et al. [13] recommended the use of solutions with relatively low NaCl concentration, in the range of 15 –140 mM (i.e., of similar or lesser strength as "normal saline solution" (154 mM), as tDCS at these concentrations is more likely to be perceived as comfortable, requires low voltage, and still allows good conduction of current. Applications of topical analgesics/anesthetics at the site of stimulation may be a promising means to enhance tolerability and to alleviate local adverse effects associated with tDCS [12, 14].

The size of the electrodes may influence discomfort. Turi et al. [15] compared different subject groups that received tDCS with 25 or 35 cm^2-sized electrodes. When current density (averaged across the electrode surface) was kept constant, larger electrodes were associated with greater cutaneous discomfort. However, when current intensity was kept constant, there was no difference. This suggests that higher current intensity is related to more cutaneous discomfort, even when electrode size is increased to compensate. Fertonani et al. [5] in a post hoc analysis of more than 600 tES sessions suggested that both current intensity and electrode size affected discomfort. Ambrus et al. [16] observed that, in contrast, electrode shape does not matter in terms of perception – if both have the same surface area, standard rectangle and circular electrodes induce similar skin sensations.

35.2.3 Acceptability in Clinical Trials

Acceptability is a term used in controlled clinical trials to evaluate the number of dropouts that occur in the experimental treatment compared to the control intervention. Acceptability is low if dropouts occur significantly more frequently in the experimental treatment, since this suggests that the excess dropouts happened due to intolerable adverse effects. It is important to assess if a

new treatment is not only effective but also well tolerated by the patients, otherwise the intervention would only be applied to a restricted number of individuals.

Meta-analyses that investigated this issue by collecting data from randomized, sham-controlled tDCS clinical trials for depression found that the drop-out rate of patients in the active versus sham arms of tDCS was similar [17, 18]. These results suggest that consecutive daily application of tDCS for several days is an acceptable and tolerable procedure at least for depression studies. In fact, studies evaluating acceptability of tDCS for other neurologic and psychiatric conditions did not report a higher rate of dropouts following active stimulation [19].

35.3 Safety

35.3.1 Serious Adverse Effects

No serious adverse events/effects, according to the FDA literature, regarding tDCS have been reported in any tDCS clinical study performed from 2000 onward, including induction of seizure, stroke, cardiac arrest, and other life-threatening events. Moreover, safety studies revealed that standard tDCS does not change heart rate variability at rest [20], does not increase the serum levels of neuron-specific enolase, a brain enzyme associated with neuronal death [21], and does not qualitatively alter electroencephalographic activity [22]. According to the last recent evidence-based update [6] and guidelines [7] on tDCS safety aspects, no serious adverse events are reported across over 32,000 tDCS sessions and 1000 subjects with repeated sessions and over 18,000 sessions administered neurological/psychiatric patients and healthy subjects.

TDCS safety was also explored in animal studies (see corresponding chapter in this book). One important study was performed by Liebetanz et al. [23] that explored the safety limits of tDCS in rats by using increasingly larger current intensities and thereafter performing histological evaluations. The authors found that the threshold necessary to induce brain lesions in rats was 52,400 C/m^2, two orders of magnitude larger than the charge density applied in humans. Although these results cannot be assumed to directly apply to human brain tissue, they corroborate clinical studies showing that the technique is safe when used according to standardized parameters. Stimulation over holes or fissures of the cranial bone (for instance, due to trepanation procedures, skull fractures, brain surgery, and other reasons), which can result in an increase of current density, should be carefully investigated prior to stimulation [24] – for instance, by performing computer simulation studies.

35.3.2 Skin Lesions

Palm et al. [25] reported five cases of skin lesions in a tDCS study on depressed patients. After 5 days of 2 mA stimulation using tap water-soaked sponges, patients presented lesions showing extensive redness and brown crusty lesions under the cathode. Lesions seemed also to be associated with high skin impedance. Frank et al. [26] reported three cases of skin lesions under the anode in patients with tinnitus. The current intensity was 1.5 mA and tap water-soaked sponges were used. Rodriguez et al. [27] reported three cases of skin burn under the cathode. In these cases, saline-soaked sponges were used, and the impedance was adequate. Finally, Wang et al. [28] reported a skin lesion under the cathode after a single tDCS session, using a 2 mA current and sponges soaked in 46 mM NaCl.

To conclude, skin damage caused by tDCS has been occasionally reported. It is unclear whether this adverse effect is more common under the anode or the cathode or which factors increase its risk, although it seems that tap water-soaked sponges and high impedance were more frequently associated with it – in fact, a higher impedance is observed in tap water (vs. saline)-soaked sponges [29]. To avoid this side effect, Loo et al. [30] suggested some precautions, such as screening patients for skin diseases and checking the skin site where the electrode is placed for lesions before each session. The authors also

advised to avoid abrasion of the skin and to ask patients to report during stimulation whether tDCS induced pain; the latter may serve as a potential early indicator of risk of skin damage. This approach, however, may not be fool-proof; Palm and colleagues noting that cutaneous sensation was not related to the development of skin lesions [29].

35.3.3 Safety in Neuropsychiatric Samples

The majority of tDCS studies have been performed so far in healthy participants and not in neuropsychiatric samples, although this number is rapidly changing given the increasing number of ongoing clinical trials. In patients with clinical conditions, not only should the physical adverse events of tDCS be considered but also whether tDCS can cause specific cognitive or behavioral side effects when used in a disorder. For instance, in patients with depression, some cases of hypomania/mania have been reported after tDCS treatment, although it is difficult to infer whether tDCS *caused* these symptoms or they occurred as part of the natural course of the disease [31–33] (see corresponding chapter in this book).

Anodal (excitability increasing) tDCS has not been associated with seizures in healthy subjects, although this event has been reported in two young patients with pre-existing neurological conditions. A 4-year-old male with a history of left dominant spastic tetraparesis and infantile spasms had been seizure-free for 2 years on anti-epileptic medication [34]. Anodal tDCS (1.2 mA, 20 min) was performed over the right paracentral region. Four hours after the third session of stimulation, the patient developed a partial onset seizure characterized by speech arrest, confusion, leftward eye gaze deviation, left arm clonic movements, and secondary generalization, which required administration of intravenous midazolam. The patient's lateralized semiology suggested that the seizure onset was from the frontocentral region, corresponding to the region of anodal stimulation. Importantly, the patient was weaned off the anti-epileptic drug topiramate, 2 weeks prior to commencing tDCS. The partial onset seizure may therefore have been partly due to this change in medication prior to tDCS.

The second case report documented the occurrence of a first generalized tonic-clonic seizure in a 13-year-old subject in the week following tDCS application [35]. Further investigations of the past medical history by the authors showed the presence of daily muscle jerks during wakening over the past 2 years in the patient which was undiagnosed before recruitment, suggesting the diagnosis of juvenile myoclonic epilepsy. In this line, a post-seizure investigation of the scalp EEG in awake and sleep deprivation conditions by the authors showed abnormal patterns (diffuse bilateral abortive spike and wave discharges, eye closure sensitivity, and photosensitivity). Given that the seizure occurred 5 days following tDCS, no causal relationship could be confirmed between the tDCS and seizure. However, the result of this report suggests that patients should be asked about the presence of daily muscle jerks and relevant behavioral indicators (e.g., dropping objects from hand, falls) before inclusion in a tDCS study, and that this symptom should be added as an exclusion criterion. Therefore, though the occurrence of seizures or other serious adverse effects is rare, extra caution may be warranted in neuropsychiatric patients and further studies assessing the safety of tDCS in patients with neuropsychiatric disorders are warranted. Nonetheless, the frequency of adverse effects in these populations is still rare.

35.3.4 Safety of Remotely Supervised tDCS

In recent years, researchers and clinicians have recognized that the portability of tDCS, unique among other noninvasive brain stimulation modalities, allows for home-based stimulation. Advances in technology have ensured that tDCS can be delivered safely without compromising efficacy through remote video observation of treatment sessions and the development of devices that prevent unsafe usage. To reduce the

risk of patients "overdosing" through excessive exposure to stimulation, many tDCS manufacturers now offer devices that can be restricted in the number of sessions or total duration of stimulation allowed per day or can be locked until a code is generated by the tDCS technician. Additionally, improvements in the methodology used to fix tDCS electrodes to the scalp in an accurate and consistent manner through custom-built caps and straps have ensured that patients can receive stimulation as effectively as if they were in a research or clinical setting. Collectively, these advances allow individuals to self-administer tDCS with only minimal intervention from tDCS experts in the form of remote supervision. Experts in the field have developed written and video-based guidelines for tDCS technicians seeking to commence remote-supervised tDCS [36, 37]. These have been put into practice in studies investigating the feasibility of remote applications in clinical applications for various neuropsychiatric disorders, for example, in the treatment of multiple sclerosis [38, 39] and depression [40]. Indeed, a meta-analysis of this nascent development in the tDCS field suggests that side effects associated with home-based tDCS mirror those conducted under research conditions in a laboratory setting [41]. Further research is still needed, including larger randomized controlled clinical trials, investigations of the safety of long-term usage, and feasibility of conducting combined interventions (e.g., tDCS with concurrent behavioral training or psychotherapy). Nevertheless, remotely supervised tDCS presents an exciting opportunity to increase the reach and therapeutic potential of stimulation in clinical populations.

35.3.5 Functional Impairment

Functional safety encompasses the induction of cognitive, behavioral, or other disturbances (particularly permanent function reductions), which are not intended by the application of tDCS. Respective functional distortions might occur because different brain networks interact with each other, and the enhancement of the activity of one region can occur at the expense of a decrease in activity of another one. In one study with healthy subjects, it was shown that tDCS over the posterior parietal cortex enhanced numerical learning whereas automaticity for learned materials decreased. Vice versa, tDCS over the dorsolateral prefrontal cortex impaired the learning process and improved automaticity [42]. Another study in depressed subjects found that a single session of bilateral tDCS over the dorsolateral prefrontal cortex impaired implicit learning acquisition compared to sham [43].

35.4 Contraindications

There are few, relative contraindications for tDCS. As the electrodes are placed over the skin, they should not be placed directly above areas of impaired skin (including areas with chronic skin diseases) to avoid skin damage and skin burn. TDCS should also not be applied directly over areas with implanted metallic plates, or cranial bone discontinuities, to avoid heating or preferential conduction over respective areas. Encouragingly, new research has found that tDCS may not interfere with the performance of some devices located distant from tDCS-induced current flow, including cardiac pacemakers [44]. Nevertheless, care should be taken to place electrodes such that the current pathway is as far from implanted devices, such as deep brain stimulators, as possible. For patients with a history of previous neurosurgical procedures, neurologic malformations, or brain neoplasias, it is proposed that the tDCS current pathways should be modeled for that individual patient – using high-definition, computational forward models based on that patient's head anatomy, reconstructed from MRI scans – to inform on the brain area that will receive most of the electrical current [45]. However, such approaches have not been extensively empirically validated. Likewise, the use of tDCS in specific populations, such as children and pregnant women, should be carefully considered, with recommendations that lower current intensities are used in the young [46]. Finally, there is no data to support the use of tDCS beyond

the standard parameters tested so far in research settings, that is, tDCS sessions given: (a) more than twice daily; (b) more than 40 min per session, or (c) using current densities above 0.125 A/m^2 [12, 14]. In such cases, the protocol should be tested first under controlled settings.

35.5 Safety and Tolerability of tDCS in Children and Adolescents

Although tDCS has been increasingly used in children and adolescents in recent years, the number of currently available studies in these populations is still limited compared to adults. According to a review of tDCS studies up to 2015, less than 2% of subjects who underwent tDCS interventions were under 18 years of age [6]. This would warrant further investigation of tDCS safety in children and adolescents. Furthermore, there are important considerations with regard to tDCS use and parameter adaptation in the developing brain. These aspects are discussed in more detail in Chap. 17. Here, we discuss recent findings and reports of the safety of tDCS use in children and adolescents.

The first comprehensive review of the safety of noninvasive brain stimulation (NiBS; 48 studies), including tDCS (16 studies), in children and adolescents reported redness of the skin, tingling, and itching [47]. Redness was most commonly observed on the electrode sites. Tingling and itching were found to occur at the beginning of stimulation and were the most frequently experienced adverse effects. As with adult populations, these paresthetic effects do not result in structural tissue damage and are not thought to pose any safety issues. No major adverse effects were reported. The results of this review thus support the safety and tolerability of tDCS for children and adolescents. In agreement, the largest comprehensive review so far of tDCS delivered to children, including at least 2800 tDCS sessions applied to nearly 500 individuals, reported no serious adverse effects [6]. A more recent report reviewed 612 tDCS sessions (1 mA stimulation intensity) over the last 10 years (Jan 2009 to May 2018), and also reported that tDCS was well tolerated, without serious adverse events. Mild itching/tingling was reported in 37% of all sessions, supporting the safety and tolerability of tDCS in children [48]. Another recent report of 170 tDCS sessions with higher intensities (2 mA intensity) in adolescents with early-onset schizophrenia reported mild, transient, and well-tolerated adverse effects, including itching (33.3%), burning (33.3%), and tingling sensations (20%), and no serious adverse effects [49]. In addition to these safety-driven reports, recently published reviews of tDCS use in child and adolescent psychiatric and neurodevelopmental disorders [50–52], including autism spectrum disorder [53], and attention-deficit hyperactivity disorder (ADHD) [54] confirm the safety and tolerability of tDCS. The latter review investigated 449 sessions of tDCS (1–2 mA current intensity) in 143 ADHD children and adolescents (from nine studies) and found no reported serious adverse effect, but the usually observed skin sensations (i.e., tingling and itching sensation) [54]. Taken together, the reported side effects are related mainly to the tolerability of tDCS, and deliver no hints for safety issues, such as structural or functional damages as a result of tDCS interventions.

While the published studies to date broadly confirm the overall safety and excellent tolerability of tDCS in children and adolescents, two case reports of seizures occurring in the context of pre-existing neurological disorder have been reported (see above). These reports confirm that epilepsy should be an exclusion criterion for tDCS unless tDCS is intended as a treatment for epilepsy, in which case caution and additional monitoring are required.

Another relevant aspect of tDCS safety in the underaged population is dosage determination, considering the specific anatomy and physiology of the developing brain. Results of computational modeling studies suggest that the induced electrical field in the brain of a child is different from adults. Applying the same electrical current induces higher electric fields in children compared to adults, and results also in different electrical field intensities, dependent on the age of children [55]. A recent systematic review of the

induced electrical field in attention-deficit/hyperactivity disorder patients showed that the required stimulation intensity to generate an electrical field comparable to that achieved in adults (2 mA, 0.8 V/m, 25 cm electrode size, anodal F3 cathodal Fp2) is almost half in children (1 mA, 0.6 V/m) [54]. Although higher electrical field intensities in this range do not necessarily constitute a safety problem, this should be nevertheless taken into account for stimulation protocol designs [55]. Another emerging trend in tDCS studies is focalizing stimulation by use of smaller electrodes, as compared to the relatively large conventional ones. Using smaller electrodes increases current density at least at the level of the skin, if current strength is not adjusted, and might enhance uncomfortable sensations especially in children. Given the higher sensitivity of children's skin, it may be advisable to adjust stimulation protocols and electrode numbers to reduce discomfort during stimulation.

Taken together, the results of increasing numbers of tDCS studies in children and adolescents in recent years support the previously held assumption about the safety and tolerability of tDCS in these populations. Accordingly, the currently applied conventional tDCS parameters (protocols with 0.5–2 mA current intensity, stimulation duration of 10–20 min, up to 10 once-daily sessions) can be rated as safe, considering the absence of serious adverse effects in healthy as well as vulnerable populations, with appropriate screening for seizure risk (as above). At present, no safety concerns have been identified for protocols using higher intensities, durations, and repetition rates. However, the number of available studies is relevantly lower, and thus, respective evidence is weaker, as compared to the adult population. Considering the available reports to date, the use of tDCS in children and adolescents is safe if the general safety rules for NiBS are complied with.

Systematic investigations of the reported side effects with specific focus on relevant parameters (intensity, duration, repetition rate) and long-term monitoring are needed to improve evidence-based information about safety and tolerability. Suggestions for reducing side effects, improving safety monitoring, and increasing transparency of the field include the following: (1) systematic monitoring of the experienced sensations under the electrodes during stimulation by asking for verbal feedback, (2) systematic reporting of the type, duration, and severity (mild, moderate, severe) of adverse effects [56], (3) avoiding high stimulation intensities, where reasonable, as this might produce more painful sensations at the level of the skin, or using topical anesthetics in case of high intensities, (4) and considering developmental aspects for determination of stimulation parameters (e.g., electrode size, between-electrode distance, stimulation intensity) [54, 55].

35.6 Conclusion

Within the standard parameters of use outlined above, available evidence indicates that tDCS is a well-tolerated technique, with few, mild side effects. Although tDCS is considered to be "safe," as the (battery-driven) tDCS device is limited to delivering a low-dose current which has effects on cortical excitability (though not to the extent of directly inducing action potentials), and no major or serious adverse effects for tDCS have been reported, such findings do not imply that tDCS is "universally safe" and should therefore be used without limits or controls. First, there are no data regarding tDCS use beyond the limits commonly used in experimental settings regarding current intensity, session duration, and intervals between sessions. Second, it is possible that tDCS enhances activity in one brain area at the expense of decreasing activity in another brain area – for instance, in a clinical trial in which tDCS presented antidepressant effects, we also found that it prevented implicit-learning acquisition during a probabilistic classification learning task, possibly by decreasing activity in brain areas responsible for implicit memory learning [43]. In this context, it is possible that "wrong" stimulation parameters for several days may have unwanted consequences leading to maladaptive plasticity. Finally, tDCS is a relatively novel technique and longer term follow-up studies are still warranted for fully addressing the clinical safety of tDCS.

Taken together, currently applied tDCS protocols seem to be safe, and well tolerated in adults

and developing populations (children and adolescents). This assumption does not, however, necessarily apply for all tDCS protocols, particularly for those extending beyond tested stimulation parameters and clinical populations. Thus, general statements such as "tDCS is safe" independent from protocol specifications should be avoided. Moreover, this assumption is only valid if common exclusion criteria for tDCS/noninvasive brain stimulation (metal in the head, pacemaker, no stimulation over fissures, or cranial holes, causing locally enhanced current density, excluding patients with epilepsy, if the disease is not the treatment target) are respected. Special consideration should also be given when determining safety and tolerability in children, where parameters safely used in adults may have a different safety and tolerability profile.

References

1. Poreisz C, et al. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 2007;72(4-6):208–14.
2. Brunoni AR, et al. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14(8):1133–45.
3. Kessler SK, et al. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul. 2012;5(2):155–62.
4. Russo R, et al. Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. Brain Stimul. 2013;6(6):946–51.
5. Fertonani A, Ferrari C, Miniussi C. What do you feel if I apply transcranial electric stimulation? Safety, sensations and secondary induced effects. Clin Neurophysiol. 2015;126(11):2181–8.
6. Bikson M, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9(5):641–61.
7. Antal A, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9):1774–809.
8. Nikolin S, et al. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul. 2018;11(2):278–88.
9. Durand S, et al. Prostaglandins participate in the late phase of the vascular response to acetylcholine iontophoresis in humans. J Physiol. 2004;561(Pt 3):811–9.
10. Guarienti F, et al. Reducing transcranial direct current stimulation-induced erythema with skin pretreatment: considerations for sham-controlled clinical trials. Neuromodulation. 2014;18(4):261–5.
11. Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol. 2010;121(11):1908–14.
12. Nitsche MA, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1(3):206–23.
13. Dundas JE, Thickbroom GW, Mastaglia FL. Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes. Clin Neurophysiol. 2007;118(5):1166–70.
14. Brunoni AR, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95.
15. Turi Z, et al. When size matters: large electrodes induce greater stimulation-related cutaneous discomfort than smaller electrodes at equivalent current density. Brain Stimul. 2014;7(3):460–7.
16. Ambrus GG, Antal A, Paulus W. Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. Clin Neurophysiol. 2011;122(4):803–7.
17. Berlim MT, Van den Eynde F, Daskalakis ZJ. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J Psychiatr Res. 2013;47(1):1–7.
18. Shiozawa P, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int J Neuropsychopharmacol. 2014;17(9):1443–52.
19. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. NeuroImage. 2013;85(Pt 3):948–60.
20. Vandermeeren Y, Jamart J, Ossemann M. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci. 2010;11:38.
21. Nitsche MA, et al. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol. 2003;114(4):600–4.
22. Tadini L, et al. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. J ECT. 2011;27(2):134–40.
23. Liebetanz D, et al. Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol. 2009;120(6):1161–7.
24. Bikson M, Rahman A, Datta A. Computational models of transcranial direct current stimulation. Clin EEG Neurosci. 2012;43(3):176–83.
25. Palm U, et al. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul. 2008;1(4):386–7.

26. Frank E, et al. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul. 2010;3(1):58–9.
27. Rodriguez N, et al. Skin lesions induced by transcranial direct current stimulation (tDCS). Brain Stimul. 2014;7(5):765–7.
28. Wang J, et al. Skin burn after single session of transcranial direct current stimulation (tDCS). Brain Stimul. 2015;8(1):165–6.
29. Palm U, et al. The role of contact media at the skin-electrode interface during transcranial direct current stimulation (tDCS). Brain Stimul. 2014;7(5):762–4.
30. Loo CK, et al. Avoiding skin burns with transcranial direct current stimulation: preliminary considerations. Int J Neuropsychopharmacol. 2011;14(3):425–6.
31. Arul-Anandam AP, Loo C, Mitchell P. Induction of hypomanic episode with transcranial direct current stimulation. J ECT. 2010;26(1):68–9.
32. Baccaro A, et al. Hypomanic episode in unipolar depression during transcranial direct current stimulation. Acta Neuropsychiatrica. 2010;22(6):316–8.
33. Brunoni AR, et al. Manic psychosis after sertraline and transcranial direct-current stimulation. J Neuropsychiatry Clin Neurosci. 2011;23(3):E4–5.
34. Ekici B. Transcranial direct current stimulation-induced seizure: analysis of a case. Clin EEG Neurosci. 2015;46(2):169.
35. Splittgerber M, et al. First generalized tonic clonic seizure in the context of pediatric tDCS – a case report. Neurophysiol Clin. 2019;50(1):69–72.
36. Shaw MT, et al. Remotely supervised transcranial direct current stimulation: an update on safety and tolerability. J Vis Exp. 2017;128:e56211.
37. Charvet LE, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. Front Syst Neurosci. 2015;9:26.
38. Charvet LE, et al. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. Mult Scler J. 2018;24(13):1760–9.
39. Charvet L, et al. Remotely supervised transcranial direct current stimulation increases the benefit of at-home cognitive training in multiple sclerosis. Neuromodulation. 2018;21(4):383–9.
40. Alonzo A, et al. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–83.
41. Palm U, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. Neuromodulation. 2018;21(4):323–33.
42. Iuculano T, Cohen Kadosh R. The mental cost of cognitive enhancement. J Neurosci. 2013;33(10):4482–6.
43. Brunoni AR, et al. Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free patients with major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;43C:146–50.
44. Roncero C, et al. Investigation into the effect of transcranial direct current stimulation on cardiac pacemakers. Brain Stimul. 2020;13(1):89–95.
45. Bikson M, et al. High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. Neuromodulation. 2012;15(4):306–15.
46. Moliadze V, et al. Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. Clin Neurophysiol. 2015;126(7):1392–9.
47. Krishnan C, et al. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 2015;8(1):76–87.
48. Zewdie E, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: prospective single center evidence from 3.5 million stimulations. Brain Stimul. 2020;13(3):565–75.
49. Chhabra H, et al. Tolerance of transcranial direct current stimulation in psychiatric disorders: an analysis of 2000+ sessions. Psychiatry Res. 2020;284:112744.
50. Lee JC, et al. Transcranial direct current stimulation in child and adolescent psychiatric disorders. Child Adolesc Psychiatr Clin N Am. 2019;28(1):61–78.
51. Finisguerra A, Borgatti R, Urgesi C. Non-invasive brain stimulation for the rehabilitation of children and adolescents with neurodevelopmental disorders: a systematic review. Front Psychol. 2019;10:135.
52. Grohs MN, Hilderley A, Kirton A. The therapeutic potential of non-invasive neurostimulation for motor skill learning in children with neurodevelopmental disorders. Curr Dev Disord Rep. 2019;6(1):19–28.
53. Osório AAC, Brunoni AR. Transcranial direct current stimulation in children with autism spectrum disorder: a systematic scoping review. Dev Med Child Neurol. 2019;61(3):298–304.
54. Salehinejad MA, et al. Transcranial direct current stimulation in ADHD: a systematic review of efficacy, safety, and protocol-induced electrical field modeling results. Neurosci Bull. 2020;36(10):1191–212. https://doi.org/10.1007/s12264-020-00501-x.
55. Kessler SK, et al. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112.
56. Ciechanski P, Kirton A. Chapter 5 – transcranial direct-current stimulation (tDCS): principles and emerging applications in children. In: Pediatric brain stimulation. Oxford: Academic Press; 2016. p. 85–115.

36 Home-Based tDCS: Applications and Approaches, Design, Feasibility, and Safety

Angelo Alonzo and Leigh Charvet

36.1 Introduction

Until recently, the availability of tDCS for therapeutic applications was limited only to research centers or clinic-based settings with treatment administered by trained staff. Within the past few years, advances in tDCS device and equipment design have enabled an increase in studies investigating the use of home-based, self-administered tDCS in many neurological and psychiatric conditions [1, 2].

There are many features of tDCS, such as portability of equipment, relative ease of operation, and tolerability of side effects, that lend themselves to being more readily adaptable for home use compared to other noninvasive brain stimulation techniques. Despite its potential, however, there remains much to learn about the optimization of therapeutic parameters and whether there should be limits to its use. Support of its wider use, therefore, specifically in the context of home use, should be tempered by an awareness that tDCS is still not yet a fully developed treatment.

Nonetheless, given the burgeoning clinical, commercial, and popular interest in neuromodulation that are more accessible, convenient, and, to some extent, controlled by the end user, consideration of guidelines for the home use of tDCS is necessary. Moreover, the unique challenges to healthcare access due to the quarantine and physical distancing measures imposed by the COVID-19 pandemic have put into focus the need for innovations in telehealth and remote clinical treatments that could potentially lead to enduring changes in practice, minimizing the need for face-to-face appointments, and allowing patients to receive and implement treatment at home [3]. This chapter presents issues for consideration when adapting tDCS for home use particularly with regard to therapeutic applications, operator training, patient safety and monitoring, and device design. Recommendations here are put forward with the view that tDCS will ultimately be more widely available as a treatment option under standard clinical care and supervision.

36.2 Clinical Guidelines

Recognition by professional and governing bodies of tDCS as a clinical treatment is currently limited but growing. For instance, the National Institute for Health and Care Excellence (UK) and the Royal Australian and New Zealand College of Psychiatrists currently recognize emerging

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evidence of tDCS efficacy only for depression [4, 5]. Likewise, an advisory group commissioned by the European Chapter of the International Federation of Clinical Neurophysiology has proposed a Level B recommendation (probable efficacy) for tDCS in major depression without drug resistance as well as in addiction/craving [6]. Probable or possible efficacy has also been recognized for some neurological conditions including fibromyalgia and neuropathic pain [6].

Notwithstanding, all such guidelines acknowledge that further research is needed to develop tDCS treatment protocols to enhance its efficacy and further evidence is needed to support the use of tDCS for other conditions. In addition, in recognizing the adaptability of tDCS for home use, there is a consensus that tDCS should only be administered under the clinical supervision of a qualified health professional (e.g., medical doctor) trained in tDCS principles, and patients be informed of the current evidence base for tDCS, to safeguard against inappropriate applications.

In the United States, tDCS remains for investigational use only. tDCS has not gained approval for clinical use and also generally does not meet institutional criteria to be considered for compassionate use. This regulatory status does not reflect an evaluation of efficacy by the Federal Drug Administration (FDA), but instead is pending a response to commercial interest. There are two potential FDA pathways to market: a premarket approval (PMA) or a 510(k) clearance. The PMA is an extensive process that requires the collection of both safety and efficacy data, and has not yet (as of June 2020) been issued for any tDCS device. For the less rigorous 510(k) clearance, the device must be demonstrated to have the same intended use and technical specifications as a device currently on the market, without the requirement for safety and efficacy data. tDCS devices have been cleared through the 510(k) pathway, based on iontophoresis devices that were on the market prior to the establishment of the PMA regulations. However, this clearance does not provide the option for indicated clinical use and the corresponding option for billable codes for healthcare reimbursement, for either on- or off-label use. With commercial PMA applications pending FDA review, the future regulatory status of tDCS in the United States is likely to evolve in the near future.

36.3 tDCS for Home Use

tDCS is typically administered via battery-powered devices that can be easily hand-held. Due to their portability, tDCS devices (including their attendant equipment – electrodes, cables, and headgear) have the most potential of all brain stimulation techniques for distribution and use outside clinical centers (see Fig. 36.1 for examples). Although operation of tDCS devices is not particularly complex, operation has been further simplified to as simple as pressing a start button as stimulation parameters (i.e., current intensity, duration, and number of sessions) can be preprogrammed. This allows clinicians to ensure that the stimulation applied is kept within standard protocols that are known to be safe and prevents patients from using the device beyond their prescribed course.

When adhering to standard stimulation parameters based on investigational use to date (typically no more than 2.5 mA and 30-min duration), repeated sessions of tDCS are known to have a benign side effects profile and are well tolerated [7, 8] (also see Chap. 17 of this book that discusses safety aspects of tDCS). The most commonly reported side effects include tingling, skin redness, itching, and/or a heat sensation at the electrode site. Side effects do not normally last beyond the stimulation period but if so (e.g., headache, dizziness, and fatigue) [7, 8], are usually transient and rarely require specific treatment. Provided that patients follow standard operation, are made aware of common side effects, and are aware of reporting procedures and instructions for seeking help should an adverse event arise, tDCS administered at home should be as safe and well tolerated as tDCS administered in research and clinical centers.

Costs of tDCS equipment and administration also compare favorably to other brain stimulation techniques. As tDCS as envisaged for home use can be self-administered, there are no costs asso-

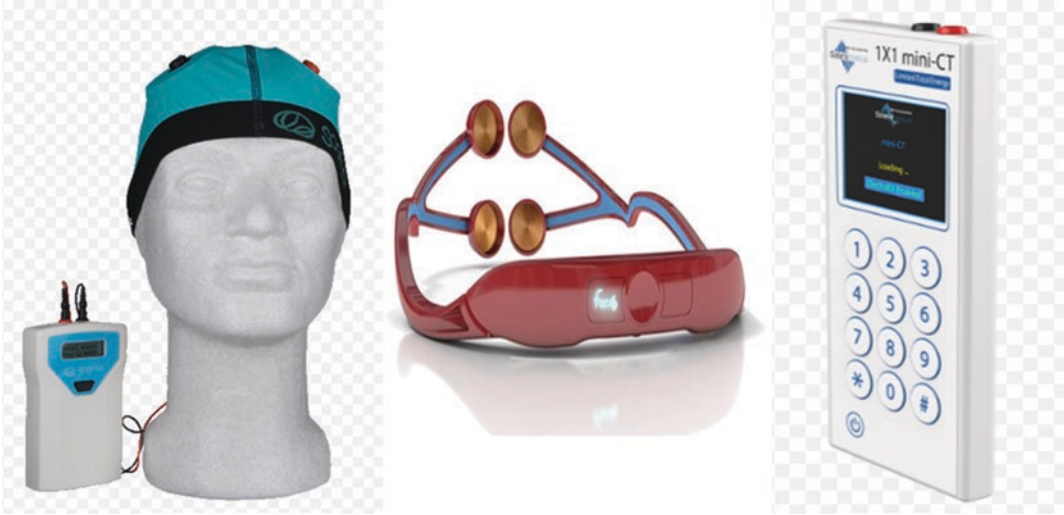

Fig. 36.1 Examples of tDCS devices developed for self-administration either autonomously or under clinical supervision

ciated with clinic staff or facilities nor costs of travelling to and from a treatment center, which usually involves attending every weekday for several weeks. Home-based tDCS would also afford greater accessibility for patients living in remote areas or patients who are less mobile or home bound, thereby encouraging better treatment adherence. With the cost of a home-based tDCS device and consumables costing much less than other brain stimulation devices, its relative affordability makes it a viable option for a greater number of people as a treatment that can be purchased outright or rented and used as needed under clinicians' guidance.

36.4 Clinical Applications of Home-Based tDCS

A relatively recent survey of do-it-yourself (DIY) tDCS users has found that although the majority of respondents (59%) used tDCS for cognitive enhancement and treatment, of those who used tDCS to treat a medical condition, the most common medical condition was depression (58%), followed by attention deficit hyperactivity disorder (15%), pain (13%), obsessive-compulsive disorder (6%), and stroke (6%) [9]. This study, conducted in 2013–2014, included use of two major DIY tDCS internet websites (www.reddit.com/r/tDCS and www.diytdcs.com) subscribed by DIY tDCS users to conduct: (1) an online questionnaire survey to which 121 people responded, (2) a content analysis of web postings on DIY tDCS, comprised of 825 postings and 4756 comments, and (3) five in-depth interviews with users who were identified as being able to provide a general overview and information on DIY tDCS users. Although preliminary, such findings not only bring to attention the use of tDCS among healthy people as well as unwell patients for some conditions that currently have little data to support the use of tDCS but also highlight a need for more rigorous studies to assess tDCS efficacy that can also contribute toward the development of protocols and guidelines for the protection of users.

The past few years alone have shown promising steps in the rapid growth in protocol-guided, home-based tDCS studies investigating its use for neurological and psychiatric conditions [10]. There is also growing evidence supporting the use of home-based tDCS for treatment of a range of neuropsychiatric symptoms and in the context of rehabilitation, especially when targeting extended dosing regimens [2].

In neurological conditions, there have now been many completed trials in many disorders

demonstrating the feasibility of home-based tDCS to test the benefits of repeated treatment for improving symptoms, either alone or in combination with rehabilitative exercises. For example, randomized sham-controlled trials have used home-based tDCS to demonstrate cognitive improvement in Alzheimer's disease ($n = 17$, 6 months of daily treatment) [11], reducing pain and other symptoms of fibromyalgia ($n = 20$, 60 daily sessions) [12], reducing tinnitus severity ($n = 35$, 10 daily sessions) [13], reducing fatigue in multiple sclerosis (MS) ($n = 28$, 20 daily sessions) [14], increasing arousal in minimally conscious state ($n = 37$, 20 daily sessions) [15], and improving upper extremity functioning following stroke ($n = 15$, 5 daily sessions) [16]. Additional studies have used home-based tDCS in single-blind and randomized crossover designs for improving dizziness in *Mal de Debarquement* syndrome ($n = 24$, 20 daily sessions) [17], increasing recall in mild vascular dementia ($n = 21$, 4 daily sessions) [18], and reducing trigeminal neuralgic pain ($n = 10$, 14 daily sessions) [19].

Open-label studies have utilized home-based tDCS to demonstrate improvements in cognitive functioning in Parkinson's disease [20, 21] and MS [22] and pain in fibromyalgia [12, 23]. Taken together, this body of work provides a supportive framework for the feasibility of home-based tDCS in even those patients with more advanced age or more severe levels of neurological impairment. tDCS including home-based use is also emerging as an adjuvant therapeutic option particularly in the context of cognitive and motor rehabilitation [2, 10]. However, many questions remain to achieve and maintain optimal clinical benefits, particularly in terms of dosing parameters. Home-based tDCS will continue to be a valuable tool in reaching participants and providing the number of treatments needed for studies to provide the answers.

In contrast to clinic-based tDCS studies, there have been far fewer studies that have investigated home-based tDCS for psychiatric applications and no randomized, controlled trials to date. The few studies that exist, however, suggest home-based tDCS for conditions such as depression and hallucinations in schizophrenia is feasible, safe, and as well tolerated as previous, clinic-based studies [24–28]. In an open-label pilot trial to treat depression [24], participants were trained and credentialed by research staff before self-administering daily tDCS at home over 4 weeks followed by a 4-week taper phase of 1 tDCS session per week. Depressive symptoms improved significantly up to at least 1 month after completing the acute daily sessions. Side effects were typical of tDCS (e.g., tingling, burning sensation, skin redness, and itching), predominantly mild and transient, and comparable to clinic/research center-based tDCS [29, 30]. Treatment adherence was excellent, with a 93% completion rate.

Further, two case reports of home-based tDCS for hallucinations in schizophrenia support the safety and efficacy of tDCS on a long-term basis [25, 26]. In one report, a schizophrenia patient with severe, clozapine-refractory auditory hallucinations received daily to twice-daily tDCS at home for at least 3 years with symptoms worsening only when the frequency of sessions was reduced [25]. Moreover, at the time of publication, treatment was still ongoing, supporting the viability of extended home treatment with tDCS. Despite these findings, however, further studies are evidently needed to confirm the efficacy of home-based tDCS.

36.5 Models for Providing Home-Based tDCS

As opposed to self-directed home use (e.g., a patient or participant using tDCS on their own), there is consensus among investigators for ongoing monitoring and supervision for either clinical or research use of home-based tDCS [31, 32]. In initial consensus guidelines [31], conditions for home use were described to ensure patient or participant safety and tolerability, recommending ongoing monitoring to ensure that the tDCS was used as intended and for reliable and uniform dosing in study protocols. These were refined following implementation across studies [32]. Central to these recommendations is specially designed equipment that both carefully regulates and records use. Extensive training pro-

cedures and safety checks at each step overseen by a study technician can guide safe application to ensure the safest and most tolerable use. In a systematic review of home use of tDCS [2], while the specific protocols varied across trials, the studies with ongoing supervision (e.g., with each session) had markedly high compliance and completion rates (e.g., >90%).

In the treatment of neurological disorders, an example of these guidelines is with the rigorous remotely supervised or RS-tDCS protocol, in which all tDCS is provided with a real-time technician supervising all aspects of use via live videoconference [33–35]. In this telemedicine platform, patients or participants are first cleared for safe use, guided for correct headset placement, and then provided a one-time use "unlock" code for their device (Soterix mini-CT) to deliver a preprogramed dose (set for intensity and duration, and can include delivery of sham stimulation for controlled trials). Using a structured "stop" criteria, participants are monitored for side effects before, during, and after the stimulation. Any session in which pain is reported (reaching a "7" on a scale of 1–10) is immediately aborted. The RS-tDCS protocol has been used in trials demonstrating the benefit of tDCS for the treatment of fatigue [14] and cognitive impairment [22] in MS and Parkinson's disease [20, 21], with several large randomized controlled trials currently underway to treat fatigue and improve cognitive and motor functioning. Given that the MS population represents patients across a broad range of age (e.g., 18–80 years in the studies) and neurological disabilities (minimal to severe cognitive and/or motor involvement), the protocol has been demonstrated to be generalizable for use across most neurological disorders. RS-tDCS has been used to demonstrate feasibility and initial benefit in Parkinson's disease [20, 21] and in conditions such as cerebellar ataxia [36], following ECT [27], post-stroke aphasia [37], and traumatic brain injury [38] among others. The protocol is also now in use at a site in the United States for clinical telerehabilitation of cognitive and motor impairments on a limited exception basis.

Another option is adapting a more individualized approach, combining initial supervision of sessions either in the clinic or remotely with video monitoring, and then graduating the participant to more self-directed use with additional real-time monitoring conducted as needed [24, 28, 39, 40]. This approach entails less intensive real-time monitoring by the treating team but would still crucially involve monitoring via other avenues to ensure treatment compliance and safety. Monitoring may include participants' self-directed use reported in a treatment diary [15, 19, 24], a daily check via phone or email [17], and/or automatic usage logs stored on the tDCS device or linked to a central server managed by the treating team [11, 41, 42]. These monitoring aims may also be combined into one modality as recently reported by a study of home-based tDCS to treat mild cognitive impairment that used a smart phone application as a platform by which device operation was detected, patients reported safety information, and remote support was provided via phone/video communication [40]. Such modified approaches have now been trialed and found to be feasible for a number of conditions including pain conditions [39, 41, 42], Alzheimer's disease [11], mild cognitive impairment [40], hallucinations in schizophrenia [25, 26], Mal de Debarquement syndrome [17], tinnitus [13], depression [24], and chronically ill patients [15, 28], with some studies demonstrating feasibility, safety, and efficacy over an extended treatment period ranging from 6 months in clinical to over 3 years in individual cases [11, 25, 26].

With home-based tDCS now being trialed in various clinical applications and contexts, the degree of monitoring may depend on the treatment protocol, risk assessment of the condition being treated, individual patient characteristics as well as available technology. Treatment protocols that involve administration of tDCS with a concurrent task as part of the therapeutic approach may be more likely to necessitate real-time monitoring for every session [20, 22, 43, 44] while other approaches that use home-based tDCS as the sole treatment may require less real-time monitoring, especially with experienced patients provided that appropriate clinical oversight and monitoring are maintained. Overall, however,

in-person training before home use along with monitoring in real time for each home session has been found to lead to the highest study retention and completion rates [2, 12].

