Chapter 14
Transcranial Direct Current Stimulation Ethics and Professional Conduct

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Introduction

Low intensity transcranial direct current stimulation (tDCS) is increasingly used in research and clinical practices around the world including a wide range of neurological and psychiatric conditions, where patients have no or few alternative treatment options. In parallel, the regulatory, safety and ethical considerations (Maslen et al. 2014, 2015; Maslen et al. 2013, 2014; Wexler 2016) and related problems using this methodology started to grow rapidly. Nevertheless, important ethical concerns with regard to different kind of electrical stimulation methods emerged already more than 200 years ago, since electrophysiology was born, mainly through incidental findings. E.g. Aldini travelled through Europa promoting his belief that electrical stimulation could reanimate the dead (Parent 2004). In early clinical applications the risk-benefit ratio was frequently ignored: a well-known example is a case study in 1874, when Dr. Bartholow applied electrical current to the exposed dura in a female patient. After the induction of muscular twitches, he increased the applied current intensity until distress, convulsion and finally coma were reported (Harris and Almerigi 2009). About 100 years later in the twentieth century, one of

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the most shocking and ethically unacceptable incident raised relevant public attention. Two physicians at the Tulane University aimed to treat a patient because of his homosexuality. Combining electrical stimulation applied over the septum with sexual interactions provided by a female prostitute, they reported a 10-month suppression of the homosexual behavior (Moan and Heath 1972). However, by evaluating these events in the past, we have to consider that the ethical awareness was/is always linked to the social definitions and moral, both in health and disease. Nowadays a very careful assessment of the Institutional Review Boards and Ethical Committees of a given clinic or university is required before a study is initiated. Nevertheless, the main responsibility with regard to the appropriate conduct and keeping a rigorous ethical framework remains always by the investigators. In this chapter we provide an overview of the present ethical issues associated with the scientific and therapeutic application of tDCS, including recommendations, in which ways these issues should be addressed.

Regulatory Framework and System of Regulations

As research involving human subjects must comply with ethical principles and standards. Although the regulatory framework differs among countries, the leading principles revolve around topics of protection and safety of participating subjects, and professional conduct. This in general involves multiple aspects addressed by a complex system of regulations, recommendations and principles, for example Good Practices in Clinical Research, Code of Federal Regulations (CFR) or Food and Drug Administration (FDA) in the USA, the Medical Devices Directive (MDD) and European health authorities in the EU. CFR is accessible to public online and regulations pertaining to protection of human subjects appear in CRF Titles 21 and 45. At present, tDCS is not approved in the United States by the FDA as a medical treatment for any indication. Devices from two companies, Soterix or Neuroconn, whose have an ‘investigational device exemption’ from the FDA, can be obtained by researchers and by medical personnel for investigational use.

Generally, non-invasive brain stimulation medical devices (NIBS), like transcranial magnetic stimulator (TMS), are classified as class IIa devices according to the Council Directive 93/42/CEE for medical devices and should conform to standards and directives. The MDD distinguishes two main cases for medical devices made available to the user, with and without CE marking. Devices without CE marking are either custom-made devices or devices intended for clinical evaluation. All other devices necessitate CE marking. Devices intended for clinical evaluation should be evaluated by the manufacturer with regard to the possibility of undesirable side effects during use. All medical devices must fulfill the Essential Requirements for safety and performance described in Annex I of the MDD, which state that a device used for its intended purpose shall not compromise the safety of any person (patients and professional users, who are applying the stimulation. The manufacturer should trace each device on the market in order to perform post-market surveillance by

implementing a systematic procedure (with regard to malfunction of the stimulators, appearance and frequency of side and adverse effects, etc). Medical practitioners are required to report all incidents, related to the use of stimulator.

In 2016 the European Parliament and Council reached an agreement for better surveillance and traceability of medical devices, the Commission published a communication concerning the position of the Council on the adoption of the regulation on 9 March, 2017. The medical devices regulation will enter into force 3 years after publication, on 26 May 2020 (http://www.europarl.europa.eu/legislative-train/theme-environment-public-health-and-food-safety/file-regulation-on-medical-devices).

Ethical Considerations Pertaining to tDCS Personnel

It is the responsibility of the clinician and researcher to obtain appropriate training to insure optimal safety of patients and participants receiving tDCS. In the absence of such training, the patients or participants are exposed to an unnecessary increased risk of burn or other adverse event (AE) that would be otherwise avoidable. Suitable training should involve formal knowledge acquisition including lectures, hands-on training, and supervised administration. At a minimum, training should include: (1) knowledge of relevant background (2) knowledge of information relevant to common safety concerns, (3) knowledge of necessary precautions for reduction of AEs and serious AEs (SAEs), and the correct documentation of these, if they occur, (4) hands on training with the preparation and application of tDCS electrodes, (5) hands on training with tDCS stimulator operation, (6) supervised preparation and application of tDCS electrodes, (7) supervised operation of the tDCS stimulator, and (8) demonstration of mastery of the above training components.

