HHS Public Access

Author manuscript

Clin Neurophysiol. Author manuscript; available in PMC 2018 June 04.

Published in final edited form as:

Clin Neurophysiol. 2017 September ; 128(9): 1774–1809. doi:10.1016/j.clinph.2017.06.001.

Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines

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Abstract

Low intensity transcranial electrical stimulation (TES) in humans, encompassing transcranial direct current (tDCS), transcutaneous spinal Direct Current Stimulation (tsDCS), transcranial alternating current (tACS), and transcranial random noise (tRNS) stimulation or their combinations, appears to be safe. No serious adverse events (SAEs) have been reported so far in over 18,000 sessions administered to healthy subjects, neurological and psychiatric patients, as summarized here. Moderate adverse events (AEs), as defined by the necessity to intervene, are rare, and include skin burns with tDCS due to suboptimal electrode-skin contact. Very rarely mania or hypomania was induced in patients with depression (11 documented cases), yet a causal relationship is difficult to prove because of the low incidence rate and limited numbers of subjects in controlled trials. Mild AEs (MAEs) include headache and fatigue following stimulation as well as prickling and burning sensations occurring during tDCS at peak-to-baseline intensities of 1–2 mA and during tACS at higher peak-to-peak intensities above 2 mA.

The prevalence of published AEs is different in studies specifically assessing AEs vs. those not assessing them, being higher in the former. AEs are frequently reported by individuals receiving placebo stimulation. The profile of AEs in terms of frequency, magnitude and type is comparable in healthy and clinical populations, and this is also the case for more vulnerable populations, such as children, elderly persons, or pregnant women. Combined interventions (e.g., co-application of drugs, electrophysiological measurements, neuroimaging) were not associated with further safety issues.

Safety is established for low-intensity 'conventional' TES defined as <4 mA, up to 60 min duration per day. Animal studies and modeling evidence indicate that brain injury could occur at predicted current densities in the brain of 6.3–13 A/m^2 that are over an order of magnitude above those produced by tDCS in humans. Using AC stimulation fewer AEs were reported compared to DC. In specific paradigms with amplitudes of up to 10 mA, frequencies in the kHz range appear to be safe.

In this paper we provide structured interviews and recommend their use in future controlled studies, in particular when trying to extend the parameters applied. We also discuss recent regulatory issues, reporting practices and ethical issues. These recommendations achieved consensus in a meeting, which took place in Göttingen, Germany, on September 6–7, 2016 and were refined thereafter by email correspondence.

Keywords

tDCS; tACS; TES; Safety; Adverse events

1. Introduction

The aim of this review is to update the safety of low-intensity electric stimulation based on available published research and clinical data in animal models and in human studies until the end of 2016. The essentials of the present manuscript were agreed upon at a two-day safety conference held in Göttingen, Germany on 6–7th September, 2016. Participants included research and clinical experts from neurophysiology, neurology, cognitive neuroscience and psychiatry. Representatives of transcranial electrical stimulation (TES) equipment manufacturers contributed to regulatory issues.

For the purposes of this review, data from published articles that encompassed more than 18,000 stimulation sessions in ~8000 subjects, according to a recent review (Bikson et al., 2016), using low intensity stimulation (<4 mA; see definitions below) up to 60 min duration/day were included. Literature searches investigated by experts on the related fields covered studies using transcranial direct current stimulation (tDCS), alternating current stimulation (tACS) and random noise stimulation (tRNS), with key words Adverse Events (AE) or Reactions (AR) and/or safety (see definitions below), in order to assess stimulation-related risks and to better understand of the risk-benefit ratio of these procedures. We relied on summarizing and interpreting data on (1) available animal studies, (2) computational modeling and (3) testing in human trials, including reports on healthy subjects, patients and on theoretically vulnerable populations, such as children, elderly and pregnant women. With

regard to animal data the main effort was devoted to understanding the translation of findings to human applications (e.g., the relationship of dose of the stimulation and safety). Concerning patients, only the most frequently investigated clinical groups were included (major depression, chronic pain and stroke), because of lack of data in other populations. Special stimulation conditions that are increasingly used during the last years, e.g., combination of TES with other methods, such as stimulating patients with intracranial implants, combination of TES with transcranial magnetic stimulation (TMS) or functional magnetic resonance imaging (fMRI), as well as “do it yourself” use of TES for neuro-enhancement purposes, were also considered, because of the theoretical increased risk in these conditions. Furthermore, other stimulation settings than ‘transcranial’, in which recent safety data are available, were also integrated (e.g., using transcutaneous spinal direct current stimulation (tsDCS) and applying optic nerve stimulation (ONS)).

In general, human studies that evaluate parameters of neuronal damage, such as neuron specific enolase (NSE), magnetic resonance imaging (MRI) (Nitsche et al., 2004), electroencephalography (EEG), and neuropsychological tests (Iyer et al., 2005; Tadini et al., 2011) support the safety of tDCS. However, it is also important to underscore the fact that the safety of low intensity TES is mostly derived from an analysis of secondary outcomes in TES clinical trials assessing efficacy as the primary outcome.

In this paper, we first provide an overview of the technical parameters and basic principles of low intensity TES used alone or combined with other methods, safety aspects of the stimulation with a summary of the published AEs in healthy subjects and different patient populations. The presumed mechanisms of TES and the efficacy of TES in eliciting desired outcomes are not relevant for the scope of this review except for instances, in which they inform about safety. Other stimulation methods that are applying specific (brand) waveforms or conditions, such as cranial electrical stimulation (CES) are also not incorporated here, but have been comprehensively reviewed by other authors (Mindes et al., 2015). We also present recent regulatory issues and recommend rules for reporting in research and clinical practice, and finally we summarize existing data and provide recommendations for future safety monitoring. Consensus with regard to the definitions, recommendations, etc. were reached by using a modified Delphi method, in this case a structured interactive communication technique (Kleymeyer, 1976). The experts first summarized safety data related to their fields and answered questions in more rounds. The key results were presented and discussed in Göttingen at the meeting. After that the experts were encouraged to support or revise their earlier answers in light of the replies of other members of the panel and in response to reviewers’ critiques.

1.1. Basic aspects: nomenclature and explanations

We adopt suggested definitions as already published (e.g., Bikson et al., 2016; Woods et al., 2016) except that we chose the term “burden” instead of “tolerability” in accordance with the Declaration of Helsinki (1964) (Last revision 2013). The following terms are used in this paper:

Low intensity TES: This is defined as intensities <4 mA, a total stimulation duration of up to 60 min per day, and using electrode sizes between 1 cm^2 and 100 cm^2 (delivering ≤7.2

coulombs of charge) (Bikson et al., 2016) to apply frequencies between 0 and 10,000 Hz. The intensity of tDCS is always defined as peak-to-baseline, while with tACS peak-to-baseline or peak-to-peak intensities can be used. The type of current is direct current or bipolar alternating current (Guleyupoglu et al., 2013).

Safety can probably only be considered in relative terms. According to the definition of the European Medical Device Directive, 'safe' is a condition where all risks are accepted risks (Annex I; § I. General Requirements). However, all stimulation protocols carry a certain degree of risk and could cause problems in specific circumstances. Many problems cannot be detected until extensive research or clinical experience is gained. The current approach in this field is to estimate the potential of a protocol becoming a hazard that could result in safety problems (e.g., using too high intensities or too long durations of stimulation). Hazard is a potential for an AE. Risk is a measure of the combination of the hazard, the likelihood of occurrence of the AE and the severity (Altenstetter, 2003; McAllister and Jeswiet, 2003) (See also: http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf). The conclusion that a procedure is safe is based on a comprehensive and unbiased documentation of all AEs in relation to the frequency of application of the procedure. Risk must be differentiated from burden, a procedure may be burdensome (e.g., produce much discomfort) but nevertheless safe (e.g., not having any relevant risk for permanent damage).

Generally and according to the Common Terminology Criteria for **Adverse Events** (AEs) (https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_5x7_Locked.pdf), AEs are undesirable, uncomfortable or harmful effects that are observed after a medical intervention that may or may not be causally related to it. Here, we prefer the term AE to the term **Side Effect** (SE), which is frequently employed synonymously to describe AEs. A SE should be a consequence different than the intended effect, and might be good or bad (beneficial or adverse). An example of a good SE might be an improvement of memory by an intervention for depression. An AE is by definition always bad. In the context of the present paper the term SE will not be used in accordance with recommendations in the ICH guidelines (Baber, 1994; Food and Drug Administration, 2011). According to this classification, a **mild AE** (MAEs – grade 1) is defined as involving mild symptoms for which no medical treatment is necessary (i.e. skin redness or tingling during tDCS), while a **moderate AE** (grade 2) indicates the need of local or noninvasive treatment (e.g., in the case of TES, the local application of a cream after a skin burn). **Serious AEs** (grade 3) (SAE) are severe or medically significant but not immediately life-threatening events, include the requirement for inpatient hospitalization or prolongation of hospitalization. ***Life threatening SAEs*** include any event that may be life threatening (grade 4) or death from the AE (grade 5).

Suspected Adverse Reaction (AR) means any AE for which there is a reasonable possibility (causality is probable, likely or certain) that the intervention caused the AE (Baber, 1994; Food and Drug Administration, 2011). The distinction between AE and AR is not always clear, first because causality often cannot be proven unambiguously, and second because some effects (e.g., sedation) may be in some instances good but in other instances bad for the patient. Another point to be considered is unexpectedness. An AE or suspected AE is generally considered unexpected if it is not listed in the information brochure or is not

listed at the specificity or severity level that has been observed or it is not consistent with the risk information described in the investigational plan (FDA regulations, 21CFR312.32, safety reporting). Unexpected ARs require particular attention because their correlation with the procedure may be neglected. If for example, someone is treated using tDCS and is hit by a car an hour later, this is usually not considered as AR. However, if it is due to sedation and cognitive impairment it may indeed be an AR. Corresponding to the definitions above, mild, moderate and severe ARs may be defined. **The risk-benefit ratio** is the overall ratio of all potential benefits of a procedure divided by all the ARs of a procedure. Usually, a procedure is only acceptable if the beneficial effects outweigh the risks.

2. Assumptions regarding dose-response relationship, animal studies

TES dose is defined by all of the parameters of the stimulation device that affect the generated electric field (EF) in the body with units of V/m (or, equivalently, mV/mm) (Peterchev et al., 2012). This includes the parameters of the electrode montage (skin contact area), the waveform applied to the electrodes and at the case of tACS, the stimulation frequency.

The parameters delivered by the stimulation equipment are well defined and reproducible, while other influencing factors are not (e.g., individual tissue properties and anatomy, age, gender, baseline neurotransmitter concentrations, genetics, dynamic state of the brain before and during stimulation) or only barely controllable. Nevertheless, they shape the physiological responses to the stimulation and should therefore be considered along with the dose selection. Due to the high individual variability of these factors the electrical stimulation dose cannot fully determine the magnitude of the physiological or therapeutic outcome since it cannot be guaranteed that given the same doses the outcomes of stimulation will be the same. Furthermore, the indirect effects of TES, e.g., afferent low threshold stimulation of peripheral nerves, cranial nerves and retina cannot be avoided and can lead to neuro-modulatory effects of their own or in conjunction with brain stimulation. This presents a challenge to researchers and clinicians when finding the ‘optimal’ dose for a given application. Unfortunately, due to these uncontrollable factors and additional putative mechanisms that are initiated during stimulation (activation of glial cells, vasodilation, changes in blood-barrier permeability, etc.), the current state of knowledge of the physiological mechanisms of TES remains limited. At present, in most studies the dose is chosen based on previously published data, prior clinical experience, individual measures such as thresholds, computational models, summary metrics (including all parameters: intensity, electrode size, stimulation duration) and safety considerations based on human and animal experimental data.

In vivo, the dosage induced by tDCS may, in a first approximation, be the EF as described by the charge density, given as (current [A] * stimulation duration [s])/electrode contact size [m^2]). However, the relation of this to EF or time integrated EF on the cortex is not simple and certainly not linear (Miranda et al., 2009; Ruffini et al., 2013a). In humans, tDCS with approximately 1 mA using standard contact electrodes (sizes between 16 and 35 cm^2) results in charge densities ranging from 170 to 480 C/m^2 (Liebetanz et al., 2009). In animal experiments, much higher charge densities, sometimes exceeding the doses in human low

intensity TES studies by several orders of magnitude, have been applied. In an animal study, safety limits were determined histologically by applying DC of increasing intensities directly to the rat cortex using an epicranial wet electrode (Liebetanz et al., 2009). At current densities between 14.3 and 28.7 mA/cm^2, corresponding to a charge density threshold below 52,400 C/m^2, no histologically detectable brain lesions were induced. In a histology-based (hematoxylin & eosin staining) study, safety limits were determined by applying increasingly powerful tDCS regimes through an open epicranial wet electrode (Liebetanz et al., 2009). Combined with updated safety data in rats, this threshold approximation obtained from the rat experiments was estimated to be over one order of magnitude higher compared to current clinical protocols (Bikson et al., 2016). But many uncertainties in the translation of animal studies to human experiments remain.

3. Interaction of EF with tissue, electroporation, galvanotaxis

A variety of montages ranging from two large, pad electrodes to arrays of smaller electrodes are used for tDCS (Alam et al., 2016) with a typical current of 1–2 mA (0.03–2 mA/cm^2 current to electrode area ratios depending on the electrode size); this results in cortical EF strengths of up to 0.4–0.8 V/m (Ruffini et al., 2013b) with typical durations of 10–30 min. Both the applied current and the resulting brain EFs are ~1000-fold lower than those for pulsed stimulation used for electroconvulsive therapy (ECT) (Alam et al., 2016). These small EFs are considered to be below the intensity required to evoke action potentials in a resting cell (Radman et al., 2009), but likely modify spontaneous firing rates and ongoing processes such as plasticity that are sensitive to polarization levels (Fritsch et al., 2010; Jackson et al., 2016; Ranieri et al., 2012), and over time may induce molecular or structural changes. Indeed, neuronal network activity generates its own endogenous EFs in brain extracellular spaces and these, in turn, influence network firing (Frohlich and McCormick, 2010). The measured field strength in the ferret visual cortex was around 2–4 V/m and altered the neuronal transmembrane potential (Vmem) by 0.5 and 1.3 mV, respectively (Frohlich and McCormick, 2010).

Many developing and regenerating tissues generate steady electrical gradients, and many cell types respond to these signals with directed migration, enhanced migration rates and regulated proliferation and differentiation. This migration is termed galvanotaxis and occurs at physiological field strengths of 5–150 mV/mm. With very long stimulation duration, galvanotaxis may play a role in the safety of tDCS. The mechanisms that drive cell migration in an EF include induced asymmetries of electrically charged membrane proteins and local activation of downstream signaling pathways, e.g., the neuronal nicotinic ACh receptor in nerve growth cones coupled to cAMP signaling, and the EGF receptor at the leading edge of corneal epithelial cells coupled to ERK1/2 and PI3K signaling (McCaig et al., 2005). Recent additions to this array of molecular players include ATP and the P2Y1 receptor, which transduce the EF into cathodal neuronal migration. The concept involves EF-induced neuronal ATP release and autocrine feedback on its own asymmetrically distributed receptors (Cao et al., 2015), a concept first raised for ACh in neuronal growth cones (Erskine and McCaig, 1995).

The brain microenvironment modulates migration. Keratinocyte fragments migrate anodally and intact parent cells cathodally. Anodal migration is myosin II dependent, whilst the PI3kinase pathway underpins cathodal cell migration (Sun et al., 2013). In cytoskeletal terms, the Arp2/3 complex is required for oligodendrocyte precursors to migrate cathodally (Li et al., 2015). Glioblastoma cells migrate anodally in 2D culture, but switch to cathodal migration in 3D hyaluronic acid plus collagen cultures. Myosin II is not needed for the 2D anodal migration, but is required for 3D cathodal migration. By contrast, PI3kinase regulates the 2D anodal response (Huang et al., 2016).

Hypoxia enhances galvanotaxis of mouse keratinocytes, which is important in wound healing (Guo et al., 2015). Hypoxia is likely not to be present in the healthy brain but it may play a specific role in acute stroke. DC stimulation markedly increases tissue oxygen consumption (Pulgar, 2015), so galvanotaxis could theoretically be enhanced, or its threshold reduced in brain regions that are excessively stimulated by tDCS. Besides this, hypoxia can stimulate stem cell differentiation, and tDCS of regions containing neural or cancer stem cells, such as glioblastomas, may raise specific problems (Bath et al., 2013; Guo et al., 2015). However, at the present stage it is unclear if this needs specific considerations in terms of safety aspects, since longer stimulation durations and intensities higher than those applicable in human tDCS usually have be used for the effects reported in animal studies.

Finally, several studies found that glia cells are involved in the mechanisms underlying tDCS (Gellner et al., 2016; Monai et al., 2016; Ruohonen and Karhu, 2012). Rat cortical astrocytes migrate anodally and show increased proliferation in an EF of 40 mV/mm (Baer et al., 2015). Nerves and Schwann cells have a galvanotaxis threshold of ca. 5 mV/mm (McCaig et al., 2005), which is close to the field generated by tDCS (~1 mV/mm). However, tDCS does not induce directed migration of labeled neural stem cells transplanted into the rat brain (Keuters et al., 2015).

At much higher EF strengths, pulses of DC stimulation have been used for electroporation to create nanopores in the plasma membrane to deliver chemotherapeutic drugs or gene therapies intracellularly, to sterilize foodstuffs and to ablate tumor tissue. Irreversible electroporation (IRE) uses DC short pulses of high voltage 3000 V and 50 A current delivered to a target volume of around 50–70 mm^3. This gives rise to EFs of around 8000 V/m, which are about 1000 times stronger than the endogenous, steady DC EFs that drive galvanotaxis. IRE uses msec pulses, is minimally invasive and carried out under visual control using CT or MRI imaging. Tumor ablation requires ~100 pulses and these are delivered between heartbeats to avoid arrhythmias. This non-thermal technique has also been used to ablate tumors in pancreas, lung, kidney, gastrointestinal tract, brain, breast, cervix, prostate and sarcomas (Lu et al., 2013; Paiella et al., 2015; Ting et al., 2016).

Conclusions and recommendations: Although with very long stimulation and much higher intensity than in currently applied approaches galvanotaxis may possibly play a role in tDCS, there is yet no conclusive *in vivo* evidence in either animal models or humans whether any cells close to the stimulation site have migrated away from or toward the electrodes, therefore, more research is needed in this field. While studies on electroporation

have shown additive effects of pulsed DC electrical fields, the intensities needed for electroporation remain orders of magnitude above tDCS. Furthermore, the relative sensitivity of cell types (neurons, astrocytes, endothelial cells, etc.) have not been well studied either.

3.1. TES and tissue inflammation

Inflammation in the central nervous system (CNS), i.e., neuroinflammation, is mediated by both brain-resident microglia and invading blood-borne immune cells. Neuroinflammation plays a pathophysiological role not only in classic neuroimmunological diseases, but also in various other neurological disorders such as stroke (Le Thuc et al., 2015) and traumatic brain injury (Loane and Kumar, 2016), as well as in neurodegenerative diseases such as Parkinson's disease (PD) (Tansey and Goldberg, 2010) and Alz-heimer's disease (AD) (Heneka et al., 2015).

DC fields affect the alignment and migration of various cultured immune cells (Pelletier and Cicchetti, 2014). Resting murine BV2 microglia cells change their morphology in the EF at 100 V/m and adopt an activated phenotype (Pelletier et al., 2014). Of note, activated BV2 microglia cells do not respond to high-voltage EFs (50–100 V/m) in the same way as resting microglia, but rather react with a decrease in their viability (Pelletier et al., 2014).

