Chapter 1
Transcranial Direct Current Stimulation Among Technologies for Low-Intensity Transcranial Electrical Stimulation: Classification, History, and Terminology

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Classification of tDCS Among Other Brain Stimulation Techniques

Classification of tDCS Among Techniques

The field of brain stimulation dates to the discovery of electrical phenomena, which is not surprising given that human and animal responses to electrical shock are among the earliest evidence for the existence of electricity (Bischoff 1801; Galvani and Aldini 1792; Volta 1800). Research and human trials on electrical brain stimulation, and underling bioelectric phenomena, has been continuous. Modern brain stimulation as a field has branched and evolved into many different categories of devices and tech-

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niques, but whose commonality remains to alter brain or specific nervous system functions by introducing electrical currents through electricity or magnetism. The contemporary landscape of stimulation techniques covers a vast expanse of applications and nomenclatures, many with overlapping aspects. An introduction to tDCS should therefore place it among this landscape of brain stimulation techniques. This includes presenting a simplified mapping and categorization of selected historical and contemporary stimulation techniques and showing how they are categorically interrelated. This by no means should be taken as a complete assortment of stimulation techniques (Guleyupoglu et al. 2013), but rather to clarify the unique features and historical role of tDCS in modern neuromodulation.

When it comes to the categorizing methods of stimulation, several different approaches can be taken. A first simple arrangement is to group stimulation methods into invasive and non-invasive procedures (Fig. 1.1). At this level of division, the obvious distinction lies in the placement of stimulating electrodes. Invasive brain stimulation techniques involve patients undergoing anesthesia or receiving analgesics and having stimulating electrodes surgical implanted in specified regions of the brain, spinal cord, subcutaneously, or around nerves. These implanted electrodes are then activated and used to deliver electrical stimulation to specific regions of the brain, the spinal cord, or specific nerves. Primary stimulation targets are considered local and adjacent to implanted electrodes (McIntyre et al. 2004). Noninvasive techniques, on the other hand, involves the external placement of electrodes (or magnetic coils) without breaking the skin or entering the body cavity, and do not require surgical procedures for application. These noninvasive electrodes or stimulation apparatuses are placed on areas like the scalp, forehead, or shoulders, though which electricity or magnetism is then delivered. Regions that are influenced by stimulation depend on both the electrode montage and individual anatomy (Dmochowski et al. 2011).

Both invasive and noninvasive categorizations can be further divided into techniques intended to either stimulate the brain (transcranial or intracranial) and those techniques targeting extra-cranial structures (non-transcranial or non-intracranial). For non-invasive brain stimulation (NIBS), transcranial encompasses stimulation techniques that intend to pass electricity, magnetism, or sound through the skull and have specific sub-cranial brain (cortical) targets, whereas non-transcranial encompasses delivering current to extra-cranial targets and thus having non-cortical targets. For invasive brain stimulation (IBS), intracranial techniques include deep brain stimulation (DBS), which targets but is not exclusive to specific limbic, basal ganglia, and thalamic brain areas. Non-intracranial IBS techniques include implants such spinal cord stimulation (SCS) – used to treat chronic pain – (Cameron 2004) and direct peripheral nerve stimulation (DPNS) that involves the implantation of an electrode on a nerve (Oh et al. 2004). Other examples of non-intracranial IBS techniques include invasive cranial nerve electrical stimulation (iCNES) techniques. Some iCNES techniques include vestibular prostheses (VP; Golub et al. 2014); optic nerve stimulation (ONS), used for the restoration of vision (Brelen et al. 2010); vagus nerve stimulation (VNS), first approved by the FDA to treat epilepsy (Beekwilder and Beems 2010); and direct trigeminal nerve stimulation (DTNS), which involves implanting electrode cuffs or arrays directly on a nerve (Slavin et al. 2006). In terms

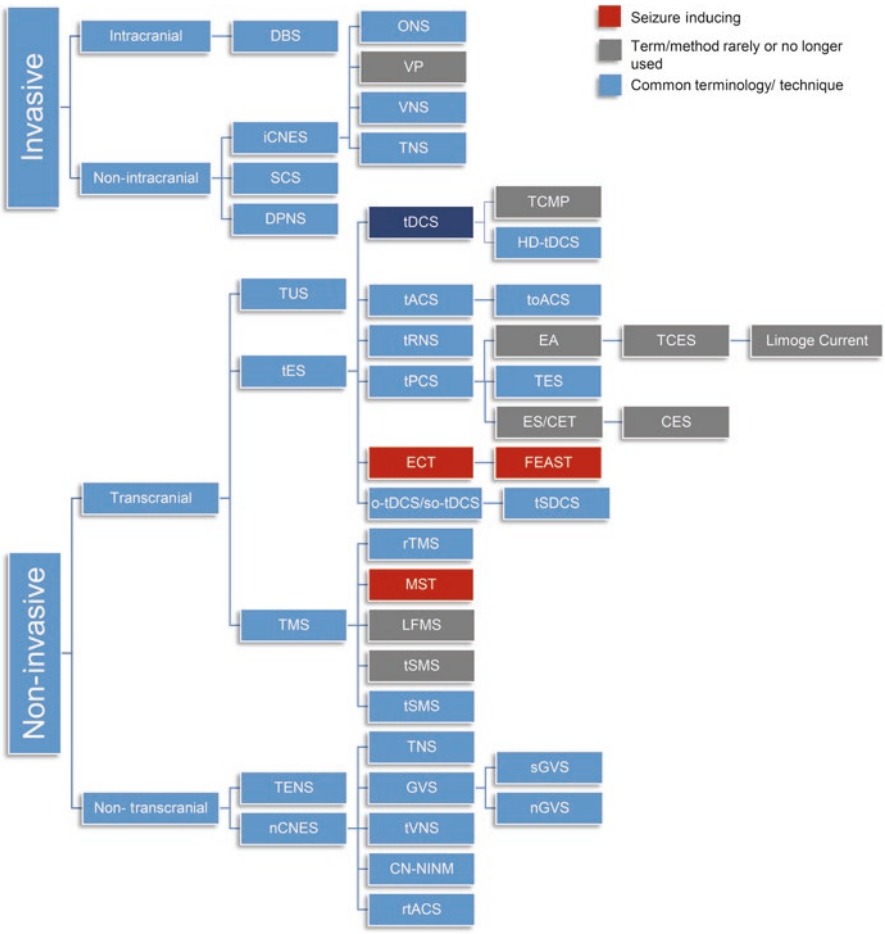

Fig. 1.1 Arrangement of stimulation techniques with common terminology (light blue), terms and methods that are rarely or no longer used (gray), and highlights of seizure-inducing techniques (red). tDCS is highlighted (dark blue) to show its place among the selected techniques

of noninvasive brain stimulation (NIBS) that targets sub-cranial regions, techniques can involve the use of electrical stimulation through electrodes on the scalp, magnetic stimulation with a coil near the scalp, or stimulation with ultrasonic sound through an ultrasound transducer placed on the scalp. Thus, NIBS with transcranial targets is divided into the broad categories of transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and the emerging field of transcranial ultrasound (TUS) modulation (Fig. 1.1; Legon et al. 2014).

Non-transcranial electrical stimulation techniques include transcutaneous electrical nerve stimulation (TENS; Robertson et al. 2006), and noninvasive cranial nerve electrical stimulation (nCNES); both of which utilize electrical currents to stimulate nerves. TENS targets all peripheral nerves, whereas nCNES techniques specifically target cranial nerves. nCNES can be subdivided into repetitive transorbital alternative

current stimulation (rtACS; Gall et al. 2010; Bola et al. 2014), trigeminal nerve stimulation (TNS; DeGiorgio et al. 2011; Schoenen et al. 2013), galvanic vestibular stimulation (GVS; Fitzpatrick and Day 2004), transcutaneous vagus nerve stimulation (tVNS; Frangos et al. 2015; Hein et al. 2013; Kraus et al. 2013), and cranial nerve noninvasive neuromodulation (CN-NINM; Danilov et al. 2014). As the name implies, GVS is historically applied using direct current, however with different vestibular targets emerging, the technique has expanded to include stochastic/noisy GVS (Samoudi et al. 2012; Yamamoto et al. 2005) and sinusoidal GVS (Coats 1972).

TMS techniques' main distinction from tES is the use magnetic coils to induce electrical current in the brain (George and Aston-Jones 2010). TMS can be sub-categorized to include repetitive TMS (rTMS; Lefaucheur et al. 2014), seizure-inducing magnetic seizure therapy (MST; Kayser et al. 2015; Lisanby et al. 2003), and the relatively new transcranial static magnetic stimulation (tSMS; Gonzalez-Rosa et al. 2015) and low-field magnetic stimulation (LFMS; Rohan et al. 2004).