1. Knowledge of relevant background. This element of training should include information regarding the physiological mechanisms underlying tDCS, with specific focus on the impact of tDCS on tissue properties including all of the neuronal elements, neurotransmitters, and possible interaction with common medications and medical conditions.
2. Knowledge of information relevant to common safety concerns. Training should also include information on how variations on contact medium, electrode properties, electrode preparation, equipment sanitization, and other tDCS parameters and their interactions that could impact the overall efficacy and safety of tDCS application.
3. Knowledge of necessary precautions for reduction of AEs and SAEs. In addition, training should involve information for optimizing safety of tDCS electrode preparation and application, medical conditions that may increase the likelihood of adverse events or serious adverse events (e.g., existing skin lesions, history of epilepsy, etc.), and special considerations for potentially vulnerable populations (e.g., children, persons with skull defects) and the correct documentation and process in case of these occur.

4. Hands on training with the preparation and application of tDCS electrodes. Training should include demonstration and hands on practice with the preparation and application of electrodes. This should include appropriate localization of electrodes (e.g., 10–20 International Electrode Measurement System, by using neuronavigation or TMS), application of contact medium to electrodes, placement of electrodes on the head, safe removal of electrodes, and equipment sanitization procedures.
5. Hands on training with tDCS stimulator operation. This element of training should involve demonstration and hands on experience with the tDCS stimulator and all of the possible settings on the device. This should include, at least, methods for powering on and off the device, knowledge of the unit power supply, how to check impedance or contact quality metrics, blinding procedures, ramp-up and down, stimulation intensity and duration settings, and emergency procedures for stopping stimulation in the middle of a session.
6. Supervised preparation and application of tDCS electrodes. This component of training must take place before a person is allowed to independently stimulate a patient or participant. This should involve supervision of the trainee in the full preparation and application of electrodes to a patient or participant, with guided feedback when necessary. A single observation is not sufficient, at least two, but preferably three or more, sessions should be supervised.
7. Supervised operation of the tDCS stimulator. Similar to the preceding component, trainees should be supervised in operation of the tDCS stimulator with guided feedback on at least two occasions, but preferably three or more.
8. Demonstration of mastery of the above training components. Following completion of components 1–7, trainees should be required to demonstrate independent mastery of each component through demonstration of necessary knowledge and skills. This demonstration of mastery should ideally involve a formal test of relevant knowledge and observation of expertise through independent application of electrodes and stimulator operation. Only after this demonstration of mastery should the trainee be allowed to work independently.

Until recently, relatively few formal courses were available for tDCS training. Several courses have become available that meet the above criteria. These courses provide the best opportunity for optimal training of clinicians and researchers new to tDCS. In the absence of a formal course work, materials with the relevant information for items 1–3 can be obtained from the literature (e.g., Antal et al. 2004; Batsikadze et al. 2013; Bikson et al. 2010; Boggio et al. 2007; Datta et al. 2009; Kessler et al. 2013; Minhas et al. 2012; Monte-Silva et al. 2010; Nitsche et al. 2000, 2003a, b, 2004a, b, 2005, 2007, 2008; Palm et al. 2008; Stagg and Nitsche 2011; Stagg et al. 2009, 2013; Woods et al. 2015, 2016) or in textbooks like this one. However, hands-on training and supervision must be acquired from either a formal course or in the lab of someone with extensive expertise in tDCS application. To reiterate, it is never advised for persons without training to apply tDCS to another person. Whether it is in a research, clinical or at-home settings, the administrator of tDCS has an ethical responsibility to protect the person receiving tDCS from AEs to

the best of their ability, even when that person is administrator stimulation to him or herself.

Any research team carrying out a tDCS study has to be arranged for several specific functions and roles, some pertaining to general research activities and some specific to the tDCS use. Although one individual may assume more than one role and responsibilities associated with the role, the duties have to be clearly described, assigned, accepted and documented. Key roles within the research team and a typical scope of responsibilities include:

Principal investigator (PI) bears the overall responsibility for the whole research project. An important aspect from the regulatory and ethical point of view is that PI can delegate specific responsibilities and duties to others, such as co-investigators, but *the PI's accountability pertaining to the project is not transferable*. Therefore, it is in the best interest of PI to have the process of duty delegation well-defined and documented, so that an effective oversight of the personnel and quality checks can be made. Co- investigators substantially contribute to the scientific component of the project (such as contributing to design of the study) and/or to day-to-day study procedures (such as participant's screening). Co-investigators as all study personnel must comply with mandatory regulatory requirements clearly stated in the ethic proposals and report to the PI.

Study coordinator is mainly responsible for day-to-day study activities, such as contact with study participants, deployment of equipment, carrying out study procedures, and maintaining study documentation including participants individual study files, mandatory regulatory files, and study database. An important consequence pertaining to study coordinator's responsibilities is that the study coordinator is the core person dealing with regulatory files and associated documents and processes, such as mandatory time-frames pertaining to reporting or standard operating procedures to be followed. Thus, misconduct, negligence or insufficient training will likely have direct effects on the regulatory compliance of the study. Therefore, assigning duties to study coordinator for a specific study should emphasize this aspect and should be discussed in detail before the duty is assigned, and through training pertaining to regulatory agenda should be issued and documented. In many research teams the day-to-day study procedures are carried out by post-graduate trainees (such as post-doctoral students), it is important to keep in mind that still all duties that typically belong to the study coordinator have to be covered. They can either be assigned in full to the trainee, or can be split with a co-investigator or other senior member of the team, so that the trainee carries out the day-to-day study procedures and the senior member is responsible for maintaining the mandatory regulatory files.