36.6 Device and Equipment Design

Besides some differences in approaches to monitoring protocols, present devices also vary in terms of strict dose control. Most tDCS devices have been primarily designed for clinician-administered stimulation within the context of a medical or research setting. However, the rapidly growing interest in home use necessitates devices that lend themselves to self-administration and take into consideration practical design issues as well as additional safety features. This has resulted in increased development of devices that can be used away from the clinic, typically including a meter to control stimulation delivery outside of prescribed use (e.g., one-time use unlock code to operate, stimulation delivered at a prescheduled time).

As described in consensus guidelines for home use of tDCS in clinical and research applications [31, 32], devices should meet regulatory requirements for commercial medical devices as a compromise in quality standards could lead to reduced overall safety and unanticipated side effects. Maintenance of these standards should also provide assurance that findings from clinical studies may be applicable to home-based use. Device safety features should include measures to restrict use within prescribed limits; that is, manual alterations of the intended stimulation parameters should be prevented by, for instance, locking devices to specific stimulation parameters (e.g., current intensity, duration, number of sessions).

In terms of design, devices should feature large, clearly labelled buttons and cable slots for easy operation, and be accompanied by plainly written but comprehensive directions for use. The device interface should include an easily readable screen to monitor device performance with helpful readouts such as the stimulation time remaining, current intensity, and impedance in real time. A dynamic impedance readout in particular will allow the user to be continuously aware of their "dose" quality and if in case of any irregularities, discontinue stimulation or make adjustments according to prescribed guidelines. For safety, it is necessary to include a feature to immediately abort the stimulation to allow the user to safely terminate at any point. As an additional safety feature, devices could also be designed to either be paused or automatically power down if abnormalities in impedance are detected. To preserve battery charge, devices should automatically shut off after a specific period of inactivity.

Headset design and electrode placement is an equally important consideration for home-based administration. Size of the headset is important to ensure proper fit and can be confirmed on-site before providing for home use. Electrode placement is one of the critical determinants in achieving behavioral results [45]. If incorrectly positioned, unanticipated negative side effects may occur, including the reversing of polarity that could lead to unintentional disturbance of certain functions [46]. However, with proper supervised guidance, including visual markers on the headset to confirm placement, self-placed headsets have been shown to replicate the same current flow as when placed on-site by lab staff [47].

Also important for headset design is the electrode montage to be used. Some montages would be more readily self-administered than others such as a bifrontal montage in which the user can directly see the electrode positioning in a mirror and make adjustments as needed. A montage in which electrodes need to be placed on the occipital or temporal area would be more difficult to directly check, though not impossible with, for example, the use of a second mirror to enable a rear view. However, the electrode placement process for any montage could be facilitated by having a headset specifically designed for the montage to be used where electrodes can be fastened onto the headset at particular sites possibly standardized according to the 10–20 EEG system. Training users to identify key anatomical landmarks such as the nasion and inion as addi-

tional reference points should also assist in the relative positioning of the headset and electrodes. As technology continues to advance, augmented reality applications may become available to guide precise self-positioning of electrodes.

Regarding electrode preparation, it would be important to have a standardized procedure for moistening the electrode sponges with saline as the recommended conducting solution. Electrode sponges that are too dry could lead to poor conductance or skin discomfort at the electrode sites. Conversely, excessive moisture could lead to the current being shunted away from the intended target, unintentional weakening of the current intensity by being diffused over a wider area, or even a distant skin lesion not located at the electrode site [48]. To facilitate adequate moisture, sponges could be provided pre-moistened with saline and in sealed plastic until opened for use, or at the very least, the saline could be premeasured via syringe. Sponges could also be designed to indicate (e.g., by change of color), when optimal saturation has been reached.

Additional considerations for supervised home use of tDCS include the supporting equipment [49], especially when the tDCS is to be paired with a rehabilitative activity (e.g., for cognitive or motor rehabilitation). At the minimum, patients and participants will need a computer or phone connected to the Internet to facilitate Health Insurance Portability and Accountability Act (HIPAA) compliant communication with clinical lab staff. It is ideal to complete a tDCS and technology training and orientation on-site, including administration of first treatment session, before sending the user home. In addition, particularly for patients who have greater challenges (e.g., older in age, less computer literacy, cognitively impaired), clinical lab staff may travel to the participant's home to ensure adequate setup for home use [2, 32].

tDCS has a growing DIY community with many instructions for the design and use of devices already available on the Internet. These devices can be purchased directly without a prescription, training, or supervision. The potential safety concerns are apparent, and their unsupervised use is not advisable given that there is an absence of safety standards with regard to prevention of device malfunction, governance to prevent overuse, and sanitary practices [50]. Some devices on the market may meet minimal manufacturing standards and/or include safety features (e.g., meters to prevent overuse), but little is known concerning their design and safety apart from information provided by the companies. Any claims for benefit may be made independent of any governing oversight in some countries as there is no regulation of these devices or any certification process. These direct-to-consumer devices in the United States are not currently regulated by the US FDA, and any stated therapeutic claims or guidance for therapeutic use remain unverified. Despite the ongoing marketing, few devices have been directly studied in clinical trials. Therefore, the safety, tolerability, and reliability of the use of the commercial devices remain largely unknown.

36.7 Patient Selection and Contraindications

While patient- and condition-specific criteria such as symptom profile, severity, and comorbid conditions will determine the suitability of home-based tDCS in addition to the current evidence base for a specific condition, there are a number of common criteria that should be considered when assessing patient suitability.

The most practical consideration is the likelihood of the patient adhering to the prescribed course and capacity to self-administer or receive tDCS from a care provider as failure to meet basic treatment requirements would result in suboptimal, if not ineffectual, treatment at best. Of greater concern, although there are few absolute contraindications that would preclude a patient from receiving tDCS, there should be particular note of conditions that could interfere with the normal current flow or affect the conductance. The presence of metal or implanted medical devices in the head is widely accepted as absolute contraindications as their conductivity can affect current density and/or shunt the current away from the intended target. A history of seri-

ous brain injury or neurological surgery can be considered more on a case-by-case basis depending on the location and extent of anatomical changes as the size of skull defects could influence the distribution of peak cortical fields [51]. Other conditions such as history of headache or migraine, stroke, or seizure would not necessarily be considered absolute contraindications but may be application specific as such conditions may themselves be the target for tDCS treatment.

Attention should also be given to any existing skin disorder and the condition of the scalp particularly at the intended electrode sites as skin burns can result from multiple tDCS sessions applied to the same scalp area if skin integrity is compromised [52, 53]. tDCS should not be applied if there are skin breakages, lesions, cuts, rashes, acne, pitting or excessive sensitivity, and dryness at the electrode sites as the current may become focalized around the damaged area and potentially result in skin burns. Even using a lower current intensity to that originally intended would not be advisable as there is no guarantee that this will prevent further damage. However, as there is some degree of latitude with tDCS to slightly adjust electrode positioning without drastically changing the resultant stimulated cortical area, the electrodes could be moved if appropriate to avoid directly stimulating the affected skin.

There are no medications that are contraindicated for use with tDCS although the effects of certain medications should be considered when assessing the likelihood of tDCS benefitting a patient. Benzodiazepines have been associated with a worse outcome in depressed patients receiving tDCS [54] although the exact mechanism by which they modulate tDCS effects has not been fully elucidated and could depend on a combination of factors such as their effect on GABA receptors and downstream modulation of remote cortical and subcortical areas [55]. Carbamazepine and flunarizine have been found to selectively eliminate the excitatory effects of anodal tDCS, while dextromethorphane prevented induction of prolonged effects of tDCS irrespective of polarity [56]. These results suggest that any medications that affect neuroplasticity via actions on sodium and calcium channels as well as NMDA receptors could modulate tDCS effects. However, whether concurrent use of such medications is permitted would depend on the intended use of tDCS as mitigating or potentiating effects of anodal or cathodal tDCS could have specific beneficial applications.

36.8 Training and Credentialing

While tDCS devices developed for home use have been designed to make electrode placement as simple and reliable a process as possible via headbands or caps to fasten the electrodes, it is nonetheless recommended that patients at least attend an initial training and credentialing session before being approved to take home a tDCS device. The purpose of such a visit would not only be to ensure that a patient can competently operate a tDCS device and safely administer tDCS but also to give the patient a working knowledge of tDCS principles and safety as well as giving an opportunity for the overseeing clinician to address aspects of the tDCS procedure and technique that may be specific to the patient.

Patients should first be given a demonstration of how the tDCS device is set up and operated, familiarizing them with the device features and interface as well as use and maintenance of the associated equipment (i.e., headband, cable leads, electrodes, sponge sleeves, and saline solution). This would also include checking the equipment for wear and tear that could affect stimulation quality such as oxidation and residue forming on the leads, and tears or scratches on the electrodes.

Demonstration of the actual tDCS procedure should cover routine preparation for tDCS such as checking the scalp sites for any skin irritation or breakage, gently swabbing the skin with alcohol swabs to remove surface oils or dirt, and preparing the sponge electrodes in the conducting solution (usually saline). Correct electrode

and headband placement should then be demonstrated with particular attention on ensuring consistent positioning of the electrodes as well as maintaining firm and even contact between the entire surface area of the sponge electrode and the scalp. As tDCS devices for home use are designed to automatically run pre-programmed parameters once started, the only routine procedures for patients to follow during tDCS would be to periodically add saline to the sponge electrodes to avoid drying and maintain conductance, wipe dry any excess saline dripping from the sponge electrodes as this may lead to reduced current density at the intended target site or even a skin burn away from the electrode site [48], and check the stimulation contact quality (if available via the device readout).

To formalize the training process and ensure consistent standards, a credentialing session may then be conducted to assess the patient's demonstrated competence against specific criteria, which may include items outlined below.

Skin and Electrode Preparation
- Parting hair to expose stimulation area and gently wiping the skin with alcohol swabs
- Checking skin for irritation and breakage
- Checking equipment for wear and tear
- Preparing sponge electrodes with the appropriate amount of saline solution
- Attaching the sponge electrodes onto the headband
- Placing and securing the band on the head with the electrodes in the correct position and orientation
- Adjusting band placement and tightness as needed

Machine Preparation
- Connecting the cable leads to the tDCS device
- Connecting the leads to the electrodes
- Understanding the electrode contact quality readout (if available) and adjusting the electrode and headband setup if needed
- Activating the stimulation session

During tDCS
- Monitoring contact quality
- Adding appropriate amount of saline at designated intervals
- Drying excess saline

After Stimulation
- Removing the headband and electrodes
- Rinsing and cleaning equipment

Following satisfactory completion of training and credentialing, patients may also be supplied with a treatment diary (hardcopy or electronic) to record the date/time of their treatment sessions and any side effects experienced. The diary may also include a procedural checklist that patients can follow and check off in sequence as they self-administer tDCS.

It is also recommended that the patient undergoes their first tDCS session at the initial training/credentialing visit so that the patient is familiarized with the typical sensations of tDCS (e.g., tingling, itching) and be monitored by a clinician to assess how well the treatment is tolerated and whether any unexpected side effects emerge. On the very rare occasion, a patient's skin may be particularly sensitive to the point where the patient is unable to tolerate the paresthetic effects of tDCS even beyond the first few minutes of stimulation. In such a case, the availability of a clinician is ideal in order to quickly assess the viability of proceeding with treatment and whether use of a topical cream designed to reduce skin discomfort [57] would be beneficial. Any other concerns the patient may have about the procedure can also be immediately addressed.

36.9 Ongoing Monitoring and Oversight

Patients should remain under the supervision of a clinician during a course of home-based tDCS. This oversight is important for technical and safety reasons. For patients inexperienced

with tDCS, even after being credentialed to take a device home, there can still be a learning process to streamline the device setup and operation. Oversight and coaching via real-time monitoring can greatly assist in this learning process especially during the first few home-based tDCS sessions while ensuring the treatment can still be administered reliably in the patient's home environment. Whether ongoing monitoring is required for all subsequent sessions or only as needed (e.g., instances where a patient encounters a technical problem or experiences unusual side effects) may depend on the treatment prescribed. For example, if the patient is required to undertake a concurrent task during tDCS, real-time monitoring for all sessions may be necessary to oversee administration of the concurrent task or verify the data being collected [22].

Periodic monitoring by a clinician during the tDCS course is also important to check for adverse or unintended effects of the stimulation and other possible changes in the patient's status where continued stimulation may not be beneficial. Furthermore, as stimulation may also be administered concurrently with other treatments, the monitoring process should include checking for potential unexpected interactions (e.g., with a medication) [58].

Monitoring of efficacy outcomes has also been recommended in clinical guidance issued by some professional bodies especially in the context of further building the evidence base of tDCS for clinical use [4, 5]. It may, however, be difficult for a patient to objectively evaluate their degree of improvement. Therefore, change in clinical or cognitive functioning may best be assessed by a clinician-administered scale conducted at least prior to starting a treatment course and then following course completion.

36.10 Patient Safety

The primary safety considerations with home-based tDCS relate to ensuring the safe administration of tDCS in the patient's home environment and their health and welfare during the treatment course. When approved to use a tDCS device at home, patients should be given a list of standard safety precautions to minimize any risk of harming themselves or damaging the tDCS device. Such a list may include the following:

- When administering tDCS, the rubber electrodes must always be covered by the sponges and never directly in contact with the scalp as this could lead to skin burns. Typical tDCS side effects such as tingling or itching should never be painful. If any pain is concentrated in one area, stimulation should be aborted immediately. The headband should be removed and skin checked for any redness or discoloration. The treating team should be notified before proceeding any further.
- tDCS will automatically stop if the contact quality between the sponge electrodes and scalp drops to a critical level. The current intensity will quickly drop to zero and transient light-headedness or even a phosphene flash may be experienced. In such an event, such symptoms are not unusual, but the treating team must be contacted so that the cause of the poor contact quality (e.g., insufficient contact between sponge electrodes and scalp; rubber electrodes cracking; wear and tear on the leads) can be investigated.
- Over repeated use or after rough handling of the rubber electrodes if inserting into or taking out of sponge sleeves/covers, the rubber electrodes may start to scratch or tear. This can lead to poor contact quality and tDCS not able to be initiated. At the start of each session, the rubber electrodes should be checked for any tears and the treating team notified if any are present before proceeding any further.
- Avoid spilling any liquids on the tDCS device. The device should not be used if it has been exposed to any liquids and the treating team notified if this has occurred.
- The tDCS device should be kept on a flat, secure surface during tDCS and sudden head movements should be avoided as this could

lead to pulling on the cables, causing the tDCS device to fall if not secured.
- tDCS should not be administered over skin that is irritated or damaged including any cuts, scars, scratches, or pimples as this could lead to the current becoming concentrated in one area and potentially causing skin burns. The treating team must be notified if any of these are present at the electrode sites.

As part of a patient's treatment diary, a structured questionnaire checking for typical side effects that may arise during or after tDCS should be included with patients instructed to record the presence/absence of each side effect as well as the severity and duration. Any side effect that is rated as severe or atypical of tDCS, regardless of whether the patient feels it is related to the tDCS treatment, should be reported and assessed by the treating team before any further tDCS sessions are administered.

tDCS is a low-risk procedure and is not expected to cause serious adverse events. However, guidelines that help patients to identify and document adverse events may be useful in managing any potential risks. An adverse event may be defined as any untoward medical occurrence that is temporally associated with the use of tDCS regardless of whether it results in the patient's hospitalization. Any worsening of a pre-existing condition may also potentially be considered an adverse event. Occurrence of any adverse event should be reported by the patient to the treating team and assessed before any further sessions are conducted.

As patients will be receiving tDCS as a treatment for an existing psychiatric, neurological, or other health condition, clear instructions should be communicated to patients, their families, and/or carers in case of an emergency. While details of the safety plan may be specific to the patient's condition, information regarding an emergency contact number and contact details for the nearest clinic or hospital should be provided in the event that the patient may not be able to obtain immediate help from their primary treating doctor.

36.11 Further Approaches Using Home-Based tDCS

While there is growing evidence that tDCS as a stand-alone treatment is efficacious for some conditions such as depression [59], as with tDCS treatment in general, home-based tDCS requires further investigations to optimize treatment parameters. Its capacity to be self-administered, in particular, may facilitate such investigations by allowing researchers to provide greater convenience and accessibility to tDCS for patients and therefore recruit potentially more representative clinical samples, while also reducing the demand on staff resources that face-to-face treatment sessions would entail.

One approach to enhance tDCS efficacy has been to administer it as a concurrent treatment. At least for the treatment of depression, some studies support the use of tDCS in combination with some antidepressant medications as a better treatment than either one alone [60, 61]. Other studies have investigated additional avenues to further enhance the antidepressant efficacy of tDCS by combining it with a psychological therapy such as cognitive behavior therapy or a cognitive training task with positive results [62–64], the rationale being that by administering a concurrent activity that engages the same brain regions targeted by tDCS, synergistic antidepressant effects may be produced. A similar approach has been implemented in other clinical applications with promising findings including combining tDCS with cognitive training to treat cognitive impairment in multiple sclerosis [22] and motor symptoms in Parkinson's disease [20], mindfulness-based meditation or physical therapy for pain [44, 65], notched music training for chronic tinnitus [66], and occupational therapy for motor impairment [16]. However, such studies are typically characterized by an open-label design with small sample sizes and there have been some mixed findings [67, 68]. More rigorous, randomized, controlled trials are needed to assess the added benefits of using tDCS as an adjunct treatment but by enabling a completely decentralized treat-

ment delivery, home-based tDCS is well placed to support the feasibility of such investigations.

Aside from being utilized as the primary, acute treatment, tDCS may also have the potential to be used as a maintenance treatment following response to another treatment technique. There is already evidence that tDCS can be effective as a long-term maintenance or ongoing treatment following initial response in conditions such as depression and hallucinations in schizophrenia [25, 26, 69, 70]. tDCS has also been trialed on an extended basis to treat fibromyalgia [12], cognitive decline in Alzheimer's disease [11, 71], and a case of cerebellar ataxia [36] with encouraging results. However, a case series of six patients [72] investigating if another type of brain stimulation treatment, transcranial magnetic stimulation (TMS), could be a viable substitute for maintenance electroconvulsive therapy (ECT), offers a treatment paradigm by which tDCS could also be potentially utilized. In this study, self-reported outcomes indicated all patients, following response to a course of ECT, maintained or improved their clinical state up to at least 6 months with maintenance TMS although two patients had relapsed by 9 months. To date, no trial has directly compared the relative efficacy of TMS and tDCS. However, if found to be comparable, tDCS, as a maintenance treatment, can offer the added advantage of a more affordable, easily accessible alternative due to it being more amenable for home use. Moreover, having a home-based device may afford a clinician greater agility in adjusting their patient's tDCS "dose" (specifically, the frequency of sessions) in response to any symptom fluctuations as treatment would not depend on the patient's ability to travel to a treatment center nor on the availability of clinic staff. tDCS has also been trialed with other conditions to maintain improvement following initial treatment with other modalities including in prior responders to TMS to treat neuropathic pain [42] or Mal de Debarquement syndrome [17], patients undergoing methadone maintenance treatment following opioid dependence [73], and recently abstinent cocaine-dependent users [74]. To this point, such studies have been exploratory, and findings vary in terms of whether further trials of tDCS maintenance treatment are warranted, but if promising, home-based tDCS would be well placed to offer a sustainable and safe maintenance treatment as needed.

Among brain stimulation techniques currently available, tDCS is best positioned to be made available as a home-based, self-administered treatment option. Provided that tDCS devices intended for home use can be designed to ensure reliable and consistent delivery of stimulation in a less controlled, non-clinical environment, tDCS has the potential to be an easily accessible and affordable treatment for a broad range of patients who may be limited from accessing other clinic-based treatments due to distance, cost, or time constraints. Given these prospects and the burgeoning interest from consumers, larger scale randomized, controlled trials of home-based tDCS are greatly anticipated.

References

1. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Worsching J, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. Neuromodulation. 2018;21(4):323–33.
2. Sandran N, Hillier S, Hordacre B. Strategies to implement and monitor in-home transcranial electrical stimulation in neurological and psychiatric patient populations: a systematic review. J Neuroeng Rehabil. 2019;16(1):58.
3. Bikson M, Hanlon CA, Woods AJ, Gillick BT, Charvet L, Lamm C, et al. Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. Brain Stimul. 2020;13(4):1124–49.
4. Royal Australian and New Zealand College of Psychiatrists (RANZCP). Clinical Memorandum: Transcranial direct current stimulation (tDCS) 2018. Available from: https://www.ranzcp.org/files/resources/college_statements/clinical_memoranda/cm-transcranial-direct-current-stimulation-(tdcs).aspx
5. National Institute for Health and Care Excellenece. Transcranial direct current stimulation (tDCS) for depression: Interventional procedures guidance [IPG530] 2015. Available from: https://apastyle.apa.org/style-grammar-guidelines/references/examples/clinical-practice-references
6. Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial

direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.
7. Chhabra H, Bose A, Shivakumar V, Agarwal SM, Sreeraj VS, Shenoy S, et al. Tolerance of transcranial direct current stimulation in psychiatric disorders: an analysis of 2000+ sessions. Psychiatry Res. 2020;284:112744.
8. Nikolin S, Huggins C, Martin D, Alonzo A, Loo CK. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul. 2018;11(2):278–88.
9. Jwa A. Early adopters of the magical thinking cap: a study on do-it-yourself (DIY) transcranial direct current stimulation (tDCS) user community. J Law Biosci. 2015;2(2):292–335.
10. Gough N, Brkan L, Subramaniam P, Chiuccariello L, De Petrillo A, Mulsant BH, et al. Feasibility of remotely supervised transcranial direct current stimulation and cognitive remediation: a systematic review. PLoS One. 2020;15(2):e0223029.
11. Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12(5):1222–8.
12. Brietzke AP, Zortea M, Carvalho F, Sanches PRS, Silva DPJ, Torres I, et al. Large treatment effect with extended home-based transcranial direct current stimulation over dorsolateral prefrontal cortex in fibromyalgia: a proof of concept sham-randomized clinical study. J Pain. 2019;S1526-5900(19):30770–9.
13. Hyvarinen P, Makitie A, Aarnisalo AA. Self-administered domiciliary tDCS treatment for tinnitus: a double-blind sham-controlled study. PLoS One. 2016;11(4):e0154286.
14. Charvet LE, Dobbs B, Shaw MT, Bikson M, Datta A, Krupp LB. Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. Mult Scler. 2018;24(13):1760–9.
15. Martens G, Lejeune N, O'Brien AT, Fregni F, Martial C, Wannez S, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. Brain Stimul. 2018;11(5):982–90.
16. Mortensen J, Figlewski K, Andersen H. Combined transcranial direct current stimulation and home-based occupational therapy for upper limb motor impairment following intracerebral hemorrhage: a double-blind randomized controlled trial. Disabil Rehabil. 2016;38(7):637–43.
17. Cha YH, Urbano D, Pariseau N. Randomized single blind sham controlled trial of adjunctive home-based tDCS after rTMS for mal de debarquement syndrome: safety, efficacy, and participant satisfaction assessment. Brain Stimul. 2016;9(4):537–44.
18. Andre S, Heinrich S, Kayser F, Menzler K, Kesselring J, Khader PH, et al. At-home tDCS of the left dorsolateral prefrontal cortex improves visual short-term memory in mild vascular dementia. J Neurol Sci. 2016;369:185–90.
19. Hagenacker T, Bude V, Naegel S, Holle D, Katsarava Z, Diener HC, et al. Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. J Headache Pain. 2014;15:78.
20. Agarwal S, Pawlak N, Cucca A, Sharma K, Dobbs B, Shaw M, et al. Remotely-supervised transcranial direct current stimulation paired with cognitive training in Parkinson's disease: an open-label study. J Clin Neurosci. 2018;57:51–7.
21. Dobbs B, Pawlak N, Biagioni M, Agarwal S, Shaw M, Pilloni G, et al. Generalizing remotely supervised transcranial direct current stimulation (tDCS): feasibility and benefit in Parkinson's disease. J Neuroeng Rehabil. 2018;15(1):114.
22. Charvet L, Shaw M, Dobbs B, Frontario A, Sherman K, Bikson M, et al. Remotely supervised transcranial direct current stimulation increases the benefit of at-home cognitive training in multiple sclerosis. Neuromodulation. 2018;21(4):383–9.
23. Sivaramakrishnan A, Datta A, Bikson M, Madhavan S. Remotely supervised transcranial direct current stimulation: a feasibility study for amyotrophic lateral sclerosis. NeuroRehabilitation. 2019;45(3):369–78.
24. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–83.
25. Andrade C. Once- to twice-daily, 3-year domiciliary maintenance transcranial direct current stimulation for severe, disabling, clozapine-refractory continuous auditory hallucinations in schizophrenia. J ECT. 2013;29(3):239–42.
26. Schwippel T, Wasserka B, Fallgatter AJ, Plewnia C. Safety and efficacy of long-term home treatment with transcranial direct current stimulation (tDCS) in a case of multimodal hallucinations. Brain Stimul. 2017;10(4):873–4.
27. Clayton AM, Howard J, Dobbs B, Shaw MT, Charvet LE. Remotely supervised transcranial direct current stimulation after ECT improves mood and cognition in a patient with multiple sclerosis: a case study. J ECT. 2018;34(1):e15.
28. Riggs A, Patel V, Paneri B, Portenoy RK, Bikson M, Knotkova H. At-home transcranial direct current stimulation (tDCS) with telehealth support for symptom control in chronically-ill patients with multiple symptoms. Front Behav Neurosci. 2018;12:93.
29. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200(1):52–9.
30. Loo CK, Husain MM, McDonald WM, Aaronson S, O'Reardon JP, Alonzo A, et al. International randomized-controlled trial of transcranial direct current stimulation in depression. Brain Stimul. 2018;11(1):125–33.
31. Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for

clinical trials: guidelines for technology and protocols. Front Syst Neurosci. 2015;9:26.
32. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: a guide for clinical research and practice. Brain Stimul. 2020;13(3):686–93.
33. Kasschau M, Sherman K, Haider L, Frontario A, Shaw M, Datta A, et al. A protocol for the use of remotely-supervised transcranial direct current stimulation (tDCS) in multiple sclerosis (MS). J Vis Exp. 2015;106:e53542.
34. Shaw M, Pilloni G, Charvet L. Delivering transcranial direct current stimulation away from clinic: remotely supervised tDCS. Mil Med. 2020;185(Suppl 1):319–25.
35. Shaw MT, Kasschau M, Dobbs B, Pawlak N, Pau W, Sherman K, et al. Remotely supervised transcranial direct current stimulation: an update on safety and tolerability. J Vis Exp. 2017;128:56211.
36. Pilloni G, Shaw M, Feinberg C, Clayton A, Palmeri M, Datta A, et al. Long term at-home treatment with transcranial direct current stimulation (tDCS) improves symptoms of cerebellar ataxia: a case report. J Neuroeng Rehabil. 2019;16(1):41.
37. Richardson JD, Charvet, L., Shaw, M., Galletta, E. Remotely supervised transcranial direct current stimulation (RS-tDCS) for people with stroke-induced and progressive aphasia. American Speech-Language-Hearing Association. July; Atlanta, GA2019.
38. Eilam-Stock T, George A, Charvet L. Cognitive telerehabilitation with transcranial direct current stimulation (tDCS) improves cognitive and emotional functioning following a traumatic brain injury: a case study. Arch Clin Neuropsychol. 2020;36(3):442–53.
39. Carvalho F, Brietzke AP, Gasparin A, Dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. J Vis Exp. 2018;137:57614.
40. Park J, Oh Y, Chung K, Kim KJ, Kim CO, Park JY. Effect of home-based transcranial direct current stimulation (tDCS) on cognitive function in patients with mild cognitive impairment: a study protocol for a randomized, double-blind, cross-over study. Trials. 2019;20(1):278.
41. Garcia-Larrea L, Perchet C, Hagiwara K, André-Obadia N. At-home cortical stimulation for neuropathic pain: a feasibility study with initial clinical results. Neurotherapeutics. 2019;16(4):1198–209.
42. O'Neill F, Sacco P, Bowden E, Asher R, Burnside G, Cox T, et al. Patient-delivered tDCS on chronic neuropathic pain in prior responders to TMS (a randomized controlled pilot study). J Pain Res. 2018;11:3117–28.
43. Van de Winckel A, Carey JR, Bisson TA, Hauschildt EC, Streib CD, Durfee WK. Home-based transcranial direct current stimulation plus tracking training therapy in people with stroke: an open-label feasibility study. J Neuroeng Rehabil. 2018;15(1):83.
44. Ahn H, Zhong C, Miao H, Chaoul A, Park L, Yen IH, et al. Efficacy of combining home-based transcranial direct current stimulation with mindfulness-based meditation for pain in older adults with knee osteoarthritis: a randomized controlled pilot study. J Clin Neurosci. 2019;70:140–5.
45. de Berker AO, Bikson M, Bestmann S. Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. Front Hum Neurosci. 2013;7:613.
46. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res. 2012;216(1):1–10.
47. Knotkova H, Riggs A, Berisha D, Borges H, Bernstein H, Patel V, et al. Automatic M1-SO montage headgear for transcranial direct current stimulation (TDCS) suitable for home and high-throughput in-clinic applications. Neuromodulation. 2019;22(8):904–10.
48. Kortteenniemi A, Lehto SM, Javadi A-H. Delayed, distant skin lesions after transcranial direct current stimulation. Brain Stimul. 2019;12(1):204–6.
49. Cucca A, Sharma K, Agarwal S, Feigin AS, Biagioni MC. Tele-monitored tDCS rehabilitation: feasibility, challenges and future perspectives in Parkinson's disease. J Neuroeng Rehabil. 2019;16(1):20.
50. Fitz NS, Reiner PB. The challenge of crafting policy for do-it-yourself brain stimulation. J Med Ethics. 2015;41(5):410–2.
51. Datta A, Bikson M, Fregni F. Transcranial direct current stimulation in patients with skull defects and skull plates: high-resolution computational FEM study of factors altering cortical current flow. NeuroImage. 2010;52(4):1268–78.
52. Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul. 2010;3(1):58–9.
53. Palm U, Keeser D, Schiller C, Fintescu Z, Nitsche M, Reisinger E, et al. Skin lesions after treatment with transcranial direct current stimulation (tDCS). Brain Stimul. 2008;1(4):386–7.
54. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the major depressive episode: findings from a naturalistic study. Eur Psychiatry. 2013;28(6):356–61.
55. Nitsche MA, Liebetanz D, Schlitterlau A, Henschke U, Fricke K, Frommann K, et al. GABAergic modulation of DC stimulation-induced motor cortex excitability shifts in humans. Eur J Neurosci. 2004;19(10):2720–6.
56. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553(Pt 1):293–301.
57. McFadden JL, Borckardt JJ, George MS, Beam W. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. Brain Stimul. 2011;4(1):38–42.

58. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91.
59. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Benseñor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99:109836.
60. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of electrical direct-current therapy versus escitalopram for depression. N Engl J Med. 2017;376(26):2523–33.
61. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, et al. The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70(4):383–91.
62. D'Urso G, Mantovani A, Micillo M, Priori A, Muscettola G. Transcranial direct current stimulation and cognitive-behavioral therapy: evidence of a synergistic effect in treatment-resistant depression. Brain Stimul. 2013;6(3):465–7.
63. Martin DM, Teng JZ, Lo TY, Alonzo A, Goh T, Iacoviello BM, et al. Clinical pilot study of transcranial direct current stimulation combined with cognitive emotional training for medication resistant depression. J Affect Disord. 2018;232:89–95.
64. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014;7(2):325–31.
65. Sakrajai P, Janyacharoen T, Jensen MP, Sawanyawisuth K, Auvichayapat N, Tunkamnerdthai O, et al. Pain reduction in myofascial pain syndrome by anodal transcranial direct current stimulation combined with standard treatment: a randomized controlled study. Clin J Pain. 2014;30(12):1076–83.
66. Lee HY, Choi MS, Chang DS, Cho CS. Combined bifrontal transcranial direct current stimulation and tailor-made notched music training in chronic tinnitus. J Audiol Otol. 2017;21(1):22–7.
67. Teismann H, Wollbrink A, Okamoto H, Schlaug G, Rudack C, Pantev C. Combining transcranial direct current stimulation and tailor-made notched music training to decrease tinnitus-related distress–a pilot study. PLoS One. 2014;9(2):e89904.
68. Vanderhasselt MA, De Raedt R, Namur V, Lotufo PA, Bensenor IM, Boggio PS, et al. Transcranial electric stimulation and neurocognitive training in clinically depressed patients: a pilot study of the effects on rumination. Prog Neuro-Psychopharmacol Biol Psychiatry. 2015;57:93–9.
69. Aparicio LVM, Rosa V, Razza LM, Sampaio-Junior B, Borrione L, Valiengo L, et al. Transcranial direct current stimulation (tDCS) for preventing major depressive disorder relapse: results of a 6-month follow-up. Depress Anxiety. 2019;36(3):262–8.
70. Martin DM, Alonzo A, Ho KA, Player M, Mitchell PB, Sachdev P, et al. Continuation transcranial direct current stimulation for the prevention of relapse in major depression. J Affect Disord. 2013;144(3):274–8.
71. Bystad M, Rasmussen ID, Gronli O, Aslaksen PM. Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. Neurocase. 2017;23(2):146–8.
72. Cristancho MA, Helmer A, Connolly R, Cristancho P, O'Reardon JP. Transcranial magnetic stimulation maintenance as a substitute for maintenance electroconvulsive therapy: a case series. J ECT. 2013;29(2):106–8.
73. Sadeghi Bimorgh M, Omidi A, Ghoreishi FS, Rezaei Ardani A, Ghaderi A, Banafshe HR. The effect of transcranial direct current stimulation on relapse, anxiety, and depression in patients with opioid dependence under methadone maintenance treatment: a pilot study. Front Pharmacol. 2020;11:401.
74. Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci. 2014;8:661.

37 Ethical Aspects of tDCS Use in Neuropsychiatry and the Risk of Misuse

Rachel P. Wurzman, Leah M. Friedman, and Roy H. Hamilton

37.1 Introduction: Is tDCS Hope or Hype?

There is growing enthusiasm about the potential of transcranial direct current stimulation (tDCS) to be of value for clinical and cognitive enhancement purposes. With headlines like "Learning faster might be possible with this wearable headseat," or "Got a problem—put your electric thinking cap on," hundreds of enthusiastic print media articles have been published in the last few years [1–4]. The majority of media attention to tDCS has been optimistic and has praised the putative benefits of the technology [2]. However, while the tone of such coverage speaks in part to the considerable therapeutic potential of tDCS for disorders of cognition and mood, it also highlights the need to distinguish hope from hype. More than that, the science of tDCS and its potential applications present practical and ethical obstacles that warrant serious contemplation.

In many ways, practical and ethical considerations for tDCS mirror those of other forms of brain stimulation or neural interventions more broadly, but there are a few key features about tDCS that set it apart. Compared with other forms of noninvasive brain stimulation such as transcranial magnetic stimulation (TMS), tDCS is cheap, accessible, and portable. These factors multiply the contexts and applications for tDCS, some of which could present ethical, legal, and social problems if tDCS use were to become more widespread. At the same time, its very high level of accessibility also limits the range of potential actions that can be taken to prevent potentially problematic developments. Its low cost and relative technological simplicity make tDCS applicable to a broader set of contexts than other forms of invasive or even noninvasive brain stimulation, as it does not require surgery and can be easily self-administered. Consequently, tDCS is highly amenable to direct-to-consumer product development and marketing, as well as to increased use in so-called para-clinical contexts for enhancing cognitive and behavioral abilities, such as in the workplace, on the battlefield, or as a cosmetic enhancement in daily life. Recent years have witnessed a substantial proliferation of available devices and companies that are making tDCS products for recreational and "wellness" purposes, some of which blur the boundary between clinical and daily enhancement application [5–7]. This potential for broad use both inside and outside of medical contexts calls for special consideration of the promises, potential perils, and implications for tDCS in the

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field of neuropsychiatry—both in how it is practiced and how it is perceived.

This chapter starts by exploring the promise of tDCS, first as a tool in cognitive neuroscience research, then as a clinical intervention, and finally as a technology to enhance normal cognition. Next, the scientific and ethical perils of tDCS are discussed in terms of the current state of the science, and how that informs the ways we think about the ethical challenges that tDCS poses with respect to safety, justice, humanity and character, and autonomy. For example, how can and should (or should not) knowledge learned in controlled research contexts be translated for potential safe and effective tDCS administration to complex real-world patients with multiple diagnoses, often on multiple medications? If cognitive self enhancement becomes a social norm, what effects will that have on social structures, personal development, perhaps even clinical norms for what is considered normal versus pathological? Finally, we consider the ways in which tDCS presents specific advantages as well as challenges to neuropsychiatry and its role in society.

The field and scope of tDCS use (and other noninvasive brain stimulation and cognitive enhancement interventions) may already be developing at a rate that exceeds the pace of our scientific understanding [4]. One needs only to look at the recent and upcoming products released by the companies like Halo Neuroscience (Halo Neuroscience, San Francisco, CA), LIFTiD (LIFTiD Neurostimulation, Ossining, NY—https://www.getliftid.com/index.html), and Brain Driver (The Brain Driver, Chicago, IL—https://thebraindriver.com/)—not to mention their marketing approaches—to glimpse the future role that tDCS could come to play in daily life. We may not be able to predict the rate at which the potential pitfalls may develop, but we can be sure that if tDCS continues to develop along its present trajectory, ethical, legal, and social issues will eventually arise. It is therefore important to consider these issues now, so that we can take proactive steps to mitigate against potentially unintended and undesirable consequences.

37.2 tDCS as a Cognitive Neuroscience Tool

Noninvasive brain stimulation (NIBS) methods are highly useful to cognitive neuroscience, in that they are used to modulate activity in brain regions or networks with varying degrees of anatomical selectivity and functional specificity. In general, NIBS add significant inferential strength to the ability of cognitive neuroscience to decipher causal brain region-function and network-function relationships. Following stimulation, subsequent changes in cortical activity, measured directly or indirectly by probing sensorimotor or cognitive behavioral functions, afford improved understanding of how brain activity in one region or network contributes to cognition and behavior. In recent years, tDCS has seen increasing use in the cognitive neuroscience community, with the number of publications published per year increasing approximately twentyfold over the last decade [2]. An overview and methodological guidelines for using tDCS as a tool of cognitive neuroscience was published by Reinhart and colleagues in 2017 to help guide new users and researchers in setting up tDCS studies to probe cognitive processes [8]. TDCS has been applied to a variety of cognitive domains, including but not limited to skill learning, memory, executive functions, cognitive control, numerical cognition, creativity, language, spatial processing, social cognition, and moral cognition [9–13]. This section provides a brief partial review of studies in which tDCS has been shown to manipulate cognition in informative ways, some of which have possible clinical applications.

With respect to learning and memory, acquisition and retention of new procedural skills has been experimentally enhanced using tDCS. One study found that, compared to sham stimulation, increased motor cortex excitability and enhanced learning of motor movements resulted when simple repetitive practice was paired with anodal tDCS [14]. Similarly, in multiple studies, tDCS delivered over 5 days paired with training on a complex motor task resulted in increased improvement between daily stimulation sessions and persistent superior skill retention 3 months

after stimulation in both healthy and aging populations [15, 16]. The implications of this are that repeated administration of tDCS may have "offline" effects that consolidate skill acquisition, effectively enhancing the long-term effects of rehearsal on performance or reducing the rate of performance decline [17]. Safety studies on repeated tDCS administration have not identified any immediate safety issues with repeat administration, indicating that multi-session tDCS is a viable future direction for brain stimulation [18]. Demonstrably increased interest in and feasibility of administering tDCS remotely for treatment and research [19] will yield more safety information about the effects of repeated stimulation over time.

Declarative verbal memory has also been investigated using tDCS. Five days of tDCS stimulation in older and younger adults was shown to improve verbal associative learning, with effects maintained over 1–3 months [20]. Similarly, stimulation applied to the left dorsolateral prefrontal cortex had the effect of increasing the rate of verbal learning [21]. Consistent with this, another study found that tDCS delivered to the same site but with the opposite polarity had an inhibitory effect on verbal learning [22].