Transcranial electrical stimulation approaches pass electrical current directly to the brain via electrodes on the head (Paulus et al. 2013). These techniques include tDCS, transcranial alternating current stimulation (tACS; Antal and Paulus 2013), transcranial random noise stimulation (tRNS; Terney et al. 2008), transcranial pulsed current stimulation (tPCS; Morales-Quezada et al. 2015; Fitzgerald 2014), oscillating tDCS (o-tDCS D'Atri et al. 2015) or sinusoidal oscillating tDCS (so-tDCS; Eggert et al. 2013), and seizure-inducing electroconvulsive therapy (ECT) with the subset, focal electrically administered seizure therapy (FEAST; Spellman et al. 2009). The o-tDCS /so-tdcs technique can further be broken down to include transcranial sinusoidal stimulation (tSDCS). On the other hand, tPCS can be further broken down into "TES", a supra threshold form of tPCS (Kalkman et al. 1992; Zentner et al. 1989); transcutaneous cranial electrical stimulation (TCES; Limoge et al. 1999), a derivative of electroanesthesia (EA; Smith et al. 1967; Wilson et al. 1968) which can include high frequency currents (Limoge et al. 1999); and cranial electrotherapy stimulation (CES; Schmitt et al. 1986), which was derived from electrosleep (ES; Dimitrov and Ralev 2015) and later called cranial electro-stimulation therapy (CET; Knutson et al. 1956). Though ECT can also involve the use of pulsed waveforms, it involves unique stimulation schemes, and is not a tPCS subcategory here.

tDCS, like other techniques, is associated with derivative nomenclature and variants. These variants are rooted in the same principles of tDCS (delivering direct current across the head); however, they both take different approaches to how direct current is delivered. For instance, High Definition-tDCS (HD-tDCS) aims to focalize current distribution across the brain so that specific regions are better targeted. There are numerous montage variations of HD-tDCS (Borckardt et al. 2012; Dmochowski et al. 2011; Kuo et al. 2013; Nikolin et al. 2015) including the most common 4 × 1 HD-tDCS montage (Alam et al. 2016; Datta et al. 2009; Hill et al. 2017; Shekhawat et al. 2015; Shen et al. 2016). Another tDCS derivative is transcranial micropolarization (TCMP), which aims to deliver current intensities (700–1000 μA) on that are much less than conventional tDCS (Ilyukhina et al. 2005; Shelyakin et al. 1998). Other terminology associated with tDCS exists, such as

"anodal/cathodal tDCS" or "lateralized" montages, however these are descriptive of the intended outcome of stimulation and not necessarily distinct technique categories (see below).

The fundamental distinction between tDCS and other categorizations of tES is the waveform delivered to the brain during stimulation (Fig. 1.2). tDCS is the only class of neuromodulation technique that delivers a sustained direct current (DC). Almost all other techniques (and essentially all invasive and magnetic techniques) use pulsed stimulation (such as tPCS) while other non-invasive variants include AC waveforms (such as tACS) or random noise (such as tRNS). Thus, the use of a sustained direct current is a characteristic feature of tDCS, and one that should be kept in mind when considering any unique neurophysiologic, cognitive, or behavioral outcomes.

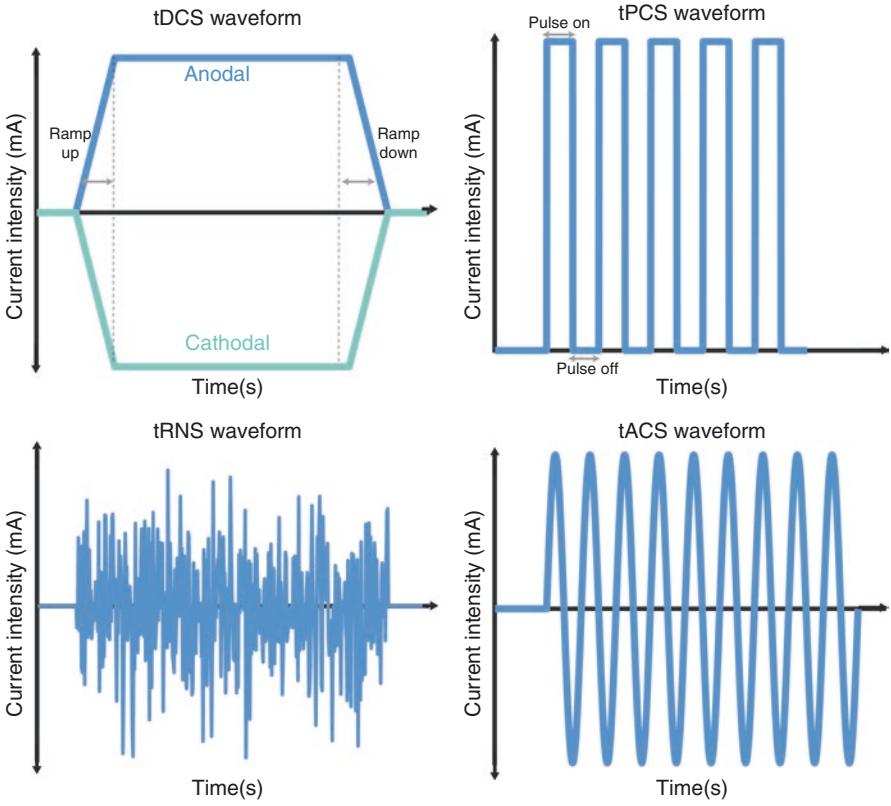

Fig. 1.2 Waveforms of different tES techniques. The tDCS waveform is shown for anodal (blue) and cathodal (light blue) electrodes, which must always be active concurrently. Typically, the current is increased to or ramped up to the desired current intensity and when said intensity is reached the current intensity is held at that level for the duration of stimulation. The tACS waveform shows a typical oscillatory current delivery between electrodes. The tRNS waveform shows a generalized random noise current intensity being delivered during stimulation. The tPCS waveform shows a generalized pulse train of current. Here the duration of pulse on and pulse off time can vary depending on the type of tPCS being done

The Case for Simplicity of tDCS

Direct current represents the most simplistic waveform – though this does not preclude tDCS from producing unique and profound neuromodulatory effects that arise from a sustained current. Nonetheless, regarding the development and adoption of tDCS, we propose that this simplicity underpins the unique role of tDCS in the emergence of modern non-invasive neuromodulation and its grounding in science. Decades of modern work have firmly established that direct current stimulation (DCS) changes neuronal excitability and plasticity. To explain the unique role of tDCS in modern neuromodulation, some historical context is necessary.

Direct current was the first form of brain stimulation generated using a device (as opposed to electric fish or static electricity) since it was the simplest to build – connecting a "voltaic pile" (early battery) to the body. Thus, this approach was the earliest example of electrical stimulation in humans and animals (leading to early theories of the role of electricity in physiology). Later, the first demonstration of long term potentiation was made using direct current (Bindman et al. 1964; Gartside 1968; Gartside and Lippold 1967), preceding the well cited studies of Bliss and Lomo (1973). Monophasic pulse stimulation later integrated mechanical methods to rapidly connect and disconnect the DC battery.

The emergence of other stimulation waveforms (e.g. complex pulsed patterns) paralleled development in electronics (Guleyupoglu et al. 2013). For example, the emergence of the microcontroller allowed for the generation of any arbitrary waveform. Enabled by this flexibility, the twentieth century saw the emergence of numerous variations in waveforms, most of which were claimed to be unique and proprietary. The purported uniqueness facilitated marketing of devices but also resulted in reduced transparency of performance. For example, at the end of the twentieth century, devices FDA-cleared for CES each promised a unique waveform (Fig. 1.3). In a sense this uniqueness (exclusivity) impeded clinical research which benefits from uniformity across labs (reproducibility) and transparency. At the turn of the century though, even career researchers in neuromodulation often could not explain the difference in nomenclature (e.g. does electro-sleep use direct current? is CES and CET the same? Guleyupoglu et al. 2013).

In this context, the early work on tDCS that emerged circa 2000 was characterized by (1) high transparency in a simple and reproducible waveform (e.g. 1 mA sustained for 10 min); and (2) a foundation based, not on clinical experience, but on neurophysiological data (e.g. modulation of TMS evoked responses; Fig. 1.4). These two fundamental characteristics, followed by dozens of rigorous human neurophysiology trials (including multiple independent replications) and animal electrophysiology (steming from our own group; Bikson et al. 2004) established the scientific foundation of tDCS. Work on tDCS, in turn, supported a new era in modern NIBS research. For example, modern tACS approaches mimicked tDCS montages, similarly used a basic and well-defined waveform (single sinusoid), and identical neurophysiology markers of response prior to clinical trials. Clinical trials that used tDCS (starting from our group; Fregni 2005; Fregni et al. 2006b) were

Fig. 1.3 The evolution of transcranial stimulators spanning 1900 to present day. Early ES/EA devices were developed between 1900 and 1960. These early devices were followed NeuroElectric Therapy (NET) devices between 1970 and 1980. Later more established tDCS, tACS, and iontophoresis devices were developed, some of which are still used today. During the early aughts, more advanced and modern stimulation techniques were developed starting from 2004 to present day

rationalized based on these human and animal neurophysiology studies. In the past 15 years, hundreds of studies on tDCS mechanisms have shown that the effects of tDCS are – not surprisingly – more complex than initially hypothesized. But this ongoing work should be understood as building on the broad scientific base of tDCS, rather than somehow challenging it. In this regard, work on tDCS mechanisms continues to be a touching stone for other neuromodulation techniques (Brunoni et al. 2012b; Fertonani and Miniussi 2016; Giordano et al. 2017; Jackson et al. 2016; Paulus et al. 2013).