Assisting personnel supports day-to-day study operations. Ethical and regulatory issues pertaining to assisting personnel encompass mostly two broad areas: (i) the supporting personnel have to have sufficient knowledge of the study so that they input is in compliance with the study protocol and regulatory requirements, and (ii) responsibilities on a specific study have to be really clearly defined. Although it seems to be trivial, substantial difficulties may arise if the responsibilities of supporting personnel are in the "gray zone", not clearly clarified. For example: Is assisting

personnel allowed to contact study participants? If yes, for all which purpose? A phone call for scheduling purpose has an entirely different regulatory framework than a call to follow-up on a serious adverse event. In real life, the issue of responsibility of assisting personnel gets more complicated due to possible multitude of studies that the assisting personnel support. Thus, a clear check list of activities/support provided and not provided for each study helps keep track and ease the compliance oversight for the assisting personnel, and an at-a-glance duty delegation log provides an overview of specific responsibilities of each individual contributing to the study.

It is a frequently discussed issue whether researchers have a responsibility to laypersons who appropriate their research, or not. Many scientists agree that research results should be made freely available in order to better inform e.g. those engaging in do-ot yourself (DIY) practices. Indeed, a lay summary in scientific publications might help to avoid misinterpretation and misuse of the methodology by individuals who may lack the scientific background to understand the details. Nevertheless, there is no clear agreement with regard to these points.

Ethical Considerations Concerning Recipients, Including Research Participants and Patients

As the research and clinical value of tDCS grows, questions concerning treatment guidelines and the continuous updating of these guidelines must be considered. First, have to contemplate what criteria should we adopt before recommending tDCS, and not another treatment as a possible option. Furthermore, the scientific actuality about what tDCS can and cannot do must be explicitly stated, and every effort to balance a patient's hopes and expectations should be fairly done. Informed consent and any kind of communication with potential participants must be clear, and the objectives transparent. Risk – benefit determinations, (including an evaluation of the possible and probable risks the type, magnitude, and duration of benefit; the level of uncertainty, patients' tolerance for risk and perception of benefit) should always part of the informed consent. Moreover, participants should fully understand that they have the option to choose another alternative treatment options. Here, the basic ethical and legal requirements for inclusion of human subjects to tDCS are summarized.

Informed Consent

In the USA and in the EU the federal regulations for the protection of human subjects require investigators to obtain legally effective informed consent (IC) from individuals participating in research. IC is considered legally effective if (a) all federally required elements of IC (discussed below) as set forth in the Code of Federal Regulations, section 45 CFR 46.116 (USA) are contained in the consent form document, *and* (b) the consent of the participant is obtained prior to conducting any

study-related procedure or intervention, *and* (c) the person signing the consent form is the participant or the participant's legally authorized representative. Although there are exceptions to this requirement, such as a waiver of consent, these exceptions are limited and must be approved by the IRB or Ethical Committee before the commencement of the study. Importantly, IC is not a single event or form to be signed, but an educational process that takes place between the authorized study personnel and the prospective participant. The process should include providing information in several sessions or phone calls, providing written information and allowing enough time, so that the information can be reviewed by the prospective participant. Further, sufficient time has to be allowed for questions and answers before the consent is obtained. The following are the required conditions and elements of IC:

1. Consent must be sought under circumstances that provide the participant or the legally authorized representative sufficient opportunity to consider whether or not to participate, and to minimize the possibility of coercion or undue influence.
2. Consent may not include any exculpatory language (a) through which the participant or the legally authorized representative is made to waive or appear to waive any of the participant's legal rights, or (b) which releases, or appears to release, the investigator, the Sponsor, or its agents from liability for negligence.
3. The consent must include the following elements:

   – Explicit statement that the subject is consenting to research (including prominent use of the term "research").
   – The purposes of the research, including the name of the study and who is conducting the study.
   – The description of the procedures to be followed/what will happen to the participant and the methods will be used. The ethics application must specify what other measures or stimulation methods (if any) will be employed in conjunction with tDCS. It must indicate the expected duration of the participant's involvement, including the time commitment for each component of the study and the total expected time to complete the study. If there are experimental procedures as part of the research, these must be identified.
   – Description of any reasonably foreseeable risks, AEs, SAEs, or discomforts to the participant.
   – Description of any benefits to the participant or others, which may be reasonably expected from the research.
   – Disclosure of appropriate alternative procedures or courses of treatment/therapy, if any, that might be advantageous to the participant.
   – Description of the manner and extent to which the confidentiality of records identifying the participant will be maintained.
   – Statement as to what audio or visual recording devices will be used, if any, and what will be done with such recordings upon completion of the study. The

consent form should include a separate signature line for the participant to agree to be video- or audio-taped or photographed.
- Explanation as to whether and what compensation is provided and schedule of payments.
- When appropriate, contact information and emergency contact information for the participant in the event of a research-related injury to the participant.
- When appropriate, information about the insurance during the experiments, available medical treatments for research-related injuries, payments for these treatments, and contact information for additional information about these issues.
- Name and contact information of the PI and contact persons for answers to pertinent questions by the participant about the research and his or her rights as a participant, at any time before or during the research.
- Statement that participation is voluntary, that refusal to participate will not involve any penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
- IRB and Ethic Committee contact information and statement that the participant may contact the IRB and Ethic Committee at any time with any questions or complaints.
- Statement that the participant will be given a copy of the consent form.

