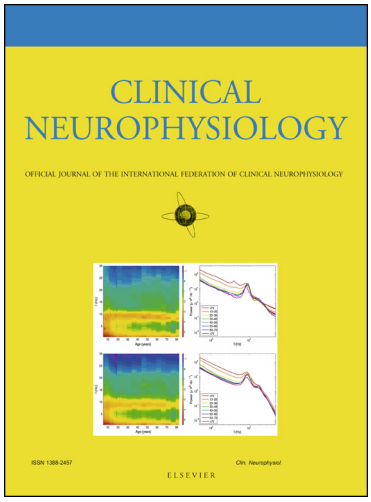


Review

# A technical guide to tDCS, and related non-invasive brain stimulation tools

A.J. Woods, A. Antal, M. Bikson, P.S. Boggio, A.R. Brunoni, P. Celnik, L.G. Cohen, F. Fregni, C.S. Herrmann, E.S. Kappenman, H. Knotkova, D. Liebetanz, C. Miniussi, P.C. Miranda, W. Paulus, A. Priori, D. Reato, C. Stagg, N. Wenderoth, M.A. Nitsche

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# A technical guide to tDCS, and related non-invasive brain stimulation tools

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**Abstract**

Transcranial electrical stimulation (tES), including transcranial direct and alternating current stimulation (tDCS, tACS) are non-invasive brain stimulation techniques increasingly used for modulation of central nervous system excitability in humans. Here we address methodological issues required for tES application. This review covers technical aspects of tES, as well as applications like exploration of brain physiology, modelling approaches, tES in cognitive neurosciences, and interventional approaches. It aims to help the reader to appropriately design and conduct studies involving these brain stimulation techniques, understand limitations and avoid shortcomings, which might hamper the scientific rigor and potential applications in the clinical domain.

**Keywords:** Transcranial electrical stimulation (tES), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), technical guide, methodology review, safety, design.

**Highlights**

- A review of technical aspects of transcranial electrical stimulation (tES) techniques.
- Recommendations for safe and replicable application of tDCS and other tES methods.
- Discussion of state-of-the-art methodology and design considerations in tES.

## 1. Introduction

Transcranial direct current stimulation (tDCS) was re-introduced as a non-invasive brain stimulation (NIBS) technique applicable in humans approximately 15 years ago (Priori et al. 1998; Nitsche and Paulus 2000). Its principal mechanism of action is a subthreshold modulation of neuronal membrane potentials, which alters cortical excitability and activity dependent on the current flow direction through the target neurons (Purpura and McMurtry 1965). Other biological effects of the electric field are also likely relevant (changes in neurotransmitters, effects on glial cells and on microvessels, modulation of inflammatory processes).

In analogy to pharmacological neuromodulators, tDCS does not induce activity in resting neuronal networks, but modulates spontaneous neuronal activity (Fritsch et al. 2010). Consequently, the amount and direction of effects critically depend on the previous physiological state of the target neural structures (Antal et al. 2014a; Thirugnanasambandam et al. 2011) In this sense, tDCS, transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) represent neuromodulatory techniques. They do not induce massive synchronized discharge of action potentials as TMS or paired associate stimulation (PAS) do. DCS changes the threshold for discharge of stimulated neurons, thus changing the likelihood of their discharge (Nitsche et al. 2000, 2003; Nitsche and Paulus 2001; Fritsch et al. 2010). DCS at intensities comparable to those modelled in humans does not induce LTP in slices of mouse primary motor cortex. However, when combined with a second input, for example thalamocortical stimulation, DCS results in powerful elicitation of LTP (Fritsch et al. 2010). This basic science work suggested that, in human application, LTP-like effects may be better accomplished by pairing DCS with the behavior intended to modulate. Thus, DCS effects depend on the baseline status of the brain at the time of its application. This dependency could possibly influence interindividual variability in DCS effects previously reported (López-Alonso et al. 2014; Wiethoff et al. 2014) and the fact that differences in experimental protocols such as stimulation intensity or use of

different versions of the same or different behavioural tasks, result in different outcomes (Antal et al. 2004a; Batsikadze et al. 2013). In the case of tACS, the neuromodulatory intent is to entrain brain oscillations (Antal et al. 2008; Ali et al. 2013b; Neuling et al. 2013; Cecere et al. 2014; Helfrich et al. 2014b). In case of such entrainment, one oscillation, e.g. the tACS sine wave, modulates the power and/or phase of another oscillation, e.g. an endogenous brain oscillation.

In the following sections, we will discuss technical aspects of tDCS and related techniques, covering basic methodological issues, including modelling aspects, but also interventional approaches in cognitive neurosciences and clinical trials. We hope that hereby this review will contribute to enhancing the methodological quality of research within this emerging field.

## 2. Transcranial direct current stimulation

tDCS is a tES technique that involves the application of a weak direct electrical current (e.g., 1-2 mA) scalp through two or more electrodes placed on the scalp (Priori et al. 1998; Nitsche et al. 2000).

### 2.1 Selecting and preparing electrodes and contact medium

The purpose of electrodes in tDCS is to facilitate delivery of current from the stimulation device to the scalp. With rigorous control of electrode selection and preparation, along with adherence to established tDCS protocols, operator training, and use of certified devices, teams of clinical trial researchers have reported application of thousands of tDCS sessions without any skin injury (Brunoni et al. 2011b, 2013b; Kalu et al. 2012; Loo et al. 2012; Fertonani et al. 2015). The electrode assembly most commonly used for tDCS comprises 1) a metal or conductive rubber electrode, 2) an electrode sponge, and 3) an electrolyte-based contact medium (e.g., saline, gel, or conductive cream) to facilitate delivery of current to the scalp, as well as 4) any materials used to shape these components or otherwise direct current flow (plastic casing, rivets).

During tDCS, the metal or conductive rubber electrode is the site of electrochemical reactions (Merrill et al. 2005) and should not directly contact the skin. Rather, an electrolyte is used as a buffer between the electrode and the skin – with sufficient electrolyte volume preventing chemicals formed at the electrode from reaching the skin (Minhas et al. 2010). The electrolyte can be placed in a sponge encasing the electrode (i.e., saline) or, in the case of electrode cream, placed directly on the electrode surface. However, in the case of saline, oversaturation of the electrode sponge significantly undermines the reproducibility of tDCS application and effects. When sponges are over-saturated, saline is evacuated from the sponge and covers an area of the scalp outside of the surface area electrode sponge. Rather than delivering current through a specified surface area on the scalp under the electrode (e.g., 5x5 cm), the electrode surface area and area of current delivery now encompasses the entire area of the scalp that is covered in saline. This creates an amorphous area of current delivery that is not reproducible within or between subjects. It is important to obtain good contact under, and only under, the electrode with the electrode sufficiently, but not overly saturated. Methods allowing quantification of saline (e.g., syringes) can assist in achieving a consistent and appropriate amount of contact medium.

Consistent with issues introduced by oversaturation of sponges, the shape/size of electrodes/sponges significantly alter the distribution of current delivered to the scalp and the brain (Minhas et al. 2011; Kronberg and Bikson 2012). At a constant current intensity level (e.g., 1 mA), increases in electrode size or differences in electrode assembly shape result in differences in the distribution of the current across the surface area of the scalp, resulting in differences in the distribution of current throughout the brain (Minhas et al. 2011; Kronberg and Bikson 2012). Thus, it is critical for investigators to consistently report not only the current intensity applied and the amount of contact medium used, but also the shape and size of the electrode assembly.

### 2.2 Selecting and preparing electrode placement

Another critical consideration for tDCS is determining where to place electrodes on the head. Studies monitoring physiological changes following tDCS and computational modeling studies of predicted current flow demonstrate that the relative location of electrodes results in significant differences in where and how much current is delivered to the brain (Minhas et al. 2012; Kessler et al. 2013b; Woods et al. 2015). For example, Nitsche and Paulus (2000) demonstrated that relative differences in electrode locations altered whether or not tDCS impacted TMS generated motor-evoked potentials (MEPs). Numerous modeling studies have demonstrated significant differences between relative locations of electrodes, with results varying from stimulation of the whole brain to more selective stimulation of particular lobes of the brain (Minhas et al. 2012; Kessler et al. 2013b; Woods et al. 2015). Woods et al. (2015) further demonstrated that as little as 1cm of movement in electrode position significantly altered the distribution of predicted current flow in the brain, as well as the intensity of stimulation in specific brain regions Computational modeling (discussed in detail in a later section) can be a useful tool for the a priori design of tDCS electrode positions for a given study. In this same context, the importance of electrode location also highlights yet another critical consideration, preparation of a stable electrode placement on the head.

As head size and shape vary from person to person, it is important to use a method for common localization of electrode position. There are several methods for addressing this issue: 1) International 10-20 (or 10-5) Electrode Placement System (Klem et al. 1999; Oostenveld and Praamstra 2001), or another gross anatomical coordinate system (Seibt et al.), 2) neuronavigation systems (e.g., MRI guided; Feurra et al., 2011, 2013; Santarnecchi et al., 2014), or 3) physiology-based placement (e.g., TMS generated MEPs). At present, physiology based placement can only be performed for motor and other primary cortices (e.g., sensory). However, further options may become available in the future (e.g., TMS-EEG methods). Regardless, these methods can be used to reproducibly center each electrode on the head, accommodating varied head shape or size.