An unintended consequence of the perceived "simplicity" of tDCS is that new groups adopting the technique may assume that precision and careful control in technology, training, and protocols is not critical for rigor. In fact, reproducibility requires the selection of only appropriate equipment and accessories, certification

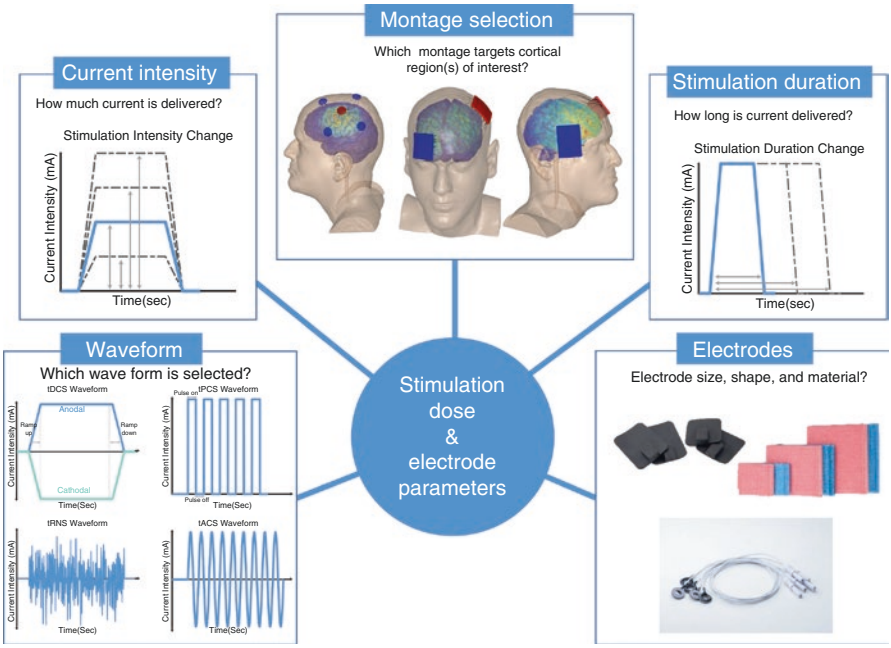

Fig. 1.4 Stimulation dose and electrode parameters include the selection of the stimulation waveform, the current intensity, the montage, stimulation duration, and electrodes. With waveform selection several different waves can be selected, ranging from a direct current waveform to alternating current, pulsed current, or random noise current. In the case of intensity, the amount of current to be delivered is defined. With montage, the placement of electrodes on the scalp are selected. In the case of duration, the amount of time that current is introduced to the body is defined. With electrodes, the size and type of electrodes are selected. Each parameter is an essential part to defining and reporting dose in tES

of staff on experimental equipment, and adherence to well established protocols (Woods et al. 2016). Failure to do so leads to variable and potentially inconsequential results that have little or no relevance to the tDCS field.

tDCS Terminology Including Components and Stimulation Parameters

The broad landscape of stimulation approaches – in many cases with subtle variations in waveform – make the need for standardized nomenclature critical. Such standardization help to foster proper understanding of tDCS techniques, aid in clinical trial development, break down the barrier to adoption, and encourage higher scientific validation. Better understanding and definitive nomenclature would in turn allow patients and healthcare providers to make improved and informed decisions when it comes to various tDCS technique options. Here, we present some

key terminology used in the tDCS literature, and as relevant, broader tES terms which help position (distinguish) tDCS.

Our approach was to define terms as used conventionally in the tDCS field – and we do not propose new or altered terminology. Nonetheless, inconsistent, and at times confusing use of terminology, required us to constrain definitions. In defining tDCS itself there is a compromise between broad definitions – which allows for needed dose exploration and optimization such as higher currents – and more restrictive definitions that create the least possible ambiguity – such as limited current levels that have been extensively tested. In our approach, we adopted broader definitions, even including dose ranges yet to be tested, while also defining "conventional" practices that are limited to the most common conventions. This approach to taxonomy is intended neither to imply safety nor efficacy.

We note that following conventions of use in the field, tES classifications are not simply literal – meaning a classification is rarely the literal amalgamation of each word in the technique name. Rather, the classifications provided here are proper names. Compared to a definition based strictly on semantics, tES classifications are typically more restrictive based on both dose and intent. The use of lower case "t" emphasizes classifications are proper names.

Dose

The classification of a brain stimulation technique is itself based on the definition of dose. Following the method of Peterchev et al. (2012), tES dose is defined "by all parameters of the stimulation device that affect the electromagnetic field generated in the body." Dose thus includes stimulation waveform (e.g. AC/DC), intensity, and duration; as well as the number of electrodes and their shape (Peterchev et al. 2012).

Each class classification of tES (e.g. tDCS, tACS, CES) is restricted in part by dose and intended outcomes. For example, tDCS is understood to be a modulatory technique which may exclude approaches intended to directly induce neuronal firing. While dose is defined by describing *all* relevant parameters of stimulation (Fig. 1.5), classification may relate to only a selection of these parameters (i.e. tDCS is defined by the waveform irrespective of electrode montage). We emphasize, the classification of a study does not reduce the need to fully report the complete dose applied to allow interpretation and reproduction of methods (Peterchev et al. 2012). Every tDCS trial must fully document dose. The method used to select the dose (e.g. subject titration, prior experience) and summary metrics (e.g. electrode current density or total charge) are important, but does not diminish the need to fully report the final dose applied.

Furthermore, though not always part of "dose", complete details of the electrode assembly including electrode material, coupling medium, electrode size (area), electrode thickness, and any relevant details on electrode age/prior-use must be

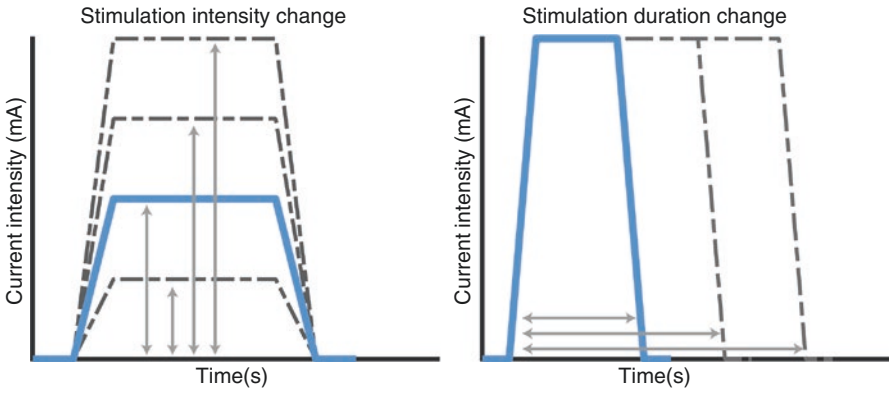

Fig. 1.5 Stimulation intensity changes alters the amount of current that is delivered. Current intesites in tDCS can range from (but are not limited to) 0.5–2 mA. Stimulation duration changes alteres the time over which current is delivered. With tDCS current delivery times can range from (but are not limited to) 10–30 min, with ramp up and ramp down times between 10 and 30 s

provided or referenced for reproducibility. To this end, our definition attempts to disambiguate how terms of tDCS technology are used and defined.

tES

The term *transcranial electrical stimulation* (tES) is the preferred nomenclature for any non-invasive medical device intended to directly change brain function by passing low- or high-amplitude electrical currents, of any waveform, through at least one electrode on the scalp.

Though variants of tES as a global classification have been proposed, a review of relevant historical (Guleyupoglu et al. 2013) and modern literature confirms tES is the most conventional terminology. Non-Invasive brain electrical stimulation and transcranial current stimulation (first used in only 2008; Datta et al. 2008) are comparatively rare. Upper-case first letter "TES" is not preferred because of association with supra-threshold single pulse waveforms (Merton and Morton 1980).

The intended outcome of tES includes direct actions on the central nervous system (even if peripheral actions such a cranial nerve stimulation, peripheral vascular and muscle actions, etc. cannot be excluded). Specific intended outcomes often appear in definitions of tES classifications. Devices that use any implanted electrodes, including intracranial or subcutaneous, should not be included in tES – regardless of whether such techniques result in current passage across the cranium.

Non-invasive medical procedures are typically defined as not breaking the skin or entering the body cavity. Non-invasive medical devices do not involve an invasive medical procedure. tES is thus non-invasive. While the current delivered by tES

crosses into the body and produces physiologic responses (including changing skin properties), this does not meet the standard for an invasive medical procedure/device, any more than a stone used for massage (which transfers physical force into the body) or a heating blanket (transferring heat into the body).

Session

A session of tDCS refers to a set program of stimulation, provided over a limited (fixed) time. Repetitive, when used in the context of tDCS, typically refers to multiple sessions.

tDCS

Transcranial direct current stimulation (tDCS) is a tES technique in which the dose waveform is a sustained direct current (DC) applied to the head (at least one cephalic electrode) to produce a direct change in brain function. The intensity of tDCS is limited with the intention of modulating excitability and/or ongoing activity rather than triggering action potentials (as the brain is active, tDCS will change the ongoing firing rate of neurons; Reato et al. 2013). The sustained waveform of tDCS reflects this intention. Thus, our definition of tDCS includes both a dose component (specifically a waveform characterized by a sustained current) and the intended mechanisms of action (specifically sustained polarization and neuromodulation).