In the USA and in Europa the IRB or Ethical Committee has the final authority as to the content of the consent form presented to the prospective study participants and may require adding additional elements to the consent, for example if the research involves potentially vulnerable population, such as chronically ill patients, children, pregnant women and prisoners; or subjects with sensory disabilities, language barrier, or if inclusion of subjects without decisional capacity is planned. Further, the IRB and Ethical Committee have the authority to determine the way how IC will be obtained and documented. For example, they may approve obtaining verbal IC or an abbreviated written IC, but in most studies IC is obtained in written using a full length consent form.

The process of the consent must be documented in the participant's study files. As the study files are confidential and do not bear the participant's name (only an individual study participation code), the signed consent has to be kept in a separate location from the individual study files in order to maintain confidentiality.

It is mandated that no study procedures take place until the IC is obtained. Thus, screening for the full Inclusion/Exclusion criteria is carried out after obtaining the IC and those who do not fully meet the Inclusion/Exclusion criteria are noted in the study files as screen failures and discharged from the study. It is important to note that any study participant may withdraw from study at any time. In addition, participants may be removed from the study by study personnel for specified reasons. A clear criteria for removal of a participant from the study by the study personnel have to be in place, noted in written in the study protocol as well as in the text of the

informed consent. Criteria for removal from the study vary among studies, but often include the following events:

- Not following the study protocol or instructions from study personnel.
- If a SAEs or repeated AEs related or potentially related to the study procedure occurs.
- For administrative reasons, such as if the study closes.

Screening of Subjects

It is of the utmost importance that subjects or patients be carefully screened using the Inclusion/Exclusion criteria that maximize their safety during tDCS in a research or clinical protocol, as discussed above. For a study investigating the role of a brain regions in a given behavior in healthy adults would include common items, including but not limited to: absence of head injury or neurological disease, no personal or family history of seizures, a minimum age or a specific age-range for participants, no metal implanted in the head (e.g., stent, plate, metal shavings in the eye, hearing aids, etc.) or body (e.g., pacemaker, insulin pump, etc.) that could be affected or the function altered by current flow, no pregnancy, drug and alcohol abuse, no glutamatergic or GABA-ergic medications that could alter tDCS effects, no major psychiatric illness (depression, schizophrenia, etc.). However, some of these criteria will differ based on the intended application or treatment use of tDCS. For example, a depression trial would specifically target persons with a clinical diagnosis of depression, but might maintain all other criteria.

Appropriate screening methods of the population of study or treatment must use appropriate methods. For research studies in otherwise healthy populations, a detailed self-reported medical history is the typical method for acquiring this information. When using this method, it is important to stress in the consenting process or phone interview prior to consent, the importance and relevance of the screening criteria and how they can impact the person, is critical. For example, relaying how metal in the head could interact with the electrical current flow to cause damage helps to fully inform the participant of risks, should they misreport information on the self-reported medical screening. In addition, and when possible, permission to review of the person's medical records can help the researcher to cross-validate self-reported information and further enhance study/participant safety. However, the availability of medical records is not universal when working with healthy populations.

In contrast, when working in patient populations, self-report can be used, but should also be verified using medical records and/or in collaboration with the person's physician. These materials should be reviewed by a study physician and the subject should optimally be interviewed by the study physician before study entry and after they have had the opportunity to review the medical records. In clinical treatment studies, the availability of medical records will provide much of the

needed information for study screening. However, medical records are often incomplete, especially when patients use different health care systems for treatment across the lifespan (extremely common). Thus, it is also important to cross validate this information with self-reported information to identify discrepancies that deserve further investigation.

In the case of patients or participants with compromised cognitive abilities, self-report information should be obtained from the caregiver and cross-validated with medical records. Nonetheless, it is not always easy to identify compromised cognitive function, thus matching medical records to self-report from the patient/participant and the caregiver provides optimal insight into premorbid conditions or other factors that may prevent a participant from participating in a study or treatment.

Ethical Issues Related to Choosing Subject Population

Choosing a sample size For prospective research applications of tDCS, sample size calculations should be performed prior to initiation of a study using either pilot data or best available data in the literature to estimate the necessary minimum sample size for appropriate tDCS effect estimation. If a study is underpowered with no potential for appropriate effect estimation, subjects are exposed to study risks, even if minimal, without any potential for scientific benefit. However, in the absence of appropriate data, a pilot study in a small sample of subject may be used to acquire the data needed for appropriate estimation. Again, the minimum number of subjects necessary for initial effect size estimation should be used in pilot studies, minimizing any exposure to risk for the participants. Furthermore, appropriate sample size estimation is critical for avoiding an oversampling of the population and, in effect, the unethical process of "chasing a statistical p-value." As is the case with parametric statistics, a significant effect can be "found", if a study collected enough subjects. This issue highlights the importance of not only reporting test-statistics, but also measures of effect size. Simply put, if a test statistic is significant, but the effect size estimate is small (e.g., Cohen's d less than 0.2), this is an indication of a small and perhaps negligible effect of stimulation even in the presence of statistical significance. Nevertheless, the scientific aim should always be considered, e.g. with regard to clinical studies including a small number of patients for the global test comparing primary and secondary endpoints of the study among treatment groups a p value less than 0.2 indicates a possible treatment effect and warrants further studies (Kianifard and Islam 2011),

