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Review article

Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction

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ABSTRACT

Non-invasive brain stimulation (NIBS) has been gaining increased popularity in human neuroscience research during the last years. Among the emerging NIBS tools is transcranial electrical stimulation (tES), whose main modalities are transcranial direct, and alternating current stimulation (tDCS, tACS). In tES, a small current (usually less than 3 mA) is delivered through the scalp. Depending on its shape, density, and duration, the applied current induces acute or long-lasting effects on excitability and activity of cerebral regions, and brain networks. tES is increasingly applied in different domains to (a) explore human brain physiology with regard to plasticity, and brain oscillations, (b) explore the impact of brain physiology on cognitive processes, and (c) treat clinical symptoms in neurological and psychiatric diseases. In this review, we give a broad overview of the main mechanisms and applications of these brain stimulation tools.

1. Introduction

Over the past few decades, the introduction and development of non-invasive brain stimulation (NIBS) techniques have provided researchers and clinicians a valuable means to modulate activity of cerebral areas in humans and thereby contribute to the exploration of brain-behavior relations and develop treatment for various neurological and psychiatric disorders. NIBS has been shown to not only alter neural activity during application, but can also induce long-lasting alterations of cortical excitability and activity. Transcranial Electrical Stimulation (tES) and Magnetic Stimulation (TMS) are two of the most well-known forms of NIBS which influence neural activity based on different electromagnetic principles.

tES is a generic term that designates several techniques based on the modality of the applied electricity, which can be direct currents (transcranial direct current stimulation, tDCS), alternating currents (transcranial alternating current stimulation, tACS), or random noise currents (transcranial random noise stimulation, tRNS). tDCS, which is the most widely used form of tES, delivers weak direct currents to the scalp through two or more electrodes. tACS involves application of a balanced sinusoidal current across the scalp, and tRNS, a specific type of tACS, typically involves the application of a current which randomly fluctuates between a frequency range 0.1–640 Hz (Antal et al., 2008; Antal and Paulus, 2013; Deans et al., 2007; Helfrich et al., 2014b; Nitsche and Paulus, 2000; Nitsche and Paulus, 2001).

Acute effects of modern NIBS techniques distinguish tES from TMS, where the activation of neurons is pertinent. TMS induces high intensities of short-lasting electromagnetic currents in the cerebral cortex, which subsequently generate a supra-threshold activation of the neurons. In contrast, tES does not generate action potentials in neurons, but bi-directionally modulates their spontaneous firing activity via subthreshold alterations of resting membrane potentials (Barker et al., 1985; Nitsche and Paulus, 2000; Nitsche et al., 2003b; Purpura and McMurtry, 1965; Wagner et al., 2007). With regard to the after-effects, although the presumed induction procedure differs between respective stimulation protocols, which are theta-burst TMS, repetitive TMS (rTMS) and tDCS applied for some minutes, all are able to produce long-lasting facilitatory or inhibitory plastic changes in neural systems depending on the stimulation parameters (Dayan et al., 2013; George and Aston-Jones, 2010; Nitsche and Paulus, 2001; Rossini and Rossi, 2007; Rothwell, 1993). Concurrent application of stimulation with behavioral tasks is more difficult with rTMS compared to tES, as suprathreshold activations may inevitably disrupt task-relevant activity, whereas the subthreshold polarization induced by tDCS allows the online stimulation to enhance or reduce task-dependent neuronal activation. Whereas the spatial and temporal resolution of TMS is more superior, tES tools

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are generally more cost-effective, easier to operate, and easily adaptable for double-blind, sham-controlled studies. Both techniques are valuable adjunctive tools in neuroscience research and have the potential to overcome an inherent limitation of neuroimaging techniques: the difficulty to infer causal involvement of brain areas or functional networks in specific motor, perceptual, or cognitive processes.

In the following, we focus on tES as a re-introduced technique in the NIBS field. We first describe the main physiological mechanisms of excitability alterations and neuroplasticity induced by tES, which affect both regional and network levels. We then show some examples of how tES may be applied in healthy humans to alter cognitive and behavioral effects, or in patients to treat neurological or psychiatric disorders. In the last part of this introductory review, we discuss critical open questions and future directions of research.

2. tDCS – from the "classical" protocols

Electrical brain stimulation has a long history, starting from the ancient Greeks, who were using electric fish to treat migraine (Kellaway, 1946). In the same line, in the 11th century, the physician Ibn-Sidah suggested to treat epilepsy with a living electric catfish (Kellaway, 1946). With the introduction of the electric battery in the 18th century, it became possible to systematically evaluate and report clinical applications of transcranial stimulation for treatment of neurological and psychiatric conditions. Aldini applied electrical stimulation in a patient with major depression, and described that galvanic currents improved his mood (Parent, 2004). Direct current (DC) stimulation was routinely applied for the treatment of mental disorders during the 19th century and the early part of the 20th century, but because of many unknowns about its mechanisms of action and a lack of reliable neurophysiological markers, which led to variable and/or inconsistent results, its use became disregarded for a while from the 1930s (Parent, 2004). In the 1950s, DC (mostly pulsed currents) reappeared as a therapeutic technique to induce a sleep-like state (Smith, 2008). Animal studies in 1960s showed the ability of low intensity DC currents to modulate the firing rate of neurons and cortical excitability (Bindman et al., 1964). Cathodal stimulation of the rat's medial cortex abolished retention (Albert, 1966b) and anodal stimulation improved memory consolidation (Albert, 1966a). In 1964, psychological effects of 50–500 μA DC currents over the forehead region of 32 healthy subjects were systematically investigated. It was reported that anodal current increased alertness, mood and motor activity, while cathodal current induced quietness and apathy (Lippold and Redfearn, 1964). However, subsequent double-blind studies failed to replicate these findings (Sheffield and Mowbray, 1968). Lack of significant effects of polarizing currents may have been due to either observer expectation bias in Lippold and Redfearn's work (Lippold and Redfearn, 1964), or a small sample size in Sheffield and Mowbray's study (Sheffield and Mowbray, 1968). In 1964, in a preliminary clinical study, anodal currents (20–250 μA) were applied over the forehead of 29 chronic depressed patients who had failed to respond satisfactorily to other forms of interventions. Most of these patients showed clinical improvements and felt better during current application, and the effect was usually sustained for one or two days (Redfearn et al., 1964). These findings were also confirmed by double-blind clinical trials (Costain et al., 1964).

Direct evidence for the generation of electric potential difference over the cortex by transcranially applied pulsed currents was provided by recordings from deep EEG (electroencephalography) electrodes in three patients with temporal lobe epilepsy. Anodal current of 0.1–1.5 mA was applied bilaterally over the frontal poles of patients (four small electrodes, two placed over the frontal poles and two over the mastoids) and about 50% of the transcranially applied direct current was shown to reach the brain through the skull (Dymond et al., 1975). Despite several promising reports from the 1960s and 1970s, this technique was once again almost abandoned, likely due to the lack of evidence of direct physiological effects in humans. In 1980, it was shown that application of a brief, high voltage capacitative discharge to the scalp over the primary motor cortex could elicit cortico-spinal activations, and result in cortically elicited muscle twitches (Merton and Morton, 1980). Although this technique, termed transcranial electric stimulation (TES), marked a paradigm shift in physiological assessments of brain stimulation, it was also associated with uncomfortable perceptions by the subject, likely due to the passage of high intensity currents through dermal pain receptors. In 1985, Barker et al. devised the novel concept of TMS. This technique marked a further breakthrough in the field, as it circumvented the involvement of pain receptors due to application of a strong, short-lasting electromagnetic current. Supra-threshold activation of neuronal populations within the motor cortex using single-pulse TMS could elicit an involuntary muscular contraction (motor evoked potential – MEP), whose amplitude could be recorded electromyographically. This important TMS measure of corticospinal excitability made it possible to monitor changes in cortical excitability following plasticity induction protocols (Rothwell, 1993). As such, application of low-intensity tDCS as a non-invasive, painless, and well-tolerated brain stimulation technique in the intact human brain was renewed at the turn of the 20th century by the seminal studies of Priori et al. (1998) followed by work of Nitsche and Paulus (Nitsche and Paulus, 2000). These studies investigated the impact of tDCS on cortical excitability using TMS and showed that tDCS could induce polarity-dependent, prolonged shifts in cortical excitability. Since then, tES applications have increased across various research and clinical areas over the past decade, with over 700 publications in the last year alone (Bikson et al., 2016). Subsets of the tDCS technique have also been introduced, such as transcranial micropolarization technique developed by Russian researchers, which employs smaller electrodes (100–600 mm^2) with currents of less than 1 mA (Guleyupoglu et al., 2013; Nitsche et al., 2003a; Sheliakin et al., 2005). In 2008, Antal and co-workers developed the concept of applying an alternating current – tACS (Antal et al., 2008)—which was shown to effectively entrain endogenous brain oscillatory activity (Antal and Paulus, 2013; Deans et al., 2007; Helfrich et al., 2014b). These techniques have proven to be valuable in clinical and research settings. In the next section, we discuss the underlying physiological mechanisms of these techniques.

3. Physiology of tES

Transcranial direct current stimulation can induce both acute and neuroplastic alterations of cortical excitability at the macroscopic level. Duration and direction of these effects are determined by stimulation parameters such as current density, polarity, stimulation duration and/or geometrical montage of electrodes (Nitsche et al., 2008; Woods et al., 2016). Stimulation in the order of a few seconds only induces excitability alterations during intervention (Nitsche and Paulus, 2000). If, however, tDCS is conducted for some minutes, both anodal and cathodal stimulation are able to induce neuroplastic after-effects. For instance, long-lasting changes of cortical excitability are induced by applying 13 min of anodal tDCS and 9 min of cathodal tDCS (Nitsche et al., 2003b; Nitsche and Paulus, 2001).

The primary effect of tDCS is a subthreshold modulation of resting membrane potentials (Nitsche and Paulus, 2000). Depending on the orientation of the neurons relative to the direction of current flow, neuronal compartments are de- or hyper-polarized (Bikson et al., 2004). Early animal studies demonstrated that anodal or cathodal tDCS increased or decreased spontaneous neuronal activity, likely caused by subthreshold changes in membrane polarization (Bindman et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965). Studies in humans hint for comparable effects.

Acute effects of anodal tDCS appear to primarily depend on changes in membrane potential. Pharmacological studies demonstrated elimination or reduction of anodal tDCS online effects (increase in cortical excitability) after calcium and sodium channels blockade (Nitsche et al.,

2003a). On the other hand, neither an NMDA receptor antagonist (Nitsche et al., 2003a) nor a $GABA_A$ receptor agonist (Nitsche et al., 2004a) influenced tDCS online effects. Absence of changes in intracortical facilitation [ICF] and short-interval cortical inhibition [SICI], which are respectively TMS measures of glutamatergic and GABAergic interneurons, suggest that tDCS online effects do not depend on modulation of these interneuronal pools either (Nitsche et al., 2005).