Once desired locations are identified, the electrode assembly must be affixed to the head for delivery of current. Non-conductive headgear used to position the electrodes on the body or scalp (e.g., elastic straps) are not included in the electrode assembly but are critical for appropriate electrode placement (Woods et al. 2015). For tDCS using sponge-covered electrodes, elastic straps are the most commonly used headgear for electrode placement. If these straps are under- or over-tightened, electrodes have a high tendency to move over the course of a tDCS session. Thus, the distribution of current delivery changes over the duration of a tDCS session (Woods et al. 2015). This too undermines tDCS replicability. Furthermore, if electrode straps are over-tightened, there is an increase in the probability of evacuation of saline from the electrode sponges. Regardless, the contour at the base of the skull below the inion and the flat of forehead provide for stable placement of a strap around the head. For participants with long hair, placement of the back of the strap under the hairline also improves stability of the strap preparation, whereas placement over the hair leads to a high probability of upward drift of the strap and the electrodes placed on the head. Use of cross straps over the head should also avoid over-tightening of the cross-strap to avoid this same issue. Use of a cross-strap under the chin can counteract this tendency, but may be uncomfortable to participants. If under-chin straps are used, these should be used for all participants to maintain consistency of participant experience in the study.

**2.3 Selecting a stimulation protocol**

If the purpose is to modulate neurophysiological measures (e.g., MEP amplitudes) for resting motor cortex stimulation in healthy young humans (1 mA intensity, electrode size 35 $cm^2$), tDCS for 4 s induces acute excitability alterations, which do not result in after-effects.(Nitsche and Paulus 2000) Short-lasting after-effects for up to 10 min are accomplished by 5 and 7 min stimulation, whereas 9 min stimulation of the motor cortex under the cathode electrode, and 13 min stimulation under the anode electrode result in after-effects lasting for approximately 1h (5x7 cm electrodes, motor cortex-contralateral supraorbital ridge electrode

arrangement (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003); for an overview about the physiological foundation of after-effects see Stagg and Nitsche 2011. Further extension of stimulation duration and/or intensity will not necessarily result in a relative increase, but can invert stimulation effects (Batsikadze et al. 2013, Monte-Silva et al. 2013b). For the induction of relevantly longer-lasting tDCS effects, spaced stimulation with intervals ≤ 30 min is suited (Monte-Silva et al. 2013b; Goldsworthy et al. 2014). It remains to be determined to what extent parameters of stimulation that modify physiological responses to TMS stimulation impact motor behaviour or can be applied with similar success to other brain regions and behaviours.

While these stimulation parameters can serve as a rule of thumb for tDCS of other areas, participant groups, and experimental conditions, a one-to-one transferability of effects found in studies of motor cortices cannot be taken for granted due to state-dependency of tDCS effects, anatomical differences, and other factors (Nitsche and Paulus 2000; Kessler et al. 2013b; Gill et al. 2014). Thus, if no reference study exists for a specific experimental protocol, titration of stimulation parameters is recommended (Boggio et al. 2006; Iyer et al. 2005a; Cuypers et al. 2013). Furthermore, these stimulation protocols elicit respective effects at the group level. Individual efficacy varies considerably (Wiethoff et al. 2014). Individual adjustment of stimulation protocols due to state, and anatomical factors, such as electrode-brain-distance, and cortical folding, might be an attractive solution in future studies.

The above-mentioned electrodes will result in relatively widespread stimulation of brain regions, physical, and probably also physiological effects (Minhas et al. 2010; Kuo et al. 2013). If less widespread effects are intended, different options do exist. Efforts to improve focality of DCS are under way, like high-definition (HD) tDCS, a small central electrode positioned over the target is surrounded by 4 return electrodes (Minhas et al. 2010). Other options include decreasing target electrode size, while keeping current density constant, increasing return electrode size (Nitsche et al. 2007a), or moving the return electrode to an

extracephalic region, which might require higher stimulation intensity (Moliadze et al. 2010). In addition, other work has investigated the benefit of personalized electrode shape and size for stimulation of desired brain regions (Tecchio et al. 2013). However, if these approaches induce different current flow direction, physiological effects might not be identical, as distribution of currents and behavioural effects of tDCS critically depends on the relation between current flow direction and neuronal orientation in the target areas (Kabakov et al. 2012). Furthermore, reduction of electrodes size might over-proportionally reduce current flow into the brain, thus an adjustment of current intensity to slightly larger relative values might be required (Miranda et al. 2009). That said, one of the useful features of tDCS, particularly in relation to potential therapeutic applications, may be its lack of focality. On the other hand, it should be recognized that if the attempt is to deliver more focal stimulation, the choice of TMS with a figure-of-eight magnetic coil is likely to induce much more focal currents than tDCS.

**2.4 Use of Blinding and Sham**

The usual approach of blinding participants for plasticity-inducing protocols is to apply a "sham" stimulation protocol, which encompasses ramping stimulation up and down like in the real stimulation condition, but to stimulate with the target intensity only for a few seconds. Participants will feel the initial itching/tingling sensation, but the stimulation duration is too short to induce after-effects. For 1 mA tDCS with an electrode size of 25 $cm^2$, this method has been shown to reliably blind participants (Gandiga et al. 2006; Ambrus et al. 2012). Stronger stimulation will induce larger sensations, and thus compromise blinding, especially under repeated measures conditions (O'Connell et al. 2012; Palm et al. 2013). In parallel studies, this might however not be a relevant problem (Russo et al. 2013). Alternative approaches are application of topical anaesthetics to abolish skin sensations (Guleyupoglu et al. 2014) or, probably much more valuable, an active control condition (i.e., stimulation over an area irrelevant for the task under study). Since the occurrence of skin damage seems to be not reliably associated with cutaneous sensation (Palm et al. 2008), local anaesthetics

should not put participants specifically at risk. Blinding of the experimenter with regard to the specific stimulation protocol is accomplished by use of stimulators that include a sham stimulation function, thus keeping the experimenter unaware of the specific stimulation condition. Even here, however, the presence of skin erythema, which is due to tDCS-induced vasodilation (Durand et al. 2002), can compromise blinding. Skin erythema is reliably reduced by acetylsalicylate, or topical application of ketoprofen (Durand et al. 2002)(Guarienti et al. 2014). Thus, for reliable double blinding, a couple of approaches are available, which should be chosen carefully due to the specific experimental design. Other approaches for testing the specificity of the effects are assessing the effects of opposite stimulation polarities, or testing the effect on different central nervous system areas. Overall, when the goal is to demonstrate that stimulation applied over one cortical region induces a particular effect, an active control in which a different brain region is stimulated provides a strong foundation for interpretation of results in this context. If the goal is to demonstrate a polarity-specific effect, use of the opposite polarity for the same stimulated region is an appropriate control choice. The choice of the control has a profound impact on the conclusion that can be drawn from a particular study and should be highly hypothesis-driven.

**2.5 Safety versus Tolerability**

It is important to discern between tolerability and safety aspects in a strict sense. Tolerability refers to the presence of uncomfortable and unintended effects (e.g. tingling, and itching sensation under the electrodes), which in case of tDCS are however not inducing structural or functional damage, whereas safety refers to damaging effects. Comfort ratings for presently used protocols show a favourable tolerability profile. Most often reported effects are tingling and itching sensations under the electrodes, headache, and tiredness (Poreisz et al. 2007; Fertonani et al. 2015). The sensation of phosphenes elicited by abrupt current on- or offset is avoided by ramping current intensity. Erythema under the electrodes are caused by tDCS-induced vasodilation, and thus are not a safety issue (Durand et al. 2002). For safety

aspects in a strict sense, structural damage of brain tissue can be ruled out for motor cortex stimulation protocols introduced by Nitsche and colleagues (Nitsche and Paulus 2001; Nitsche et al. 2003). Furthermore, unlike repetitive TMS (rTMS), no cases of seizure induction have been reported to date. In vivo rat models favour a safety margin of about 2 orders of magnitude of the currently used protocols (Liebetanz et al. 2009). However, stimulation over holes or fissures of the cranial bone, which results in local enhancement of current density, should be approached with caution (Agnew and McCreery 1987). Skin damage has been reported occasionally (Palm et al., 2008), but was in most cases associated with protocol shortcomings, like drying of the contact media under the electrodes. In a recently conducted study, tap water increased the risk of skin damage (i.e., burns) as compared to physiological saline solution. Thus, tap water as a contact medium should be avoided. For use of electrode cream, a sufficiently thick film, which prevents direct contact between skin and electrodes, is mandatory (Nitsche et al. 2010; Voss et al. 2014). Thus, electrode gels are not appropriate as a contact medium for conventional flat electrodes, as they do not provide a sufficiently thick film for necessary electrode to scalp spacing – unless a container is used to control thickness and electrode-skin distance. Functional safety encompasses the induction of cognitive, behavioural, or other disturbances, which are not intended by, or can be derived from the principle physiological effect of tDCS, and are not self-limiting. In healthy populations no specific effects of this kind were described with currently used protocols. When present, decreases in performance have been transient (Antal et al. 2004a; Iuculano and Cohen Kadosh 2013). Taken together, customarily applied tDCS protocols using relatively well-defined electrodes, stimulus durations and intensities seem to be safe, and well tolerated. Moreover, modelling studies also showed that the use of an extracephalic electrode on the shoulder should not influence cardiac or brainstem activities (Parazzini et al. 2013a, 2013b). This assumption does, however, not necessarily apply for any tDCS protocol, independent from current intensity, and stimulation duration, and without regard for inclusion/exclusion criteria. Thus, any general statements that “tDCS is safe” independent of protocol characteristics should be entirely avoided. Moreover, this

assumption is only valid if common exclusion criteria for tDCS/NIBS (metal in the head, pacemaker, no stimulation over fissures, or cranial holes, causing locally enhanced current density) are followed. Special consideration should also be given when determining safety and tolerability in children, where parameters safely used in adults may have a different safety and tolerability profile (Minhas et al. 2012; Kessler et al. 2013b). On the other hand, it is important not to confuse calls for excessive caution in susceptible populations (children, brain injury) with the existence of any data suggesting safety risks.