Another point of consideration is the use of appropriate statistical procedures to investigate tDCS effects. If a sample size does not allow for assumptions necessary for parametric statistics (and a normal distribution of the data is a necessary condition related to the study aim) non-parametric statistics should be used. Furthermore, general or generalized linear modeling approaches accounting for covariates of interest and non-interest are important for understanding the meaning and potential

impact of data. The use of t-tests as primary test statistics for data analyses is generally not the best choice, unless used as a planned contrast following prior appropriate statistical procedures (e.g., ANOVA, ANCOVA, multiple linear regression).

Choosing appropriate inclusion/exclusion criteria Identifying the appropriate population and selecting inclusion/exclusion criteria to minimize subject risk is an important part of the overall study design and ethical execution of a study or clinical treatment using tDCS. Inclusion/exclusion criteria will vary significantly depending on the population of interest and the applied experimental procedures. For example, while personal or family history of epilepsy would be major exclusion criteria for a study using tDCS to enhance cognitive function in older adults, it would be an inclusion criteria for a study seeking to enhance cognitive function in patients with epilepsy. Very few inclusion/exclusion criteria are universal, except for exclusion of persons with metal implanted or lodged in the head, neck or face. In the case of metal piercings or studs that cannot be removed, these persons should also be excluded from tDCS. Stimulation of persons with face tattoos that may use inks containing metals should be avoided as well. Another exclusion criteria important to consider is the exclusion of persons with implanted devices in the body that control autonomic function or perform a function that, if altered by introduction of current, could endanger the patient (e.g. pacemaker, implanted medication pump, etc). In the absence of technical and medical specialist that can verify the continued functionality of such devices during and after tDCS, these persons should be excluded from research or clinical applications of tDCS.

Other criteria important for consideration to minimize risk and maximize possible benefit include significant medical histories that may predispose a person to seizure activity. While no cases of seizure have been reported to date from tDCS, introduction of electrical current to the brain, no matter how small, requires careful consideration and minimization of risk when considering of the study outweigh the possible increased risk profile of including someone with a personal history or family history of epilepsy. Conditions related to vascular, traumatic, tumoral, infectious or metabolic lesions of the brain, even without history of seizure, administration of drugs that potentially lower seizure threshold, sleep deprivation, alcoholism should always carefully evaluated. As in the example above, it is possible that seizure history can be an inclusion criteria in a clinical study, but for most applications it is a common exclusion criteria.

Medications that can alter the impact of tDCS on brain function are yet another criteria important for consideration. For example, prior research shows that 1 mA stimulation while a person is on an selective serotonin reuptake inhibitor (SSRI) changes the typical inhibitory effects related to cathodal stimulation in the motor system to a net excitatory effect and enhances and prolongs the efficacy of anodal stimulation (Nitsche et al. 2009). Depending on the study goals (e.g., adjunctive depression treatment), this may be a desirable effect. However, in other applications where selective inhibition and excitation under different electrodes is desired (e.g., some inhibitory control paradigms), use of concurrent SSRI could have unintended consequences and change the potential benefit/risk profile for specific sub-

jects. Another careful consideration is exclusion of persons on drugs that either block NMDA receptors or GABA agonists, as these have been shown to undermine the overall neuroplastic effect of tDCS (Nitsche et al. 2004a, b). This would mean that a person may have limited to no potential benefit from tDCS in the presence of such drugs, and this would alter the benefit/risk ratio for the participant or patient, too. As dose-response relationships are relatively poorly understood in many applications of tDCS, careful consideration and caution are required to maximize safety of participants and patients.

Ethically, it is also important not to use biased inclusion/exclusion criteria, providing equitable access to tDCS studies or treatments. For example, exclusion based on gender or ethnic background must be clearly justified by the scientific aims of a study. For example, a study examining ethnic differences between analgesic tDCS response for two ethnic groups with differing pain profiles could be justified in a series of ethnicity based inclusion/exclusion criteria. In contrast, ethnic or gender-based inclusion/inclusion criteria are never acceptable for consideration of clinical treatment options of tDCS. Age of participant is another factor that must be carefully considered regarding potential for benefit vs. risk. Several studies suggest (Kessler et al. 2013; Minhas et al. 2012) that application of 'adult' tDCS protocols to children does not result in the same effects that were observed in adults. For example, application of 2 mA tDCS can produce current density much higher in the brain of an 8 year old a child versus an adult. Aside from parameter considerations, inclusion/exclusion of children should be considered very carefully relative to potential benefit vs. risk. It is entirely unknown what long-term effects of repeated applications of tDCS in a developing brain might have on the plastic development of neuronal tissue. While no negative data have been produced, no data exist to support or refute possible long-term effects. Thus, inclusion of participants that are still in a phase of neural development must be strongly justified by potential benefit to the participant. The human brain is reported to continue development in frontal regions into the mid-twenties. However, most work in tDCS has been applied to college age students participating in research studies. While the effects on a "mostly" developed brain may be negligible or even positive, there is yet again an absence of data supporting either notion. Nevertheless, here a distinction should be made between repeated stimulation sessions and a single application that does not induce a long lasting physiological change.