Conventional tDCS

Conventional tDCS would include protocols (e.g. waveform intensities and durations) that are commonly used in current human and clinical exploratory studies, as well as formal trials. Conventional current intensities span 0.1 (used often in sham) to 3.0 mA; with most efforts between 1.0 and 2.5 mA (Fig. 1.6). Conventional durations span 4 s (used only for transient changes; Nitsche and Paulus 2000) to several minutes (typically 10–40 used for durable changes; Ohn et al. 2008). However, tDCS intensity and current is not restricted per our general definition above. Conventional intensities are limited to a few milliamps relating to tolerability of skin using existing electrode technologies (Minhas et al. 2010). Stimulation is applied over skin which is not compromised by a pre-existing burn or injury (e.g. open wound) and is thus largely homogenous. However, acne or non-injurious spots are typically not exclusions for electrode placement locations. Skin preparation typically excludes significant abrasion (intend to remove epidermis; Shiozawa et al. 2013), though cleaning of the skin/hair with saline or alcohol is sometimes used

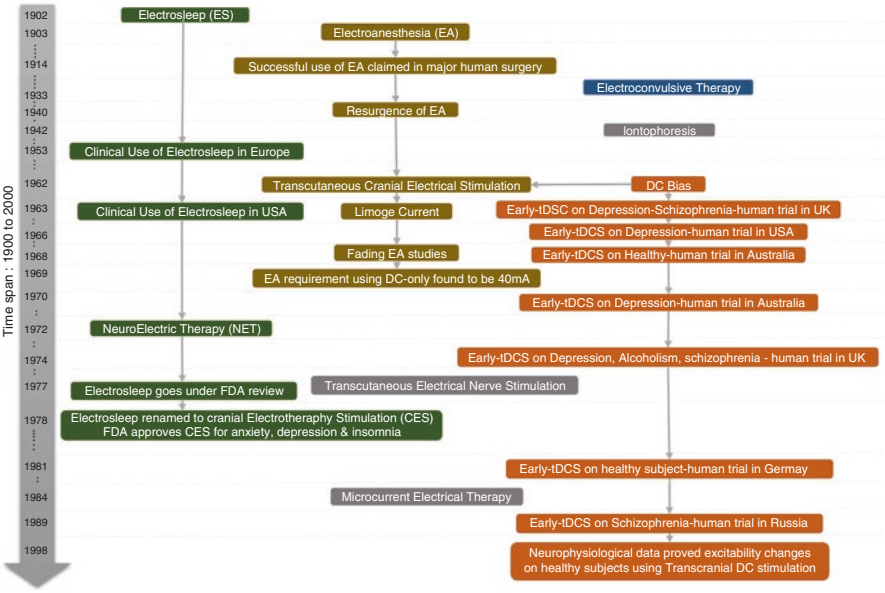

Fig. 1.6 A brief history of tES stimulation spanning 1902 to 1998. Cranial stimulation methods used in twentieth century are categorized in five lines including methods with direct current

(DaSilva et al. 2011). Any advancement in the development of electrodes used for conventional tDCS may permit current amplitudes to exceed 3 mA, assuming improvements in skin tolerability, which in turn would expand intensity limits for conventional tDCS with potential impacts on outcomes. In any given session, conventional tDCS uses a single current amplitude with minimal variation during stimulation, except for one ramp up and ramp down period (typically a 10–30 s linear ramp).

Conventional tDCS uses electrode assemblies of 5 × 5 cm to 5 × 7 cm to interface with skin-electrolyte contact areas, though both smaller and larger electrode assemblies have been explored (Nitsche et al. 2007). Conventional tDCS electrode assemblies use either a metal or conductive rubber electrodes (Kronberg and Bikson 2012). Electrolytes or more commonly isotonic saline (saturated in a sponge) gels and/or creams have also been used. The details of electrode assembly (see definition) design is considered important for tolerability. Conventional tDCS commonly uses two electrodes, though three or four electrode montages are conceivable. tDCS limits on the number of electrodes is related to the conventional size of electrodes, since using larger electrodes limits the number that can be positioned on the scalp (see also HD-tDCS).

A single tDCS session is defined as the period from initiation of current flow (start of ramp up) to end of current flow (end of ramp down). However, conventionally the "duration" of a tDCS session is exclusive of the ramp up or ramp down period and thus refers to the period when tDCS is sustained at the target current (e.g. 2 mA).

tDCS must involve at least one electrode on the scalp. The anode is defined as any electrode where current (positive charge) enters the body and the cathode is defined as any electrode where the current (positive charge) exits the body. tDCS must have at least one anode and at least one cathode.

Anode/Cathode

The anode (also called Anode Electrode) is the electrode where positive current enters the body. For two electrodes in tDCS, the anode has a positive voltage relative to the cathode. The cathode (also called Cathode Electrode) is the electrode from which positive current exits the body.

In other approaches, such as tACS, when the current controlled waveform is applied to any given electrode, changes polarity of each electrode is seen (e.g., a biphasic sinusoid applied such that the current direction to any given electrode changes in direction) where the electrodes switch from being an anode to a cathode during stimulation based on the frequency of stimulation. For this reason, an "anode" is not used in biphasic stimulation. However, for tDCS as defined here, polarity should not change within a session and so electrodes that are the anode and the cathode remain fixed as such.

"Anodal-tDCS" (a-tDCS), "Cathodal-tDCS" (c-tDCS)

While semantically transcranial direct current stimulation could include any waveform that does not change polarity (e.g. even a monophasic triangle wave), tDCS as used across current human trials involves only sustained direct current. The lower-case "t" in tDCS is thus important to emphasize a proper name. As tDCS dose is defined as a waveform of a sustained direct current, only the intensity (in milliamps), duration (in seconds or minutes), and ramp up/down details, are needed to specify the waveform to each electrode. Fundamentally, the mechanisms of tDCS are speculated to derive from the sustained polarization of neuronal assemblies (Bikson et al. 2004; Bindman et al. 1964; Nitsche and Paulus 2000), which in turn results from sustained current delivery. Use of waveforms that are speculated to produce physiologic changes – even in part – based on the change in current, are thus not strictly tDCS as defined here. Hence trains of monophasic pulses are not tDCS as defined here, rather they are classified as tPCS, even when a DC offset is included. Similarly, an oscillating transcranial direct current stimulation (a monophasic square waveform), or a rectified or monophasic sinusoidal waveform are not included in tDCS as defined here, but they can be considered as variants of tDCS (e.g. see transcranial oscillating direct current stimulation, toDCS).

The terminology "anodal-tDCS" (a-tDCS) and "cathodal-tDCS" (c-tDCS), though common, should be used with caution. All tDCS methods involve at least one anode and one cathode (to complete a minimal circuit), and all current entering the cortex

must exit (and pass through intermediary brain regions). There is no pure unipolar tDCS (effects exerted under one electrode only), as may be implied by the terms anodal-tDCS or cathodal-tDCS in describing an intervention. Anodal-tDCS or cathodal-tDCS in this context, thus reflect the *intended* outcome of stimulation by the specific electrode that is assumed to be more relevant, and thus these terms are understood as only an expected outcome (or hypothesis). However, the extent to which anodal and cathodal sources produce net effects on excitation and inhibition, especially in the context of brain processing and behavior, are complex and unresolved. The preferred language should be "the anodal-tDCS *over* brain region X" (Clemens et al. 2014) or "anode at scalp coordinate X defined by EEG 10-10" rather than "anodal tDCS *of* brain region X" since the latter incorrectly implies that current is delivered to just that brain region (Datta et al. 2009) and moreover over-simplistic intended outcomes. Still more precise semantics would consist of stating "anodal-*electrode over* brain region X".

Just because there are well established, montage specific effects on bio-markers (e.g. TMS MEPs) or behaviors associated with brain regions nominally targeted by tDCS, this does not imply that current was restricted to or solely influential by the brain area "under" the electrode.

"Active", "Stimulating", "Return" or "Reference" Electrode

The terms "return" or "reference" electrode is typically used to describe an electrode with presumed "physiological inertness" or perceived lack of importance – (e.g. not being in proximity to the brain regions of interest). However, all electrodes are functional – even when they are not related to the hypothesis tested – in the engineering sense that they are used to carry current. The physiological activity of "return" electrodes can be theoretically reduced for example by increasing electrode size or using a ring of electrodes (Datta et al. 2008; Nitsche et al. 2007); nonetheless, the configuration of these electrodes needs to be explicit and their polarity and configuration must be indicated. The configuration and position of the "return" electrode has a profound effect on current flow near the "active" electrode and use of an extra-cephalic electrode evidently does not cancel the role of this electrode in brain current flow (Bikson et al. 2010; Truong et al. 2014).

Analogous to how anodal-tDCS and cathodal-tDCS are descriptive, the terms "active" or "stimulating" electrode refers to those electrodes presumed to be physiologically active – or more specifically that a physiological/behavioral outcome of interest is due to current passed through these electrodes. The terms "active", "stimulating", "return", and "reference" are thus terms that typically relate to the "intent" of stimulation and if they are used it should be (i) with the recognition that despite intent, the physiological actions of stimulation may be unexpected (ii) the complete stimulation dose is documented (e.g. it is never appropriate to exclude details of reference electrode size, placement, and materials). The term "reference" may also be used in the mathematical context of defining polarity (e.g. 5 V relative to the reference electrode), without presumptions of "intent", which is sound.

Electrode Assembly, Electrode, and Electrolyte

The electrode assembly refers to all components that carry current between the device lead wire and the scalp (such as metal electrode, conducting rubber electrode, electrolyte, sponge) and/or materials used to shape these components or otherwise direct current flow (casing, sponge, rivets). The headgear used to position the electrodes on the body or scalp is not included in the electrode assembly. The headgear must include some components that do not conduct current flow.