Various executive functions such as cognitive and behavioral impulse control and working memory have also been investigated with tDCS, especially tDCS in combination with working memory training [23, 24]. One study found that orbitofrontal cortex stimulation with tDCS enhanced decision making and improved cognitive impulse control, without any concurrent effects on attention, mood, or motor impulse control [25]. In another study, tDCS improved response inhibition, which refers to the ability to inhibit an action once initiated [26]. For working memory (WM) and related functions, tDCS-induced improvements of performance on some tasks appear to depend in part on the level of cognitive demand of the tasks. For example, one group found that stimulation over the right cerebellum or left DLPFC increased accuracy and decreased response times for an arithmetic task that was more difficult and attentionally demanding, but not for an easier arithmetic task [27, 28]. Another group found that cathodal tDCS improved word naming and categorical perception when tasks are more complex, providing further support for the interaction between tDCS and task load or difficulty [29]. Importantly, these effects also required that domain-specific cognitive behaviors be engaged during stimulation; stimulation-induced improvements were absent when tDCS was not paired with a relevant behavioral task [30, 31]. A study by Hill and colleagues (2019) demonstrated that HD-tDCS over the left DLPFC results in different event-related potentials when administered during a working memory task compared to stimulation without a task [32]. Other studies have also found an interaction between task context and type of stimulation on tDCS effects. For example, Weissengruber and colleagues (2019) found that these variables influence how tDCS modulates switching between model-based and model-free reinforcement learning systems [33].

Some studies have found that cathodal tDCS may influence creativity and cognitive flexibility, presumably by inhibiting certain frontal lobe functions. Two studies have found that subjects could come up with more uncommon uses for everyday objects and improve set shifting with inhibitory stimulation of the left, but not right (and in one study, also excitatory stimulation to the right), prefrontal cortex [34, 35]. These findings suggest that creativity could be enhanced by stimulation that increases the influence of unfiltered bottom-up information. Other work in augmenting creative cognition suggests that tDCS can enhance creativity by promoting self-focused attention, creative thinking, and artistic enactment or follow-through [36].

It may be possible to significantly enhance the ability to learn new languages using tDCS. For example, anodal tDCS over language cortical regions enhanced new vocabulary learning in healthy young adults [37]. Even without a reference object to associate with a novel "nonword," tDCS facilitated the acquisition of the phonological form of the nonwords into long-term memory, beyond the stimulation session [38]. tDCS may also play a facilitative role in integrating word meaning when applied to the left angular gyrus

[39]. Reading skills may also be enhanced using tDCS [40–43]. Compared with sham stimulation, subjects receiving real tDCS subjects exhibited significantly better nonword reading efficiency. Curiously, this seemed only to apply consistently to below-average readers in the cohort; subjects who were more efficient readers to begin with saw much more variable changes in reading performance during real tDCS [44].

TDCS has been used to manipulate and enhance aspects of visuospatial processing. For example, we showed [45] that anodal tDCS over the right posterior parietal cortex could be used to selectively enhance detection of left-sided allocentric targets, which is to say that stimulated subjects were better able to detect the left side of visual targets independent of where the targets were in the subjects' visual fields. Interestingly, tDCS has also been used to manipulate how spatial and temporal processing contribute to higher order mental representations, such as the perception of cause and effect. In a study by Woods and colleagues [46], subjects were asked to make judgments about the causal relationship between two virtual objects (i.e., did one object cause the other to move by striking it), while the spatial and temporal features of the objects' motions were manipulated. Consistent with the role of the parietal cortex in spatial processing, the authors found that parietal tDCS selectively influenced how sensitive subjects were to spatial manipulation as it related to their perception of causality. On the other hand, frontal cortex stimulation influenced both spatial and temporal judgments with respect to causality, consistent with the overarching role of the frontal cortex in cause-and-effect reasoning [47].

Brain stimulation has also been used to alter social cognition and behaviors, including those that affect moral decision making that balances self-interest with social values [13]. For example, individuals will often reject an offer that they perceive as highly unfair, although accepting the offer would still be to their benefit, as reciprocal punishment for the perceived unfairness (a concept known as "altruistic punishment"). Noninvasive inhibitory stimulation of the right DLPFC makes people less likely to reject marginally beneficial but unfair offers, even when consciously recognized as highly unfair [13, 48, 49], suggesting that direct current stimulation might also be used to calibrate the impact of economic self-interest on people's enforcement of social norms [48, 49]. In another study, left anodal/right cathodal tDCS was found to decrease "corruption behavior" in an investment-like game [50]. Gross et al. (2017) revealed that tDCS to the right lateral prefrontal cortex increases complementary prosocial "fairness" behaviors that, depending on the polarity, either entailed rule following at participants' own expense (cathodal), or rule violating in order to preserve fairness (anodal) [51].

In research on lie detection, tDCS has been demonstrated to alter individuals' deception skills in fairly specific ways, such as influencing someone's deceptive abilities when trying to conceal one's guilt or in situations such as card games. Early studies found that the act of lying increases cortical excitability on both sides of the brain [52]. People became better liars in a simulated interrogation task when cathodal tDCS was used to inhibit the anterior prefrontal cortex. Not only did stimulation make people better at concealing guilty knowledge, decreasing the kinds of signals that a polygraph detects when someone is lying, it also decreased their feelings of guilt over deceiving the experimenter [53]. On the other hand, anodal excitation of the dorsolateral prefrontal cortex made people worse at pretending not to have knowledge about something true, like whether a particular card is in their hand; interestingly, this effect did not extend to subject's behavior when bluffing or telling the truth [54]. Another study replicated this finding and found differential effects by gender [55]. Other studies have similarly found that anodal stimulation to the right tempo-parietal junction decreases deceptive abilities [56, 57].

One of the advantages of NIBS compared to classical methods in cognitive neuroscience and cognitive neurology like lesion studies is that these technologies can be used both to interfere with and enhance cognitive functions, at least temporarily. For example, the aforementioned studies on executive function and creativity

illustrate how inverting the polarity of stimulation over brain regions responsible for cognitive control can either result in favoring of cognitive abilities that require heavy filtering of extraneous information, such as sustained attention and working memory, or in favoring cognitive abilities that benefit from unfiltered intrusion of extraneous information, such as divergent thinking and creativity [10, 25–28, 30, 31, 34–36].

While enhancing aspects of cognition using such manipulation is a powerful tool for making inferences about brain function, it also opens the door to considering whether technologies like tDCS could be used to facilitate cognitive processes in patients with neurologic or psychiatric disorders of cognition, as well as in cognitively healthy individuals. For example, the ability of tDCS to manipulate perception of cause and effect could have implications for understanding and treatment of psychiatric disorders such as schizophrenia and obsessive compulsive disorder (OCD), where abnormal causal perceptions can contribute to symptoms [58, 59]. Moreover, the enhancement of allocentric spatial processing found by Medina and colleagues (2013) could have important implications for the treatment of spatial neglect in stroke patients [47], and studies related to executive function could lead to applications in a wide range of neurologic and psychiatric disorders [25–28, 30, 31]. Further research will be required so that group level results from cognitive neuroscience studies, which are principally designed to reveal brain function, can be translated to clinical applications in which the goal is to alter specific functions in single individuals.

37.3 tDCS as a Clinical Intervention

With respect to clinical contexts, a growing body of literature suggests that tDCS is a potentially effective therapy for a wide variety of neuropsychiatric syndromes and symptoms, as well as other neurologic conditions affecting cognition [60–62]. Depression and chronic pain in particular are two areas in which a substantial number of clinical trials support the utility of tDCS to alleviate symptoms [63–65]. For depression, tDCS to the prefrontal cortex has shown promise as a treatment and medication adjunct to improve therapeutic outcomes [66–72] for patients who are both treatment-resistant and non-treatment-resistant [64]. With respect to tDCS as a treatment for pain, clinical trials for tDCS have been performed for chronic lower back pain [73–76], chronic pain in the elderly [77, 78], chronic temporomandibular disorders [79–82], chronic pain in irritable bowel syndrome [83, 84], neuropathic pain [85, 86] such as in fibromyalgia [87, 88], or multiple sclerosis [89–93], and chronic pain associated with CNS damage from spinal cord injury [94, 95] or stroke [96–98]. Newer research has also investigated tDCS to alleviate symptoms of pain from osteoarthritis [99, 100], migraines and headaches [101, 102], phantom limb pain [103], and chronic orofacial pain [104]. Although the results of clinical trials have in some cases been mixed [105, 106], the potential utility of tDCS for clinical pain applications has been demonstrated in studies that show tDCS can affect aspects of nociception, pain thresholds, and affective (i.e., emotional) components of pain processing in healthy individuals [107–111]. tDCS has also been investigated at length in other neuropsychiatric conditions [112–114]. These conditions include attention deficit hyperactivity disorder (ADHD) [115, 116], schizophrenia [112, 117–121], Alzheimer's disease [122, 123] and mild cognitive impairment (MCI) [124, 125], tinnitus [126, 127], obsessive compulsive disorder (OCD) [128, 129], Tourette syndrome [130], and generalized anxiety disorder [131, 132]. TDCS is also being considered for PTSD, based on observed effects in fear extinction and attentional bias for threat in anxiety [112, 133–135]. There is even some preliminary evidence that tDCS may provide clinical benefits in patients with epilepsy [136].

Other clinical applications for tDCS include disorders characterized by problematic behaviors related to abnormal executive function, including addictions and impulsive behaviors [137–140]. Studies have shown that tDCS may be useful for decreasing cigarette cravings and smoking

behavior [141–145]. Interestingly, one study of risk-taking behavior in smokers versus nonsmokers found that tDCS was associated with personality-dependent effects [146], which emphasizes that existing cognitive patterns influence the specific nature of tDCS effects. Similarly, tDCS has been potentially effective in diminishing risk-taking behaviors in clinically impulsive patients [147] but has had mixed effects in healthy populations [148, 149]. Substance abuse and cravings in alcoholism [150–154] and drug addiction to methamphetamine [137, 155] and crack cocaine [137, 156–158] were also responsive to tDCS. Preliminary clinical studies of tDCS applied to DLPFC to intervene in obesity and disordered eating behavior have seen positive results. These have mostly examined acute tDCS effects on subjective reports of food craving, attentional bias for food as probed with eye tracking following a single session of stimulation, and caloric intake following tDCS [159–166]. An 8-day, randomized, sham-controlled, crossover study found that anodal DLPFC stimulation decreased appetite and specifically reduced the consumption of carbohydrates at a standardized test buffet [167]. While clinical studies have also begun to investigate whether tDCS can bolster treatment of eating disorders such as anorexia nervosa, treatment effects remain ambiguous [166, 168].

Substantial promise has been found for tDCS in post-stroke neurorehabilitation [169]. Following stroke, tDCS has been shown to assist in upper and lower motor limb recovery from paresis [169–171], and had beneficial effects in visuospatial hemineglect and dysphagia [172, 173]. In another study the response to prism adaptation therapy was improved when therapy was paired with tDCS [174]. Anodal tDCS to the right premotor cortex also restored one patient's awareness of hemiplegia during stimulation [175], and in another case study, cognitive neglect therapy paired with biparietal tDCS, but not sham stimulation, enhanced the patient's response to therapeutic cognitive training [176]. Additionally, multiple studies have shown that when tDCS is paired with speech and language therapy, naming ability can be improved in stroke patients with aphasia [177–188], specifically in patients with more severe impairments at baseline [189]. Another neurorehabilitation application may be to post-stroke attentional decline, as anodal tDCS to the left DLPFC also improved attention in stroke patients, resulting in increased accuracy on a cognitive task of executive function [190]. Finally, tDCS is also being explored as enhancement to learning and memory in normal aging and in states of cognitive impairment [191–195], particularly in neurodegenerative dementias [196, 197]. Specifically, tDCS has shown promise and continues to be investigated for mediating improvements in primary progressive aphasia and anomia in combination with speech language therapy techniques [188, 198–202].

Not coincidentally, tDCS has been explored clinically in many areas where the underlying impaired cognitive constructs have been shown in cognitive neuroscience research to be manipulable using stimulation. For example, cognitive neuroscience studies showing effective tDCS modulation on decision-making, including risk taking, reward-seeking, impulsivity, and fairness consideration are considered as promising for addictive disorders, in which the hallmarks of clinical symptomatology are compromises in such decision-making capacities [203].

There are many practical reasons to favor tDCS in clinical settings. In addition to being small and portable, tDCS is inexpensive compared to other neuromodulation technologies like TMS. As currently used tDCS protocols are also safe, tDCS is an ideal form of neuromodulation to pair with existing therapies, and could potentially be self-administered by patients who may benefit from repeated stimulation on a regular basis [19, 204, 205].

37.4 tDCS to Enhance Normal Cognition

In addition to clinical applications and cognitive neuroscience studies designed to elucidate brain function (described above), there has been growing interest in explicitly enhancing normal cognition. In particular, tDCS joins a variety of

neuroscience tools applied to so-called neuroergonomic purposes, referring to applications intended to aid human operators in the performance of their work duties [45, 206]. Academic investigations for this purpose include—and in many cases expand upon—cognitive neuroscience studies of effects on isolated cognitive abilities, by examining tDCS effects on the performance of more complex tasks. Frequently, these experiments involve more naturalistic paradigms with clear applications to specific occupational functions, and assess improvements in the cognitive functions of implicit memory (e.g., procedural and motor learning; probabilistic learning), explicit learning and memory (e.g., declarative memory encoding with retrieval), working memory, attention, and perception [207]. For example, tasks in which tDCS has shown accelerated learning, enhanced performance, and/or prolonged training effects include threat detection in virtual reality simulated urban warfare scenes [208–210], simulated air traffic controller games [211], a complex multitask game "Space Fortress" [212], and an image analysis task in which target objects must be identified from synthetic aperture radar images of terrain with buildings and vehicles [213]. Research in the neuroergonomics realm has also demonstrated the ability of tDCS to sustain wakefulness and improve mood in night shift workers for longer than caffeine [214].

Not surprisingly, much of this research has been funded by the US Department of Defense (DoD) [215]. The Department of Defense has actively begun to evaluate the feasibility, benefits, and trade-offs of tDCS for war-fighting and defense settings [216–218], considering tDCS as part of the "third offset" which aims to gain an advantage over adversaries through human enhancement [219]. DoD research funding is also pushing toward the creation of nonsurgical neurotechnology with programs like N3 (https://www.darpa.mil/program/next-generation-nonsurgical-neurotechnology), which seeks to create closed-loop brain stimulation systems capable of "writing" and "reading" to the brain. While this program is not explicitly clinical in application, the resulting technologies are certain to be dual-use, with easily imagined translation to clinical contexts.

On the other end of the spectrum from defense and security organizations, a community of individual "do-it-yourself" (DIY) tDCS users are also actively pursuing cognitive self- improvement [220]. The practices of this community have been described in detail by Wexler [5, 221]. The DIY community refers collectively to tDCS use outside of professional or academic settings, and can be subdivided into those who seek to enhance their cognition and those who intend to alleviate clinical symptoms of neuropsychiatric disorders [5]. In a study of 308 individuals who purchased and used a tDCS device on themselves at least once (representing 3.9 percent of all device purchasers contacted), one-third reported using the device to self-treat depression (2018). It is worth noting that in this study by Wexler (2018), people who use tDCS for treatment purposes rate it as more effective than those who self-administer tDCS for cognitive enhancement. Possible explanations offered for this are that tDCS may have stronger effects on depression than other conditions or cognitive functions, that there may be more room for functional improvement in those who use tDCS for treatment versus enhancement, or that there is a greater placebo effect when used for treatment than for enhancement [221].

Alongside this DIY community, a burgeoning wearables market for at-home tDCS is emerging, producing tDCS products controlled by companion apps for cognition and athletic performance enhancement, in both healthy individuals and clinical populations. Several of these companies supply direct-to-consumer devices for recreational and lifestyle indications (Thync, Foc.us, PaltoWork—https://www.indiegogo.com/projects/platowork-brain-stimulator#/, among others). Thync (https://www.thync.com/) has begun to produce electrical "energy patches" to sustain wakefulness while the startup PlatoWork (https://www.indiegogo.com/projects/platowork-brain-stimulator#/) offers the ability to buy a pack of tDCS devices for teams in the workplace or otherwise. Another company has a stimulator intended for healthy and "impaired" populations

in a well-funded development pipeline (Halo Neuroscience; http://haloneuro.com/#science) [215]. Other companies like Capturon (https://caputron.com/) act as tDCS "wholesalers," providing the DIY community with an array of tDCS devices at various price points. These companies are at the forefront of trends that could potentially lead to widespread, if not ubiquitous, use of neuromodulatory technologies in daily life. However, it is worth noting that compared with other products like "brain training games," the number of tDCS users are still orders of magnitude smaller [6]. Despite a surge in enthusiastic media attention (and subsequently, users) in 2014 and 2015, Wexler (2017) observed that actually there is "little evidence to support the notion that home use of tDCS is increasing."

Some of the most popular applications of DIY tDCS are in wellness and athletic applications, where tDCS may work to enhance both physical and mental performance [222–224]. For instance, Halo devices have been found to enhance components of sprint cycling [225], and other tDCS devices may improve muscle endurance in professional bodybuilders [226]. It was originally thought that these effects might be driven by increased excitatory output from the primary motor cortex that delays supraspinal fatigue, or elsewise reduced perception of affective obstacles like pain or fatigue. However, follow-up studies have produced mixed results that may be due to the particulars of each experimental setup, and many of these studies were not designed to probe specific mechanisms for performance enhancement by tDCS [107]. Therefore, while athletic performance enhancement is one of the most heavily marketed tDCS applications, the science behind whether or why it works is still uncertain.

tDCS has also shown promise in enhancing effects of mindfulness meditation, alone and in combination with yoga practices, with increased positive affect, mood, and mindfulness measurements [227, 228]. However, it is unclear what role expectations and placebo may be playing in these results. Stimulation for meditative applications are often combined with a phone app or other cues, which both set expectations for, and might directly mediate, results. However, as noted, this does not necessarily mean that such an intervention is not useful; it simply emphasizes the importance of attention to the context for stimulation delivery in achieving consistent results.

At present the effects of tDCS are far from established. Even at-home and DIY users are not entirely convinced of its efficacy; of the at-home users studied by Wexler (2018), 40% had stopped using the device they purchased, most commonly due to a lack of perceived efficacy [221]. The same study found that perceived efficacy was also lower when the use intention was enhanced cognition, compared with self-treatment. Despite growing excitement about the possibility of using tDCS for enhancement of otherwise normal cognition, caution is warranted before extrapolating observations and lessons learned in cognitive neuroscience and clinical research contexts to cognitive enhancement in healthy individuals due to fundamental differences in the theoretical, practical, and ethical issues related to each (as will be discussed in the next section). Exercising caution may take the form of increased regulation of consumer brain stimulation devices as recommended by researchers like Anna Wexler, who have taken critical looks at DIY and consumer practices to inform future tDCS regulatory directions [5, 229, 230]. Clinicians and scientists may also promote caution by directing patients and other interested parties to the open letter published by 4 neuroscientists and signed by 39 other tDCS researchers in 2016 [231]. This letter employs a measured tone to clearly communicate with the public about the risks posed both by what is known and unknown about tDCS.

37.5 The Perils of tDCS

Despite its promise, the use of tDCS in cognitive neuroscience, clinical research, and para-clinical applications faces several scientific and ethical challenges, which must be considered to protect against unanticipated or even adverse effects on the bio-psycho-social health of individuals and communities. Some of these challenges are

driving the development of emerging technologies that may have more potent and specific effects compared with tDCS as described above. It is especially important to accurately assess the state of the science, and reflect upon the way that the present degree of scientific understanding of tDCS motivates, justifies, and sometimes cautions against tDCS use.

37.6 Scientific Challenges

Scientific challenges stem from the fact that there is much that we do not yet understand about the underlying neural mechanisms of tDCS. Our incomplete understanding of tDCS mechanisms is underscored by data that indicates that the effects of stimulation on brain function are neither monotonic nor invariant. The initial dogma based on studies in motor cortex, which attributed enhancement or diminishment of cortical excitability to anodal or cathodal stimulation, respectively, often conflicts with experimental results. In fact, dose-response relationships are still poorly understood [216, 232]. For example, one study found that 1 mA cathodal stimulation diminished motor cortex excitability, but 2 mA cathodal stimulation enhanced it [233]. Similarly, doubling the time of stimulation can reverse the behavioral and cortical excitability effects [234, 235]. As Esmaeilpour and colleagues (2018) noted, "Put simply, we still do not know whether more intensity of electric field in a given brain area supports greater neurophysiological or behavioral outcomes" [232]. The "anodal-facilitation versus cathodal-disruption" schema is also a clear oversimplification; particularly beyond motor cortex, anodal and cathodal stimulation do not have equal and opposite effects on behavior. In cognitive studies, anodal and cathodal stimulation is sometimes found to have the same net facilitative effect on behavior, or only one stimulation polarity over the target will be found to influence a given behavior [26, 236].

More broadly, we know that stimulation parameters matter a lot, but we are limited in our knowledge of what difference they actually make. Studies confirm that differences in behavioral outcomes are related to changes in cortical excitability induced by stimulation, but it remains a problem to predict how excitability of specific neuronal tissue will change in any one individual under a common set of stimulation parameters [237]. For example, finite element models of tDCS-induced electrical current flow tell us that the size and location of the "reference" electrode strongly influences the effects of stimulation [238, 239]. Small changes in electrode position and individual head shapes can also greatly modify current flow patterns [240–244]. However, the results of these models vary considerably based on model assumptions [245]. In other words, the best tools we have for understanding what stimulation is doing are themselves quite limited.

In addition to head shape, individual differences in brain morphology and neurochemistry cause individual responses to tDCS to vary widely between people. For example, the shape and thickness of the cortical tissue varies between individuals, and this accounts for as much as one-third of the variance of stimulation efficacy between individuals [246]. This variance makes it extremely challenging to assess the efficacy of tDCS as an intervention, and the heterogeneity of responses may lead us to underestimate the actual potential of tDCS to deliver useful neuromodulation.

Attempts to solve this problem have focused on combining MRI-based electrical field modeling and tDCS as well as improving the use of biomarkers to predict individual tDCS dose-responses. Functional biomarkers tested to predict cortical excitability include an individual's transcranial magnetic stimulation (TMS) motor threshold, which reflects the amount of energy required to elicit neuronal firing in motor cortex using TMS stimulation, as well as the amounts of excitatory and inhibitory neurotransmitters detected from specific brain areas using magnetic resonance spectrography [247, 248]. Integration between tDCS and both functional magnetic resonance imaging (fMRI) and magnetoencephalography, which respectively measure the blood-oxygen level-dependent (BOLD) response and magnetic field strength generated by electrical activity in task-related brain areas,

have also been explored as a tool to reduce the variability in tDCS response [249, 250]. By predicting sensitivity to stimulation, and more directly tracking the changes in cortical excitability that stimulation elicits, neuroscientists hope to achieve rational design of stimulation for more precise dosing in individuals, which will facilitate a more accurate assessment of tDCS efficacy.

In addition to questions about dose and mechanism, there are unresolved questions pertaining to predicting how both individuals and phenotypic groups will respond to tDCS under any particular set of stimulation parameters. In healthy populations, heterogeneous groups have been found to respond variably to tDCS depending on subtype. This heterogeneity may be behavioral, as in one study that found only low-performers to be negatively affected by anodal tDCS [251]. Individual differences may also be genetic or morphological in nature. Individuals with different genetic polymorphisms may react variably to identical stimulation parameters [252], underlying cortical morphologies might affect the efficacy of tDCS to prefrontal areas [246], and heterogeneous neurochemical excitability could influence responses to tDCS [247]. This heterogenicity likely applies to neuropsychiatric populations as well, which highlights the need for further clinical research investigating which clinical sub-phenotypes might respond best to specific applications of tDCS. For example, when using tDCS for ADHD, there may be a need to consider the inattentive subtype differently than the hyperactive subtype.

Other unknown variables when considering the perils of broader applications of tDCS to enhance cognition are the interactions that brain stimulation may have with comorbid diagnoses and the concurrent use of medications (for a review of studies reporting medication effects on tDCS, see [253]. The interaction of brain stimulation with agents that act on different neurotransmitters is of special concern in neuropsychiatry, since many (or perhaps most) people who suffer from these problems are taking one or more such medications. Some drugs have been found to have profound, complex and varied influences on tDCS-induced neuromodulation [254–257]. In one very large clinical study of tDCS and depression, an additional naturalistic study systematically evaluated how tDCS responses were affected by concurrent treatment with psychiatric medications, including benzodiazepines, serotonin-noradrenergic reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), first- and second-generation antipsychotics, and mood stabilizers, and found that medication-stimulation interactions are significant considerations [258]. Specifically, they confirmed that antidepressants generally increased tDCS effects, but found that taking benzodiazepines actually worsened outcomes. They also found that tDCS did not interact with nonbenzodiazepine anticonvulsants and antipsychotics, which are frequently used as mood stabilizers in patients with depression. Considering that there have been reports of hypomanic switches after tDCS in depression patients [259, 260], including an episode of manic psychosis in a stimulated patient taking sertraline [68], these findings warrant further investigation in order to develop safety guidelines for treating mood disorders with tDCS [261].

In sum, we have an incomplete understanding of how stimulation parameters and other dose variables act on the brain or interact with medications. This lack of precise mechanistic understanding limits our ability to predict the effects of tDCS in individuals. It is essential that clinicians and self-applicators of tDCS temper their enthusiasm with an understanding of these limitations. There are ethical and pragmatic obligations to resolve these uncertainties and to seek a more detailed mechanistic understanding of tDCS.

37.7 Emerging Trends and Technologies

Newer trends and emerging technologies are being developed in response to some of the scientific challenges, particularly those involving interindividual differences and tDCS's imprecise targeting of stimulated tissue. While better dose precision in terms of stimulation parameters such

as electrode placement and current strength will help better evaluate the potential of tDCS to treat and enhance brain function, tDCS still remains a fairly nonspecific intervention in the sense that it most likely facilitates preexisting or task-generated brain network activity by making it easier or harder for neurons to fire [216]. While this may generate effects on oscillatory dynamics between brain areas, which are specifically linked to behavioral outcomes, tDCS alone does not target frequency-specific dynamics between brain areas. tDCS devices are also largely incapable of integrating feedback and modifying stimulation parameters in real time to produce or maintain a behavioral outcome. Some of the scientific challenges pertaining to variable dose response and efficacy with tDCS are being addressed by innovating newer NIBS applications with these capabilities, such as transcranial alternating current stimulation (tACS) and closed-loop tDCS (or other electrical neurostimulation), respectively. Given that the evidence for tDCS efficacy has been mixed, their mention here is relevant to a discussion of the ethical challenges posed by tDCS because these emerging technologies may afford more specific and powerful neuromodulation, which increases the likelihood of some of the foreseeable ethical problems.

Transcranial alternating current stimulation (tACS) is closely related to tDCS and has been used as a more specific probe of how oscillatory dynamics are involved in cognitive functions. In domains of working memory, tACS may be even more effective than tDCS in improving associative working memory and performance on n-back tasks [262, 263]. tACS has also been used to investigate domains beyond working memory. One study found that 5 Hz theta tACS stimulation to the frontal eye fields enhanced reading speed and decreased fixation on words [264]. Motor performance on a visuo-motor task improved with high-frequency gamma oscillations to the primary motor cortex [265]. In the visual memory domain, one tACS study demonstrated that in-phase 6 Hz stimulation of the left prefrontal and parietal cortices significantly improved visual memory-matching and reaction times [266]. Like tDCS, tACS may also have domain-specific cognitive effects, with one study showing tACS to improve object but not spatial working memory [267].

A landmark study by Reinhart and Nguyen (2019) demonstrated that declining working memory could be revived in older adults by using tACS (with the frequency of the alternating current tuned to individuals) to restore efficient coordination of rhythmic neuronal activity between brain areas in frontotemporal networks [268]. Most exciting, the improvement in working memory performance after 25 minutes of stimulation outlasted all post-stimulation measurements up to 50 minutes. This is tantalizing because it demonstrates the potential of tACS, if properly tuned to individuals and aimed at specific coupling dynamics within cortical networks, to induce longer-lasting plasticity that could mitigate cognitive decline.

While fairly new in clinical application, one notable innovation (prompted in part by DoD interest) has been the development of closed-loop tDCS systems. The idea behind these systems is that they are better able to guide personalization of timing and stimulation settings without the need for a human operator [269]. This is accomplished by utilizing a feedback signal (either neural signals or behavior) to drive or modify stimulation parameters, in order to sustain the desired effect. In this way closed-loop systems may enhance otherwise unstable effects of stimulation on cognitive behavior. The fact that the system would respond to the particular conditions in each brain with the aim of steering activity toward a particular functional state could theoretically result in more uniform responses to tDCS.

Currently, the focus has been on developing systems that make brain stimulation compatible with measurements from EEG, MEG, fNIRS, and other brain imaging modalities than to create entirely closed-loop systems [106, 249, 270–274]. Closed-loop technological advances have led to preliminary studies using tDCS for drowsiness management, memory consolidation, and responsiveness in disorders of consciousness [275–277]. While ultimately closed-loop systems may be limited in effect size by the diffuse nature

of tDCS effects compared with more focal stimulation methods like DBS, they may still have a useful purpose in helping to achieve and maintain brain states in clinically useful ways. For example in patients with ADHD, brain networks might be assisted to more readily stay in functional configurations that serve to increase focused, goal-directed behavior. A theoretical advantage to closed-loop systems for cognitive enhancement purposes is that neural control strategies can be developed without needing precise understanding of how neural activity in brain regions/networks serves various functions (which likely differs between individuals anyways). The system simply adapts the stimulation in response to sensed conditions to favor a targeted, observable outcome [278].

When considering the potential applications of closed-loop systems, it is important to note that the effects of tDCS may be to amplify or facilitate brain activity that is dependent upon the task or state that the user is in during stimulation [33, 251, 279]. Studies have found that active tDCS amplifies the effects of expectation priming compared with sham stimulation, and in the active stimulation condition positive expectation priming caused the subject to rate the perceived effectiveness of cognitive effects to be lower after receiving tDCS [279]. This latter finding emphasizes the subjectively subtle effects of tDCS, while the former suggests that tDCS effects might be mediated by the amplification of a placebo effect. Far from being less useful, this simply emphasizes the importance of targeted intervention in the subject's behavior and mentality when receiving tDCS in order to achieve more consistent results. Clinically, this could translate into tDCS being a useful adjunct to cognitive-behavioral, mindfulness-based dialectical, and compassion/acceptance oriented treatments. By actively responding to states of neural activity in ways that maintain a certain range of function, closed-loop systems may ultimately augment the potential of tDCS to assist with behaviorally driven plasticity in patients' patterns of brain activity. This is also an example of ways that the distinction between enhancement and treatment is often unclear, given that brain network activity already exists on a spectrum of dysfunctional to functional. One might think of the action of these interventions as "tuning" a metaphorical dial; rather than controlling the song that comes out, such stimulation may merely guide the expression of "songs" that can be received/processed within a functional "station frequency" [278].

Substantial technical obstacles remain that must be overcome to develop effective closed-loop systems for electrical non-invasive brain stimulation. But particularly when combined with the greater specificity of neuromodulation afforded by tACS, closed-loop systems may represent a leap forward in neuromodulatory power by sidestepping some of the problems with dose-response variability and the need to understand what drives interindividual differences in the response to tDCS. Such systems could have more potent effects and accordingly, more potent ethical consequences.

Another trend with neuroethical consequences involves the at-home use of tDCS, viewed within a larger social context that includes the neurohacker, biohacker, and lifehacker movements [6]. Users of DIY and direct-to-consumer tDCS devices are often "neurohackers," individuals associated with a subculture concerned with brain optimization [6]. Neurohacking includes noninvasive brain self-stimulation methods, although it is more heavily focused on other methods such as brain-training games and nootropics (i.e., "smart drugs"). According to Wexler (2017), the neurohacking movement is somewhat related to but different from the "biohacking" movement, which seeks to democratize scientific tools in order to redistribute the power associated with limits to how scientific inquiry is accomplished, although the subculture and focus of each movement are distinct. The neurohacking movement is also related to the "lifehacking" (aka, "quantified self") movement, which is concerned with collecting and analyzing highly detailed personal and behavioral data in order to perform self-experiments designed to optimize productivity, mood, and performance. As with neurohacking, lifehacking has become commercialized and commodified, with an endless stream of sophisticated sensors and apps

to collect behavioral data. Like neurohacking, the quantified self movement's experiments are limited by having a sample size of one, but the multiplication of apps and platforms to aggregate and track personal data enables the "crowdsourcing" of data that has more significant utility when aggregated [6]. A timely example during this writing is the use of data from app-paired body temperature sensors to model the distribution of fevers, which permitted the company owning the application to estimate spread of influenza and COVID-19 infections. These trends have inspired both neurohackers and academic researchers to consider the possibility of filling knowledge gaps through "crowdsourced" tDCS research, in which at-home users would become active research participants [280]. However, the methodological variability would pose problems for study replication and data aggregation, and study reliability would likely vary depending on whether DIY, scientific, or funding bodies led such projects [280].

As the trends continue to unfold with increasingly potent and specific neuromodulatory technologies, military-sponsored development of closed-loop NIBS systems, commercialization of at-home stimulation and neural signal recording devices, and democratized science, ethical tensions will inevitably arise that will impact clinical practice. By anticipating some of these, we gain the ability to contemplate potential courses of action to avoid some of the more severe ethical pitfalls.

37.8 Ethical Challenges

The potential for tDCS use to become widespread raises a number of social and existential risks that must be carefully weighed against its benefits. By their nature, the effects of tDCS on cognition and affect blur the distinctions between treatment and enhancement. Moreover, its accessibility makes its use especially difficult to confine within the bounds of clinical medicine. Thus, ethical issues raised by tDCS cannot be viewed solely through a clinical ethics lens. Like pharmacological treatments that also have the potential to be used for enhancement purposes, the use of tDCS has not and will not remain in the medical realm. However, there is much still unknown about cognitive enhancement [281], both in terms of the science and in terms of its broader effects in ethical, legal, and social spheres. As discussed below, the ethical issues surrounding tDCS can be broadly categorized into concerns regarding safety, justice, character, and autonomy. The latter three concerns deal with potential trajectories of tDCS technology development and use patterns that are, at present, still somewhat speculative. However, it is important to consider the ethical implications of possibilities so that the negative consequences can be anticipated, and if possible, avoided.

37.9 Safety

In most traditional ways of thinking about safety, tDCS is of low concern; all current evidence indicates that tDCS delivery by currently applied protocols is very safe. While there are some recognized minor risks associated with tDCS such as mild headache and a mild itching or burning sensation under the electrodes [282], the risk of obvious physical injury from tDCS is extremely low. The most severe recognized potential medical risks associated with tDCS are burns to the skin and complications resulting from electrical equipment failures [283–285], but these are very rare and more likely to result from DIY systems than commercially manufactured stimulators. However, it is worth noting that in a study of 339 users of direct-to-consumer at-home tDCS devices, 10 participants reported serious skin burns [221].

In recent years, research has explored the feasibility and requirements to safely implement at-home administration of tDCS, both with and without remote supervision of administration by clinical or research technicians [19, 204, 205]. This research highlights special safety requirements of specific populations whose symptoms may interfere with self-administration of tDCS, such as attentional deficits or motor deficits in ADHD and MS, respectively. It is clear that

further work is needed to carefully consider what additional procedures need to be in place for safe remote clinical administration of tDCS, and to this extent a few articles have been published with specific guidelines and procedures for remotely supervised tDCS in various clinical populations [19, 65, 205]. At the time of this writing, global events such as the COVID-19 pandemic have affected clinical practice across medicine by increasing the demand for telehealth services, and established treatment procedures using remotely supervised tDCS could be usefully incorporated in both clinical research and neurological telemedicine under similar circumstances in the future.

The main potential concern with safety is that tDCS may alter cognition in unintended ways [286, 287]. Evidence suggests that stimulation at different sites may benefit some cognitive abilities but impair others [288]. Additionally, inhibiting or exciting the same region of brain can elicit different types of benefits. For example, anodal stimulation to the lateral prefrontal cortex not only improved working memory but also related fronto-executive functions that require a high degree of cognitive control, such as selective attention and set-switching. However, some aspects of cognitive flexibility and divergent thinking could be more consistent with a loosening of cognitive control, resulting in less "top-down" regulatory filtering of low-level information. Accordingly, cathodal stimulation to lateral prefrontal cortex has been shown to enhance cognitive flexibility in tool use [34]. Viewed together, these studies raise theoretical concerns that stimulation delivered with the intent of enhancing attention or working memory could have detrimental tradeoffs for cognition associated with creativity.

These kinds of tDCS-induced mental tradeoffs have been demonstrated for other aspects of cognition [288]. For instance, Iulcano and Kadosh (2013) explored how tDCS affected two dissociable aspects of learning that were relevant to mastery of a novel mathematical task: skill acquisition rate, and skill automaticity whereby tasks are performed quickly, effortlessly, and without conscious intention. Using tDCS to brain regions associated with learning (posterior parietal cortex; PPC) or automaticity (DLPFC) the investigators demonstrated a double dissociation wherein tDCS to the PPC enhanced learning rate but impaired automaticity while tDCS of the DLPFC enhanced automaticity at the expense of learning rate [288].

The nature of stimulation benefits may be specific to certain traits or states. For example, tDCS improved arithmetic decision-making efficiency in healthy subjects who had high levels of preexisting math anxiety, but it slowed reaction times in healthy subjects who had low-math anxiety and whose arithmetic efficiency was already unimpaired [289]. In several studies, state-dependent tDCS effects were linked to one's starting level of ability, with factors that lead to better performance at baseline associated with less improvement, and potentially impairment [193, 290, 291]. In a related fashion, the effects of tDCS on learning and memory task may depend on the stage of training [292].

In some cases where tDCS is associated with worse outcomes, stimulation does not directly cause cognitive degradation, but rather may block typical improvement by factors such as practice. One group discovered this while looking at the effects of tDCS on repeated IQ testing, employed as a means to simultaneously assess multiple domains for cognition. The study found that practice-related improvements for subtests of fluid intelligence (e.g., perceptual reasoning) were specifically attenuated when right, left, or bilateral anodal tDCS was delivered before retesting [293]. While in retrospect these results are consistent with expected effects of frontal anodal tDCS on cognitive flexibility, the authors initially hypothesized that tDCS would improve IQ test performance because previous studies had found that other types of task performance were improved by such stimulation. Such evidence highlights that tDCS is not a panacea, and further suggests that perhaps we should consider a more nuanced notion than "cognitive enhancement" for framing tDCS applications.

One of the challenges in understanding the risks, benefits, and trade-offs of using tDCS to enhance cognition is that, while many in the DIY

stimulation community and elsewhere look toward the cognitive neuroscience community to inform how stimulation for enhancement could be pursued, the fundamental approach taken by most cognitive neuroscience studies does not adequately address the "cognitive safety" of enhancement with tDCS in at least two ways. First, the scientific methodology used in most cognitive neuroscience studies of tDCS only test one or a very limited number of cognitive functions in order to test specific hypotheses about the relationships between the brain areas stimulated and those specific mental operations. They do not test to make sure there are no deleterious effects on every other intellectual function. Second, cognitive neuroscience studies generally do not test for the durations that one might consider relevant if one was trying to make long-term changes in cognition. We simply do not know what the effects of increased frequencies and durations of stimulation are for individuals with healthy cognition. While this is not terribly relevant for basic cognitive neuroscience studies, it is extremely relevant for cognitive enhancement studies, due to the increased likelihood of repeated and potentially prolonged stimulation sessions in the latter. Similarly patient studies do not wholly inform what the likely effects of neural enhancement with brain stimulation are because the brains in which therapeutic stimulation is being applied have already been altered by disease. Thus, safety considerations for tDCS underscore that the science has yet to support the technical application of tDCS for unmitigated cognitive enhancement.

37.10 Justice

Distributive justice refers to the equitable distribution of benefits. The development of "cosmetic" tDCS as a boutique service for cognitive remediation or enhancement could exacerbate social disparities by introducing a new type of "cognitive" privilege for those who can afford to exogenously treat or augment their own intellect [294]. This type of development is no longer idle futuristic speculation. As of 2020, this boutique type administration of tDCS at "fancy, resort-style clinic" already exists, for example the Sha Wellness Clinic on the Mediterranean coast of Spain, with accommodations ranging from $360 to $8200 per night, and brain stimulation treatment packages costs starting at $4000. The clinic disclosed that over 50,000 people from around the world have visited the spa, among them executives and CEOs, although this number may not reflect the number of guests who opted for tDCS services while there (weight loss and detox services are also offered). According to a CNN article on the spa, the brain stimulation program has packages marketed toward aging individuals who wish to keep their maximal cognitive function as they age (prices starting at $8300) as well as a "Business Reset" program for senior management teams to boost productivity.

If boutiqued cognitive enhancement becomes a norm that is taken for granted, expectations regarding a "normal" range of cognitive abilities could become distorted to the point where unaugmented cognition is perceived as pathological. This could result in (further) medicalization of systemic disadvantage, which may introduce further obstacles to the remediation of social inequality, since access to education, medical care, and nutrition are already inequitable. Thus, explicit "cognitive health" disparities might further entrench systems of privilege and socioeconomic inequality. In many ways, this problem is not new or unique to enhancement with NIBS, but is symptomatic of the already vast separation in privilege between the haves and the have-nots.