Ethical Considerations Related to the tDCS Implications of Involuntary or Coercive Use

As tDCS becomes more commonly applied in clinical settings, the potential for coercive use of tDCS as a treatment becomes a realistic possibility that deserves careful consideration. tDCS has been shown effective in treating a number of symptoms and disease states that have potential for impact on this issue. For example, some studies have shown efficacy in treating symptoms of schizophrenia. As such, it is possible that a psychiatrist could order treatment within a mental health facility,

as is the case with electroconvulsive therapy (ECT) or pharmaceutical treatment. It is within the purview of informed and trained clinicians to make medically relevant decisions regarding treatment of their patients when that treatment has a potential for alleviating the medical condition afflicting the patient. There is also the potential for clinicians or researchers to apply tDCS to children at the request of their parents. Prior to the age of consent within a given country, this is within the legal rights of the parents, as they are deemed best qualified to dictate the treatment of their child in collaboration with a trained and certified clinician. This is not disputed here. However, a strong word of caution is needed regarding such applications – as the long-term consequences of tDCS for developing tissue is yet undetermined. In cases where the clinician and parents deem the potential benefit to the child to outweigh unknown risks to the developmental process, these applications may be warranted. However, the quantification of unknown risk is difficult at best, similarly to many other interventions in children.

Furthermore, as tDCS is a technology that can be acquired by the community at large with little effort, yet using devices that have inferior or no device qualifications (discussed further in a following section below), there is also the possibility of tDCS being applied without consent to children by their parents, without consultation of a clinician. This is both ill-advised and unethical, as the technology's consequences are not at a stage where this process could be considered safe – due to unknown optimal dosing parameters, unknown long-term effects and risks, and increased potential for harm when using uncertified devices available to the public. At a future date where these factors are better understood, this application may become possible within an ethical space, but this is currently not the case.

Ethical Aspects of Reimbursement (and Methods How to Mitigate Coercive Effect)

It has been widely accepted that participants in research may be reimbursed for their time or discomfort, but ethical considerations are needed to mitigate coercive effect of the reimbursement. It is recommended (and in some studies required) to derive the level of reimbursement from the characteristics of each involved study procedure, such as time-demand, burden for the participant, or need for frequent travel to the research facility. It is recommended to dispense the reimbursement at time points along the study protocol (e.g. at each study visit), avoiding all-in-once payment at the beginning or end of a study, in order to avoid potential bias of "buying participants to the study" or potential coercive effect as some participants may tend to under-report AEs in order to be eligible for the reimbursement at the end of study. Importantly, the process of reimbursement must be planned and codified in the approved study protocol, and each reimbursement transaction must be documented and kept on files.

Ethics Pertaining to tDCS Procedures

Independently from the type of the study, stimulation parameters and schedules must always be chosen with clear clinical goals and safety considerations in mind and these parameters and protocols must be accepted by the IRB and Ethical Committee before initiation of a study. However, it could happen that during a given study the approved research protocol cannot be or was not followed, i.e. due to a change in a research activity. If an unanticipated or unintentional divergence from the approved protocol happens (e.g. higher intensity, longer stimulation duration was applied) it must be reported to the IRB/ Ethical Committee (usually within 7 days of their discovery). Generally, the only ethically acceptable intentional protocol deviation is when urgent action is required to eliminate an immediate hazard to a subject.

Other single occurrence deviations could occur e.g. in inclusion/exclusion criteria that are often planned exceptions in clinical studies. They should receive IRB or Ethical Committee approval before being implemented.

Like in every research and clinical application, the potential benefit of the tDCS must be found by an independent assessment to outweigh the risk. In any case, the decision on the risk-benefit ratio of a given study needs to be made by each PI and the local IRB or Ethical Committee. The requirement of equal distribution of the burdens and benefits of research can be violated when tDCS is conducted on seriously ill patients or patients made vulnerable by physical or social or conditions, bearing only its burdens. Nevertheless, in these patients alternative therapies also have significant risks (e.g. neurosurgical procedures). It is not only sufficient that the subject be willing to accept the risk involved and it is advised that the likelihood of clinical benefit must always outweigh the potential risks.

tDCS studies in patients with primary therapeutic objective, including the development of new protocols that have been not yet tested for safety, e.g. cumulative daily or weekly applications of tDCS for therapeutic purposes, has a potential resulting in direct individual clinical benefit, nevertheless with potential risk(s). Studies with indirect benefit and related moderate risk might involve patients where the potential clinical benefit is speculative or where no clinical benefit is anticipated, but the study might result in a better understanding of pathophysiological mechanisms of different disorders. Here the exposure to AEs (when clinical benefit is uncertain) for patients and many times healthy controls subjects should carefully be evaluated by the PI and the IRB or Ethical Committee.