Technically the electrode in an electrode assembly refers only to the material (or surface) where charge carried by electrons is converted to charge carried by electrodes. For tES, this is limited to the metal and/or conductive rubber in contact with the electrolyte (such a saline or gel). In electrochemistry literature (Merrill et al. 2005), electrode refers only to the one element in the electrode assembly that is conductive and, in almost all applications of tES, does not touch the skin. However, in the tDCS (and broader tES) literature electrode has been used to refer to the entire electrode assembly. Ambiguity in this regard limits reproducibility. For example, it should be made clear if provided dimensions (e.g. 5 × 5 cm) refer to the electrode (e.g. the conductive rubber or metal) or rather the overall electrode assembly or sponge (the skin contact area).

It is conventional to discuss montage and waveform in terms of electrode (rather than electrode assembly). For example, delivery of 1 mA to an electrode implies delivery of 1 mA through the electrode assembly. Use of an electrode as an "anode" is correct and implied the electrode assembly functions as an anode. The conventions in the literature describing montage and waveform referencing "electrode" are typically appropriate if (i) the distinction between electrode and electrode assembly is clear to the writer and readers and (ii) details of the electrode assembly, including the electrode design, are explicit.

The electrolyte is the component of the electrode assembly where charge is carried by ions. It is in contact with both the electrode and the skin and completes a circuit of electricity flow. The electrolyte may be saline or other salt containing solution (Dundas et al. 2007) or the electrolyte may be a salt-containing hydrogel or fatty (oily) cream. To prevent spread, the electrolyte may be suspended in a porous material like a sponge and/or contained by a holding vessel like a cup. In some cases, such as with fatty creams, the electrolyte may be sufficiently viscous not to require a suspension. Notably though, oily creams or fats may change the impedance properties of the skin stressing the importance of attending to the resistivity of preparations. Regardless, the electrolyte is always a barrier between the electrode and the skin. The minimum path distance between the electrode and the skin that passes through the electrolyte is the minimum electrode-skin distance. This minimum distance may be determined by a physical non-conductive (e.g. plastic) separator or holder, by sponge thickness, or by the thickness of the paste (where special care must be taken to ensure the electrode does not approach skin).

Some studies have used water to saturate tES electrodes and in such cases the water presumably either contains some ions or absorbs it from the skin. "Salt-free"

gels and creams have also been evaluated for tES (Minhas et al. 2010), but often have other chemical substitutes for supporting charge transfer and should not be used without validation.

Headgear

All components that are used to position and hold the electrode to the body are part of the head-gear. As defined here the headgear is primarily fabricated using non-conductive components (e.g. elastic or fabric). However, some conductive components like the electrode assembly and the lead (wires) may be integrated into the headgear. The head-gear serves to hold these components in place, position them relative to the scalp, and/or facilitate set-up.

Resistance (Impedance)

Resistance is a ubiquitous term in tDCS and is considered important in pre-testing and monitoring of stimulation, though clarification on its usage is useful. As tDCS is current controlled, the voltage output (across two electrode and tissue) of the stimulator is adjusted to maintain a controlled current application. When the term "resistance" is used in the context of tDCS what is generally being referred to is the voltage at the output of the current source divided by the current applied – through the application of Ohm's law. Typically, prior to stimulation, as the stimulator probes resistance, a small imperceptible test current is applied and the resulting voltage noted; here again, division of the voltage by the test current is similarly used to calculate resistance. However, neither before nor during stimulation, is the electrode and tissue simply resistive (e.g. explained only by ohms law). For example, prior to stimulation, the "resistance" calculated will depend on the current test applied (Hahn et al. 2013). The term "impedance" refers to the broader relation between current applied and the voltage need to maintain this current flow. Linear impedance includes frequency specific responses (e.g. the response to sinusoids of varied frequency). The electrode and tissue are complex non-linear impedance. For example, the impedance may change over time.

What does all this subtlety mean for the simple and consistent use of "resistance" in tDCS? It is accepted that during tDCS a significantly increased voltage (at the current source output) is associated with an overall impedance increase, which would indicate non-optimal conditions at the electrode or electrolyte-skin interface. This is biophysically justified since maintaining a low electrode "over-potential" voltage – a voltage that occurs specifically across the electrode interface as a result of electrochemical conditions (for detailed discussion, see Merrill et al. 2005) – and high conductivity (e.g. good gel/saline contact with the electrode and skin) are associated with minimized chemical reactions and good contact. These

factors, in turn, promote but do no guarantee tolerable stimulation. Variability in the outcomes of tDCS methods can come about due to differences in the resistance – or more properly the impedance – of the skin. While "resistance" may be reported, investigators should recognize the impedance value is not a fixed property of the system but reflects how the measurement is obtained. The pre-stimulation "resistance" reported is a function of the device used while the "resistance" during stimulation is a global measure integrating several factors. In this qualified sense, "resistance" may be used interchangeably with "impedance" in conventional tDCS. To compensate for these issues some devices adopt "quality units" which may also be reported as a substitute for resistance, but only when noting the type of device.

High-Definition Transcranial Direct Current Stimulation (HD-tDCS)

HD-tDCS is defined as any tDCS montage using electrodes with a compact (e.g. < 5 cm^2) skin-electrolyte that is defined by a rigid holder (e.g. comparable to EEG designs). In some cases, the increased current density necessitates use of specially designed electrodes (Minhas et al. 2010) that are called High-density electrodes.

Two or more electrodes may be used for HD-tDCS. A feature of smaller electrodes is the potential to use a higher number of electrodes and/or electrodes in closer proximity; this in turn provides increased flexibility in montage design (Dmochowski et al. 2013) as well as facilitates simultaneous recording of EEG during tDCS (Roy et al. 2014).

HD-tDCS may use a varied number of electrodes, including 2, 5, or more depending on the stimulation objectives and device constraints (Dmochowski et al. 2011, 2013). HD-tDCS may be optimized for focality (sparring non-targeted brain regions) or for overall intensity (with diffuse brain current flow).

4 × 1 HD-tDCS Montage

The 4 × 1 Montage is a deployment of HD-tDCS where one center electrode is surrounded by four electrodes of the opposite polarity (Datta et al. 2009; Kuo et al. 2013) – thus forming a ring around the center electrode. If the center is an anode, the four surround electrodes are cathodes. If the center is a cathode the four surround electrodes are anodes. The 4 × 1 HD-tDCS montage is intended to restrict current predominantly to the cortex circumscribed by the ring (Edwards et al. 2013) and can produce more unidirectional stimulation since the role of the polarity of the four return electrodes is distinct and so presumed diminished. Whereas 4 × 1 refers to a particular electrode configuration, HD-tDCS indicates any montage with small ("HD") electrodes.

(Slow) Oscillating Transcranial Direct Current Stimulation, Transcranial Sinusoidal Direct Current Stimulation (tSDCS)

Oscillatory tDCS (o-tDCS) is a form of tDCS using direct current stimulation where the intensity of stimulation is regularly modulated but which remains monophasic such that the polarity of stimulation is never inverted. The stimulation waveform is typically a monophasic square or a monophasic sinusoidal wave. o-tDCS and its variants conventionally use electrode montages adapted from tDCS.

Slow oscillatory tDCS (so-tDCS) conventionally refers to a signal with a frequency below 1 Hz (e.g. 0.75 Hz; Groppa et al. 2010). Often, so-tDCS is applied between a supra-orbital electrode and an electrode on the mastoid. Transcranial sinusoidal direct current stimulation (ts-DCS) is a form of o-tDCS where the waveform is a monophasic (biased) sinusoid. so-tDCS may also be used to describe protocols with sinusoidal waveforms and low frequency (Eggert et al. 2013; Groppa et al. 2010). ts-DCS frequencies and intensities span those used in tACS (Antal et al. 2008).

The duty cycle of o-tDCS and its derivatives may be varied (e.g. 5 intervals with 1 min gap; Eggert et al. 2013). The distinction between o-tDCS and forms of tDCS which is applied intermittently and repeatedly (repetitive tDCS; e.g. 15 s on tDCS, 15 s off tDCS, repeated; Marshall et al. 2004) is, as defined here, one of intended outcome – where o-tDCS is expected to produce changes in part through the change in current (namely the neurophysiologic intended outcomes are assumed to reflect the non-static nature of current flow), while tDCS is assumed to produce its outcome primarily during the sustained phase (namely the neurophysiologic outcomes are assume to reflect actions when the current is sustained, even if interactions across tDCS sessions are expected). Evidently, this distinction of intention is subtle (and subject to change/interpretation) and we emphasize that all studies would report the dose applied regardless of terminology used.