Extending the duration of tDCS leads to long-lasting aftereffects on cortical activity and excitability (Bindman et al., 1964; Cambiaghi et al., 2010; Koo et al., 2016; Ranieri et al., 2012; Stagg and Nitsche, 2011). Initial studies showed that anodal tDCS over the left motor cortex with a return electrode over the contralateral supraorbital area increased motor cortical excitability, while cathodal tDCS decreased it (Nitsche et al., 2003b; Nitsche and Paulus, 2001). These studies proposed the involvement of neuroplastic mechanisms, as previously obtained from animal experiments, which revealed that the establishment of neuroplastic after-effects depend on protein expression (Gartside, 1968; Islam et al., 1994; Islam et al., 1997) and changes of intracellular cyclic AMP concentration (Hattori et al., 1990). It has also been shown that early gene activity (Islam et al., 1995b), brain-derived neurotrophic factor concentration (Fritsch et al., 2010), and intracellular calcium level (Islam et al., 1995a) are altered by anodal DC stimulation, the latter likely caused by glutamatergic receptors (Koo et al., 2016; Ranieri et al., 2012). Although stimulation in humans is in most cases conducted with lower current densities, as compared to respective animal experiments (Bikson et al., 2016), the principal results fit with the above-mentioned animal experiments. The physiological mechanism underlying the induction of LTP- and LTD-like plasticity induced by anodal and cathodal tDCS is primarily a glutamatergic process, involving NMDA receptors (Aroniadou and Keller, 1995; Castro-Alamancos et al., 1995; Hess et al., 1996; Liebetanz et al., 2002; Nitsche et al., 2003a; Nitsche et al., 2004b). Pharmacological studies revealed that blockage of NMDA receptors prevents increased excitability after anodal tDCS and decreased excitability after cathodal tDCS (Nitsche et al., 2003a), while the partial NMDA receptor agonist d-cycloserine enhanced the excitability enhancement achieved by anodal tDCS (Nitsche et al., 2004b). Furthermore, NMDA receptor-mediated calcium influx is also thought to be essential for tDCS-induced plasticity (Batsikadze et al., 2013; Cho et al., 2001; Lisman, 2001). In animal models, early LTP and LTD depend on activation of calcium-dependent kinases to control insertion or removal of AMPA receptors to or from the subsynaptic membrane (Malenka and Bear, 2004). Likewise, the after-effects of tDCS have also been shown to be calcium dependent (Nitsche et al., 2003a). Moreover, a recent animal study using calcium imaging linked the involvement of astrocytes to the influx of calcium generated by anodal tDCS (Monai et al., 2016). Induction of glutamatergic plasticity by tDCS requires further involvement of other neurotransmitters and neuromodulators (Stagg, 2014). In case of both anodal and cathodal tDCS, reduction of GABA seems to gate the respective plasticity of the glutamatergic system (Stagg et al., 2009), and reduction of dopaminergic activity prevents tDCS-induced plasticity (Nitsche et al., 2006). These pharmacological mechanisms conclude that primarily GABA-controlled intracortical inhibition is reduced, and glutamate-driven facilitation is enhanced by anodal tDCS, while cathodal tDCS has antagonistic effects. In accordance with the observed GABA reduction by anodal and cathodal tDCS, it was also shown that both anodal and cathodal tDCS resulted in I-wave facilitation, which depends on the GABAergic system (Nitsche et al., 2005).

Beyond these “classic” plasticity effects, i.e. LTP-like effects of anodal, and LTD-like effects of cathodal tDCS, antagonistic effects of these protocols have also been recently described, which appear to critically depend on the specific stimulation protocols (Bastani and Jaberzadeh, 2013; Batsikadze et al., 2013; Jamil et al., 2017; Monte-Silva et al., 2013). Whereas application of anodal tDCS for 13 min over the motor cortex significantly enhanced motor cortical excitability (Monte-Silva et al., 2013; Nitsche and Paulus, 2000), doubling this stimulation duration to 26 min decreased it (Monte-Silva et al., 2013). Similar nonlinear effects have been obtained for cathodal stimulation, where 2 mA stimulation for 20 min induced an excitability enhancement (Batsikadze et al., 2013). These nonlinearities in tDCS aftereffects might be explained based on the dependency of the direction of plasticity from the amount of neuronal calcium influx initiated by the particular stimulation protocol. Differing levels of activation of NMDA receptors, and membrane polarization result in different degrees of intracellular calcium concentration, which will result in different effects on subsequent synaptic modulation. Low and prolonged Ca^{2+} influx into postsynaptic neurons causes LTD, moderate increase of Ca^{2+} influx induces no synaptic modulation, and larger calcium increases result in LTP. Excessive calcium will again reduce plasticity due to potassium channel-dependent counter-regulation (Lisman, 2001; Misonou et al., 2004). In accordance, in the previously mentioned study where anodal tDCS was applied for 26 min, blockage of NMDA receptors, which will reduce calcium influx, abolished the inhibitory after-effects of this tDCS protocol (Monte-Silva et al., 2013). For the excitability-enhancing effects of 2 mA cathodal tDCS, it was suggested that this stimulation intensity increases calcium to concentrations which induce LTP-like plasticity (Batsikadze et al., 2013).

Despite the relatively well-known physiological mechanisms of tDCS, less is known about the effects and underlying physiological mechanisms of tACS. Similar to tDCS, the primary mechanism of tACS is a subthreshold alteration of the neuronal resting membrane potential, whose direction depends on the direction of the current flow (Kuo and Nitsche, 2015). Due to its symmetric sinusoidal currents, tACS is assumed to be de- or hyper-polarizing according to the respective stimulation frequency. tACS modulates brain oscillations in a frequency-specific manner. Several animal and human studies have suggested that tACS applied within the EEG frequency range mainly acts by entraining ongoing brain oscillations or synchronizing neuronal networks, thereby altering, but not inducing, oscillatory brain activity (Antal and Herrmann, 2016; Helfrich et al., 2014a; Helfrich et al., 2014b). tACS may modulate the amplitude (Helfrich et al., 2014b), frequency (Fröhlich and McCormick, 2010), or phase/phase coherence (Helfrich et al., 2014a) of brain oscillations. In the resting primary motor cortex, for instance, where the beta frequency range is predominant, it was shown that tACS only when applied at a beta frequency could increase motor-cortical excitability (Feurra et al., 2011).

Neuroplastic effects of tACS have thus far only been demonstrated with higher frequencies, such as 140 Hz tACS (Moliadze et al., 2010; Moliadze et al., 2012). In the latter study, the direction of plasticity appears to depend on the stimulation intensity, where low intensities (0.4 mA) result in diminution of motor cortex excitability, and higher intensities (1 mA) result in enhanced motor cortical excitability. These results may be due to differences in the sensitivity of excitatory and inhibitory synapses to different stimulation intensities (Moliadze et al., 2012). Increases in cortical excitability are also observed following 1, 2, and 5 kHz tACS over the primary motor cortex (1 mA, 10 min, with reference electrode over the contralateral orbit) which might be explained by mechanisms similar to tDCS, i.e., alteration in the neuronal membrane potential (Chaieb et al., 2011). To summarize, depending on stimulation frequency, intensity, and duration, tACS may non-linearly modify cortical excitability, both during and after intervention.

4. Remote effects of tES

tES results in not only regional effects as described so far, but also in widespread, network-level changes across the brain which can be monitored with fMRI and EEG. Recent evidence suggests that tDCS affects cortical regions not only beneath the electrodes, but also other cortical and subcortical structures (Keeser et al., 2011; Polania et al., 2012a). Moreover, effects of tDCS on remote regions that are functionally connected to the stimulated area can be in the same (Antal et al., 2011) or opposite (Stagg et al., 2009) direction compared to the

area underneath the electrodes.

A tDCS-fMRI and also a tDCS-EEG study showed enhanced motor network activation, including premotor areas and posterior parietal areas by anodal stimulation of the left primary motor cortex (Polania et al., 2011; Polania et al., 2012b). Moreover, the combined tDCS-fMRI study showed enhanced functional connectivity between the left motor cortex and the ipsilateral thalamus, and caudate nucleus by anodal, and reduced connectivity between the left motor cortex and the contralateral putamen by cathodal stimulation of the left motor cortex (Polania et al., 2012b). Another tDCS-fMRI study showed that bilateral stimulation of the sensorimotor cortices results in extensive changes in functional connectivity, particularly in primary and secondary motor as well as prefrontal cortices (Sehm et al., 2012). In another study by Polania and co-workers (Polania et al., 2011), EEG signals were recorded from 62 channels to analyze tDCS effects on network cortical functions. EEG data were recorded before and after application of anodal tDCS over the left M1 both during performance of voluntary hand movements (finger tapping) and during rest. Results showed that tDCS is not only able to affect resting state networks, but also has a boosting effect on motor-task related cortico-cortical functional circuits, especially in the gamma frequency range (Polania et al., 2011).

Likewise, tACS also induces changes in remote oscillatory activity and long-distance, area-to-area interactions. In a study by Polania and co-workers, in-phase and anti-phase 6 Hz tACS over the left prefrontal and parietal cortices were employed to induce theta synchronization and desynchronization between these regions. Respective stimulation protocols had improving/deteriorating effects on performance of a working memory (WM) task. This effect was interpreted as evidence for the causal relevance of theta phase-coupling between prefrontal and parietal areas for WM performance in healthy humans (Polania et al., 2012a). In another study, bihemispheric anti-phase tACS was applied over occipital-parietal areas in the gamma frequency band (40 Hz) while participants fixated on the center of a display presenting a stroboscopic alternative motion (SAM) pattern and pressing response buttons in the case of change in the perceived direction of horizontal or vertical motion (Struber et al., 2014). Increased interhemispheric gamma band coherence during perceived horizontal compared to vertical motion of the SAM display was previously shown in correlative EEG studies (Rose and Buchel, 2005). Elevated interhemispheric coherence (phase synchronization), and thereby increased perception of horizontal compared to vertical motion by tACS, demonstrated the causal role of gamma oscillations for bistable perception (Struber et al., 2014). In a study on rats, Ozen and co-workers applied tES with a sinusoidal waveform (0.8, 1.25 or 1.7 Hz) and performed extracellular and intracellular recordings from neocortical and hippocampal neurons. Entrainment of neuronal activity by tES was observed in both cortical regions and in distant hippocampal sites. Distant neurons might be affected directly by tES or activated by polysynaptic pathways involving neurons in the neighborhood of the stimulating electrodes (Ozen et al., 2010).

These findings provide evidence that tES may not affect only localized regions, but may have widespread remote effects on functional networks at both cortical and subcortical levels, likely transmitted via cortico-cortical and cortical–subcortical connections. The relevance of these network alterations for cognition and behavior needs to be explored in future studies.

5. Functional effects of tES

Considering its capability to modulate cortical excitability, plasticity, and brain oscillations (Antal and Paulus, 2013; Nitsche and Paulus, 2000; Nitsche et al., 2005), tES is presumed to also affect cognition- and motor-associated brain functions. In this section, we review some studies that investigated neuromodulatory effects of tES on motor processes and cognitive functions in healthy volunteers. Our intention here is not to present a broad overview, but to discuss the principle mechanisms (a more comprehensive overview can be found in (Floel, 2014; Kuo and Nitsche, 2012; Nitsche et al., 2008; Reis and Fritsch, 2011; Reis et al., 2008)).