Anodal tDCS with 4 kC/m^2, a charge density about 10 times higher than a regular human dose, down-regulates inflammatory mediators in the hippocampus of rats subjected to chronic, stress-induced pain (Spezia Adachi et al., 2012). Likewise, anodal tDCS with a charge density of 99 kC/m^2 – about 200 times higher than a regular human dose – decreases the number of activated microglia in the healthy mouse brain (Pikhovych et al., 2016). In contrast, electric stimulation with an even higher charge densities may up-regulate inflammatory processes (Rueger et al., 2012), suggesting that higher charge densities may induce subtle tissue damage and trigger an inflammatory response.

TES could enhance functional recovery after stroke and considering the potentially beneficial effects in the sub-acute phase after cerebral ischemia (Floel and Cohen, 2010), this could be consistent with the time line of post-ischemic neuroinflammatory processes (Dirnagl et al., 1999). Cathodal tDCS at ~66 kC/m^2 – around 200 times higher than a regular human dose – applied after focal cerebral ischemia in mice reduces activated microglia in the peri-infarct cortex as well as infiltrating mononuclear cells and neutrophils in both peri-infarct cortex and striatum (Peruzzotti-Jametti et al., 2013). Multi-session cathodal tDCS applied for ten consecutive days after stroke in the rat accelerates recovery of function and a shift in microglia polarization (Braun et al., 2016). However, all of these studies were conducted in young rodents in contrast to the older human stroke population. Moreover, chronic neuroinflammatory processes may go on for even 6–12 months or longer after a stroke (Walberer et al., 2014).

Conclusions and recommendations: Current data suggest that both anti-inflammatory and pro-inflammatory effects of TES depend on pre-existing inflammation and TES current density. TES seems to not only affect activation levels of brain-resident and invading immune cells, but also alter their specific phenotype and polarization. However, current

research in animals used between 4 and 200 kC/m^2 charge densities, which is about 10–500 times higher than levels of tDCS given in humans so far (Liebetanz et al., 2009). For currently applied protocols, there are no hints for neuroinflammations in human studies. So far, tDCS studies did not intend to address long-term chronic neuroinflammatory processes, but rather focused on transient neuroinflammatory response, such as occurring in the sub-acute phase after stroke, or were geared toward promoting neuroplastic processes or cortical excitability changes. More research is needed in this field and the interpretation in term of "changes in neuroinflammation" should be treated with caution.

4. Modeling (heating, induced voltages)

Computational models of current flow relate tDCS surface dose with subject-specific brain current density (Peterchev et al., 2012; Ruffini et al., 2014; Truong et al., 2013). The precision of the prediction depends on the accuracy of the model (not simply the com plexity; (Bikson and Datta, 2012). For a given electrode montage, increasing the current results in a proportional increase in the EF throughout the head – such that, for any given montage, 2 mA will produce an EF in each brain region double that with 1 mA. The local tissue current density is equal to the EF multiplied by the tissue's conductivity, and thus follows the above dose-response rule for the EF. Because current density is predicted to be much higher in the skin than in the brain, and assuming equal sensitivity to injury of skin and brain, lack of skin injury may indirectly support the claim that the brain current flow is safe (Bikson et al., 2016; Faria et al., 2011; Saturnino et al., 2015).

All models predict that the EF in the cortex is strongly affected by the complex arrangement of its folds and by the electrode montage (e.g., Datta et al., 2009a; Miranda et al., 2013; Opitz et al., 2015; Parazzini et al., 2011; Sadleir et al., 2010; Salvador et al., 2010; Wagner et al., 2014a). The EF generally decreases with distance from the electrodes but is non-uniform, with hotspots on the crowns of the gyri that lie between and close to the electrodes, and at the bottom of sulci under the electrodes (Fig. 1). Computational approaches are available to calculate maximal current densities in any area in the brain with a defined stimulation parameter space (Bortoletto et al., 2016; Lee et al., 2016; Seibt et al., 2015; Wagner et al., 2016).

Changes in individual EF distribution can also be calculated in the presence of skull defects or skull plates (Datta et al., 2010), in stroke patients with large defects filled by CSF (Datta et al., 2011) and in children with thinner skulls (Gillick et al., 2014; Kessler et al., 2013; Parazzini et al., 2015). For typical bipolar montages, and in the absence of skull defects or brain lesions, the values predicted for the maximum EF strength in the cortex of realistic head models often fall between 0.2 and 0.5 V/m using 1 mA (e.g., Datta et al., 2009a; Metwally et al., 2015; Miranda et al., 2013; Parazzini et al., 2017; Rampersad et al., 2014; Saturnino et al., 2015; Shahid et al., 2013). The maximal value so far reported by some investigators in a normal brain is 1.6 V/m and can be attributed to the conductivity values used in this particular model (Parazzini et al., 2011). Anatomical variations can have a substantial impact on field strength (Datta et al., 2012; Kessler et al., 2013; Laakso et al., 2015; Truong et al., 2013) and may lead to variations by a factor of 2 or more for a fixed stimulation intensity. Predicted EF strengths of about 0.4 V/m in the cortex are in good

agreement with data obtained in epilepsy patients with EF strengths of 0.6–1.6 V/m per 1 mA (Dymond et al., 1975), and ≤0.5 V/m per 1 mA (Opitz et al., 2016). These EFs may be sufficient to modulate neuronal network activity in hippocampal slices (~0.3 V/m, Francis et al., 2003), or to induce entrainment at low frequencies in neocortical slices (~0.7 V/m, Anastassiou et al., 2011). They are slightly lower than the endogenous EFs measured in the ferret's neocortex (~3 V/m, Frohlich and McCormick, 2010).

The EF strength and its spatial distribution in tACS are expected to be similar to that observed with tDCS. It remains unclear whether the high electric permittivity of brain tissues can significantly affect the strength of the EF in the brain and shift the phase of the sinusoidal waves, in particular with higher frequencies (Logothetis et al., 2007; Opitz et al., 2016; Wagner et al., 2014b). Montages with (multiple) small electrodes do not affect the maximal V/m range with respect to safety considerations (Dmochowski et al., 2011, 2013; Edwards et al., 2013; Ruffini et al., 2014; Sadleir et al., 2012). Because electric current is conducted about 10 times better tangentially along a fiber than perpendicular to it, computational models can take fiber orientation into account by calculating on the basis of diffusion tensor image data in the MRI (e.g., free shareware www.simnibs.de) (Metwally et al., 2012; Opitz et al., 2015; Shahid et al., 2013, 2014).

Heating of the brain during tDCS is considered to be insignificant. For a current of 1 mA, and assuming an EF strength of 0.5 V/m and a conductivity of 0.4 S/m, the power dissipated in the cortex would be about 0.1 mW/kg, which is 5 orders of magnitude less than the metabolic heat production rate in the brain, which is about 11 W/kg (Nelson and Nunneley, 1998). Assuming that the resistance of the extracranial tissue between the two electrodes is about 300 Ω, then the total power dissipated in the whole head would be 0.3 mW. In practice, the resistance between the two electrodes is more likely to be around 10 kΩ due to the contact impedance at the electrode-skin interfaces. In this case, the total power would be 10 mW, dissipated almost entirely in the scalp under the electrode edges. In agreement with these considerations, Datta et al. (2009b) predicts no significant temperature increase ($\Delta T <$ 0.003 °C) in the brain or in the scalp for conventional or multichannel tDCS montage for current intensities currently employed. Using multichannel tDCS, several brain regions are targeted in parallel using e.g., arrays of small electrodes on the scalp.

Conclusions and recommendations: Current flow calculation models allow a reasonable estimation of the electric field and current density, including in deep brain areas. Models also allow the design of new montages including electrode arrays. Therefore, EF modeling for targeting predefined areas for stimulation can be helpful. The main potential strength of modeling lies in subject-specific current optimization, which may lead to more reproducible results across individuals and increased safety.

5. Electrode design for TES

A bipolar electrode configuration is the minimal requirement and customarily used for tDCS, with one target electrode placed over the site of the desired cortical stimulation and one remote "return" electrode (but see: Bikson et al., 2010). The return electrode may be placed on the scalp (the most frequently used site), concentrically around the target electrode

(Laplacian montage) (Bortoletto et al., 2016; Datta et al., 2009a), extracephalically (e.g., Moliadze et al., 2010; Schambra et al., 2011) or distributed over several sites (Faria et al., 2009).

These electrodes are typically made of conducting materials, some using plastic such as conductive (filled) silicone, while others are metal, usually non-polarizable silver/silver chloride (Ag/AgCl) (Faria et al., 2012; Minhas et al., 2010). The size of the electrode contact area (which for tDCS/tACS is defined as the electrolyte/skin interface) ranges between about 1 cm^2 and up to about 100 cm^2 (Bortoletto et al., 2016; Ho et al., 2016; Kronberg and Bikson, 2012; Nitsche et al., 2007a). Target and return electrode may be differentiated by size and thus current density, but for bipolar montages the total current is equal across electrodes. Neurophysiological studies indicate that smaller electrodes produce more targeted outcomes while larger electrodes decrease the current density below a given stimulation threshold, such that tDCS no longer has a physiological effect (Nitsche et al., 2007a). Imaging and modeling suggest that electrode placement may play a more significant role than size (Faria et al., 2011).

A recent study has compared scalp sensations using the classical bipolar and HD-tDCS montages over the prefrontal cortex using 1 mA for 20 min (Hill et al., 2017). Stronger sensations were reported after 5 min of stimulation with HD-tDCS compared to either bipolar tDCS or sham tDCS, and this is likely due to the higher current densities produced with this montage using smaller electrodes. After 15 min of stimulation, sensations did not differ between the three conditions and participants were not able to guess at a level better than chance, which type of stimulation they had received.

Conclusions and recommendations: A multitude of possible electrode placements, using either bipolar montage or arrays, permit shaping current flow patterns through the head or targeted stimulation of cortical areas. From available data, no specific safety issues apply for different electrode designs used in tDCS studies. There is no evidence for brain injury following conventional tDCS and multichannel-tDCS protocols. The low to moderate scalp sensation ratings documented in these studies indicate a good overall level of stimulation tolerability provided proper electrode design, preparation, and conventional dose guidance are followed (Woods et al., 2016). For extended protocols (higher intensities, longer duration), a rationale should be given, and it would be advantageous to gather safety information systematically for these protocols before extensive human applications (Bikson et al., 2016).

5.1. Electrochemistry of electrodes

The electrode acts as a transducer between the electron currents in the technical system (stimulator) and the ion currents in the biological system (body). Current can be transmitted across the electrode/electrolyte interface by capacitive charging of the Helmholtz double layer or by electrochemical (faradaic) reactions (Cogan, 2008). Even with large electrodes and thus very low charge densities, one cannot inject a DC of 1–2 mA over a period of several minutes by capacitive charging alone. For instance, the Helmholtz double layer of a 6 cm^2 electrode has a capacitance of ca. 120 μF (Kronberg and Bikson, 2012). To charge such a capacitance with a constant current of 1 mA for 15 min would require a voltage of up

to 7500 V (1 mA * 15 min/120 μF). The Helmholtz double layer reaction is not associated with any transfer of charge carriers across the interface, but results in an increase in the electrode potential (overpotential), which may cause the onset of unwanted electrochemical reactions such as gas formation by hydrolysis. This is of importance in implanted systems such as cochlear or retinal implants, where the net electrochemical reactions at the electrode interface must be kept at an absolute minimum in order to avoid hydrolysis and electrode corrosion (Merrill et al., 2005). For this reason, invasive neural stimulation is usually performed with very short (60–1000 μs, Howell et al., 2015), charge-balanced, biphasic pulses, in which a cathodic pulse that induces the desired neural stimulation is followed by an anodic pulse to reverse the electrochemical reactions. The charge injection capacity is defined as the maximum charge per pulse and electrode area that can be “safely” injected with an electrode without inducing irreversible electrochemical reactions that would cause electrode corrosion and/or tissue damage. It is mainly dependent on the electrode material and can reach values of several mC/cm^2 for materials such as iridium oxide or conductive polymers (Cogan, 2008). Since the capacitive charging is limited to about 20 $\mu F/cm^2$ (Merrill et al., 2005), and since in transcranial stimulation larger current densities are usually required, capacitive charging of the Helmholtz double layer does not play a major role.

Biphasic sinusoidal pulse currents are mostly used for tACS. Due to the large electrode areas in transcranial applications, the applied charge densities are low (<100 $\mu A/cm^2$), resulting in an injected charge density of less than 1 $\mu C/cm^2$ per phase (Woods et al., 2016). No irreversible electrochemical products are known to accumulate at the electrode with such low current densities, although the effective phase (“pulse”) duration during low-frequency tACS (e.g., 1 Hz tACS has a 500 mS phase duration) is much longer and increases the possibility of irreversible reactions. Sinusoidal stimulation is thus not used for implants. The electrodes used for tACS are adapted from tDCS and, hence, provide the same compensation for any potential electrochemical changes. tRNS is not considered here in detail but the use of high-rate charge-balanced pulsing would minimize concerns about electro chemical changes (Merrill et al., 2005), and tRNS seems relatively well tolerated by subjects (Ambrus et al., 2010; Curado et al., 2016; Terney et al., 2008).

In the case of tDCS, current across the interface is unidirectional, of course, and neural stimulation paradigms such as the above mentioned charge injection capacity (Cogan, 2008; Merrill et al., 2005) can therefore not be safely transferred directly to this type of stimulation. The use of DC for stimulation does not allow for reversal of electrochemical reactions during stimulation, but effects such as corrosion and hydrolysis at the electrode may not have as severe consequences for the patient as with implantable stimulators. The essential aspect of electrodes used for tDCS (and tACS) is that metal or conductive rubber where electrochemical reactions may occur are not placed directly on the skin; an electrolyte (saline of gel) always separates the two (Minhas et al., 2010). Therefore, in TES, the current is mainly injected by faradaic reactions but the products of these reactions are kept away from the skin. Conductive rubber electrodes are convenient for macro tDCS/tACS as they are flexible and can be inserted into a saline soaked sponge “pocket”. As an alternative, especially when smaller electrodes are used (e.g., for multichannel stimulation), Ag/AgCl electrodes are well suited due to their non-polarizable character, i.e., their low faradaic resistance results in almost no capacitive charging of the double layer (Merrill et al., 2005).

This keeps the electrode potential constant, preventing unwanted faradaic reactions such as gas formation. The reaction mainly responsible for charge transmission at the Ag/AgCl electrode is the formation of AgCl by dissolution and oxidation of solid silver at the anode, and the formation of solid silver by decomposition of AgCl along with a reduction of silver ions at the cathode (Merrill et al., 2005; Minhas et al., 2010). The formation of AgCl requires a suffi-cient amount of free chloride ions in the vicinity of the electrode, which is provided by the electrode gel applied between the electrode and the skin. For this reason, electrode gels containing Cl ions are typically used with Ag/AgCl electrodes.

Small Ag/AgCl electrodes (1–3 cm^2, 1–2 mA) with electrode gel, typically containing salts, such as sodium chloride or potassium chloride, are being used more frequently for tDCS with no AEs (e.g. Borckardt et al., 2012; Faria et al., 2012; Murray et al., 2015). Twenty minutes of real (n = 13) or sham (n = 11) 2 mA HD-tDCS over the motor cortex using 1 cm^2 electrodes (Borckardt et al., 2012) or 3 × 20 min sessions with 1–2 mA using 3 cm^2 PiStim electrodes (hybrid Ag/AgCl EEG/tDCS electrodes with a circular contact area, Starstim, Neuroelectrics) (Murray et al., 2015) resulted in no AEs.

For the sponge electrode design the function of the sponge is to fix the conductive rubber away from the skin and contain the saline. The salinity is important (Dundas et al., 2007), and gel can be substituted for saline. When using a paste electrolyte the sponges may not be necessary but then extreme care must be taken to ensure the conductive rubber does not accidently push through and contact the skin. For HD designs, a holder fixes the distance between the Ag/AgCl electrode and the skin, and also holds the gel. The composition of the electrolyte (saline, gel, or paste) is important as it influence the uniformities of current flow through the skin as well as acting as a chemical (diffusion) buffer between changes at the surface of the metal/rubber and skin (Dundas et al., 2007; Kronberg and Bikson, 2012; Minhas et al., 2010). For both sponge-based Ag/AgCl electrodes the materials and shapes of electrode assembly are thus critical for burden (Minhas et al., 2010). Equally important is adherence to established protocols for electrode preparation and application (Woods et al., 2016).

Recommendations: Use either sponge-like electrodes soaked in saline solution that contain an electrode pad made of conductive rubber (filled silicone), or Ag/AgCl electrodes with appropriate cream. Tap water is not recommended, and care should be taken, even when using saline solution in longer lasting experiments as increased contact resistance may also arise from drying of the sponges (Woods et al., 2016). In such cases an electrode gel or cream is a possible alternative. Abrading the skin (scalp) before electrode placement is not recommended (Loo et al., 2011).

6. The application of low intensity TES in human studies: AEs in human studies

6.1. Historical background of electrical stimulation

The history of electric stimulation starts with the application of electricity generated by electric fish, which are able to generate 2 ms long pulses, up to 600 V and up to 1 A.

Because the purpose of this feature is to stun prey, electric fish are unsafe by design. Immediately after the invention of the voltaic pile around 1800, several books were published on the use of the pile in a variety of mostly neurological diseases (Althaus, 1860; Augustin, 1801; Grappengiesser, 1801; Hellwag and Jacobi, 1802; Kluge, 1811; Ziemssen, 1864). Due to unknown details in the chemical composition and construction of the voltaic piles, it is almost impossible to determine, which intensities were used at that time. In addition, AEs were not documented systematically in these early studies, and most of the reported AEs referred to stimulation of peripheral nerves (Table 1). Thus, they will not be considered in the present context. This also applies to electrostimulation techniques for electroanaesthesia and electrosleep originally developed in Russia and summarized partially by Guleyupoglu and his coworkers (Guleyupoglu et al., 2013). Major known AEs associated with TES in humans (healthy and clinical populations) published between 2000 and 2016 are summarized in Tables 2–8.

6.2. Local pain, headache, discomfort

The first evaluation of tDCS-induced AEs summarized data from approximately 500 healthy subjects between 2000 and 2003 (Nitsche et al., 2003). In most of the studies a 5 × 7 cm stimulation electrode was positioned over M1 and the return electrode positioned over the contralateral supraorbital area. Weak direct currents (1 mA; current density 0.029 mA/cm^2) were applied for up to 20 min. Typical events were slight transient tingling sensations under the electrodes or light flashes when the stimulation was switched on or off abruptly. In an evaluation of 103 healthy volunteers with currents of 1 mA or 2 mA (current densities 0.04 and 0.08 mA/cm^2) applied for up to 20 min with the stimulus electrode over the prefrontal cortex and the return electrode over the contralateral supraorbital area, only a transient erythema was seen under the stimulus electrode in two subjects (Iyer et al., 2005). It was suggested that this might be related to local vasodilatation (Guarienti et al., 2015). Nevertheless, it is still unknown why vasodilatation under the anode is often different than under the cathode. Possible mechanisms include pH changes in different directions depending on stimulation polarity (Almalty et al., 2013; Ezquerro et al., 2017; Minhas et al., 2010).