Early and Modern History of tDCS, Alongside Historical tES Developments

Early History of tDCS and tES (Before 1900)

Early uses of electrical stimulation to modify brain function predates the invention of man-made electricity. Observations from 43–48 A.C. showed that placing a live torpedo fish induced a strong discharge over scalp that resulted in pain relief in headache. Later in the eleventh century, this method was used in patients with epilepsy by Ibn-Sidah. He suggested that stimulation of frontal bone could be used as a treatment for epileptic patients (Priori 2003). Thus, studies with electric fish included the initial attempts of brain stimulation which continued until voltaic piles were invented. In the late eighteenth century, Luigi Galvani invented the voltaic cell

and together with his experiments involving animal electricity, he conducted foundational bioelectrical (electrophysiology) studies. As early as 1755, Charles Le Roy conducted experiments in a blind man with the purpose of restoring sight. In this experiment wires were placed around the subject's head and leg. Although he perceived phosphenes and the experiment was repeated several times, the subject remained blind. In terms of early stimulation techniques for treatment, Giovanni Aldini (Zaghi et al. 2009) recommended galvanism for patients with deafness, amaurosis, and "insanity"; reporting good results with this technique especially when it was used in patients with "melancholia". Aldini also treated patients with personality disorders and reported complete rehabilitation following transcranial administration of electrical currents (Parent 2004). These early studies used rudimentary batteries and were inherently constant voltage stimulation, where the resulting current depended on the variable body resistance. During the nineteenth century several studies utilized electrical stimulations in various parts of the world. The variability among such studies made drawing concise conclusion about their findings extremely difficult. In addition, these studies failed to report crucial information including patients' diagnosis, stimulation parameters as well as lack of scientific rigor in study design. These studies also made no attempt to estimate the amount of electricity each case received (Newth 1873). The potential value of electrical therapy was recognized and remarked upon by Dr. Alexander Robertson in the late nineteenth century, when he advised the following:

> *…The therapeutic value of electricity in mental disease is not by any means hypothetical only; it has been repeatedly proved to be of real value by numerous observers in this country (UK), in America, and especially on the continent. So long ago as 1804, Galvani's nephew, Aldini, is reported as having cured two cases of melancholia by galvanism to the satisfaction of several disinterested physicians who watched the cases. Galvanism is not a remedy to be used indiscriminately, or in a hazard way. It is not a toy, but a very potent means of doing good or harm, and must be used very cautiously and scientifically…*

Late History of tDCS and tES (1900–2000)

Over the course of the twentieth century, direct voltage continued to be intermittently tested, but electro-medicine involved pulsed stimulation became dominant. Early efforts began with simple circuits and basic devices, where a crank intermittently connected the mechanical connection between the battery and the subject; and later evolved into to modern current control circuits. The increasingly complex waveforms that were made possible by this advance in electrical engineering including Cranial Electrotherapy Stimulation and its variants (Guleyupoglu et al. 2013). We categorized tES in the twentieth century into fives streams (Fig. 1.6), four of which spans decades plus one additional stream of contemporary approaches. These streams are: (1) CES that descended from ES or CET; (2) EA, which went through several periods of waning interested and resurgence when new waveform variations were proposed including TCES, and Limoge Current; (3) Polarization or direct current stimulation, which includes tDCS, TCMP, and HD-tDCS; (4) ECT, initially

called Electroshock Therapy; and (5) Contemporary approaches that have been explored intensively over last decades such as tACS, tSDCS, and tRNS. As discussed above, many contemporary approaches developed following the emergence and methodology of tDCS.

Electrosleep (ES), the method of stimulating brain to produce a sleep-like state, was initiated in 1902 (Robinovitch 1914). Most of the work related to this topic was conducted mainly in Russia, until 1953 when clinical usage of this method began in Europe (Smith 2006). In 1977 ES and its derivatives went under review by FDA and in 1978 it was classified as a class III device for treatment of insomnia, anxiety, and depression. Modern CES is thus a historical descendant of ES with continuous use and development over the century.

In parallel with initiation of ES, EA which induced anesthesia using high frequency stimulation, was first described in 1903 (Leduc and Rouxeau 1903). One of the first published claims of EA's success during surgeries was made in the 1914 by Leduc (1914), however safety and tolerability concerns, as well as the development of early chemical anesthetics may have contributed to quelling of interest in EA. In the 1940s research on EA focused on chemical primers being used in conjunction with EA and soon after its use appeared to largely halt due to side effects. Although side effects were discovered, research into variants of EA continued and the term TCES was adopted around 1960–1963 with the intended use to potentiate some drug effects with the goal of drastic reduction in pharmacologic anesthetic agents. Circa 1965, interferential stimulation (IS) was proposed by Russian scientists who had two pairs of electrodes that could apply sinusoidal waves with slightly different frequencies. The intention of this approach was that through pulsation, higher frequencies would create a lower frequency where the two frequencies intersect. This was clinically desired as low frequencies were presumed more efficacious in inducing EA whereas higher frequencies were more desirable for tolerability. Historical EA and TCES used current intensities that were typically well above those used in contemporary tES.

Direct current stimulation has been used intermittently as a component in both ES and EA. In 1957, a DC bias was added to ES. In 1964, Redfearn and Lippold investigated polarizing current for treatment of neuropsychiatric diseases; their use of prolonged stimulation was motivated by animal studies showing that prolonged direct current stimulation could produce lasting changes in excitability (Bindman et al. 1964). The majority of studies after Lippold were relatively small and used comparable dose (Table 1.1). Commonly used current intensities from 1964 to 1998 raged from 0.5 to 0.1 mA; though Redfearn and his colleagues used up to 3 mA in one patient. The most common electrode montage was active electrode(s) above eyebrow (supra-orbital) and reference electrode in an extra-cephalic position (e.g., leg, hand). In alternative montages, the active electrodes could be placed on occipital and temporal areas of the scalp. Apart from the leg and arm, the return electrodes were also placed on the mastoid bone or collarbone. Active electrode size was 0.1 to 0.2 cm^2 (mean 1.26 cm^2). The reference electrode area was often larger than the active ones (Baker 1970; Lifshitz and Harper 1968), but in some cases they were the same size (Elbert et al. 1981).

Table 1.1 tDCS studies published between 1960 and 1998

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration Of stimulation	Electrode	Findings	Side effects
Lippold et al. (1964), UK	32	Depression/ Schizophrenia	Uncontrolled double-blind	Anodes over each eyebrows and cathode over right knee	0.1–3[a]	0.5–5[b] h (duration of stimulation varied in subjects based on their condition and improvement).	1.26 cm^2 Chloride silver discs covered with saline-soaked gauze	In scalp-positive polarization patients became more alert and more involved with the environment; in scalp-negative polarization quietness and withdrawal was seen. They have often found an effect at 0.25 mA for each anode whereas there had repeatedly been no effect at 0.15 mA scalp positive stimulation[c].	Tremor during scalp-positive, nausea, sleepiness
Costain et al. (1964), UK	24	Depression	Controlled double-blind, crossover	Anodes over each eyebrows and cathode over one knee	0.25 for each anode %current was started from 0.1 for each eyebrow and gradually increased	8 h per day for 12 days	1.26 cm^2 Silver discs covered with saline-soaked gauze	Improvement of anxiety, agitation and somatic symptoms.	Faint, blue flashes, skin sensitivity, mild headaches
Redfearn et al. (1964),UK	29	Refractory depression	Open label	Anodes over each eyebrows and cathode over one knee	0.1–0.25 for each anode	0.5–11[b] h (duration for each person was based on side effects), 5 times a week for 6 months.	1.26 cm^2 Chlorided silver discs covered with saline-soaked gauze	13 cases showed clinical improvement that lasted only 1-2 days It has been suggested that a dosage of 0.4 mA in each lead for period on 8 hours per day was more effective in many patients.	Mild headache, skin sensitivity

(continued)

Table 1.1 (continued)

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration Of stimulation	Electrode	Findings	Side effects
Ramsay et al. (1966), USA	20	Depression	Open label	Anodes over each eyebrows and cathode over one knee	0.15–0.3 for each anode	4–6[b] h per day. Total stimulation time varies.	–	14 definitely improved, 4 equivocal improved, 2 did not improve	Few side effects reported (does not mention which)
Herjanic et al. (1967), Unknown location	20	Depression/ Schizophrenia	Uncontrolled Open label	–	0.1–0.5	–	–	All patients improved their depressive symptoms	None reported
Lifshitz and Harper (1968), USA	5	Schizophrenia	Controlled double-blind crossover	Anodes over eyebrows and cathodes over homolateral thighs.	0.33 for each channel of stimulation	6 h per day for 2 weeks only on week days followed by 2 week rest period.	Pure silver electrodes covered by surgical gauze soaked with normal saline. Anode = 1 × 2.5 cm and cathode = 2 × 4 cm	No significant effects either for scalp positive or scalp negative stimulation.	Skin irritation was fairly marked for 3 patients. Skin lesion consisted of erythema, papules and pustules which principally appeared under negative electrode.
Sheffield et al. (1968), Australia	6	Healthy	Controlled double-blind	Anodes over eyebrows and cathode over one leg	0.25 for each lead% current started from 0.03 mA and gradually increased in 90 min	3 h, each person was stimulated twice (positive and negative) in different days.	Chlorided silver discs covered with saline soaked lint pads. Anode= 0.5 inch diameter, cathode= 0.75 inch diameter.	Happier and more alert with scalp-positive polarization but results don't show significant changes in mood in subjects compared to control.	Moody and sleepy with scalp-negative polarization

Carney et al. (1970), Australia	119	Depression	Open label, uncontrolled	–	0.25	–	–	Improvement in excited behavior and mood; relapse on stopping treatment and improvement on recommencing.	None reported
Arfai et al. (1970), USA	19	Depression	Controlled double-blind clinical trial	Anodes over eyebrows and cathodes over thighs	0.25 for each independent channel	8 h per day during 6 days each week (totally 12 applications)	Chlorided silver discs	No significant effects	None reported
Hall et al. (1970), USA	18	Healthy	Controlled double-blind	Anodes over each eyebrows and cathode over knee	0.15 and 0.3 for each lead	2 h, each person was stimulated 3 times (scalp positive, scalp negative and sham) in different days.	Metallic mesh electrodes. Skin was rubbed by alcohol and local anesthetic was used.	No significant effect.	None reported
Baker (1970), Rhodesia	107	Depression	Random group of patients treated with brain polarization.	Anodes over each eyebrows and cathode over upper arm or forearm	0.4 for each $lead_{\%}$ current started with 0.2 mA and gradually reached 0.4 in half an hour	5[b] h per day for 6–8 sessions.	Silver plates covered with lint soaked in saline and gel was used for skin Anode= 10 cm^2 and cathode= 20 cm^2.	84% reported sustained improvement. Anxiety was not relieved.	Skin sensitivity, tachycardia and migraine
Nias and Shapiro (1974), UK	1	Schizophrenia with Depression	Controlled double-blind clinical trial	Anodes over each eyebrows and two cathodes attached to right knee	0.4 for each lead	3–4 h per day for 14–120 sessions.	–	Improvement with negative and worsening with positive stimulation	Tingling on the forehead.
	1	Alcoholism with Depression			0.5 for each lead			Improvement with positive stimulation	