Appropriate safety measures related to a given study must permanently be introduced. It is important to assess the subject/patient's acute condition prior to each tDCS application. Thus, participants would answer a series of questions regarding their experience with various symptoms prior to the first stimulation session, to establish a baseline. Furthermore, subjects must be continuously monitored during and after the stimulation sessions. It is advised that following each session participants should complete an Adverse Effects Questionnaire, (http://www.neurologie.uni-goettingen.de/downloads.html) which requires participants to rate of any

AEs such as local pain, tingling, burning, headaches, perception, or cognitive effects before, during and after stimulation. At the next session, they would report on these questions regarding the interval between the last stimulation to immediately before the day's stimulation session. After stimulation, they would again report on the experience during and immediately after stimulation. This approach provides the researcher or clinician to assess for AEs or changes that could warrant concern for study continuation. These questionnaires typically query participants using either a visual analog scale or a basic Likert scale that can be quickly evaluated by the researcher or clinician and quantified for further analyses. These data might also provide information important for validating effectiveness of sham versus real tDCS stimulation in both clinical and research settings.

Participants should remain in the laboratory for min. fifteen minutes after stimulation has ended. If they feel unwell, they should be seen by a medical doctor. With respect to the skin contact, there is a possibility of electrochemical production of toxins and electrode dissolution products at the electrode tissue interface that occurs very rarely, probably due to using non-suitable electrode material. Repeated applications of tDCS over several days might cause skin irritation under the electrodes in some individuals. Participants should therefore be interviewed for the existence of skin diseases and the condition of the skin under the electrodes should be inspected before and after stimulation. In the case of notable skin irritation caused in sensitive individuals it should be decided at case by case basis whether to proceed with the experiment.

Long-term negative cognitive and neuropsychological changes of single tDCS applications seem negligible. However, at least one study has suggested that using tDCS to "enhance" certain functions may impair others (Iuculano and Kadosh 2013). Therefore, neuropsychological monitoring is strongly recommended when repeated daily sessions of tDCS are administered for therapeutic purposes, or when new parameters of stimulation (e.g. higher intensities) are investigated (even in healthy subjects). Many laboratories apply physiological monitoring (TMS, EEG) of every subject undergoing new tDCS protocols. It is responsibility of the PI to decide the most appropriate tests to be applied. These additional procedures should also be approved by the IRB.

Open Questions and Gray Areas in the tDCS Ethics

There is much discussion about the difference between treatment and neuroenhancement. Where does tDCS treatment versus neuroenhancement differ? Does it matter? On the one hand, tDCS has been shown efficacious in addressing a variety of clinical issues in patient populations: depression, pain, post-stroke cognitive or motor deficits, etc. When the case of tDCS as a neuroenhancer is discussed, it is more often the situation that this refers to the use of tDCS by otherwise healthy adults or young adults in an attempt to enhance their abilities beyond their normal aptitude. In contrast, others are currently using the technique to address cognitive decline associated with the normal aging process. Thus, otherwise healthy older

adults that experience a natural decline in cognitive abilities are treated with tDCS, typically in conjunction with another therapy, such as cognitive training, to help alleviate symptoms of cognitive aging. While this case falls under the category of neuroenhancement, in many ways it also fits with examples of tDCS use that treat symptoms associated with a given disorder. To researchers who are investigating the process of aging, it is a disorder that affects all systems in the body and its preclusion may prevent the development of debilitating diseases, like Alzheimer's.

Where is the fine line between neuroenhancement and treatment? This most likely exists in the overall "intent" of the tDCS application by the user. From a simple perspective, an application to recover function (e.g., aging, stroke) is a treatment approach, whereas, an attempt to enhance function beyond baseline levels fits within the category of neuroenhancement. Does this distinction between treatment and neuroenhancement matter? In and of itself, perhaps not. However, there are caveats based on our current knowledge in the field that must be considered. From one perspective, adults attend higher education to enhance their fluid abilities beyond their current stage. This is not unethical. We take caffeine to enhance our current state of arousal to optimize performance. Thus, the simple act of neuroenhancement itself is not unethical, as it represents a fundamental component of human life and development. However, the current lack of understanding of long term consequences of tDCS and poor understanding of its effect on developing brain tissue suggests that application of this technique as a neuroenhancer may or may not have the intended consequences. Thus, while neuroenhancement in and of itself is likely not unethical by definition, its application at the current state of our understanding of tDCS deserves extreme caution. Thus, application as a neuroenhancer prior to necessary understanding of the technologies long-term consequences could be viewed as ethically questionable outside of research applications exploring impact. As the longitudinal consequences of this technology become more clearly defined, both treatment and neuroenhancement approaches will become viable avenues of use.

Ethical Aspects of Using Neuromodulation Devices Outside of Therapeutic Use

Should the ability to facilitate brain function be reserved for clinical treatment and research applications or should it be available to the community at large? There are different perspectives that are important to consider.

1. *Should we self-stimulate because we can stimulate?* There is a long human history of performing techniques or consuming substances to enhance function/performance. The use of caffeine serves as an example of self-stimulating behavior common across the world. Indeed, many people take supplements to potentially enhance health. Furthermore, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly taken without a prescription for treatment of pain.

Thus, if tDCS can provide some form of health benefit, alleviate pain, or enhance cognition, one perspective would argue that it should be available to all persons that might benefit. However, while tDCS can affect the domains from these examples, the long-term consequences remain relatively unknown. Further still, optimal dosing parameters require further study to evaluate what long-term effects tDCS might have on the brain. In fact, few studies have stimulated participants outside of a 2-week window of stimulation for 10 out of 14 days (Loo et al. 2012). E.g. Loo et al. in one study investigated 3 weeks of treatment (15 days over 3 weeks). This means that there is little to no evidence of stimulation consequences for extended long-term use. Until these data become available, a level of regulation is necessary. Thus, the absence of knowledge for long-term consequences suggests that tDCS as a self-administered neuroenhancer or treatment requires regulation for the time being.