5.1. Functional effects of tES on the motor system in healthy subjects

Diverse neuroimaging and neuromodulation studies (Grafton et al., 1992; Honda et al., 1998a; Pascual-Leone et al., 1994) have revealed that changes in the activity, plasticity, and functional connectivity of a distributed neural network, including the primary motor, premotor and supplementary motor cortices, the cerebellum, thalamic nuclei and the striatum, are associated with motor skill learning (Honda et al., 1998b; Seidler, 2010; Ungerleider et al., 2002). As discussed previously, the NMDA-receptor-dependent neuroplastic after-effects of tES share a certain similarity with LTP and LTD which are recognized as important substrates of learning and memory formation (Liebetanz et al., 2002; Rioult-Pedotti et al., 2000). Therefore, tES may be a promising tool for modulating the activity of presumed task-relevant brain areas, and thereby identifying their causal significance for motor learning and adaptation.

To investigate the contribution of motor and frontal cortices in implicit motor learning, Nitsche et al. combined tDCS with serial reaction time task (SRTT) (Nitsche et al., 2003c). In SRTT, subjects implicitly learn to perform a finger movement sequence. Functional imaging and TMS studies suggest involvement of the primary motor cortex, supplementary motor area, the prefrontal cortex, and the rostral inferior parietal cortex in this task (Honda et al., 1998b; Pascual-Leone et al., 1994). To explore the causal relevance of these areas for the learning process, 1 mA anodal or cathodal tDCS was applied over either the primary motor (M1), premotor, lateral prefrontal, or medial prefrontal cortices during SRTT performance (online tDCS). Anodal tDCS of M1 improved motor learning, whereas stimulation of the remaining cortices had no effect. These observations suggest critical role of neuroplasticity in the motor learning process, and also the involvement of the primary motor cortex in the acquisition and early consolidation phases of motor learning (Nitsche et al., 2003c). Further tDCS-SRTT studies revealed a critical role of timing of stimulation for the effects of tDCS on motor learning. In contrast to online tDCS, offline stimulation before SRTT performance of either anodal or cathodal tDCS over M1 did not modulate performance in this task (Kuo et al., 2008). These differences might be due to a more unspecific priming effect of tDCS in this case, which −in contrast to online tDCS– will not be focused on task-related activated neurons.

Previous literature has suggested that the premotor cortex is primarily involved in consolidation of SRTT-related learning, which takes place during rapid eye movement (REM) sleep (Maquet et al., 2000). Given that consolidation also involves plasticity of contributing neuronal connections, and that online boosting of plasticity is superior to offline intervention, it could be hypothesized that stimulation of this area during REM sleep might improve sequence consolidation. In one study, healthy participants learned the SRTT in the evening and stimulation was applied over premotor cortex during REM sleep. In two control experiments, tDCS was delivered during performance of a SRTT-like task, but without repeating sequences (to control for the specificity of stimulation effects on motor learning consolidation), and while subjects were awake (to control for time-dependent but not sleep-dependent consolidation). Premotor anodal tDCS during sleep enhanced consolidation compared to sham, while no improvement was observed in the other conditions. These results suggest an involvement of the premotor cortex in REM sleep-associated consolidation of procedural memory (Nitsche et al., 2010). Further evidence of this involvement was found in a study by Stagg et al. (2011). Here, sequence learning was investigated by a similar sequential finger press task combined with 1 mA anodal/cathodal tDCS over M1 (10 min, with the return electrode over the contralateral supraorbital ridge). Their results show that stimulation applied during motor practice modulated learning rates in a

polarity-specific manner: anodal tDCS increased, while cathodal stimulation decreased the rate of motor sequence learning. The results further showed the dependency of effects on the relative timing of stimulation and motor task performance as anodal or cathodal tDCS applied *prior* to the motor task slowed learning when compared to sham stimulation (Stagg et al., 2011).

The aforementioned studies investigated the effects of tDCS within a single session. To explore the effects of tDCS on long-term retention of motor memory and also explore distinct mechanistic processes for temporal components of skill learning, Reis et al. examined the effect of tDCS on sequence learning over an extended time course (Reis et al., 2009). During five consecutive days, 1 mA anodal tDCS was applied for 20 min over the left M1 while subjects performed a sequential visual isometric pinch force task. The impact of tDCS on performance was assessed both within and between training sessions (online and offline effects, respectively). Anodal in comparison to sham tDCS led to greater total (online plus offline) skill acquisition. Moreover, these skill measures remained improved in the anodal as compared to sham group over a 3-month follow-up. The stability of these learning effects suggests tDCS may be a promising tool in long-term skill consolidation (Reis et al., 2009).

In addition to tDCS, other modes of tES have also been explored for the modulation of motor functions. Specifically, modulating brain oscillations in a frequency-specific manner by tACS may be relevant for investigating the neurophysiological underpinnings of motor processes. Motor learning is associated with changes in oscillatory activity and synchronization at alpha (8–12 Hz) (Zhuang et al., 1997), and beta (13–30 Hz) (Boonstra et al., 2007) frequencies within and between brain regions in the motor network. The amplitude of beta activity in contralateral motor areas has been shown to decrease during motor performance and increase after movement cessation (Pfurtscheller, 1981). The causal role of these brain oscillations for motor performance can be explored by their modulation with tACS (Antal and Paulus, 2013). In a pioneer tACS study, Antal et al. (2008) evaluated the effects of different AC stimulation frequencies on sequence learning (SRTT, see above). The electrodes were positioned over the left motor cortex and the contralateral orbit and 400 μA current was applied for 5 min with frequencies of 1, 10, 15, 30, and 45 Hz. The results showed a frequency-specific effect on SRTT performance where only 10 Hz tACS combined with SRTT improved motor learning compared to sham stimulation. In another study, Wach and coworkers targeted alpha and beta oscillations in the motor cortex −which have been suggested to be relevant for movement velocity and timing accuracy- by applying 10 or 20 Hz tACS at 1 mA for 10 min through two 35 cm^2 electrodes (Wach et al., 2013). Movement speed and accuracy of the right hand during a fast finger tapping task were assessed before and at three time points after tACS (immediately, after 30 min, and 60 min). In addition, M1 excitability was evaluated by measuring the cortical silent period (CSP), and TMS-elicited MEPs. 10 Hz tACS increased movement variability and 20 Hz tACS resulted in movement slowing. These effects were present at different time-points: immediately after stimulation for 20 Hz, and 30 min after tACS for the 10 Hz stimulation condition. Behavioral measures and neurophysiological changes induced by 10 Hz stimulation were also correlated: shortening of CSP was significantly associated with increased behavioral variability. Altogether, the results of this study show that frequency-dependent AC stimulation affects both motor cortical excitability as well as motor function, and further supports the hypothesis that alpha and beta oscillations have differential effects on motor behavior. The association of beta tACS with movement slowing in this study extends previous correlative evidence (Gilbertson et al., 2005). Increased behavioral variability after 10 Hz tACS, on the other hand, was attributed by the authors to disruption of internal pacing, which is crucial in some motor tasks like fast finger tapping (Wach et al., 2013).

tES can modulate activity of specific cortical areas involved in motor learning to induce enduring improvements in motor function. Stimulation effects might critically depend on the timing of stimulation in relation to motor training, where it may be more optimal to apply stimulation at the time point when a targeted area is involved in performance. tES has been widely used to identify the functional relevance of specific brain regions in different phases of motor skill learning. Though most of the studies which have employed tES to study the role of motor areas in motor learning have focused on M1, stimulation effects are not restricted to this area. Taken together, the results of these studies show that tES can contribute to gaining a deeper knowledge of mechanisms underlying motor learning and motor memory formation. This knowledge could help in developing new strategies for improving specific stages of learning and memory processing in both healthy and patient populations.

5.2. Functional effects of tES on emotional and cognitive processing systems in healthy humans

The prefrontal cortex (PFC) provides the neuronal basis for many high level cognitive functions. For example, the dorsolateral prefrontal cortex (DLPFC) is involved in mood and emotional processes (Dolcos et al., 2004; Grimm et al., 2006; Nitsche et al., 2012; Weigand et al., 2013). Positive emotional stimuli and happier mood are associated with higher activity in the left DLPFC (Habel et al., 2005; Herrington et al., 2005; Sergerie et al., 2005), while higher activity in the right cortex is associated with negative affect (Belyi, 1987; Perini, 1986; Robinson and Lipsey, 1984). Neuroimaging and electrophysiological data have further identified the left DLPFC as a core region in emotional processing, specifically in the down-regulation of negative emotional conditions (Davidson et al., 2000). As such, tES has been employed in various emotion-related studies as a potentially useful tool to regulate mood and emotional processes through alteration of prefrontal activity and excitability.

A number of studies have shown that tDCS application over the DLPFC does not modulate mood in healthy subjects (Morgan et al., 2014; Motohashi et al., 2013; Nitsche et al., 2012; Plazier et al., 2012), but may suppress negative feelings and affect when subjects are exposed to negative stimuli (Rego et al., 2015) or frustration (Plewnia et al., 2015). Nitsche et al. (2012a) applied tDCS over the left DLPFC to evaluate its effect on subjective emotional state and emotional state-related information processing in healthy individuals. First, they applied anodal, cathodal, or sham tDCS to the left DLPFC with a return electrode above the contralateral orbit (1 mA, 20 min) and examined changes immediately after compared to before tDCS using a self-report questionnaire monitoring actual mood states (Hampel, 1977). In a second experiment, participants performed an emotional face recognition task before, during, and after tDCS (1 mA, 10 min). tDCS applied to the prefrontal cortex improved emotional face processing (more remarkably for anodal tDCS and emotionally positive faces), but did not influence subjective emotional state. These findings support the hypothesis that the DLPFC might contribute more directly to the cognitive aspects of emotional processing and not the emotional state itself.

In another study, Mungee et al. (Mungee et al., 2014) explored the contribution of the right DLPFC to fear memories via tDCS. On day one, fear acquisition was performed with a Pavlovian fear conditioning paradigm with partial reinforcement. Blue and yellow squares were used as conditioned stimuli, and a low-intensity electric shock to the right wrist acted as the unconditioned stimulus. The conditioned stimulus was paired with the shock. On the second day, the fear memory was first retrieved by a single presentation of the conditioned stimulus, which had been paired with the shock on day one. Then participants received anodal or sham tDCS over the right DLPFC (cathode over the contralateral supraorbital area, 1 mA intensity, 20 min duration, and 15 cm^2 electrodes). Effects of tDCS on the conditioned fear response were assessed on the third day. In this study, tDCS enhanced fear memory. This might have been caused by strengthening of the respective memory trace via anodal tDCS of the right DLPFC or by down-

regulating the left ventromedial prefrontal cortex via the cathodal electrode positioned over this area, which is involved in extinction, retention, and recall of fear memories. The ability of tDCS to modulate emotional memories might suggest new therapeutic applications in diseases for which fear plays a critical role.