The AEs seen in 567 tDCS sessions (1 mA; 9–15 min; current density 0.029 mA/cm^2; electrode placement occipital, temporal or parietal; motor or non-motor cortex) in 102 subjects (77 healthy volunteers and 25 patients with migraine, post-stroke, or tinnitus) were mild tingling sensation (70.6%), moderate fatigue (35.3%), slight itch under the stimulus electrode (30.4%), headache (11.8%), nausea (2.9%) and insomnia (0.98%) (Poreisz et al., 2007). The incidence of AEs, all belonging to the class of MAEs, such as transient headache was consistently lower after tDCS than after rTMS (11.8% vs. 23% in rTMS) (Machii et al., 2006; Rossi et al., 2009; Rossini et al., 2015).

A review of 209 tDCS studies (Brunoni et al., 2011a) described the primary MAEs as itching (active vs. sham tDCS group: 39.3% vs. 32.9%), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensations (8.7% vs. 10%) and discomfort (10.4% vs. 13.4%), with no significant differences between active and control groups. The latter received only a short stimulation at the beginning of the treatment session. However, in a

prospective comparison of active and sham tDCS in 131 subjects (277 tDCS sessions with the standard protocol using 1–2 mA stimulation intensity) (Kessler et al., 2012) found a statistically significant higher incidence of AEs in the active stimulation group as compared to the sham group with tingling (89% versus 53%), itching (81% versus 42%), burning sensation (65% versus 33%), pain (31% versus 11%) and headache (15% versus 9%). Also, as expected, the incidence of AEs in the prospective study was higher than that in a retrospective study (Kessler et al., 2012).

Repeated daily tDCS (up to five sessions), mostly with sponge electrodes, with a current density of about 0.06 mA/cm^2 (i.e., electrodes 25–35 cm^2, currents 1.5–2.1 mA) caused persisting skin lesions under the electrodes in some subjects, typically on the forehead or over frontal cortical areas (Frank et al., 2010; Nitsche et al., 2008; Palm et al., 2008b; Riedel et al., 2012; Rodriguez et al., 2014; Wang et al., 2015) (Table 2). Vitiligo does not seem to increase the risk (Shiozawa et al., 2013). Contact dermatitis following tDCS has also been reported (Riedel et al., 2012). Contributing factors are electrode position, pre-existing conditions such as allergies to skin creams, extensive skin heating, high impedance (electrode dry or defect, solution salinity of electrode sponges and deterioration of the sponges, inappropriate contact solution, incorrect electrode fixation, non-uniform contact pressure of electrodes to skin), prolonged duration or repeated sessions, high current density (high current, small electrode) (Dundas et al., 2007; Frank et al., 2010; Guleyupoglu et al., 2014; McFadden et al., 2011; Norris et al., 2010; Palm et al., 2014, 2008a; Riedel et al., 2012; Rodriguez et al., 2014; Turi et al., 2014; Wang et al., 2015).

Conclusions and recommendations: Minimizing skin reactions due to active stimulation is a readily realizable but important consideration in the management of the treatment. Irritation can be prevented by best possible preparation of skin and stimulation electrode. Abrading the skin before the fixation of the electrode is not recommended, only light cleaning with a pad, if it is necessary (Loo et al., 2011). The application of the stimulation over non-homogenous (e.g., scars) or inflamed skin areas should be avoided. To minimize serious skin damage, investigators need to pay close attention to electrode application, and participants should be instructed to report discomfort immediately, particularly when higher intensities are used.

6.3. Perceptual and cognitive AEs

No obvious individual AEs in either perceptual or cognitive domains causing changes (impairment) in performance on neurocognitive tests have been reported following TES. At the perceptual level, undesired online secondary effects are related to the protocol used. tACS with frequencies of 8–40 Hz and currents above 1 mA, as well as tDCS that it is not ramped up and down in the initial and final seconds of stimulation are likely to induce phosphenes, depending on the distance of the electrode to the eye, and tingling sensations under the electrode during stimulation (Fertonani et al., 2015; Turi et al., 2013). Depending on TES intensity phosphenes can significantly interfere with visual perception (Schwiedrzik, 2009).

Almost all reported cognitive effects in controlled studies were related to the primary or secondary study target, and hence were more physiological reactions than AEs. They are

associated with specific stimulation effects, either in down-regulating and up-regulating cortical states or degrading the signal-to-noise ratio that can impair or improve performance (e.g., Macher et al., 2014; Mathys et al., 2010; Peters et al., 2013; Plewnia et al., 2013; Rogalewski et al., 2004; Zwissler et al., 2014). This implies changes in neuronal activity that continue beyond stimulation and rely on mechanisms comprising inhibitory homeostasis of the system, long-term depression and metaplasticity (Muller-Dahlhaus and Ziemann, 2015).

The reported cognitive "AEs" of TES may not capture all effects. It is impossible to quantify all aspects of cognition at one time during TES, only the functions tested can be quantified. TES-induced improvement in one function may be associated with the simultaneous decline of another cognitive function (Iuculano and Cohen Kadosh, 2013; Younger et al., 2016). In this context a zero-sum model has been proposed claiming that every gain in cognitive functioning is necessarily accompanied by a loss in some other domain (Brem et al., 2014; Fertonani and Miniussi, 2017; Luber, 2014).

Conclusion: TES does not appear to cause apparent perceptual or cognitive AEs effects in healthy subjects.

6.3.1. Neuroenhancement—Neuroenhancement can be defined as any augmentation of core information processing systems in the brain apart from natural training, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning and motor performance. Pharmacological neuroenhancement refers to the use of substances or devices by healthy subjects with the purpose of cognitive enhancement, e.g., of vigilance, concentration, memory, or mood. "Brain doping" raises numerous ethical and social concerns. In particular, liberalization demands are continuously being discussed (Franke and Lieb, 2010). Almost every TES method has been proposed for neuroenhancement. Theories behind a potential neuroenhancement include the following mechanisms:

1. Balance effect: Balance effects are based on the model of inter-hemispheric rivalry between homologue areas. They have been investigated particularly for complex motor-and space-related functions in healthy subjects and patients. Inter-hemispheric balance effects have been used to account for the paradoxical enhancement of ipsilateral motor function, ipsilateral visuospatial attention, or lateralized verbal memory and language abilities, when using brain stimulation to suppress activity in specific cortical regions.
2. Entrainment theory: The entrainment theory is based on the notion that oscillatory activity in brain networks is associated and causally related to specific functions. According to this model, stimulation mimics brain oscillations and has an effect by entraining the brain's natural state. For instance, applying tACS during sleep promoted lucid dreaming at specific frequencies of 25 and 40 Hz with a concomitant increase of 25 and 40 Hz EEG activity (Voss et al., 2014).
3. Stochastic resonance: Stochastic resonance refers to the notion that injection of subthreshold noise into a system can serve to enhance signal detection (Fertonani and Miniussi, 2017; Stacey and Durand, 2000; van der Groen and Wenderoth, 2016).

4. Net zero-sum framework: Applied to the brain, this model suggests a situation whereby neural “gains” must be matched by neural “losses”. Accordingly, if stimulation induces a “facilitation”, a detrimental opposite effect should occur somewhere else in the brain (Brem et al., 2014).

Single or repetitive studies have claimed an improvement of a given cognitive function following brain stimulation sessions. The reported motor and cognitive (attention, risk-taking, planning and deceptive abilities) enhancements in healthy volunteers were described as follows: DLPFC – attention, risk-taking/impulsivity, planning and deceptive abilities; IFC: Inferior Frontal Cortex – attention and deceptive abilities; PPC: Posterior Parietal Cortex – attention; M1: motor cortex – reaction time, motor learning; TPJ: temporoparietal junction – working memory. However, appropriate control conditions were frequently lacking, in particular the real stimulation of a non-target area in order to prove site-specificity as compared to generalized and non-specific mechanisms related, for example, to increasing alertness/vigilance.

Altogether, the conclusions from a previous study by Bikson et al. (2013) seem appropriate: “…Controlled investigation of tDCS for treating neuropsychiatric disorders or for neurorehabilitation should not be confused with improvised devices or practices that apply electricity to the brain without reference to established protocols … Experimentation outside established and tested norms may put subjects at risk. …Meddling with the tDCS dose is potentially as dangerous as tampering with a drug’s chemical composition. Painstaking efforts by researchers to understand the risks and benefits of tDCS should never be interpreted as encouraging such practices.”

6.4. Safety of tACS

Sensations under the electrodes are generally less intense during tACS than during tDCS (Fertonani et al., 2015). This may in part be due to less intense electrochemical effects, and one might speculate that cell membranes of sensory neurons act as low-pass filters (Deans et al., 2007) and are thus less susceptible to high-frequency signals. Skin sensations and phosphenes are strongest with frequencies between 10 and 30 Hz with a peak at 20 Hz and diminish at higher and lower frequencies (Turi et al., 2013). The most pronounced phosphenes were seen with frontal electrode montages and the most intense skin sensations with central montages; both phosphenes and skin sensations increased with stimulation intensity. Similarly, dizziness appeared to (non-significantly) increase with stimulation intensity (Raco et al., 2014). No pathological changes in EEG or anatomical MRI, and no increase in NSE-levels were observed after tACS at 5 kHz with 1 mA applied for 10 min (Chaieb et al., 2011, 2014).

The *highest stimulation intensity* applied to date in a human study was administered using an electrical current theta-burst protocol (ecTBS) (Kunz et al., 2016). Using the same design as Huang et al. (2005), the authors applied three altered ecTBS protocols: 5 mA ecTBS with sinusoidal bursts of 5 ms duration, 10 mA ecTBS with sinusoidal bursts of 1 ms and 10 mA ecTBS with sinusoidal bursts of 5 ms, using a 5 kHz carrier frequency in order to avoid or at least minimize skin pain as known from high pulse electric stimulation and to achieve greater field strengths. Six of the 17 subjects reported MAEs after stimulation, mainly

headache. In another study during a combined stimulation with tDCS and 60 Hz tACS (ratio 2:1) using a stimulation intensity of 5 mA administered for 35 min, the stimulation was well tolerated with one patient (out of twenty) reporting a post-stimulation headache lasting 15 min (Nekhendzy et al., 2010).

The longest tACS stimulation duration applied to date in humans in the course of one day was 45 ± 10 min of 1.5 mA at 40, 60, and 80 Hz (Laczo et al., 2012). None of the sessions had to be interrupted because of AEs; two of the 20 subjects complained of a mild post-stimulation headache.

The longest stimulation duration over several days was applied to healthy volunteers using 1.5 mA at their individual alpha frequency for 20 min per day on five consecutive days. No AEs were reported (Muller et al., 2015). The subjects were unable to determine whether they had been assigned to the stimulation or the sham group. The sham group received a short stimulation at the beginning of the session.

Electrophysiological assessment methods, such as EEG or magnetoencephalography (MEG), can be used sequentially or simultaneously (provided detailed attention to potential artifact; Noury et al., 2016) to monitor the effects and efficacy of tACS on brain activity (Antal et al., 2008a; Zaehle et al., 2010) similarly to tDCS (Cunillera et al., 2016; Faria et al., 2012; Luft et al., 2014; Mancini et al., 2015). Recording electrophysiological data during stimulation requires methods for artifact elimination (Helfrich et al., 2014; Neuling et al., 2015). Manufacturers need to ensure that tACS and EEG/MEG devices can be safely operated together.

Conclusions and recommendations: There is an agreement with regard to the safety of applying tACS at the intensities and durations tested in published experimental protocols in healthy populations. When tACS is combined with EEG or MEG, one must prevent conductive fluids between electrodes in order to avoid short circuiting adjacent electrodes and, in this regard, electrode gel is preferable to saline solution (Helfrich et al., 2014). Similarly to previously published tDCS-EEG studies, no AEs have been reported for this combination other than those seen in tACS without additional electrophysiological monitoring.

6.5. Safety of combinations of TES with evaluation methods in clinical neurophysiology

6.5.1. Combined TES and rTMS—Theoretically, priming with tDCS might intensify the AEs of sub-sequent repetitive TMS (rTMS) (cf. Rossi et al., 2009). Studies combining TES with rTMS in healthy subjects reported no AEs during and after the combined interventions (see Table 3) (Karabanov et al., 2015; Muller-Dahlhaus and Ziemann, 2015). Similarly, no AEs were reported in any of the reviewed small clinical studies applying a combination of tDCS and rTMS (see Table 4), apart from increased scalp pain with rTMS, when preceded by tDCS, in one pilot study (Loo et al., 2009). In summary, there is currently no evidence that the combination of tDCS and rTMS is unsafe or is associated with burden.

6.5.2. tDCS in MRI—MR-compatible stimulation devices allow functional MRI and magnetic resonance spectroscopy (MRS) with only minor effects on image quality (Antal et

al., 2011b; Gbadeyan et al., 2016; Woods et al., 2016) predominantly in 3-tesla MR systems, but also without noticeable problems in 7-tesla fields (Barron et al., 2016). Neuroimaging studies with tDCS before (Baudewig et al., 2001; Lang et al., 2005; Stagg et al., 2009) or during neuroimaging (Antal et al., 2011b; Hone-Blanchet et al., 2015; Rae et al., 2013; Stagg et al., 2013) or combined with magnetic resonance electrical impedance tomography (Kwon et al., 2016) reported no AEs.

Specific safety precautions do apply. The study protocol must always comply with the safety standards for both tDCS and MRI. As for all metal containing devices, the tDCS stimulator MUST ALWAYS remain outside the MR cabin to avoid the stimulator coming too close to the static magnetic field. The stimulator is connected to the MR-compatible electrodes by specially designed, MR-compatible (non-ferrous or appropriately shielded and radio-translucent) leads. In some devices the stimulating leads are passed through a radio-frequency filter tube in the MR cabin wall and through a radiofrequency filter module, consisting of two filter boxes (Antal et al., 2011b). In other devices (see: http://wiki.neuro-electrics.com/images/c/c5/NEWP201505-MRI_tCS_compatibility.pdf) there is only one filter attached to the patch panel of the MRI machine to ensure that the filtered currents flow through the ground and to ensure that the faraday cage of the MRI room is not opened and there is no noise during normal MRI image acquisition.

The filter module is necessary to suppress the radio-frequency noise that is brought into the scanner room via the stimulating leads. If tDCS is applied with the subject in the MR bore, the radio-frequency pulses generated by the MR may induce eddy currents in the stimulation leads, causing heating of the leads with the risk of skin burns. Each lead must therefore be fitted with protective, high-ohmic resistors (ca. 5 kOhm) and the leads should always run parallel to the axis of the scanner bore without forming any loops (Meinzer et al., 2014a; Woods et al., 2016). Unshielded cables inside the MRI room should be as short as possible to avoid crossing wires and loops that might induce current to the patient. Longer cables should be designed for the MRI room and therefore shielded.

For tDCS in the MR cabin, biocarbon electrodes and thick layers of electrical conductance paste should be used rather than saline-soaked sponges or low viscosity electrode gel. The reason for this is that tDCS-MRI experiments may take longer and electrodes cannot easily be accessed in the scanner to prevent the electrodes from drying with the associated risk of thermal injury (Woods et al., 2016).

In contrast to tDCS, tACS is less likely to cause artifacts (Antal et al., 2014). No AEs other than those with tACS alone have been reported for this combination (Alekseichuk et al., 2016; Cabral-Calderin et al., 2016; Vosskuhl et al., 2016).

6.6. Optic nerve stimulation

Animal studies apply crush and transection models of the optic nerve in order to investigate new treatment options for glaucoma and other optic neuropathies, such as electrical optic nerve stimulation (eONS or ONS) (Fu et al., 2015). The studies indicate that eONS may induce structural neurorestoration (axonal regenera tion), functional neurorestoration (visual evoked potentials), and neuroprotection (survival of ganglion cells) (Miyake et al., 2007;

Morimoto et al., 2005; Tagami et al., 2009; Yin et al., 2016), which are assumed to be mediated by release of neurotrophic factors and increased chorioretinal blood flow (Fu et al., 2015). ONS can be achieved with many frequencies; the sensitivity peaks around 15 Hz (e.g., Brindley, 1955). One proprietary approach (EBS technologies GmbH) sets the stimulus frequency between the individual's EEG α frequency and his flicker fusion frequency. This is applied on ten consecutive days with each session lasting approx. 60–90 min (Gall et al., 2016). To date, 760 patients with optic neuropathies, e.g., following stroke or with postchiasmatic lesions, have been treated in various clinical trials using this technology (Fedorov et al., 2011; Gall et al., 2013, 2010, 2016, 2011, 2015; Sabel et al., 2011; Schmidt et al., 2013). The most common AEs were skin sensations and irritation, headache, drowsiness, and sleep disturbances. No device-related SAEs were reported. No incidents occurred since the market introduction of a commercial device for ONS in 2014, and it can be assumed that the likelihood of detrimental effects is probably extremely low.

6.7. Transcutaneous spinal direct current stimulation (tsDCS)

During transcutaneous spinal DCS (tsDCS) (Cogiamanian et al., 2008) the current is delivered through a skin electrode positioned over the spinal cord with the return electrode placed over various regions according to different protocols (mainly the shoulder, the anterior aspect of the trunk, or somewhere along the spine). It has been used in patients with spinal cord injury (Hubli et al., 2013) and with restless leg syndrome (Heide et al., 2014). The technique appears to influence ascending and descending spinal pathways and to modify the excitability of various spinal reflexes in humans and animals (for a review see Priori et al., 2014). In general, anodal tsDCS tends to suppress conduction along spinal pathways and to facilitate reflexes, while cathodal tsDCS tends to enhance responses mediated by spinal ascending pathways and inhibit reflexes (Priori et al., 2014). In addition, tsDCS may induce indirect functional changes in the brain (Bocci et al., 2015a, 2015b, 2015c).

None of these studies reported SAEs, and serum NSE levels were unchanged (Cogiamanian et al., 2008). Spinal DC stimulation did not damage the spinal cord in rats (Ahmed, 2011) with the estimated current density being well below the threshold for neural tissue damage (McCreery et al., 1990). Data concerning tsDCS have been so far been only collected in adults, usually after a single session involving the thoracic spine. Modeling data (Parazzini et al., 2014) suggest that the current density may be slightly higher in smaller subjects and children. Harmful effects due to the higher current density through spinal foramina or intervertebral space are not anticipated, but cannot be excluded.

Recommendations: tsDCS in young subjects or children, especially based on multiple stimulation sessions with intensities and/or durations greater than those conventionally used should be carefully evaluated within controlled studies. The specific case of pregnancy is addressed in the next chapter. In other conditions, there is theoretically no higher risk to stimulate the spinal cord than the brain.

6.8. TES and pregnancy

EFs attenuate rapidly with distance, so it is unlikely that the fetus would be directly affected by TES. A calculation of current intensities arriving at different parts of the body (e.g., heart, uterus) during transcranial stimulation has not been performed yet. There are only two published case reports of pregnant women who underwent tDCS treatment for depression and hallucinations related to schizophrenia (Shenoy et al., 2015; Vigod et al., 2014). The first case reported was a 25-year-old woman with schizophrenia (DSM-IV) and drug non-responsive auditory verbal hallucinations (Shenoy et al., 2015). The stimulation intensity was set at 2 mA for 20 min with sessions twice a day (separated by at least 3 h) for 5 consecutive days with an anode at F3 and FP1 and the cathode at T3 and P3 positions. The patient responded well with nearly full remission of hallucinations until follow-up at one month after tDCS. Repeated sonography at this time showed a healthy fetus (22 weeks) without any abnormalities and the pregnancy was uneventful as ascertained again by an obstetrician.