On the other hand, compared with other technologies (including pharmaceutical agents) with utility as treatments or enhancements, justice may arguably constitute less of an issue for tDCS than other neurotechnologies, because it is relatively inexpensive and easy to create and employ with only modest technical training [295]. Noninvasive brain stimulation in healthcare is currently inequitable; if tDCS could confer comparable benefits while requiring less medical or technological infrastructure, it could increase justice in medically oriented neurostimulation [296]. Outside the medical realm, some researchers have suggested that safe and cost-effective

tDCS may actually tackle, rather than cause, unfairness in sports [297].

Ethical assessment of the potential of tDCS to introduce justice issues depend on an accurate estimation of people's willingness to stimulate themselves to either enhance or repair cognition, and their moral attitudes toward others doing so. Medaglia and colleagues surveyed nearly 1000 demographically diverse individuals to probe their attitudes toward a fictional brain stimulation device [298]. They employed an experimental design that examined attitudes toward stimulation delivered either to themselves or others, comparing attitudes when the intention is to repair versus enhance cognitive functions that are considered "core" vs "peripheral" to authentic self-identity. The investigators found that individuals viewed affecting themselves with brain stimulation to be more morally acceptable, but were overall more willing to use brain stimulation on others to repair core functions essential to empathic functioning [298]. This finding suggests that the public is likely to care about the potential of tDCS to affect character, if tDCS use was considered effective and more widespread (discussed below). Overall, the study found that the public is generous in considering the moral acceptability of other people to enhance cognitive function. Interestingly, this study utilized a scenario where stimulation resources were finite, and the authors remarked that it might be interesting to probe the extent of that generosity and altruistic attitudes when required to choose between optimizing themselves or others.

37.11 Character

Issues of character relate to our essential humanity and how we find meaning in life. Ethical issues of character with brain simulation are those that impact our experience of personhood [299]. With its potential to alter our experience of behavior and cognition, brain stimulation raises two key questions. The first of these is about identity and the integral core constellation of mental and behavioral characteristics that define us. It asks, "To what extent can and should we have the ability to change the core of who and what we are?" In part, the answers depend on the degree to which the core traits that distinguish us are considered to be stable, consistent, and integrated, and whether tDCS can disintegrate or change this subjective "core." For example, some cognitive domains where tDCS has been applied such as moral cognition [13, 50] and creativity [35, 36] do raise questions about authenticity; if these can be enhanced exogenously, is that more or less valuable than the natural cultivation of such behavior? And do people intuitively support such enhancements to themselves, or others?

The study by Medaglia et al. (2019) found that people were most willing to use tDCS to restore cognition related to core identity in others, but nevertheless considered it to be more morally acceptable to use tDCS on themselves than others. This bespeaks the value placed on preserving the character of individuals in society, but also suggests that individual autonomy is also a priority. Given that past studies have found that individuals were less willing to pharmaceutically influence traits that are core (versus peripheral) to one's character, Medaglia's findings may also indicate that people's moral intuitions about neuromodulatory interventions that can affect one's authentic identity may differ when the means is electrical versus pharmaceutical. We do not currently have an in-depth understanding of how sociocultural processes shape the way people evaluate and accept different technological mechanisms with respect to character, and this is an area where more research could supply insight into technological decision-making and public policy formulation [298].

The second question is about self and the potential long-term consequences of self-enhancement on character building and other aspects of psychosocial development, both within individuals and as a society. What sort of experiences are necessary for wisdom, maturity, or virtue, and what are the consequences of avoiding them? These questions have already been deeply explored for neural interventions, in particular invasive deep brain stimulation (DBS) [300–304]. However, the scope of access to tDCS adds an additional dimension to such ethical

consideration, as the potential effects on character development or change shifts from being an issue that affects select patients and their loved ones to something that could extend more directly to everyone.

Aspects of life experience that are not necessarily subjectively positive are integral to shaping a person's bearing, demeanor, and personality [305, 306]. It is a widely accepted social norm that adversity breeds character, and experiencing some adversity often leads to superior performance and functioning [307]. If cognitive and emotional challenges can all be eased by exogenously stimulating the brain, how does that affect the resilience and moral quality of a society in which this life of convenience is available? On the other hand, how much suffering is enough, and who gets to decide? After all, we do not consider it a moral failing if a person treats pain associated with childbirth or medical procedures. At what point, if any, does relief from difficult experiences diminish us [308]? The consequence of tDCS on individual development ultimately affects society and culture in ways that are evolving and reciprocal, because social dynamics among individuals and groups influence, and are influenced by, the ambient culture. Thus, the adoption of widespread self-enhancement will bring questions about whether there should be limits to alter our fundamental nature to the forefront in formulating social and policy responses to growing use of tDCS.

Despite potential concerns, the effects of widespread tDCS use on character may not necessarily be negative. For instance, ongoing research is exploring the role of the brain in sports and fatigue (http://www.neuroelectrics.com/use-case/), and seeks to leverage this understanding to develop stimulation that could remove neural obstacles to maximum physical athletic performance. One could argue that removing obstacles to maximum performance given maximum effort is a categorically different type of enhancement than enhancement that makes something require less effort. In such a context, tDCS could be viewed as an enabling tool that could enhance character, rather than to act as a substitute for qualities that character would ordinarily supply to ensure success, such as commitment, patience, perseverance, and self-transcendence. This distinction is potentially relevant not only to athletics, but also to treatment in neuropsychiatry, wherein stimulation could potentially enable rather than substitute for self-driven efforts to cultivate positive character traits. For example, enhancement of executive function in someone with ADHD to improve impulse control and the ability to sustain attention might enable such individuals to practice acts of high character, such as finishing what one has started or keeping commitments. The cardinal distinction applying to both situations is that high sustained effort is still required, and that absent the intervention, there are limits to the degree that such effort could affect performance. Assuming that the same amount of effort is exerted with or without tDCS, what is the true nature of the effect, if any, on the character of the athlete or individual with ADHD? These are all largely philosophical and psychological questions whose answers hinge on arguments about the relative influence afforded to situational context versus personality when assessing character. Although this subject is beyond the scope of this chapter, it is worth noting that a meaningful discussion of the impact of tDCS on character may require further consideration of a broader conceptual framework to address the daunting philosophical challenge of relating concepts such as identity and self to behavior and neurobiological functions.

37.12 Autonomy

Autonomy can be thought of as the right to one's own life, to make choices based on reasons and motivations that are not the product of manipulating or distorting external forces. In the context of tDCS, autonomy can be considered in terms of two types of freedom: (1) the freedom not to be stimulated, and (2) the freedom to be stimulated.

The freedom from stimulation can be threatened by hard or soft coercion. In hard coercion, the individual is forced into an activity for the perceived "good of society." Neuropsychological

hard coercion is far from unheard of. Examples include psychopharmacologic agents given to soldiers to maintain battlefield performance and chemical castration to diminish the libido of imprisoned sex offenders [309, 310]. It is not all that hard to imagine cognitive enhancement with brain stimulation potentially following a similar course with similar vulnerable populations. Whether or not the technology actually develops to influence brain networks with enough specificity to affect moral cognition, dystopian possibilities exist whereby authorities may be tempted to use tDCS or its derivatives for "moral correction" purposes. For example, functional brain network differences have been detected in individuals who place a greater value obedience and authority [311]. It is conceivable that state-sponsored neuromodulation could be employed to influence the actions and attitudes of persons deemed to be politically or socially problematic. With soft coercion, the individual feels societal pressure to keep up with norms and mores. As we know from many examples in professional sports, in high-stakes competitive environments, individuals turn readily to performance enhancers to give themselves a competitive edge. With respect to mental performance, we can see examples of soft coercion currently in individuals who take pharmacologic cognitive agents in hopes of optimizing their performance at school or work. With respect to neuropsychology, the hazard of soft coercion again highlights that tDCS could potentially blur the distinctions between pathologically poor brain function and brain function that is normal but suboptimal for the tasks one desires to accomplish.

The indistinct boundary between optimal, declining, and pathological brain function is important to consider, as aging individuals consider using tDCS in hopes of maintaining peak cognitive performance and a competitive edge in an economy and culture that places a high value on youth and vigor. While news media gives the impression of a younger user base for at-home tDCS devices, Wexler (2017) found that the mean age of at-home tDCS users was 45.3 years. Places like the Sha Wellness Clinic specifically market toward highly educated, wealthy individuals (such as corporate executives) with anxieties about losing their "edge" due to aging. The higher-than-expected mean age of at-home tDCS users likely may reflect the pressure older individuals feel to guard against the cognitive effects of aging. This may be an early instantiation of concerns about soft coercion, given that more older adults are willing to risk experimenting with a technology that carries the risk of unknown or unintended effects. There is a need for further research into the possibility that aging and older individuals may be more vulnerable to soft coercion and increased risks as new noninvasive brain stimulation methods are increasingly marketed directly to consumers.

The freedom to be stimulated is unlikely to be overtly threatened given the accessibility of tDCS components. In this, lessons can be learned from other examples of cognitive self-enhancement, and cosmetic applications of medical technologies, including neuropharmacology. While it is important to remember that individuals are free to do as they see fit with respect to their own bodies and minds, inevitably, autonomy must necessarily be balanced with other ethical imperatives that arise from pragmatic or moral justifications, such as the need to consider the health of the community. Just as soft coercion can be used to encourage stimulation, social pressures can be exerted to influence the actions of those who would elect to use tDCS for medical or enhancement purposes. Given the complexity of the issues surrounding the use of tDCS for medical or enhancement, monolithic laws are unlikely to be helpful—or effective.

37.13 Ethical Considerations Pertaining to Neuropsychiatry

It may be taken for granted that the principal ethical considerations for tDCS with respect to the practice of neuropsychiatry boil down to whether tDCS is an acceptable way to treat patients. To this end, it is important to keep in mind that the distinction between normal and pathological is indiscrete and often culturally determined. Importantly, individuals whose thoughts and behaviors may objectively deviate

from typical behavioral norms do not always do so in a way that leads to suffering; the moral imperative to medically treat dysfunction depends on the qualitative impact it has on an individual's life rather than the mere presence of abnormality [312]. Indeed, neurodiversity is increasingly being recognized as an intrinsic and valuable part of the spectrum of human experience that confers value and vigor to our overall ability to cognitively adapt to social and environmental changes [313]. Medicalizing neurodiversity pressures individuals and professionals (to some extent) into enforcing conformity to sociocultural norms of what is considered a "valuable" life. Neuropsychiatry as a field should consider tDCS alongside other dilemmas involving neurodiversity that drive the overall societal disposition toward psychiatry. These are not necessarily different issues than those pertaining to medicating neuropsychiatric disorders, but the fact that one does not necessarily need a prescription to self-administer tDCS (in some form) could shape perspectives on whether neuropsychiatric therapeutic applications of tDCS are perceived as legitimate, relative to other contexts in which tDCS could be used for enhancement or recreation.

Neuropsychiatry as a field should also be aware of the ways that widespread and even nonmedical use of tDCS could influence perceptions of normality versus pathology. It can, at times, be difficult to distinguish between true "diseases" of the mind and more mundane dissatisfaction with mental states. Psychological aspects of individuals that are considered to be symptoms can often be conceptualized as traits that vary along a continuous spectrum of expression, for example, from inattentiveness to an attention deficit, or from sadness or emotional exhaustion to depression. This slippery slope of spectrum is especially problematic considering the capacity of tDCS to alter intellectual performance or mood. While most neuroscientists would argue that we are still far from being able to reliably alter mental states on an individualized basis using tDCS, the marketing for products like Thync and subjective experiences reported by at-home and DIY users indicate that at least the perception that tDCS can be used to induce targeted changes to mood (for example) exists presently. Having the power to so easily remedy dissatisfaction with one's mental states using tDCS—or even just believing that one has that power—has the potential to further obscure boundaries between what is considered normal, subclinical, or pathological.

Clinical fields that purport to distinguish between normal and pathological mental functioning face special obstacles when clinical values conflict with sociocultural norms, such as individuality or self-reliance. This has implications for clinical uses of tDCS. It is already difficult to determine when it is ethical to use technology to intervene in one's mental functioning. Widespread use of neural enhancement technologies like tDCS could further pathologize aspects of cognitive performance that would otherwise be considered along a spectrum of normalcy. This distortion could have the effect of decreasing individual autonomy by exerting positive pressure on clinical professionals to treat patients using neurostimulation or on individuals to "treat" themselves. As with pharmacological self-enhancement, some individuals might seek neuropsychiatric treatment for the purpose of procuring access to such technology as opposed to alleviating the suffering caused by illness. Thus neuropsychiatrists run the theoretical risk of becoming dispensers of cognitive commodities in tDCS as well as neuropharmacology. On the other hand, if there is general cultural pushback to increasing use of NIBS for self enhancement, the application of tDCS in neuropsychiatric contexts, even where therapeutically beneficial, could come to be seen as problematic. Consider, for example, the stigma that popular culture has placed on electroconvulsive therapy (ECT), a highly effective treatment for refractory and life-threatening cases of depression, and how that stigma has had a sustained negative influence on its acceptance and use as a therapy. If tDCS becomes similarly stigmatized, this could raise obstacles to the development of effective treatments for a variety of neurologic and neuropsychiatric conditions.

Several points raised in this chapter also have ethical implications for clinician-patient encounters. Because tDCS is not yet approved for specific clinical indications, we will here consider

concerns that apply primarily to users of DIY or direct-to-consumer products. As public use of these technologies becomes more widespread, patients may sometimes confide to their neurologists or psychiatrists that they are experimenting with tDCS for self-treatment. In this situation, it is important that patients understand the safety consequences tDCS, including possible unintentional alteration of cognition or emotions. It will also be important for patients to recognize the current limits of the scientific literature, which cannot reliably predict what effects tDCS will have in the context of polypharmacy or other concurrent treatments. Conversations about the state of tDCS science and what is and is not known about tDCS might help patients to make better-informed decisions for themselves. In 2016, an open letter authored by 4 neuroscientists and signed by 39 others was published to communicate with the public about the risks posed both by what is known and unknown about tDCS [231]. However, insofar as there is currently no compelling evidence of serious medical risk posed by tDCS, some patients may be inclined to disregard the advice of their clinician and continue to self-administer tDCS in ways that, at least theoretically, seem potentially deleterious. This raises ethical issues of how best to engage with the patients regarding the risk of tDCS misuse in the absence of clear evidence for or against long term harms. The issue of clinical misuse or overuse is similarly likely to arise in the event that tDCS is approved for specific indications such as depression or pain. While there is no clear one-size-fits-all strategy for navigating this topic with patients, it is an issue that neurologists and psychiatrists should be aware and ask about in their patients, especially as awareness of the therapeutic potential of tDCS becomes much more widespread in the public sphere.

37.14 Conclusion

In sum, there are pragmatic considerations specific to the practice of neuropsychiatry that bear weight in assessing both the utility and risks of employing tDCS as therapy. As it is presently understood, the mechanism of tDCS effects may be of particular utility for disorders in which coincident dysfunction and overlapping neural circuits lead to a range of psychiatric and cognitive symptoms. Targeting those common neural substrates with tDCS may lead to a variety of salutary effects in patients with complex disorders of mood, affect, and cognition. However, stimulation of overlapping neural circuits may also give rise to cognitive trade-offs that should prompt caution, particularly when the intent is to use tDCS to enhance normal cognition as opposed to treat disease. It is important to consider what is known versus what is not known about tDCS when designing clinical and cognitive research studies, and even more so when developing public policy and communicating with potential tDCS users (both consumers and patients). Clinicians and neuroscientists alike have an ethical responsibility to ensure that the lay public can access accurate information about what is and is not known about the mechanisms, effects, and safety of tDCS. In some cases, this may mean tempering unbridled enthusiasm for tDCS expressed in media coverage. The benefits and risks of tDCS clearly vary according to the context of administration, both with respect to the research, clinical, and cosmetic purposes for stimulation, as well as the states and traits of individual recipients.

All these considerations prompt a need to anticipate the trajectories of current and potential future use of tDCS both within and outside of clinical contexts, as there are likely to be dynamic broader social and cultural consequences of tDCS use within neuropsychiatry. Likewise, neuroethical consequences from nonclinically oriented tDCS use are also likely to have an impact on the way tDCS is used and sought out by patients. Thus, the use of tDCS in neuropsychiatry may have profound impacts not only on the social-cultural milieu but also on the perceptions and practices of neuropsychiatry as a field.

References

1. Adee S. Zapping the brain to get with the flow. The Washington Post [Internet]. Feb 13, 2012. [https://www.washingtonpost.com/national/healthscience/zapping-the-brain-to-get-with-the-flow/2012/02/09/gIQAuiSeBR_story.html] Accessed June 19, 2021.

2. Dubljević V, Saigle V, Racine E. The rising tide of tDCS in the media and academic literature. Neuron [Internet]. 2014;82(4):731–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24853934&retmode=ref&cmd=prlinks.
3. Sample I. Got a problem – put your electric thinking cap on. Guardian Unlimited [Internet]. 2011. Available from: http://guardian.co.uk.
4. Livni E. Learning faster might be possible with this wearable headset. Quartz. 2019.
5. Wexler A. The practices of do-it-yourself brain stimulation: implications for ethical considerations and regulatory proposals. J Med Ethics [Internet]. 2016;42(4):211–5. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26324456&retmode=ref&cmd=prlinks.
6. Wexler A. The social context of "do-it-yourself" brain stimulation: Neurohackers, biohackers, and lifehackers. Front Hum Neurosci. 2017;11(May):224.
7. Wexler A, Reiner PB. Oversight of direct-to-consumer neurotechnologies. Science (80-). 2019;363(6424):234–5.
8. Reinhart RMG, Cosman JD, Fukuda K, Woodman GF. Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. Atten Percept Psychophys [Internet]. 2017;79(1):3–23. Available from: https://doi.org/10.3758/s13414-016-1224-2.
9. Hamilton RH, Zreik J. Wired for thought. Sci Am [Internet]. 2014. Available from: http://www.nature.com/scientificamerican/journal/v310/n2/full/scientificamerican0214-12.html.
10. Shah-basak PP, Hamilton RH, Nitsche MA, Woods AJ. Transcranial direct current stimulation in cognitive neuroscience. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 509–39.
11. Kelley NJ, Gallucci A, Riva P, Lauro LJR, Schmeichel BJ. Stimulating self-regulation: a review of non-invasive brain stimulation studies of goal-directed behavior. Front Behav Neurosci. 2019;12(January):1–20.
12. Mosbacher JA, Brunner C, Nitsche MA, Grabner RH. Effects of anodal tDCS on arithmetic performance and electrophysiological activity. Front Hum Neurosci. 2020;14(February):17.
13. Darby RR, Pascual-Leone A. Moral enhancement using non-invasive brain stimulation. Front Hum Neurosci. 2017;11(February):1–10.
14. Galea JM, Celnik P. Brain polarization enhances the formation and retention of motor memories. J Neurophysiol [Internet]. 2009;102(1):294–301. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19386757&retmode=ref&cmd=prlinks.
15. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci [Internet]. 2009;106(5):1590–5. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19164589&retmode=ref&cmd=prlinks.
16. Dumel G, Bourassa M-E, Charlebois-Plante C, Desjardins M, Doyon J, Saint-Amour D, et al. Motor learning improvement remains 3 months after a multisession anodal tDCS intervention in an aging population. Front Aging Neurosci. 2018;10(October):1–9.
17. Greeley B, Barnhoorn JS, Verwey WB, Seidler RD. Multi-session transcranial direct current stimulation over primary motor cortex facilitates sequence learning, chunking, and one year retention. Front Hum Neurosci. 2020;14(March):1–18.
18. Nikolin S, Huggins C, Martin D, Alonzo A, Loo CK. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul. 2018;11(2):278–88.
19. Gough N, Brkan L, Subramaniam P, Chiuccariello L, De Petrillo A, Mulsant BH, et al. Feasibility of remotely supervised transcranial direct current stimulation and cognitive remediation: a systematic review. PLoS One. 2020;15(2):e0223029.
20. Perceval G, Martin AK, Copland DA, Laine M, Meinzer M. Multisession transcranial direct current stimulation facilitates verbal learning and memory consolidation in young and older adults. Brain Lang [Internet]. 2020;205(August 2019):104788. Available from: https://doi.org/10.1016/j.bandl.2020.104788.
21. Nikolin S, Loo CK, Bai S, Dokos S, Martin DM. Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning. Neuroimage [Internet]. 2015;117:11–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25987365&retmode=ref&cmd=prlinks.
22. Elmer S, Burkard M, Renz B, Meyer M, Jäncke L. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. Behav Brain Funct [Internet]. 2009;5:29. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19604352&retmode=ref&cmd=prlinks.
23. Imburgio MJ, Orr JM. Effects of prefrontal tDCS on executive function: methodological considerations revealed by meta-analysis. Neuropsychologia. 2018;117(April):156–66.
24. Mancuso M, Ilieva IP, Hamilton RH, Farah MJ. Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. J Cogn Neurosci [Internet]. 2017;28(8):1063–89. Available from: https://www.apa.org/ptsd-guideline/ptsd.pdf%0A; https://www.apa.org/about/offices/directorates/guidelines/ptsd.pdf.
25. Ouellet J, McGirr A, Van den Eynde F, Jollant F, Lepage M, Berlim MT. Enhancing decision-making and cognitive impulse control with transcranial direct current stimulation (tDCS) applied over

the orbitofrontal cortex (OFC): a randomized and sham-controlled exploratory study. J Psychiatr Res [Internet]. 2015;69:27–34. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26343591&retmode=ref&cmd=prlinks.
26. Jacobson L, Javitt DC, Lavidor M. Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. J Cogn Neurosci [Internet]. 2011;23(11):3380–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21452949&retmode=ref&cmd=prlinks.
27. Pope PA, Miall RC. Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum. Brain Stimul [Internet]. 2012;5(2):84–94. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22494832&retmode=ref&cmd=prlinks.
28. Pope PA, Brenton JW, Miall RC. Task-specific facilitation of cognition by anodal transcranial direct current stimulation of the prefrontal cortex. Cereb Cortex [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25979089&retmode=ref&cmd=prlinks.
29. Rodrigues de Almeida L, Pope PA, Hansen PC. Task load modulates tDCS effects on language performance. J Neurosci Res. 2019;97(11):1430–54.
30. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul [Internet]. 2015;8(2):253–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25465291.
31. Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul [Internet]. 2011;4(2):84–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1935861X10000628.
32. Hill AT, Rogasch NC, Fitzgerald PB, Hoy KE. Impact of concurrent task performance on transcranial direct current stimulation (tDCS)-induced changes in cortical physiology and working memory. Cortex [Internet]. 2019;113:37–57. Available from: https://doi.org/10.1016/j.cortex.2018.11.022.
33. Weissengruber S, Lee SW, O'Doherty JP, Ruff CC. Neurostimulation reveals context-dependent arbitration between model-based and model-free reinforcement learning. Cereb Cortex. 2019;29(11):4850–62.
34. Chrysikou EG, Hamilton RH, Coslett HB, Datta A, Bikson M, Thompson-Schill SL. Noninvasive transcranial direct current stimulation over the left prefrontal cortex facilitates cognitive flexibility in tool use. Cogn Neurosci [Internet]. 2013;4(2):81–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23894253&retmode=ref&cmd=prlinks
35. Hertenstein E, Waibel E, Frase L, Riemann D, Feige B, Nitsche MA, et al. Modulation of creativity by transcranial direct current stimulation. Brain Stimul [Internet]. 2019;12(5):1213–21. Available from: https://doi.org/10.1016/j.brs.2019.06.004.
36. Lucchiari C, Sala PM, Vanutelli ME. Promoting creativity through transcranial direct current stimulation (tDCS). A critical review. Front Behav Neurosci. 2018;12(August):167.
37. Floel A, Rösser N, Michka O, Knecht S, Breitenstein C. Noninvasive brain stimulation improves language learning. J Cogn Neurosci [Internet]. 2008;20(8):1415–22. Available from: http://www.mitpressjournals.org/doi/abs/10.1162/jocn.2008.20098.
38. Savill N, Ashton J, Gugliuzza J, Poole C, Sim Z, Ellis AW, et al. tDCS to temporoparietal cortex during familiarisation enhances the subsequent phonological coherence of nonwords in immediate serial recall. Cortex [Internet]. 2015;63:132–44. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25282052&retmode=ref&cmd=prlinks.
39. Price A, Bonner M, Hamilton R, Peelle J, Grossman M. Modulating language comprehension using HD-tDCS. Brain Stimul [Internet]. 2017;10(1):e12. Available from: https://doi.org/10.1016/j.brs.2016.11.056.
40. Cummine J, Boliek CA, McKibben T, Jaswal A, Joanisse MF. Transcranial direct current stimulation (tDCS) selectively modulates semantic information during reading. Brain Lang [Internet]. 2019;188(October 2018):11–7. Available from: https://doi.org/10.1016/j.bandl.2018.11.002.
41. Younger JW, Wagner MR, Booth JR. Weighing the cost and benefit of transcranial direct current stimulation on different reading subskills. Front Neurosci. 2016;10(June):1–9.
42. Bhattacharjee S, Chew A, Kashyap R, Wu C, Yeo M, O'Brien B, et al. Could tDCS modulate bilingual reading? Brain Stimul. 2019;12(2):569.
43. Costanzo F, Rossi S, Varuzza C, Varvara P, Vicari S, Menghini D. Long-lasting improvement following tDCS treatment combined with a training for reading in children and adolescents with dyslexia. Neuropsychologia [Internet]. 2019;130(March 2018):38–43. Available from: https://doi.org/10.1016/j.neuropsychologia.2018.03.016.
44. Turkeltaub PE, Benson J, Hamilton RH, Datta A, Bikson M, Coslett HB. Left lateralizing transcranial direct current stimulation improves reading efficiency. Brain Stimul [Internet]. 2012;5(3):201–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22305346&retmode=ref&cmd=prlinks.
45. McKinley RA, Bridges N, Walters CM, Nelson J. Modulating the brain at work using noninvasive transcranial stimulation. Neuroimage [Internet]. 2012;59(1):129–37. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21840408&retmode=ref&cmd=prlinks.

46. Woods AJ, Hamilton RH, Kranjec A, Minhaus P, Bikson M, Yu J, et al. Space, time, and causality in the human brain. Neuroimage [Internet]. 2014;92:285–97. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24561228&retmode=ref&cmd=prlinks.
47. Medina J, Beauvais J, Datta A, Bikson M, Coslett HB, Hamilton RH. Transcranial direct current stimulation accelerates allocentric target detection. Brain Stimul [Internet]. 2013;6(3):433–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22784444&retmode=ref&cmd=prlinks.
48. Knoch D, Pascual-Leone A, Meyer K, Treyer V, Fehr E. Diminishing reciprocal fairness by disrupting the right prefrontal cortex. Science (80-) [Internet]. 2006;314(5800):829–32. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17023614&retmode=ref&cmd=prlinks.
49. Nihonsugi T, Ihara A, Haruno M. Selective increase of intention-based economic decisions by noninvasive brain stimulation to the dorsolateral prefrontal cortex. J Neurosci [Internet]. 2015;35(8):3412–9. Available from: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.3885-14.2015.
50. Fan B, Mao W, Jin J, Ma Q. Modulating activity in the dorsolateral prefrontal cortex alter corruption behavior: a transcranial direct current stimulation study. Behav Brain Res [Internet]. 2020;382(October 2019):112479. Available from: https://doi.org/10.1016/j.bbr.2020.112479.
51. Gross J, Emmerling F, Vostroknutov A, Sack AT. Manipulation of pro-sociality and rule-following with non-invasive brain stimulation. Nat Sci Rep. 2018;8(1827):1–10.
52. Lo YL, Fook-Chong S, Tan EK. Increased cortical excitability in human deception. Neuroreport [Internet]. 2003;14(7):1021–4. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=12802195&retmode=ref&cmd=prlinks.
53. Karim AA, Schneider M, Lotze M, Veit R, Sauseng P, Braun C, et al. The truth about lying: inhibition of the anterior prefrontal cortex improves deceptive behavior. Cereb Cortex [Internet]. 2010;20(1):205–13. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19443622&retmode=ref&cmd=prlinks.
54. Priori A, Mameli F, Cogiamanian F, Marceglia S, Tiriticco M, Mrakic-Sposta S, et al. Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cereb Cortex [Internet]. 2008;18(2):451–5. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17584853&retmode=ref&cmd=prlinks.
55. Gao M, Yang X, Shi J, Lin Y, Chen S. Does gender make a difference in deception? The effect of transcranial direct current stimulation over dorsolateral prefrontal cortex. Front Psychol. 2018;9(AUG):1–7.
56. Tang H, Ye P, Wang S, Zhu R, Su S, Tong L, et al. Stimulating the right temporoparietal junction with tDCS decreases deception in moral hypocrisy and unfairness. Front Psychol. 2017;8(NOV):1–7.
57. Noguchi Y, Oizumi R. Electric stimulation of the right temporo-parietal junction induces a task-specific effect in deceptive behaviors. Neurosci Res [Internet]. 2018;128:33–9. Available from: https://doi.org/10.1016/j.neures.2017.07.004.
58. Dèttore D, O'Connor K. OCD and cognitive illusions – Springer. Cogn Ther Res [Internet]. 2013. Available from: http://link.springer.com/article/10.1007/s10608-012-9440-0.
59. Tschacher W, Kupper Z. Perception of causality in schizophrenia spectrum disorder. Schizophr Bull [Internet]. 2006;32 Suppl 1:S106–12. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16896057&retmode=ref&cmd=prlinks.
60. George MS, Padberg F, Schlaepfer TE, O'Reardon JP, Fitzgerald PB, Nahas ZH, et al. Controversy: repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-complusive disorder, panic, posttraumatic stress disorder). Brain Stimul [Internet]. 2009;2(1):14–21. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20633399&retmode=ref&cmd=prlinks.
61. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology [Internet]. 2013;64:566–78. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22749945&retmode=ref&cmd=prlinks.
62. Zhao H, Qiao L, Fan D, Zhang S, Turel O, Li Y, et al. Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): clinical applications and safety concerns. Front Psychol. 2017;8(MAY):685.
63. Pinto CB, Costa BT, Duarte D, Fregni F. Transcranial direct current stimulation as a therapeutic tool for chronic pain. Physiol Behav. 2018;176(1):139–48.
64. Yadollahpour A, Jalilifar M, Rashidi S. Transcranial direct current stimulation for the treatment of depression: a comprehensive review of the recent advances. Int J Ment Health Addict. 2017;15(2):434–43.
65. Knotkova H, Borckardt JJ, Riggs A, Dasilva AF. Transcranial direct current stimulation potential for pain management. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019.
66. Blumberger DM, Tran LC, Fitzgerald PB, Hoy KE, Daskalakis ZJ. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front Psychiatry [Internet]. 2012;3:74. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/

elink.fcgi?dbfrom=pubmed&id=22912618&retmode=ref&cmd=prlinks.
67. Valiengo L, Benseñor IM, Goulart AC, De Oliveira JF, Zanao TA, Boggio PS, et al. The sertraline versus electrical current therapy for treating depression clinical study (SELECT-TDCS): results of the crossover and follow-up phases. Depress Anxiety 2013;30(7):646–53.
68. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry [Internet]. 2011;35(1):96–101. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20854868&retmode=ref&cmd=prlinks.
69. Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacopuzzi M, et al. Transcranial direct current stimulation in severe, drug-resistant major depression. J Affect Disord [Internet]. 2009;118(1–3):215–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19286265&retmode=ref&cmd=prlinks.
70. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety [Internet]. 2006;23(8):482–4. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16845648&retmode=ref&cmd=prlinks.
71. Loo C, Martin D, Pigot M, Arul-Anandam P, Mitchell P, Sachdev P. Transcranial direct current stimulation priming of therapeutic repetitive transcranial magnetic stimulation: a pilot study. J ECT [Internet]. 2009;25(4):256–60. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19440158&retmode=ref&cmd=prlinks.
72. Rigonatti SP, Boggio PS, Myczkowski ML, Otta E, Fiquer JT, Ribeiro RB, et al. Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur Psychiatry [Internet]. 2008;23(1):74–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18023968&retmode=ref&cmd=prlinks.
73. Hazime FA, de Freitas DG, Monteiro RL, Maretto RL, de Almeida Carvalho NA, Hasue RH, et al. Analgesic efficacy of cerebral and peripheral electrical stimulation in chronic nonspecific low back pain: a randomized, double-blind, factorial clinical trial. BMC Musculoskelet Disord [Internet]. 2015;16:7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25636503&retmode=ref&cmd=prlinks.
74. Luedtke K, Rushton A, Wright C, Juergens TP, Mueller G, May A. Effectiveness of anodal transcranial direct current stimulation in patients with chronic low back pain: design, method and protocol for a randomised controlled trial. BMC Musculoskelet Disord [Internet]. 2011;12:290. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22204615&retmode=ref&cmd=prlinks.
75. Mariano T, Burgess F, Bowker M, Kirschner J, van't Wout-Frank M, Halladay C, et al. T187. Transcranial direct current stimulation (tDCS) for the affective symptoms of chronic low back pain (CLBP): a double-blinded, randomized, placebo-controlled trial. Biol Psychiatry [Internet]. 2018;83(9):S200–1. Available from: https://doi.org/10.1016/j.biopsych.2018.02.524.
76. Luedtke K, Rushton A, Wright C, Jürgens T, Polzer A, Mueller G, et al. Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain: sham controlled double blinded randomised controlled trial. BMJ [Internet]. 2015;350:h1640. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25883244&retmode=ref&cmd=prlinks.
77. Harvey M, Martel M, Houde F, Daguet I, Séguin M, Leonard G. Using transcranial direct current stimulation to reduce chronic pain in elderly individuals. Innov Aginig. 2017;1:240.
78. Concerto C, Al Sawah M, Chusid E, Trepal M, Taylor G, Aguglia E, et al. Anodal transcranial direct current stimulation for chronic pain in the elderly: a pilot study. Aging Clin Exp Res [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26174129&retmode=ref&cmd=prlinks.
79. Silva T dos SF, Galdino MKC, Andrade SMM dos S, Lucena LBS de, Aranha REL de B, Rodrigues ET de A. Use of non-invasive neuromodulation in the treatment of pain in temporomandibular dysfunction: preliminary study. Brazilian J Pain. 2019;2(2):147–154.
80. Brandão Filho RA, Baptista AF, Brandão R de AFS, Meneses FM, Okeson J, de Sena EP. Analgesic effect of cathodal transcranial current stimulation over right dorsolateral prefrontal cortex in subjects with muscular temporomandibular disorders: study protocol for a randomized controlled trial. Trials [Internet]. 2015;16(1):415. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26381733&retmode=ref&cmd=prlinks.
81. Oliveira LB, Lopes TS, Soares C, Maluf R, Goes BT, Sá KN, et al. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: a blind randomised-controlled trial. J Oral Rehabil [Internet]. 2015;42(10):723–32. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25891021&retmode=ref&cmd=prlinks.
82. Buja S, Baroni A, Straudi S, Pavarelli C, Galiè M, Basaglia N. Effects of transcranial direct current stimulation (tDCS) on patients with chronic temporomandibular joint disorders: a case series. J Pain Manag. 2018;11(2):187–91.

83. Bayer KE, Neeb L, Bayer A, Wiese JJ, Siegmund B, Prüß MS. Reduction of intra-abdominal pain through transcranial direct current stimulation: a systematic review. Medicine (United States). 2019;98(39):e17017.
84. Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease via transcranial direct current stimulation: a randomized controlled trial. Pain [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26469395&retmode=ref&cmd=prlinks.
85. Lewis GN, Rice DA, Kluger M, McNair PJ. Transcranial direct current stimulation for upper limb neuropathic pain: a double-blind randomized controlled trial. Eur J Pain (United Kingdom). 2018;22(7):1312–20.
86. O'Neill F, Sacco P, Nurmikko T. Evaluation of a home-based transcranial direct current stimulation (tDCS) treatment device for chronic pain: study protocol for a randomised controlled trial. Trials [Internet]. 2015;16:186. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25902771&retmode=ref&cmd=prlinks.
87. Castillo Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, et al. Clinically effective treatment of fibromyalgia pain with HD-tDCS - Phase II open-label dose-optimization. J Pain [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26456677&retmode=ref&cmd=prlinks.
88. Fregni F, Gimenes R, Valle AC, Ferreira MJL, Rocha RR, Natalle L, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum [Internet]. 2006;54(12):3988–98. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17133529&retmode=ref&cmd=prlinks.
89. Ayache SS, Chalah MA. Transcranial direct current stimulation: a glimmer of hope for multiple sclerosis fatigue? J Clin Neurosci. 2018;55:10–2.
90. Mattioli F, Bellomi F, Stampatori C, Capra R, Miniussi C. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Mult Scler. 2016;22(2):222–30.
91. Mori F, Codecà C, Kusayanagi H, Monteleone F, Buttari F, Fiore S, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J Pain [Internet]. 2010;11(5):436–42. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20018567&retmode=ref&cmd=prlinks.
92. Ayache SS, Palm U, Chalah MA, Al-Ani T, Brigno A, Abdellaoui M, et al. Prefrontal tDCS decreases pain in patients with multiple sclerosis. Front Neurosci. 2016;10(APR):1–12.
93. Workman CD, Kamholz J, Rudroff T. Transcranial direct current stimulation (tDCS) for the treatment of a multiple sclerosis symptom cluster. Brain Stimul [Internet]. 2020;13(1):263–4. Available from: https://doi.org/10.1016/j.brs.2019.09.012.
94. Li S, Stampas A, Frontera J, Davis M. Combined transcranial direct current stimulation and breathing-controlled electrical stimulation for management of neuropathic pain after spinal cord injury. J Rehabil Med. 2018;50:814–20.
95. Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. Brain [Internet]. 2010;133(9):2565–77. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20685806&retmode=ref&cmd=prlinks.
96. O'Brien AT, Amorim R, Rushmore RJ, Eden U, Afifi L, Dipietro L, et al. Motor cortex neurostimulation technologies for chronic post-stroke pain: Implications of tissue damage on stimulation currents. Front Hum Neurosci. 2016;10(NOV2016):1–8.
97. De Souza JA, Corrêa JCF, Agnol LD, Dos Santos FR, Gomes MRP, Corrêa FI. Effects of transcranial direct current stimulation on the rehabilitation of painful shoulder following a stroke: protocol for a randomized, controlled, double-blind, clinical trial. Trials. 2019;20(1):1–8.
98. Morishita T, Hyakutake K, Saita K, Takahara M, Shiota E, Inoue T. Pain reduction associated with improved functional interhemispheric balance following transcranial direct current stimulation for post-stroke central pain: a case study. J Neurol Sci [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26349403&retmode=ref&cmd=prlinks.
99. Ahn H, Woods AJ, Kunik ME, Bhattacharjee A, Chen Z, Choi E, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: an experimenter- and participant-bl. Brain Stimul [Internet]. 2017;10(5):902–9. Available from: https://doi.org/10.1016/j.brs.2017.05.007.
100. Tavares DRB, Okazaki JEF, Rocha AP, Santana MVDA, Pinto ACPN, Civile VT, et al. Effects of transcranial direct current stimulation on knee osteoarthritis pain in elderly subjects with defective endogenous pain-inhibitory systems: protocol for a randomized controlled trial. JMIR Res Protoc. 2018;7(10):e11660.
101. Riachi N, Mansour A, Ahdab R. Transcranial direct current stimulation as a prophylactic therapy in migraine patients. J Neurol Sci. 2017;381:939.
102. Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial magnetic and direct current stimulation (TMS/tDCS) for the treatment of headache: a systematic review. Headache. 2019;59(3):339–57.