**2.6 Considerations for transcutaneous spinal DC stimulation (tsDCS)**

In 2008, Cogiamanian et al. found that weak DC delivered over the dorsal spinal cord modulates in a polarity-dependent manner the amplitude of the somatosensory evoked potential (SEPs) elicited by tibal nerve stimulation (Cogiamanian et al. 2008). The effect was specific because SEPs elicited by median nerve stimulation were not influenced by thoracic transcutaneous spinal DC stimulation. Several further studies replicated the observation that weak DC delivered over the spinal cord can influence different physiological variables of spinal cord function in humans and animals, both intact and injured (for a review see (Priori et al. 2014).

In applying tsDCS, researchers used certain key technical features (Toshev et al. 2014). For lumbar spinal cord modulation, the electrodes (measuring about 5 cm × 7 cm) are usually placed over the spinous process of the tenth thoracic vertebra and above the right shoulder (Cogiamanian et al. 2008, 2011; Lamy et al. 2012; Lamy and Boakye 2013). For cervical spinal cord modulation, one electrode was positioned on the seventh cervical vertebra and the other on the anterior part of the neck (Lim and Shin 2011). An influential variable that needs to be systematically investigated when applying tsDCS is the effect of electrode positioning on the arm or elsewhere (see below). Also, stimulation intensity and duration were kept relatively constant across the various studies from different groups: intensities between 2 and 2.5 mA were usually applied for 15/20 min. Like tDCS, spinal DC often elicits

short-lasting tingling sensations when stimulation begins and ends, and sometimes redness under the electrode. The effect of polarity on physiology is complex (Priori et al. 2014). In general, in humans it can be assumed that thoracic transcutaneous DC under the anode electrode decreases responses involving spinal tract compartments below the stimulating electrode and increases segmental reflex responses, whereas the cathode electrode induces opposite effects. This polarity convention (opposite from conventional tDCS) simplistically appears to follow that expected for long axons, but could also reflect the underlying neuronal morphology. Thus, the polarity of the electrodes is critical for physiological effects.

Like in cortical tDCS, the position of the return electrode may influence the effects of spinal DC stimulation. Parazzini et al. (2014b) assessed three electrode montages in a modeling study, with the anode always over the spinal process of the tenth thoracic vertebra and the cathode: (1) on the right arm, (2) on the abdominal wall 2 cm above the umbilicus on the median line and (3) on the vertex. Within the spinal cord, the electric field was primarily directed longitudinally along the vertebral column. On transverse spinal cord sections, current density distributed uniformly. This finding suggests that the ventral (motor) and dorsal (sensory) axonal tracts receive identical electric field strength. The return electrode position over the right arm results in current prevailing at the thoracic level. Conversely, the return electrode position over Cz results also in supra-spinal effects at the bulbar level (see also Priori et al. 2014 for a discussion). Hence, the type of montage should be selected according to the aim of the study.

**2.7 Considerations for cerebellar tDCS**

When delivering cerebellar tDCS (ctDCS) it is important to consider which region of the cerebellum is being targeted as well as the underlying cellular morphology (Rahman et al. 2014). Similar to the neuromodulation of any other CNS structure, the focality of ctDCS effects is presumably relatively limited, however recent studies aimed also for relatively focal stimulation. In this section we will describe the two most common electrode montages

utilized in different laboratories (for a detailed review on the technique and cerebellar tDCS applications see Ferrucci and Priori 2014a; Grimaldi et al. 2014; Priori et al. 2014).

### 2.7.1 Targeting the whole cerebellum

This montage includes the use of a large electrode measuring about 7×5 cm (area 35 cm2). One electrode is centered horizontally on the median line over the whole cerebellum (1–2 cm below the inion) with its lateral borders about 1 cm medially to the bilateral mastoid apophysis. The second electrode is placed over one of the buccinator muscles, the right shoulders or over the scalp (Ferrucci et al. 2015). tDCS over the whole cerebellum modulates implicit learning (Ferrucci et al. 2013), working memory (Ferrucci et al. 2008), emotion recognition (Ferrucci and Priori 2014b) and pain perception (Bocci et al. 2015) in healthy subjects.

### 2.7.2 Targeting the cerebellar hemispheres

This montage includes two 5x5cm electrodes (area 25 cm2 for each electrode). One electrode is centered 3cm lateral to the inion with half of the electrode covering an imaginary line above the inion, and the other half below. In other words, a 5x5cm electrode will have the medial border at 0.5cm from the inion, with the superior and inferior border 2.5cm above and below the inion. The second electrode is placed ipsilaterally over the face cheek. Thus, a 5x5cm electrode lays 1 or 2cm behind the angle of the mouth with the midline crossing an imaginary line going from the mouth angle to the tragus (Grimaldi et al. 2014; Celnik 2015).

The same precautions for electrode preparation and placement described above should also be observed for cerebellar tDCS. The cerebellar electrode is typically fixed with a headband or ace wrap in the axial plane, whereas the face electrode is fixed with a headband on the coronal or vertical plane (Galea et al. 2009; Cantarero et al. 2015). Both electrodes are connected to a standard tDCS stimulator, delivering DC for the desired amount of time (typically 15–25 min), at an intensity ranging from 1 to 2 mA. Modeling studies show that,

using the whole cerebellum montage with the return electrode over the right shoulder, cerebellar tDCS targets the posterior cerebellum in the adult bilaterally, with a slight spread to the brainstem in children (Parazzini et al. 2014c); while the lateral cerebellar montage affects only one hemisphere with little spreading to other regions (Rampersad et al. 2014). The validity of these modeling results should be evaluated with human experiments.

### 2.8 Selecting a Stimulator

Currently a limited set of certified tDCS-stimulators are available (e.g., produced/distributed by Brainstim, Magstim, Neuroconn, Neuroelectrics, Newronika and Soterix Medical). All of these devices deliver constant current (Agnew and McCreery 1987; Bronstein et al. 2015). Stimulators differ for specific features, like suitability for other stimulation protocols (e.g., tACS, tRNS), programming capabilities, number of channels, size, weight, portability, suitability for magnetic resonance imaging (MRI), and blinding options. All certified tDCS-stimulators provide the basic features required for tDCS. Thus, which stimulator to choose depends on planned application (e.g., need for blinding protocols, desired intensity level, number of electrodes, portability, wearability, etc.). In any case, exactness of delivered current, as programmed, is of crucial importance, and should be tested (e.g., by aid of an oscilloscope), since, as discussed, minor deviances can result in prominent alterations of experimental outcomes.

## 3. Transcranial alternating current stimulation (tACS)

tACS is a method of tES, which shares basic electrode montage and low-intensity features with tDCS. However, in case of tACS a sinusoidal current is applied to the scalp. This results in a few important differences to tDCS that shall be discussed below.

### 3.1 Selecting tACS Electrode Placement

One of the main technical differences between tDCS and tACS is the functional interpretation of the two or more electrodes mounted on the scalp. In case of tDCS, these two electrodes

are referred to as anode and cathode because of the current crossing into the body being positive and negative, respectively. For tACS the concept of how to place the stimulation electrodes is quite different due to the applied alternating current. During one half cycle of a tACS oscillation, one electrode will serve as anode and the other one as cathode and current strength will increase and decrease following a half sine wave. During the other half cycle, the pattern will reverse and the former anode must now be considered the cathode and vice versa. Thus, on average, the membrane potential is not affected and tACS is not intended to excite or inhibit cortical activity monotonously. Instead, the main goal of tACS is to influence brain oscillations (Herrmann et al. 2013). In contrast to tDCS, all cortical areas that receive stimulation, i.e. at least two areas if two electrodes are used, are modulated in a similar way.

**3.2 Selecting Experimental Design**

Compared to tDCS, tACS requires a different rationale for planning an experiment or intervention. At first, experimenters will identify a cognitive or other process that is characterized by a specific brain oscillation. Next, it has to be defined what parameter of this brain oscillation is responsible or is thought to be responsible for which aspect of the respective process. It is possible to enhance the amplitude of an electroencephalography (EEG) oscillation by applying tACS at the frequency of that oscillation (Zaehle et al. 2010). Note that the changes that result from tACS may outlast the duration of stimulation due to synaptic plasticity (Antal and Paulus 2013). In addition, the frequency of an EEG oscillation can be modulated towards the frequency of tACS if the frequencies of tACS are close to the intrinsic frequency of the EEG (Helfrich et al. 2014a). Furthermore, the phase of the EEG could become phase-locked to the alternating current of tACS. Thus, the phase at a certain brain location can be modulated as well as the phase coherence between multiple brain areas that are stimulated by different electrodes. It is important to be aware that the two sine waves applied at the two tACS electrodes have a phase difference of 180°. Using a third electrode can then bring a cortical region in-phase or out-of-phase with respect to the brain region stimulated by one of the other electrodes (Polanía et al. 2012a). Thus, if the intent of

stimulation were to stimulate two distant areas in phase, dependent on the type of stimulator, it would be necessary to split one of the channels and connect it to two electrodes, which would then be in phase. In this case, a third electrode (the other channel) will serve as the return electrode. Last but not least, cross-frequency effects can be achieved. It has been shown that stimulating the brain with 40 Hz tACS reduces oscillatory power at 10 Hz representing cross-frequency coupling and supporting the known antagonism between gamma and alpha oscillations (Helfrich et al. 2014a).

**3.3 Selecting Stimulation Parameters**

The effect of increasing the intensity of tACS results in non-linear excitability modulation of cortical tissue when 140 Hz tACS is applied to the primary motor cortex (M1) and MEPs are recorded in response to TMS pulses (Moliadze et al. 2012). Low intensities of 0.4 mA result in a decrease of the amplitudes of MEPs. Intermediate intensities of 0.6 and 0.8 mA showed no significant effect, and a high amplitude of 1 mA resulted in elevation of the MEP amplitude. This was interpreted as inhibitory neurons being more sensitive to 140 Hz tACS than excitatory neurons that dominate the overall effect at high intensities. At intermediate intensities excitation and inhibition cancel each other out. Thus, non-linearities of the effects of different tACS intensities should be taken into account.