The second case was a 23-year-old woman with depression from her 6th week of pregnancy who was successfully treated using a bifrontal electrode placement with anode corresponding to the F3 area and the cathode corresponding to the F4 area on the scalp (Sreeraj et al., 2016). A direct current of 2 mA was delivered for 30 min daily for 10 days. Here a minor AR was reported, in 3 out of 10 tDCS sessions during the fade-in phase the patient experienced transient, mild burning sensations at the site of application and fleeting experience of phosphenes. There was no detailed information reported on the course of pregnancy including the fetus in terms of malformations and growth.

Recommendation: In controlled studies the entrance questionnaire should ask about pregnancy, and pregnant subjects should be stimulated only if the benefit is higher than the risk. Due to the higher field intensities and the location of stimulation, direct stimulation over the lumbar spine should likely be avoided in pregnant women. Furthermore, although risks for the embryo or fetus during TES are logically negligible, the risk is actually unknown, and it should be recognized that any research on medical products in pregnant women is regulated by law.

6.9. TES-associated AEs in pediatric populations

tDCS may play an important future role in the treatment of developmental disorders (Ciechanski and Kirton, 2017; Palm et al., 2016). If the intention is to approximate brain current densities produced in adults, then the tDCS dose in children needs attenuation in order to compensate for the thinner skull and lower resistance (Gillick et al., 2014; Kessler et al., 2013; Moliadze et al., 2015b), though 2 mA has been tested without incident in children (Ciechanski and Kirton, 2017; Mattai et al., 2011). The main findings of tDCS applications in this population are summarized in Tables 5 and 6.

In 48 studies on transcranial magnetic and electric stimulation, involving more than 513 children and adolescents (Krishnan et al., 2015), AEs were generally mild and transient, and very similar to those in adults. In patients with congenital hemiparesis (7–18 years; $n = 13$) a

single session of tDCS (0.7 mA for 10 min) was well tolerated with no changes in vital signs or worsening of motor function (Gillick et al., 2015).

Children suffering from various neuropsychiatric disorders (n = 14; 5–12 yrs) were given multiple-session tDCS (2 mA; 30 min daily for ten days) (Andrade et al., 2014). The main AEs reported were mood changes, skin sensations (itching, tingling, burning), headache and sleepiness, but it is uncertain whether or not these complaints might not be attributed to the neuropsychiatric disorders themselves rather than to the stimulation.

Twelve patients (mean age = 15.4, range 10–17 yrs) with childhood-onset schizophrenia were treated with repeated 2 mA tDCS (2 mA, 20 min, ten sessions) (Mattai et al., 2011). There was no clinically significant improvement of mood, arousal, or verbal output. A randomized, controlled, crossover study of the AEs of tDCS in healthy children and adolescents (mean age 13.9, range 11–16 yrs) showed that tDCS with 1 mA intensity over 10 min is well tolerated in children and adolescents. No pathological oscilla tions, and in particular, no markers of epileptiform activity, after 1 mA tDCS were detected in any of the EEG analyses (Moliadze et al., 2015a). Long-term EEG monitoring was not performed (Bogdanov et al., 1994; Moliadze et al., 2015a).

No AEs were seen in young patients, even after tDCS was applied with a higher than usual current density (0.497 mA/cm^2) and/or repeated over several days (Breitling et al., 2016; Mattai et al., 2011; Munz et al., 2015; Schneider and Hopp, 2011; Soff et al., 2016). tDCS was applied to some children during sleep without awakening them, and none reported AEs the following morning (Munz et al., 2015; Prehn-Kristensen et al., 2014).

All studies in both adults and children showed that tDCS does not elicit epileptic seizures or provoke epileptic EEG activity in patients with known epilepsy (Varga et al., 2011). A four-year-old boy with a history of idiopathic infantile spasms suffered a probably unrelated partial onset seizure 4 h after his third anodal tDCS session (anodal tDCS of right M1, 1.2 mA, 20 min, 25 cm^2 electrodes) (Ekici, 2015). The child had been free from seizures under medication with valproic acid and topiramate for the previous two years. Topiramate had been tapered off two weeks prior to tDCS and he was receiving escitalopram (2.5 mg) prior to tDCS to facilitate excitatory effects, so the situation was complicated. No firm conclusions can be drawn regarding a potential epileptogenic interaction of serotonergic medication and anodal tDCS (Ekici, 2015).

Major reported AEs and related stimulation protocols in children are summarized in Table 6.

Recommendations: The type and magnitude of reported AEs does not differ between children/adolescents and adults, available evidence delivers no established risks specific to tDCS, and thus recommendations match those for adult populations. There are no published data concerning long-term after-effects of TES in children/adolescents.

6.10. TES-associated AEs in aging populations

The majority of studies of tDCS in healthy, older adults do not differ from those in younger adults methodologically (standard electrode montages with prefrontal, precentral, temporal,

or parietal locations of the target electrode (size 25–35 cm^2) with a supraorbital or vertex return electrode (same size or up to 100 cm^2)). A weak (1–2 mA) anodal current was usually applied for 15–30 min. About one-third of the studies published until 2016 in aging populations reported no occurrence of tDCS-related AEs without giving details (Table 7). The most commonly reported AEs were typical tingling and itching that usually occurred when stimulation began but were also reported under sham conditions, where stimulation was applied only for a short duration at the beginning of the session (Boggio et al., 2010; Fertonani et al., 2014; Gandiga et al., 2006; Harty et al., 2014; Hoff et al., 2015; Holland et al., 2011; Learmonth et al., 2015; Manenti et al., 2013; Parikh and Cole, 2014; Sandrini et al., 2014, 2016).

Anodal tDCS (2 mA, 15 min) applied over the cerebellum (return electrode over the buccinator muscle) was not significantly more painful than sham stimulation (Hardwick and Celnik, 2014) (see Table 7). Similar results were seen in a study of anodal tDCS (1 mA, 20 min) over the M1 with a supraorbital return electrode (20 min, 1 mA) with regard to attention, discomfort and fatigue (Hoff et al., 2015).

Burning sensations and slight “pinching” were reported by 72% and 32%, respectively, following tDCS of the left DLPFC (2 mA, 10 min, shoulder reference electrode) but there was no difference between active and sham stimulation (Fertonani et al., 2014). Pruritus was reported after cathodal and anodal stimulation with the same active electrode placement (1 mA, 37.5 min, vertex return electrode) and was more intense following active stimulation (Harty et al., 2014). There was no correlation between pruritus and task performance. Similarly, Learmonth et al. (2015) observed slightly more burning sensations during active stimulation sessions in older adults that received parietal anodal tDCS with a supraor-bital reference for 15 min with 1 mA (Learmonth et al., 2015).

The only study of AEs during tACS in healthy older adults (Antonenko et al., 2016) used 5 × 7 cm^2 or 10 × 10 cm^2 electrodes with a temporo-parietal/supraorbital montage. tACS was administered at 6 Hz for 20 min. The sensations experienced by the twelve older participants were tingling ($n = 3$), itching ($n = 1$), fatigue ($n = 2$) and loss of concentration ($n = 2$) during either active or sham tACS. Participants were unable to reliably identify the active stimulation session.

Conclusions and recommendations: The quality of reported AEs does not differ between young and old subjects; they are milder in older adults and tend to disappear during stimulation, and do not significantly affect task performance (Fertonani et al., 2014; Hardwick and Celnik, 2014; Learmonth et al., 2015) (see Table 7). The incidence does not differ significantly between active and sham stimulation, indicating the effectiveness of the standard fade-in fade-out sham stimulation at least in naïve subjects (Hummel et al., 2010; Lindenberg et al., 2013; Manor et al., 2016; Parikh and Cole, 2014; Sandrini et al., 2014, 2016; Zimerman et al., 2013). Not surprisingly, the identification of the actually applied stimulation paradigm is more accurate after repeated sessions (Nilsson et al., 2015; Wallace et al., 2016). Validated standardized questionnaires are required for assessing AEs in older adults. From pharmacological interventions, it is well-known that older adults are more

susceptible to negative effects on cognition, mood, or increased dizziness, than younger subjects (Thiem, 2012) and these issues should be better evaluated in future studies.

6.11. Special considerations for intracranial implants

Simulations suggest TES in the present of DBS will not result in significant concentration of current in the brain (Bikson et al., 2016). In 10 subjects with intracranial EEG electrodes, 0.5–2 mA tACS with frequencies up to 100 Hz was applied with no AEs, producing 0.4 V/m electric field/mA (Huang et al., 2017). In a separate study, in two epilepsy patients with implanted electrode grids, 1 Hz alternating current of 1 mA was applied to the bitemporal area for 2 min (Opitz et al., 2016). Patient 1 had bilateral stereotactic EEG electrodes and patient 2 had left subdural grid, strip and depth electrodes. No AEs were reported. The highest magnitudes of EFs were found in superficial sites near the stimulating electrodes, with maximum EF strength of ~0.36 mV/mm for patient 1 and ~0.16 mV/mm for patient 2. These results from intracranial recording are in the range predicted by modeling studies for tDCS (Datta et al., 2009a; Miranda et al., 2013). The study also tested tACS in two monkeys with stereotactic EEG electrodes, and here, similarly, no adverse physiological reactions were identified.

ECT has been performed in 24 patients with implants (eight with cerebral clipping systems, two with cerebral coils, four with DBS, seven with other types of metallic implants, and three with foreign bodies), with no AEs related to the presence of these objects (Gahr et al., 2014). As of July 2016, at least ten patients with DBS for treatment of PD, cervical dystonia, essential tremor, depression and obsessive compulsive disorder have been treated with ECT without AEs (Rosenthal et al., 2016). In most cases, the DBS system was turned off during ECT to prevent inadvertent DBS activation, but ECT has also been performed with the device on (Vila-Rodriguez et al., 2014). In some cases, the ECT protocols were modified to maximize the distance between the ECT electrodes and the DBS electrodes or the subcutaneous leads.

Several *ex vivo* studies showed that TMS over DBS leads did not induce sufficient current to cause tissue damage or damage to the pulse generator (Kuhn and Huebl, 2011; Kumar et al., 1999), although stimulation over lead loops could potentially produce current large enough to be dangerous (Deng et al., 2010; Shimojima et al., 2010). At least 20 TMS studies in patients with DBS have been published since 2001 (Chen et al., 2001) and no AEs have been reported. TMS-induced current in the DBS stimulator leads has been claimed to be sufficient to activate the internal capsule (Hidding et al., 2006; Kuhn et al., 2002) as demonstrated by shorter latencies MEPs. However, this was not found in other studies (Kuriakose et al., 2010). These differences may be related to the location of the TMS coil relative to the DBS leads and the presence of lead loops. An ex vivo study and testing in a patient found no safety concerns with rTMS over subdural cortical electrodes (Phielipp et al., 2017). The current TMS safety recommendation states that TMS can be safely applied to patients with implanted stimulators of the central and peripheral nervous system (Rossi et al., 2009). Therefore, tDCS with its much lower intensities is unlikely to be associated with significant heating, current induction or movement of implanted devices. Induction of chemical reactions with galvanic currents in implanted electrodes is an unsolved issue when tDCS is

applied close to subdural or epidural electrodes, or to the leads of DBS electrodes. This effect may be amplified by the lower resistance of the burr hole if the transcra-nial electrode is closer than approximately 2 cm (Datta et al., 2010). Another concern could be the still unknown combined biological effects of tDCS with intracranial stimulation since both tDCS and DBS (Kim et al., 2015; Udupa et al., 2016) can induce cortical plasticity alterations.

Recommendation: TES should be performed on humans carrying any implants in the brain or in the skull only in well-supervised and controlled studies.

6.12. Safety concerns: illness-therapy-stimulation interactions

TDCS can be combined with basically any other therapeutic intervention. Pairing tDCS with motor or cognitive training or behavioral interventions (Bajbouj and Padberg, 2014; Wessel et al., 2015) or the application of selective serotonin reuptake inhibitors (SSRI) combined with tDCS in depression (Brunoni et al., 2013b) are examples of meaningful combinations. Combinations of tDCS with motor or cognitive training or behavioral interventions appear to be safe (in stroke and in neurorehabilitation). However, some behavioral interventions might increase the risk of AEs, e.g. excitatory tDCS after sleep deprivation may amplify cortical excitability changes. No such interaction has been reported so far.

In the following sections we concentrate on reported AEs in the most frequently TES-treated patient groups: major depressive disorder (MDD), stroke and chronic pain. From other patient populations we have less information, and even in these major groups there is a considerable heterogeneity in AE reporting.

6.13. Published AEs in depression

The burden associated with TES in MDD trials was basically the same as in all other trials with tDCS, i.e., cutaneous symptoms and sensations occurring with the same frequency (Aparicio et al., 2016). Four RCTs (Bennabi et al., 2015; Brunoni et al., 2013b; Loo et al., 2012, 2010) described treatment-emergent mania/hypomania in a total of ten cases: nine in the active and one in the sham groups (Table 8). Loo et al. (2010) described a tDCS-induced hypomanic episode (anode over the left DLPFC, cathode over the right supraorbital region, 20 min/day, 1 mA) after eight sessions of active tDCS in a 57-year old woman who was not using any medications (Arul-Anandam et al., 2010). In their second trial using active tDCS (same montage as previously described, 20 min/day, 2 mA), Loo et al. (2012) induced a hypomanic episode after six sessions of tDCS in a type I bipolar, 78-year-old woman who was on lithium, quetiapine and fluoxetine. Brunoni et al. (2013b) later reported six cases of tDCS-induced hypomania/mania. All patients (two male, four female, aged between 25 and 62 year-old) were antidepressant-free before trial onset. In one case, a hypomanic episode was triggered by tDCS-only. In the other five cases, the combination of tDCS with sertraline 50 mg/day induced hypo-manic (three cases) or manic episodes (two cases, one of them with psychotic symptoms, as described in Brunoni et al. (2011b)). The treatment protocol was anode over the left, cathode over the right DLPFC, 30 min/day, 2 mA stimulation session. Finally, Bennabi et al. (2015) reported one case of tDCS-induced mania in the active group, using a treatment protocol of anode over the left DLPFC, cathode over the right supraorbital region, 30 min/day and 2 mA current intensity.

Besides the abovementioned RCTs, there are two additional case reports of tDCS-induced hypomania. Baccaro et al. (2010) reported a tDCS-induced hypomanic episode in a 58-year-old man with a depressive episode secondary to gastric cancer. The hypomanic episode was triggered after five sessions of bifrontal tDCS (2 mA intensity, 30 min/day) and resolved only after discontinuing treatment and initiating lamotrigine treatment. Galvez et al. (2011) described the case of a 33-year-old female with bipolar II disorder on mood stabilizer medication who underwent bifrontal tDCS without incident, however later became hypomanic when receiving a second course of frontoextracephalic tDCS. In this context, it is also worth noting a case series of five bipolar depressed patients treated with bifrontal tDCS (2 mA intensity, 30 min/day, 10 sessions) (Pereira Junior Bde et al., 2015). A patient who was at baseline in a mixed depressive state exhibited an initial improvement, but with recrudescence of depressive and manic symptoms during the trial, showing overall no improvement with tDCS. Another patient presented an increase of the Young Rating Manic Scale (YMRS) from 2 to 11 during the trial, although no clinical diagnosis of hypomania/mania was performed.

In summary, 11 cases of tDCS-induced hypomania/mania episodes have been described, of which only two occurred in patients with a bipolar disorder. Five patients out of these 11 cases started receiving tDCS and sertraline simultaneously. In a recent meta-analysis on the topic, Brunoni et al. (2017) found that the treatment-emergent hypomania/mania rates were not statistically different between active and sham stimulation, although they were higher in active (3.5%) vs sham (0.5%) stimulation.

Treatment-emergent suicidal ideation or behavior is a risk in the treatment of any depressed patient. One patient committed suicide during a clinical tDCS trial, but this was most likely unrelated to tDCS intervention (Loo et al., 2010). A PubMed search failed to find other psychiatric AEs induced by tDCS (hallucinations, psychosis, anxiety, etc.).

Recommendation: patients should be carefully assessed for a history of bipolar disorder or of switching into mania with past antidepressant treatments, as these factors may indicate a higher risk of manic switch with tDCS. In these patients, concurrent treatment with mood stabilizer medications during the tDCS treatment course should be considered. In this context, the use of lithium and antipsychotic drugs should be preferred over anticonvulsant medications, which can decrease or abolish anodal tDCS effects (Brunoni et al., 2013a).

6.14. Review of published AEs in chronic pain

In the period 2005–2016, 43 of the 54 tDCS studies performed in pain patients reported the incidence of AEs (Lefaucheur, 2016). Of these 43 studies, 34 reported AEs without having used a questionnaire or without details of the questions or the results obtained with the questionnaire. Three-quarters of these studies reported AEs occurring during or after their tDCS protocols, mainly tingling at the stimulation site (44% of active procedures and 47% of sham procedures) and sleepiness or fatigue (31% after active procedures and 21% after sham procedures). In many case, the occurrence of AEs in chronic pain patients was significantly higher during or after active tDCS condition than during or after sham tDCS. With regard to skin redness at the electrode site, it was observed more frequently for active tDCS than for sham tDCS (20% vs. 11%).

Four dropouts in pain studies were the result of AEs such as skin reaction at stimulation site (n = 3) or increased pain (n = 1). The latter event could be interpreted as a lack of tDCS efficacy in treating the pain syndrome rather than as an AE produced by the stimulation. These pain therapy studies also reported three cases of skin burn due to the electrodes, which healed within a few days, leaving a small scar in one patient (Oliveira et al., 2015).

In nine studies using a structured questionnaire on the occurrence of AEs in migraine (Antal et al., 2011a; Dasilva et al., 2012; Poreisz et al., 2007; Wickmann et al., 2015), fibromyalgia (Fagerlund et al., 2015; Mendonca et al., 2016), temporomandibu-lar disorders (Donnell et al., 2015), irritable bowel syndrome (Volz et al., 2016), or a mixture of various neuropathic and non-neuropathic pain syndromes (Antal et al., 2010) the frequency of reported AEs was 20–50% higher than in studies with spontaneous reporting. Here also the most frequent AEs were tingling at the stimulation site (51% of either active or sham), and sleepiness or fatigue (39% after active and 45% after sham). The incidence of skin redness at the electrode site was high in both the active tDCS (50%) and sham tDCS (46%). However, it should be noticed that sham stimulation usually includes a very brief stimulation period at the beginning of each session.

Conclusion: patients with pain syndromes do not have a lower tolerance for TES than other patients. Furthermore, there is currently no solid evidence to suggest that the AEs in these patients are significantly higher in the active condition than in the placebo condition.

6.15. Published AEs in post-stroke treatment

In the stroke domain, 58 of the 86 tDCS studies published in the period 2005–2016 containing the data of 788 patients reported the incidence of mild and transient AEs. Fourteen events led to discontinuation of the treatment (Gillick et al., 2015; Jo et al., 2009; Kim et al., 2010; Làdavas et al., 2015; Mortensen et al., 2016; Polanowska et al., 2013; Rosso et al., 2014; Shigematsu et al., 2013; Smit et al., 2015; Sparing et al., 2009; Straudi et al., 2016; Sunwoo et al., 2013; Triccas et al., 2015; Wang et al., 2014; You et al., 2011).

The most common AEs were headache in 16 of the 788 patients (Kim et al., 2010; Mortensen et al., 2016; Sunwoo et al., 2013), burning and aching (12/788), skin irritation (14/788), tingling and itching under or around the electrode (5/788), and nonspecific discomfort (4/778) (Gillick et al., 2015; You et al., 2011). One patient suffered a possibly allergic skin reaction (Triccas et al., 2015), probably to the applied crème, while one required a lotion for skin dryness following the stimulation session (Smit et al., 2015). One patient experienced a “sudden psychological disturbance” during bi-hemispheric stimulation of the parietal cortex (2 mA, 20 min, 1 session) similar to that seen with application of TMS to the same location (Schutter et al., 2009).