Working memory is another fundamental cognitive ability which has been extensively explored using tES. Considering the available evidence showing the crucial role of the left DLPFC in WM (Carpenter et al., 2000), early tDCS studies on WM targeted this area and found that WM performance is enhanced through anodal stimulation of the left DLPFC. In a pioneer study, Fregni et al. (2005a, 2005b) found a significant effect of left DLPFC anodal stimulation on WM performance in a 3-back task (Fregni et al., 2005b). Recent meta-analyses gathering available tDCS-WM experiments showed significant effects of anodal tDCS over DLPFC (Hill et al., 2016) and left anodal DLPFC stimulation coupled with WM training (Mancuso et al., 2016) with regard to WM enhancement.

More recently, tACS has also been employed to modulate WM. EEG and MEG (magnetoencephalography) studies have reported enhanced theta power in the frontal and parietal cortices and theta phase coupling within a distributed fronto-parietal network during executive and working memory task performance (Gevins et al., 1997; Mizuhara and Yamaguchi, 2007). Looking for empirical evidence supporting the causal role of frontoparietal theta phase-coupling in working memory performance, Polania and coworkers utilized tACS to exogenously induce synchronized or desynchronized frontoparietal theta coupling (Polania et al., 2012a). Application of synchronized 6 Hz (theta band) tACS over the left prefrontal and parietal cortices, while subjects performed a delayed letter discrimination task, improved reaction times in the task, whereas desynchronized stimulation over the same regions slowed down reaction times. These results were frequency-specific, as application of 35 Hz stimulation over the same regions did not produce any significant effects on task performance. These findings provide empirical evidence for the causality between frontoparietal theta phase-coupling and cognitive performance in healthy humans. tACS can also be applied with two different frequencies to modulate interaction of different brain rhythms. Cross-frequency coupling between different brain areas is important in many cognitive processes. For instance, based on a multiplexing buffer model of WM, maintaining multiple items in WM is organized by theta-nested gamma cycles (Lisman and Jensen, 2013). Correlative findings have shown the importance of cross-structural and cross-frequency coupling mechanisms between theta and gamma neural oscillations in WM functioning. Alekseichuk and co-workers used cross-frequency tACS (co-stimulation of theta and gamma frequencies) over the left prefrontal cortex to explore if theta-gamma phase-amplitude coupling has a causal role in visual-spatial WM. They showed that cross-frequency tACS boosted WM task performance, which demonstrates the causal dependence of spatial working memory function on the theta-gamma coupling (Alekseichuk et al., 2016).

The presented overview about application of tES on WM and affective processes highlight tES as a valuable tool which can identify causal relations between brain physiology and behavior, and thus a means to complement current knowledge in this field. The majority of tES studies in affective neuroscience have targeted cortical areas. Considering the crucial role of many subcortical structures in affective processing, it seems plausible to target deep brain regions via alterations of cortico-subcortical connections in future studies (Nonnekes et al., 2014). Single- and multiple-frequency tACS can be used for frequency-specific entrainment of neuronal activity and/or to modulate cross-frequency coupling and thereby pave the causal link between neuronal oscillations and perception and behavior at local and network levels. More standardized methodologies regarding electrode position, stimulation intensity, frequency, and stimulation duration, as well as the employed cognitive tasks, would help to decrease heterogeneity of findings, integrate the results, and draw a more definitive picture about stimulation effects.

5.3. Functional effects of tES in patient populations

The promising results of studies conducted on healthy subjects led to the hypothesis that tES might be suited as an adjuvant therapy in neurological and psychiatric disorders. Indeed, alterations of neuroplasticity, cortical excitability, and neural oscillations are pathophysiological underpinnings of many neurological and psychiatric disorders, and tES may provide a promising therapeutic venue by modifying these abnormalities. To demonstrate its rationale, in this section, we briefly review some of the studies which have used tES in selected patient populations to modulate motor, emotional, or cognitive functions (for comprehensive overviews, see (Floel, 2014; Kuo et al., 2014a)).

5.3.1. tES and motor rehabilitation after stroke

Interhemispheric interaction between the primary motor cortices is impaired after stroke. The extent of motor impairment after stroke is associated with the amount of inhibition directed from the contralesional to the lesioned hemisphere (Loubinoux et al., 2003; Nair et al., 2007). Typically after stroke, excitability of the lesioned M1 decreases and excitability of the non-lesioned M1 increases (Traversa et al., 1998; Ward et al., 2003). Enhanced activity of the unaffected primary motor cortex in combination with reduced activity of the lesioned one constitutes maladaptive plasticity (Rossini et al., 2003) which limits motor recovery after stroke (Takeuchi and Izumi, 2012). Based on these pathophysiological alterations, several animal and human studies suggest that learned non-use of the paretic limb is relevant for the deficit in motor abilities resulting from brain damage. Learned non-use involves the progressive suppression in the use of the affected extremity and the dominant use of the nonparetic limb. As a consequence, reliance on the unaffected limb will increase, and the mobility of affected limb will continue to decrease (Taub et al., 2006). Neural circuits not actively engaged in task performance for a prolonged period of time begin to degrade (Kleim and Jones, 2008), which leads to a vicious cycle, by which immobility of the affected limb, changes in cortical representation, and changes in muscle atrophy facilitate each other and limit the capacity for subsequent gains in motor function of the paretic limb. Recovery is associated with the return of activity of the lesioned cortical areas (Heiss et al., 1999). By altering the interhemispheric balance of cortical activity and excitability, tES might be useful for blocking or reducing the maladaptive plasticity via normalizing imbalanced interhemispheric inhibition through either the upregulation of excitability of the damaged (ipsilesional) motor cortex, the downregulation of excitability of the intact (contralesional) motor cortex, or both.

In a pioneer study, Hummel and coworkers investigated the effect of tDCS on motor function improvement in patients with chronic stroke using a double blind, sham-controlled, crossover design (Hummel et al., 2005). One session of anodal stimulation was applied over the primary motor cortex of the affected hemisphere (1 mA, 20 min). Evaluation of paretic hand function using the Jebsen-Taylor Hand Function Test (a standardized seven-part test of manual dexterity which evaluates a broad range of everyday hand functions using common items such as paper clips, cans, pencils, etc.) showed significant improvement in performance after tDCS (Hummel et al., 2005). Later, to explore the efficiency of cathodal/anodal stimulation over unaffected/affected hemispheres in the improvement of motor performance after stroke, Fregni and coworkers (Fregni et al., 2005a) applied cathodal tDCS over the non-lesioned M1 of six patients with chronic stroke, and compared the results with anodal stimulation of the lesioned M1 and sham stimulation (1 mA, 20 min, 35 cm^2 electrodes). The Jebsen–Taylor Hand Function Test was used as a measure of hand function. The authors found that both montages yielded similar motor improvements and both are significantly more efficient in improving hand motor function compared to sham stimulation (Fregni et al., 2005a). A potentially more

effective montage for restitution of interhemispheric balance after stroke may be to enhance excitability of the damaged M1 and simultaneously decrease excitability of the undamaged one. Efficiency of this bilateral stimulation was first investigated in a study by Lindenberg et al. (Lindenberg et al., 2010). During five consecutive days, bilateral motor cortex stimulation was combined with physical and occupational therapy in a group of chronic stroke patients (1.5 mA, 30 min duration, 16.3 cm^2 electrodes). The results showed that the bilateral modulation significantly enhanced motor function scores compared to the sham group, and the beneficial effects lasted for at least one week. Thus, a combination of stimulation with physical and occupational therapy, as conducted in this study, may augment advantageous effects of stimulation (Hesse et al., 2007; Kim et al., 2010; Nair et al., 2011). In a double-blind study by Kim et al., three groups of patients with subacute stroke underwent combined tDCS and occupational therapy for 10 sessions: one group received anodal tDCS over the affected motor cortex, one group received cathodal stimulation over the unaffected motor cortex, and the third group received sham stimulation (Kim et al., 2010). Although neither cathodal nor anodal stimulation elicited changes in improvement compared to sham immediately after 10 sessions, a large improvement was observed after a six-month follow-up for the cathodal stimulation condition. Absence of beneficial effects immediately after stimulation might originate from heterogeneity in the small number of patients (subcortical or cortical ischemic), and also insensitive outcome measures (Kim et al., 2010). Outlasting effects of single- or multiple-session anodal tDCS over the lesioned M1 and/or cathodal tDCS over the non-lesioned M1 have been reported by some other studies as well (Boggio et al., 2007; Hesse et al., 2007; Nair et al., 2011).

Systematic reviews and meta-analyses have shown long-term beneficial effects of anodal stimulation over the ipsilesional hemisphere, cathodal stimulation over the contralesional hemisphere, and bilateral stimulation over both (Butler et al., 2013; Kang et al., 2016; Ludemann-Podubecka et al., 2014). These studies lend support to the effectiveness of tDCS as a useful adjuvant to traditional interventions for motor recovery. The magnitude of improvement differs somewhat between studies, and might depend on factors such as stimulation parameters, type of task performed in conjunction with stimulation, and stages of recovery (acute, sub-acute, and chronic). Finding the optimal stage of stroke recovery for application of stimulation to be both effective and safe, requires more systematic investigations. Future directions would benefit from further evaluation of outcomes and stimulation parameters and lead toward finding the most effective and prudent protocol.

5.3.2. Depression

Depression is accompanied by profound alterations of neural structure and function. Imbalance between the activity of left and right DLPFC, namely hypoactivity of the left, and hyperactivity of the right DLPFC, has been suggested as important factors for major depressive disorder (MDD) (Grimm et al., 2008). In accordance, it has been demonstrated that lesions by tumors and epileptogenic zones of the left and right hemisphere are accompanied by depressed mood and euphoria, respectively (Belyi, 1987; Perini, 1986; Robinson and Lipsey, 1984). Furthermore, increasing evidence points to a dysregulation or disruption of neuroplasticity, especially compromised LTP, in mood-relevant networks which may contribute to the pathophysiology of depression (Brunoni et al., 2013; D'Ostilio and Garraux, 2016). Considering these sources of evidence, and also the ability of tES to modify cortical excitability and neuroplasticity, various approaches may be taken to treat depression, such as enhancing excitability in left DLPFC, reducing excitability in the right DLPFC, or rebalancing the interaction between two hemispheres.

In a proof-of-principle pioneer study, anodal tDCS was applied over the left DLPFC in 10 patients with major depression for five consecutive days (1 mA, 20 min, 35 cm^2 electrodes with the return electrode positioned over the contralateral supraorbital area). Evaluation by the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) scores revealed four responders in the active group versus no responders in the sham group. Improvement was suggested to be associated with enhanced excitability of left DLPFC, which is pathologically hypoactive in major depression (Fregni et al., 2006). In a subsequent double-blind study in 40 patients, the number of sessions was extended to 10 days and stimulation intensity was increased to 2 mA (Boggio et al., 2008). Anodal tDCS of the occipital cortex and sham tDCS were performed as active and placebo control conditions, respectively. Here, only prefrontal tDCS significantly reduced depression scores evaluated by HDRS and BDI, which persisted for at least 30 days after the last stimulation session. Effectiveness of the same stimulation protocol was compared with standard medical treatment (fluoxetine) in another randomized, double-blind clinical trial (Rigonatti et al., 2008). Assessment of patients was performed at baseline and 2, 4, and 6 weeks after the beginning of treatment. Results showed an equally significant reduction of depressive symptoms with both active tDCS and six-week pharmacological treatment. Moreover, alongside the clinical effectiveness of tDCS, the beneficial effects emerged faster compared to the pharmacological treatment (Rigonatti et al., 2008).