Concerns have been raised about the applicability of placebo protocols in tACS studies (Raco et al.; Schutter and Hortensius 2010), as alternating current applied in the EEG frequency range - dependent on electrode position and stimulation intensity – can evoke phosphene perception during the entire application of stimulation (Turi et al. 2013). Phosphenes during tACS are most probably induced by retinal stimulation, as computational modeling studies of the path of the current flow suggest (Kar and Krekelberg 2012a). It was found that some portion of the AC can reach the retina by passing through the eyes, due to the current spread-effect, which is sufficiently strong to induce phosphene perception in many subjects. Future experimental work may concentrate on developing and optimizing

tACS placebo protocols specifically for stimulation frequencies between the alpha and gamma ranges.

### 3.4. Transcranial Random Noise Stimulation (tRNS)

tRNS is also an alternating current stimulation technique, but at a stimulation frequency continuously changing within a spectrum of oscillations ranging from 0.1 Hz to 640 Hz. This technique is more recent than the other types of tES, with very few studies regarding mechanisms of action (Terney et al. 2008; Paulus 2011). In general, it has been shown that tRNS, if applied over the motor cortex, can increase MEP size. However, the effect of stimulation is likely intensity-dependent (Moliadze et al. 2012). Since tRNS is a repetitive stimulation, random and subthreshold, it has been hypothesized that tRNS can induce mechanisms of temporal summation of neural activity because the time constant of a neuron is long enough to allow the sum of two or more stimuli in close temporal sequence (Fertonani et al. 2011). Indeed, in a recent pilot study the $Na^+$ channel blocker carbamazepine trendwise inhibited MEPs after tRNS application over the motor cortex (Chaieb et al. 2015). Furthermore, the effects of tRNS can also be explained in reference to the phenomenon of stochastic resonance (Miniussi et al. 2013). Stochastic resonance refers to the phenomenon that a signal that is too weak to exceed a threshold is amplified by adding noise (McDonnell and Abbott 2009). For example, if random noise is added to the sub-threshold neural oscillation in the brain, the sum of the two signals will exceed the threshold at several timepoints, resulting in improved cognitive performance (Cappelletti et al. 2015).

## 4. Monitoring physiological effects of tES

### 4.1 Monitoring physiological effects of tES with TMS

TMS is one of the major tools used to monitor cortical excitability alterations induced by tES. To explore the physiological effects of tES, TMS is most frequently applied over the motor cortex. Beyond motor cortex stimulation, TMS can be used to monitor visual cortex excitability alterations via phosphene thresholds (Antal et al. 2003; Kanai et al. 2008). TMS-

EEG is suited to obtain excitability alterations independent from cortical areas, which deliver motor or sensory output (Pellicciari et al. 2013).

#### 4.1.1 Monitoring of tES-induced motor cortex plasticity

The typical course of respective experiments is (a) determination of the motor cortex hot spot of the target muscle, and baseline TMS intensity, (b) obtaining baseline excitability, (c) tES intervention, and (d) obtaining intervention-induced excitability alterations.

For (a), correct determination of the target muscle hot spot is crucial to obtain reliable results. Neuronavigated coil placement is helpful to guarantee constant coil position, and reduce variability. Baseline MEP amplitudes before tES should be of medium size to avoid ceiling or bottom effects. This is accomplished by a mean MEP amplitude of about 1 mV, or a TMS intensity of 120% of resting motor threshold (Nitsche and Paulus 2000, 2001; Nitsche et al. 2001; Rossini et al. 2015). The threshold-dependent method might result in somewhat larger interindividual variability of MEP amplitudes. For reliable baseline MEP amplitude determination (b), it is crucial that the target muscle is completely relaxed, and that alertness of the participants is stable. Because of the intrinsic variability of MEP amplitudes, a minimum of 20 MEPs should be obtained. Especially the first MEPs are prone to artifacts caused by arousal or suboptimal coil position (Schmidt et al. 2009), thus these should be excluded from further analysis, if contamination is suggested. The same holds true for other MEP affected by muscle activity, instable arousal or other sources of artifactual MEP. (c) During intervention, TMS is rarely applied, since it was suspected that TMS might affect tES-effects. This however seems not to be the case, at least for tDCS (Nitsche et al. 2007b). If TMS is performed during tES, baseline TMS measures should be performed with the tES electrodes on the head to avoid differences of coil-brain distance, which would affect MEP size. Furthermore, flat electrodes are preferable to guarantee constant coil position. If TMS protocols are applied requiring muscle contraction for baseline determination of TMS parameters, these should be performed about 20 min before intervention, because muscle

contraction alters tDCS effects (Thirugnanasambandam et al. 2011). For (d), post-intervention TMS has been performed for up to over 24h (Monte-Silva et al. 2010, 2013a). Especially for these prolonged measures, coil and EMG electrode position have to be guaranteed to be constant throughout the experiment, e.g., by marking the respective positions, or use of neuronavigation. For protocols that require a constant test pulse, or conditioning pulse intensity, post-tES adjustment of TMS parameters is advantageous (Nitsche et al. 2005). For monitoring neuroplastic effects, follow-up measures should be conducted for a sufficiently long time, otherwise delayed effects can be missed (Nitsche et al. 2004; Batsikadze et al. 2013). Sufficiently long breaks between MEP blocks are required to prevent subjects from becoming sleepy (e.g., 20 MEPs every 5 min for 30 min, then every 30 min for up to 120 min after intervention).

In general, especially naïve subjects might have problems to relax completely, and to stay in identical states of alertness throughout the experiments. This enhances variability, and reduces validity, of the outcome measures. This problem can be circumvented by establishing a first session that is not included in the terminal data analysis. In multiple session approaches, for short-term plasticity effects (5 or 7 min stimulation) an inter-session interval of one hour is sufficient (Nitsche et al. 2005; Fricke et al. 2011). For long-term plasticity effects, an interval of one week should avoid interferences, whereas a 24 h break is insufficient (Monte-Silva et al. 2010, 2013a). In all cases, it is crucial to describe in detail if tDCS experiments were implemented in naïve subjects and if specific inclusion criteria were implemented (i.e., responders vs. nonresponders, subjects with MEP > than a certain value, subjects with/without phosphenes, etc.). A complete description of the strategy utilized for subject selection is crucial to allow replicability of results and to allow meaningful comparisons across studies.

Many of the suggestions made for motor cortex TMS protocols are also relevant for visual cortex TMS and TMS-EEG studies, thus for the sake of brevity we avoid an extensive discussion.

### 4.2 Monitoring physiological effects of tES with electroencephalography (EEG) and event-related potentials (ERPs)

EEG is one of many methods available to study the state and function of the human brain. Although EEG lacks the spatial resolution of other techniques, such as functional MRI (fMRI), it possesses several qualities that can provide unique insight on how tES changes brain activity. The clear utility of integrating EEG with tES lies in the fact that EEG is a measure of electrical activity, directly reflecting the electric state of neurons. Specifically, the scalp-recorded EEG signal measures voltage fluctuations resulting from ionic current flow (Kappenman and Luck 2011) –current flow that can be directly modulated with tES. Moreover, the excellent temporal resolution of EEG offers the potential to identify specific brain responses to tES and how they evolve throughout stimulation, elucidating changes in processing over time within an area or across circuits (Miniussi et al. 2012; Bortoletto et al. 2014). The objective of this section is to outline the technical steps necessary to successfully combine EEG recordings with tES based on currently available evidence in the field. It should be noted, however, that this is a relatively new area of investigation, and there are many aspects of EEG-tES combination that have yet to be systematically investigated. . For a discussion of how tES-EEG can inform about products of excitability changes induced by tES, see Miniussi et al. 2012.

#### 4.2.1 Selecting an Approach

Experiments that combine tES and EEG can be divided into two methodological approaches: the offline or sequential method, which evaluates the short- and long-term after-effects of brain stimulation, and the online or simultaneous/concurrent method, which evaluates the immediate and ongoing changes that occur during stimulation. Only the online approach,

which involves recording EEG concurrently with brain stimulation, can be defined as tES-EEG coregistration. These two approaches provide different information about mechanisms and create unique technical challenges. Therefore, it is important to clearly specify which method was used when describing an experiment. Additionally, it is also very important to explicitly describe the temporal relation between tES and the EEG recording. In the case of sequential tES-EEG, it is important to report how much time separated the tES and EEG recording sessions. For concurrent tES-EEG, it should be specified how much of the tES overlapped with the EEG recording. This information is relevant to the interpretation of results and has significant implications for potential replication attempts.

#### 4.2.2 Integrating tES and EEG electrodes

There are a number of challenges that exist in integrating tES with EEG recordings. At present, a few dedicated commercial systems are available that are specifically designed to integrate tES with EEG (Schestatsky et al. 2013). In the following section, we will primarily consider how to integrate tES with EEG in the event that such a combined system is not used.

The first challenge we face in integrating tES with EEG is how to interface the tES electrodes with the EEG electrodes without causing interference or bridging between electrode sites. The first and simplest solution is to place the tES electrodes underneath the EEG electrode cap, making sure that the EEG electrodes are not directly on top of or close to the tES electrodes. However, this approach does not allow access to the tES electrodes during stimulation, making it difficult to fix issues that may arise throughout the session, such as drifting of the electrodes, evaporation of saline/drying of electrode gel, or increases in impedance at the electrode sites. This approach is also subject to potential bridging between tES and nearby EEG electrode locations. An alternative solution is to create specific “windows” in the electrode cap (e.g., cut outs) for placement of the tES electrodes. This approach would permit direct access to the stimulation area; however, there are a limited

number of cuts that can be performed on the caps, and removing sections of the electrode cap may alter the location of remaining electrode sites by disrupting the overall fit of the cap. Moreover, although bridging is less likely with this arrangement than in the case of placing tES electrodes underneath the electrode cap, gel/saline can still spread over the tES electrode and cause bridging with adjacent EEG electrodes. To reduce bridging, it is possible to use self-adhesive tape on the cap over the border of the cuts between the cap and the skin to minimize the spreading of the conductive medium. More recently, it has become possible to deliver tES by means of small electrodes that are similar in size to EEG electrodes. This approach, called high definition tES (Datta et al. 2009), can be easily integrated with EEG by mounting both EEG and tES electrodes in the same cap. This approach minimizes many of the issues described above, providing continued access to the tES electrodes throughout the session, and minimizing the potential for electrical bridging between adjacent electrode locations (although care should still be used to ensure that gel does not spread to adjacent sites).