No patient reported fatigue (Ang et al., 2012; Bae et al., 2012; Giovannella et al., 2017; Kongthong et al., 2011; Ridder and Vanneste, 2012; Schestatsky et al., 2013; Smit et al., 2015). Since tDCS may affect sympathetic tone (Rossi et al., 2016) and cardiovascular stability is crucial, particularly in the acute post-stroke period (Al-Qudah et al., 2015; Beeli et al., 2008; Makovac et al., 2016; Santarnecchi et al., 2014; Vandermeeren et al., 2010; Vernieri et al., 2010) there might be a theoretical risk of arrhythmias or hypertensive crisis in

stroke patients. However, prolonged monitoring during and after tDCS in healthy subjects failed to show an influence on vital functions. A short lasting linear increase of systolic/diastolic blood pressure in healthy subjects unrelated to the polarity of stimulation and to tDCS-induced changes on corti-cospinal excitability (Santarnecchi et al., 2014) awaits confirmation.

Another issue that has been raised is whether tDCS in stroke patients would have a higher risk of inducing seizures. Indeed, about one third of tDCS clinical trials in stroke exclude patients with history of seizures and/or epilepsy (Russo et al., 2017). However there have been no cases of confirmed seizures induced by tDCS regardless of the risk of seizures. A recent study provides initial evidence for the safety of tDCS intensities up to 4 mA in stroke treatment (Chhatbar et al., 2017).

6.16. Pharmacological interventions combined with tDCS: interactions between tDCS and concomitant drug treatments

Interactions between TES and concomitant treatment with centrally acting drugs may potentially augment the efficacy of TES. However, this may also increase AEs (or conversely might reduce them). First, local drug application may ameliorate AEs associated with tDCS. Topical ketoprofen reduced erythema under the electrodes (Guarienti et al., 2015), and a topical local anesthetic emulsion (e.g., 2.5% lidocaine or prilocaine) reduced discomfort during stimulation (McFadden et al., 2011). EMLA® cream is also very effective in anesthetizing normal skin. This could help to improve blinding in controlled studies. Blunting cutaneous sensation does not correlate with the degree of skin injury (Palm et al., 2014), and with correctly performed stimulation technique, therefore topical anesthesia should not increase the risk of injury (Woods et al., 2016).

Second, tDCS has been applied together with pharmacological interventions in healthy humans as well as in patient populations to explore and potentially boost the effects of stimulation (for an overview see Brunoni et al., 2013a; Nitsche, 2012). Also, the standard pharmacotherapy for the disorder for which tDCS is employed as an adjuvant measure should usually be continued. Drugs such as benzodiazepines may interfere with a beneficial outcome in depressive disorders (Brunoni et al., 2013a). The reported effects were either AEs typical of tDCS or of the medication, e.g., vertigo, tiredness, vomiting, (dopaminergics, NMDA receptor antagonists or benzodiazepines). No SAEs have been reported with combinations, e.g., tDCS and clozapine (Arumugham et al., 2016). Thus, currently there is no evidence that the combination of pharmacotherapy with TES results in enhanced risks exceeding AEs, which can attributed to the respective single interventions.

6.17. Interactions between TES and concomitant treatment in neurorehabilitation

A PubMed search of the literature from 2000 to 2016 was conducted for neurorehabilitation studies using “tDCS” in combination with “neurorehabilitation” and “rehabilitation” as the search terms followed by searches on symptoms or disorders such as “aphasia” or “multiple sclerosis” treated with tDCS. Pain treatment studies were included in cases where the pain had a central nervous system etiology (e.g., spinal cord injury). A total of 232 studies met the criteria, of which 115 studies (49.6%) explicitly reported safety outcomes in sufficient

detail to allow for quantification of AEs across studies. The remaining 117 were unsuitable for the analysis of safety issues.

In the 115 suitable studies, the number of participants per study condition (real or sham tDCS) was tallied. Participants were counted once for each study condition (i.e., twice in crossover stud ies), giving a total of 2260 participants x conditions (hereafter referred to as "subjects"). A total of 506 tDCS-related AEs were reported for an overall incidence of 22.4%. The actual incidence of AEs is probably somewhat lower because some subjects may have reported multiple complaints. The most common reported AEs were mild sensory phenomena that only occurred during stimulation at or near the electrodes (tingling, itching, phosphenes) that occurred in 253 (11.2%) subjects (e.g., Grecco et al., 2014a; Triccas et al., 2015). Transient events included skin irritation (75 subjects; 3.3%, Ferrucci et al., 2014; Triccas et al., 2015), issues with sleep or energy level, including sleepiness, fatigue, and insomnia (74 subjects; 3.3%; e.g., Lesniak et al., 2014; Murray et al., 2015), headache or nausea (56 subjects; 2.5%; Khedr et al., 2014; Kim et al., 2014), problems with concentrating (15 subjects; 0.7%; e.g., Wrigley et al., 2013), and neck pain (4 subjects; 0.2%; e.g. Straudi et al., 2016). An additional ten subjects (0.4%) experienced AEs that were deemed by investigators to be 'adverse' but were not well described (Fusco et al., 2014). A total of 19 subjects (0.84%) withdrew from their respective studies because they did not tolerate the AEs. Subjects who received real tDCS reported a higher overall incidence of AEs (342 of 1323; 25.9%) than those with sham tDCS (164 of 397; 17.5%), which might be due to the fact that the conditions were not satisfactorily blinded in some studies. The rate of study withdrawal was higher among subjects who received real stimulation than those with sham stimulation (16 vs. 3 subjects), although the drop-out rate was low for both conditions (1.2% and 0.3%, respectively).

6.18. Conclusions of human trials and recommendations

No SAEs were reported for either real or sham TES between 2000 and 2016 with the exception of an epileptic seizure in an epileptic child (Ekici, 2015) and suicide in a depressed patient in a clinical trial (Loo et al., 2010) – in both cases the causality to tDCS was not proven. When reviewing only conventional bipolar tDCS in human applications and clinical trials no reports of an SAE or irreversible injury attributable to tDCS were found in over 33,200 sessions and 1000 subjects with repeated sessions (Bikson et al., 2016).

About 300 publications using low intensity TES between 2000 and 2016 reported mild AEs, mainly in the category of skin sensations; however, several studies were not placebo controlled and double blinded. At present there is no solid evidence to suggest that the AEs in patients or in vulnerable populations are significantly higher and different in magnitude in comparison to healthy subjects. However, in several individual clinical trials a higher prevalence is reported. For example, in MDD some RCTs (Brunoni et al., 2013b; Loo et al., 2012, 2010) actively surveyed for AEs, and therefore the reported AE prevalence was much higher compared to other RCTs (Bennabi et al., 2015; Blumberger et al., 2012; Palm et al., 2012). In fact, in a recent systematic review of 64 tDCS trials (Aparicio et al., 2016), it was found that the quality of AE reporting was quite low – MDD trials only complied with 31.3% of the items described by CONSORT-harms (a "gold-standard" questionnaire for

adequate AE reporting). Lack of adequate AE reporting is a concern because this usually leads to an underestimation of the true rate of AEs, which can, in turn, result in safety and blinding issues. Therefore, better reporting of AE both in clinical and investigational applications of TES is warranted.

7. Ethical, legal and regulatory issues

7.1. Ethics

Previous studies using transcranial stimulation suggest that ethical awareness was and is always linked to the social definitions and moral issues, both in health and disease (Harris and Almerigi, 2009; Moan and Heath, 1972). Nowadays a very careful assessment of the Institutional Review Boards (IRB) and Ethical Committees of a given institute is required before a study is initiated. Nevertheless, the main responsibility with regard to the appropriate conduct and maintenance of a rigorous ethical framework remains the responsibility of the investigators. Similar to other interventions, in the TES area three basic ethical and legal requirements pertain to all research studies and clinical use: (1) Informed consent; (2) Risk-benefit ratio; (3) Equal distribution of burdens and benefits of research.

Analogous to magnetic stimulation studies (Rossi et al., 2009), TES studies could be divided into categories dependent on the requirements for protection of the participants and what benefits they might expect. Here, we introduce a new category (high benefit, low risk, see 4):

1. Direct benefit, high risk: studies with diagnostic or therapeutic primary objective, including new therapeutic indications or protocols with potential direct clinical benefit for the participant. The acceptable risk for participants could possibly be high for such procedures that have not been tested for safety. Healthy subjects usually do not participate in these studies.
2. Indirect benefit, moderate risk: studies with little or no expectation of a clinical benefit. The study is anticipated to provide valuable data for the development of treatments, for safety assessment, or for improving the understanding of the pathophysiology of neurological or psychiatric diseases. Healthy subjects do not usually participate in these studies but could be included as controls. However, if the risk of AEs is high, healthy subjects should not be recruited.
3. Indirect benefit, low risk: studies expected to yield important data on brain physiology, general pathology or on safety, but without any immediate relevance for clinical problems. Healthy subjects and clinical population can participate.
4. High benefit, low risk: studies expected to yield important data on cognition and brain physiology in healthy subjects and patient populations, with an immediate relevance for cognitive or motor improvement. Studies targeting neuroenhancement would fall into this category.

Independently from the type of the study (research or clinical), stimulation parameters and protocols must always be chosen with clear goals and safety considerations in mind, and be accepted by the Ethical Committee before initiation of a study. Alterations in research protocols should always be documented. When an unanticipated divergence from the

approved protocol happens (e.g., higher intensity of stimulation was applied accidentally) it must be reported to the Ethical Committee (timing depends on the legal regulations, usually after 7 days of their discovery).

There are application specific concerns in the TES-ethics. One of the most discussed concerns the difference between treatment and neuroenhancement (see Section 6.3.1). Some has suggested a theoretical, socially important problem is that the use of TES for cognitive and athletic enhancement of healthy subjects could increase natural differences between people, or even create new differences, leaving some individuals in a disadvantaged condition (Lavazza, 2017). In fact, if TES methods were to be widespread in competitive contexts (e.g., exams, sport, job interviews), those who do not benefit from stimulation (or cannot afford to be stimulated for financial reasons) would be more disadvantaged compared to those able to enhance their skills thanks to neuromodulation.

Other issues are associated with unlimited self-administration and related long-term consequences of stimulation. At present, there is little to no evidence of stimulation consequences for extended long-term use. The possible TES interactions with behavior, such as impulsivity, moral decisions, risk taking behavior (e.g., Darby and Pascual-Leone, 2017; Fecteau et al., 2012) are also frequently discussed points.

Recommendations: Before entering a patient in a TES study, investigators should screen exclusion criteria by a standard questionnaire; consensus has been reached for the questionnaire in Table 9. (http://www.neurologie.uni-goettingen.de/downloads.html) Additional questions and information can be inserted according to particular experimental demands. An affirmative answer to one or more of the questions does not indicate an absolute contraindication to TES, but the risk-benefit ratio should be carefully checked and balanced by the principal investigator (PI) or by the responsible researcher/physician. If participants feel indisposed during or after the stimulation, they should be seen by a medical doctor. Self- or proxy-administration of tDCS at locations remote from the clinicians or investigator benefits from careful consideration of risks and mitigating factors (Charvet et al., 2015).

7.2. Regulatory aspects of TES in the USA and EU

Though the regulatory frameworks differ among countries, the common principles include emphasis on the safety of participating subjects and on professional conduct. Here the regulatory approaches taken in USA and Europe are addressed; nevertheless similar regulations and principles prevail in other parts of the world.

In the USA, the framework comprises a complex system of regulations and recommendations issued by the Good Practices in Clinical Research, Code of Federal Regulations (CFR), and/or the Food and Drug Administration (FDA). CFR is accessible to everyone; regulations pertaining to protection of human subjects appear in Titles 21 and 45. The FDA (Neurostimulation Devices Branch in the Division of Neurological and Physical Medicine Devices at the Office of Device Evaluation) defines medical devices as products that are “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or intended to affect the structure or

any function of the body of man and which does not achieve any of its primary intended purposes through chemical action." Medical devices not cleared by the FDA in the US are required to follow the Investigational Device Exemptions (IDE) regulation (21 CFR Part 812). This regulation describes three types of devices studies: significant risk (SR), non-significant risk (NSR), and exempt studies. Under 21 CFR 812.3(m), a SR device study is defined as a clinical investigation using a device that is intended as an implant, is represented to be for a use in supporting human life, is for a use of substantial importance in mitigating and treating disease or presents a potential for serious risk to the health, safety or welfare of a subject. A NSR device study is one that does not comply with the definition for an SR device study. Certain studies are exempt from the requirements of 21 CFR Part 812, for example: studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling. So far, clinical studies using tDCS devices in the US have been classified as NSR. Sponsors of investigational SR device studies are required to get an approved IDE from the FDA before starting their study. In addition, in accordance with the regulations at Part 812, the study may not start until both FDA and the Institutional Review Board (IRB) of clinical setting have given their approval.

The European Union (EU) with its 28 member states, represented by "Competent Authorities" (similar to the FDA but for individual countries, and while they do not clear/approve products they ensure that the products are built to a certain standard and that any clinical utility is evidenced), pursues the regulation of neuromodulatory devices in different ways. In the EU, equipment intended for medical use is regulated by the Medical Devices Directive 93/42/EEC, which is implemented in each member state in the form of a national act or regulations governing medical devices. The Medical Devices Directive defines a medical devices as "…any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception…" (Medical Devices Directive 93/42/EEC). However, if a manufacturer specifies an intended purpose of a device that is not covered by the above definition, e.g., for wellness, well-being or even for neuroscience research (e.g., for the investigation of physiological processes) the device does not fall under this directive and is therefore not regulated by the Medical Devices Directive (third intent of Article 1(2)(a) of the Medical Devices Directive; European Court Reports 2012: ECLI:EU: C:2012:742). One can thus find the same types of devices in versions for the regulated medical market and for the general market, where other regulations such as consumer safety regulations apply. Another important case, which also might not be covered by the Directive is Compassionate Use, i.e., discretionary therapeutic use of a medical device for which it was not explicitly intended. The regulatory approach to assess risks and benefits for non-therapeutic devices, including enhancement devices, diverges from the approach used for medical devices. Neither the FDA nor the EC regulate the off-label use of stimulators.

The EU Medical Devices Directive distinguishes two important 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 application. All other devices require CE marking. Making a device available is called “placing it on the market,” regardless of whether the device is new or refurbished, for payment or free of charge. Devices intended for clinical evaluation are to be used to test the performance intended by the manufacturer and to determine undesir able AEs during use. Such evaluations are part of the risk assessment of a device and are carried out by a duly qualified practitioner or other authorized person based on the virtue of her/his professional qualifications. The equipment for TES falls in the category of active medical devices, which depend on a source of electrical energy or any source of power. All active therapeutic devices intended to administer or exchange energy are in Class IIa, thus TES devices are Class IIa (MDD, Annex IX, rule 9). Any Class IIa device requires CE marking including the number of the notified body.

All medical devices must fulfill the Essential Requirements for safety and performance described in Annex I of the Medical Devices Directive, which state that a device used for its intended purpose shall not compromise the safety of any person (patients, professional users, and other persons such as visitors). These requirements apply to both design and manufacturing. All risks associated with the use of the device shall constitute acceptable risks. The latter requirement leads to the necessity of a risk analysis, including risks due to the ergonomic features of the product, taking into account the user environment and knowledge (i.e., risk of user error). Consequently, manufacturers need to establish a risk management process, define acceptable levels of risk and demonstrate that the remaining risk is acceptable or mitigated against in the design process. Manufacturers should participate in clinical evaluations of stimulators. These can consist in a critical evaluation of the relevant scientific literature or in a critical evaluation of the results of all clinical investigations, or a combination of both. The critical evaluation of the relevant scientific literature includes all aspects of safety, performance, design characteristics and intended purpose of the TES device. For literature evaluations, the equivalence of the considered devices and the compliance with the relevant essential requirements must be demonstrated.

The Essential Requirements of the Medical Devices Directive require that the device be state of the art and that the manufacturer adhere to world-wide, European and national standards, such as the IEC 60601 family of standards. The IEC 60601 family consists of a series of technical standards for safety, performance and effectiveness of medical electrical devices. Part 60601-1 includes the general requirements for basic safety and essential performance for all medical electrical devices. The collateral standards (60601-1-X; X stands for a specific number) include requirements for specific aspects of safety and performance such as electromagnetic compatibility, and the particular standards (60601-2-Y) provide requirements for specific products. While there is a particular standard for electroconvulsive therapy equipment (60601-2-14) and also a particular standard for nerve and muscle stimulators excluding the head (60601-2-10), there is not yet a standard for TES. Consequently, the definition of the state of the art, as required by the Medical Devices Directive, is given by the basic and collateral standards, and the state of the art described in

the scientific literature. As the latter is naturally quite dynamic and sometimes contradictory, a particular norm for TES would be helpful.

It is the responsibility of the manufacturer or its responsible representative on the European market to affix CE marking for a freely moving product within Europe. There are four ways to obtain the CE marking for Class IIa products: implementing full quality assurance (Annex II of the Medical Devices Directive), or EC declaration of conformity set out in Annex VII in combination with either the procedure relating to the EC verification (Annex IV), the production quality assurance (Annex V), or the product quality assurance (Annex VI).

An important step in fulfilling the Essential Requirements is a documented clinical evaluation (Annex X). The EC gives explicit guidelines for the evaluation of clinical data in the context of medical devices both for manufacturers and notified bodies (MEDDEV. 2.7.1, rev 4, since 28/06/2016) (http://ec.europa.eu/DocsRoom/documents/17522/attachments/1/translations/en/renditions/native). Post-market surveillance by the manufacturer is required for products already on the market and the gathered data must be used to update the clinical evaluation and its documentation. Such surveillance is supported by the European Databank on Medical Devices (Eudamed) (European Commission Decision 2010/227/EU of 19 April 2010 on the European Databank on Medical Devices) and by the responsible authorities of each EU member state and is freely accessible. In the near future, the Global Medical Device Nomenclature (GMDN), which was developed by the European Standards body CEN, will completely replace the separate codes of medical devices in the EU member states. The GMDN code for a continuous current TES system is 62056.

The manufacturer must be able to trace each device on the market and to perform continuing post-market surveillance. The manufacturer must implement a systematic procedure for reviewing experience gathered from devices in the market. It is mandatory that incidents leading to, or possibly leading to, death, or a serious deterioration in the health of a patient or user be reported to the responsible authorities. This is required independent of whether a malfunction or deterioration in the characteristics and/or performance of the device occurred, or the labeling or the instructions for use were inadequate. Medical practitioners are also required to report such incidents. Reporting is also required for systematic recalls of a device by the manufacturer.

Recommendations: Practitioners should know the basic regulatory aspects of the type of stimulator they are using. Practitioners must report all incidents related to the malfunction of a stimulator to the responsible authorities. In June 2016, the European Parliament and the Council reached an agreement for better surveillance and traceability of medical devices. Consequently, new regulations are expected for 2017 and will apply for three years following their publication. We warn against the use of devices and methods unless they have shown both efficacy and safety in appropriately designed clinical trials.