The idea of combining tES with pharmacological treatments is interesting from both safety and efficacy aspects. The network model of depression suggests that conjunctive pharmacological and neuromodulation treatments might generate synergistic influences on mood through increased cortico-limbic stimulation-induced plasticity (D'Ostilio and Garraux, 2016). In a four-arm factorial trial, Brunoni et al. (2013) aimed to investigate the safety and efficacy of tDCS combined with sertraline hydrochloride in 120 patients with MDD. Serotonin has a notable influence on neuroplasticity and affects learning and memory formation in animals and humans. Previous studies showed that acute application of a selective serotonin reuptake inhibitor (SSRI) enhances and prolongs anodal tDCS-induced LTP-like plasticity in healthy humans (Nitsche et al., 2009). Moreover, chronic application of a SSRI in healthy humans extends the duration of LTP-like plasticity induced by anodal tDCS for more than 24 h after intervention (Kuo et al., 2016a). In the study by Brunoni and co-workers, participants were divided into four groups and each group received real or sham tDCS combined with either real SSRI (sertraline) or placebo medication. In all groups, anode was placed over the left DLPFC and cathode over the right DLPFC. Stimulation was performed for 10 consecutive working days. The combination of tDCS with sertraline was found to be significantly superior compared to all other intervention groups. A potential mechanism underlying the more efficacious response achieved by combined therapy might be the modulation of key nodes of the mood-relevant cortico-limbic network, which are disrupted during MDD, i.e., synergistic regulation of DLPFC activity by tDCS and limbic system activity by SSRI (Brunoni et al., 2013; D'Ostilio and Garraux, 2016).

In contrast to the above-mentioned results, some studies have shown no superior effects of active tDCS compared to sham stimulation (Loo et al., 2010; Palm et al., 2012), despite using the same parameters as studies with favourable results (Boggio et al., 2008; Fregni et al., 2006). Potential explanations for this apparent inconsistency may be the role of pharmacological history, as patients in the sham group were on antidepressant medication (Loo et al., 2010), inter-study differences in the severity of symptoms, and/or a small sample size resulting in insufficient statistical power.

Taken together, the available evidence suggests a clinically relevant potential of tDCS as an intervention to treat major depression, which has been demonstrated by meta-analyses and systematic reviews (Berlim et al., 2013; Brunoni et al., 2016; Shiozawa et al., 2014). However, various aspects which are relevant for its efficacy need to be systematically explored in future researches. These include specifics of the stimulation protocol such as intensity, duration, number of sessions, and the envisaged target region for stimulation. Furthermore, the

influence of clinical and patient characteristics, interaction between antidepressive medication and stimulation, neurobiological underpinnings of stimulation, and persistency of its effects require controlled investigations.

6. Concluding remarks and future directions

Applications of tES, as it is used for exploring basic aspects of human brain physiology, cognitive functions or suitability as a therapeutic agent, have experienced significant growth in the past years (Kuo and Nitsche, 2012; Kuo et al., 2014b; Shin et al., 2015; Woods et al., 2016). Stimulation can be used in combination with neuroimaging techniques, such as fMRI and EEG, to closely identify underlying functional brain networks relevant for many cognitive processes and behaviours. Furthermore, tDCS has been probed as a promising therapeutic intervention for diverse psychiatric and neurological conditions. This technique has appealing characteristics, such as being non-invasive, well-tolerated, and so far, absent of any serious adverse effects (Bikson et al., 2016).

tES has multilevel effects on the brain and brain-related functions, including modulation of cortical excitability, oscillatory activity, neuroplasticity, network connectivity, and cognitive processes. The precise effects of stimulation depend on various aspects, such as the stimulation protocol, brain state of the individual, and the nature of the specific task if combined with stimulation. The timing of applying tES (before, during or after a cognitive or motor task) is also a critical aspect. The classic assumptions of enhancement/diminution of cortical excitability by anodal/cathodal tDCS, and increase in stimulation efficacy with larger and longer stimulation are simplifications which may not hold across all applications. Neuroplastic after-effects of tES critically depend on stimulation parameters, are in most instances relatively short lasting, and not uniform between individuals. The need for longer-lasting effects, and presence of marked inter-individual variability, necessitates a deeper understanding of the relationship between stimulation parameters and physiological effects. Furthermore, more profound knowledge about basic neurophysiological mechanisms underlying tES is still required to understand the extent of its potential in therapeutic applications and cognitive neuroscience research. Several studies have investigated the stimulation parameter- (intensity, duration, interval, electrode size and position, etc.) response relationship by systematic titration of these parameters (Bastani and Jaberzadeh, 2013; Jamil et al., 2017; Monte-Silva et al., 2013; Monte-Silva et al., 2010; Nitsche and Paulus, 2000; Nitsche et al., 2007). Furthermore, various studies have exploited other aspects of the stimulation parameter space. For instance, for enhancing stimulation focality and efficiency, innovative shapes and arrangements of electrodes such as multi-channel tDCS in a Laplacian arrangement for more focal effects (Datta et al., 2009; Datta et al., 2008), fractal electrodes (Mahdavi et al., 2015), and electrodes individually reshaped to the target cortical region (Tecchio et al., 2013) have been introduced. Methodological guidelines, through consensus of expert groups, have also been introduced for appropriate design and conduction of studies in cognitive neurosciences and clinical trials involving tES (Antal and Herrmann, 2016; Woods et al., 2016; Woods and Martin, 2016).

Though a large portion of studies on neuroplasticity-inducing effects of tES and its basic physiology originates from motor cortex stimulation, it seems able to induce a variety of excitability changes also in areas outside the motor system. Combined TMS-EEG, fMRI, MEG, PET, and other neuroimaging techniques have been employed to investigate transferability of the results to other brain regions. These methods can provide real-time and direct information about cortical reactivity of brain areas where a direct physiological read-out such as TMS-induced MEPs is not available. While a similar functional and physiological impact of tDCS on a multitude of cortical regions has already been demonstrated (Dieckhofer et al., 2006; Matsunaga et al., 2004), a one-to-one transferability of effects in motor cortices to other regions cannot be presumed due to state-dependency of tES effects, anatomical differences, and other reasons (Accornero et al., 2007; Kuo et al., 2016b).

Transferability of results from healthy humans to patients is another important topic for extending its clinical application. Because of differences of neuromodulator activities and cortical excitability between healthy subjects and patients suffering from neuropsychiatric diseases, this is not a trivial issue. Here, computational modelling approaches based on individualized MRIs to account for disorder-related atrophy and damages may be useful in designing patient specific stimulation protocols (Datta et al., 2011; Gillick et al., 2014; Mahdavi et al., 2014). Similarly, considerable inter-individual variability in healthy adults has also been reported for tES effects, which is an inherent component of all neuromodulatory interventions, including stimulation and pharmacological approaches. Such variability may be caused by numerous factors such as head anatomy, genetics, age, and/or organization of local inhibitory and excitatory circuits (Li et al., 2015; Ridding and Ziemann, 2010). Therefore, a “one-size-fits-all” strategy, i.e., employing the same intervention across all individuals, may not result in optimal effects (Ashley, 2015). On the other hand, the large-scale parameter space of tES provides an opportunity for tailoring tES interventions to maximise its benefits. Thus, an important goal would be to systematically identify key parameters which produce a reliable and reproducible modulation in physiological effects, which may involve titrating stimulation for a particular population or even specific individuals. Existing knowledge in the NIBS field is mostly obtained via open-loop approaches, where a pre-defined stimulation protocol is usually applied for all participants (Zrenner et al., 2016). Closed-loop protocols, i.e., online adjustment of stimulation parameters according to “intra-subject” dynamic brain states, is also an ongoing development and goal of the field. One example here would be to adaptively change tACS frequency based on the subject’s endogenous oscillatory activity derived from EEG recordings (Boyle and Frohlich, 2013; Wilde et al., 2015).

Regarding clinical applications of tES, well-designed and larger-scale trials are required for careful investigation of efficacy. Here, considerable opportunities exist for further enhancements in future clinical trial designs, such as utilizing common outcome measures, and obtaining appropriate sample sizes, which allows to draw definitive conclusions about the use of this technique for therapeutic purposes. Furthermore, combination of tES with other interventions might create synergistic effects and clinical benefits beyond each intervention independently. This has already been shown for a variety of cases such as the combination of tDCS with cognitive-behavioural therapy for depression (D’Urso et al., 2013), the combination of tDCS with virtual reality therapy for rehabilitation of patients with subacute stroke (Lee and Chun, 2014), and the combination of tDCS with sertraline for depressed patients (Brunoni et al., 2013). Interaction of interventions might augment functional improvement caused by each intervention alone, e.g. by improving the response of the target regions to the stimulation (Wagner et al., 2014) or boosting task-related plasticity by stimulation (Nitsche et al., 2003c). For augmenting the effects of each therapy and synergistically improving clinical effects, more systematic explorations are required to determine appropriate protocols with respect to factors such as relative timing of each therapeutic program, type and intensity of interventions, and phase and severity of target disorder.

Taken together, research conducted in the last years has relevantly helped to improve our understanding about mechanistic effects of tES, and this non-invasive intervention tool is increasingly used to improve our understanding of the basic foundation of psychological processes, motor functions, and behaviour. Moreover, numerous proof-of-concept studies have been conducted to explore its clinical potential to treat neurological and psychiatric diseases. Crucial for the future development and usefulness of this intervention is further understanding of mechanisms of action, and a complete development of stimulation protocols which exert optimal effects.

Conflict of interest statement

M. Nitsche is member of Advisory Board of Neuroelectrics. None of the remaining authors have potential conflicts of interest to be disclosed.