#### 4.2.3 Recording EEG during tES

Concurrent tES-EEG recordings face additional challenges over the sequential method. Importantly, EEG involves recording electrical activity on the surface of the head, and tES involves the application of electrical current on the surface of the head. Therefore, these two techniques can interfere with each other in important ways. This is true even in the case of tDCS, which involves application of a DC current outside of the typical AC range examined in EEG/ERP experiments. One issue faced in simultaneous tES-EEG recordings is that the tES is orders of magnitude stronger than the signals recorded with EEG, resulting in saturation of an EEG recording amplifier that does not have a sufficient input range. In some cases, saturation may appear only in the EEG channels located nearby to the tDCS electrodes (Accornero et al. 2014). Noise can also be introduced by the tES system during the EEG recording. Specifically, the tES system contains an electronic circuit that can be the source of

external noise, and this noise can be recorded in the EEG. This noise can be minimized or eliminated by using a stimulator that has adequate isolation.

It is relatively easy to determine whether these external sources of noise described above may impact EEG recordings by testing with a phantom head (see below). Therefore, it is recommended that individuals interested in recording EEG during tES follow a set of simple procedures to evaluate their tES equipment/stimulation parameters in the context of the EEG system. These procedures simply involve recording EEG both without tES and during application of tES using a phantom head, eliminating the influence of biological artifacts. The EEG recordings can then be compared between the session with tES and the session without tES to identify any unwanted artifacts or induced frequencies present in the recorded signals with simultaneous tES. One easy phantom head is to use a small melon (e.g., a cantaloupe melon, of about the dimension of a small head), that can be stimulated with tES, allowing the recording of any artifacts induced by the tES device (Veniero et al. 2014). Alternatively, a fake head can be created by connecting three resistors together to form a triangle, and connecting each corner of the triangle to wires leading to the active, ground, and reference inputs in the EEG system (Luck 2014). However, it is important to note that tES may also induce biological artifacts, and therefore not all artifacts will appear in testing with a phantom head. It is therefore also recommended that the same procedures be completed with a human research participant to fully examine the potential for artifacts.

In some cases, filtering the EEG with a 0.5- to 70-Hz band pass filter may effectively attenuate artifacts related to tDCS (Accornero et al. 2014). In the case of residual artifacts, it is recommended to follow the general guidelines provided by the Society for Psychophysiological Research for artifact rejection/correction procedures for EEG/ERP studies (Keil et al. 2014). In addition, all artifacts should be sufficiently described in publications, along with any procedures used to remove or correct for the artifacts. There are no specific acquisition parameters in terms of sampling rate, impedance, or online filtering

outside of the general recommendations for EEG recordings (Keil et al. 2014; Luck 2014). The recording of EEG is traditionally performed with electrodes made of tin, silver, silver-chloride, gold or more recently sintered silver/silver-chloride electrodes. The sintered electrodes seem to be ideal in this respect because they are less sensible to polarization effects, and therefore they have long-term stability and minimal low-frequency noise (Tallgren et al. 2005).

The application of tACS or tRNS is even more challenging because these modalities of stimulation induce an oscillation that impacts the whole recorded signal. Nevertheless, thanks to the development of dedicated algorithms it might be possible to remove the signal from tACS-induced artifacts in cases in which the tACS frequency does not overlap with frequencies examined in the EEG/ERP signals (Helfrich et al. 2014b). Therefore, in the case of tACS, an additional algorithm is likely necessary to remove the tES-induced signal without altering the cortical signal, although it should be noted that the effectiveness of these algorithms at removing the artifact signals has not been systematically evaluated yet in these domains.

**4.3 Monitoring physiological effects of tES with Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS)**

Integration of tES with human magnetic resonance (MR) provides a novel avenue for investigating the neural mechanisms underlying tES. To date, the majority of research integrating tES with MR has focused on integration of tDCS. This section will discuss how tDCS has been integrated with fMRI, both in terms of Blood Oxygen Level Dependent (BOLD) fMRI (Baudewig et al. 2001) and Arterial Spin Labeling (ASL; Zheng et al. 2011; Stagg et al. 2013); as well as proton and non-proton MR Spectroscopy (MRS; Rango et al. 2008; Stagg et al. 2009; Binkofski et al. 2011; Clark et al. 2011; Stagg and Nitsche 2011; techniques hereafter collectively referred to as MR in this section). tDCS and MR have to date been combined in a number of ways depending on the nature of the question posed,

from the technically most simple where fMRI is used to guide subsequent tDCS application (Woods et al. 2014) to approaches where tDCS and MR are performed in the same session. tDCS can be applied in the bore of the magnet, with the option of acquiring data during stimulation (concurrent acquisition) or subjects can be removed from the scanner, tDCS applied, and then replaced in the scanner (sequential acquisition).

#### 4.3.1 Integration of tDCS with MR

Prior to the advent of MR compatible tDCS systems, studies were limited to sequential acquisition. This presents logistical and analytical issues for BOLD fMRI and MRS data, although these issues can be at least partially overcome. However, with the advent of MR-compatible tDCS systems, both sequential and concurrent acquisitions are possible. Thus, participants can undergo baseline scans prior to stimulation, simultaneous acquisition of data during stimulation, and/or post-stimulation scanning while remaining in the same position throughout the scan. This has obvious advantages for studies where the reproducibility of voxel placement, or high-resolution fMRI is required. However, integration of the tDCS device into an MRI system is not without complications, and a number of aspects should be considered. Importantly, MR-compatible systems should have high-ohmic resistors in the stimulating circuit (commonly 10kOhm) to prevent the induction of eddy currents within the stimulating leads.

When tDCS is integrated with MR, subject safety standards for both MR and tDCS should be adhered to (e.g., no metal on or in the head, no implants susceptible to electrical current or magnetic fields, etc.). In order to acquire good data, the localization of electrodes, careful preparation/placement of electrodes, stable fixation of the electrodes to the head, etc. remain critical considerations for tDCS combined with MR, as they are with tDCS alone (see section on electrodes above for detailed description of these considerations).

However, some specific issues need to be addressed when using tDCS in the MR bore. Firstly, biocarbon electrodes should be attached to the participant using thick electrical conductance paste (e.g., Ten-20 paste), rather than saline soaked sponges or low viscosity electrode gel. As sponges begin to dry after ~20 minutes, but scanner sessions commonly last one or more hours in duration, conductance paste avoids premature drying of electrode sponges when using saline. Drying of the sponge leads to an increase in resistance and runs the risk of pain and skin burning to the subject. Furthermore, electrode paste, rather than electrode gel, allows preparation of a thick coating (≥3mm) of paste to provide sufficient distance between biocarbon electrodes and scalp, ensuring that stimulation is delivered evenly across the electrode. Paste should be applied directly to the biocarbon electrode and thickness of paste prep kept consistent, preferably measured for precision. The adhesive quality of the paste assists in affixing the electrode to the targeted location/scalp, but also requires additional elastic straps for fully secure placement.

Care should be taken at this stage to ensure that the electrodes do not move, and electrodes can be marked with oil-capsules so their position can be checked on the resulting images. It is vital to ensure that electrodes are not in contact with the head coil, or headphones, to prevent electrode displacement and unexpected interactions between the stimulator and the scanner.

Additionally, tDCS within the MR bore requires careful insertion of specially designed MRI-compatible (non-ferrous or appropriately shielded) tDCS cables and electrodes through the magnet suite waveguide and into the magnet bore. These should run parallel to the bore, without loops and away from the subject to prevent the risk of eddy current induction and potential RF burns.

**4.3.2 Considerations for Concurrent MR Acquisition**

Introduction of an electrical current into the scanner's magnetic field results in further warping of the magnetic field (i.e., field artifact). This artifact is of critical concern for BOLD fMRI protocols, as it may result in false positive patterns in BOLD signal. The impact of field artifacts may also alter MRS and ASL-based sequences as well. The magnitude and nature of any artifacts are likely to depend on the exact experimental setup and therefore will in all probability vary from center to center. One study demonstrated evidence of BOLD signal within brains of two cadavers during a concurrent tDCS and fMRI protocol (Antal et al. 2014b). Another study demonstrated visual evidence of change in echo-planar imaging (EPI) field maps that was limited to the scalp and cortical tissue near to the electrode site (Holland et al. 2011). To date, very few studies have provided data on change in the magnetic field in relation to concurrent tDCS-MR. These contrasting cases demonstrate the need for careful consideration of concurrent data and acquisition of appropriate field map data to allay concerns over false positive functional results from perturbation of the magnetic field. Specifically, brief acquisition of EPI field maps with and without stimulation within participants (~1 minute per field map) should become standard procedure for concurrent data, as absence of this data undermines interpretation of data.

#### *4.3.3 Other Considerations for tDCS integrated with MR*

At present, most published studies using combined tDCS and MRI/MRS methods have used limited sample sizes (average sample size of all tDCS-MR papers published between 2001-2014 = 10.8±5.7). While these sample sizes were also common in early MR studies over a decade ago, sample sizes of this scope have proven insufficient in most modern MR studies, leading to underpowered and difficult to replicate findings. Future tDCS-MR studies should strive to adhere to appropriate MR and tDCS specific sample sizes, or internal replication, to insure clear interpretation of data and potential for future replication.