103. Bocci T, De Carolis G, Ferrucci R, Paroli M, Mansani F, Priori A, et al. Cerebellar transcranial direct current stimulation (ctDCS) ameliorates phantom limb pain and non-painful phantom limb sensations. Cerebellum. 2019;18(3):527–35.
104. Herrero Babiloni A, Guay S, Nixdorf DR, De Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. J Pain Res. 2018;11:1445–57.
105. Kumru H, Murillo N, Benito-Penalva J, Tormos JM, Vidal J. Transcranial direct current stimulation is not effective in the motor strength and gait recovery following motor incomplete spinal cord injury during Lokomat® gait training. Neurosci Lett [Internet]. 2016;620:143–7. Available from: https://doi.org/10.1016/j.neulet.2016.03.056.
106. O'Connell NE, Wand BM. Transcranial direct current brain stimulation for chronic pain. BMJ [Internet]. 2015;350:h1774. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25883106&retmode=ref&cmd=prlinks.
107. Angius L, Hopker JG, Marcora SM, Mauger AR. The effect of transcranial direct current stimulation of the motor cortex on exercise-induced pain. Eur J Appl Physiol [Internet]. 2015 [cited 2020 Apr 23];115(11):2311–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26148882&retmode=ref&cmd=prlinks.
108. Bocci T, Santarcangelo E, Vannini B, Torzini A, Carli G, Ferrucci R, et al. Cerebellar direct current stimulation modulates pain perception in humans. Restor Neurol Neurosci [Internet]. 2015;33(5):597–609. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25777683&retmode=ref&cmd=prlinks.
109. Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia [Internet]. 2009;47(1):212–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18725237&retmode=ref&cmd=prlinks.
110. Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol [Internet]. 2008;15(10):1124–30. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18717717&retmode=ref&cmd=prlinks.
111. Ihle K, Rodriguez-Raecke R, Luedtke K, May A. tDCS modulates cortical nociceptive processing but has little to no impact on pain perception. Pain [Internet]. 2014;155(10):2080–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25083928&retmode=ref&cmd=prlinks.
112. Brunoni AR, Palm U. Transcranial direct current stimulation in psychiatry: mood disorders, schizophrenia and other psychiatric diseases. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019.
113. Kekic M, Boysen E, Campbell IC, Schmidt U. A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. J Psychiatr Res [Internet]. 2016;74:70–86. Available from: https://doi.org/10.1016/j.jpsychires.2015.12.018.
114. Gupta T, Kelley NJ, Pelletier-Baldelli A, Mittal VA. Transcranial direct current stimulation, symptomatology, and cognition in psychosis: a qualitative review. Front Behav Neurosci. 2018;12(May):1–10.
115. Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: a meta-analysis of neuropsychological deficits. PLoS One. 2019;14(4):1–26.
116. Cosmo C, Baptista AF, de Araújo AN, do Rosário RS, Miranda JGV, Montoya P, et al. A randomized, double-blind, sham-controlled trial of transcranial direct current stimulation in attention-deficit/hyperactivity disorder. PLoS One [Internet]. 2015;10(8):e0135371. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26267861&retmode=ref&cmd=prlinks.
117. Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. Brain Stimul [Internet]. 2014;7(6):813–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25442152&retmode=ref&cmd=prlinks.
118. Hasan A, Aborowa R, Nitsche MA, Marshall L, Schmitt A, Gruber O, et al. Abnormal bihemispheric responses in schizophrenia patients following cathodal transcranial direct stimulation. Eur Arch Psychiatry Clin Neurosci [Internet]. 2012;262(5):415–23. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22318337&retmode=ref&cmd=prlinks.
119. Hoy KE, Arnold SL, Emonson MRL, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res [Internet]. 2014;155(1–3):96–100. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24703529&retmode=ref&cmd=prlinks.
120. Schretlen DJ, van Steenburgh JJ, Varvaris M, Vannorsdall TD, Andrejczuk MA, Gordon B. Can transcranial direct current stimulation improve cognitive functioning in adults with schizophrenia? Clin Schizophr Relat Psychoses [Internet]. 2014;1–27. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25367166&retmode=ref&cmd=prlinks.
121. Strube W, Bunse T, Nitsche MA, Wobrock T, Aborowa R, Misewitsch K, et al. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimula-

tion study. Neuropsychopharmacology [Internet]. 2015;40(4):822–30. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25308351&retmode=ref&cmd=prlinks.
122. Cai M, Guo Z, Xing G, Peng H, Zhou L, Chen H, et al. Transcranial direct current stimulation improves cognitive function in mild to moderate Alzheimer disease: a meta-analysis. Alzheimer Dis Assoc Disord. 2019;33(2):170–8.
123. Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimul [Internet]. 2012;5(3):223–30. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21840288&retmode=ref&cmd=prlinks.
124. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Floel A. Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms. Alzheimers Dement [Internet]. 2015;11(9):1032–40. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25449530&retmode=ref&cmd=prlinks.
125. Martin DM, Mohan A, Alonzo A, Gates N, Gbadeyan O, Meinzer M, et al. A pilot double-blind randomized controlled trial of cognitive training combined with transcranial direct current stimulation for amnestic mild cognitive impairment. J Alzheimers Dis. 2019;71(2):503–12.
126. Yuan T, Yadollahpour A, Salgado-Ramírez J, Robles-Camarillo D, Ortega-Palacios R. Transcranial direct current stimulation for the treatment of tinnitus: a review of clinical trials and mechanisms of action 11 medical and health sciences 1103 clinical sciences. BMC Neurosci. 2018;19(1):1–9.
127. Faber M, Vanneste S, Fregni F, De Ridder D. Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex. Brain Stimul [Internet]. 2012;5(4):492–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22019079&retmode=ref&cmd=prlinks.
128. Palm U, Leitner B, Kirsch B, Behler N, Kumpf U, Wulf L, et al. Prefrontal tDCS and sertraline in obsessive compulsive disorder: a case report and review of the literature. Neurocase [Internet]. 2017;23(2):173–7. Available from: https://doi.org/10.1080/13554794.2017.1319492.
129. Volpato C, Piccione F, Cavinato M, Duzzi D, Schiff S, Foscolo L, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. Neurocase [Internet]. 2013;19(4):360–70. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22554168&retmode=ref&cmd=prlinks.
130. Eapen V, Baker R, Walter A, Raghupathy V, Wehrman JJ, Sowman PF. The role of transcranial direct current stimulation (tDCS) in tourette syndrome: a review and preliminary findings. Brain Sci. 2017;7(12):1–13.
131. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. Neurosci Biobehav Rev [Internet]. 2019;96(August 2018):219–31. Available from: https://doi.org/10.1016/j.neubiorev.2018.12.012.
132. Shiozawa P, Leiva APG, Castro CDC, da Silva ME, Cordeiro Q, Fregni F, et al. Transcranial direct current stimulation for generalized anxiety disorder: a case study. Biol Psychiatry [Internet]. 2014;75(11):e17–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23958182&retmode=ref&cmd=prlinks.
133. Marin M-F, Camprodon JA, Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: implications for PTSD treatment and beyond. Depress Anxiety [Internet]. 2014;31(4):269–78. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24634247&retmode=ref&cmd=prlinks.
134. Heeren A, Baeken C, Vanderhasselt M-A, Philippot P, de Raedt R. Impact of anodal and cathodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex during attention bias modification: an eye-tracking study. PLoS One [Internet]. 2015;10(4):e0124182. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25909846&retmode=ref&cmd=prlinks.
135. Ironside M, O'Shea J, Cowen PJ, Harmer CJ. Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety. Biol Psychiatry [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26210058&retmode=ref&cmd=prlinks.
136. Regner GG, Pereira P, Leffa DT, de Oliveira C, Vercelino R, Fregni F, et al. Preclinical to clinical translation of studies of transcranial direct-current stimulation in the treatment of epilepsy: a systematic review. Front Neurosci. 2018;12(MAR):189.
137. Lapenta OM, Marques LM, Rego GG, Comfort WE, Boggio PS. tDCS in addiction and impulse control disorders. J ECT. 2018;34(3):182–92.
138. Naish KR, Vedelago L, Mackillop J, Amlung M. Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviors : a systematic review. Drug Alcohol Depend. 2018;192:338–51.
139. Bashir S, Yoo WK. Neuromodulation for addiction by transcranial direct current stimulation: opportunities and challenges. Ann Neurosci. 2016;23(4):241–5.
140. Teti Mayer J, Chopard G, Nicolier M, Gabriel D, Masse C, Giustiniani J, et al. Can transcranial direct current stimulation (tDCS) improve impulsivity in healthy and psychiatric adult populations? A systematic review. Prog Neuro-Psychopharmacology

Biol Psychiatry [Internet]. 2020;98(November 2019):109814. Available from: https://doi.org/10.1016/j.pnpbp.2019.109814.

141. Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: a preliminary study. Drug Alcohol Depend [Internet]. 2014;140:78–84. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24814566&retmode=ref&cmd=prlinks.
142. Fraser PE, Rosen AC. Transcranial direct current stimulation and behavioral models of smoking addiction. Front psychiatry [Internet]. 2012;3:79. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22969733&retmode=ref&cmd=prlinks.
143. Fregni F, Liguori P, Fecteau S, Nitsche MA, Pascual-Leone A, Boggio PS. Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. J Clin Psychiatry [Internet]. 2008;69(1):32–40. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18312035&retmode=ref&cmd=prlinks.
144. Grundey J, Thirugnanasambandam N, Kaminsky K, Drees A, Skwirba AC, Lang N, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J Neurosci [Internet]. 2012;32(12):4156–62. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22442079&retmode=ref&cmd=prlinks.
145. Meng Z, Liu C, Yu C, Ma Y. Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. J Psychiatr Res [Internet]. 2014;54:19–25. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24731752&retmode=ref&cmd=prlinks.
146. Pripfl J, Neumann R, Köhler U, Lamm C. Effects of transcranial direct current stimulation on risky decision making are mediated by "hot" and "cold" decisions, personality, and hemisphere. Eur J Neurosci [Internet]. 2013;38(12):3778–85. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24124667&retmode=ref&cmd=prlinks.
147. Gilmore CS, Dickmann PJ, Nelson BG, Lamberty GJ, Lim KO. Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimul [Internet]. 2018;11(2):302–9. Available from: https://doi.org/10.1016/j.brs.2017.11.011.
148. Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci [Internet]. 2007;27(46):12500–5. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18003828&retmode=ref&cmd=prlinks.
149. Russo R, Twyman P, Cooper NR, Fitzgerald PB, Wallace D. When you can, scale up: large-scale study shows no effect of tDCS in an ambiguous risk-taking task. Neuropsychologia [Internet]. 2017;104(December 2016):133–43. Available from: https://doi.org/10.1016/j.neuropsychologia.2017.08.008.
150. da Silva MC, Conti CL, Klauss J, Alves LG, do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J Physiol Paris [Internet]. 2013;107(6):493–502. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23891741&retmode=ref&cmd=prlinks.
151. den Uyl TE, Gladwin TE, Wiers RW. Transcranial direct current stimulation, implicit alcohol associations and craving. Biol Psychol [Internet]. 2015;105:37–42. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25541515&retmode=ref&cmd=prlinks.
152. Herremans SC, Baeken C. The current perspective of neuromodulation techniques in the treatment of alcohol addiction: a systematic review. Psychiatr Danub [Internet]. 2012;24(Suppl 1):S14–20. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22945180&retmode=ref&cmd=prlinks.
153. Klauss J, Penido Pinheiro LC, Silva Merlo BL, de Almeida Correia Santos G, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol [Internet]. 2014;17(11):1793–803. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25008145&retmode=ref&cmd=prlinks.
154. Bhandal A, Sultana T, Janjua K. Transcranial direct current stimulation: a potential novel treatment for alcohol addiction and abuse. Bangladesh J Med Sci. 17(01):7–15.
155. Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimpoor M, Keshvari F, Nejati V, et al. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int J Neuropsychopharmacol [Internet]. 2014;17(10):1591–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24825251&retmode=ref&cmd=prlinks.
156. Batista EK, Klauss J, Fregni F, Nitsche MA, Nakamura-Palacios EM. A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. Int J Neuropsychopharmacol [Internet]. 2015. Available from: http://eutils.ncbi.nlm.nih.gov/

entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26065432&retmode=ref&cmd=prlinks.
157. Conti CL, Nakamura-Palacios EM. Bilateral transcranial direct current stimulation over dorsolateral prefrontal cortex changes the drug-cued reactivity in the anterior cingulate cortex of crack-cocaine addicts. Brain Stimul [Internet]. 2014;7(1):130–2. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24139147&retmode=ref&cmd=prlinks.
158. Conti CL, Moscon JA, Fregni F, Nitsche MA, Nakamura-Palacios EM. Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. Int J Neuropsychopharmacol [Internet]. 2014;17(9):1465–75. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24776374&retmode=ref&cmd=prlinks.
159. Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FAM, Nitsche MA, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite [Internet]. 2008;51(1):34–41. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18243412&retmode=ref&cmd=prlinks.
160. Goldman RL, Borckardt JJ, Frohman HA, O'Neil PM, Madan A, Campbell LK, et al. Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite [Internet]. 2011;56(3):741–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21352881&retmode=ref&cmd=prlinks.
161. Kekic M, McClelland J, Campbell I, Nestler S, Rubia K, David AS, et al. The effects of prefrontal cortex transcranial direct current stimulation (tDCS) on food craving and temporal discounting in women with frequent food cravings. Appetite [Internet]. 2014;78:55–62. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24656950&retmode=ref&cmd=prlinks.
162. Lapenta OM, Di Sierve K, de Macedo EC, Fregni F, Boggio PS. Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. Appetite [Internet]. 2014;83:42–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25128836&retmode=ref&cmd=prlinks.
163. Montenegro RA, Okano AH, Cunha FA, Gurgel JL, Fontes EB, Farinatti PT V. Prefrontal cortex transcranial direct current stimulation associated with aerobic exercise change aspects of appetite sensation in overweight adults. Appetite [Internet]. 2012;58(1):333–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22108669&retmode=ref&cmd=prlinks.
164. Mostafavi SA, Khaleghi A, Mohammadi MR, Akhondzadeh S. Is transcranial direct current stimulation an effective modality in reducing food craving? A systematic review and meta-analysis. Nutr Neurosci. 2020;23(1):55–67.
165. Dendy R, Stinson EJ, Guerithault N, Gluck ME. Brain stimulation to modulate food intake and eating behavior. Curr Diab Rep. 2019;19(12):1–11.
166. Hall PA, Vincent CM, Burhan AM. Non-invasive brain stimulation for food cravings, consumption, and disorders of eating: a review of methods, findings and controversies. Appetite [Internet]. 2018;124:78–88. Available from: https://doi.org/10.1016/j.appet.2017.03.006.
167. Jauch-Chara K, Kistenmacher A, Herzog N, Schwarz M, Schweiger U, Oltmanns KM. Repetitive electric brain stimulation reduces food intake in humans. Am J Clin Nutr [Internet]. 2014;100(4):1003–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25099550&retmode=ref&cmd=prlinks.
168. Dalton B, Bartholdy S, Campbell IC, Schmidt U. Neurostimulation in clinical and sub-clinical eating disorders: a systematic update of the literature. Curr Neuropharmacol. 2018;16(8):1174–92.
169. Awosika OO, Cohen LG. Transcranial direct current stimulation in stroke rehabilitation: present and future. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019.
170. Butler AJ, Shuster M, O'Hara E, Hurley K, Middlebrooks D, Guilkey K. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. J Hand Ther [Internet]. 2013;26(2):162-70-quiz 171. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22964028&retmode=ref&cmd=prlinks.
171. Wu D, Qian L, Zorowitz RD, Zhang L, Qu Y, Yuan Y. Effects on decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: a randomized sham-controlled study. Arch Phys Med Rehabil [Internet]. 2013;94(1):1–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22878231&retmode=ref&cmd=prlinks.
172. Sunwoo H, Kim Y-H, Chang WH, Noh S, Kim E-J, Ko M-H. Effects of dual transcranial direct current stimulation on post-stroke unilateral visuospatial neglect. Neurosci Lett [Internet]. 2013;554:94–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24021804&retmode=ref&cmd=prlinks.
173. Salazar APS, Vaz PG, Marchese RR, Stein C, Pinto C, Pagnussat AS. Noninvasive brain stimulation improves hemispatial neglect after stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2018;99(2):355–66.e1.
174. Làdavas E, Giulietti S, Avenanti A, Bertini C, Lorenzini E, Quinquinio C, et al. a-tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment in neglect. Restor Neurol Neurosci [Internet]. 2015;33(5):647–62. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/

elink.fcgi?dbfrom=pubmed&id=25855132&retmode=ref&cmd=prlinks.
175. Gandola M, Sedda A, Manera M, Pingue V, Salvato G, Spitoni GF, et al. Selective improvement of anosognosia for hemiplegia during transcranial direct current stimulation: a case report. Cortex [Internet]. 2014;61:107–19. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25481469&retmode=ref&cmd=prlinks.
176. Brem A-K, Unterburger E, Speight I, Jäncke L. Treatment of visuospatial neglect with biparietal tDCS and cognitive training: a single-case study. Front Syst Neurosci [Internet]. 2014;8:180. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25324736&retmode=ref&cmd=prlinks.
177. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke [Internet]. 2010;41(6):1229–36. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20395612&retmode=ref&cmd=prlinks.
178. Floel A, Meinzer M, Kirstein R, Nijhof S, Deppe M, Knecht S, et al. Short-term anomia training and electrical brain stimulation. Stroke [Internet]. 2011;42(7):2065–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21636820&retmode=ref&cmd=prlinks.
179. Jung I-Y, Lim JY, Kang EK, Sohn HM, Paik N-J. The factors associated with good responses to speech therapy combined with transcranial direct current stimulation in post-stroke aphasic patients. Ann Rehabil Med [Internet]. 2011;35(4):460–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22506160&retmode=ref&cmd=prlinks.
180. Kang EK, Kim YK, Sohn HM, Cohen LG, Paik N-J. Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. Restor Neurol Neurosci [Internet]. 2011;29(3):141–52. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21586821&retmode=ref&cmd=prlinks.
181. Marangolo P, Caltagirone C. Options to enhance recovery from aphasia by means of non-invasive brain stimulation and action observation therapy. Expert Rev Neurother [Internet]. 2014;14(1):75–91. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24308276&retmode=ref&cmd=prlinks.
182. Monti A, Ferrucci R, Fumagalli M, Mameli F, Cogiamanian F, Ardolino G, et al. Transcranial direct current stimulation (tDCS) and language. J Neurol Neurosurg Psychiatry [Internet]. 2013;84(8):832–42. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23138766&retmode=ref&cmd=prlinks.
183. Santos MD, Gagliardi RJ, Mac-Kay APMG, Boggio PS, Lianza R, Fregni F. Transcranial direct-current stimulation induced in stroke patients with aphasia: a prospective experimental cohort study. Sao Paulo Med J [Internet]. 2013;131(6):422–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24346782&retmode=ref&cmd=prlinks.
184. Volpato C, Cavinato M, Piccione F, Garzon M, Meneghello F, Birbaumer N. Transcranial direct current stimulation (tDCS) of Broca's area in chronic aphasia: a controlled outcome study. Behav Brain Res [Internet]. 2013;247:211–6. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23538068&retmode=ref&cmd=prlinks.
185. You DS, Kim D-Y, Chun MH, Jung SE, Park SJ. Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. Brain Lang [Internet]. 2011;119(1):1–5. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21641021&retmode=ref&cmd=prlinks.
186. Ulanov MA, Shtyrov YY, Stroganova TA. Transcranial direct current stimulation as a tool to induce language recovery in patients with post-stroke aphasia. Neurosci Behav Physiol. 2019;49(9):1169–80.
187. Wortman-Jutt S, Edwards DJ. tDCS in post-stroke aphasia recovery. Stroke. 2017;48(3):820–6.
188. Norise C, Hamilton RH. Non-invasive brain stimulation in the treatment of post-stroke and neurodegenerative aphasia: parallels, differences, and lessons learned. Front Hum Neurosci. 2017;
189. Norise C, Sacchetti D, Hamilton R. Transcranial direct current stimulation in post-stroke chronic aphasia: the impact of baseline severity and task specificity in a pilot sample. Front Hum Neurosci. 2017;11(May):260.
190. Kang EK, Baek MJ, Kim S, Paik N-J. Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci [Internet]. 2009;27(6):645–50. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20042788&retmode=ref&cmd=prlinks.
191. Brambilla M, Manenti R, Ferrari C, Cotelli M. Better together: left and right hemisphere engagement to reduce age-related memory loss. Behav Brain Res [Internet]. 2015;293:125–33. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26200716&retmode=ref&cmd=prlinks.
192. Floel A, Suttorp W, Kohl O, Kürten J, Lohmann H, Breitenstein C, et al. Non-invasive brain stimulation improves object-location learning in the elderly. Neurobiol Aging [Internet]. 2012;33(8):1682–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21684040&retmode=ref&cmd=prlinks.

193. Learmonth G, Thut G, Benwell CSY, Harvey M. The implications of state-dependent tDCS effects in aging: behavioural response is determined by baseline performance. Neuropsychologia [Internet]. 2015;74:108–19. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0028393215000445.
194. Prehn K, Floel A. Potentials and limits to enhance cognitive functions in healthy and pathological aging by tDCS. Front Cell Neurosci [Internet]. 2015;9:355. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26441526&retmode=ref&cmd=prlinks.
195. Woods AJ, Antonenko D, Flöel A, Hampstead BM, Clark D, Knotkova H. Transcranial direct current stimulation in aging research. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 569–95.
196. Rahman-filipiak A, Reckow JM, Woods AJ, Nitsche MA, Hampstead BM. The use and efficacy of transcranial direct current stimulation in individuals with neurodegenerative dementias. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 473–507.
197. Ferrucci R, Mrakic-Sposta S, Gardini S, Ruggiero F, Vergari M, Mameli F, et al. Behavioral and neurophysiological effects of transcranial direct current stimulation (tDCS) in fronto-temporal dementia. Front Behav Neurosci. 2018;12(October):1–11.
198. Cotelli M, Manenti R, Ferrari C, Gobbi E, Macis A, Cappa SF. Effectiveness of language training and non-invasive brain stimulation on oral and written naming performance in primary progressive aphasia: a meta-analysis and systematic review. Neurosci Biobehav Rev. 2020;108:498–525.
199. Hosseini, M., McConathey, E.M., Ungrady, M. Grossman, M., Coslett, H.B., Hamilton, R.H. Transcranial direct current stimulation mediates improvements in verbal fluency for patients with primary progressive aphasia (published proceedings). Brain Stimul. 2019;12:e69–e70.
200. McConathey EM, White NC, Gervits F, Ash S, Coslett HB, Grossman M, et al. Baseline performance predicts tDCS-mediated improvements in language symptoms in primary progressive aphasia. Front Hum Neurosci. 2017;11:347.
201. Hung J, Bauer A, Grossman M, Hamilton RH, Coslett HB, Reilly J. Semantic feature training in combination with transcranial direct current stimulation (tDCS) for progressive anomia. Front Hum Neurosci. 2017;11:253.
202. Gervits F, Ash S, Coslett HB, Rascovsky K, Grossman M, Hamilton R. Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study. Brain Lang. 2016;162:35–41.
203. Levasseur-Moreau J, Fecteau S. Translational application of neuromodulation of decision-making. Brain Stimul [Internet]. 2012;5(2):77–83. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22537866&retmode=ref&cmd=prlinks.
204. Knotkova H, Clayton A, Stevens M, Riggs A, Charvet LE, Bikson M. Home-based patient-delivered remotely supervised transcranial direct current stimulation. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 379–405.
205. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: a guide for clinical research and practice. Brain Stimul. 2020;13(3):686–93.
206. Ayaz H, Dehais F. Neuroergonomics: the brain at work and in everyday life. 1st ed. London: Elsevier; 2019.
207. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. Neuroimage [Internet]. 2014;85 Pt 3:895–908. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23933040&retmode=ref&cmd=prlinks.
208. Clark VP, Coffman BA, Mayer AR, Weisend MP, Lane TDR, Calhoun VD, et al. TDCS guided using fMRI significantly accelerates learning to identify concealed objects. Neuroimage [Internet]. 2012;59(1):117–28. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21094258&retmode=ref&cmd=prlinks.
209. Coffman BA, Trumbo MC, Flores RA, Garcia CM, van der Merwe AJ, Wassermann EM, et al. Impact of tDCS on performance and learning of target detection: interaction with stimulus characteristics and experimental design. Neuropsychologia [Internet]. 2012;50(7):1594–602. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22450198&retmode=ref&cmd=prlinks.
210. Falcone B, Coffman BA, Clark VP, Parasuraman R. Transcranial direct current stimulation augments perceptual sensitivity and 24-hour retention in a complex threat detection task. PLoS One [Internet]. 2012;7(4):e34993. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22511978&retmode=ref&cmd=prlinks.
211. Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage [Internet]. 2014;85(Pt 3):909–17. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23235272&retmode=ref&cmd=prlinks.
212. Scheldrup M, Greenwood PM, McKendrick R, Strohl J, Bikson M, Alam M, et al. Transcranial direct current stimulation facilitates cognitive multitask performance differentially depending on anode location and subtask. Front Hum Neurosci [Internet]. 2014;8:665. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25249958&retmode=ref&cmd=prlinks.
213. McKinley RA, McIntire L, Bridges N, Goodyear C, Bangera NB, Weisend MP. Acceleration of image analyst training with transcranial direct

current stimulation. Behav Neurosci [Internet]. 2013;127(6):936–46. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24341718&retmode=ref&cmd=prlinks.
214. McIntire L, McKinley A, Nelson J, Goodyear C. P285 using transcranial direct current stimulation (tDCS) as a fatigue countermeasure. Clin Neurophysiol [Internet]. 2017;128(3):e149–50. Available from: https://doi.org/10.1016/j.clinph.2016.10.393.
215. Nelson JT, Tepe V. Neuromodulation research and application in the U.S. Department of Defense. Brain Stimul [Internet]. 2015;8(2):247–52. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25468072&retmode=ref&cmd=prlinks.
216. Giordano J, Bikson M, Kappenman ES, Clark VP, Coslett HB, Hamblin MR, et al. Mechanisms and effects of transcranial direct current stimulation. Dose-Response. 2017;15(1):1–22.
217. Davis SE, Smith GA. Transcranial direct current stimulation use in warfighting: benefits, risks, and future prospects. Front Hum Neurosci. 2019;13(April):1–18.
218. Feltman KA, Hayes AM, Bernhardt KA, Nwala E, Kelley AM. Viability of tDCS in military environments for performance enhancement: a systematic review. Mil Med. 2020;185(1–2):E53–60.
219. Peltier C, Pettijohn K, Blacker K. Developing the third offset: transcranial direct current stimulation can improve the human operator. Mil Med. 2019;184(1–2):11–3.
220. Fitz NS, Reiner PB. The challenge of crafting policy for do-it-yourself brain stimulation. J Med Ethics [Internet]. 2015;41(5):410–2. Available from: http://jme.bmj.com/cgi/doi/10.1136/medethics-2013-101458.
221. Wexler A. Who uses direct-to-consumer brain stimulation products, and why? A study of home users of tDCS devices. J Cogn Enhanc. 2018;2(1):114–34.
222. Colzato LS, Nitsche MA, Kibele A. Noninvasive brain stimulation and neural entrainment enhance athletic performance—a review. J Cogn Enhanc. 2017;1(1):73–9.
223. Edwards DJ, Cortes M, Wortman-Jutt S, Putrino D, Bikson M, Thickbroom G, et al. Transcranial direct current stimulation and sports performance. Front Hum Neurosci. 2017;11:243.
224. Park K. Neuro-doping: the rise of another loophole to get around anti-doping policies. Cogent Soc Sci [Internet]. 2017;3(1). Available from: https://doi.org/10.1080/23311886.2017.1360462.
225. Huang L, Deng Y, Zheng X, Liu Y. Transcranial direct current stimulation with halo sport enhances repeated sprint cycling and cognitive performance. Front Physiol. 2019;10(FEB):1–7.
226. Kamali AM, Saadi ZK, Yahyavi SS, Zarifkar A, Aligholi H, Nami M. Transcranial direct current stimulation to enhance athletic performance outcome in experienced bodybuilders. PLoS One. 2019;14(8):1–20.
227. Badran BW, Austelle CW, Smith NR, Glusman CE, Froeliger B, Garland EL, et al. A double-blind study exploring the use of transcranial direct current stimulation (tDCS) to potentially enhance mindfulness meditation (E-meditation). Brain Stimul. 2017;10(1):152–4.
228. Danilewitz M, Pang C, Aur D, Shalbaf R, Ge R, Brown J, et al. The acute effects of a combined yoga and transcranial direct current stimulation on neurophysiological markers: preliminary data. Brain Stimul. 2017;10(2):494.
229. Wexler A. A pragmatic analysis of the regulation of consumer transcranial direct current stimulation (TDCS) devices in the United States. J Law Biosci. 2016;2(3):669–96.
230. Zettler PJ. What lies ahead for FDA regulation of tDCS products? J Law Biosci. 2016;3(2):318–23.
231. Wurzman R, Hamilton RH, Pascual-Leone A, Fox MD. An open letter concerning do-it-yourself users of transcranial direct current stimulation. Ann Neurol. 2016;80(1):1.
232. Esmaeilpour Z, Marangolo P, Hampstead BM, Bestmann S, Galletta E, Knotkova H, et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. Brain Stimul [Internet]. 2018;11(2):310–21. Available from: https://doi.org/10.1016/j.brs.2017.12.002.
233. Batsikadze G, Moliadze V, Paulus W, Kuo M-F, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol [Internet]. 2013;591(Pt 7):1987–2000. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23339180&retmode=ref&cmd=prlinks.
234. Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul [Internet]. 2013;6(3):424–32. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22695026&retmode=ref&cmd=prlinks.
235. Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. Front Psychiatry [Internet]. 2011;2:45. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21811474&retmode=ref&cmd=prlinks.
236. Dedoncker J, Brunoni A, Baeken C, Vanderhasselt M. The effect of stimulation parameters in prefrontal tDCS research on cognition. Brain Stimul. 2017;10(2):362.
237. Falcone B, Wada A, Parasuraman R, Callan DE. Individual differences in learning correlate with modulation of brain activity induced by transcranial direct current stimulation. PLoS One. 2018;13(5):e0197192.

238. Moliadze V, Antal A, Paulus W. Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. Clin Neurophysiol [Internet]. 2010;121(12):2165–71. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20554472&retmode=ref&cmd=prlinks.
239. Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol [Internet]. 2007;97(4):3109–17. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17251360&retmode=ref&cmd=prlinks.
240. Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. Front psychiatry [Internet]. 2012;3:91. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23097644&retmode=ref&cmd=prlinks.
241. Wagner T, Fregni F, Fecteau S, Grodzinsky A, Zahn M, Pascual-Leone A. Transcranial direct current stimulation: a computer-based human model study. Neuroimage [Internet]. 2007;35(3):1113–24. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17337213&retmode=ref&cmd=prlinks.
242. Alam M, Truong DQ, Khadka N, Bikson M. Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). Phys Med Biol. 2016;61(12):4506–21.
243. Laakso I, Tanaka S, Mikkonen M, Koyama S, Hirata A. Variability in TDCS electric fields: Effects of electrode size and configuration. 2017 32nd Gen Assem Sci Symp Int Union Radio Sci URSI GASS 2017. 2017.
244. Rampersad S, Jansen V, van Asseldonk E, Stegeman D. Evaluating the effects of model-based optimal bipolar tDCS configurations on cortical excitability. Brain Stimul [Internet]. 2017;10(1):e11–2. Available from: https://doi.org/10.1016/j.brs.2016.11.055.
245. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. Neuroimage [Internet]. 2014;89:216–25. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24345389&retmode=ref&cmd=prlinks.
246. Filmer HL, Ehrhardt SE, Shaw TB, Mattingley JB, Dux PE. The efficacy of transcranial direct current stimulation to prefrontal areas is related to underlying cortical morphology. Neuroimage [Internet]. 2019;196(November 2018):41–8. Available from: https://doi.org/10.1016/j.neuroimage.2019.04.026.
247. Filmer HL, Ehrhardt SE, Bollmann S, Mattingley JB, Dux PE. Accounting for individual differences in the response to tDCS with baseline levels of neurochemical excitability. Cortex [Internet]. 2019;115:324–34. Available from: https://doi.org/10.1016/j.cortex.2019.02.012.
248. Caulfield KA, Badran BW, DeVries WH, Summers PM, Kofmehl E, Li X, et al. Brain stimulation transcranial electrical stimulation motor threshold can estimate individualized tDCS dosage from reverse-calculation electric- field modeling. Brain Stimul. 2020;13:961–9.
249. Garcia-Cossio E, Witkowski M, Robinson SE, Cohen LG, Birbaumer N, Soekadar SR. Simultaneous transcranial direct current stimulation (tDCS) and whole-head magnetoencephalography (MEG): assessing the impact of tDCS on slow cortical magnetic fields. Neuroimage [Internet]. 2016;140:33–40. Available from: https://doi.org/10.1016/j.neuroimage.2015.09.068.
250. Esmaeilpour Z, Shereen AD, Ghobadi-Azbari P, Datta A, Woods AJ, Ironside M, et al. Methodology for tDCS integration with fMRI. Hum Brain Mapp. 2020;41(7):1950–67.
251. Hsu TY, Juan CH, Tseng P. Individual differences and state-dependent responses in transcranial direct current stimulation. Front Hum Neurosci. 2016;10(DEC2016):1–12.
252. Wiegand A, Nieratschker V, Plewnia C. Genetic modulation of transcranial direct current stimulation effects on cognition. Front Hum Neurosci. 2016;10(DEC2016):1–7.
253. McLaren ME, Nissim NR, Woods AJ. The effects of medication use in transcranial direct current stimulation: a brief review. Brain Stimul [Internet]. 2018;11(1):52–8. Available from: https://doi.org/10.1016/j.brs.2017.10.006.
254. Chaieb L, Antal A, Terney D, Paulus W. Pharmacological modulation of the short-lasting effects of antagonistic direct current-stimulation over the human motor cortex. Front psychiatry [Internet]. 2012;3:67. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22783210&retmode=ref&cmd=prlinks.
255. Monte-Silva K, Kuo M-F, Thirugnanasambandam N, Liebetanz D, Paulus W, Nitsche MA. Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. J Neurosci [Internet]. 2009;29(19):6124–31. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19439590&retmode=ref&cmd=prlinks.
256. Nitsche MA, Lampe C, Antal A, Liebetanz D, Lang N, Tergau F, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur J Neurosci [Internet]. 2006;23(6):1651–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16553629&retmode=ref&cmd=prlinks.

257. Agarwal SM, Bose A, Shivakumar V, Narayanaswamy JC, Chhabra H, Kalmady S V., et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatry Res [Internet]. 2015;235:97–103. Available from: https://doi.org/10.1016/j.psychres.2015.11.042.
258. Brunoni AR, Ferrucci R, Bortolomasi M, Scelzo E, Boggio PS, Fregni F, et al. Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the major depressive episode: findings from a naturalistic study. Eur Psychiatry [Internet]. 2013;28(6):356–61. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23182847&retmode=ref&cmd=prlinks.
259. Arul-Anandam AP, Loo C, Mitchell P. Induction of hypomanic episode with transcranial direct current stimulation. J ECT [Internet]. 2010;26(1):68–9. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19483641&retmode=ref&cmd=prlinks.
260. Gálvez V, Alonzo A, Martin D, Mitchell PB, Sachdev P, Loo CK. Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS). J ECT [Internet]. 2011;27(3):256–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21206371&retmode=ref&cmd=prlinks.
261. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul [Internet]. 2012;5(3):175–95. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22037126&retmode=ref&cmd=prlinks.
262. Lang S, Gan LS, Alrazi T, Monchi O. Theta band high definition transcranial alternating current stimulation, but not transcranial direct current stimulation, improves associative memory performance. Sci Rep. 2019;9(1):1–11.
263. Klink K, Peter J, Wyss P, Klöppel S. Transcranial electric current stimulation during associative memory encoding: comparing tACS and tDCS effects in healthy aging. Front Aging Neurosci. 2020;12(March):1–12.
264. Pammer K, Archer K, Bairnsfather J. Using tDCS and tACS to understand the role of dorsal processing and theta signals in word recognition and natural reading. Brain Stimul [Internet]. 2019;12(2):587–8. Available from: https://doi.org/10.1016/j.brs.2018.12.953.
265. Santarnecchi E, Biasella A, Tatti E, Rossi A, Prattichizzo D, Rossi S. High-gamma oscillations in the motor cortex during visuo-motor coordination: a tACS interferential study. Brain Res Bull [Internet]. 2017;131:47–54. Available from: https://doi.org/10.1016/j.brainresbull.2017.03.006.
266. Lavidor M. TES stimulation as a tool to investigate cognitive processes in healthy individuals. Eur Psychol. 2016;21(1):15–29.
267. Jones KT, Arciniega H, Berryhill ME. Replacing tDCS with theta tACS provides selective, but not general WM benefits. Brain Res [Internet]. 2019;1720(May):146324. Available from: https://doi.org/10.1016/j.brainres.2019.146324.
268. Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci. 2019;22(5):820–7.
269. Thut G, Bergmann TO, Frohlich F, Soekadar SR, Brittain J-S, Valero-Cabre A, et al. Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: a position paper. Clin Neurophysiol. 2017;128(5):843–57.
270. Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. Neuroimage [Internet]. 2016;140:4–19. Available from: https://doi.org/10.1016/j.neuroimage.2016.02.012.
271. An J, Lee S, Jin S. Fully closed-loop neuromodulation approach in real-time. Brain Stimul. 2019;12(2):567.
272. Miao Y, Koomson VJ. A CMOS-based bidirectional brain machine interface system with integrated fdNIRS and tDCS for closed-loop brain stimulation. IEEE Trans Biomed Circuits Syst. 2018;12(3):554–63.
273. Dmochowski JP, Koessler L, Norcia AM, Bikson M, Parra LC. Optimal use of EEG recordings to target active brain areas with transcranial electrical stimulation. NeuroImage. 2017;157:69–80.
274. Wunder S, Hunold A, Fiedler P, Schlegelmilch F, Schellhorn K, Haueisen J. Novel bifunctional cap for simultaneous electroencephalography and transcranial electrical stimulation. Sci Rep [Internet]. 2018;8(1):1–11. Available from: https://doi.org/10.1038/s41598-018-25562-x.
275. Li G, Chung WY. Combined EEG-gyroscope-TDCS brain machine interface system for early management of driver drowsiness. IEEE Trans Human-Machine Syst. 2018;48(1):50–62.
276. Jones AP, Choe J, Bryant NB, Robinson CSH, Ketz NA, Skorheim SW, et al. Dose-dependent effects of closed-loop tACS delivered during slow-wave oscillations on memory consolidation. Front Neurosci. 2018;12(NOV):1–20.
277. Martens G, Barra A, Carrière M, Soria-Frisch A, Ruffini G, Ibáñez D, et al. Closed-loop application of tDCS to promote responsiveness in patients with disorders of consciousness. Brain Stimul. 2019;12(2):459.
278. Medaglia JD, Zurn P, Sinnott-Armstrong W, Bassett DS. Mind control as a guide for the mind. Nat Hum Behav. 2017;1(6):1–8.

279. Rabipour S, Wu AD, Davidson PSR, Iacoboni M. Expectations may influence the effects of transcranial direct current stimulation. Neuropsychologia [Internet]. 2018;119(April): 524–34. Available from: https://doi.org/10.1016/j.neuropsychologia.2018.09.005.
280. Wexler A, Hamilton RH. Crowdsourced tDCS research: feasible or fanciful? AJOB Neurosci. 2017;8(1):50–3.
281. Farah MJ. Neuroscience. The unknowns of cognitive enhancement. Science (80-) [Internet]. 2015;350(6259):379–80. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26494744&retmode=ref&cmd=prlinks.
282. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 2007;72(4–6):208–14.
283. Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. Brain Stimul. 2010;3(1):58–9.
284. Loo CK, Martin DM, Alonzo A, Gandevia S, Mitchell PB, Sachdev P. Avoiding skin burns with transcranial direct current stimulation: preliminary considerations. Int J Neuropsychopharmacol. 2011;14(3):425–6.
285. Shiozawa P, Da Silva ME, Raza R, Uchida RR, Cordeiro Q, Fregni F, et al. Safety of repeated transcranial direct current stimulation in impaired skin a case report. J ECT. 2013;29(2):147–8.
286. Kuersten A, Hamilton RH. The brain, cognitive enhancement devices, and European regulation. J Law Biosci [Internet]. 2014. Available from: http://jlb.oxfordjournals.org/content/1/3/340.short.
287. Maslen H, Douglas T, Kadosh RC, Levy N, Savulescu J. The regulation of cognitive enhancement devices: extending the medical model. J Law … [Internet]. 2014. Available from: http://jlb.oxfordjournals.org/content/1/1/68.abstract.
288. Iuculano T, Cohen Kadosh R. The mental cost of cognitive enhancement. J Neurosci [Internet]. 2013;33(10):4482–6. Available from: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.4927-12.2013.
289. Sarkar A, Dowker A, Cohen Kadosh R. Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. J Neurosci [Internet]. 2014;34(50):16605–10. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25505313&retmode=ref&cmd=prlinks.
290. Benwell CSY, Learmonth G, Miniussi C, Harvey M. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: evidence from biparietal tDCS influence on lateralized attention bias. Cortex [Internet]. 2015. Available from: http://www.sciencedirect.com/science/article/pii/S0010945215001665.
291. Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. Neurosci Lett [Internet]. 2012;521(2):148–51. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22684095&retmode=ref&cmd=prlinks.
292. Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci [Internet]. 2009;29(22):7271–7. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19494149&retmode=ref&cmd=prlinks.
293. Sellers KK, Mellin JM, Lustenberger CM, Boyle MR, Lee WH, Peterchev AV, et al. Transcranial direct current stimulation (tDCS) of frontal cortex decreases performance on the WAIS-IV intelligence test. Behav Brain Res [Internet]. 2015;290:32–44. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25934490&retmode=ref&cmd=prlinks.
294. Hamilton R, Messing S, Chatterjee A. Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation. Neurol Int. 2011;76(2):187–93. Available from: http://www.neurology.org/cgi/doi/10.1212/WNL.0b013e318205d50d.
295. Cabrera LY, Evans EL, Hamilton RH. Ethics of the electrified mind: defining issues and perspectives on the principled use of brain stimulation in medical research and clinical care. Brain Topogr [Internet]. 2014;27(1):33–45. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23733209&retmode=ref&cmd=prlinks.
296. Pascual-Leone A, Fregni F, Steven-Wheeler MS, Forrow L. Non-invasive brain stimulation as a therapeutic and investigative tool: an ethical appraisal. In: Oxford handbook of neuroethics. New York: Oxford University Press; 2012.
297. Imperatori LS, Milbourn L, Garasic MD. Would the use of sage, cost-effective tDCS tackle rather than cause unfairness in sports? J Cogn Enhanc. 2018;2:377–87.
298. Medaglia JD, Yaden DB, Helion C, Haslam M. Moral attitudes and willingness to enhance and repair cognition with brain stimulation. Brain Stimul [Internet]. 2019;12(1):44–53. Available from: https://doi.org/10.1016/j.brs.2018.09.014.
299. Farah MJ, Wolpe PR. Monitoring and manipulating brain function: new neuroscience technologies and their ethical implications. Hastings Cent Rep [Internet]. 2004;34(3):35–45. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=15281725&retmode=ref&cmd=prlinks.
300. Heinrichs JH. The promises and perils of non-invasive brain stimulation. Int J Law Psychiatry [Internet]. 2012. Available from: http://www.sciencedirect.com/science/article/pii/S0160252711001543.