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References

Accornero, N., Li Voti, P., La Riccia, M., Gregori, B., 2007. Visual evoked potentials modulation during direct current cortical polarization. Exp. Brain Res. 178, 261–266.
Albert, D., 1966a. The effects of polarizing currents on the consolidation of learning. Neuropsychologia 4, 65–77.
Albert, D.J., 1966b. The effect of spreading depression on the consolidation of learning. Neuropsychologia 4, 49–64.
Alekseichuk, I., Turi, Z., de Lara, G.A., Antal, A., Paulus, W., 2016. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr. Biol. 26 (12), 1513–1521.
Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., Paulus, W., 2008. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 1, 97–105.
Antal, A., Herrmann, C.S., 2016. Transcranial alternating current and random noise stimulation: possible mechanisms. Neural Plast. 2016, 3616807.
Antal, A., Paulus, W., 2013. Transcranial alternating current stimulation (tACS). Front. Hum. Neurosci. 7.
Antal, A., Polania, R., Schmidt-Samoa, C., Dechent, P., Paulus, W., 2011. Transcranial direct current stimulation over the primary motor cortex during fMRI. Neuroimage 55, 590–596.
Aroniadou, V.A., Keller, A., 1995. Mechanisms of LTP induction in rat motor cortex in vitro. Cereb. Cortex 5, 353–362.
Ashley, E.A., 2015. The precision medicine initiative: a new national effort. JAMA 313, 2119–2120.
Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. Lancet 1, 1106–1107.
Bastani, A., Jaberzadeh, S., 2013. Differential modulation of corticospinal excitability by different current densities of anodal transcranial direct current stimulation. PLoS One 8, e72254.
Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A., 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591, 1987–2000.
Belyi, B., 1987. Mental impairment in unilateral frontal tumours: role of the laterality of the lesion. Int. J. Neurosci. 32, 799–810.
Berlim, M.T., Van den Eynde, F., Daskalakis, Z.J., 2013. Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. J. Psychiatr. Res. 47, 1–7.
Bikson, M., Grossman, P., Thomas, C., Zannou, A.L., Jiang, J., Adnan, T., Mourdoukoutas, A.P., Kronberg, G., Truong, D., Boggio, P., Brunoni, A.R., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R.H., Hampstead, B.M., Jankord, R., Kirton, A., Knotkova, H., Liebetanz, D., Liu, A., Loo, C., Nitsche, M.A., Reis, J., Richardson, J.D., Rotenberg, A., Turkeltaub, P.E., Woods, A.J., 2016. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 9, 641–661.
Bikson, M., Inoue, M., Akiyama, H., Deans, J.K., Fox, J.E., Miyakawa, H., Jefferys, J.G., 2004. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J. Physiol. 557, 175–190.
Bindman, L.J., Lippold, O.C., Redfearn, J.W., 1964. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J. Physiol. 172, 369–382.
Boggio, P.S., Nunes, A., Rigonatti, S.P., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2007. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor. Neurol. Neurosci. 25, 123–129.
Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., Myczkowski, M.L., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int. J. Neuropsychopharmacol. 11, 249–254.
Boonstra, T.W., Daffertshofer, A., Breakspear, M., Beek, P.J., 2007. Multivariate time-frequency analysis of electromagnetic brain activity during bimanual motor learning. Neuroimage 36, 370–377.
Boyle, M.R., Frohlich, F., 2013. EEG feedback-controlled transcranial alternating current stimulation, Neural Engineering (NER). 2013 6th International IEEE/EMBS Conference On. IEEE 140–143.
Brunoni, A.R., Moffa, A.H., Fregni, F., Palm, U., Padberg, F., Blumberger, D.M., Daskalakis, Z.J., Bennabi, D., Haffen, E., Alonzo, A., Loo, C.K., 2016. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br. J. Psychiatry 208, 522–531.
Brunoni, A.R., Valiengo, L., Baccaro, A., Zanao, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Bensenor, I.M., Fregni, F., 2013. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial randomized, controlled trial. JAMA Psychiatry 70, 383–391.
Butler, A.J., Shuster, M., O'Hara, E., Hurley, K., Middlebrooks, D., Guilkey, K., 2013. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. J. Hand Ther. 26, 162–170 (quiz 171).
Cambiaghi, M., Velikova, S., Gonzalez-Rosa, J.J., Cursi, M., Comi, G., Leocani, L., 2010. Brain transcranial direct current stimulation modulates motor excitability in mice. Eur. J. Neurosci. 31, 704–709.
Carpenter, P.A., Just, M.A., Reichle, E.D., 2000. Working memory and executive function: evidence from neuroimaging. Curr. Opin. Neurobiol. 10, 195–199.
Castro-Alamancos, M.A., Donoghue, J.P., Connors, B.W., 1995. Different forms of synaptic plasticity in somatosensory and motor areas of the neocortex. J. Neurosci. 15, 5324–5333.
Chaieb, L., Antal, A., Paulus, W., 2011. Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. Restor. Neurol. Neurosci. 29, 167–175.
Cho, K., Aggleton, J.P., Brown, M.W., Bashir, Z.I., 2001. An experimental test of the role of postsynaptic calcium levels in determining synaptic strength using perirhinal cortex of rat. J. Physiol. 532, 459–466.
Costain, R., Redfearn, J.W., Lippold, O.C., 1964. A controlled trial of the therapeutic effects of polarization of the brain in depressive illness. Br. J. Psychiatry 2, 786–799. http://dx.doi.org/10.1192/bjp.110.469.786.
Creutzfeldt, O.D., Fromm, G.H., Kapp, H., 1962. Influence of transcortical d-c currents on cortical neuronal activity. Exp. Neurol. 5, 436–452.
D'Ostilio, K., Garraux, G., 2016. The network model of depression as a basis for new therapeutic strategies for treating major depressive disorder in Parkinson's disease. Front. Hum. Neurosci. 10.
D'Urso, G., Mantovani, A., Micillo, M., Priori, A., Muscettola, G., 2013. Transcranial direct current stimulation and cognitive-behavioral therapy: evidence of a synergistic effect in treatment-resistant depression. Brain Stimul. 6, 465–467.
Datta, A., Baker, J.M., Bikson, M., Fridriksson, J., 2011. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimul. 4, 169–174.
Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., Bikson, M., 2009. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2, 201–207 (e201).
Datta, A., Elwassif, M., Battaglia, F., Bikson, M., 2008. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. J. Neural Eng. 5, 163.
Davidson, R.J., Putnam, K.M., Larson, C.L., 2000. Dysfunction in the neural circuitry of emotion regulation?a possible prelude to violence. Science 289, 591–594.
Dayan, E., Censor, N., Buch, E.R., Sandrini, M., Cohen, L.G., 2013. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat. Neurosci. 16, 838–844.
Deans, J.K., Powell, A.D., Jefferys, J.G., 2007. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J. Physiol. 583, 555–565.
Dieckhofer, A., Waberski, T.D., Nitsche, M., Paulus, W., Buchner, H., Gobbele, R., 2006. Transcranial direct current stimulation applied over the somatosensory cortex — differential effect on low and high frequency SEPs. Clin. Neurophysiol. 117, 2221–2227.
Dolcos, F., LaBar, K.S., Cabeza, R., 2004. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. Neuroimage 23, 64–74.
Dymond, A.M., Coger, R.W., Serafetinides, E.A., 1975. Intracerebral current levels in man during electrosleep therapy. Biol. Psychiatry 10, 101–104.
Feurra, M., Bianco, G., Santarnecchi, E., Del Testa, M., Rossi, A., Rossi, S., 2011. Frequency-dependent tuning of the human motor system induced by transcranial oscillatory potentials. J. Neurosci. 31, 12165–12170.
Floel, A., 2014. tDCS-enhanced motor and cognitive function in neurological diseases. Neuroimage 85 (Pt 3), 934–947.
Fregni, F., Boggio, P.S., Mansur, C.G., Wagner, T., Ferreira, M.J., Lima, M.C., Rigonatti, S.P., Marcolin, M.A., Freedman, S.D., Nitsche, M.A., 2005a. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport 16, 1551–1555.
Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005b. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp. Brain Res. 166, 23–30.
Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 8, 203–204.
Fritsch, B., Reis, J., Martinowich, K., Schambra, H.M., Ji, Y., Cohen, L.G., Lu, B., 2010. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 66, 198–204.
Fröhlich, F., McCormick, D.A., 2010. Endogenous electric fields may guide neocortical network activity. Neuron 67, 129–143.
Gartside, I.B., 1968. Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. Nature 220, 383–384.
George, M.S., Aston-Jones, G., 2010. Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology 35, 301–316.
Gevins, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of