## 5. Monitoring functional effects of tES

### 5.1 Monitoring functional effects of tES in healthy subjects

An increasing number of studies have applied tDCS to modulate neuroplasticity in the motor system or in other cortical networks of interest. Since memory formation and retention are processes that cannot be measured directly, their state is typically inferred indirectly using electrophysiological markers or measures of behavioral performance that change in response to practice and reflect increased efficacy of task performance. When using behavioral outcome measurements, the choice of task and the associated performance metric are critical for reliably detecting tDCS effects. Important parameters include task complexity, type of task (e.g., tDCS can have antagonistic effects in noisy and non-noisy tasks; Antal et al. 2004b) and the amount of training, which must be appropriate for the skill level of the participant otherwise facilitatory tDCS effects might be masked by ceiling effects in performance measures (Furuya et al. 2014a). Moreover, the brain's ability to undergo neuroplastic changes differs across populations. Applying tDCS with the goal of up-regulating learning tends to induce smaller effects in young adults who exhibit a near-optimal level of neuroplasticity than, for example, in elderly (Zimerman et al. 2013). Similarly, using 1mA tDCS under the cathode electrode to down-regulate plasticity seems to be most effective in individuals that exhibit maladaptive plasticity that is too high, as it is the case with dystonia (Furuya et al. 2014b). Note, however, that pathology might also change a patient's responsiveness to tDCS. For example, multiple sclerosis patients whose motor learning ability is impaired did not benefit from tDCS during motor training, even though the stimulation protocol is suitable to enhance plasticity when applied in healthy populations (Meesen et al. 2014).

Modulatory effects of tDCS on neuroplasticity are small compared to the large inter-individual variability in learning typical in humans. For example, consider a common design where tDCS is applied during a single practice session to boost learning in comparison to a sham control group. Given that subject samples are often of moderate size, the observed behavioral effects might be too small to differ significantly from sham stimulation. However, there is evidence that modulatory effects accumulate when tDCS is applied during multiple,

consecutive sessions (Reis et al. 2009; Alonzo et al. 2012; Waters-Metenier et al. 2014), and that tDCS effects might require a consolidation period to be fully expressed (Reis et al. 2009; Reis et al. 2013). It was initially thought that tDCS applied at rest prior to practice can prime the cortex for learning, and that tDCS applied after practice can facilitate consolidation. However, experimental evidence that supports this idea is sparse. Notably, when tDCS is applied immediately before or after motor practice, effects are rarely additive because the interventions might interact according to homeostatic principles (i.e., facilitating protocols might suddenly suppress plasticity and vice versa; Müller-Dahlhaus and Ziemann 2014) thus leading to counter-intuitive results. On the other hand, there is mounting evidence that applying tDCS during practice triggers effects that outlast the stimulation period and facilitate neuroplasticity and long-term memory formation. (Fritsch et al. 2010; Reis et al. 2013; Saucedo Marquez et al. 2013)

Functional effects of tDCS are also monitored via cognitive tasks. Indeed, tDCS has been added to the technical arsenal of cognitive neuroscientists and has revealed important evidence on both the relationship between brain and behavior as well as on its efficacy as a cognitive neuroenhancement tool (Kuo and Nitsche 2012; Miniussi et al. 2013). However, several aspects should be considered when establishing cognitive assessment protocols for testing technical safety or for investigating its role as a cognitive intervention method. First, the effect of tDCS on cognition has been frequently assessed by classical neuropsychological tasks that are not necessarily sensitive to the subtle changes it induces. Secondly, different tests are often used by different authors making comparisons across studies difficult. Importantly, standard tDCS protocols have only a moderate level of spatial specificity; for example, a positive effect on working memory is observed when stimulating DLPFC, but not M1 (Fregni et al. 2005). However, the spatial resolution of tDCS is too low to precisely stimulate functional subdivisions of a cortical area so that different cognitive functions have been modulated even though similar tDCS protocols were applied (i.e., similar target areas, electrode size, stimulation parameters). This highlights that caution is required

when interpreting cognitive findings. Also, little is known about the additive effects of tDCS and cognitive tasks (Andrews et al. 2011; Miniussi et al. 2013; Carvalho et al. 2014). Thus, further studies are needed to explicitly compare the effects of cognitive assessment during and after stimulation. Finally, cognitive tDCS protocols should consider the possibility that differences in polarity, current intensity, electrode size, time of stimulation and volunteer group lead to different modulatory effects (Boggio et al. 2006; Jacobson et al. 2012; Kuo and Nitsche 2012; Carvalho et al. 2014). For example, a positive effect on working memory in healthy young participants can be obtained with 1mA tDCS (Fregni et al. 2005) whereas the same effect is only observed with 2mA stimulation in patients with Parkinson's disease (Boggio et al. 2006). Another example is the differential effect of tDCS on risk behavior when applied in healthy young or elderly subjects. Using the same methodology Fecteau et al. (2007) showed that tDCS applied over DLPFC decreased risk behavior in younger subjects while Boggio et al. (2011) showed the opposite effect in elderly.

It has been shown that tACS is an appropriate tool to modulate a wide range of cognitive functions (Antal and Paulus 2013; Herrmann et al. 2013; Fröhlich et al. 2015) including perception (Feurra et al. 2011), attention (Laczó et al. 2012), working memory (Jaušovec and Jaušovec 2014), declarative memories (Marshall et al. 2006), fluid intelligence (Santarnecchi et al. 2013), decision making (Sela et al. 2012) and self-awareness when dreaming (Voss et al. 2014). Most previous studies applied tACS with the goal of entraining intrinsic brain oscillations that are essential for successfully performing a behavioural task. The basic idea is that applying alternating currents simultaneously to a large number of neurons modulates oscillatory network activity in a frequency specific manner (Frohlich and McCormick 2010; Ali et al. 2013a) even if the externally applied current is small (Reato et al. 2013).

In order to apply this principle within an experimental context, efficacy of tACS is best when tailored to the specific oscillatory signature observed within the targeted brain area and for the investigated behavioural task. tACS entrainment has been demonstrated for a large

variety of tasks (Antal and Paulus 2013; Herrmann et al. 2013; Fröhlich et al. 2015), however, the observed behavioral effects were largest when appropriate frequency bands were stimulated while stimulation with control frequency had no or minor effects (Pogosyan et al. 2009; Joundi et al. 2012; Santarnecchi et al. 2013; Lustenberger et al. 2015). Most of these previous studies applied tACS for "typical" frequency bands reflecting a population average for a specific task. However the efficacy of tACS might be further increased by considering inter-individual differences of intrinsic oscillations (e.g. the frequency peak of alpha-oscillation can vary between 8 and 14 Hz), i.e. by matching the tACS frequency to *individual* peak frequencies over the cortical area of interest. Otherwise, deviations from the individual intrinsic frequency, even if small, might induce other effects than intended (e.g., by slightly shifting alpha frequency; Cecere et al. 2014) or reduce the efficacy of tACS entrainment (Ali et al. 2013a). Nevertheless, even in the same subject, individual intrinsic oscillatory activity slightly varies during the course of a given task or exercise (e.g. due to attentional load, learning effect, emotional and motivational changes, etc) and might decrease the effectivity of the stimulation even when the individual peak frequency is applied. Furthermore, when tailoring the tACS stimulation frequency to a specific task it is important to keep in mind that entrainment effects might not be restricted to the stimulation frequency per se, but might also affect neural activity within other frequency bands, which are influenced via cross-frequency interactions (Helfrich et al. 2014b) or are higher harmonics of the stimulation frequency (Miniussi et al. 2013; Reato et al. 2013).

Most higher-order cognitive functions are associated with long-range communication between different brain regions that depend not only on oscillation frequency, but also the phase coupling between the two neuronal populations. Modulating the phase relationship for a given frequency band has been shown to modulate cognitive function (Polanía et al. 2012b; Helfrich et al. 2014b). Thus, consideration of the phase-relationship between different cortical areas is important, particularly when using a two-electrode setup with both electrodes mounted over the cortex, since this setup can only provide out-of-phase (180deg)

stimulation. By contrast, using a multi-electrode montage (three or more electrodes) provides better experimental control over the phase relationship between remote yet interacting oscillating neuronal populations. Finally, it is well known that tACS at frequencies below 30 Hz induces visual phosphenes in most participants, however dependent on electrode position and stimulation intensity (Kanai et al. 2008). Phosphenes emerge most likely because a substantial part of the applied current is shunted via the skin to the eyes where it either affects retinal cells or the optical nerve (Kar and Krekelberg 2012b). In order to exclude that functional effects are driven by supra- or subthreshold stimulation of the retina/optical nerve rather than by modulating neural activity of a specific cortical area, it is strongly recommended to include a control experiment where both electrodes are placed over control sites.

**5.2 Monitoring functional effects of tES in patients**

tES – particularly tDCS – has been increasingly investigated as a treatment option for neurological and psychiatric disorders in the past years. The interest in using tES for treatment purposes relies on several compelling characteristics for clinical use, such as safety, tolerability, ease of use, cost and portability. As discussed in 2.6, currently applied protocols are safe and well tolerated by subjects. For instance, in a recent literature review, data from all tDCS clinical studies performed from 1998 to August 2010 were collected (Brunoni et al. 2011a). Of 209 studies (172 articles, encompassing almost 4000 subjects), similar rates in frequency of adverse effects in the active vs. sham arms were observed. The most common adverse effects were headache, itching, burning, discomfort and tingling, occurring in 10-40% of patients regardless of treatment group.