301. Jotterand F, Giordano J. Transcranial magnetic stimulation, deep brain stimulation and personal identity: ethical questions, and neuroethical approaches for medical practice. Int Rev Psychiatry [Internet]. 2011;23(5):476–85. Available from: http://www.tandfonline.com/doi/full/10.3109/09540261.2011.616189.
302. Lipsman N, Glannon W. Brain, mind and machine: what are the implications of deep brain stimulation for perceptions of personal identity, agency and free will? Bioethics [Internet]. 2013;27(9):465–70. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22681593&retmode=ref&cmd=prlinks.
303. Mathews DJH. Deep brain stimulation, personal identity and policy. Int Rev Psychiatry [Internet]. 2011;23(5):486–92. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22200138&retmode=ref&cmd=prlinks.
304. Witt K, Kuhn J, Timmermann L, Zurowski M, Woopen C. Deep brain stimulation and the search for identity. Neuroethics [Internet]. 2013;6:499–511. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24273620&retmode=ref&cmd=prlinks.
305. Seery MD, Leo RJ, Lupien SP, Kondrak CL, Almonte JL. An upside to adversity? Moderate cumulative lifetime adversity is associated with resilient responses in the face of controlled stressors. Psychol Sci [Internet]. 2013 [cited 2020 Jun 1];24(7):1181–9. Available from: http://journals.sagepub.com/doi/10.1177/0956797612469210.
306. Taylor S. Transformation through suffering. J Humanist Psychol [Internet]. 2012 [cited 2020 Jun 1];52(1):30–52. Available from: http://journals.sagepub.com/doi/10.1177/0022167811404944.
307. Sarkar M, Fletcher D, Brown DJ. What doesn't kill me: adversity-related experiences are vital in the development of superior Olympic performance. J Sci Med Sport. 2015;18(4):475–9.
308. Wielenberg EJ. Pleasure, pain, and moral character and development. Pacific Philos Q [Internet]. 2002 [cited 2020 Jun 1];83(3):282–99. Available from: http://www.blackwell-synergy.com/links/doi/10.1111%2F1468-0114.00152.
309. Eliyahu U, Berlin S, Hadad E, Heled Y, Moran DS. Psychostimulants and military operations. Mil Med [Internet]. 2007;172(4):383–7. Available from: http://publications.amsus.org/doi/10.7205/MILMED.172.4.383.
310. Meyer W J III, Cole CM. physical and chemical castration of sex offenders. J Offender Rehabil [Internet]. 1997;25(3–4). Available from: http://www.tandfonline.com/doi/abs/10.1300/J076v25n03_01.
311. Amodio DM, Jost JT, Master SL, Yee CM. Neurocognitive correlates of liberalism and conservatism. Nat Neurosci. 2007;10(10):1246–7.
312. Welie JVM. In the face of suffering: the philosophical-anthropological foundations of clinical ethics [Internet]. the philosophical-anthropological foundations of clinical ethics. Creighton University Press; 1998. 304 p. Available from: http://books.google.com/books?id=wDVrAAAAMAAJ&q=In+the+Face+of+Suffering+The+Philosophical+Anthropological+Foundations+of+Clinical+Ethics&dq=In+the+Face+of+Suffering+The+Philosophical+Anthropological+Foundations+of+Clinical+Ethics&hl=&cd=1&source=gbs_api.
313. Kapp SK, Gillespie-Lynch K, Sherman LE, Hutman T. Deficit, difference, or both? Autism and neurodiversity. Dev Psychol [Internet]. 2013;49(1):59. Available from: http://proxy.library.upenn.edu:2192/journals/dev/49/1/59.html.

tDCS-Pharmacotherapy Interactions

38

Min-Fang Kuo and Michael A. Nitsche

38.1 Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique which induces cortical excitability alterations via application of continuous, weak direct current through the scalp, leading to bidirectional plasticity induction according to the stimulation protocols [1, 2]. Neuroplasticity induced by tDCS also shares common features with synaptic plasticity in animal studies. The process involves glutamatergic mechanisms and can be modulated by different transmitters, including dopamine, acetylcholine, serotonin, and noradrenaline, which are also associated with a broad range of psychiatric diseases. In recent years, tDCS has been increasingly implemented as an adjuvant to conventional clinical therapy with promising results. As the majority of psychiatric disorders is connected to dysfunctions of specific neuromodulator systems, respective pharmacotherapy is a primary option for treatment. It is therefore crucial to consider the possible interacting factors between tDCS and medications, in order to maximize treatment efficacy. Here we briefly review the neurochemistry of tDCS effects and discuss the knowledge obtained so far from pharmacological experiments with healthy participants, as well as clinical trials and pilot studies, with the aim to inform future combined pharmaco-stimulation approaches in basic research, and clinical application.

38.2 tDCS Physiology: Ion Channel- and Neurotransmitter-Dependent Mechanisms

tDCS induces neuroplasticity via a primary effect on neuronal membrane polarization, which involves modulation of neuronal ion channel activities. Prolonged stimulation over some minutes results in excitatory plasticity, similar to long-term potentiation (LTP), following anodal tDCS, while cathodal stimulation induces excitability inhibition comparable to long-term depression (LTD). Pharmacological studies revealed an abolishment of the acute effects of anodal tDCS via calcium and sodium channel block, but not NMDA receptor antagonists, and GABA receptor activity enhancement [3], which

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is in accordance with an involvement of ion channels, but not synaptic mechanisms, in these immediate polarization-dependent tDCS effects. Furthermore, the neuroplastic after-effects of anodal tDCS-induced LTP-like plasticity were blocked by the respective calcium and sodium channel blockers carbamazepine and flunarizine, which stresses the relevance of the initial polarization effects for the induction of plasticity by tDCS [3]. Neuroplasticity elicited by tDCS is also dependent on NMDA receptors, and thus glutamatergic mechanisms, as the blockade of these receptors results in diminution of cortical plasticity [3, 4], while enhancing NMDA activity via the partial agonist d-cycloserine prolonged and consolidated LTP-like plasticity following anodal tDCS [5]. The mechanism underlying glutamatergic plasticity is associated with the dynamics of calcium concentration [6]. Animal research revealed an alteration of the neuronal calcium profile after direct current stimulation [7, 8]. Accordingly, anodal tDCS-induced excitatory plasticity in humans was abolished by calcium channel block, and the nonlinearity of tDCS effects has been shown to be associated with calcium dynamics [3, 9]. In addition to the involvement of NMDA receptors, tDCS effects are also associated with regulation of AMPA receptor activities [10].

The neuroplasticity-inducing effect of tDCS is also related to GABA activity, which is one of the key regulators of the cortical excitation/inhibition balance. In the primary motor cortex, anodal, and cathodal tDCS reduces local GABA, as revealed by magnetic resonance spectroscopy (MRS) [11], and also by the enhancement of I-wave facilitation following anodal, and cathodal tDCS, as this specific TMS measure is determined by the GABAergic system [12]. Reduction of GABA might thus have a gating effect on tDCS-induced glutamatergic plasticity. It also explains the relatively minor effect of benzodiazepines on tDCS-induced plasticity, as these work only on active GABA receptors. For prefrontal stimulation, MRS results however revealed no change of the GABA level at the left dorsolateral PFC (dlPFC) after anodal tDCS, with the return electrode attached to contralateral right dlPFC [13]. This might mean that the modulatory effect of tDCS on GABAergic activity is different across cortical areas. It should however be noted that stimulation parameters were not identical between studies, and more studies are required for more conclusive comparisons. The recent development of noninvasive brain research techniques such as the combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) allows direct excitability measures also in associative cortical modalities [14]. Specific components of TMS-evoked potentials (TEP) have been shown to be related to the dynamics of neurotransmission, including the GABAergic system [15], and might help to further clarify mechanisms.

As the involvement of glutamate/GABA neurotransmitter systems in psychiatric disorders came increasingly into attention recently, both have been targeted for the purpose of more efficient treatment. For instance, pathological connectivity alterations in glutamatergic and GABAergic systems have been proposed to partially explain the pathophysiology of depression, and corresponding medication such as ketamine or GABA-targeting compounds have shown therapeutic potential in clinical trials [16, 17]. Given the increasing implementation of tDCS in psychiatry, it is crucial to obtain a better understanding about the modulation of tDCS effects by these neurotransmitters also in clinical populations, which might require an adjustment of treatment in case of combined application.

38.3 Modulation of tDCS Effects by Neuromodulators

In contrast to the abovementioned neurotransmitters, which are involving fast-acting signals across the synaptic cleft to induce excitatory and inhibitory postsynaptic potentials, neuromodulators are associated with diffuse, volume-transmitted mechanisms, which have no large effects on their own, but modulate neuronal activities at a slower time course. In this section, the impact of neuromodulatory systems which are critically involved in the majority of neuropsychiatric diseases, including dopamine, acetylcholine, serotonin,

and noradrenaline, on tDCS-induced plasticity will be covered.

38.4 Dopamine

As one of the most important neuromodulators in the category of monoamines, dopamine is a key player in many cognitive functions, including reward, decision making, or working memory. The disturbance of respective operations leads to behavioral dysfunctions, which are linked to many neuropsychiatric diseases. Physiological and cognitive studies in both animal models and humans have demonstrated complex modulatory effects of dopamine on brain physiology, which underlie respective psychological processes. At the molecular level, dopamine mediates brain physiology via clusters of receptors on neuronal membranes, classified as D1- and D2-like receptors, which can be distinguished by pharmacological agonists and antagonists. It is proposed that dopamine exerts its function as a result of the dynamic balance between D1 and D2 activation, revealed as differential modulatory effects of the two receptor subtypes on cortical activity and neuroplasticity [18], which are thought to account for nonlinear effects of dopamine on physiological, psychological, and motor functions [19].

38.4.1 Dopaminergic Effects on Neurophysiology and Cognition in Humans

Evidence from animal studies indicates that dopamine modulates neuroplasticity via its impact on the specific interaction between NMDA and GABA receptors, based on distinct D1 and D2 receptor contributions on the activity of these receptors [18, 20]. A biphasic effect of dopamine on synaptic plasticity has been shown in numerous studies [21, 22], which is assumed to be caused by its impact on NMDA and GABA receptors. DA potentiates NMDA currents or membrane depolarization via D1 receptor activation [23, 24], although an inverted U-shaped dose-dependency has also been described [18]. On the other hand, D2 receptors have a suppressing effect on NMDA receptors, and neuronal calcium influx [25]. Dopamine has also the capacity to evoke a biphasic modulation of GABA-mediated currents: D2-like receptors reduce, while D1-like receptors increase GABAergic activity [26–28]. The dopaminergic effects on NMDA and GABA responses are furthermore neuronal activity-dependent. In case of low network activity, it is assumed that the D1 receptor exerts synaptic plasticity-reducing effects, as the increase of low-level NMDA activation is outweighed by concurrent, large-range GABA currents enhanced by D1 receptor activity [27]. On the other hand, higher network activity results in persistent stronger NMDA receptor activation [29], which is further strengthened by D1 receptors [21, 27]. The opposite effect is observed with D2 activation, where glutamatergic plasticity is reduced via reduction of activation of NMDA receptors, but enhanced by D2-decreased GABA responses when higher network activity is present. Dopamine is thus assumed to have a complex modulatory effect on synaptic plasticity, based on its effects on glutamatergic and GABAergic transmission.

For the human brain, the impact of dopamine on brain physiology was studied most extensively for the motor cortex as a model system. The contribution of dopamine to motor cortical plasticity in humans is complex, and seems to depend on a couple of factors, such as receptor subtype activation, amount of activation (i.e., dosage of respective dopaminergic substances), as well as history and state of activation of the target structures. Dopamine has been shown to be essential for neuroplasticity induction by tDCS. The D2 antagonist sulpiride abolished tDCS-induced cortical plasticity [30]. Results of further studies suggest—similarly to those of related animal models (see above)—that dopamine enhances the signal-to-noise ratio in the human brain, and that this effect depends on the amount of receptor activation, and receptor subtypes. Whereas dopamine abolishes diffuse LTP-like plasticity, as induced by tDCS, or converts it into LTD-like plasticity, it preserves or enhances focal plastic-

ity, as generated by paired associative stimulation (PAS), if dopaminergic activity is moderately enhanced [31–33]. D1- and D2-like receptors contribute in discernible ways to this global dopamine effect. While D2 receptors have a similar impact on plasticity as dopamine itself, D1-like receptor activation fosters facilitatory plasticity independently from its focality [34, 35]. In addition, results from these studies also revealed a dose-dependency of dopaminergic modulation on neuroplasticity, where medium dosage resulted in most prominent effects, whereas low and high dosages reduced tDCS-induced plasticity. In case of low-dose dopaminergic enhancement, the respective plasticity-abolishing effect might be due to the activation of presynaptic, inhibitory autoreceptors [32, 33, 36].

38.4.2 Clinical Aspects

Dysfunctions of the dopaminergic system have been related to many psychiatric disorders including schizophrenia, where treatment with dopamine antagonists improves symptoms. tDCS has been probed for the treatment of schizophrenia symptoms, and improved negative symptoms, attention, and reduced auditory hallucinations [37–41]. Given the impact of DA-affecting substances on tDCS-induced plasticity, it would be important to learn about respective interactions also with respect to clinical studies. In one study, the efficacy of tDCS to reduce auditory hallucinations was compared in patients treated with neuroleptics with high and low D2 receptor affinity [40]. The result revealed less therapeutic efficacy when tDCS was combined with high-affinity antipsychotics, which is in accordance with the plasticity-abolishing effect of D2 receptor block described before [30].

Repetitive disorders, such as the Tourette syndrome, are also associated with imbalanced dopamine activity [42]. Beyond the modulation of tDCS effects by dopaminergic and antidopaminergic agents, the stimulation itself might affect dopaminergic activity, and thereby elicit clinical effects. Application of tDCS in an animal model of Tourette syndrome has been shown to alleviate pathological repetitive behavior via reducing dopaminergic hyperresponsivity in a sensorimotor cortico-striatal circuitry which has been targeted for therapy with deep brain stimulation [43]. Similarly, tDCS has also been shown in human studies to modulate dopaminergic activity in subcortical striatal regions, indicating the opportunity to apply tDCS for dopaminergic enhancement in clinical syndromes caused by dopamine deficiency [44, 45].

38.5 Acetylcholine

Acetylcholine (ACh) is involved in the arousal/attentional system as well as in many other cognitive functions, such as working and long-term memory. Apart from its wide distribution in both subcortical and cortical regions, cholinergic signaling also acts in a temporal- and spatial-specific manner [46, 47]. Dysfunction of cholinergic, particularly nicotinic receptor transmission, can lead to cognitive impairment or dementia, in which abnormal regulation of synaptic plasticity is thought to be involved at the neurophysiological level [48, 49]. Moreover, cholinergic function varies in healthy humans according to brain states, and nicotine consumption, which can explain partially its observed complex and heterogeneous effects on cognition.

38.5.1 Cholinergic Modulation of Cortical Excitability, Plasticity, and Cognition

Cholinergic activation alters cortical excitability, and thereby regulates neuroplasticity [50–52]. These effects are directly induced via cholinergic transmission, but also based on its impact on other neurotransmitters, such as glutamatergic, GABA-ergic and dopaminergic systems [53, 54]. In animal experiments, it has been shown that neuronal excitability can be enhanced by the activation of nicotinic ACh receptors (nAChRs) via the increase of glutamate release, or by muscarinic ACh receptors (mAChRs), which reduce presynaptic GABAergic inhibition on pyramidal

neurons [55, 56]. On the other hand, nAChRs also facilitate GABAergic inhibition, possibly via downregulation of Ca^{2+} signaling [57, 58]. This inhibitory effect of nicotine is reflected in human cortical excitability, as it significantly enhances GABA-associated cortical inhibition in nonsmokers [59]. An important role of nAChRs in synaptic plasticity has been also revealed (for review, see [52]). The activation of nAChRs enhances LTP induction with or without NMDA receptor involvement [49, 60, 61], but it has also been demonstrated to diminish LTP [62]. This heterogeneous effect, which underscores the neuromodulatory role of this system, might be explained by different factors, including specifics of the stimulation protocol, and brain states. With respect to the impact of cholinergic modulation on tDCS-induced plasticity, global cholinergic activation by application of rivastigmine, an acetylcholinesterase inhibitor, diminished LTP-like plasticity induced by anodal tDCS and slightly prolonged LTD-like plasticity following cathodal tDCS [63]. A similar pattern of results was also demonstrated for nAChR activation when applying nicotine or the α4β2-receptor partial agonist varenicline [64, 65]. The mechanisms underlying the LTP-like plasticity-diminishing effects of nicotinic receptor activation might involve calcium dynamics, since reduction of nicotine-induced calcium overflow by an NMDA antagonist as well as calcium channel blocker restituted neuroplasticity [9, 66]. Beyond these effects of nicotinic activation on nonsmoking healthy humans, in smokers LTP-like plasticity was not induced by anodal tDCS under nicotine withdrawal, most likely to nicotinic receptor desensitization induced by chronic nicotine application [67]. Administration of nicotine or varenicline however reestablished compromised plasticity in these participants [67, 68].

38.5.2 Implications for Basic and Clinical Research

For studies in healthy humans, the results imply that inclusion of smokers should be avoided in basic studies which do not aim to explore the effects of nicotine, because of the relevant effect of smoking, and especially nicotine withdrawal, on the physiological effects of tDCS. For clinical studies with tDCS application, the situation might be more complex, as excluding smokers would mean to reject a relevant portion of the patients. Here it would be crucial to implement nicotine consumption, that is, smoking, during experimental sessions, as well as the timing since last consumption, at least as confounding factors for control. Indeed, it has been shown that smoking has a relevant impact of tDCS effects in clinical populations. tDCS-induced motor cortical plasticity was reduced in schizophrenia patients who are nonsmoking or smokers under nicotine withdrawal, while in smoking patients the tDCS effect was restored by nicotine application [69, 70]. Smoking state also had a relevant impact on the therapeutic effect of tDCS. In one study where multiple-session tDCS was applied in schizophrenia patients to reduce auditory hallucinations, the results demonstrated a lack of response in smokers when compared to nonsmoking patients, possibly due to partial self-regulated abstinence in smokers before treatment sessions [71]. In contrast, under proper control of nicotine consumption during the experimental course, tDCS did improve cognitive performance in chronic smoking schizophrenics without withdrawal [72]. These results underline the importance of nicotine levels for tDCS efficacy, particularly for long-term smoking patients in clinical studies.

Based on the cholinergic hypothesis, pro-cholinergic drugs are applied to improve pathological cognitive decline in patients with mild cognitive impairment and dementia [73–75]. As cumulative evidence also suggests beneficial effects of tDCS for cognitive functions, it has been applied recently to augment the efficacy of respective pharmacological treatment in patients with cognitive deficits. Combination of the acetylcholinesterase inhibitor donepezil with 6-months tDCS treatment significantly improved global cognitive performance in patients with Alzheimer's disease, as compared to pharmacotherapy alone [76]. This approach provides initial evidence for a potential synergistic effect of both

interventions to prevent or diminish cognitive decline in dementia. At the first look, this effect is surprising, given that in healthy humans, cholinergic activation diminishes plasticity. The likely explanation is however that respective patients have a hypofunctional cholinergic system, similar to smokers under nicotine withdrawal, which is counteracted upon by pharmacological activation of the system, and thus reestablishes plasticity induction by tDCS.

38.6 Serotonin and Noradrenaline

38.6.1 Neuromodulatory Effect of Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) has been classified as a neurotransmitter or -modulator [77]. The serotonergic system is involved in cognition, mood, behavior, motor processes [78] and also linked to executive functions [79]. Increased serotonin levels improve learning, memory, and motor functions in healthy and post-stroke patients [80, 81]. Dysfunction of this system contributes to the pathophysiology of psychiatric diseases, such as depression [82]. Studies in humans and animals have provided evidence for a relevant role of 5-HT in neuroplasticity [83, 84]. Animal studies have revealed that 5-HT interferes with LTP and LTD, and these effects are related to drug dosage, receptor subtypes, and duration of 5-HT receptor activation [85, 86]. Activation of 5-HT2 receptors results in calcium release from intracellular storages, while 5-HT3 activation increases conductance of calcium influx, and both effects contribute to LTP induction [87]. It was also shown that LTD in hippocampal slices was converted to LTP vis 5-HT4 enhancement, suggesting an excitatory modulation of serotonin on neuroplasticity [86]. In humans, it was shown that the enhancement of serotonin levels by a selective serotonin reuptake inhibitor (SSRI) modulates neuroplasticity in different modalities. In the visual area, long-term SSRI administration augmented visual plasticity in healthy participants [88]. A related LTP-like plasticity-enhancing effect was also observed in the motor cortex, where application of citalopram resulted in enhanced LTP-like plasticity induced by tDCS or PAS, and reduction or even conversion of LTD-like into LTP-like plasticity [89–91]. Moreover, similar, but stronger effects have been shown under chronic application of the same SSRI, which might be associated with long-term therapeutic effects of respective pharmacological treatment in clinical settings [90]. A recently published study also showed beneficial influences of SSRI on cognitive functions in both healthy young and aging humans, and revealed a more prominent effect when medication was combined with anodal tDCS over the right temporoparietal region [92]. These results indicate a potential of combined treatment with SSRI and tDCS in associated basic and clinical domains, which might be due to synergistic effects on LTP-like plasticity.

38.6.2 Neuromodulatory Effect of Noradrenaline

Similar to serotonin, cortical excitability and plasticity, both LTP and LTD, are modulated by noradrenergic activation via its impact on various intracellular processes. Animal studies have shown that neuronal excitability is enhanced by the activation of β-adrenoreceptors via suppressing GABAergic inhibition and facilitating the activation of NMDA receptors [93]. On the other hand, α-adrenoreceptors decrease neural excitability by facilitating GABAergic inhibition, possibly via downregulation of calcium signaling [94]. Similar results have been found in human studies. Here, noradrenergic enhancement increases cortical excitability via enhancement of NMDA receptor-dependent facilitation and reduction of GABAergic inhibition, in principle accordance with a primarily ß-adrenergic enhancing effect [95]. Regarding synaptic plasticity, animal studies have shown that activation of β-adrenoreceptors strengthens LTP, while α-adrenoreceptors promote LTD [96, 97]. In a human study, enhancement of monoamine availability fostered noninvasive brain stimulation-induced LTP-like plasticity, whereas

stimulation-induced plasticity was reduced by a ß-adrenergic antagonist [98]. Acute and chronic administration of the selective noradrenaline reuptake inhibitor (NRI) reboxetine increased and prolonged stimulation-induced LTP-like plasticity, whereas it converted LTD-like plasticity into LTP-like plasticity [99, 100]. Similar to adrenergic effects on excitability, this pattern of results is in accordance with a primary impact of ß-adrenoceptors on plasticity in humans [98].

38.6.3 Clinical Aspects

Pathophysiological disturbances or lesions of the prefrontal cortex are closely related to numerous neuropsychiatric disorders. Major depression is associated with a task-associated dysbalance of bilateral prefrontal cortex activation, where lower activity was shown in the left dorsolateral prefrontal cortex [101]. Moreover, reduced LTP is also suggested as a pathological agent in depression, and might involve large parts of the brain, since a reduction of visual cortical plasticity was observed in depression [88]. These findings might explain the therapeutic benefit of serotonin for depression, as 5-HT exerts excitatory effects on LTP-like neuroplasticity as shown in healthy participants [89–91]. Furthermore, the observed facilitation of LTP-like plasticity resulting from the combination of drugs and stimulation establishes a rationale for combined application in depression. Indeed, it has been demonstrated that sertraline combined with tDCS over the dorsolateral PFC had a superior impact on major depression when compared with placebo and the respective single interventions [81]. Interestingly, patients who received only tDCS treatment also showed significantly better improvement than placebo. This approach to augment clinical treatment effects is currently further explored in ongoing clinical trials [102]. Following a similar rationale, as discussed in the previous section, noradrenergic medication has also been implemented in treating depression, as well as other psychiatric diseases such as attention-deficit/hyperactivity disorders or panic disorder, although consensus over its efficiency remains to be established (see [103] for an overview). Combining NRIs with tDCS might be a way to enhance treatment outcomes, following the rationale outlined above, which however needs validation in clinical trials.

38.7 Conclusion

As a noninvasive brain stimulation tool which modulates cortical excitability and induces plasticity, tDCS has been implemented in psychiatry to normalize pathological excitability and plasticity alterations. Technically it is often combined with conventional pharmacological therapy, because patients are under routine medication, or in a targeted way to further enhance therapeutic efficacy. Hence it is crucial to better understand the synergies, as well as interaction of tDCS and pharmacotherapy. Evidence from both basic and clinical studies has provided important information about the co-application of tDCS and medication, as discussed above. The outcomes of combined interventions are heterogeneous, and manifested as diminished, enhanced, or stratified tDCS effects, which is explained by the neurophysiological mechanisms of stimulation effects, and their association with the sites of action of respective medications. Neuroplasticity induced by tDCS is determined by NMDA receptors and modulated by several neuromodulators such as dopamine, acetylcholine, serotonin, and noradrenaline. The effects of neuromodulators on tDCS-induced plasticity can be further classified into two principle patterns of action: for dopamine and acetylcholine, the activation of both neurochemical systems strengthened LTD-like plasticity induced by tDCS, and reduced LTP-like plasticity, or even converted it into inhibition, while serotonin and noradrenaline exerted an overall facilitatory effect, resulting in LTP-like plasticity enhancement, and a conversion of LTD-like plasticity into LTP-like plasticity. These effects are also determined by the applied dosage and the balance between receptor subtypes, for which the mechanisms have not been fully identified, particularly in humans. It should also be noted that most of the findings from human

studies so far are based on the motor cortex as model system. A one-to-one translation to the prefrontal cortex, which is involved in the majority of psychiatric disorders, as well as translation from healthy humans to patients requires caution and further exploration for support and guidance of clinical applications.

In general, the design of patient studies should take into consideration the concurrent treatment with different types of medication, as well as consumption of recreational substances such as nicotine, which affect the outcome of tDCS. This is relevant to elucidate synergistic, and antagonistic effects of combined stimulation, and pharmacological interventions, which is crucial to tailor therapeutic approaches for improvement of treatment success. Specifically, tDCS has revealed potential as an adjunctive therapy in psychiatry, and results from clinical experiments combining stimulation and pharmacology are encouraging. Such combination might be extended in future to a synergistic, multimodal treatment module, especially when tDCS protocols could be adapted to normalize pathological plasticity. It is expected that accumulating results from future studies will bring more insight into therapeutic mechanisms and thereby benefit the field (Fig. 38.1).

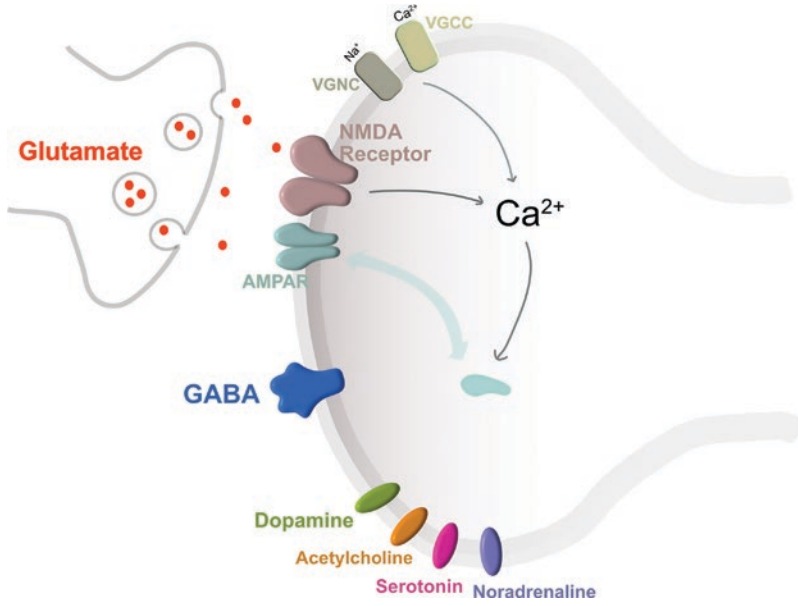

Fig. 38.1 Neurophysiology and modulation of tDCS-induced neuroplasticity
Shown are the main plasticity mechanisms of glutamatergic synapses, and the modulation of ion channels as well as neuromodulators relevant for tDCS-induced plasticity. NMDA receptors are activated via glutamate release in combination with tDCS-induced neuronal membrane depolarization, which results in neuronal calcium influx through the subsynaptic membrane. In addition to NMDA receptors, the activity of voltage-gated calcium channels (VGCCs) contributes to respective intracellular calcium alterations via polarization effects of tDCS. The enhanced intracellular calcium concentration activates enzyme cascades and consequently AMPA receptor trafficking, which further determines the probability of supra-threshold postsynaptic activation upon a given presynaptic activity level. Hereby, the amount of calcium concentration determines if AMPA receptors are inserted into or removed from the subsynaptic membrane. As such, the modification of AMPA receptor density is the main basis of LTP and LTD. Various neurotransmitters such as GABA, dopamine, acetylcholine, serotonin, adrenaline, and noradrenaline influence these mechanisms of action in a complex, sometimes nonlinear way via their specific receptors, and impact on glutamatergic receptors and ion channels.

References

1. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
2. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology. 2001;57:1899–901.
3. Nitsche MA, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301.
4. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125:2238–47.
5. Nitsche MA, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology. 2004;29:1573–8.
6. Lisman J, Three E. Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. J Physiol. 2001;532:285.
7. Monai H, et al. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat Commun. 2016;7:11100.
8. Islam N, Aftabuddin M, Moriwaki A, Hattori Y, Hori Y. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 1995;684:206–8.
9. Grundey J, et al. Nicotine modulates human brain plasticity via calcium-dependent mechanisms. J Physiol. 2018;596:5429.
10. Martins CW, de Melo Rodrigues LC, Nitsche MA, Nakamura-Palacios EM. AMPA receptors are involved in prefrontal direct current stimulation effects on long-term working memory and GAP-43 expression. Behav Brain Res. 2019;362:208–12.
11. Stagg CJ, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29:5202–6.
12. Nitsche MA, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005;568:291–303.
13. Hone-Blanchet A, Edden RA, Fecteau S. Online effects of transcranial direct current stimulation in real time on human prefrontal and striatal metabolites. Biol Psychiatry. 2016;80:432–8.
14. Chung SW, Rogasch NC, Hoy KE, Fitzgerald PB. Measuring brain stimulation induced changes in cortical properties using TMS-EEG. Brain Stimul. 2015;8:1010–20.
15. Du X, et al. TMS evoked N100 reflects local GABA and glutamate balance. Brain Stimul. 2018;11:1071–9.
16. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. Neuron. 2019;102:75–90.
17. Wilkinson ST, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discov Today. 2019;24:606–15.
18. Seamans JK, Yang CR. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 2004;74:1–58.
19. Goto Y, Grace AA. The dopamine system and the pathophysiology of schizophrenia: a basic science perspective. Int Rev Neurobiol. 2007;78:41–68.
20. Tritsch NX, Sabatini BL. Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron. 2012;76:33–50.
21. Seamans JK, Durstewitz D, Christie BR, Stevens CF, Sejnowski TJ. Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. Proc Natl Acad Sci U S A. 2001;98:301–6.
22. Beurrier C, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. J Neurosci. 2002;22:5817–22.
23. Chen G, Greengard P, Yan Z. Potentiation of NMDA receptor currents by dopamine D1 receptors in prefrontal cortex. Proc Natl Acad Sci U S A. 2004;101:2596–600.
24. Jocoy EL, et al. Dissecting the contribution of individual receptor subunits to the enhancement of N-methyl-d-aspartate currents by dopamine D1 receptor activation in striatum. Front Syst Neurosci. 2011;5:28.
25. Higley MJ, Sabatini BL. Competitive regulation of synaptic Ca2+ influx by D2 dopamine and A2A adenosine receptors. Nat Neurosci. 2010;13:958–66.
26. Gribkoff VK, Ashe JH. Modulation by dopamine of population responses and cell membrane properties of hippocampal CA1 neurons in vitro. Brain Res. 1984;292:327–38.
27. Seamans JK, Gorelova N, Durstewitz D, Yang CR. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J Neurosci. 2001;21:3628–38.
28. Gorelova N, Seamans JK, Yang CR. Mechanisms of dopamine activation of fast-spiking interneurons that exert inhibition in rat prefrontal cortex. J Neurophysiol. 2002;88:3150–66.

29. Lisman J, Grace AA, Duzel E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends Neurosci. 2011;34:536–47.
30. Nitsche MA, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur J Neurosci. 2006;23:1651–7.
31. Kuo MF, Paulus W, Nitsche MA. Boosting focally-induced brain plasticity by dopamine. Cereb Cortex. 2008;18:648–51.
32. Monte-Silva K, Liebetanz D, Grundey J, Paulus W, Nitsche MA. Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. J Physiol. 2010;588:3415–24.
33. Thirugnanasambandam N, Grundey J, Paulus W, Nitsche MA. Dose-dependent nonlinear effect of L-DOPA on paired associative stimulation-induced neuroplasticity in humans. J Neurosci. 2011;31:5294–9.
34. Fresnoza S, Paulus W, Nitsche MA, Kuo MF. Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:2744–53.
35. Fresnoza S, et al. Dosage-dependent effect of dopamine D2 receptor activation on motor cortex plasticity in humans. J Neurosci. 2014;34:10701–9.
36. Galloway MP, Wolf ME, Roth RH. Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies in vivo. J Pharmacol Exp Ther. 1986;236:689–98.
37. Gögler N, et al. Parameter-based evaluation of attentional impairments in Schizophrenia and their modulation by prefrontal transcranial direct current stimulation. Front Psych. 2017;8:259.
38. Gomes JS, et al. Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in Schizophrenia. Brain Stimul. 2015;8:989–91.
39. Mondino M, Haesebaert F, Poulet E, Suaud-Chagny MF, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. Schizophr Res. 2015;161:515–6.
40. Agarwal SM, et al. Impact of antipsychotic medication on transcranial direct current stimulation (tDCS) effects in schizophrenia patients. Psychiatry Res. 2016;235:97–103.
41. Valiengo LDCL, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in Schizophrenia a randomized clinical trial. JAMA Psychiat. 2020;77:121–9.
42. Singer HS, Minzer K. Neurobiology of Tourette's syndrome: concepts of neuroanatomic localization and neurochemical abnormalities. Brain and Development. 2003;25(Suppl 1):S70–84.
43. Edemann-Callesen H, et al. Non-invasive modulation reduces repetitive behavior in a rat model through the sensorimotor cortico-striatal circuit. Transl Psychiatry. 2018;8:11.
44. Fonteneau C, et al. Frontal transcranial direct current stimulation induces dopamine release in the ventral striatum in human. Cereb Cortex. 2018;28:2636–46.
45. Meyer B, et al. Increased neural activity in meso-striatal regions after prefrontal transcranial direct current stimulation and l-DOPA administration. J Neurosci. 2019;39:5326–35.
46. Sarter M, Parikh V, Howe WM. nAChR agonist-induced cognition enhancement: integration of cognitive and neuronal mechanisms. Biochem Pharmacol. 2009;78:658–67.
47. Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology. 2011;36:52–73.
48. Rasmusson DD. The role of acetylcholine in cortical synaptic plasticity. Behav Brain Res. 2000;115:205–18.
49. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience. 2002;111:815–35.
50. Mansvelder HD, van Aerde KI, Couey JJ, Brussaard AB. Nicotinic modulation of neuronal networks: from receptors to cognition. Psychopharmacology. 2006;184:292–305.
51. Lucas-Meunier E, et al. Involvement of nicotinic and muscarinic receptors in the endogenous cholinergic modulation of the balance between excitation and inhibition in the young rat visual cortex. Cereb Cortex. 2009;19:2411–27.
52. McKay BE, Placzek AN, Dani JA. Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. Biochem Pharmacol. 2007;74:1120–33.
53. Pistillo F, Clementi F, Zoli M, Gotti C. Nicotinic, glutamatergic and dopaminergic synaptic transmission and plasticity in the mesocorticolimbic system: focus on nicotine effects. Prog Neurobiol. 2015;124:1–27.
54. Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology. 2006;184:523–39.
55. Lambe EK, Picciotto MR, Aghajanian GK. Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. Neuropsychopharmacology. 2003;28:216–25.
56. Kruglikov I, Rudy B. Perisomatic GABA release and thalamocortical integration onto neocortical excitatory cells are regulated by neuromodulators. Neuron. 2008;58:911–24.
57. Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature. 1996;383:713–6.
58. Léna C, Changeux JP. Role of Ca2+ ions in nicotinic facilitation of GABA release in mouse thalamus. J Neurosci. 1997;17:576–85.
59. Grundey J, et al. Cortical excitability in smoking and not smoking individuals with and without nicotine. Psychopharmacology. 2013;229:653–64.