processing, and practice. Cereb. Cortex 7, 374–385.
Gilbertson, T., Lalo, E., Doyle, L., Di Lazzaro, V., Cioni, B., Brown, P., 2005. Existing motor state is favored at the expense of new movement during 13–35 Hz oscillatory synchrony in the human corticospinal system. J. Neurosci. 25, 7771–7779.
Gillick, B.T., Kirton, A., Carmel, J.B., Minhas, P., Bikson, M., 2014. Pediatric stroke and transcranial direct current stimulation: methods for rational individualized dose optimization. Front. Hum. Neurosci. 8, 739.
Grafton, S.T., Mazziotta, J.C., Presty, S., Friston, K.J., Frackowiak, R., Phelps, M.E., 1992. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J. Neurosci. 12, 2542–2548.
Grimm, S., Beck, J., Schuepbach, D., Hell, D., Boesiger, P., Bermpohl, F., Niehaus, L., Boeker, H., Northoff, G., 2008. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. Biol. Psychiatry 63, 369–376.
Grimm, S., Schmidt, C.F., Bermpohl, F., Heinzel, A., Dahlem, Y., Wyss, M., Hell, D., Boesiger, P., Boeker, H., Northoff, G., 2006. Segregated neural representation of distinct emotion dimensions in the prefrontal cortex—an fMRI study. Neuroimage 30, 325–340.
Guleyupoglu, B., Schestatsky, P., Edwards, D., Fregni, F., Bikson, M., 2013. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. J. Neurosci. Methods 219, 297–311.
Habel, U., Klein, M., Kellermann, T., Shah, N.J., Schneider, F., 2005. Same or different? Neural correlates of happy and sad mood in healthy males. Neuroimage 26, 206–214.
Hampel, R., 1977. Adjektiv-Skalen zur Einschätzung der Stimmung (SES).
Hattori, Y., Moriwaki, A., Hori, Y., 1990. Biphasic effects of polarizing current on adenosine-sensitive generation of cyclic AMP in rat cerebral cortex. Neurosci. Lett. 116, 320–324.
Heiss, W.D., Kessler, J., Thiel, A., Ghaemi, M., Karbe, H., 1999. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. Ann. Neurol. 45, 430–438.
Helfrich, R.F., Knepper, H., Nolte, G., Struber, D., Rach, S., Herrmann, C.S., Schneider, T.R., Engel, A.K., 2014a. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. 12, e1002031.
Helfrich, R.F., Schneider, T.R., Rach, S., Trautmann-Lengsfeld, S.A., Engel, A.K., Herrmann, C.S., 2014b. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr. Biol. 24, 333–339.
Herrington, J.D., Mohanty, A., Koven, N.S., Fisher, J.E., Stewart, J.L., Banich, M.T., Webb, A.G., Miller, G.A., Heller, W., 2005. Emotion-modulated performance and activity in left dorsolateral prefrontal cortex. Emotion 5, 200.
Hess, G., Aizenman, C.D., Donoghue, J.P., 1996. Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. J. Neurophysiol. 75, 1765–1778.
Hesse, S., Werner, C., Schonhardt, E.M., Bardeleben, A., Jenrich, W., Kirker, S.G., 2007. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. Restor. Neurol. Neurosci. 25, 9–15.
Hill, A.T., Fitzgerald, P.B., Hoy, K.E., 2016. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-Analysis of findings from healthy and neuropsychiatric populations. Brain stimulation 9, 197–208.
Honda, M., Deiber, M.-P., Ibáñez, V., Pascual-Leone, A., Zhuang, P., Hallett, M., 1998a. Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. Brain 121, 2159–2173.
Honda, M., Deiber, M.P., Ibanez, V., Pascual-Leone, A., Zhuang, P., Hallett, M., 1998b. Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. Brain: J. Neurol. 121 (Pt 11), 2159–2173.
Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W.H., Gerloff, C., Cohen, L.G., 2005. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain: J. Neurol. 128, 490–499.
Islam, N., Aftabuddin, M., Moriwaki, A., Hattori, Y., Hori, Y., 1995a. Increase in the calcium level following anodal polarization in the rat brain. Brain Res. 684, 206–208.
Islam, N., Aftabuddin, M., Moriwaki, A., Hori, Y., 1997. Effects of anodal polarization on protein kinase Cγ (PKCγ) in the rat brain. Indian J. Physiol. Pharmacol. 204–210.
Islam, N., Moriwaki, A., Hattori, Y., Hayashi, Y., Lu, Y.F., Hori, Y., 1995b. c-Fos expression mediated by N-methyl-D-aspartate receptors following anodal polarization in the rat brain. Exp. Neurol. 133, 25–31.
Islam, N., Moriwaki, A., Hattori, Y., Hori, Y., 1994. Anodal polarization induces protein kinase C gamma (PKC gamma)-like immunoreactivity in the rat cerebral cortex. Neurosci. Res. 21, 169–172.
Jamil, A., Batsikadze, G., Kuo, H.I., Labruna, L., Hasan, A., Paulus, W., Nitsche, M.A., 15 February 2017. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J. Physiol. 595 (4), 1273–1288.
Kang, N., Summers, J.J., Cauraugh, J.H., 2016. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry 87, 345–355.
Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., Brunelin, J., Moller, H.J., Reiser, M., Padberg, F., 2011. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J. Neurosci. 31, 15284–15293.
Kellaway, P., 1946. The part played by electric fish in the early history of bioelectricity and electrotherapy. Bull. Hist. Med. 20, 112.
Kim, D.Y., Lim, J.Y., Kang, E.K., You, D.S., Oh, M.K., Oh, B.M., Paik, N.J., 2010. Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. Am. J. Phys. Med. Rehabil. 89, 879–886.
Kleim, J.A., Jones, T.A., 2008. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J. Speech Lang. Hear. Res. 51, S225–239.
Koo, H., Kim, M.S., Han, S.W., Paulus, W., Nitche, M.A., Kim, Y.H., Kim, H.I., Ko, S.H., Shin, Y.I., 2016. After-effects of anodal transcranial direct current stimulation on the excitability of the motor cortex in rats. Restor. Neurol. Neurosci. 34, 859–868.
Kuo, H.I., Paulus, W., Batsikadze, G., Jamil, A., Kuo, M.F., Nitsche, M.A., 2016a. Chronic enhancement of serotonin facilitates excitatory transcranial direct current stimulation-induced neuroplasticity. Neuropsychopharmacology 41, 1223–1230.
Kuo, M.-F., Paulus, W., Nitsche, M.A., 2014a. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 85, 948–960.
Kuo, M.-F., Polanía, R., Nitsche, M., 2016b. Physiology of Transcranial Direct and Alternating Current Stimulation, Transcranial Direct Current Stimulation in Neuropsychiatric Disorders. Springerpp. 29–46.
Kuo, M.F., Nitsche, M.A., 2012. Effects of transcranial electrical stimulation on cognition. Clin. EEG Neurosci. 43, 192–199.
Kuo, M.F., Nitsche, M.A., 2015. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. Neurosci. Bull. 31, 198–206.
Kuo, M.F., Paulus, W., Nitsche, M.A., 2014b. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 85 (Pt 3), 948–960.
Kuo, M.F., Unger, M., Liebetanz, D., Lang, N., Tergau, F., Paulus, W., Nitsche, M.A., 2008. Limited impact of homeostatic plasticity on motor learning in humans. Neuropsychologia 46, 2122–2128.
Lee, S.J., Chun, M.H., 2014. Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. Arch. Phys. Med. Rehabil. 95, 431–438.
Li, L.M., Uehara, K., Hanakawa, T., 2015. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front. Cell. Neurosci. 9, 181.
Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W., 2002. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125, 2238–2247.
Lindenberg, R., Renga, V., Zhu, L., Nair, D., Schlaug, G., 2010. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology 75, 2176–2184.
Lippold, O., Redfearn, J., 1964. Mental changes resulting from the passage of small direct currents through the human brain. Br. J. Psychiatry 110, 768–772.
Lisman, J.E., 2001. Three Ca2+ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. J. Physiol. 532, 285.
Lisman, J.E., Jensen, O., 2013. The theta-gamma neural code. Neuron 77, 1002–1016.
Loo, C.K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G.S., Lagopoulos, J., Mitchell, P., 2010. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int. J. Neuropsychopharmacol. 13, 61–69.
Loubinoux, I., Carel, C., Pariente, J., Dechaumont, S., Albucher, J.-F., Marque, P., Manelfe, C., Chollet, F., 2003. Correlation between cerebral reorganization and motor recovery after subcortical infarcts. Neuroimage 20, 2166–2180.
Ludemann-Podubecka, J., Bosl, K., Rothhardt, S., Verheyden, G., Nowak, D.A., 2014. Transcranial direct current stimulation for motor recovery of upper limb function after stroke. Neurosci. Biobehav. Rev. 47, 245–259.
Mahdavi, S., Towhidkhah, F., Fatouraee, N., 2015. Efficacy of fractal electrodes in transcranial direct current stimulation: A computational modeling study. 2015 23rd Iranian Conference on Electrical Engineering. IEEE 99–103.
Mahdavi, S., Yavari, F., Gharibzadeh, S., Towhidkhah, F., 2014. Modeling studies for designing transcranial direct current stimulation protocol in Alzheimer's disease. Front. Comput. Neurosci. 8, 72.
Malenka, R.C., Bear, M.F., 2004. LTP and LTD: an embarrassment of riches. Neuron 44, 5–21.
Mancuso, L.E., Ilieva, I.P., Hamilton, R.H., Farah, M.J., 2016. Does transcranial direct current stimulation improve healthy working memory?: a meta-analytic review. J. Cogn. Neurosci. 28 (8), 1063–1089. http://dx.doi.org/10.1162/jocn_a_00956.
Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., Aerts, J., Del Fiore, G., Degueldre, C., Meulemans, T., Luxen, A., Franck, G., Van Der Linden, M., Smith, C., Cleeremans, A., 2000. Experience-dependent changes in cerebral activation during human REM sleep. Nat. Neurosci. 3, 831–836.
Matsunaga, K., Nitsche, M.A., Tsuji, S., Rothwell, J.C., 2004. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. Clin. Neurophysiol. 115, 456–460.
Merton, P.A., Morton, H.B., 1980. Stimulation of the cerebral cortex in the intact human subject. Nature 285, 227.
Misonou, H., Mohapatra, D.P., Park, E.W., Leung, V., Zhen, D., Misonou, K., Anderson, A.E., Trimmer, J.S., 2004. Regulation of ion channel localization and phosphorylation by neuronal activity. Nat. Neurosci. 7, 711–718.
Mizuhara, H., Yamaguchi, Y., 2007. Human cortical circuits for central executive function emerge by theta phase synchronization. Neuroimage 36, 232–244.
Moliadze, V., Antal, A., Paulus, W., 2010. Boosting brain excitability by transcranial high frequency stimulation in the ripple range. J. Physiol. 588, 4891–4904.
Moliadze, V., Atalay, D., Antal, A., Paulus, W., 2012. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul. 5, 505–511.
Monai, H., Ohkura, M., Tanaka, M., Oe, Y., Konno, A., Hirai, H., Mikoshiba, K., Itohara, S., Nakai, J., Iwai, Y., Hirase, H., 2016. Calcium imaging reveals glial involvement in transcranial direct current stimulation-induced plasticity in mouse brain. Nat. Commun. 7, 11100.
Monte-Silva, K., Kuo, M.F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., Nitsche, M.A., 2013. Induction of late LTP-like plasticity in the human motor cortex