(continued)

Table 1.1 (continued)

Study	N	Disease	Design	Electrode montage	Intensity (mA)	Duration Of stimulation	Electrode	Findings	Side effects
Elbert et al. (1981), Germany	48	Healthy	Single-blinded	Anode over vertex and cathodes over earlobes	0.26	1 h in a session (half of task was done in cathodal and the rest was done in anodal stimulation).	1.5 cm diameter Silver discs	Vertex positive current tends to develop faster reaction times and higher skin conductance responses than vertex-negative currents.	None reported
Elbert et al. (1981), Germany	32	Healthy	Single-blinded	Anode over vertex and cathode over collarbone to both sides which were linked	0.25	1 h in a session (half of it was anodal and the other half was cathodal stimulation).	1.5 cm diameter Silver discs	Results suggest that subjects reacted after a shorter interval when negative pole was applied compared to positive stimulation.	None reported
Korsakov (1989), Russia	48	Schizophrenia	Open label clinical trial	Anode over Occipital cortex OR anode over frontal CORTEX cathode=mastoid	0.05–0.2	–	Silver cup electrodes	Cathodal on occipital cortex increased visual sensitivity (discrimination of the brightness of a pair of light flashes), anodal decreased.	None reported

[a]Just for one person 3 mA was used and it was applied while putting local anesthetic under electrode
[b]Device was portable and patients could go about their normal hospital business and returning to the lab at pre-arranged times
[c]They has two other failed trials before the present study. The essential difference between this trial and two others were electrodes placed over eyebrows, currents were lower and they were passed for much longer time

These early studies employed several sessions of stimulation, with a median of 14 sessions (ranging from 1 to 120 sessions). The median of the total duration of stimulation was 30 h. Redfearn et al. conducted among the highest total dose studies, with 960 h total time of stimulation across sessions (Redfearn et al. 1964). The median duration of sessions was 4.5 h, with a maximum of 11 h (Redfearn et al. 1964). Reflecting the long duration of stimulation in many studies, the devices were often portable and patient could move around the hospital or go home. In most studies from this era, stimulation apparatus was made of low voltage dry batteries in a pack with a potentiometer to produce constant current. In one early study (Elbert et al. 1981), an optocoupled system driven by the analog output provided constant current which had a ramp up period of 6 s to increase current from zero to 0.25 mA. In all the studies, electrodes were metallic, either pure silver or silver chloride disks.

We note that in direct current stimulation methods before the modern period (before 1998), the active electrode's mean size was smaller, current was lower, and session durations were higher. As discussed next, approaches used in the modern era was heavily derived from canonical neurophysiological studies (circa 2000), which were in fact not intended to optimize clinical benefit. It is thus interesting that contemporary efforts to enhance clinical efficacy now consider using longer duration sessions along with more sessions which benefit from home-use devices (Charvet et al. 2015), and are thus closer to these early clinical efforts.

Modern tDCS 2000+

The Canonical Methodological Paradigm

While research using low-intensity currents continued throughout the twentieth century, the modern resurgence in the investigation of weak direct and alternating currents is linked to seminal neurophysiology work circa 2000 (Nitsche and Paulus 2000). This work and subsequent neurophysiologic studies (Clark et al. 2012; Leite et al. 2013) established the foundations of modern tDCS as evidenced through the establishment of certain canonical dose paradigms. These include use of currents in the 1 mA range, use of large sponge based electrodes (in the 30 cm^2 range), use of long duration stimulation (tens of minutes), and intention to produce polarity specific modulation with the anode/cathode placed over the region to be excited/inhibited (often with the other electrodes in a forehead/SO position). While the understanding of brain response to a given tDCS dose have continued to evolve through rigorous investigations (Monte-Silva et al. 2010; Ohn et al. 2008; Reis et al. 2015) and new techniques have been invented (Nikolin et al. 2015), the basic rational for tDCS design has continued to dominate the design of trials. Namely aspects like 1–2 mA, 10–20 min of "anodal/cathodal" tDCS to "increase/decrease" function using a large sponge electrode placed on the scalp over the target with the functional

role of the other electrode assumed unimportant. In both neurophysiological studies and clinical trials, there has been only a conservative escalation of both dose and sessions.

Brief Overview of Current Understanding of Neurophysiological Mechanisms

While passage of current through surface electrodes results in some shunting of current at the scalp as well as cerebrospinal fluid (CSF), a portion of current will penetrate to the brain, producing a peak electric field of approximately 0.3 V/m per 1 mA applied (Datta et al. 2009; Huang et al. 2017). While the resulting electric fields are low intensity (for comparison, TMS produces an almost 100 V/m electric field), the sustained "DC" electric field produced during tDCS will polarize the transmembrane neuronal potential (Jackson et al. 2016). This polarization, in turn, can influence "excitability" including the responsiveness to synaptic input (Rahman et al. 2013), modulate the firing rate of individual neurons (Miranda et al. 2006; Wagner et al. 2007), and change information processing by cells (Huang et al. 2017) and networks (Reato et al. 2013).

Importantly, when sustained for several minutes and present during ongoing LTP, direct currents can modulate plasticity (Jackson et al. 2016). tDCS-modulated neuro-plastic changes may be associated with alteration of neuronal ionic channels, such as the L-type voltage gated calcium channel (L-VGCC), and N-methyl-D-aspartate (NMDA) receptors (Paulus 2011; Stagg and Nitsche 2011). Mechanisms analogous to long-term potentiation (LTP) or long-term depression (LTD) have thus been attributed to tDCS effects on plasticity. Notably, since the current used in tDCS is subthreshold, it does not induce action potentials (Bikson et al. 2004); instead it modulates spontaneous neuronal activity (evoked, ongoing/endogenous activity) in a polarity-dependent fashion. Since tDCS does not necessarily produce, but instead modulates activity, it has the feature of being "functionally selective" where only paired plasticity (e.g. the training matched with stimulation) is boosted (Bikson and Rahman 2013).

The effects of tDCS are stimulation polarity dependent. Surface anodal stimulation will typically produce inward current flow at the cortex, which is expected to produce somatic depolarization of pyramidal cortical neurons and apical dendrite hyperpolarization, while surface cathodal stimulation will typically produce outward current flow at the cortex and is expected to result in somatic hyperpolarization of pyramidal cortical neurons and apical dendrite depolarization (Radman et al. 2009; Zaghi et al. 2010). Changes in brain excitability were classically assumed to track somatic polarization, at least for moderate stimulation intensities (e.g. 1 mA) and durations (e.g. 15 min). However, ongoing and rigorous investigation of tDCS cellular targets and dose response indicate a more nuanced

mechanism. For example, the cellular targets of tDCS may include axons (Rahman et al. 2013), dendrites (Kronberg et al. 2017), glia (Monai et al. 2016), or endothelial cells (Lopez-Quintero et al. 2010). New cellular targets, in turn, suggest varied and more nuanced dependence on tDCS stimulation polarity (Rahman et al. 2013). The dose response to increasing tDCS intensity may be nonlinear with increasing current, duration, or brain activity (Jamil et al. 2017).

There is also increasing sophistication about the anatomical targets of tDCS and montage design. While the nominal targets of tDCS are often simplistically assumed to be under the electrodes, the current flow produced using conventional tDCS in fact spans all cortical regions between and around the electrodes (Datta et al, 2009; Huang et al. 2017; Jog et al. 2016). It is therefore important to take care to distinguish between stimulating with an electrode "over" a region and specifically targeting "of" that region. Moreover, current flow with conventional montages is expected to reach deep structures (Bikson et al. 2010; Brunoni et al. 2012a; DaSilva et al. 2012; Keeser et al. 2011; Miranda et al. 2006; Salvador et al. 2010; Zaghi et al. 2010). In addition to tDCS having effects on brain regions distant from the electrode due to physical diffusion of current flow, tDCS may also modulate distant networks which are functionally connected to directly stimulated regions (Nitsche et al. 2005). For example, tDCS has been found to modulate resting-state functional connectivity after prefrontal stimulation (Keeser et al. 2011). As noted, to counteract diffusivity, tDCS may be "functionally" focalized by timing stimulation with specific tasks (Cano et al. 2013; Cohen Kadosh et al. 2010) – this combination with training is relevant for clinical applications as discussed next.

There are arguably no neuromodulation techniques that have been subject to as extensive neurophysiological investigation at the animal and human level as tDCS. In just the last decade, there have been dozens of human trials addressing nuance in dose response (Giordano et al. 2017; Jamil et al. 2017; Woods et al. 2016), which are supported by animal trials indicating the effects of tDCS are pathway and state specific (Bikson and Rahman 2013). While challenges remain, including in addressing individual dose response, it is important that the basic rationale for using direct current to alter brain function is exhaustively tested.