7.3. Safety of freely available (direct-to-consumer) brain stimulation devices

Devices used by non-professionals for self-stimulation, which are available “over-the-counter” on the internet are not at the main focus of this report. Nevertheless, approximately a dozen companies, mostly American, are at present marketing and selling ready-to-use

brain stimulation devices directly to consumers (Wexler, 2016). These direct-to-consumer tDCS companies range from small shoestring operations to larger Silicon Valley start-ups with significant venture capital funding. Furthermore, because TES can be performed with relatively simple devices, laypersons have begun to build their own tDCS devices for use on themselves, with the main goal of self-improvement. They are part of a movement, informally known as the “do-it-yourself (DIY) tDCS” online community (such as Reddit.com or diytdcs.com).

To date, only two studies of direct to consumer TES-users exist. Jwa (2015) conducted a survey of those who use brain stimulation at home, and Wexler (2016) presented a preliminary sketch of the practices of home users, based on qualitative research. In the Jwa (2015) sample (n = 121), respondents were mostly males (94%) in their 20s and 30s (71%) who resided in North America (74%). Wexler (2016) studied how users attempt to measure the effects of tDCS, finding that those who use tDCS for cognitive enhancement often attempt to measure the effect by assessing their performance in cognitive tests that are freely available online. In contrast, those who use tDCS for self-treatment, typically for mood disorders, often rely on a subjective sense of self-improvement as evidence of efficacy (Wexler, 2016). To some extent, home users adhere to the current levels employed in scientific studies, though they tend to experiment with the duration and frequency of stimulation.

There is little reliable data on the safety or effectiveness of direct-to-consumer brain stimulation devices. The only study to-date conducted outside the commercial realm found that stimulation with the Foc.us v1 device caused subjects to perform worse on the accuracy component of a working memory task than subjects who received sham stimulation (Steenbergen et al., 2016). Companies such as Thync® and Halo Neuroscience® have conducted in-house studies, both on safety and efficacy, and have posted some of their data online, though little has been published in academic journals. Further, evaluations have been over several weeks of use, while many in the DIY community apply stimulation over longer periods.

In the USA a fundamental legal issue is whether direct-to-consumer brain stimulation devices should be considered medical devices, and therefore be subject to relatively stringent regulations, or instead be considered consumer products and thus subject to more lenient regulations (in the EU this is no issue: if the manufacturer specifies an intended use other than medical, the Medical Devices Directive does not apply). The crux of the problem lies in the legal definition of a medical device, which depends not on a product’s mechanism of action but rather on its “intended use,” which is determined from a product’s advertising and labeling. In the United States, for example, a product is considered a medical device if it is intended for use in the diagnosis or treatment of disease or other medical conditions, or if it is intended to affect the structure or function of the body.

Since many direct-to-consumer brain stimulation device manufacturers do not make medical claims, instead marketing their products for “enhancement” or “wellness,” it is unclear whether these products meet the first part of the definition of a medical device in the USA. Whether consumer tDCS devices meet the second part of the definition is a more difficult

issue discussed in detail elsewhere (Wexler, 2015). To date, the only instance of regulatory enforcement was by the California Department of Public Health, which in May 2013 took action against a company called tDCS Device Kit, Inc., for violating California's Sherman Food, Drug, and Cosmetic Law. No other regulatory authorities, in the United States or elsewhere, have issued formal statements or taken any kind of regulatory action with regard to direct-to-consumer tDCS devices.

Many of the ethical questions that arise from the consumer use of brain stimulation go hand-in-hand with the regulatory ones, particularly with regard to safety. Although a device or technique might informally be referred to as "safe" or "unsafe," it may be better to consider safety as the outcome of a constellation of variables that include users (i.e., who is using the device), devices (what kind of device they utilize), and stimulation parameters (how they are using the device). In addition, safety may refer to acute issues (such as headache that may occur during stimulation) or long-term ones (such as potentially deleterious effects on cognition).

With regard to short-term safety issues, no SAEs have been reported by tDCS home users either, at least not on the Reddit forum. In one survey of home users, approximately half of the respondents reported experiencing mild AEs during stimulation (Jwa, 2015). The long-term effects of tDCS on cognition are more difficult to measure. At least one study has suggested that using tDCS to "enhance" certain functions may impair others, however, it was detected immediately after the application (Iuculano and Cohen Kadosh, 2013). Thus, one of the main points of contention with regard to consumer tDCS is whether a technique that may —or may not—have detrimental effects on cognition should be freely available to the public. Along these lines, researchers and ethicists have been particularly concerned about the use of tDCS on children, especially since few laboratory studies have examined the effects of brain stimulation in this vulnerable population.

Summary and recommendation: More data is needed on the consumer neurotechnology market with regard to the prevalence of AEs related the home use of tDCS, and the effects of repeated stimulation to help illuminate the most prudent pathway forward through the ethical and legal complexities of consumer brain stimulation. Thus, the International Federation of Clinical Neurophysiology (IFCN) warns against the use of DIY devices and methods unless they have shown both efficacy and safety (https://goo.gl/uZsXAb), and a recent open letter from researchers to the DIY community outlined the risks of the home use of electrical brain stimulation (Wurzman et al., 2016).

7.4. Where should/could TES be performed and by whom?

No legal obligations exist to prevent application of TES outside a hospital environment. However, the manufacturer of the medical device determines the scope the medical device including labeling, indented use, user and environment. That means that the manufacturer might specify a particular device for hospital use only. In clinical studies a decision on the risk-benefit ratio has to be made by the investigator and approved by the Ethical Committee or IRB. There are no fundamental scientific objections against home use exist either, since successful scientific studies on that topic have been published (e.g., Andre et al., 2016; Wickmann et al., 2015).

The first consideration in dealing with the question of where TES should be performed is the establishment of a risk profile. If the risk is more than minimal, as e.g., in patient populations, then it is suggested that stimulation is performed in a hospital setting. Risk should be assessed not only for the nature of the technique, but also for the subjects being studied (e.g., whether the population is vulnerable or whether there might be an interaction with concurrent medication). If there is no more than minimal risk, stimulation could be performed in a research setting outside a hospital or at home. The research setting should be approved by the responsible IRB or Ethics Committee, and written, informed consent should be obtained. If there were approved medical indications for home use, a signed document confirming that the subject understands the instructions and intends to use the device as prescribed, would be needed.

In a situation that is deemed to pose no more than minimal risk, in which stimulation is conducted at a research center or at home, the critical issue should be the proper use of the equipment, and this would require adequate training. Training of researchers is considered below, but training is just as important for subjects if tDCS is to be performed at home. Remote supervision, possibly using the internet, would be important in order to help prevent protocol violations and assure maximal safety (see e.g., (Perez-Borrego et al., 2014) for an example of successful telemonitoring of long term home use of tDCS therapy in a patient). To assist subjects with home delivery of tDCS, equipment functions could be restricted and/or simplified to encompass only specific stimulation needs. Stimulators should internally record and document stimulation parameters of each stimulation session; this would permit complete monitoring of what was done and also identify noncompliance.

7.4.1. Training—Training has two facets: (1) the correct use of the device, and (2) safety issues, i.e., knowing how to prevent and monitor for AEs, and how to deal with them should they arise. While physicians should be involved in any procedure that poses more than minimal risk, there is no requirement that persons performing the stimulation should have a specific profession. Researchers should know about the principles of TES and the physiology of its desired and undesired effects. Researchers, technicians and even the subjects themselves, in the setting of home use, would need to know how to set up the equipment, how to place the electrodes correctly, and how to assure the prescribed dose of stimulation. After a period of instruction, individuals should be assessed to make sure that they are able to perform all the procedures correctly. At present, the teachers are persons with the most experience in the field; both self-declared and recognized by others usually on the basis of their publications. In the long run, teachers might need a kind of certification such as warranted country-specific in other areas of the public health service.

Recommendations: Persons performing TES should also know how to prevent, assess, report, and deal with AEs, when they occur. Skin burns are an acute moderate risk if electrodes are improperly employed, and operators and patients should be alert to any feeling of pain or heat under the electrodes. In certain circumstances, it would be appropriate to know how to deal with cognitive or emotional changes. Since so far no confirmed incidence of seizures has ever occurred in the context of TES, training in dealing with seizures is not necessary at present.

8. How to assure safety in the future?

AEs have been rare and minor in the course of thousands of hours of TES in controlled settings. CE certified stimulation devices are current-controlled; they limit the maximum current delivered per electrode (<2–4 mA), the maximum stimulation voltage with an auto-abort option if the pre-set current cannot be delivered beyond a defined voltage level and the maximum total current delivered through all electrodes at any moment. They force users to set the program duration, and check impedance before and during stimulation. The following additional measures could further increase safety:

1. Verification (visual inspection) of the stimulation parameters should be done before each stimulation session, when it is possible (e.g., when the study is not double blinded). Additionally, because, like any device, a TES device can malfunction without visible signs, a regular performance verification check by operators or manufacturers is also warranted (e.g., in every second year depending on country specific regulations).

2. A standard system for reporting the multidimensional parameter space used for an experiment. Clearly defined protocols with specification of electrode type, positions, current type (DC/AC) and intensity, duration, and session sequencing allow for better reproduction, interpretation and comparison of results among laboratories, and facilitate the development of new applications. A longer, comprehensive and shorter, basic checklist can be found in Table 10. The lists can be downloaded from the website http://www.neurologie.uni-goettingen.de/downloads.html.

3. Specifically querying for known AEs: The use of standardized questionnaires that query about the occurrence of specific AEs and offer numeric scales for rating the intensity (e.g., Fertonani et al., 2015; Poreisz et al., 2007). We propose the publication of completed questionnaires even if no AEs occurred. Consensus was reached with the questionnaire in Table 11, which contains detailed questions regarding a thorough list of known AEs. It can be modified according to specific experimental conditions. The documents can be downloaded from the website: http://www.neurologie.uni-goettingen.de/downloads.html.

4. Analyzing potential differences in specific populations such as between age-groups. Validated questionnaires for assessing AEs or any type of stimulation-associated sensation in older adults are not widely acknowledged as part of the research routine, and, if applied, are not standardized. From the realm of pharmacological interventions, it is well-known that older adults are more susceptible to negative effects on cognition or mood, or increased dizziness, in response to almost any central-nervous system-active drugs (Thiem, 2012).

5. Unknown AEs: AEs not yet encountered or reported may be detected by explicitly asking about “other AEs/sensations.” For a better understanding and sorting beyond these categories of causality and severity, one may adopt a classification that was initially employed to target drug AEs (Rawlins, 1981). In this classification, type A AEs correspond to an excess of the intended effects

(e.g., too much sedation, too much blood pressure lowering). Type B AEs occur in an unexpected form, with individual administrations or doses of an intervention, usually in subjects with a particular susceptibility, and type C AEs only occur in chronic application of a procedure or substance.

6. Reporting each patient's guess for type of stimulation (active/sham) and reporting the researcher's assessment of the patient's propensity to complain (cf. Fertonani et al., 2015; Wallace et al., 2016) is required in controlled blinded studies.

9. Summary

Given the growing interest in the non-invasive TES technologies, in this paper a range of researchers, clinicians, ethicists and developers of devices/new technologies summarized safety and ethical issues surrounding the use of TES for the treatment of nervous system disorders as well as for non-therapeutic uses, including cognitive and functional enhancement. Low intensity TES so far appears to be a safe technique. Typical AEs are itching, burning sensations under the electrode or transient, mild headaches. MAEs are mainly skin burns, which can be controlled by preventing electrodes from drying, and improving skin-electrode contact. As in drug studies, the incidence of AEs increases with the use of questionnaires, in parallel with the increase of incidence of AEs under placebo stimulation.

Modeling and imaging studies suggest that the effects of TES are not limited to the targeted brain area, and some behavioral and therapeutic effects are probably mediated by distant brain regions affected via trans-synaptic connections and non-neuronal effects. Better understanding of these connections and effects, e.g., by pre-stimulation EF modeling for targeting definition, would enable us to improve the therapeutic approaches. Individual subject-specific modeling may lead to more reproducible results across individuals, increasing safety further by minimizing current flow in non-target regions.

Similarly, a better understanding of why some people do not respond to neuromodulation is needed. The determination of dose – biological effect relationships, optimal duration and repetition rate of stimulation in clinical studies, and definition of appropriate washout periods for different stimulation protocols are required. Simultaneous registration of EEG or fMRI to study physiological effects in these studies should be informative. It seems clear that a single session of tDCS is safe if done properly, however, much less is known about repeated sessions in the long-term, which is how it will be used for treatment and enhancement. Home use of TES could enable a more individualized treatment and probably increase efficacy, but requires a better understanding of the effects of more frequent patterns of stimulation and raises concerns about clinical supervision and regulations. Tele-monitoring of home use should help to better appraise and control the impact of tDCS therapy in a familiar surrounding.

The safety of the method has mostly been verified in adults with intact skulls, no implants, etc. Other groups are less well studied, and even less is known about the long-term effects and safety for the use of tDCS in children or elderly populations. Future research should

carefully specify and limit duration, intensity, and repetition of sessions in these populations. More detailed and sensitive examinations for potential safety issues are required. Minor to moderate alterations in features such as mood, cognitive functions or motoric functions cannot be assessed using questionnaires completed by the stimulation subjects themselves. Depending on the possible range of AEs, sensitive neurological, psychological tests should be performed in studies using a double blind design, especially when higher stimulation intensities and/or longer durations are used that can strongly interfere with brain functions.

Other forms of low intensity TES methods, such as tACS, tRNS, have been studied less extensively. However, in case of generally using accepted tACS protocols, potentially induced AEs do not include structural or functional damage. For example, no seizure induction has been reported to date for tACS.

Cognitive enhancement is perhaps the most widely publicized, non-therapeutic application of brain stimulation. The alleged effects of TES on attention, memory, learning, visuomotor performance and other neuropsychological functions have led to a growing industry in non-therapeutic enhancement tools, even though the long-term effects of TES are not well documented and the possible negative consequences of the technique are not completely ruled out.

The regulatory landscape for TES devices is important and will likely evolve. We discussed the significance of potential outcome measures for therapeutic uses in the regulatory process, and explored strategies for obtaining the approval of therapies utilizing a combination of TES and pharmaceuticals. During the safety meeting differences in the regulatory pathways in different countries, and the benefits of harmonizing the regulatory policies were also mentioned. The question remained open whether the regulatory policies for medical devices should be extended to TES devices for neuroenhancement in order to promote the safe use of such devices.

Questions pertaining to ethics and patient safety with regard to off-label and over-the-counter uses of tDCS are very complex. One reason is that there is no clear distinction between medical and non-medical approaches (e.g., neuroenhancement applications in healthy individuals cover potential therapeutic indications in patients). Other problems are related to the diverse and multifaceted regulations in different countries and to the quality of performed trials. For example, recent findings even suggest that other electrical stimulation devices and methods that are cleared for use in psychiatric disorders are supported by low-quality data only (Philip et al., 2017).

An emerging market for direct-to-consumer non-therapeutic products raises questions about safety and efficacy in the home setting, since the safety of unsupervised use is an area of concern. On the most popularly used Reddit tDCS forum, many comments can be seen that indicate a lack of understanding of tDCS uses and effects, and which suggest that the application of stimulation by some users may be unsafe.

In summary, in this guideline we provided an overview of the technical parameters and basic principles of TES, either used alone or combined with other methodologies. We addressed safety aspects of the stimulation, including reporting of AEs in healthy subjects and different

patient populations. Finally, we summarized recent regulatory issues and recommended checklists and questionnaires for reporting. These forms are available and can be downloaded freely from the internet: http://www.neurologie.uni-goettingen.de/downloads.html.

Acknowledgments

We would like to thank Prof. Dr. Michael Siniatchkin for his helpful comments in the chapter summarizing the AEs of tDCS in pediatric populations and to Dr. Oluwole Awosika for his contribution in the chapter Published AEs in the post-stroke treatment. We thank Christine Crozier and Dr. Thomas Crozier for language editing of the manuscript. Felipe Fregni is supported by NIH research grants and also a grant from Labuschagne Foundation. Dr. Hallett is supported by the NINDS Intramural Program. Michael A. Nitsche receives grants from the German Federal Ministry for Education and Research (GCBS, grant 01EE1403C, TRAINSTIM, grant 01GQ1424E), and from the EC FET program (LUMINOUS project, grant 686764). Marom Bikson receives grants from the National Institutes of Health (1R01NS101362-01, 1R01MH111896-01, 1R01NS095123-01, 1R01MH109289-01).

Conflict of interest: Mark S. George has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands, and has received research funds from Brainsway, Mecta, Neuronetics, Neo-sync and TAL medical. Hartwig R. Siebner has served on a scientific advisory board for Lundbeck A/S, Valby Denmark, and has received honoraria as speaker from Biogen Idec, Denmark A/S, Genzyme, Denmark and MerckSerono, Denmark, has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, has received travel support from MagVenture, Denmark, and has received a research fund from Biogenidec. Marom Bikson has patents on brain stimulation and equity in Soterix Medical Inc. Walter Paulus is a member of the scientific advisory board of Precisis and has a patent on tran-scranial deep brain stimulation. He and Friedhelm C. Hummel are members of the scientific board of EBS technologies. Ulf Ziemann has received honoraria from Biogen Idec Deutschland GmbH, Bayer Vital GmbH, Bristol Myers Squibb GmbH, CorTec GmbH, Medtronic and Servier for advisory work, and grants from Biogen Idec and Janssen Pharmaceuticals NV for supporting investigator initiated trials. Mark Hallett may accrue revenue on US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He has received honoraria from publishing from Cambridge University Press, Oxford University Press, and Elsevier. Dr. Hallett has research grants from UniQure for a clinical trial of AAV2-GDNF for Parkinson Disease, Merz for treatment studies of focal hand dystonia, and Allergan for studies of methods to inject botulinum toxins. Michael A. Nitsche serves on a scientific advisory board for Neuroelectrics. Pedro C. Miranda serves on the scientific advisory board for Neuroelectrics, Barcelona, Spain, receives license fee payments for US Patent #7,407,478, and receives research funds from Novocure, Israel. Christoph Herrmann has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands, and has filed a patent application on brain stimulation. Klaus Schellhorn works as a full-time employee (Chief Technical Officer) of neuroCare Group. Alberto Priori founded Newronika srl Company (Italy), he has patents on brain stimulation and is stakeholder of the company. Giulio Ruffini holds patents on multichannel brain stimulation and the combination of EEG and brain stimulation, and is a Neuroelectrics shareholder. Rafal Nowak works as a full-time employee for Neuroelectrics. Colleen Loo has received equipment support from Soterix Medical for investigator-initiated research. Jens Ellrich has received honoraria from Autonomic Technologies Inc. (ATI), WISE Neuro Srl, and Nuviant GmbH for advisory work, and is an employee (Chief Medical Officer) of EBS Technologies GmbH. Dr. Ugawa has received grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 22390181, No. 25293206, No. 15H05881), the Ministry of Health, Labour and Welfare of Japan, the Support Center for Advanced Telecommunications Technology Research, the Association of Radio Industries Businesses, and the NOVARTIS Foundation (Japan) for the Promotion of Science, Nihon Kohden, LTD, Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd., Mit-subishi Tanabe Pharma Corporation. Dr. Ugawa received honoraria from the Taiwan Movement Disorders Society, Chinese Neurology Society, Astellas Pharma Inc., Eisai Co., Ltd., FP Pharmaceutical Corporation, Otsuka Pharmaceutical Co., Ltd., Elsevier Japan K. K., KIS-SEI PHARMACEUTICAL CO., Ltd., KYORIN Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline K. K., Sanofi-Aventis K.K., DAIICHI SANKYO Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, TEIJIN PHARMA LIMITED, Nippon Chemiphar Co., Ltd., NIHON PHARMACEUTICAL Co., Ltd., Nippon Boehringer Ingel-heim Co., Ltd., Novartis Pharma K.K., Bayer Yakuhin, Ltd., and MOCHIDA PHARMACEUTICAL Co., Ltd. and received royalties from CHUGAI-IGAKUSHA, Igaku-Shoin Ltd, Medical View Co. Ltd., and Blackwell Publishing K.K. Gary Dowthwaite is a full time employee of the Magstim Company Ltd. John Rothwell has received honoraria as deputy editor from Elsevier Publishers, Amsterdam, The Netherlands and from the Movement Disorders Society.