60. Placzek AN, Zhang TA, Dani JA. Nicotinic mechanisms influencing synaptic plasticity in the hippocampus. Acta Pharmacol Sin. 2009;30:752–60.
61. Matsuyama S, Matsumoto A, Enomoto T, Nishizaki T. Activation of nicotinic acetylcholine receptors induces long-term potentiation in vivo in the intact mouse dentate gyrus. Eur J Neurosci. 2000;12:3741–7.
62. Couey JJ, et al. Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. Neuron. 2007;54:73–87.
63. Kuo MF, Grosch J, Fregni F, Paulus W, Nitsche MA. Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. J Neurosci. 2007;27:14442–7.
64. Thirugnanasambandam N, et al. Nicotinergic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans. Neuropsychopharmacology. 2011;36:879–86.
65. Batsikadze G, Paulus W, Grundey J, Kuo MF, Nitsche MA. Effect of the nicotinic α4β2-receptor partial agonist Varenicline on non-invasive brain stimulation-induced neuroplasticity in the human motor cortex. Cereb Cortex. 2015;25:3249–59.
66. Lugon MD, et al. Mechanisms of nicotinic modulation of glutamatergic neuroplasticity in humans. Cereb Cortex. 2017;27:544–53.
67. Grundey J, et al. Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. J Neurosci. 2012;32:4156–62.
68. Batsikadze G, et al. Compromised neuroplasticity in cigarette smokers under nicotine withdrawal is restituted by the nicotinic $\alpha_4\beta_2$-receptor partial agonist varenicline. Sci Rep. 2017;7:1387.
69. Hasan A, et al. Impaired long-term depression in schizophrenia: a cathodal tDCS pilot study. Brain Stimul. 2012;5:475–83.
70. Strube W, et al. Smoking restores impaired LTD-like plasticity in schizophrenia: a transcranial direct current stimulation study. Neuropsychopharmacology. 2015;40:822–30.
71. Brunelin J, Hasan A, Haesebaert F, Nitsche MA, Poulet E. Nicotine smoking prevents the effects of frontotemporal transcranial Direct Current Stimulation (tDCS) in hallucinating patients with schizophrenia. Brain Stimul. 2015;8:1225–7.
72. Smith RC, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. Schizophr Res. 2015;168:260–6.
73. Buckley JS, Salpeter SR. A risk-benefit assessment of dementia medications: systematic review of the evidence. Drugs Aging. 2015;32:453–67.
74. Newhouse P, et al. Nicotine treatment of mild cognitive impairment A 6-month double-blind pilot clinical trial. Neurology. 2012;78:91–101.
75. Mehta M, Adem A, Kahlon MS, Sabbagh MN. The nicotinic acetylcholine receptor: smoking and Alzheimer's disease revisited. Front Biosci (Elite Ed). 2012;4:169–180.
76. Im JJ, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12:1222–8.
77. Iversen L, Iversen S, Bloom FE, Roth RH. Introduction to neuropsychopharmacology. Oxford University Press; 2008.
78. Pereira M, Martynhak BJ, Andreatini R, Svenningsson P. 5-HT6 receptor agonism facilitates emotional learning. Front Pharmacol. 2015;6:200.
79. Enge S, Fleischhauer M, Lesch KP, Strobel A. On the role of serotonin and effort in voluntary attention: evidence of genetic variation in N1 modulation. Behav Brain Res. 2011;216:122–8.
80. Acler M, Robol E, Fiaschi A, Manganotti P. A double blind placebo RCT to investigate the effects of serotonergic modulation on brain excitability and motor recovery in stroke patients. J Neurol. 2009;256:1152–8.
81. Brunoni AR, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383–91.
82. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev. 2017;77:317–26.
83. Ogren SO, et al. The role of 5-HT(1A) receptors in learning and memory. Behav Brain Res. 2008;195:54–77.
84. Bert B, Fink H, Rothe J, Walstab J, Bönisch H. Learning and memory in 5-HT(1A)-receptor mutant mice. Behav Brain Res. 2008;195:78–85.
85. Kojic L, Gu Q, Douglas RM, Cynader MS. Serotonin facilitates synaptic plasticity in kitten visual cortex: an in vitro study. Brain Res Dev Brain Res. 1997;101:299–304.
86. Kemp A, Manahan-Vaughan D. The 5-hydroxytryptamine4 receptor exhibits frequency-dependent properties in synaptic plasticity and behavioural metaplasticity in the hippocampal CA1 region in vivo. Cereb Cortex. 2005;15:1037–43.
87. Reiser G, Donié F, Binmöller FJ. Serotonin regulates cytosolic Ca2+ activity and membrane potential in a neuronal and in a glial cell line via 5-HT3 and 5-HT2 receptors by different mechanisms. J Cell Sci. 1989;93:545–55.
88. Normann C, Schmitz D, Fürmaier A, Döing C, Bach M. Long-term plasticity of visually evoked potentials in humans is altered in major depression. Biol Psychiatry. 2007;62:373–80.
89. Nitsche MA, et al. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol Psychiatry. 2009;66:503–8.
90. Kuo HI, et al. Chronic enhancement of serotonin facilitates excitatory transcranial direct current stimulation-induced neuroplasticity. Neuropsychopharmacology. 2016;41:1223–30.

91. Batsikadze G, Paulus W, Kuo MF, Nitsche MA. Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex. Neuropsychopharmacology. 2013;38:2260–7.
92. Prehn K, et al. Effects of anodal transcranial direct current stimulation and serotonergic enhancement on memory performance in young and older adults. Neuropsychopharmacology. 2017;42:551–61.
93. Lei S, Deng PY, Porter JE, Shin HS. Adrenergic facilitation of GABAergic transmission in rat entorhinal cortex. J Neurophysiol. 2007;98:2868–77.
94. Marzo A, Bai J, Otani S. Neuroplasticity regulation by noradrenaline in mammalian brain. Curr Neuropharmacol. 2009;7:286–95.
95. Wójtowicz AM, Fidzinski P, Heinemann U, Behr J. Beta-adrenergic receptor activation induces long-lasting potentiation in burst-spiking but not regular-spiking cells at CA1-subiculum synapses. Neuroscience. 2010;171:367–72.
96. McElligott ZA, Winder DG. Alpha1-adrenergic receptor-induced heterosynaptic long-term depression in the bed nucleus of the stria terminalis is disrupted in mouse models of affective disorders. Neuropsychopharmacology. 2008;33:2313–23.
97. Kemp A, Manahan-Vaughan D. Beta-adrenoreceptors comprise a critical element in learning-facilitated long-term plasticity. Cereb Cortex. 2008;18:1326–34.
98. Nitsche MA, et al. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb Cortex. 2004;14:1240–5.
99. Kuo HI, et al. Acute and chronic noradrenergic effects on cortical excitability in healthy humans. Int J Neuropsychopharmacol. 2017;20:634–43.
100. Kuo HI, et al. Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation-induced neuroplasticity in humans. J Physiol. 2017;595:1305–14.
101. Grimm S, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol Psychiatry. 2008;63:369–76.
102. Padberg F, et al. Prefrontal transcranial direct current stimulation (tDCS) as treatment for major depression: study design and methodology of a multicenter triple blind randomized placebo controlled trial (DepressionDC). Eur Arch Psychiatry Clin Neurosci. 2017;267:751–66.
103. Sepede G, Corbo M, Fiori F, Martinotti G. Reboxetine in clinical practice: a review. Clin Ter. 2012;163:e255–62.

39 Combination of tDCS with Psychotherapy and Neurobehavioral Interventions: Systematic Review and Mechanistic Principles for Future Clinical Trials

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39.1 tDCS as an Intervention in Neuropsychiatry

Transcranial direct current stimulation (tDCS) is considered a safe nonpharmacological tool able to improve several neuropsychiatric symptoms, cognitions, and behavior (see, for example, Valiengo and co-workers [1] in schizophrenia; Moffa and co-workers [2] in depression). Yet, the overall effect sizes and clinical significance of tDCS effects have been modest to moderate, especially for psychiatric patients not responding to or not tolerating psychotropic medication (see meta-analysis of individual patient data [3] and European evidence-based guidelines [4]). Hence, there is currently a worldwide quest to develop new treatment procedures that would augment the therapeutic efficacy of tDCS.

39.2 Principle of Combining tDCS with Psychological Interventions

A promising avenue for optimized treatment is the combination of tDCS with psychological interventions. These psychological interventions can be neurobehavioral or psychotherapeutic. *Neurobehavioral* refers to cognitive interventions that are known to modulate neural correlates underlying cognitive and emotional processes [5]. *Psychotherapeutic* refers to psychotherapy (e.g., cognitive-behavioral therapy, CBT) or its components, such as exposure therapy. This combination is promising, from both a practical and a mechanistic point of view. *The practical aspect* refers to the appealing safety profile of both tDCS and psychological interventions and the feasibility of combining these interventions. As compared to other Noninvasive brain stimulation

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(NIBS) techniques, such as transcranial magnetic stimulation (TMS) and theta burst stimulation (TBS), tDCS causes no distraction, as it mostly elicits a tingling sensation [6]. It is therefore well suited to be combined with other interventions that require good focus and concentration. Moreover, tDCS interventions as well as psychological interventions are based on repeated sessions, which are applied for a short period of time (e.g., 10–60 min) [7]. Administering tDCS for multiple sessions is tolerable and not found to increase adverse effects for any diagnostic group [8]. Finally, tDCS interventions can be done remotely, implying that the psychological therapist does not need to be at the brain stimulation center, or tDCS can be done at home while the psychological intervention is delivered via the internet.

The mechanistic aspect refers to the potential additive or synergistic effects of both treatments on neuroplasticity, and hence restoring neural functioning. Both tDCS and psychological interventions are known to induce longer-lasting changes in neuronal processing in order to restore basic (e.g., working memory, executive functioning) and associated higher-order psychological mechanisms (e.g., decision-making, self-regulation, reappraisal, and emotion regulation) that have been implicated in psychopathology. It is well known that the efficacy of tDCS depends on the functional state of the brain at the time of stimulation [9], and neuroplastic effects may be greater when tDCS is delivered to an already actively engaged brain (i.e., the activity-selectivity hypothesis) [10–12]. The potential for neuroplastic effects may therefore increase when combining "passive" membrane polarization by means of tDCS, with neuronal activation from psychological tasks, trainings, or therapies, especially if they co-activate a (disease-related) targeted neural network [13–15]. In other words, when a specific neural network is engaged by means of a psychological intervention, these neurons are primed for eliciting action potentials. The neural membrane polarization elicited by the weak tDCS-induced electric fields may then be sufficient to make these synchronized neurons more sensitive to synaptic inputs and may thus modulate the likelihood of neuronal firing even further. Once the neurons are activated, they may synaptically trigger the firing of other neurons, causing tDCS to exert network effects, rather than focal effects [16].

Altogether, the combination of tDCS with psychological interventions may lead to additive or synergistic effects and could increase the clinical utility and overall efficacy of tDCS. The combination of interventions might also reduce the interindividual variability in tDCS effects [17], making it an appealing treatment adaptation for personalized interventions in psychiatry [18] (see also Conclusion for a more detailed discussion). The current chapter provides a systematic review of the available literature reporting the combination of tDCS with psychological interventions, both neurobehavioral and psychotherapy, in patients with psychiatric disorders (major depression, anxiety, addiction, schizophrenia, posttraumatic stress disorder, and attention-deficit hyperactivity disorder (ADHD)). Case reports as well as one-session studies (i.e., proof of concept, no intervention) were excluded.

39.3 Overview of Combination Trials in Neuropsychiatry

We also refer to Table 39.1 for a structured overview of these studies, listing the timing of application (concurrent, sequential), the number of sessions, tDCS parameters, characteristics of the psychological intervention, and treatment arms.

39.3.1 Major Depression

Most trials combining tDCS with psychological interventions have been performed in the field of major depression. From two independent research groups, two similar randomized sham-controlled trials of combining tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) with cognitive control training (CCT) were published in 2014 [19, 20]. In short, the CCT is a neurobehavioral intervention based on the training of cognitive control functions (i.e., working memory

Table 39.1 A structured overview of studies regarding the combination trials in neuropsychiatry, listing the timing of application (concurrent, sequential), number of sessions, tDCS parameters, characteristics of the psychological intervention and treatment arms

				tDCS characteristics		Psychological intervention characteristics		Treatment arms			
Population	Study	Timing	N of sessions	Montage (Anode – Cathode)	Intensity/ Duration	Type	Duration	Active tDCS + Active intervention	Sham tDCS + Active intervention	Active tDCS + Control intervention	No treatment
Depression	Brunoni et al., 2014	C	10 (consecutive workdays)	Left DLPFC – Right DLPFC	2 mA/30 min	Neurobeh. – CCT	15 min	Active tDCS + CCT ($N = 20$)	Sham tDCS + CCT ($N = 17$)	.	.
	Martin et al., 2018	C	18 (3 each week for 6 weeks)	Left DLPFC – Right upper arm	2 mA/30–40 min	Neurobeh. – CET	40 min	Active tDCS + CET ($N = 17$)	.	.	.
	Monnart et al., 2019	S	8 (consecutive workdays) + 1 two weeks later	Left DLPFC – Right DLPFC	2 mA/20 min	Psychotherapy – MBCT	120 min	Active tDCS + MBCT ($N = 15$)	.	Active tDCS + Relaxation ($N = 16$)	.
	Nikolin et al., 2019	C	18 (3 each week for 6 weeks)	Left DLPFC – Right upper arm	2 mA/40 min	Neurobeh. – CET	40 min	Active tDCS + CET ($N = 20$)	.	.	.
	Nord et al., 2019	C/S	8 (1 each week for 8 weeks)	Left DLPFC – Ipsilateral deltoid	1 mA/20 min	WM during tDCS/ Psychotherapy – CBT	60 min	Active tDCS + CBT ($N = 20$)	Sham tDCS + CBT ($N = 19$)	.	.
	Segrave et al., 2014	C	5 (consecutive workdays)	Left DLPFC – F8 (contralateral orbit)	2 mA/24 min	Neurobeh. – CCT	30 min	Active tDCS + CCT ($N = 9$)	Sham tDCS + CCT ($N = 9$)	Active tDCS + Control training ($N = 9$)	.
	Welch et al., 2018	C	12 (3 each week for 4 weeks)	Left DLPFC – Right DLPFC	2 mA/30 min	Psychotherapy – CBT	30 min	Active tDCS + CBT ($N = 5$)	Sham tDCS + CBT ($N = 4$)	.	.
Anxiety/ Depression	Nasiri et al., 2020	C	12 (first two without tDCS)	Contralateral deltoid – Right DLPFC	2 mA/30 min	Psychotherapy – UP	60 min	Active tDCS + UP ($N = 15$)	No tDCS + UP ($N = 13$)	.	Waitlist control ($N = 15$)
Addiction	Claus et al., 2019	C	4 (1 each week for 4 weeks)	Right IFG – Left upper arm	2 mA/20 min	Neurobeh. – CBM	18 min	Active tDCS + CBM ($N = 22$)	Sham tDCS + CBM ($N = 16$)	Active tDCS + Control CBM ($N = 20$)	Sham tDCS + Control CBM ($N = 20$)

(continued)

Table 39.1 (continued)

Population	Study	Timing	N of sessions	tDCS characteristics		Psychological intervention characteristics		Treatment arms			
				Montage (Anode – Cathode)	Intensity/ Duration	Type	Duration	Active tDCS + Active intervention	Sham tDCS + Active intervention	Active tDCS + Control intervention	No treatment
	Den Uyl et al., 2018	C	4 (consecutive workdays)	Left DLPFC – Right DLPFC	2 mA/20 min	Neurobeh. – ABM	15-20 min	Active tDCS + ABM ($N = 20$)	Sham tDCS + ABM ($N = 19$)	Active tDCS + Control ABM ($N = 20$)	Sham tDCS + Control ABM ($N = 22$)
	Kooteh et al., 2019	S	8 (2 each week for 4 weeks)	Right DLPFC – Left DLPFC	2 mA/45 min	Psychotherapy – Group ER training	45-60 min	Active tDCS + ER ($N = 28$)	.	.	.
Schizophrenia	Nienow et al., 2016	C	48 CT (3 each week for 16 weeks), 28 tDCS (2 each week for 14 weeks)	Left DLPFC – Right supraorbital (SO)	1 mA/20 min	Neurobeh. – working memory (WM)	60 min	Active tDCS + Training ($N = 6$)	Sham tDCS + Training ($N = 4$)		
	Orlov et al., 2017	C	8 CT (at days 1, 2, 14, and 56) and 2 tDCS (days 1 and 14)	Left DLPFC – Right SO	2 mA/30 min	Neurobeh. – WM	22 min	Active tDCS + Training ($N = 19/22$)	Sham tDCS + Training ($N = 21/25$)	.	.
	Shiozawa et al., 2016	C	10 on 5 days (min interval of 3 h)	Left DLPFC – Right DLPFC	2 mA/20 min	Neurobeh. – WM	?	Active tDCS + Training ($N = 5$)	Sham tDCS + Training ($N = 5$)	.	.
PTSD	Saunders et al., 2014	S	5 tDCS (1 each week)/25 CT (5 each week for 5 weeks)	Left DLPFC – Right SO	1 mA/20 min	Neurobeh. – CT	30–45 min	Active tDCS + CT ($N = 4$)	.	.	.
	Van 't Wout-Frank et al., 2019	C	6 (3 each week for 2 weeks)	AF3 – PO8 (vmPFC target)	2 mA/25 min	Psychotherapy – VRExp	24 min	Active tDCS + VR exposure ($N = 6$)	Sham tDCS + VR exposure ($N = 6$)	.	.
ADHD	Allenby et al., 2018	C	3 in one week (days 1, 3, and 5)	Left DLPFC – Right SO	2 mA/20 min	Neurobeh. – WM	15 min	Active tDCS + Training ($N = 37$)	Sham tDCS + Training ($N = 37$)	.	.

updating, sustained attention, etc.) that has been found to enhance activation in the DLPFC during a cognitive task, and at the same time decrease activation in the amygdala during an emotional task [5]. Segrave and co-workers [20] observed that five sessions of tDCS stimulation (anode applied to the left DLPFC, cathode to the contralateral orbit) concurrently with CCT, as well as sham tDCS combined with CCT and tDCS combined with control training, all resulted in acute antidepressant effects. However, only the double active treatment condition was associated with ongoing therapeutic benefit 3 weeks after cessation of treatment. Interestingly, over all treatment arms, those patients showing early cognitive gain in an affective 2-back working memory task showed the greatest clinical improvement at 3 weeks follow-up. However, this study employed a small number of depressed patients ($n = 27$) and a limited number of intervention sessions ($n = 5$).

Using a larger group ($n = 37$) and double the number of training sessions ($n = 10$), Brunoni and co-workers [19] similarly observed that bifrontal tDCS stimulation (anode applied to the left DLPFC, cathode to the right DLPFC) as well as sham tDCS stimulation concurrently combined with CCT ameliorated depressive symptoms (i.e., 25% decrease), both immediately after the treatment and at 2 weeks follow-up. Yet, older patients and those who showed larger improvements in cognitive control throughout the intervention – possibly indicating increased DLPFC engagement – had larger depression improvement in the double active treatment group. In addition, in a follow-up analysis of the data, the reduction in rumination pre- to postintervention showed a positive correlation with the increase in cognitive control over the course of the combined treatment [21]. Even though the combination of tDCS with a neurobehavioral intervention seems promising, these study findings must be replicated in a larger group of depressed patients, including a CCT control condition.

On the other hand, recent studies have combined tDCS with another neurobehavioral intervention that is focused on cognitive and emotion regulation processes, namely cognitive emotional training (CET) [22, 23]. To improve emotion regulation, CET is based on an emotional working memory paradigm that aims to simultaneously activate brain regions in cognitive control, such as prefrontal cortex and affective networks, such as amygdala. The first open-label study [22] in 20 treatment-resistant depressed patients suggested that 18 sessions of tDCS applied to the left DLPFC (anode applied to the left DLPFC, cathode to the right upper arm), administered over a course of 6 weeks (i.e., three times a week) concurrently with CET, were well tolerated, with promising improvement in depression scores (i.e., 38% decrease) and response rates (i.e., 41%). In a follow-up study [23], the same group confirmed improvements in mood in 20 treatment-resistant depressed patients (of whom 10 were included in the analyses of Martin and co-workers [22]) and showed near-transfer effects of the double active DLPFC-targeted tDCS + CET training to working memory accuracy on a visual 3-back task. Yet, little evidence of neurophysiological changes during resting state and task-related electroencephalogram (EEG) activity was observed. Again, as in the studies combining tDCS with CCT, more research is needed including a sham control condition, and a larger sample of patients to investigate the neurophysiological mechanisms underlying the antidepressant effects.

Another line of research is the combination of tDCS with evidence-based psychotherapy, such as CBT [18, 24, 25] and mindfulness-based cognitive therapy (MBCT) [26]. Given that tDCS has been shown to enhance cognitive functioning, such as working memory and associated higher-order cognitive processes (i.e., executive functioning, which refers to a set of prefrontal-mediated cognitive processes including inhibition, updating, flexibility, decision-making, and planning), this might improve patients' ability to benefit from psychotherapy, which itself requires higher-order cognitive processes that are often compromised in patients with depression [27]. Bajbouj and co-workers [18] registered a large ($n = 192$) randomized placebo-controlled multicenter trial to test whether the efficacy of CBT in a group setting can be augmented by concurrent application of bifrontal tDCS (i.e., anode targeted at the left DLPFC,

cathode at the right DLPFC) in the treatment of major depressive disorder. The main hypothesis is that a 6-week treatment program consisting of 12 sessions of CBT concurrently combined with tDCS is more efficacious in reducing depressive symptom severity than CBT combined with sham-tDCS or CBT alone. Results concerning the effects on depression severity, neuropsychological functioning, and neural processing are awaited. Nord and co-workers [25] recently published the results of a double-blind randomized controlled trial looking at the sequential combination of tDCS applied to the left DLPFC (cathode applied to the ipsilateral deltoid) vs. sham tDCS, followed by CBT in unmedicated patients with major depression. However, during both active and sham tDCS the patients also engaged in a working memory-based n-back task with the aim to engage prefrontal neural circuits during stimulation. tDCS and CBT were administered once per week, for a period of 8 weeks. The results revealed no clear effect of tDCS over and above CBT, even though the sample size was again small (n = 39). Yet, functional magnetic resonance imaging (fMRI) measurements revealed that tDCS combined with CBT increased DLPFC activation compared to sham, though only during emotion processing (i.e., during an emotional face task) and not during working memory (i.e., during an n-back task). Interestingly, higher left DLPFC engagement prior to the treatment was associated with better clinical response to the double active treatment [25]. These results are very interesting as they demonstrate that tDCS combined with psychological interventions might be especially effective for depressed patients with specific neural activation patterns and associated cognitive functioning at baseline. Finally, in line with the rise of eHealth, bifrontal tDCS (anode targeted at the left DLPFC, cathode at the right DLPFC) or sham tDCS has been concurrently combined with computer-based electronic CBT (eCBT) in depressed patients [24]. Results of the pilot study (n = 9 completers), in which 12 dual active treatment interventions were given spread over 4 weeks, suggest that the combination is feasible, with a significant reduction in depression scores. However, no difference between the tDCS and sham group was observed. Yet, this study was clearly underpowered to draw any conclusion and further research is warranted to look for synergistic effects of this computerized CBT combined with tDCS. As tDCS is finding its way to home-based treatment, for which dose, number of sessions can be preprogrammed by the therapist. This combination with eCBT may have good future potential.

Lastly, tDCS has been combined with the mindfulness-based cognitive therapy (MBCT) [26], a group-based intervention that was designed to enhance self-management of prodromal symptoms of depressive relapse. In this latter study, bifrontal tDCS (anode targeted at the left DLPFC, cathode at the right DLPFC) has been combined with MBCT (n = 15) or relaxation (n = 16) in treatment-resistant depressed patients. Eight sequential sessions were administered, followed by a repetition session 2 weeks later. Clinical symptoms and cognitive functioning were assessed at baseline, after eight consecutive treatment days, and at 2 weeks follow-up right after a booster session. The combination of tDCS and MBCT, as compared to relaxation, was associated with more sustained clinical improvement after 2 weeks. Again, the sample size was low, no sham condition for tDCS was used, and the follow-up period was limited to only 2 weeks. Nevertheless, results are promising as MBCT requires ongoing daily formal mindfulness-meditation practice, which can be combined with home-based tDCS.

39.3.2 Anxiety

Studies investigating the combination of tDCS with psychological interventions for anxiety disorders are scarce, even though some studies have investigated the combination of a single session of tDCS with a neurobehavioral task targeting the relevant neural correlates in patients with anxiety [28]. This absence of combination trials is surprising as the DLPFC is involved in threat processing and the imbalance between the (hyperactive) right and (hypoactive) left DLPFC

is involved in the processing of negative emotions and the generation of anxiety. Most studies have looked at transcranial magnetic stimulation (TMS) combined with fear conditioning, cue exposure paradigms, or exposure therapy. Recently however, Nasiri and co-workers [29] tested patients with generalized anxiety disorder (GAD) and comorbid depression (n = 43) using concurrent administration of the Unified Protocol for transdiagnostic treatment of emotional disorders (UP, 12 sessions, of which the first two were performed without tDCS) with cathode to the right DLPFC-targeted tDCS (10 sessions, during which the anode was placed over contralateral deltoids), UP alone or waiting list control. Relative to UP alone, the double active treatment elicited larger improvements in anxiety symptoms, worry severity, and anxiety sensitivity, as well as slightly higher remission rates posttreatment (69% vs. 60%), and even more at 3 months follow-up (77% remission rate for UP plus tDCS vs. 60% remission rate for UP alone). However, again future large-scale clinical randomized trials are warranted. Overall, as compared to the field of depression, studies combining tDCS with psychological interventions in patients with anxiety disorders are even more in their infancy. In general, more research investigating the effectiveness of tDCS in anxiety is needed, as monotherapy studies using tDCS as a treatment for a broad range of anxiety disorders are based on different methodologies, small sample sizes, nonstandard tDCS montages, and analyzed diverse behavioral outcomes [30].

39.3.3 Addiction

In the field of addiction, research has been flourishing relatively recently in which tDCS has been combined with neurobehavioral interventions. The imbalance between increased bottom-up subcortical urges combined with weakened top-down prefrontal-mediated neural processes often leads to relapse, and neurobehavioral interventions can target this neural imbalance. Den Uyl and co-workers [31] investigated the combination of four sessions of bifrontal tDCS (anode targeted at the left DLPFC, cathode at the right DLPFC; vs. sham) administered concurrently with an attention bias modification (ABM) training (vs. control) in a sample of alcohol-dependent inpatients (n = 83). The aim of ABM is to train participants to no longer focus attention on alcohol-related stimuli. tDCS was applied to the DLPFC because this region is known to underlie attentional biases. Attentional biases toward alcohol and craving (posttreatment) and relapse (treatment outcome after 1 year) were measured. The combined application only resulted in an enhanced avoidance bias, even though there was no effect of tDCS on attentional bias, implicit alcohol associations, craving, or relapse. All in all, the results of this clinical study provided no evidence of a beneficial effect of ABM or tDCS provided alone, or the combination of both. Yet, craving of the patients enrolled in the study was generally low at baseline, and the number of tDCS sessions may not have been enough to produce a clinically meaningful effect. A similar recent study evaluated the effects of four sessions spread over 4 weeks of tDCS targeted at the right inferior frontal gyrus (vs. sham), concurrently administered with a cognitive bias modification (CBM) training (vs. control training) in high-risk drinkers (AUDIT score >8) and found no effect on drinking measures or alcohol approach biases [32]. To date, it seems that tDCS combined with attentional training in the field of addition is not promising, possibly because the nature of ABM is only based on the modification of external attentional processes (i.e., toward alcohol-related cues), and not the regulation of internal processes, such as inhibition, which play an important role in craving. In a recent review paper, Schluter and colleagues [33] highlighted that response inhibition might be an important avenue for neurobehavioral interventions in addiction, also combined with tDCS, as it may reduce the chance for relapse. Future research looking at this association is warranted. A recent proof-of-concept study showed that the effects of a single session of bifrontal tDCS (anode placed on the right DLPFC) on a rewarded Go/no-Go task assessing response inhibition were predictive of the reduction in beer drinking in heavy drinkers

[34]. These results suggest that response inhibition might be an important cognitive process to consider in tDCS combination trials.

Finally, Kooteh and colleagues [35] selected a sample of opioid-dependent patients (n = 28), who sequentially received eight sessions of bifrontal tDCS (anode targeted at the right DLPFC, cathode at the left DLPFC), directly followed by eight sessions of emotion regulation training, or first the training followed by tDCS. Both sequences reduced drug craving and drug-use thoughts and fantasies in opioid-dependent patients. However, when first engaging in emotion regulation training, and then receiving bifrontal tDCS, the authors demonstrated greater tDCS efficacy. The combination of tDCS and psychological intervention was sequential, but priming the brain with a psychological intervention seems to augment the effects of tDCS [35, 36]. It should be noted that, in this study, a sham tDCS condition as well as a control emotion regulation training were absent.

39.3.4 Schizophrenia

Also in schizophrenia, the combination of tDCS with psychological interventions – mainly neurobehavioral – is finding its way to the clinic. One of the first combination trials in schizophrenia was a randomized controlled clinical study of Nienow and co-workers [37]. Seventeen schizophrenia patients (ten included in the analyses) were administered a combined adaptive working memory training with tDCS. Cognitive training was applied for 16 weeks (three sessions per week), and the concurrent combination with either tDCS or sham stimulation targeted at the left DLPFC (cathode at the contralateral supraorbital position) started in the third week (two sessions per week for 14 weeks). Findings from this pilot study demonstrate that the combination was feasible and well tolerated, and suggest enhanced cognitive functioning after the combination trial in patients with schizophrenia, even though the effect size was modest. No significant changes in the severity of psychotic or mood symptoms were observed. Furthermore, Shiozawa and co-workers [38] investigated the effects of concurrently administering bifrontal tDCS (anode left DLPFC, cathode right DLPFC; vs. sham) and a working memory (n-back) and sequence learning-based cognitive training during 10 sessions (two times a day for 5 days) on psychotic symptoms in patients with schizophrenia (n = 9). The psychological intervention was combined during one of both daily tDCS sessions. Findings did not show beneficial effects of the combined intervention on clinical outcomes in patients with schizophrenia, also not at 4 weeks follow-up. Again, the sample size was too small for firm conclusions. In another and final study, the effects of concurrently combining tDCS applied to the left DLPFC (cathode to the right supraorbital position; vs. sham) and working memory-based (i.e., n-back) and implicit learning-based (i.e., picture-word training) cognitive training were examined on the change in cognitive performance in patients with schizophrenia (n = 49) [39]. Patients received eight cognitive training sessions spread over 4 days (days 1, 2, 14, 56) during which tDCS was applied at day 1 and day 14 during the second training session. Results showed that the double active treatment improved the working memory in schizophrenic patients both immediately and at day 56, demonstrating a long-term effect. There were, however, no effects on implicit learning. These results suggest that the beneficial effects of the combined intervention require a consolidation period and that the effects would increase long-term potentiation of neuronal networks through changing synaptic strength, influencing underlying neuroplasticity, and impacting effective learning over time. It should be noted that transfer effects on psychotic or other psychiatric symptoms were not assessed. In general, further research is needed, possibly targeting other higher-order cognitive functions or combining tDCS with psychotherapy, as this has not been investigated so far.

39.3.5 PTSD

In their review, Marin and co-workers [40] proposed to combine brain stimulation – applied to

neural networks known to be dysregulated when learning and/or recalling safety memory traces – with exposure-based therapy in individuals suffering from posttraumatic stress disorder (PTSD). In four war veterans suffering from PTSD, Saunders and co-workers [41] showed that a sequential stepped care combination of tDCS targeted at the left DLPFC (cathode at the right supraorbital region, five sessions spread over 5 weeks) followed by working memory-based and attention-based cognitive training at home (25 sessions spread over 5 weeks) leads to clinical improvement and associated neurophysiological adaptation (i.e., normalization of P300 event-related potential (ERP) responses indexing improved inhibitory control). Further, Van't Wout-Frank and co-workers [42] combined tDCS with exposure-based psychotherapy using virtual reality (virtual reality exposure therapy, VRET) to male veterans with PTSD (n = 12) in order to improve extinction-based treatments. Participants were randomly assigned to receive six sessions of real or sham tDCS stimulation spread over 2 weeks (anode applied over AF3 and cathode over PO8 in an attempt to target the ventromedial prefrontal cortex, VMPFC), concurrently combined with combat-related VR exposure sessions. The VMPFC was selected as prior research showed that patients with PTSD exhibit hypoactivity in the VMPFC but hyperactivity in the amygdala [43]. Data of this small number of patients indicated that patients in the active group exhibit a faster decline in psychophysiological arousal across sessions as compared to patients in the sham group. Additionally, there was a small but clinically meaningful decrease in PTSD symptom severity. These findings suggest that VMPFC-targeted tDCS during exposure enhances habituation/extinction-based processes to reduce PTSD symptoms, possibly more than DLPFC-targeted tDCS. This might be because the VMPFC is critically involved in the extinction of conditioned responses. These efforts show the potential of tDCS during manipulations using virtual reality to provide a context for interventions based on neurobehavioral training and psychotherapy. Together, these studies suggest that dual active interventions may be promising as a treatment for PTSD, both when VMPFC-targeted tDCS is applied concurrently with psychotherapy, and when DLPFC-targeted tDCS is administered in a sequential stepped care fashion with home-based neurobehavioral training. However, the sample sizes of these studies are small and well-powered randomized controlled trials are needed to confirm these findings.

39.3.6 ADHD

To date, only one study on ADHD patients examined the efficacy of concurrently combining tDCS with a neurobehavioral treatment. Allenby and co-workers [44] showed that tDCS applied to the left DLPFC (cathode at the right supraorbital region vs. sham) while concurrently administering a working memory-based cognitive training (i.e., n-back) for three sessions showed a decrease in impulsivity rates in patients (n = 37) only in the dual active treatment condition. This effect, however, did not persist until 3 days of follow-up.

39.4 Overall Discussion and Perspectives

Based on our systematic review (see also Table 39.1 for the details of all the studies that are included in our systematic review), it can be concluded that – so far – well-powered multicenter randomized trials investigating the effectiveness of the combination of tDCS with psychological interventions in neuropsychiatric patients are lacking. This contrasts with the field of neurorehabilitation (e.g., stroke), where the concurrent application of tDCS and physical therapy has been much more studied. In addition, studies that have been performed are difficult to compare, as they show great differences in the type of psychological intervention, tDCS parameters (reference electrode montages, stimulation dose, number of sessions), the timing of administration of both interventions, the spread of individual sessions over time, and the presence of a sham intervention [17], both across and within the different

psychiatric illnesses. Moreover, as compared to the most optimal dose for each of the interventions as a monotherapy, the optimal parameters for the combination of both have never been investigated. Hence, future well-powered full factorial randomized controlled trials with long-term follow-up evaluations are essential to answer these open questions.

That being said, most research has been performed on patients with major depressive disorder (for a review, see Sathappan and colleagues [45]), even though research on addiction, schizophrenia, and PTSD is slowly increasing as well. Almost all reported studies applied tDCS to the left DLPFC (exceptions in addiction in which the inferior frontal gyrus [32] or the right DLPFC was targeted [35]; PTSD, in which the vmPFC was targeted [42]; and comorbid anxiety/depression in which cathodal tDCS was administered to the right DLPFC [29]). This is not surprising, as most psychiatric disorders show abnormal prefrontal processing related to cognitive dysfunction (see later for a discussion of the Research Domain Criteria (RDoC) framework). However, other neural targets may be worth investigating as well (see Downar and co-workers [46]). In our systematic review, a consistent finding – which has also been observed in studies applying tDCS as a monotherapy – is that, as compared to immediately after the end of the acute treatment period, a follow-up period of a couple of weeks or even months seems needed to optimally assess the beneficial efficacy of the combination trials. As discussed by Moffa and colleagues [2], tDCS effects involve long-term neuroplastic changes that keep occurring even after the acute treatment phase has ended. Further, only a couple of studies implemented maintenance sessions after the intervention with regular sessions had ended [26], which might be a promising possibility to maintain the gains.

What do future combination trials have to take into account? As the magnitude and the duration of the tDCS-aftereffects seem to depend on the functional neural activity at the time of stimulation (see also 'activity-selectivity hypothesis') [10], the characteristics of psychological interventions are of great importance. Our systematic review revealed that most tDCS combination trials in neuropsychiatry have combined tDCS with specific cognition-based neurobehavioral interventions (e.g., targeting cognitive control, (emotional) working memory, attention), as compared to combining tDCS with psychotherapy. Nevertheless, the combination of tDCS with therapeutic interventions that aim to modify more broad self-relevant emotional, as well as self-regulatory cognitive processes (i.e., anti-rumination interventions, MBCT, CBT), is flourishing as well, even though more research is absolutely needed. Examples can be found in depression (eCBT [24], CBT [25], MBCT [26]), anxiety (UP [29]), addiction (emotion regulation training [35]), and PTSD (VRET) [43]). The therapeutic synergy of 'dual active treatments' arises because, on the one hand, both tDCS and psychological interventions have to co-activate the same disease-related neural network [13–15]. On the other hand, patients are learning new abilities to regulate a variety of cognitive, emotional, and/or behavioral processes during the psychological interventions, which all depend on the neural circuitries that are modulated by tDCS applied to the prefrontal cortex. Hence, this implies that the tDCS/psychological intervention combination might enable the patient to use the restored brain function in a more efficient way, and hence benefit from the psychological intervention [27, 47]. In addition, proof-of-concept studies have shown that tDCS efficacy may depend on the psychological task during the stimulation ('what is being taught') [48]. Possibly, merely applying tDCS to the prefrontal cortex does not automatically increase cognitive and emotional capabilities, but patients have to be taught *how* to use the neural gains elicited by tDCS. This might suggest that the combination of tDCS with therapeutic interventions (as compared to neurobehavioral) might be extremely promising, as patients are learning how to regulate self-relevant impulses that arise in daily life and functioning. This might also explain why research in the domain of addiction seems a dead end, as the combination of tDCS with attentional manipulations does not seem to result in promising findings. Possibly, psychological interventions

targeting response inhibition or other higher-order cognitive control processes to regulate internal processes might be a promising avenue for tDCS combination trials in addiction.

A key question is whether tDCS and psychological interventions should be performed concurrently or sequentially. Based on our systematic review, both concurrent [24, 29, 42] and sequential [25, 26, 35] applications have been performed. Yet, most studies using a sequential application did not use a sham condition, making it difficult to draw conclusions regarding its efficacy. However, based on proof-of-concept studies, a concurrent application of both interventions may be more promising. For instance, applying one session of tDCS concurrently with a task/training has been demonstrated to lead to greater and potentially longer-lasting effects on cognition and skill acquisition as compared to a sequential application [49, 50]. Indeed, as discussed before, tDCS has been shown to preferentially modulate *already ongoing* neural activity, rather than activity in quiescent brain areas [10]. Other studies have also suggested that neural activity *during* stimulation (in the same target) is needed for longer-lasting neuroplastic effects to occur [11, 12, 51]. These findings suggest that a concurrent application is most optimal (see also meta-analysis [52]). By functionally targeting the same disease-related neural network(s) through both tDCS and the psychological intervention, greater increases in neuroplasticity may be achieved.

It is becoming ever more apparent that pre-intervention (i.e., baseline) 'endophenotypes' have to be taken into account when investigating the effects of tDCS combination trials, such as the engagement of the prefrontal cortex prior to the intervention [25] and the engagement in adaptive cognitive processing and learning at the start of or during the intervention [19, 39]. This implies that the success of the combination trial could be predicted by the cognitive processes at baseline. Moreover, the psychological intervention itself needs to be of sufficient cognitive load or intensity to have beneficial effects in combination with tDCS [14, 53–56]. But what is the optimal load? Core neurobiological mechanisms and associated psychological processes implicated in psychopathology, and that have to be modulated, show large heterogeneity [57, 58], both within patient groups (e.g., depressed patients showing variations in symptomatology) as well as between patient groups (e.g., depressed patients showing distinct symptomatology as anxiety patients). Again, this suggests the need for individualized treatment. It is clear that rigorous research is warranted. Hence, precise and personalized interventions may be advised, especially when tDCS is combined with psychological interventions. For example, after a baseline assessment of the cognitive deficits and abnormalities, a patient could be stratified to the most optimal dual active intervention for that individual. To this end, apart from neuroimaging-compatible online tDCS investigations, online EEG and other neurophysiological investigations are needed, given their high temporal resolution. Especially, investigating baseline brain states and the neural response during and after dual active treatment on event-related potentials may be a promising avenue, given that these are markers of more complex cognitive mechanisms [54].

On the other hand, patterns of neural and psychological malfunctioning may also overlap between disorders (i.e., transdiagnostic mechanisms), which may contribute to a high rate of comorbidity in psychiatry. The Research Domain Criteria (RDoC) framework of the NIMH accounts for such comorbidity [59] and may be considered to guide research into dual active tDCS psychotherapy interventions. Specifically, RDoC does not focus on a disorder, but adopts a dimensional view on the investigation of human constructs that are implicated in psychopathology (e.g., negative valence systems, positive valence systems, cognitive processing systems, social processing systems, arousal and regulatory systems). Psychopathology is then defined as malfunctioning of these constructs, related to aberrant processing in, for instance, neural networks, physiology, or behavior. Dysfunction in one of these constructs, prefrontal-mediated cognitive dysfunction, has been implicated in the development and maintenance of various psychiatric disorders (e.g., depression [47, 60, 61];

anxiety [62]; and schizophrenia [63, 64]). Cognitive dysfunction may therefore be considered a major therapeutic target [47, 65], as early improvements in cognition have also been related to better clinical outcomes [66–68]. In this context, cognitive training should be self-paced, in order to have the cognitive load individualized to the characteristics of that patient. As such, Vanderhasselt and co-workers [21] have demonstrated that the slope of the increase in cognitive control over the ten sessions of a combination trial (tDCS combined with a self-paced neurobehavioral intervention) was associated with the reduction in rumination – a core transdiagnostic cognitive mechanism. We need, however, more research to investigate which neural networks are implicated in the malfunctioning of the other core human constructs in psychiatry – which may reveal new potentially neural treatment targets. Furthermore, we need to examine more thoroughly which particular neural networks are targeted by specific tDCS setups as well as by particular neurobehavioral or psychotherapeutic interventions, and evaluate how exactly these networks are modulated (including an evaluation of the influence of specific parameters that have been used in these interventions, such as dose-response and amount of sessions). New tDCS setups as well as new psychological interventions may need to be developed that specifically target disease-related neural networks. Furthermore, in line with the RDoC framework, patient baseline processing (endophenotypes) may be of importance to predict the outcome of tDCS combined with psychological interventions.