Brief Overview of Rationale for Various Clinical Applications

Due to the neuromodulatory effects of tDCS, including its effects on excitability-measures and rate of learning (Buch et al. 2017; Kim et al. 2017; Kronberg et al. 2017) tDCS has been tested as a treatment for several neuropsychiatric disorders and to accelerate neuro-rehabilitation (Brunoni et al. 2012b) Since plasticity/excitability/activity is pathologically altered in many neurological and psychiatric diseases, tDCS is most often used to "re-adjust" or re-balance the system; examples here include epilepsy, pain, and depression, amongst others. A second rationale for testing of tDCS is the relevance of plasticity, and cortical activity/excitability

alterations, for learning and memory formation; and therefore, potential conjunctive application of tDCS during rehabilitation/training: examples include motor rehabilitation, visual restauration, dystonia (Furuya et al. 2014), and Alzheimer´s disease. Evidently the (individual) etiology of disease as well as the brain response is complex, the ability of tDCS to alter excitability and plasticity is a starting point to rationalize clinical trials (Lefaucheur et al. 2017; Naro et al. 2016).

For instance, tDCS has been used for motor learning enhancement in stroke rehabilitation (Schlaug et al. 2008), for behavioral performance enhancement with Alzheimer's patients (Boggio et al. 2009b; Ferrucci et al. 2009; see also Chap. 12), for modulation of emotional affective neural circuits in depression patients (Boggio et al. 2009b; see also Chap. 13; Bueno et al. 2011; Kalu et al. 2012), and for patients with chronic pain (Boggio et al. 2008; Fenton et al. 2009; Fregni et al. 2006c; Gabis et al. 2009; Zaghi et al. 2011). In stroke neurorehabilitation, tDCS has shown benefits when used together with other interventions such as rehabilitation training (see Chap. 11) or occupational therapy in humans (Nair et al. 2011; Zhu and Schlaug 2011). In terms of pain, tDCS has been applied to cases of chronic pain refractory to pharmacologic interventions (Lefaucheur et al. 2008; Nizard et al. 2012) and for a number of different pain conditions such as fibromyalgia, pelvic pain, and neuropathic pain (DaSilva et al. 2012; Fenton et al. 2009; Fregni et al. 2006a).

Indirect support for clinical interventions also come from experiments in healthy volunteers on cognitive function. Numerous studies have also examined the effects of tDCS on learning in healthy subjects, suggesting improvement in implicit learning (Kincses et al. 2004), motor memory (Galea and Celnik 2009), working memory (Mulquiney et al. 2011; Ohn et al. 2008), and memory retrieval (Boggio et al. 2007; see also Chap. 9; Boggio et al. 2009a; Chi et al. 2010).

The clinical effectiveness of tDCS for any given indication depends from many factors, with adoption ultimate dependent on efficacy, safety, as well as a range of regularly, commercial, and payer issues. Regarding safety, the broad consensus of researchers and clinicians is there is no evidence for a serious adverse event being caused by tDCS (Russo et al. 2017) – which is made evident, in a sense, by the routine testing of tDCS on healthy subjects (e.g. up to 6 weeks in college students; Paneri et al. 2016). Regarding efficacy, clinical trials for a broad range indications are at varied phases, through for many treatments encouraging results often support ongoing clinical trials. For some indications, notable chronic pain and depression the consensus among researcher and clinicians is for moderate evidence for efficacy (Aparicio et al. 2016; Bikson et al. 2016; Lefaucheur et al. 2017; Spagnolo and Goldman 2017; Zhu et al. 2017), which also correspond to indications for which tDCS has been approved for treatment in some regions (e.g. the EU). It should also be noted that many tDCS trials include relatively small sample sizes and clinically homogeneous populations, and often use surrogate outcomes. Moreover, clinical trials vary in dose and inclusions/exclusion (e.g. concurrent use of medication) – which can profoundly affect outcomes and there is variation in outcome measures themselves, which makes it important to draw conclusions with

care. Noting ongoing progress in addressing the mechanisms of tDCS (above), many questions remain especially in the context of treating the damages of pathophysiological brain. There is thus broad support for ongoing research especially aimed at optimization of dose (since the limited permutations tested so far could not be optimal), resolve individual responsiveness (recognizing that at useful treatment does not need to be effective for every patient), and incorporation of new technology – discussed next.

Emerging Technologies and Models

The field of tDCS is advancing, with new approaches and methodologies of tDCS recently developed. Many of these developments focus on improved method to deliver current to the brain. One such development is "High-Definition" tDCS (HD-tDCS), which utilizes an array of smaller gel-based electrodes, in contrast to the two large sponge-based electrode used in conventional tDCS. The position and current at each HD electrode can be optimized for a variety of desired outcomes, such as intensity or targeting (Dmochowski et al. 2011). One HD-tDCS configuration, the "4 × 1 ring" electrode montage, has been shown to be a more focused method of stimulation compared to conventional tDCS (Fig. 2.7; Datta et al. 2009; Edwards et al. 2013). The 4 × 1 HD-tDCS configuration has been shown to be a reliable method of targeting specific cortical areas, can produce plasticity changes that may outlast conventional tDCS (Kuo et al. 2013). Clinical application of 4 × 1 HD-tDCS are expanding, for example showing reduced perception on pain in fibromyalgia patients (Castillo-Saavedra et al. 2016; Villamar et al. 2013a, b) and in experimental pain (Borckardt et al. 2012).

A further important area of development for targeting of tDCS is use of EEG. Especially using HD-tDCS which can be integrated with EEG systems, there is compelling case for using clinical sub-population or subject-specific EEG to deliver a customized tDCS distribution. The notion of recording and HD-tDCS with the same or adjacent scalp electrodes is loosely based on the concept of reciprocity, which has only recently been formalized for non-invasive electrical stimulation (Dmochowski et al. 2013). Prior this this formalization, there have been varied empirical proposal to guide tDCS from EEG ranging from simple (Cancelli et al. 2016), to complex (Fernandez-Corazza et al. 2016; Wagner et al. 2016). EEG has also been suggested as useful to classify responders to tDCS (Al-Kaysi et al. 2016; Castillo-Saavedra et al. 2016) and broadly as a tool to diagnose the effects of tDCS (Cosmo et al. 2015; D'Atri et al. 2016; Mancini et al. 2016). The integration with EEG thus is an important frontier for tDCS optimization, but alongside this promise it is critical to consider technical concerns in implementation (Noury et al. 2016; Chap. 11).

There is a long-standing interest to use functional mapping information from fMRI to identify targets for tDCS (Clark et al. 2012; Teichmann et al. 2016) and

access outcomes (Jang et al. 2009; see Chap. 11; Clark et al. 2011; Lin et al. 2017; Cabral-Calderin et al. 2016; Cavaliere et al. 2016). However, there is a push for more sophisticated and numerically formalized methods to systematically combine spatial imaging with spatial targeting of (HD)-tDCS (Dunlop et al. 2016; Hunter et al. 2013). For example, it possible to co-register current flow and imaging data in analysis (Halko et al. 2011). A further interesting development is the use of MRI to image current flow produced by tDCS (Antal et al. 2014; Jog et al. 2016).

There have been various proposals on customized tDCS to a subject's anatomy. This is motivated by individual differences in anatomy leading to different brain current flow patterns for the same dose (Bikson et al. 2012b; Datta et al. 2012; Kim et al. 2013; Truong et al. 2013). One approach using individual MRI derived models of current flow to customize dose (Bikson et al. 2012a; Ruffini et al. 2013; Opitz et al. 2015; see Chap. 9). This approach was first suggested in stroke where individual brain lesions distort brain current flow patterns (Datta et al. 2011; Otal et al. 2016) leading to pilot clinical trials in customized tDCS in rehabilitation (Dmochowski et al. 2013). An alternative line of proposed personalization of the stimulation is by adapting the electrode shape (rather than position and current at electrodes) to fit the structural and functional features of individual subjects (Cancelli et al. 2015). Approaches used shaped concentric ring electrodes, to approximate the 4 × 1 HD-tDCS montage, are also proposed (Bortoletto et al. 2016).

One of the most promising features of tDCS is the ability to deploy to a wide range of environments, including home use. But there has been a dearth of studies using tDCS at home compared to the at the clinic/academic center, which in part reflected the need to establish efficacy in controlled environment but also the lack of availability until recently, of suitable equipment and protocols. Providing a patient with a device certified for use by an expert creates significant risk of misuse (Cabrera et al. 2014). Remote-Supervised tDCS is thus a key development to provide rigorous protocols and equipment for home-based use, including rules to maintain reproducibility and tolerability from clinic to home (Charvet et al. 2015; Knotkova et al. 2017a, Chapter 13). Efforts to develop better tDCS electrodes are often guided by simplicity and replicability for home (remote supervised) use, including single-use pre-saturated snap electrodes with single-position head-gear (Chap. 10). The need for remote based tDCS is emphasized by evidence that the effect of transcranial direct current stimulation (tDCS) is cumulative – thus treatment protocols typically require multiple consecutive sessions spanning weeks or months. The desire for remote based tDCS must be critically balanced with the development of subject/trial specific telemedicine interventions (Kasschau et al. 2015; Charvet et al. 2015; Knotkova et al. 2017b).

In the coming years, significant advances in tDCS are expected including new technology for customized stimulation in the form of more specific brain targeting (e.g. HD-tDCS), patient specific image-guided dosage parameters, and technology more easily deployable in clinical and home environments.

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