Abbreviations

AC	alternating current
AD	Alzheimer's disease
AE	adverse event
AR	adverse reaction
CFR	Code of Federal Regulations
CNS	central nervous system
DBS	deep brain stimulation
DC	direct current
DIY	do it yourself
DLPFC	dorsolateral prefrontal cortex
EC	European Commission
ECT	electroconvulsive therapy
EEG	electroencephalography
EF	electric field
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
HD-tDCS	high-definition tDCS
ICH	International Council on Harmonisation (before 2015: International Conference on Harmonisation)
IFG	inferior frontal gyrus
M1	primary motor cortex
MAE	mild adverse event
MDD	major depressive disorder
MEG	magnetoencephalography
MEP	motor evoked potential
MMSE	mini mental state examination
MRS	magnetic resonance spectroscopy
NSE	neuron specific enolase

NMDA	N-methyl-D-aspartate
ONS	optic nerve stimulation
PD	Parkinson's disease
PFC	prefrontal cortex
PPC	Posterior Parietal Cortex
RCT	randomized clinical trial
rTMS	repetitive transcranial magnetic stimulation
SAE	serious adverse event
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
tsDCS	transcutaneous spinal direct current stimulation
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
TPJ	temporoparietal junction
tRNS	transcranial random noise stimulation
Vmem	transmembrane potential

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HIGHLIGHTS

- The application of low intensity TES in humans appears to be safe.
- The profile of AEs in terms of frequency, magnitude and type is comparable in different populations.
- Structured checklists and interviews as recommended procedures are provided in this paper.

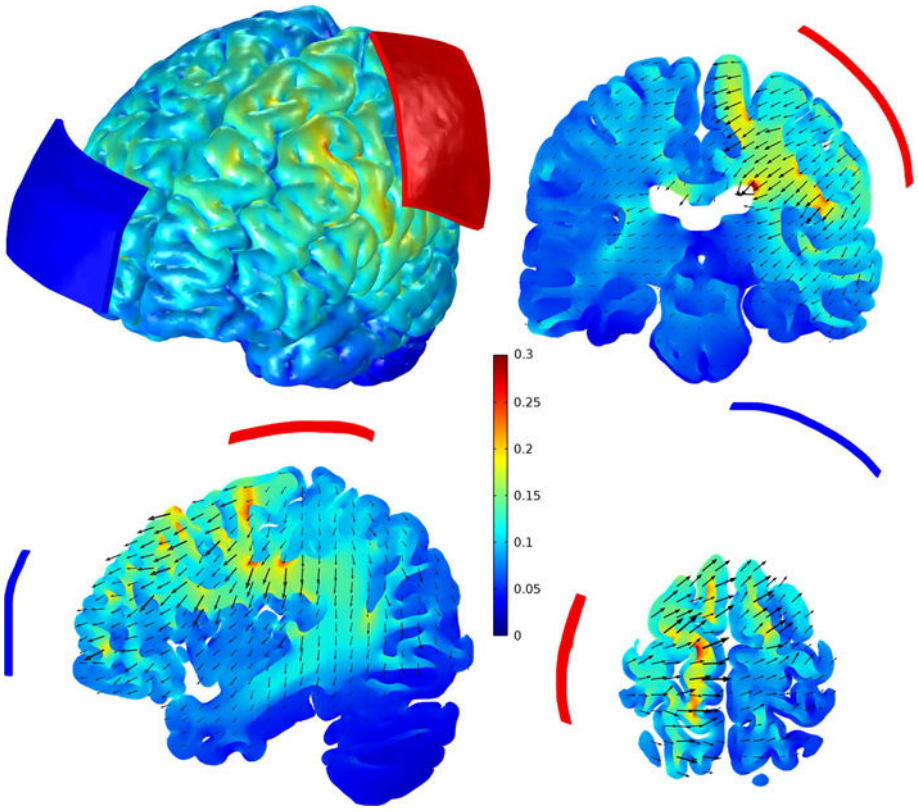

Fig. 1.

Magnitude of the electric field in the cortex, in V/m. The maximum value of the electric field in the cortex was 0.34 V/m. The 7 × 5 cm^2 electrodes were placed over the left hand knob and above the contralateral eyebrow, and the current was set to 1 mA. The three slices pass through the center of the hand knob.

Table 1

AEs of galvanism. For detailed explanation see text.

Althaus (1860)
p. 88 – Stabbing Pain on the skin which leads to an erythema
p. 89 – strong convulsions similar to a poisoning with Strychnine
p. 91 – clonic convulsions
p. 93 – tetanic convulsions of the extremities during the stimulation of the spinal cord
p. 96 – lightning sensation during stimulation of the visual organ
p. 101 – tickling and pain sensation in the olfactory organ
p. 102 – sensation of hearing sounds during the stimulation of the hearing organ
p. 104/106 – gustatory sensation and abundant secretion of saliva after stimulating the trunk of the chorda tympani
p. 162 – sympathetic reaction after galvanizing the cervical part of the sympathetic chain
p. 164 – increased heartbeat
Augustin (1801)
p. 46 – strong shock while touching the device with wet fingers
p. 55/56 – impact of the voltaic pile on the organs of the human body
p. 57 – impact of the voltaic pile on the sensory organs (burning pain, vibrating light)
p. 58 – fainting during stimulation with wire between mouth and nose with a pile constructed out of 20–30 layers
p. 58/59 – strong hearing sensation, vertigo
p. 60 – heat sensation during contact with the tongue
p. 64 – sickness after long stimulation with a battery with 100 layers, eye inflammation, vertigo, headache
p. 69 – patient becomes hypersensitive – cannot continue procedure
p. 70 – battery with 40/50 layers leads to strong pain and convulsions
Grappengiesser (1801)
p. 18 – convulsive ascending and descending of the pharynx
p. 60 – hearing sensation in the auditory passage (meatus acusticus)
p. 62 – burning pain in the auditory passage/stabbing pain in the nose
p. 72/73 – effects on the visual organ listed in tabular form
p. 82/83 – different kind of pains while contact with zinc- or silverpole
p. 88 – depression and excitation of the Nervus Ischiadicus
p. 90 – rigidity and less movement in the region of the shoulder
p. 95 – numbness while stimulating with the silverpole
p. 98 – induction of paroxysm
p. 109 – pain from feet to abdomen while stimulating the feet
p. 139 – induction of deafness and hearing sensation
p. 140 – increasing hearing sensations
p. 168 – toothache after repetitive stimulation of the jawbone
p. 169 – lightning sensation while applying brass conductors onto the cornea
p. 235 – light vertigo, light hearing sensation and lightning sensations
Hellwag and Jacobi (1802)
p. 105 – gustatory sensation on the tongue, lightning sensation
p. 108 – increased excitability of organs while stimulating with the zinc pole

p. 121/122 – patient got a concussion after stimulating the tongue with a battery

p. 123/124 – electric shock after stimulating with two conductors and one battery

p. 124 – lightning sensation with closed eyes – pain with open eyes

p. 152/153 – stimulation of a young men with a tender body with a battery with six layers. The sponge of the conductor chained with the zinc pole rests on the association of the left lacrimal bone/the other one on the Foramen supraorbitale → strong convulsions in both arms and strong lightning sensations (Pain lasted for two days)

p. 154 – hearing sensation and vertigo after stimulating with 30 layers/stimulating with up to 70–80 layers and a double-battery

p. 157 – rash on the skin similar to scabies

p. 176 – strong vertigo and hearing sensation after stimulating with 6 layers

p. 185 – strong pain in the hand after stimulating with 20 layers

Ziemssen (1864)

p. 39 – pain after stimulating branches of the N. auriculo-temporalis

p. 45 – tetanic convulsions after stimulating a hernia

p. 48 – partial anemia and spastic constriction during stimulation of vessels

p. 49 – hyperaemia of the skin

p. 77 – unpleasant sensation while stimulating the skin nerves

p. 158 – Stimulation of the median nerve leading to pain

Table 2

Examples of persisting skin lesions induced by tDCS.

Subjects/patients	Stimulation electrode position (polarity)	Return electrode position (polarity)	Current settings	Session duration (minutes)	Number of sessions	AEs	Reference
3 patients with chronic tinnitus	F3 (C)	F4 (A)	1.5 mA, 0.043 mA/cm^2	30	4	Skin lesions under anodal electrode	(Frank et al., 2010)
1 patient with tempomandibular disorder	M1 (C3 or C4) (A)	Contralateral supraorbital (C)	2 mA, electrode size is not reported	20	5	Skin burn after the fifth sessions	(Oliveira et al., 2015)
5 patients with depression	F3 (A)	Contralateral supraorbital (C)	2 mA, 0.057 mA/cm^2	20	5	Skin lesions under cathodal electrode	(Palm et al., 2008a)
1 healthy subject	Posterior superior temporal sulcus (C)	Supraorbital (A)	0.75 mA, C: 0.083 mA/cm^2 A: 0.0075 mA/cm^2	20	1	Contact dermatitis under both electrodes	(Riedel et al., 2012)
3 patients with neuropathic pain secondary to spinal cord injury	C3 or C4 (A)	Contralateral supraorbital (C)	2 mA, 0.057 mA/cm^2	20	2–10	Skin lesions under cathodal electrode	(Rodriguez et al., 2014)
1 healthy subject	F3 (A)	Contralateral supraorbital (C)	2 mA, 0.057 mA/cm^2	26	1	Skin burn under cathodal electrode	(Wang et al., 2015)

tDCS: transcranial direct current stimulation, A: anode, C: cathode; AE: adverse event.

Table 3

Adverse events in combined tDCS/rTMS studies in healthy volunteers.

Site of PS/TS	Priming stimulation	Test stimulation	Delay between PS/TS (min)	Adverse events	Reference
M1/M1	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	5 Hz rTMS, 90% RMT, 100P	~5	None	(Antal et al., 2008b)
V1/V1	atDCS, 1.5 mA, 20 min ctDCS, 1.5 mA, 20 min	5 Hz rTMS, 85% RMT, 300P 1 Hz rTMS, 85% RMT, 600P 5 Hz rTMS, 85% RMT, 300P 1 Hz rTMS, 85% RMT, 600P	15–20	None	(Bocci et al., 2014)
M1/M1	atDCS, 1.5 mA, 15 min ctDCS, 1.5 mA, 15 min	6 × 5 Hz rTMS 120% RMT, 10P	<1	None	(Cosentino et al., 2012)
M1/M1	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	5 Hz rTMS, 100% AMT, 100P	10	None	(Lang et al., 2004)
V1/V1	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	5 Hz rTMS, 90% PT, 100P	~5	None	(Lang et al., 2007)
M1/M1	atDCS, 1 mA, 7 min ctDCS, 1 mA, 7 min	PAS_{LTP} (7 min)	<1	Not reported	(Nitsche et al., 2007b)
M1/M1	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	1 Hz rTMS, 90% RMT, 15 min	10	None	(Siebner et al., 2004)

Abbreviations: PS, priming stimulation; TS, test stimulation; M1, hand area of primary motor cortex; V1, primary visual cortex; RMT, resting motor threshold; AMT, active motor threshold; PT, phosphene threshold; rTMS, repetitive transcranial magnetic stimulation; PAS, paired associative stimulation; atDCS, anodal transcranial direct current stimulation; ctDCS, cathodal transcranial direct current stimulation; P, pulses.

Table 4

Adverse events in combined tDCS/rTMS clinical studies.

Site of PS/TS	Patients	Priming stimulation	Test stimulation	Delay between PS/TS	Adverse events	Reference
M1/M1	Migraine with aura	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	5 Hz rTMS, 90% RMT, 100P	~5 min	None	(Antal et al., 2008b)
M1/M1	Migraine with aura, migraine without aura	atDCS, 1.5 mA, 15 min ctDCS, 1.5 mA, 15 min	6 × 5 Hz rTMS, 130% RMT, 10P	<1 min, or 20 min	None	(Cosentino et al., 2014)
M1/M1	Writer's cramp	atDCS, 1 mA, 10 min ctDCS, 1 mA, 10 min	1 Hz rTMS, 85% RMT, 15 min	10 min	None	(Quartarone et al., 2005)

For abbreviations, see Table 3.

Table 5

Summary of the main findings of tDCS review publications in pediatric populations.

Title of study	Main findings	Reference
Noninvasive Brain Stimulation: The Potential for Use in the Rehabilitation of Pediatric Acquired Brain Injury	NIBS may serve as a tool for pediatric neurorehabilitation, but many gaps in our knowledge must be filled before NIBS can be adopted as a clinical intervention	(Chung and Lo, 2015)
Safety of noninvasive brain stimulation in children and adolescents	TMS and TES are safe modalities in children and adolescents	(Krishnan et al., 2015)
Transcranial Direct Current Stimulation in Child and Adolescent Psychiatry	tDCS may be well tolerated and safe for children and adolescents with psychiatric and neurodevelopmental disorders, at present it is not possible to draw definite conclusions	(Muszkat et al., 2016)
Transcranial direct current stimulation in children and adolescents: a comprehensive review	Overall, tDCS seems to be safe in pediatric population	(Palm et al., 2016)
Noninvasive Brain Stimulation in Pediatric Attention-Deficit Hyperactivity Disorder (ADHD): A Review	The safety profile of tDCS is excellent and the main documented AEs are an itching sensation and skin redness under the electrode	(Rubio et al., 2016)
The use of noninvasive brain stimulation in childhood psychiatric disorders: new diagnostic and therapeutic opportunities and challenges	Although the utilization of TMS and tDCS remains limited in children, there is enough evidence for their rational, safe use in this population	(Rubio-Morell et al., 2011)
Transcranial Direct Current Stimulation in Epilepsy	Induce suppression of epileptiform activity	(San-Juan et al., 2015)
Transcranial direct current stimulation: a remediation tool for the treatment of childhood congenital dyslexia?	The studies provide preliminary evidence in support for a therapeutic potential of non-invasive stimulation techniques in children and adolescents	(Vicario and Nitsche, 2013)

NIBS: noninvasive brain stimulation, tDCS: transcranial direct current stimulation, TMS: transcranial magnetic stimulation, AE: adverse event.

Table 6

Major reported AEs and related stimulation protocols in pediatric populations.

Study population, number of subjects	Age range or mean age (years)	Montage; electrode size	Intensity, duration, # of sessions	AEs	Reference
Autism (n = 24)	5–8	F3 (A), shoulder contralateral (C); 35 cm^2	1 mA; 20 min; #2	Transient erythematous rash	(Amatachaya et al., 2015)
Autism (n = 24)	5–8	F3 (A), shoulder contralateral (C); 35 cm^2	1 mA; 20 min; #5	None	(Amatachaya et al., 2014)
Various language disorders (n = 14)	5–12	Broca area (A), right supraorbital area (C); 35 cm^2	2 mA; 30 min; #10	Slight mood changes, irritability, tingling, itching, headache, burning sensation, sleepiness, trouble concentrating	(Andrade et al., 2014)
Cerebral palsy (n = 46)	13	Left primary motor cortex (A), right shoulder (C); 35 cm^2	1 mA; 20 min; # 5	Erythematous rash in 1 patient	(Aree-uea et al., 2014)
Lennox-Gastaut Syndrome (n = 22)	6–15	Left M1 (C), right shoulder area (A), 35 cm^2	2 mA; 30 min; # 5	Mild skin burn	(Auvichayapat et al., 2016)
Epilepsy (n = 36)	6–15	Epileptogenic focus (C); right shoulder (A); 35 cm^2	1 mA; 20 min	None	(Auvichayapat et al., 2013)
ADHD (n = 9)	6–16	F3 (A); right supraorbital area (C); 35 cm^2	2 mA; 30 min; 5x	Mild headache, neck pain, tingling, itching, burning, local redness, sleepiness	(Bandeira et al., 2016)
Dystonia (n = 9)	10–21	C3 or C4 (A or C); contralateral forehead, (A or C); 28 cm^2	2 mA; 9 min; # 5	Tingling at beginning, one patient with mild headache	(Bhanpuri et al., 2015)
Infantile cerebral paralysis (n = 21)	6–18	F1 (A); C3 (C); 600 mm^2	0.2–0.8 mA, Max 35 min, #15	Slight heating under the electrodes	(Bogdanov et al., 1993)
ADHD (n = 46); healthy control (n = 21)	13–17	F8 (A), P7 (C), 35 cm^2	1 mA; 20 min	None	(Breitling et al., 2016)
Cerebral palsy (n = 1)	5	F5 (Broca's area) (A); contralateral supraorbital (C); 25 cm^2	1 mA; 20 min; # 10	None	(Carvalho Lima et al., 2016)
Neurotypical children (n = 24)	9–19	Respective primary motor cortex (A or C); contralateral forehead (A or C); 25 cm^2	A: 1 mA C: 1 mA C: 2 mA; 20 min	None	(Ciechanski and Kirton, 2017)
Cerebral palsy (n = 20)	5–10	M1 (A); supraorbital region (C); 25 cm^2	1 mA; 20 min; # 10	None	(Collange Grecco et al., 2015)
Autism, Drug-Resistant Catatonia (n = 1)	14	Left DLPFC (A) right DLPFC (C); 25 cm^2	1 mA; 20 min; #28	None	(Costanzo et al., 2015)
Dyslexia (n = 18)	10–18	Left parietotemporal (A); contralateral region (C); 25 cm^2	1 mA; 20 min; #18	None	(Costanzo et al., 2016a)
Dyslexia (n = 19)	10–18	Left parietotemporal (A); contralateral region (C); 25 cm^2	1 mA; 20 min	Mild tingling, itching, burning, sleepiness	(Costanzo et al., 2016b)
Epilepsy (n = 1)	4	Right motor cortex (A); 25-cm^2	1.2 mA; 20 min	Seizure after anodal tDCS	(Ekici, 2015)

Study population, number of subjects	Age range or mean age (years)	Montage; electrode size	Intensity, duration, # of sessions	AEs	Reference
Fibromyalgia (n = 48)	18	C3 (A); contralateral supraorbital (C); 35 cm^2	2 mA; 20 min	None	(Fagerlund et al., 2015)
Hemiparesis (n = 13)	7–18	M1 lesioned hemisphere (A); M1 nonlesioned hemisphere (C); 35 cm^2	0.7 mA; 10 min	Itching, burning, sleepiness, difficulty concentrating	(Gillick et al., 2015)
Delayed neuro-psychomotor development (n =1)	3	C3 (A); supraorbital (C), 25 cm^2	1 mA; 20 min; #10	None	(Grecco et al., 2014b)
Cerebral palsy (n = 24)	4–11	M1 (A); supraorbital (C), 25 cm^2	1 mA; 20 min; #10	Not reported	(Grecco et al., 2014a)
Cerebral palsy (n = 56), Healthy control (n = 28)	5–10	M1 (between Cz – C3 or C4) (A); contralateral supraorbital (C); 25 cm^2	1 mA; 20 min	Not reported	(Grecco et al., 2016)
Cerebral palsy (n = 12)	4–12	M1 (A); supraorbital (C); 25 cm^2	1 mA; 20 min	Not reported	(Lazzari et al., 2015)
Childhood-onset schizophrenia (n = 13)	10–17	Left and right DLPFC (n = 8) (bilateral A); left and right STG (n = 5) (bilateral C); in both cases R was placed on the non-dominant forearm; 25 cm^2	2 mA; 20 min; #10	Tingling, itching	(Mattai et al., 2011)
Healthy subjects (n = 19)	11–16	M1 (A or C); contralateral frontopolar (A or C); 35 cm^2	1 mA, 0.5 mA; 10 min	Tingling, itching	(Moliadze et al., 2015b)
ADHD (n = 14)	10–14	F3 and F4 (A); ipsilateral mastoids (C); 13 mm outer diameter; 8 mm inner diameter: 0.503 cm^2 area	0.497 mA/cm^2; 5 min; #5	None	(Munz et al., 2015)
ADHD (n = 24), Healthy Control (n = 12)	10–14	F3 and F4; M1 and M2 (C); 0.503 cm^2	0.497 mA/cm^2; 5 min; #5	None	(Prehn-Kristensen et al., 2014)
ADHD (n = 15)	12–16	Left DLPFC (A); Cz (C); round anode with a surface area of 314 mm^2 and a rectangular cathode with a surface area of 1250 mm^2	1 mA, 20 min #5	Tingling, itching	(Soff et al., 2016)
Autism (n = 10)	6–21	DLPFC (A); right supraorbital (C); 25 cm^2	0.08 mA/cm^2; 30 min	None	(Schneider and Hopp, 2011)
Focal, refractory spikes and waves during slow sleep (n =5)	6–11	T7, FT7 or TP8 (C); 25 cm^2, A: 100 cm^2	1 mA; 20 min; #2	None	(Varga et al., 2011)
Epilepsy (n = 1)	11	Area above the left orbit (A); between P4 and T4 (C); 25 cm^2	2 mA; 20 min; #10	Not reported	(Yook et al., 2011)
Dystonia (n = 14)	7–19	C3 or C4 (C); forehead contralateral (A); 35 cm^2	1 mA; 9 min; #2	None	(Young et al., 2014)
Dystonia (n = 11)	7–18	C3 or C4 (C); forehead contralateral (A); 35 cm^2	1 mA; 9 min; #2	None	(Young et al., 2013)

tDCS: transcranial direct current stimulation, A: anode, C: cathode, AE: adverse event.