by repeated non-invasive brain stimulation. Brain Stimul. 6, 424–432.
Monte-Silva, K., Kuo, M.F., Liebetanz, D., Paulus, W., Nitsche, M.A., 2010. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J. Neurophysiol. 103, 1735–1740.
Morgan, H.M., Davis, N.J., Bracewell, R.M., 2014. Does transcranial direct current stimulation to prefrontal cortex affect mood and emotional memory retrieval in healthy individuals? PLoS One 9, e92162.
Motohashi, N., Yamaguchi, M., Fujii, T., Kitahara, Y., 2013. Mood and cognitive function following repeated transcranial direct current stimulation in healthy volunteers: a preliminary report. Neurosci. Res. 77, 64–69.
Mungee, A., Kazzer, P., Feeser, M., Nitsche, M.A., Schiller, D., Bajbouj, M., 2014. Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. Neuroreport 25, 480–484.
Nair, D.G., Hutchinson, S., Fregni, F., Alexander, M., Pascual-Leone, A., Schlaug, G., 2007. Imaging correlates of motor recovery from cerebral infarction and their physiological significance in well-recovered patients. Neuroimage 34, 253–263.
Nair, D.G., Renga, V., Lindenberg, R., Zhu, L., Schlaug, G., 2011. Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tDCS. Restor. Neurol. Neurosci. 29, 411–420.
Nitsche, M., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527, 633–639.
Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 1, 206–223.
Nitsche, M.A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., Tergau, F., Paulus, W., 2007. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J. Neurophysiol. 97, 3109–3117.
Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., Paulus, W., 2003a. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J. Physiol. 553, 293–301.
Nitsche, M.A., Grundey, J., Liebetanz, D., Lang, N., Tergau, F., Paulus, W., 2004a. Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb. Cortex 14, 1240–1245.
Nitsche, M.A., Jakoubkova, M., Thirugnanasambandam, N., Schmalfuss, L., Hullemann, S., Sonka, K., Paulus, W., Trenkwalder, C., Happe, S., 2010. Contribution of the premotor cortex to consolidation of motor sequence learning in humans during sleep. J. Neurophysiol. 104, 2603–2614.
Nitsche, M.A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., Paulus, W., 2004b. Consolidation of human motor cortical neuroplasticity by D-cycloserine. Neuropsychopharmacology 29, 1573–1578.
Nitsche, M.A., Koschack, J., Pohlers, H., Hullemann, S., Paulus, W., Happe, S., 2012. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Front Psychiatry 3, 58.
Nitsche, M.A., Kuo, M.F., Karrasch, R., Wachter, B., Liebetanz, D., Paulus, W., 2009. Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol. Psychiatry 66, 503–508.
Nitsche, M.A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., Paulus, W., 2006. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. Eur. J. Neurosci. 23, 1651–1657.
Nitsche, M.A., Nitsche, M.S., Klein, C.C., Tergau, F., Rothwell, J.C., Paulus, W., 2003b. Level of action of cathodal DC polarization induced inhibition of the human motor cortex. Clin. Neurophysiol. 114, 600–604.
Nitsche, M.A., Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57, 1899–1901.
Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., Tergau, F., 2003c. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J. Cogn. Neurosci. 15, 619–626.
Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W., Tergau, F., 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J. Physiol. 568, 291–303.
Nonnekes, J., Arrogi, A., Munneke, M.A., van Asseldonk, E.H., Nijhuis, L.B.O., Geurts, A.C., Weerdesteyn, V., 2014. Subcortical structures in humans can be facilitated by transcranial direct current stimulation. PLoS One 9, e107731.
Ozen, S., Sirota, A., Belluscio, M.A., Anastassiou, C.A., Stark, E., Koch, C., Buzsáki, G., 2010. Transcranial electric stimulation entrains cortical neuronal populations in rats. J. Neurosci. 30, 11476–11485.
Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., Pogarell, O., Nitsche, M.A., Moller, H.J., Padberg, F., 2012. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul. 5, 242–251.
Parent, A., 2004. Giovanni Aldini: from animal electricity to human brain stimulation. Canad. J. Neurol. Sci. 31, 576–584.
Pascual-Leone, A., Grafman, J., Hallett, M., 1994. Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science 263, 1287–1289.
Perini, G., 1986. Emotions and personality in complex partial seizures. Psychother. Psychosom. 45, 141–148.
Pfurtscheller, G., 1981. Central beta rhythm during sensorimotor activities in man. Electroencephalogr. Clin. Neurophysiol. 51, 253–264.
Plazier, M., Joos, K., Vanneste, S., Ost, J., De Ridder, D., 2012. Bifrontal and bioccipital transcranial direct current stimulation (tDCS) does not induce mood changes in healthy volunteers: a placebo controlled study. Brain Stimul. 5, 454–461.
Plewnia, C., Schroeder, P.A., Kunze, R., Faehling, F., Wolkenstein, L., 2015. Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). PLoS One 10, e0122578.
Polania, R., Nitsche, M.A., Korman, C., Batsikadze, G., Paulus, W., 2012a. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr. Biol. 22, 1314–1318.
Polania, R., Nitsche, M.A., Paulus, W., 2011. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum. Brain Mapp. 32, 1236–1249.
Polania, R., Paulus, W., Nitsche, M.A., 2012b. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum. Brain Mapp. 33, 2499–2508.
Priori, A., Berardelli, A., Rona, S., Accornero, N., Manfredi, M., 1998. Polarization of the human motor cortex through the scalp. Neuroreport 9, 2257–2260.
Purpura, D.P., McMurtry, J.G., 1965. Intracellular activities and evoked potential changes during polarization of motor cortex. J. Neurophysiol. 28, 166–185.
Ranieri, F., Podda, M.V., Riccardi, E., Frisullo, G., Dileone, M., Profice, P., Pilato, F., Di Lazzaro, V., Grassi, C., 2012. Modulation of LTP at rat hippocampal CA3-CA1synapses by direct current stimulation. J. Neurophysiol. 107, 1868–1880.
Redfearn, J.W., Lippold, O.C., Costain, R., 1964. A preliminary account of the clinical effects of polarizing the brain in certain psychiatric disorders. Br. J. Psychiatry 110, 773–785.
Rego, G.G., Lapenta, O.M., Marques, L.M., Costa, T.L., Leite, J., Carvalho, S., Goncalves, O.F., Brunoni, A.R., Fregni, F., Boggio, P.S., 2015. Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. Neurosci. Lett. 594, 12–16.
Reis, J., Fritsch, B., 2011. Modulation of motor performance and motor learning by transcranial direct current stimulation. Curr. Opin. Neurol. 24, 590–596.
Reis, J., Robertson, E., Krakauer, J.W., Rothwell, J., Marshall, L., Gerloff, C., Wassermann, E., Pascual-Leone, A., Hummel, F., Celnik, P.A., 2008. Consensus:Can tDCS and TMS enhance motor learning and memory formation? Brain Stimul. 1, 363.
Reis, J., Schambra, H.M., Cohen, L.G., Buch, E.R., Fritsch, B., Zarahn, E., Celnik, P.A., Krakauer, J.W., 2009. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc. Natl. Acad. Sci. 106, 1590–1595.
Ridding, M.C., Ziemann, U., 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J. Physiol. 588, 2291–2304.
Rigonatti, S.P., Boggio, P.S., Myczkowski, M.L., Otta, E., Fiquer, J.T., Ribeiro, R.B., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008. Transcranial direct stimulation and fluoxetine for the treatment of depression. Eur. Psychiatry 23, 74–76.
Rioult-Pedotti, M.S., Friedman, D., Donoghue, J.P., 2000. Learning-induced LTP in neocortex. Science 290, 533–536.
Robinson, R., Lipsey, J.R., 1984. Cerebral localization of emotion based on clinical-neuropathological correlations: methodological issues. Psychiatr. Dev. 3, 335–347.
Rose, M., Buchel, C., 2005. Neural coupling binds visual tokens to moving stimuli. J. Neurosci. 25, 10101–10104.
Rossini, P.M., Calautti, C., Pauri, F., Baron, J.C., 2003. Post-stroke plastic reorganisation in the adult brain. Lancet Neurol. 2, 493–502.
Rossini, P.M., Rossi, S., 2007. Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology 68, 484–488.
Rothwell, J.C., 1993. Evoked potentials, magnetic stimulation studies, and event-related potentials. Curr. Opin. Neurol. 6, 715–723.
Sehm, B., Schäfer, A., Kipping, J., Margulies, D., Conde, V., Taubert, M., Villringer, A., Ragert, P., 2012. Dynamic modulation of intrinsic functional connectivity by transcranial direct current stimulation. J. Neurophysiol. 108, 3253–3263.
Seidler, R.D., 2010. Neural correlates of motor learning, transfer of learning, and learning to learn. Exerc. Sport Sci. Rev. 38, 3.
Sergerie, K., Lepage, M., Armony, J.L., 2005. A face to remember: emotional expression modulates prefrontal activity during memory formation. Neuroimage 24, 580–585.
Sheffield, L., Mowbray, R., Feb 1968. The effects of polarization on normal subjects. Br. J. Psychiatry 114 (507), 225–232. http://dx.doi.org/10.1192/bjp.114.507.225.
Sheliakin, A., Preobrazhenskaia, I., Tiul'kin, O., 2005. Micropolarization of the brain: a noninvasive method for correction of morphological and functional disturbances in acute focal brain lesions and their consequences. Zhurnal nevrologii i psikhiatrii imeni SS Korsakova/Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiatrov 106, 27–37.
Shin, Y.I., Foerster, A., Nitsche, M.A., 2015. Reprint of: transcranial direct current stimulation (tDCS) – application in neuropsychology. Neuropsychologia 74, 74–95.
Shiozawa, P., Fregni, F., Bensenor, I.M., Lotufo, P.A., Berlim, M.T., Daskalakis, J.Z., Cordeiro, Q., Brunoni, A.R., 2014. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 17, 1443–1452.
Smith, R.B., 2008. Cranial Electrotherapy Stimulation: Its First Fifty Years, Plus Three: a Monograph. Tate Publishing.
Stagg, C., 2014. The Physiological Basis of Brain Stimulation. The Stimulated Brain: Cognitive Enhancement Using Non-Invasive Brain Stimulation. pp. 145–177.
Stagg, C., Jayaram, G., Pastor, D., Kincses, Z., Matthews, P., Johansen-Berg, H., 2011. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia 49, 800–804.
Stagg, C.J., Best, J.G., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M., Johansen-Berg, H., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosci. 29, 5202–5206.
Stagg, C.J., Nitsche, M.A., 2011. Physiological basis of transcranial direct current stimulation. Neuroscientist 17, 37–53.
Struber, D., Rach, S., Trautmann-Lengsfeld, S.A., Engel, A.K., Herrmann, C.S., 2014. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception.

Brain Topogr. 27, 158–171.
Takeuchi, N., Izumi, S., 2012. Maladaptive plasticity for motor recovery after stroke: mechanisms and approaches. Neural Plast. 2012, 359728.
Taub, E., Uswatte, G., Mark, V.W., Morris, D.M., 2006. The learned nonuse phenomenon: implications for rehabilitation. Eura. Medicophys. 42, 241–256.
Tecchio, F., Cancelli, A., Cottone, C., Tomasevic, L., Devigus, B., Zito, G., Ercolani, M., Carducci, F., 2013. Regional personalized electrodes to select transcranial current stimulation target. Front. Hum. Neurosci. 7, 131.
Traversa, R., Cicinelli, P., Pasqualetti, P., Filippi, M., Rossini, P.M., 1998. Follow-up of interhemispheric differences of motor evoked potentials from theaffected'andunaffected'hemispheres in human stroke. Brain Res. 803, 1–8.
Ungerleider, L.G., Doyon, J., Karni, A., 2002. Imaging brain plasticity during motor skill learning. Neurobiol. Learn. Mem. 78, 553–564.
Wach, C., Krause, V., Moliadze, V., Paulus, W., Schnitzler, A., Pollok, B., 2013. Effects of 10 Hz and 20 Hz transcranial alternating current stimulation (tACS) on motor functions and motor cortical excitability. Behav. Brain Res. 241, 1–6.
Wagner, T., Valero-Cabre, A., Pascual-Leone, A., 2007. Noninvasive human brain stimulation. Annu. Rev. Biomed. Eng. 9, 527–565.
Wagner, T.A., Dipietro, L., Eden, U.T. (2014) Stimulation to guide physical therapy. Google Patents.
Ward, N., Brown, M., Thompson, A., Frackowiak, R., 2003. Neural correlates of outcome after stroke: a crossectional fMRI study. Brain 126, 1430–1448.
Weigand, A., Grimm, S., Astalosch, A., Guo, J.S., Briesemeister, B.B., Lisanby, S.H., Luber, B., Bajbouj, M., 2013. Lateralized effects of prefrontal repetitive transcranial magnetic stimulation on emotional working memory. Exp. Brain Res. 227, 43–52.
Wilde, C., Bruder, R., Binder, S., Marshall, L., Schweikard, A., 2015. Closed-loop transcranial alternating current stimulation of slow oscillations. Curr. Direct. Biomed. Eng. 1, 85–88.
Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E.S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P.C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., Nitsche, M.A., 2016. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin. Neurophysiol. 127, 1031–1048.
Woods, A.J., Martin, D.M., 2016. Clinical Research and Methodological Aspects for tDCS Research, Transcranial Direct Current Stimulation in Neuropsychiatric Disorders. Springerpp. 393–404.
Zhuang, P., Toro, C., Grafman, J., Manganotti, P., Leocani, L., Hallett, M., 1997. Event-related desynchronization (ERD) in the alpha frequency during development of implicit and explicit learning. Electroencephalogr. Clin. Neurophysiol. 102, 374–381.
Zrenner, C., Belardinelli, P., Muller-Dahlhaus, F., Ziemann, U., 2016. Closed-loop neuroscience and non-invasive brain stimulation: a tale of two loops. Front. Cell. Neurosci. 10, 92.