Some aspects have to be taken into account when applying tES in clinical populations, which are in many instances related to pathologically altered disease-related physiology. The common rationale for tES application to reduce clinical symptoms is to “normalize“ pathological brain activity and excitability. Thus, in most cases, electrodes are positioned

over the area associated with the pathology under study – for instance, in depression electrodes are placed over the dorsolateral prefrontal cortex, an area in which activity is pathologically altered (Koenigs and Grafman 2009). As discussed, although not necessarily valid in all scenarios, the rule of thumb of anode promoting increased cortical excitability and cathode inducing the opposite effects is commonly employed in clinical trials. For example, in one schizophrenia trial the cathode was placed over the left temporoparietal area, an area in which activity is supposedly increased in some schizophrenia patients with positive symptoms (Brunelin et al. 2012). However, indirect modulation of target areas via connected cortices has also been performed, as in motor cortex stimulation for pain treatment (Bolognini et al. 2015).

For the specific stimulation protocols applied, it should be taken into consideration that tDCS as a neuromodulatory intervention has effects that are brain state-dependent. Thus, similar to other plasticity-inducing stimulation protocols, stimulation might have reduced or even inverted effects in specific clinical populations (Fregni et al. 2006; Player et al. 2014). Concomitant pharmacological treatment can furthermore alter the effects of tDCS, an important consideration for all tDCS studies. For instance, it was shown in depression trials that benzodiazepines decrease tDCS clinical efficacy whereas antidepressant drugs increase it (Brunoni et al. 2013a, 2013b). Furthermore, neurophysiological studies in healthy humans (for a review, see Stagg and Nitsche 2011) showed an influence of benzodiazepines, antipsychotics, lithium, anticonvulsants and serotoninergic antidepressants on tDCS effects. Since these studies were conducted in healthy humans, and the outcome parameters were surrogate markers, the degree of transferability of these data to clinical populations is not clear at present. Thus, in most cases, the recruitment of drug-free samples would be the optimal approach to avoid confounding effects of pharmacotherapy on tDCS effects. However, this is not always feasible due to ethical and pragmatic reasons. In such cases, pharmacotherapy should remain stable for at least 4-6 weeks to minimize the confounding effects and concomitant pharmacotherapy should be reported in trial results. However, since

tDCS and pharmacotherapy have been shown to have synergistic effects in specific cases, e.g., serotonin reuptake inhibitors combined with tDCS in depression (Brunoni et al. 2013b), systematic variation of pharmacotherapy as part of the intervention protocol can also be an option.

Another factor that can influence tDCS effects is “dose”. In fact, although there is no standard definition of how to measure the “dose” of tDCS delivered in a clinical study, factors that influence the amount of current injected are the size of electrodes, the electric current intensity, the duration of the tDCS session and the total number of sessions. Some studies have shown greater cognitive improvement with higher current doses (Iyer et al. 2005b; Boggio et al. 2006). The interval between sessions (e.g., every other day, once daily, twice daily etc.) might also influence the clinical effects. Furthermore, timing of stimulation in relation to task performance, e.g., when rehabilitation should be fostered, is presumed to have an impact on the results. Similar to studies in healthy humans (see above), conductance of tES during task performance might be superior to separated interventions, especially if (re-) learning procedures are involved (Nair et al. 2011; Bajbouj and Padberg 2014).

For study design, two main types of study are used to evaluate the functional effects of tES in patients. In the first one, the functional effects of tES are evaluated immediately after or even during (“online”) stimulation. These studies commonly use a within-subjects (cross-over) design in which participants are randomized to receive the active(s) and the sham sessions with a time interval (ranging from one day to one week) between them to avoid carry-over effects. These study outcomes are usually surrogate, i.e., they compare the effects of active and sham tDCS on a biological marker or an endophenotype (e.g., changes in cortical excitability (Hasan et al. 2012), performance in a neuropsychological test (Wolkenstein and Plewnia 2013) to obtain evidence regarding the mechanisms of action of tDCS, or the pathophysiology of the disease. In the second type, typically the effects of

repeated tDCS sessions, applied once daily or more frequently for several days, are evaluated. The primary outcomes are usually clinical (although surrogate biomarkers are evaluated as well; Brunoni et al. 2012) and the research question aims to explore whether tDCS has a therapeutic effect for a neuropsychiatric condition. There are many potential study designs principally suited for this type of study: open-label trials (without a sham control, due to tricky interpretation of results only suggested for first exploratory data acquisition; Brunoni et al. 2011c) or double-blinded sham-controlled trials, such as two-arm trials (comparing active to sham tES (Brunelin et al. 2012) or, in a "double-dummy" approach, comparing active tDCS + placebo pill vs. sham tDCS + pharmacotherapy), triple-arm trial (comparing tDCS, pharmacotherapy or placebo; or two types of active tDCS and placebo; Boggio et al. 2008) and factorial designs (placebo, only tDCS, only pharmacotherapy and combined treatment; Brunoni et al. 2013b) The latter design is particularly interesting for testing two interventions simultaneously, combined and also one intervention against another. However, although comprehensive, a factorial approach requires more resources and a larger sample size. In any case, given the proneness of many diseases for placebo effects, reliable double blinding in case of sham-controlled designs, as outlined above, is of utmost importance in these studies.

Design and sample size considerations in tDCS clinical studies further depends on the methodological purpose of the study (superiority trials vs. non-inferiority ones). Especially non-inferiority tDCS trials require cautious sample-size determination, as negative findings (no difference between tDCS and the comparator) due to underpowering in non-inferiority trials could be easily misinterpreted.

## 6. tDCS/tACS/tRNS in animal preparations

Animal studies spanning decades have tried to elucidate the mechanisms by which electric currents can affect neurons. This section summarizes recent work with a special focus on

low-intensity stimulation using DC (Direct Current), AC (Biphasic Sinusoid), and RN (Noise) waveforms, highlighting findings from in-vitro and in-vivo studies.

### 6.1 DC-, AC-, RN-induced membrane polarization

Stimulation across the head with a specific waveform of current produces an electric field across neurons with a comparable waveform. When stimulation is low-intensity ("sub-threshold"), then weak changes in membrane polarization are produced that, to a first approximation, simply track the same waveform.

DC stimulation (as in tDCS) produces a tonic shift in the membrane potentials of neurons (Chan et al. 1988; Bikson et al. 2004). Changes in membrane potential will influence neuronal excitability in a stimulation polarity-specific manner. An anode at the cortical surface is expected to produce inward flow (relative to the cortical surface), producing depolarization of the pyramidal neuron soma, which may increase excitability (Radman et al. 2009). Conversely, a surface cathode will produce soma hyper-polarization, decreasing excitability. For tDCS-relevant intensities, the magnitude of this polarization is low. Importantly, dendrites and axons are also polarized, and the extent and direction of this polarization will influence net changes in excitability (Rahman et al. 2013). Though this concept is well established and supported by experimental studies, it is often misapplied in human tDCS research at macro-, meso-, and micro-scopic levels. At the macro-level, it may be disingenuous to discuss "anodal tDCS" or "cathodal tDCS" without acknowledging the presence of a return electrode. Physics dictate that the amount of current crossing in and out of the brain is equal. At the meso-scopic level, the folding of the cortex produces inversions of current flow even locally under the electrode, including inversions across single gyri (Datta et al. 2009); to assume that the current flow into the cortex is unidirectional under any electrode is misleading. Finally, at the micro-scopic level is it incorrect to refer to anodal stimulation as simply "depolarizing" when in fact there is an equal amount of compartment de- and hyper-polarized under any condition (Bikson et al. 2004; Rahman et al. 2013). The fact that these biophysical

phenomena are not convenient for simplistic interpretation and design of tDCS, does not make them less true.

AC stimulation (as in tACS) also modulates the membrane potential of neurons at the frequency of the applied stimulation (Deans et al. 2007). Thus, differently from DC stimulation, AC currents fluctuate in time, creating a temporal succession of depolarization and hyperpolarization in neuronal compartments (Radman et al. 2007). The filtering properties of the membrane (Bikson et al. 2004) also make the induced polarization frequency specific, with high frequencies less effective in modulating excitability (Deans et al. 2007). This last fact along with the delay in polarization produced during tACS is often ignored in trial interpretation or design. For example, research on optimal or customized frequency should consider that under fixed intensity, higher frequency will be less effective in producing membrane polarization (Reato et al. 2013). Studies interested in phase must consider the timing delay between maximum polarization and stimulation phase, which will also be stimulation frequency specific (Radman et al. 2007).

With RN stimulation (as in tRNS), the membrane potential is again expected to follow the waveform of the stimulation with neural compartment specific changes in sensitivity and polarity, and filtering of high frequency signals. If the RNS is biphasic, then the membranes will fluctuate between depolarization and hyperpolarization. Stochastic resonance (Moss et al. 2004) has also been suggested as a possible mechanism to mediate the effects of tRNS.

### 6.2 What can we learn from *in vitro* experiments?

Finite-element models of transcranial stimulation provide estimates of the electric fields induced in the brain when transcranial stimulation is applied with conventional current intensities and electrode montage. A current of 1 mA, using a 5x5 $cm^2$ electrode can induce an electric field with a maximum peak of less than 1 V/m (Datta et al. 2009). Ultimately, whether a stimulation protocol will be successful in modulating brain functions depends on

how electric fields of this magnitude are effective in polarizing neurons and modulate their activity. *In vitro* studies have been crucial for understanding how weak electric fields affect neurons (Jefferys 1981; Chan et al. 1988).

Obviously, the general limitation of *in vitro* studies is the difficulty to translate directly the results to humans. Brain slices have reduced neuronal populations with no inputs from other areas, reduced connectivity (due to the slicing procedure), artificial cerebrospinal fluid (CSF), and usually, cannot show spontaneous transitions to different dynamical states. However, there are specific advantages of using *in vitro* preparations depending on the scientific question being asked and in providing precise control of the electric field and slice activity. First, the effects of electric fields can be studied at the sub-cellular, cellular and population level. Second, the stimulation can be controlled in a very precise manner. Third, pharmacological manipulations can easily be used to help elucidating the effects of electric fields, especially the synaptic modifications that may underlie the long-term effects of the stimulation.