Table 7

Summary of studies of TES (tDCS, tACS) in older adults.

N	Mean age/age range (years)	Active electrode position; size (cm)	Reference electrode position; size (cm)	Current (mA)	Duration (min); # of sessions[a]	AEs[b]	References
tDCS							
25	63.7/56–80	L or R DLPFC (F3/4) (A); 35 cm^2	Contralateral cheek (C); 35 cm^2	1.5	10	N/R	(Berryhill and Jones, 2012)
28	68.4/50–85	L and R DLPFC (F3/4) (A or C); 35 cm^2	–	2	15	None/slight itching during the first 30 s of stimulation	(Boggio et al., 2010)
32	67.9	L or R DLPFC or parietal (A); 35 cm^2	Contralateral supraorbital (C); 35 cm^2	1.5	6	None	(Brambilla et al., 2015)
23	51–69	L M1 (A); 45 cm^2	R supraorbital (C)	2	20; 5x	N/R	(Dumel et al., 2016)
20	66.5/61–83	L DLPFC (A); 35 cm^2	R shoulder (C)	2	10	Itchiness (26/21%), burning (21/37%), heat (5/0%), pinching (74/68%), iron taste (11/11%), effect on performance (5/5%)[1,2B]	(Fertonani et al., 2014)
20	62.1/50–80	R temporo-parietal (A); 35 cm^2	L supraorbital (C); 100 cm^2	1	20	N/R	(Floel et al., 2012)
20	68.3	L M1 (A); 35 cm^2	R supraorbital (C); 51 cm^2	1	30	N/R	(Fujiyama et al., 2014)
11	63.0/55–80	Ipsi M1 (A); 25 cm^2, L M1-R M1 (D)	Contralateral supraorbital (C)	1	15	None	(Goodwill et al., 2013)
12	66.0	Ipsi M1 (A); 25 cm^2	Contralateral supraorbital (C)	1	15	N/R	(Goodwill et al., 2015)
22	57.5	Ipsi cerebellum (A); 25 cm^2	Ipsi buccinators muscle (C)	2	15	None Rating[2A] of discomfort: sham 1.9 ± 0.1, anodal 1.5 ± 0.1; Rating[2A] of pain: sham 1.3 ± 0.04, anodal 1.6 ± 0.2	(Hardwick and Celnik, 2014)
98	71.0/65–86	L or R DLPFC (F3/4) (A or C); 35 cm^2	Vertex (A or C)	1	37.5	Greater levels of itchiness in real compared to sham stimulation[2B]	(Harty et al., 2014)
16	73.4/65–83	L M1 (A); 25 cm^2	Contralateral supraorbital (C)	1	20	N/R	(Heise et al., 2014)
36	66.6	R M1 (A); 35 cm^2	Contralateral supraorbital (C); 100 cm^2	1	20	Itching, tingling when current was increased Rating[2A] of attention (>8), fatigue (<8), discomfort (<1.5): no differences and no changes from pre to post stimulation	(Hoff et al., 2015)
10	69.0/62–74	L IFG (A); 5×7	R supraorbital (C)	2	20	None/Mild tingling	(Holland et al., 2011)

N	Mean age/age range (years)	Active electrode position; size (cm)	Reference electrode position; size (cm)	Current (mA)	Duration (min); # of sessions[a]	AEs[b]	References
10	69.0/56–87	L M1 (A); 25 cm^2	Contralateral supraorbital (C)	1	20	None Rating[2A] of attention, fatigue, discomfort: no differences	(Hummel et al., 2010)
72	64.4/55–73	R PFC (F4) or parietal (P4) (A); 35 cm^2	Contralateral cheek (C)	1.5	10; 10x	N/R	(Jones et al., 2015)
20	66.6/60–77	L/R parietal (P3/4) (A); 25 cm^2	Contralateral supraorbital (C); 35 cm^2	1	15	Slightly more burning sensation during active stimulation sessions, tingling, itching[2B]	(Learmonth et al., 2015)
20	68.2/61–77	L M1 (C3); 5×7, L M1-R M1 (D)	Right supraorbital (A); 100 cm^2	1	30	None	(Lindenberg et al., 2013)
32	67.9	L/R DLPFC or parietal (A); 35 cm^2	Contralateral supraorbital (C)	1.5	6	Itching, irritation[2B]	(Manenti et al., 2013)
37	61	L PFC (F3) (A); 35 cm^2	Right supraorbital (C)	0.8–2[3]	20	None[2B]	(Manor et al., 2016)
20	68.0/60–76	L IFG (A)	Right supraorbital (C); 100 cm^2	1	20	None	(Meinzer et al., 2013)
18	68.4/61–77	L M1 (C3) (A); 35 cm^2, L M1-R M1 (D)	Right supraorbital (C); 100 cm^{2-}	1	30	None	(Meinzer et al., 2014b)
30	69.0/65–75	L DLPFC (F3) (A); 35 cm^2	Right supraorbital (C); 100 cm^2	1 or 2	25	None	(Nilsson et al., 2015)
38	63.2	L M1 or R cerebellum (A); 35 cm^2	Contralateral supraorbital (M1 tDCS) or L trapezius muscle (cerebellar tDCS) (C)	2	17	N/R	(Panouillères et al., 2015)
8	75.0/63–84	L M1 (A); 25 cm^2	Contralateral supraorbital (C)	1	20	Mild tingling, burning (during the initial 30 s of anodal/sham)	(Parikh and Cole, 2014)
40	69.7	L and R DLPFC (F3/4) (A); 25 cm^2	Non-dominant arm (C)	2	30; 10x	None	(Park et al., 2014)
54	66.9/60–82	L M1 (A); 25 cm^2	Contralateral supraorbital (C); 51 cm^2	1.5	20	N/R	(Puri et al., 2015)
14	65.0/55–69	L or R anterior temporal (T3/4) (A); 35 cm^2	Contralateral cheek (C)	1.5	15	N/R	(Ross et al., 2011)
36	67.2	L DLPFC (F3) (A); 35 cm^2	R supraorbital (C)	1.5	15	Itching, irritation[2B]	(Sandrini et al., 2014)
28	68.9	L DLPFC (F3) (A); 35 cm^2	R supraorbital (C)	1.5	15	Itching, irritation at the beginning of anodal/sham stimulation[2B]	(Sandrini et al., 2016)
20	63.0	L DLPFC (F3) (A); 35 cm^2	R supraorbital (C)	2	20	None	(Zhou et al., 2015)

N	**Mean age/age range (years)**	**Active electrode position; size (cm)**	**Reference electrode position; size (cm)**	**Current (mA)**	**Duration (min); # of sessions[a]**	**AEs[b]**	**References**
15	68.5/55–88	L M1 (A or C); 25 cm^2	R supraorbital (A or C)	1	20	N/R	(Zimerman et al., 2013)
N	Active electrode position; size (cm)		Reference electrode position; size (cm)	Current (mA), frequency	Duration (min); # of sessions[a]	AEs/stimulation-induced sensations[b]	
tACS							
12	L temporo-parietal (CP5); 35 cm^2		R supraorbital; 100 cm^2	1; 6 Hz	20	Tingling (3), itching (1), tiredness (2), loss of concentration (2)[2B]	(Antonenko et al., 2016)
24	Parieto-occipital (Cz-Oz); 35 cm^2		–	1.5; 8–12 Hz	20; 5x	N/R	(Muller et al., 2015)

A, anodal; bi, bilateral stimulation with two anodal plus two reference electrodes; C, cathodal; D, dual; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal cortex; Ipsi, ipsilateral to the dominant hand (mostly right-handed subjects); L, left; N/R, not reported; R, right.

[1] First number reflects AEs during anodal-offline (before task) and second number reflects sensations reported for anodal-online (during task) performance. [2A/B] Rating on 10-point/5-point scale (0/1 = none/low, 5/10 = strong/high).

[3] Determined individually.

[a] Number after semicolon indicates number of consecutive sessions.

[b] Were reported, numbers in brackets represent number/percentage of participants reporting the respective AE in active stimulation condition.

Table 8

tDCS treatment for emergent mania or hypomania.

Patients	Stimulation electrode position (polarity)	Return electrode position (polarity)	Current settings	Session duration (minutes)	Number of sessions	AEs	Reference
1 patient with unipolar depression	F3 (A)	Contralateral supraorbital (C)	1 mA, 0.029 mA/cm^2	20	10	Hypomania	(Arul-Anandam et al., 2010)
1 patient with unipolar depression	F3 (A)	F4 (C)	2 mA, 0.06 mA/cm^2	30	5	Hypomania	(Baccaro et al., 2010)
1 patient with unipolar depression	F3 (A)	F4 (C)	2 mA, 0.06 mA/cm^2	30	5	Mania	(Brunoni et al., 2011b)
1 patient with bipolar depression	F3 (A)	Contralateral arm (C)	2 mA	20	14	Hypomania	(Galvez et al., 2011)
6 patients with unipolar depression	F3 (A)	F4 (C)	2 mA, 0.08 mA/cm^2	30	12	4 hypomania and 2 mania	(Brunoni et al., 2013a)
1 patient with bipolar depression		F4 (C)	2 mA, 0.08 mA/cm^2	30	12	Hypomania	(Pereira Junior Bde et al., 2015)

tDCS: transcranial direct current stimulation, A: anode, C: cathode, AE: adverse events.

Table 9

Screening questionnaire for transcranial electrical stimulation (TES).

		YES	NO
1	Do you have metal (except titanium) or electronic implants in the brain/skull (e.g., splinters, fragments, clips, cochlear implants, deep brain stimulation etc.)? If yes, please specify the type of metal and the location _____		
2	Do you have metal or any electronic device at other sites in your body, such as a cardiac pacemaker or traumatic metallic residual fragments? If yes, please specify the device and the location: _____		
3	Did you ever have surgical procedures involving your head or spinal cord? If yes, please specify the locations: _____		
4	Have you ever had a head trauma followed by impairment of consciousness?		
5	Do you have skin problems, such as dermatitis, psoriasis or eczema? If yes, please specify the location: _____		
6	Do you have epilepsy or have you ever had convulsions, a seizure?		
7	Did you ever have fainting spells or syncope?		
8	Are you pregnant or is there any chance that you might be?		
9	Are you taking any medications? If yes, please specify: _____		
10	Did you ever undergo transcranial electric or magnetic stimulation in the past? If yes, were there any adverse events? Please specify _____		

An affirmative answer to one or more of questions do not represent an absolute contraindication to TES, but the risk-benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

Name _____ Surname _____

Date _____ Signature _____

Table 10A

Points of relevance with known influence on outcome of transcranial electrical stimulation (TES).

A – SHORT VERSION

A structured checklist increases the reproducibility of studies, minimises deviations from a given protocol and diminishes variability. A structured checklist is thus the recommended procedure for enhancing reliability and comparability in publications of TES experiments/trials.

Participant information

- Age:
- Gender:
- Handedness:
- Medication (Depending on the type of study an even more precise documentation may be necessary, measurement of drug levels may be considered), label and dose:
- Caffeine consumption: cups per day (indicate the best currently relevant estimate)
- Nicotine consumption: cigarettes per day (indicate the best currently relevant estimate)
- Alcohol consumption: drinks per day (indicate the best currently relevant estimate) (for comparability important that unit is given and comparable measures are noted)

Procedures applied, Dose parameters *(sufficient information about the stimulation parameters should be provided in order to replicate or model the stimulation dose independently based on these parameters)*

- Type of stimulation:
- Metric to be used: (e.g., behavioral, cognitive, EEG, MEP, MRI):
- Stimulation intensity (peak-to-baseline):
- Stimulation duration:
- Type and number of electrodes:
- Electrode positions:
- Electrode size:

  target electrode:

  return electrode:

Other factors to be considered

- Tasks during stimulation (if any):
- Day time of the experiment (from – to):
- Duration of the whole experiment including preparation:

  Additional comments

  _____

Table 10B

Points of relevance with known influence on outcome of transcranial electrical stimulation (TES).

B – FULL VERSION

A structured checklist increases the reproducibility of studies, minimises deviations from a given protocol and diminishes variability. A structured checklist is thus the recommended procedure for enhancing reliability and comparability in publications of TES experiments/trials.

Participant information

- Age:
- Gender:
- Racial group:
  - Caucasian/White
  - African
  - Asian
  - Hispanic
  - Other race:
  - Mixed (i.e. >1 racial type):
- Handedness:
- Head size (distance in cm: inion – nasion, ear to ear distance):
- Previous experience with TES (additional information of potential relevance):
- Medication (Depending on the type of study an even more precise documentation may be necessary, measurement of drug levels may be considered), label and dose:
  - Within last hours
  - Within last days
  - Within last months
- Caffeine consumption (cups) (indicate the best currently relevant estimate):
  - Within last 12 h
  - Average within last months
- Nicotine consumption (cigarettes per day) (indicate the best currently relevant estimate):
  - Within last 4 h (*half life of Nicotine: 2 h*)
  - Within last 48 h (*half life metabolite cotinine: 10–37 h*)
- Alcohol consumption (drinks) (indicate the best currently relevant estimate):
  - Within last 24 h
  - Average with last months (how many months?)
- Drugs (e.g. marijuana) consumption (to be specified): (for comparability important that unit is given and comparable measures are noted)
- Hormonal/menstrual cycle of female subjects
- In case of patients non-neuropsychiatric comorbidities:

Procedures applied, Dose parameters *(sufficient information about the stimulation parameters should be provided in order to replicate or model the stimulation dose independently based on these parameters)*

- Type of stimulation (complicated waveforms with drawings):
- Metric to be used (e.g., behavioral, cognitive, EEG, MEP, MRI):
- Product number and model of stimulator used (consider Nr. as encoded in case of multiple stimulators available):
- Stimulation intensity (peak-to-baseline):
- Stimulation duration:
  - Duration of ramping

Fragmented stimulation (interval duration)

- Type and number of electrodes:
- Electrode positions:
- Electrode polarities in case of tDCS:
- Position of cable fixation at electrode:
- Electrode shape:

  target electrode:

  return electrode:
- Electrode size:

  target electrode:

  return electrode:
- Method of allocation of electrode position (neuronavigation, MEP hot spot, modeling etc.):
- Electrode-skin interface (any skin preparation steps):
- Type of fixation:

  saline (molarity?), in case of cream, brand:

Other factors to be considered

- Tasks/status during stimulation (if any):
  - ○ Not specified or regulated
  - ○ Specified/regulated: details _____
- Day time of the experiment (from – to):
- Attention (level of arousal)
  1. before stimulation:
  2. during stimulation (optimal results expected with relaxation, not during arousal or sleepiness):
  3. after stimulation:
  4. Number of hours in sleep during the last night:
- Prior motor activity (i.e. cycling before stimulation, if yes, please define the duration):
- Prior rest (sleep) before stimulation:
- Duration of the whole experiment including preparation:
- Number of years in education (of interest in special, e.g. in cognitive studies):
- Additional comments:

  _____

Table 11

Questionnaire of sensations related to transcranial electrical stimulation (TES).

Questionnaire of sensations related to transcranial electrical stimulation (TES)

(To be filled in by the participants and by the investigator)

Investigator:

Participant name/code:_____ **Date:**___/____/____|

Experiment/Treatment: _____

No stimulations experienced before □ **Experienced** □

of **stimulations sessions before: .....**

Type of electrical stimulation used here_____ **Intensity** ____mA (if known)

Electrodes dimension: anode (if known) __*__ cathode (if known) __*__ (shape _____) other_____

Participant:

Did you experience any discomfort during the electrical stimulation? Please indicate the degree of intensity of your discomfort according to the following scale:

- **None =** **I did not feel the sensation addressed**
- **Mild =** **I mildly felt the sensation addressed**
- **Moderate =** **I felt the sensation addressed**
- **Strong =** **I felt the sensation addressed to a considerable degree**

In the first stimulation block I felt (to be filled in by subject, if it is possible please separate the sensations with regard to the electrode positions):				
	None	*Mild*	*Moderate*	*Strong*
Itching	□	□	□	□
Pain	□	□	□	□
Burning	□	□	□	□
Warmth/Heat	□	□	□	□
Metallic/Iron taste	□	□	□	□
Fatigue/Decreased alertness	□	□	□	□
Other	□	□	□	□

In case of perceived sensation, when did it begin? *(this part can be multiplied and completed for each sensation, e.g. one for pain, one for itching etc and could/should be modified according to the type of experiments)*

□ At the beginning; □ At approximately in the middle; □ Towards the end of the stimulation

Duration (multiple options allowed)

□ Only initially □ It stopped in the middle of the block □ It stopped at the end of the block

How much did these sensations affect your general state?

□ Not at all □ Slightly □ Considerably □ Much □ Very much

Location of sensations:

□ Diffuse □ Localized □ Close to the electrode, (which one?)_____; □ Other_____

If you would like to provide more details, please briefly describe the experimented sensations in relation to the "Other" or "Fatigue" or ..... response:

In the second stimulation block

(if there is more than one condition, repeat the list above here based on the block numbers)

To be administered at the end of the entire experiment

Do you believe that you received a real or placebo stimulation?

In the first stimulation block/day/week: □ real □ placebo □ I don't know

In the second stimulation block/day/week: □ real □ placebo □ I don't know

Investigator:

Please report any adverse event/problem (typically skin irritation and redness – separately for the electrodes -, headache, scalp pain, dizziness, or others, please specify) that occurred and rate the event/problem on a scale from 0 to 3 as previously described.