2. *Is it safe for everyone to stimulate?* The safety profile for "enhancers" like caffeine, NSAIDs, or other supplements are quite different from tDCS. When tDCS is performed incorrectly, e.g. if the scalp is broken in any way, skin lesions and deep burns can occur. The full safety profile and contraindications for tDCS are not well explored. Any metal in the head could lead to damage to brain tissue or death, if for example a metal stent was inside the head of a person. Thus, if readily available over the counter for self-use, there is a significant potential for unintended irreversible damage to person. Counter to this, one could also argue that overuse of any of the counter example products could also lead to damage of the liver, stomach, etc. However, the quantities required for irreparable damage would be high, whereas, a single session of tDCS in a person with a metal stint could cause irreparable harm. Further still, there is a possibility for parents of children to apply tDCS to enhance classroom performance, to attempt to treat some aspect of neurodevelopmental disability or to enhance the normal developmental process. As discussed above, the consequences of tDCS for developing brain tissue in children is currently unknown (Kessler et al. 2013; Minhas et al. 2012; Woods et al. 2016). Thus, ready access for self-dosing of children by parents is ill advised and should be avoided. As the application of tDCS to a human can lead to harm in a single session (e.g. using to long stimulation duration or higher intensities) and could be misused with potential for harm in those untrained or uninformed, over the counter use/off the shelf availability of tDCS outside of research or clinical settings is not advised from safety and potential for harm perspectives.
3. *Are all tDCS devices the same?* Compared to other forms of transcranial neuromodulation, tDCS relies on devices that are relatively easy to build and therefore cheaper (e.g compared to TMS). Due to this fact, a movement arose starting in 2010–2011, in which lay persons started modifying iontophoresis devices or building tDCS devices for use on themselves, with the main aims of cognitive enhancement or self-treatment. This movement, which is known as do-it-yourself (DIY) tDCS, comprises people, who are mainly communicating online, largely using the most dedicated forum called Reddit.com. Therefore, it is not surprising that in this rapidly expanding DIY culture and based on the perceived simplicity

of the engineering principles behind creating a device capable of delivering current through two or more wires to two or more electrodes, the world market is quickly becoming flooded with individuals or companies offering tDCS devices for home-stimulation or plans for construction of such devices. Furthermore, since many direct-to-consumer brain stimulation companies, mainly in the USA and Asia do not make medical claims, they are marketing their products for enhancement and/or "wellness," and they can sell them even cheaper. However, these devices often meet none of the certified device criteria discussed in Chap. 7. Thus, these devices often fail to have mechanisms for ramping current, methods for maintaining a controlled and constant current at a safe level of intensity (e.g., preventing surges/spikes in electrical current that could increase chance of burns or other harmful effects), or other features that maximize the safety of the person receiving tDCS or the DIY user (Woods et al. 2016). Through a simple internet search, one can find 9-volt batteries soldered to wires ending in bare wires or gator clips, intended to be clamped or inserted into the top of kitchen sponges or some other porous material. This should not be considered a tDCS device, as it fails to meet even the most basic safety criteria or necessary precision required for current delivery in tDCS. While such a device has limited risk of current spikes, there are in fact numerous aspects of such a device that can drastically increase the opportunity for burns by such a device (e.g., metal to skin contact, inconsistent electrode material, no ability to deliver a controlled and constant current with ramping safety features, etc.). Ethically, these devices do little to nothing to minimize the safety risks of the person being stimulated and should be avoided. Again, based on the perspective of safety, as well as the necessary engineering principles required to maintain safety, there is at least a minimum level of regulation necessary for devices made available to the public.

Conclusions

The aim of this chapter was to provide an overview of the present ethical issues associated with the scientific and therapeutic use of tDCS. Overall, the perspectives of knowledge and safety suggest that tDCS is ethically ready for supervised research and clinical applications but not for mass availability for DIY application/self/home administration. From an engineering perspective, once the devices are available, there is a minimum level of features and criteria necessary for device safety, meaning that at least a minimum level of regulation is suggested. The former argument is likely a matter of scientific and clinical research over time, while the latter is already well explored. Once the science of tDCS and our understanding of dosing and long-term consequences equal our understanding of the engineering principles behind tDCS, this is a technology that may well be suited to ready availability across the world market. Nevertheless, until this point several critical ethical issues should also be clarified, including e.g. the possible interaction with behavior by tDCS, such as impulsivity, risk taking behaviour (Cheng and Lee 2016; Fecteau et al. 2013).

Indeed, many commonly used psychiatric drugs could theoretically be understood as "personality" modifiers, nevertheless, the regulation of medical treatments using drugs have a long history and generally, the intake of these medications is relatively good regulated. Other important point is whether tDCS-induced enhancement can or should be accepted for educational purposes or not. At present, we have not reached this stage, and it is ethically questionable to make such technologies available to the public before the risks associated with their long-term use or application in vulnerable populations is understood.

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