A typical *in vitro* setup has two parallel wires or plates, usually of Ag-Ag/Cl, to create a spatially uniform electric field (same amplitude in every location between the wires; Jefferys 1981; Chan and Nicholson 1986; Bikson et al. 2004b; Radman et al. 2007b; Frohlich and McCormick 2010; Reato et al. 2010; Rahman et al. 2013b). The use of long wires ensures a uniform electrode field. The use of Ag-Ag/Cl material is intended to minimize electrode polarization providing a consistent electric field. This also minimizes electrochemical products, but actually tissue may be protected simply by putting the electrodes in the bath at a distance from the tissue. This configuration allows the experimenter to study the effects of currents on brain slices placed between the wires with a great control of the electric field magnitude, direction and waveform. Conventional electrodes can then be used to measure the electrical activity of single neurons or the average population. Changes in membrane potential, firing rate or synchrony in single neurons, evoked population responses or power

modulation in pharmacologically induced active network are typical measures to estimate the effects of electrical stimulation on neuronal activity.

In most animal studies, the electric fields used are significantly larger than those produced in the brain during tDCS, tACS, and tRNS. This may facilitate the discovery of phenomena and have produced valued predictions and insight on mechanisms (Jefferys 1981; Chan and Nicholson 1986; Bikson et al. 2004; Rahman et al. 2013; Reato et al. 2015). Only few *in vitro* studies have used electric fields comparable in magnitude to the ones induced by transcranial electrical stimulation in humans (<1 V/m). AC fields as low as 0.2 V/m have been shown to affect gamma oscillations *in vitro* (Reato et al. 2010). A previous study, using a similar preparation also reported a similar minimum value for measuring effects on gamma oscillations (0.25 V/m; Deans et al. 2007b). For entrainment of slow waves, the minimum electric field reported is 0.5 V/m (Frohlich and McCormick 2010), while for epileptic-like activity, 0.3 V/m (Francis et al. 2003). Electric fields on the order of 1 V/m have also been shown to entrain neuronal firing during slow waves *in vivo* (Ozen et al. 2010). DC fields as low as 0.75 V/m can also modulate evoked responses (Fritsch et al. 2010).

In almost all of these studies, low amplitude electric fields were able to modulate active neuronal networks. Indeed, it seems that the activity of the network can amplify the effects of the stimulation by virtue of the positive feedback of synaptically connected neurons experiencing similar polarizations (Reato et al. 2013). Results from *in vitro* studies also support the idea that the effects of weak electrical stimulation may depend on the dynamical state of the neuronal network of interest. This dynamics is often set by the balanced activity of excitatory and inhibitory neurons (Reato et al. 2010).

Interestingly, the lowest field intensities that affect neuronal activity *in vitro* are close to the maximum values of fields induced during transcranial stimulation. This may look like paradoxical considering that the stimulation parameters and the activity of the slice can be

controlled in great detail. However, the reduced level of connectivity, the absence of inputs from other brain areas and the lack of neuromodulators in brain slices is likely to reduce the sensitivity of neuronal populations to electric fields *in vitro.* Therefore, while the use of in vitro preparations is of crucial importance for understanding how neurons respond to electric fields, the key differences with *in vivo* or human experimental settings suggest caution in directly comparing electric field magnitudes.

## 7. tDCS and models of electric current through the brain

The primary use of "forward" models of tDCS is to predict the pattern of electric current through the brain for a given electrode montage (dose) and a given head anatomy (Ruffini et al. 2013). It is because the relationship between the electrode montage and current is complex that models provide value in dose design and optimization. Accurate modeling requires MRI-derived anatomy preserving gyri-level precision (Datta et al. 2009; Parazzini et al. 2011, 2012; Bikson and Datta 2012; Miranda et al. 2013; Rampersad et al. 2014; Opitz et al. 2015). Simpler geometries can be used to understand general features of the current distribution (Miranda et al. 2006, 2009; Faria et al. 2011) and to develop intuition on the dose design (Dmochowski et al. 2012).

Basic free modeling tools are available,(Truong et al.) as well as commercial software (Woods et al. 2015). However, currently advanced modeling requires access to engineering software (Windhoff et al. 2013). Whole body phantoms for dose calculations (Christ et al. 2010) are also now available and are used in modeling studies of tDCS (Parazzini et al. 2011, 2012, 2013a, 2013b, 2014a; Im et al. 2012; Laakso and Hirata 2013). A detailed anatomical head model, MIDA, has been recently made available for public use (http://dx.doi.org/10.1371/journal.pone.0124126; Iacono et al. 2015).

Models can be used to optimize conventional tDCS approaches using two large electrodes, noting that such approach will inevitably produce diffuse, if montage-specific, current

distributions (Woods et al. 2014). Models can also be used to leverage High-Definition tDCS (Datta et al. 2009), or other multi-electrode approaches for targeting, or to consider inter-individual difference across the normal adult population (Datta et al. 2012), in obesity (Truong et al. 2013), across children (Kessler et al. 2013a; Gillick et al. 2014), and in brain injury such as skull defects (Datta et al. 2010) and stroke (Dmochowski et al. 2013).

Models are ultimately used to select a "best" montage for a given indication (Brunoni et al. 2014) or, when possible, an individual (Gillick et al. 2014; Kim et al. 2014). Attempts to validate models have provided direct and indirect support for utility (Datta et al. 2013; Edwards et al. 2013). Open questions remain about how to relate predicted current density or electric field distributions with neurophysiologic, cognitive and behavioral changes (Rahman et al. 2013, 2014; Ruffini et al. 2014).

## 8. tES Ethics

As all research and medical procedures involve human subjects, tES must comply with ethical principles and standards. Although the regulatory framework differs among countries, the leading principles revolve around topics of protection and safety of participating subjects, and professional conduct. This in general involves multiple aspects addressed by a complex system of regulations, recommendations and principles, for example Good Practices in Clinical Research, or Code of Federal Regulations in the U.S. Below, we discuss selected issues highly relevant specifically to ethic pertaining to tES.

### 8.1 Education and training

Although tES is a user-friendly technique and the operation of the device, in comparison with other methods of brain stimulation, is relatively easy, skill development for consistent and safe application of tES requires comprehensive, multiple-step training. As tES has not yet been integrated into medical practice, it is not included in a formal medical graduate and postgraduate education. Availability of tES courses/workshops is growing, but they cannot

substitute for comprehensive training. Well-trained tES personnel should be proficient in the following aspects of tES application 1) the theoretical background of tES , 2) principles and rationale of tES use in specific populations, 3) dose, target, and stimulation protocol determination, 4) selection of subjects, 5) safety evidence and safety precautions pertaining to tES delivery, 6) preparation and positioning of the electrodes, preparation and operating the tES unit, 7) outcome monitoring and recording, including recording and reporting adverse events. Exposing subjects to tES delivered by personnel lacking sufficient practice and training would be a substantial lapse in professional conduct.

**8.2 Settings and procedures**

As the tES technology is rapidly developing, explorations of tES applications expand to variety of settings. For example, the conventional (1x1) tES is transitioning to clinical practices, and its modifications with enhanced safety features are being explored in remote (home-based) settings. In this context, the observance of principles of responsible professional conduct is of highest importance. Each setting (e.g., Randomized Clinical Trials, open–label or compassionate studies, remote delivery at the patient's home) requires provisions for safe tES conduct, i.e., specific procedures pertaining to monitoring of clinical status, adverse events and outcomes, as well as procedures pertaining to an access to medical assistance in case of unexpected events etc.

**8.3 Patient/subject selection**

A requirement of careful selection of subjects is a mandatory prerequisite for safe tES conduct. It is understood that tES is being explored and delivered in populations with various pathologies, and this is well justified in specific research protocols carried out by an experienced team in safety-enhanced environment. However, engaging subjects in tES procedure *ad hoc* without screening and careful considerations of conditions and factors that may alter expected tES outcomes is not consistent with the principles of responsible professional conduct.

### 8.4 Patient/subject education and informed consent

It is the tES operator responsibility to inform patients on potential risks and benefits pertaining to tES procedure, and to assure the subject's understanding, so that each potential tES participant can make an informed decision and provide informed consent for the procedure. In specific cases where decline of cognitive function is suspected, it is necessary to determine and document if the patient lack the ability to consent, and to obtain the consent from the patient's legal representative/medical proxy. However, an inclusion of research participants who lack decisional capacity has to be approved by the regulatory authority (e.g., Institutional Review Board/Independent Ethics Committee IRB/IEC) and the consenting procedure has to follow an approved study protocol.

Over all, tES has a promising potential for numerous fields of medicine and various patient-populations who do not respond to conventional therapies. Compliance with ethical principles in tES conduct facilitates further development of tES techniques and their future integration into medical practices.

## 9. Concluding remarks

In this review paper, we deliver guidance for technically sound application, and interpretation of tES results. Although the technique is seemingly simple and easy to apply, specific aspects have to be taken into consideration to obtain reliable results. This overview aims to enhance the quality of tES application in future studies, help to avoid misconceptions and -interpretation, and therefore improve the quality of scientific work in this field further.

**Conflict of Interest Statement**

M. Nitsche and P. Miranda are members of the advisory board for Neuroelectrics. W. Paulus is on the advisory board of EBS technologies and received support in terms of new tES devices by Neuroconn and EBS technologies. CUNY has patents on brain stimulation with M. Bikson as inventor. M. Bikson has equity in Soterix Medical Inc. None of the remaining authors have potential conflicts of interest to be disclosed.

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