39.5 Conclusion

In summary, coupling tDCS with simultaneously targeted cognitive interventions represents a potentially fruitful and relatively unexplored avenue to boost brain plasticity and enhance the therapeutic effects and clinical efficacy of tDCS. Yet, this requires a good understanding of the mechanistic neurobiological and cognitive-behavioral factors that drive the potential synergistic effects. As was recently pointed out by Deng and co-workers [69], acquiring knowledge of the mechanisms underlying psychiatric disorders and their neurodevelopmental origins might be one of the greatest challenges in neuropsychiatry. With this chapter, we present the current state of the art regarding tDCS combination trials, as well as avenues for future research and clinical trials based on mechanistic insights that seem to be of great importance.

References

1. Valiengo L, Goerigk S, Gordon PC, Padberg F, Serpa MH, Koebe S, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. JAMA Psychiat. 2019;77(2):121–9.
2. Moffa AH, Martin D, Alonzo A, Bennabi D, Blumberger DM, Bensenor IM, et al. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;99:109836.
3. Brunoni AR, Moffa AH, Fregni F, Palm U, Padberg F, Blumberger DM, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry. 2016;208(6):522–31.
4. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.
5. Siegle GJ, Ghinassi F, Thase ME. Neurobehavioral therapies in the 21st century: summary of an emerging field and an extended example of cognitive control training for depression. Cogn Ther Res. 2007;31(2):235–62.
6. Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul. 2012;5(2):155–62.
7. Bajbouj M, Padberg F. A perfect match: noninvasive brain stimulation and psychotherapy. Eur Arch Psychiatry Clin Neurosci. 2014;264(Suppl 1):S27–33.
8. Nikolin S, Huggins C, Martin D, Alonzo A, Loo CK. Safety of repeated sessions of transcranial direct current stimulation: a systematic review. Brain Stimul. 2018;11(2):278–88.
9. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci. 2015;9:181.
10. Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. Front Hum Neurosci. 2013;7:688.
11. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation

promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204.
12. Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts hebbian plasticity in vitro. Brain Stimul. 2020;13(2):287–301.
13. Antal A, Terney D, Poreisz C, Paulus W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci. 2007;26(9):2687–91.
14. Bortoletto M, Pellicciari MC, Rodella C, Miniussi C. The interaction with task-induced activity is more important than polarization: a tDCS study. Brain Stimul. 2015;8(2):269–76.
15. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive enhancement induced by anodal tDCS drives circuit-specific cortical plasticity. Cereb Cortex. 2018;28(4):1132–40.
16. Bikson M, Paulus W, Esmaeilpour Z, Kronberg G, Nitsche MA. Mechanisms of acute and after effects of transcranial direct current stimulation. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 81–113.
17. Spagnolo PA, Montemitro C, Pettorruso M, Martinotti G, Di Giannantonio M. Better together? Coupling pharmacotherapies and cognitive interventions with non-invasive brain stimulation for the treatment of addictive disorders. Front Neurosci. 2019;13:1385.
18. Bajbouj M, Aust S, Spies J, Herrera-Melendez AL, Mayer SV, Peters M, et al. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. Eur Arch Psychiatry Clin Neurosci. 2018;268(8):797–808.
19. Brunoni AR, Boggio PS, De Raedt R, Bensenor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–9.
20. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014;7(2):325–31.
21. Vanderhasselt MA, De Raedt R, Namur V, Lotufo PA, Bensenor IM, Boggio PS, et al. Transcranial electric stimulation and neurocognitive training in clinically depressed patients: a pilot study of the effects on rumination. Prog Neuro-Psychopharmacol Biol Psychiatry. 2015;57:93–9.
22. Martin DM, Teng JZ, Lo TY, Alonzo A, Goh T, Iacoviello BM, et al. Clinical pilot study of transcranial direct current stimulation combined with cognitive emotional training for medication resistant depression. J Affect Disord. 2018;232:89–95.
23. Nikolin S, Martin D, Loo CK, Iacoviello BM, Boonstra TW. Assessing neurophysiological changes associated with combined transcranial direct current stimulation and cognitive-emotional training for treatment-resistant depression. Eur J Neurosci. 2019;51(10):2119–33.
24. Welch ES, Weigand A, Hooker JE, Philip NS, Tyrka AR, Press DZ, et al. Feasibility of computerized cognitive-behavioral therapy combined with Bifrontal transcranial direct current stimulation for treatment of major depression. Neuromodulation. 2019;22(8):898–903.
25. Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, et al. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology. 2019;44(9):1613–22.
26. Monnart A, Vanderhasselt MA, Schroder E. Treatment of resistant depression: a pilot study assessing the efficacy of a tDCS-mindfulness program compared with a tDCS-relaxation program. Front Psychiatry. 2019;10:730.
27. De Raedt R. Contributions from neuroscience to the practice of cognitive behaviour therapy: translational psychological science in service of good practice. Behav Res Ther. 2020;125:103545.
28. Heeren A, Billieux J, Philippot P, De Raedt R, Baeken C, de Timary P, et al. Impact of transcranial direct current stimulation on attentional bias for threat: a proof-of-concept study among individuals with social anxiety disorder. Soc Cogn Affect Neurosci. 2017;12(2):251–60.
29. Nasiri F, Mashhadi A, Bigdeli I, Chamanabad AG, Ellard KK. Augmenting the unified protocol for transdiagnostic treatment of emotional disorders with transcranial direct current stimulation in individuals with generalized anxiety disorder and comorbid depression: a randomized controlled trial. J Affect Disord. 2020;262:405–13.
30. Stein DJ, Fernandes Medeiros L, Caumo W, Torres IL. Transcranial direct current stimulation in patients with anxiety: current perspectives. Neuropsychiatr Dis Treat. 2020;16:161–9.
31. den Uyl TE, Gladwin TE, Lindenmeyer J, Wiers RW. A clinical trial with combined transcranial direct current stimulation and attentional bias modification in alcohol-dependent patients. Alcohol Clin Exp Res. 2018;42(10):1961–9.
32. Claus ED, Klimaj SD, Chavez R, Martinez AD, Clark VP. A randomized trial of combined tDCS over right inferior frontal cortex and cognitive bias modification: null effects on drinking and alcohol approach bias. Alcohol Clin Exp Res. 2019;43(7):1591–9.
33. Schluter RS, Daams JG, van Holst RJ, Goudriaan AE. Effects of non-invasive neuromodulation on executive and other cognitive functions in addictive disorders: a systematic review. Front Neurosci. 2018;12:642.
34. Vanderhasselt MA, Allaert J, De Raedt R, Baeken C, Krebs RM, Herremans S. Bifrontal tDCS applied to the dorsolateral prefrontal cortex in heavy drinkers: influence on reward-triggered approach bias and alcohol consumption. Brain Cogn. 2020;138:105512.

35. Rigi Kooteh B, Bakhshani N-M, Nosratabadi M, Dolatshahi B. Effectiveness of transcranial direct-current stimulation (tDCS) and emotion regulation training in reducing current drug craving and drug-use thoughts and fantasies in opioid-dependent patients: the issue of precedence. Int J High Risk Behav Addict. 2019;8(2):53–60.
36. Silvanto J, Bona S, Marelli M, Cattaneo Z. On the mechanisms of transcranial magnetic stimulation (TMS): how brain state and baseline performance level determine behavioral effects of TMS. Front Psychol. 2018;9:741.
37. Nienow TM, MacDonald AW 3rd, Lim KO. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. Schizophr Res. 2016;172(1-3):218–9.
38. Shiozawa P, Gomes JS, Ducos DV, Akiba HT, Dias AM, Trevizol AP, et al. Effect of transcranial direct current stimulation (tDCS) over the prefrontal cortex combined with cognitive training for treating schizophrenia: a sham-controlled randomized clinical trial. Trends Psychiatry Psychother. 2016;38(3):175–7.
39. Orlov ND, Tracy DK, Joyce D, Patel S, Rodzinka-Pasko J, Dolan H, et al. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of prefrontal transcranial direct current stimulation upon memory and learning. Brain Stimul. 2017;10(3):560–6.
40. Marin M-F, Milad MR. Neuromodulation approaches for the treatment of post-traumatic stress disorder: stimulating the brain following exposure-based therapy. Curr Behav Neurosci Rep. 2015;2(2):67–71.
41. Saunders N, Downham R, Turman B, Kropotov J, Clark R, Yumash R, et al. Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. Neurocase. 2015;21(3):271–8.
42. van't Wout-Frank M, Shea MT, Larson VC, Greenberg BD, Philip NS. Combined transcranial direct current stimulation with virtual reality exposure for post-traumatic stress disorder: feasibility and pilot results. Brain Stimul. 2019;12(1):41–3.
43. Koenigs M, Grafman J. Posttraumatic stress disorder: the role of medial prefrontal cortex and amygdala. Neuroscientist. 2009;15(5):540–8.
44. Allenby C, Falcone M, Bernardo L, Wileyto EP, Rostain A, Ramsay JR, et al. Transcranial direct current brain stimulation decreases impulsivity in ADHD. Brain Stimul. 2018;11(5):974–81.
45. Sathappan AV, Luber BM, Lisanby SH. The dynamic duo: combining noninvasive brain stimulation with cognitive interventions. Prog Neuro-Psychopharmacol Biol Psychiatry. 2019;89:347–60.
46. Downar J, Blumberger DM, Daskalakis ZJ. The neural crossroads of psychiatric illness: an emerging target for brain stimulation. Trends Cogn Sci. 2016;20(2):107–20.
47. De Raedt R, Vanderhasselt MA, Baeken C. Neurostimulation as an intervention for treatment resistant depression: from research on mechanisms towards targeted neurocognitive strategies. Clin Psychol Rev. 2015;41:61–9.
48. Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain Stimul. 2014;7(1):105–12.
49. Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp Brain Res. 2014;232(10):3345–51.
50. Besson P, Muthalib M, Dray G, Rothwell J, Perrey S. Concurrent anodal transcranial direct-current stimulation and motor task to influence sensorimotor cortex activation. Brain Res. 1710;2019:181–7.
51. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125(Pt 10):2238–47.
52. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. 2016;9(4):501–17.
53. Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul. 2015;8(2):253–9.
54. Shah-Basak PP, Hamilton RH, Nitsche MA, Woods AJ. Transcranial direct current stimulation in cognitive neuroscience. In: Practical guide to transcranial direct current stimulation. Cham: Springer; 2019. p. 597–625.
55. Hsu TY, Juan CH, Tseng P. Individual differences and state-dependent responses in transcranial direct current stimulation. Front Hum Neurosci. 2016;10:643.
56. Wiegand A, Sommer A, Nieratschker V, Plewnia C. Improvement of cognitive control and stabilization of affect by prefrontal transcranial direct current stimulation (tDCS). Sci Rep. 2019;9(1):6797.
57. Morris SE, Rumsey JM, Cuthbert BN. Rethinking mental disorders: the role of learning and brain plasticity. Restor Neurol Neurosci. 2014;32(1):5–23.
58. Yee CM, Javitt DC, Miller GA. Replacing DSM categorical analyses with dimensional analyses in psychiatry research: the research domain criteria initiative. JAMA Psychiat. 2015;72(12):1159–60.
59. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:126.
60. Brockmeyer T, Bents H, Holtforth MG, Pfeiffer N, Herzog W, Friederich HC. Specific emotion regulation impairments in major depression and anorexia nervosa. Psychiatry Res. 2012;200(2-3):550–3.
61. Joormann J, Gotlib IH. Updating the contents of working memory in depression: interference from

irrelevant negative material. J Abnorm Psychol. 2008;117(1):182–92.
62. Blair KS, Geraci M, Smith BW, Hollon N, DeVido J, Otero M, et al. Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. Biol Psychiatry. 2012;72(6):476–82.
63. Barch DM, Sheffield JM. Cognitive impairments in psychotic disorders: common mechanisms and measurement. World Psychiatry. 2014;13(3):224–32.
64. Green MF, Harvey PD. Cognition in schizophrenia: past, present, and future. Schizophr Res Cogn. 2014;1(1):e1–9.
65. De Raedt R, Leyman L, Baeken C, Van Schuerbeek P, Luypaert R, Vanderhasselt MA, et al. Neurocognitive effects of HF-rTMS over the dorsolateral prefrontal cortex on the attentional processing of emotional information in healthy women: an event-related fMRI study. Biol Psychol. 2010;85(3):487–95.
66. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry. 2009;195(2):102–8.
67. Vanderhasselt MA, De Raedt R, Leyman L, Baeken C. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. J Psychiatry Neurosci. 2009;34(2):119–26.
68. Amidfar M, Ko YH, Kim YK. Neuromodulation and cognitive control of emotion. Adv Exp Med Biol. 2019;1192:545–64.
69. Deng Z-D, Luber B, Balderston NL, Afanador MV, Noh MM, Thomas J, et al. Device-based modulation of neurocircuits as a therapeutic for psychiatric disorders. Annu Rev Pharmacol Toxicol. 2020;60:591–614. https://doi.org/10.1146/annurev-pharmtox-010919-023253.

Regulatory Aspects

40

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Abbreviations

CE	Conformité Européene
CES	Cranial electrotherapy stimulation
FDA	Food and Drug Administration
HD-tDCS	High-definition transcranial direct current stimulation
IDE	Investigational device exemption
IRB	Institutional Review Board
NIBS	Noninvasive brain stimulation
NSR	Nonsignificant risk
PMA	Premarket approval
SR	Significant risk
tDCS	Transcranial direct current stimulation

40.1 Introduction

The field of noninvasive brain stimulation (NIBS) has undergone considerable advances in the last decade. The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool through the modulation of cortical excitability, and its safety and efficacy have motivated scientists to increase its use in several conditions such as stroke [1–4], chronic pain [5, 6], cognitive impairment [7–9], and neuropsychiatric disorders [10–13].

Compared to other NIBS techniques, the relative ease of use, portability, and low cost of tDCS make it an attractive technique that can be easily accessed and used without any supervision, including for nonmedical reasons. Therefore, it is important to have regulatory guidelines regarding the use of tDCS in both research and clinical practice. Currently, there is no international consensus with well-defined regulations for the use and distribution of tDCS [14]. In this chapter, we provide an overview of the regulatory process, the current status of tDCS in the USA and other countries, tDCS devices, special considerations on patient selection, and the practical aspects involving the use of tDCS.

40.2 FDA Regulation of Medical Devices

The federal agency responsible for regulating medical devices in the USA is the Food and Drug Administration (FDA). This agency has defined a medical device as an "*instrument, apparatus, implement, machine, contrivance, implant,* in vitro *reagent or other similar or related article, including a component part, or accessory which is*:

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- *Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes*" [15].

Before receiving the permission by the FDA to be legally marketed, the medical device submission enters in a review process for premarket and postmarket approvals. In the first case, the FDA classifies the medical devices according to the risk they pose to the consumers. Class I Medical Devices include devices such as elastic bandages or examination gloves for which general controls provide sufficient evidence of safety and efficacy. Class II Medical Devices include devices posing moderate risk to the patients, such as infusion pumps for the treatment of pain. Finally, for Class III Medical Devices, there is insufficient information to assure their safety or efficacy. Examples that fall in this last category are heart replacement valves or deep brain stimulating electrodes [16, 17].

Additionally, this classification determines the regulatory requirements that the manufacturer must follow. A device classified as Class I is exempt from the premarket notification. In the case of moderate and high-risk devices, the clearance is carried out through a premarket approval (PMA) or Product Development Protocol Processes [16]. The PMA process is usually longer and consists of conducting clinical studies to provide evidence of safety and efficacy of the medical device; most Class III and novel devices pass through this process in order to receive the FDA approval.

Furthermore, the premarket submission of a 510 (k) notification must be done to demonstrate that the device is substantially equivalent to a device that is already in the market. This notification includes information regarding the design and characteristics of the device and its components, as well as the clinical or nonclinical studies that were done to support the performance of the device. This is required to assess the quality of the new device and thus, be able to compare to the currently available devices. Most Class I and II devices are exempt from this submission before their sale; they do however undergo further control requirements [18]. This 510 (k) notification is also required for already marketed devices when there have been changes in their technology or a new indication for their use is foreseen.

Once the FDA approves the medical device for marketing, the manufacturer must follow other postmarket requirements: labeling and advertising, manufacturing, postmarketing surveillance, device tracking, and adverse event reporting [16].

Currently, there is no regulation of tDCS devices for therapeutic uses. The FDA regulates cranial electrotherapy stimulation (CES) devices, but does not consider tDCS as a CES due to the use of direct current stimulation and the difference in electrode placement [19]. However, considering the FDA framework on medical devices as discussed above, tDCS could be contemplated and regulated as such, considering its intended use for the treatment of different medical conditions and its effects on brain function.

40.3 tDCS in Research

All clinical evaluations of investigational devices are under the Investigational Device Exemption (IDE) regulation [20, 21]. This exemption allows the new device to be used in clinical trials to provide information regarding its safety and effectiveness. Moreover, it distinguishes between significant and nonsignificant risk device studies and, based upon this, the process for the study

approval may vary. Clinical studies using devices classified as significant risk (SR) require both the FDA and the Institutional Review Board (IRB) approval before the initiation of the study, and in order to obtain the FDA approval, the investigator must submit the IDE application. Specific information including details about the sponsor, report of prior investigations, and the investigational plan is required to apply. Furthermore, the sponsor must demonstrate that the potential risks to which the subjects may be exposed are reasonable in relation to the anticipated benefits and generation of scientific knowledge.

For studies involving nonsignificant risk (NSR) devices, only the IRB approval is required, and the sponsors' submission of the IDE is made directly to the IRB. The sponsors should also provide the study proposal and an explanation of why the device study should be considered as a NSR. If the IRB agrees, the study can begin without submission of an IDE application to the FDA. However, if the IRB determines it is a SR device, the sponsor has to report this decision to the FDA within a week (CFR Part 812.150(b)) [22, 23].

Finally, the approval of the proposed research by the IRB is based on the same criteria involving any FDA-regulated product; where the decision takes into account the risks and benefits of the investigational device and the contribution to science [24].

In the case of tDCS, these devices have been considered of NSR by the IRBs, so an IDE submission to the FDA is not required. Furthermore, its use has also been considered of minimal risk by some IRBs, which allows tDCS studies to be approved through an expedited review procedure [14, 22]. However, this is not indicative of its approval or the clearance by the FDA for the use of tDCS in scenarios other than research.

To date, the only companies having an IDE for tDCS devices by the FDA are Soterix Medical Inc. (tDCS and high-definition transcranial direct current stimulation [HD-tDCS]) and neuroConn GmbH [14]. The regulation of these devices has been subject to the FDA Quality System guidelines.

40.4 tDCS in Clinical Practice

Besides research, health care professionals in the USA can prescribe tDCS as an off-label treatment. This term refers to the use of a therapy that has proved to be safe within established parameters, for a purpose that has not been approved by the FDA. Considering that it is performed under the physician's professional and ethical judgment, the FDA has developed Clinical Practical Guidelines intended to help them make decisions regarding individual patient care [25]. Off-label uses of tDCS include motor recovery in stroke, improvement of balance and gait in cerebral palsy, and pain improvement in fibromyalgia.

Since the FDA has no legal authority to regulate clinical practice, unsupervised application of tDCS needs to be carefully reviewed for ethical and safety considerations. Off-label treatment should be applied according to the conventional protocols, with the approved devices and by trained personnel to guarantee safety and efficacy of the tDCS.

It is also important to consider that there is insufficient information regarding the long-term effects of stimulation, so this practice should be conducted with caution.

Furthermore, people who are not eligible to participate in a clinical trial may be able to get tDCS outside of a clinical trial through a "compassionate treatment." According to the FDA, it can be considered as an option in patients with serious or life-threatening conditions that do not respond to currently approved treatments [26]. To date, this option has been accepted in most countries, considering the course of neuropsychiatric diseases and the limited treatment options [14].

The application of tDCS in either scenario must be ruled by ethical and legal considerations. Every medical research involving participation of human beings should be preceded by careful assessment of the benefit–risk ratio, an equitable selection of subjects, and the obtainment of informed consent [27]. Especially for the latter, it is important to use simple and clear language to describe the tDCS procedure, as well as its potential benefits and adverse events.

40.5 tDCS Devices

The stimulation devices must meet safety requirements to be suitable for medical or scientific use. Generally, the use of battery-driven devices is preferred because it prevents the delivery of dangerous high voltages and/or currents to the patient in case of technical problems. The device must be designed to indicate and allow adjustment of the parameters by the operator, specifically the output current, voltage, and duration of the stimulation. Furthermore, the protection of the patient must be enhanced through the presence of a gradual increase or decrease ("ramp-up" and "ramp-down" phases) of the desired current over a defined time interval (e.g., 30 s) at the beginning and the end of the stimulation, respectively. Moreover, the devices should have an accessible stop button to abort the stimulation in case of any adverse events.

Finally, it is recommended that an impedance monitoring system is included in these tDCS devices. The optimization of the technique might rely as well on the quality of the electrode preparation and the voltage demands to maintain the direct current magnitude [28, 29].

FDA-approved iontophoresis devices have been used by clinicians and researchers for tDCS in the off-label program. Iontophoresis devices use direct current stimulation (approximately ≤4 mA) to introduce ions of soluble salts or other drugs through the skin. These devices lack many of the controlled elements mentioned previously, so their use as off-label treatment should be done with caution. In addition, they manage different doses and they were not designed to deliver current to the brain, and thus, they would not be ideal for performing tDCS [29].

Commercial devices claiming to have the same technology used for tDCS are already being sold to the public in the USA and other countries. Devices such as *foc.us* [30, 31] promoting the improvement of cognitive performance have raised concerns among health care professionals and researchers. In the first place, the company declares that as their product is not considered a medical device, no FDA regulation is required. In addition, these types of devices are usually designed with fixed stimulation parameters whose safety and/or efficacy have not been proved yet.

Indeed, a recent study on healthy volunteers assessed the effect of online and off-line foc.us tDCS applied over the prefrontal cortex on working memory. The authors showed that active stimulation (constant current of 1.5 mA during 20 min with a linear fade-in/fade-out of 15 s) with foc.us, compared to sham, significantly decreased the ability to monitor and update information in the working memory [31].

This device exemplifies that commercial devices may be sold without proper validation that may result in an inadequate use of the technique. In the case of foc.us, it has been presented as an alternative to "Conformité Européene" (CE)-marked tDCS devices that have shown positive results on the working memory in healthy subjects [9, 32].

Furthermore, the media has encouraged programs such as Do-It-Yourself (DIY), where step-by-step tutorials on how to build a tDCS device and its application are widely available for untrained individual users [33]. Enthusiastic benefits of these devices are promoted without taking into account the population, parameters of stimulation, and medical background of the users. This reflects the need of regulation on devices that are being advertised in the media as potential tDCS devices carrying the risk of negative neuroplastic effects and misuse.

40.6 Considerations on Patient Selection

A careful patient selection is the core for an adequate tDCS intervention, and they evolve as daily publications define and refine the specific parameters of stimulation that maximize the benefits of the tDCS therapy and reduce the adverse events. However, the patient population, the medical illness, and the interaction between concomitant treatments are factors that must be taken into account before the application of tDCS.

40.7 tDCS Candidates

The identification of subjects who are appropriate candidates either for a study or an off-label program must be conducted carefully. Although specific inclusion criteria may vary according to the specific study, certain considerations must be assessed in each patient to guarantee the safety and efficacy of tDCS:

- History of neurological and psychiatric conditions
- History of traumatic brain injury with loss of consciousness
- History of brain surgery or tumor
- History of seizures
- Presence of metallic plates in the head
- History of alcohol or substance abuse
- Use of psychopharmacological drugs
- Children
- Pregnancy

Ideally, tDCS should be adjusted in a patient-specific manner to select the best tDCS approach, reaching adequately the targeted region and avoiding safety concerns. As an example, skull defects or stroke-related lesions might need modification of tDCS dose montages [28].

General exclusion criteria include the presence of unstable medical conditions (i.e., heart disease), intracranial metallic implantation, or other conditions that may increase the risk of stimulation [28].

In addition to the appropriate patient selection, it is important to assess and report adverse events/safety during and after tDCS. The following items are included in the proposed questionnaire by Brunoni et al. to survey tDCS adverse effects: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood changes, and others. The subject should enter a value from 1 to 4 (1, absent; 2, mild; 3, moderate; 4, severe) to each item and, if present, assess if it is related to the tDCS [28, 34] (also see Chap. 23 of this book for a discussion regarding safety).

40.8 tDCS in Pediatrics

There are limited reports on the use of tDCS in the pediatric population, mainly due to safety concerns that rise when studies on adults with tDCS are extrapolated to children. To date, the optimal dose of tDCS for safety and efficacy in the pediatric population has not been well established. Studies reporting the use of tDCS in children have considered the following stimulation parameters: duration of stimulation up to 20 min, current intensities from 1 to 2 mA, and bilateral (anodal and cathodal) or cathodal montages [26, 35, 36] in conditions such as refractory epilepsy, schizophrenia, and autism. Serious adverse events have not been reported yet, and the most common adverse events are tingling and itching at the electrode site [26]. Although published data suggest that the use of tDCS in children is well tolerated, special considerations have to be taken into account.

Previous modeling studies have shown that the potential variability in the tDCS efficacy between these populations may result from differences in brain size, neuroplasticity, development, and age-dependent anatomical features (i.e., skull thickness, and white and gray matter volumes) [37–40]. For example, the scalp brain distance increases with age due to increases in extra-axial cerebrospinal fluid (CSF) space and skull thickness. Considering that the bone conductivity is low and that the skull thickness in children is decreased compared to an adult, the transmission of the current would be higher. Furthermore, the decreased amount of extra-axial CSF would provide less shunting of the current and more focal stimulation [37, 40, 41].

In the case of the white and gray matter proportion, it is important to consider that after reaching the maximum brain volume by age 5, the gray matter volume decreases approximately 1.1% per year and there is an estimated increase of 1.5% in the white matter volume until 18 years of age [39, 42–44]. The differences in this proportion, reflecting maturation in the brain structure, influence the depth of the current penetration being higher in a pediatric patient.

Another important anatomical feature dependent on age and sex is the head circumference [37]. Approximately, 98% of the total head circumference growth occurs before the age of 18 years. After the greatest gains in head growth during the first year of life, the head circumference increases at a slower pace until adulthood. At the age of 8 years, the mean head circumference for boys is 52 cm and for girls 51 cm. Once they reach the age of 18 years, the mean head circumferences are 56 and 55 cm for boys and girls, respectively [45]. This anatomical factor, as well as the size of the conventional tDCS electrodes, affects the focality of the stimulation. As the conventional tDCS protocol uses 5 cm by 5–7 cm sponge-wrapped rubber electrodes, their use in a small head circumference would end up covering the majority of the scalp, thus losing focality [37].

Based on the empirical experience with tDCS in children and the considerations mentioned previously, tDCS given within the standard parameters is well tolerated. However, due to the limited safety studies and the lack of information about the neurophysiological effects with different parameters of stimulation, caution is warranted for pediatric populations. In fact, the benefits of tDCS must be clear before designing clinical trials, especially in children with very young age (≤7 years), taking into account the phases of brain development, tDCS potential of neuroplastic changes, and the risk of inducing maladaptive plasticity in these patients.

40.9 tDCS in Pregnancy

To our knowledge, few studies have been performed on tDCS in pregnant patients. In healthy subjects, a recent study showed that tDCS does not induce any significant changes in the autonomic function, ventilation rate, or core body temperature [46–48]. These results, in addition to the localized nature of tDCS [49] and the low risk of seizures, suggest that tDCS is unlikely to cause any significant risk to the fetus. To date, a case report showed successful application of tDCS in a pregnant woman with schizophrenia, with no adverse events reported on the fetus [50]. Furthermore, a pilot study using tDCS for the treatment of major depression during pregnancy [51] provided a basis for the development of future larger multicenter studies including this population.

Although further studies are required to have solid evidence of the safety profile of tDCS in pregnancy, a conservative therapeutic approach for future clinical trials and also potential off-label use appears to be justified in the case where a clear benefit for the patient is present.

40.10 Considerations on Application of tDCS

As clinical practice and research on tDCS advance, several practical aspects such as the setting and the person who should apply this technique turn relevant. For tDCS research studies, the IRBs usually do not require the principal investigator to be a licensed physician but an expert in the tDCS technique, its principles, neurophysiological changes, and the potential side effects. Besides this, safety must be guaranteed when defining a protocol for emergency response within the study protocols in case the subject has any unexpected adverse effect.

Even though there is no consensus regarding the training and the accreditation requirements for performing tDCS, it is important that the principal investigator guarantees proper training including basic knowledge of brain physiology, mechanisms of tDCS, potential risks, and the different protocols. Trained professionals may include MDs, technicians, psychologists, physiotherapists, and engineers, as in other techniques such as transcranial magnetic stimulation [52]. In our Neuromodulation Center at Spaulding Rehabilitation Hospital in Boston, the program includes 20 hours of theoretical and training sessions given by experts in the field, followed by the corresponding assessments and certification.

In the clinical practice, a licensed physician is responsible for prescribing tDCS as an off-label or compassionate treatment. During these sessions, the trained personnel must have full access to

emergency and life-support equipment to manage any potential acute complication of the treatment.

40.11 tDCS Experience in Other Countries

For other countries leading tDCS research such as Brazil and Germany, the regulations regarding the use of tDCS in research and the clinical practice depend on the local/governmental regulations. In addition, we include the example of South Korea where the experience with tDCS has been limited.

In Brazil, the regulatory considerations for tDCS are very similar to those in the USA. Clinical trials using tDCS require the approval by the local ethics committee (Comitê de Ética em Pesquisa, CEP). As the IRBs in the USA, the CEP bases the final decision on the statement of ethical principles from the World Medical Association-Declaration of Helsinki [24]. In addition, the National Ethics Committee (CONEP) may also be involved in the statutory regulation of basic and clinical tDCS research, especially in the situation of international multicenter trials. Further regulatory assessment is the responsibility of the National Health Surveillance Agency (ANVISA) that is in charge of the supervision and administration of medical devices such as tDCS. Currently, the only device that has been registered by the ANVISA for the use of tDCS is provided by the company "neuroConn GmbH." Although the tDCS device has not been approved for clinical use, the off-label and compassionate tDCS use is considered in specific situations [14].

In the case of Germany, clinical trials, which may be initiated by the producer of the device, require the approval of the local ethics committee and the Federal Institute for pharmaceutical and medical products (BfARM), which is the corresponding federal entity. In the case of nonclinical trials, the local ethics committee is free to assess the risk–benefit ratio of the study and its decision is sufficient to approve or not the study [14]. Besides research, off-label and compassionate tDCS are provided in the context.

Finally, the South Korean regulation on tDCS has been shown to be very strict. To date, no tDCS device has been approved by the Korean Ministry of Food and Drug Safety (MFDS). tDCS has been considered to have a class II risk profile and thus, its approval requires preexistent evidence either from research studies performed in South Korea or abroad.

The application and regulation for the device approval are variable; some study protocols require approval just from the local IRB and others from the MFDS. In either case, this process is repeated for every single trial and the tDCS devices should be destroyed after the study [14]. Further uses of tDCS have not been reported.

40.12 Conclusion

We provide an overview of the regulatory aspects and special considerations for the use of tDCS in the USA. In the case of other countries leading tDCS research, the requirements for its use vary according to their local/federal laws. We consider that the involvement of the international community is crucial for the establishment of consistent tDCS regulatory aspects and the development of guidelines for its use in research and clinical practice. The active participation of the scientific community in this process of tDCS will be helpful to mitigate the potential risks of misuse and the uncertainty of long-term effects on the brain, which are not fully known.

References

1. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJL, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport. 2005;16(14):1551–5.
2. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. Arch Dis Child Fetal Neonatal Ed. 2008;65(12):1571–6.
3. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010;75(24):2176–84.
4. Hesse S, Waldner A, Mehrholz J, Tomelleri C, Pohl M, Werner C. Combined transcranial direct cur-

rent stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial. Neurorehabil Neural Repair. 2011;25(9):838–46. http://www.ncbi.nlm.nih.gov/pubmed/21825004
5. Fregni F, Boggio PS, Lima MC, Ferreira MJL, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006;122(1–2):197–209.
6. Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia : a randomized controlled trial. Pain. 2015;156:62–71.
7. Meinzer M, Lindenberg R, Phan MT, Ulm L, Volk C, Flöel A. Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms. Alzheimers Dement. 2015;11(9):1032–40. http://www.ncbi.nlm.nih.gov/pubmed/25449530
8. Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Flöel A. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci. 2013;33(30):12470–8. http://www.ncbi.nlm.nih.gov/pubmed/23884951
9. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005;166(1):23–30. http://www.ncbi.nlm.nih.gov/pubmed/15999258
10. Tortella G, Casati R, Aparicio LVM, Mantovani A, Senço N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry. 2015;5(1):88–102. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4369553&tool=pmcentrez&rendertype=abstract
11. Brunoni AR, Shiozawa P, Truong D, Javitt DC, Elkis H, Fregni F, et al. Understanding tDCS effects in schizophrenia: a systematic review of clinical data and an integrated computation modeling analysis. Expert Rev Med Devices. 2014;11(4):383–94. http://www.ncbi.nlm.nih.gov/pubmed/24754366
12. Volpato C, Piccione F, Cavinato M, Duzzi D, Schiff S, Foscolo L, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. Neurocase. 2013;19(4):360–70. http://www.ncbi.nlm.nih.gov/pubmed/22554168
13. Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, et al. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2011;35(1):96–101. http://www.sciencedirect.com/science/article/pii/S0278584610003611
14. Fregni F, Nitsche MA, Loo CK, Brunoni AR, Marangolo P, Leite J, et al. Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. Clin Res Regul Aff. 2014;11(4):383–94. http://informahealthcare.com/doi/abs/10.3109/10601333.2015.980944
15. FDA U.S. Food and Drug Administration. Is the product a medical device? Updated 2014 Sept 12. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm. Accessed 15 2015.
16. Johnson JA. FDA regulation of medical devices. 2012. https://www.fas.org/sgp/crs/misc/R42130.pdf
17. FDA U.S. Food and Drug Administration. Regulatory controls. Updated 2014 June 26. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm2005378.htm. Accessed 15 Oct 2015.
18. FDA U.S. Food and Drug Administration. Overview of device regulation [Internet]. Updated 2015 August 14. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/. Accessed 15 Oct 2015.
19. FDA U.S. Food and Drug Administration. FDA executive summary: prepared for the February 10, 2012 meeting of the neurologic devices panel. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM290787.pdf. Accessed 15 Oct 2015.
20. Administration FUSF and D. Medical devices: IDE definitions and acronyms. Updated 2014 June 26. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046698.htm. Accessed 15 Oct 2015.
21. Holbein MEB. Understanding FDA, regulatory requirements for investigational new drug applications for sponsor-investigators. J Investig Med. 2009;57(6):688–94.
22. Services USD of H and H, Administration F and D, (CDRH) C for D and RH, Research C for BE and. Information sheet guidance for IRBs, clinical investigators, and sponsors: significant risk and non-significant risk medical device studies frequently asked questions about medical devices. 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf. Accessed 15 Oct 2015.
23. Services USD of H and H, Administration F and D, (CDRH) C for D and RH, Research C for BE and. Information sheet guidance for IRBs, clinical investigators, and sponsors frequently asked questions about medical devices. 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf
24. Rickham PP. Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. Br Med J. 1964;2(5402):177.
25. Services USD of H and H, Administration F and D, (CDER) C for DE and R, (CBER) C for BE and R, (CDRH) C for D and RH. Guidance for industry dis-

tributing scientific and medical publications on unapproved new uses—recommended practices. Silver Spring; 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf
26. Mattai A, Miller R, Weisinger B, Greenstein D, Bakalar J, Tossell J, et al. Tolerability of transcranial direct current stimulation in childhood-onset schizophrenia. Brain Stimul. 2011;4(4):275–80.
27. Kapp MB. Ethical and legal issues in research involving human subjects: do you want a piece of me? J Clin Pathol. 2006;59(4):335–9. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1860367&tool=pmcentrez&rendertype=abstract
28. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95. http://www.sciencedirect.com/science/article/pii/S1935861X1100026X
29. Hahn C. Extra-low voltage and limited total energy approaches to increase patient comfort and safety during transcranial direct current stimulation. Hamburg: Hamburg University of Applied Sciences; 2012.
30. LABS ©U. FOC.US. http://www.foc.us/. Accessed 27 Jan 2016.
31. Steenberg L, Sellaro R, Hommel B, Lindenberg U, Kühn S, Colzato LS. "Unfocus" on foc.us: commercial tDCS headset impairs working memory. Exp Brain Res. 2015:1–7.
32. Kuo M-F, Nitsche M. Effects of transcranial electrical stimulation on cognition. Clin EEG Neurosci. 2012;43(3):192–9.
33. Dubljević V, Saigle V, Racine E. The rising tide of tDCS in the media and academic literature. Neuron. 2014;82:731–6.
34. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol. 2011;14(8):1133–45.
35. Varga ET, Terney D, Atkins MD, Nikanorova M, Jeppesen DS, Uldall P, et al. Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study. Epilepsy Res. 2011;97(1–2):142–5. https://doi.org/10.1016/j.eplepsyres.2011.07.016.
36. Yook S-W, Park S-H, Seo J-H, Kim S-J, Ko M-H. Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient – a case report. Ann Rehabil Med. 2011;35(4):579.
37. Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:859–62. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3641645&tool=pmcentrez&rendertype=abstract
38. Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimul. 2011;4(3):169–74.
39. Group BDC. Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI study of normal brain development. Cereb Cortex. 2012;22(1):1–12. http://cercor.oxfordjournals.org/content/22/1/1; http://cercor.oxfordjournals.org/content/22/1/1.full.pdf; http://www.ncbi.nlm.nih.gov/pubmed/21613470
40. Wanifuchi H, Shimizu T, Maruyama T. Age-related changes in the proportion of intracranial cerebrospinal fluid space measured using volumetric computerized tomography scanning. J Neurosurg. 2002;97(3):607–10. http://thejns.org/doi/abs/10.3171/jns.2002.97.3.0607?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
41. Beauchamp MS, Beurlot MR, Fava E, Nath AR, Saad ZS, Parikh N, et al. The developmental trajectory of brain-scalp distance from birth through childhood: implications for functional neuroimaging. PLoS One. 2011;6(9):1–9.
42. Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol. 1994;51(9):874–87. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8080387
43. Groeschel S, Vollmer B, King MD, Connelly A. Developmental changes in cerebral grey and white matter volume from infancy to adulthood. Int J Dev Neurosci. 2010;28(6):481–9. http://www.ncbi.nlm.nih.gov/pubmed/20600789
44. Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):1–15.
45. Nellhaus G. Head circumference from birth to eighteen years. Practical composite international and interracial graphs. Pediatrics. 1968;41(1):106–14. http://www.ncbi.nlm.nih.gov/pubmed/5635472
46. Raimundo RJS, Uribe CE, Brasil-Neto JP. Lack of clinically detectable acute changes on autonomic or thermoregulatory functions in healthy subjects after transcranial direct current stimulation (tDCS). Brain Stimul. 2012;5:196–200.
47. Nitsche M, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W, et al. Safety criteria for transcranial direct current stimulation (tDCS) in humans [1] (multiple letters). Clin Neurophysiol. 2003;114(11):2220–3.
48. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 2007;72(4–6):208–14.
49. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol. 2006;117(7):1623–9. http://www.ncbi.nlm.nih.gov/pubmed/16762592
50. Shiozawa P, da Silva ME, Cordeiro Q, Fregni F, Brunoni AR. Transcranial direct current stimulation

(tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. Brain Stimul. 2013;6(5):831–3. http://www.sciencedirect.com/science/article/pii/S1935861X13000855
51. Vigod S, Dennis C-L, Daskalakis Z, Murphy K, Ray J, Oberlander T, et al. Transcranial direct current stimulation (tDCS) for treatment of major depression during pregnancy: study protocol for a pilot randomized controlled trial. Trials. 2014;15:366.
52. Najib U, Horvath JC. Transcranial magnetic stimulation (TMS) safety considerations and recommendations. Transcran Magnet Stimul. 2014;89:15–30. http://www.springerprotocols.com/Abstract/doi/10.1007/978-1-4939-0879-0_2

Correction to: Transcranial Direct Current Stimulation in Neuropsychiatric Disorders

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The original version of chapter 3, page 29, chapter 15, page 283, chapter 35, page 667 and chapter 38, page 729 had wrongly attributed author affiliation to "University of Sao Paulo, Institute of Psychiatry, Sao Paulo, Brazil, Department of Psychiatry University of British Columbia, Vancouver, Canada, Department of Experimental Psychology, University of Oxford, Oxford, UK, Department of Neurology, University Medical Hospital Bergmannsheil, Ruhr-University Bochum, Bochum, Germany, Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany".

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