The Journal of ECT
Issue: Volume 34(3), September 2018, p 144–152

Publication Type: [Special Issue on tDCS]
DOI: 10.1097/YCT.0000000000000510
ISSN: 1095-0680
Accession: 00124509-201809000-00003
Keywords: functional connectivity, neuroplasticity, noninvasive brain stimulation

Hide Cover

[Special Issue on tDCS]

Physiology of Transcranial Direct Current Stimulation

Stagg, Charlotte J. MD, PhD[*†]; Antal, Andrea PhD[‡]; Nitsche, Michael A. MD[§[//]]

Author Information

From the [*]Nuffield Department of Clinical Neurosciences, Oxford Centre for Functional MRI of the Brain, and

[†]Department of Psychiatry, Oxford Centre for Human Brain Activity, Wellcome Centre for Integrative Neuroimaging, University of Oxford, Oxford, United Kingdom; and

[‡]Department of Clinical Neurophysiology, University Medical Center Göttingen, University of Göttingen, Göttingen;

[§]Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund; and

[[//]]Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany.
Received for publication February 10, 2018; accepted April 24, 2018.
Reprints: Michael A. Nitsche, Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Ardeystr. 67, 44139 Dortmund, Germany (e-mail: nitsche@ifado.de
).
M.A.N. receives support by the EC Horizon 2020 Program, FET Grant, 686764-LUMINOUS, grants from the German Ministry of Research and Education (GCBS grant 01EE1403C, TRAINSTIM grant 01GQ1424E), and by a grant from the Deutsche Forschungsgemeinschaft, Germany (SFB 1280 Extinction Learning). C.J.S. holds a Sir Henry Dale Fellowship, funded by the Wellcome Trust and the Royal Society (102584/Z/13/Z). The Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z). M.A.N. is in the Advisory Board of Neuroelectrics. C.J.S. and A.A. have no conflicts of interest to report.

Abstract

Abstract: Direct current stimulation is a neuromodulatory noninvasive brain stimulation tool, which was first introduced in animal and human experiments in the 1950s, and added to the standard arsenal of methods to alter brain physiology as well as psychological, motor, and behavioral processes and clinical symptoms in neurological and psychiatric diseases about 20 years ago. In contrast to other noninvasive brain

stimulation tools, such as transcranial magnetic stimulation, it does not directly induce cerebral activity, but rather alters spontaneous brain activity and excitability by subthreshold modulation of neuronal membranes. Beyond acute effects on brain functions, specific protocols are suited to induce long-lasting alterations of cortical excitability and activity, which share features with long-term potentiation and depression. These neuroplastic processes are important foundations for various cognitive functions such as learning and memory formation and are pathologically altered in numerous neurological and psychiatric diseases. This explains the increasing interest to investigate transcranial direct current stimulation (tDCS) as a therapeutic tool. However, for tDCS to be used effectively, it is crucial to be informed about physiological mechanisms of action. These have been increasingly elucidated during the last years. This review gives an overview of the current knowledge available regarding physiological mechanisms of tDCS, spanning from acute regional effects, over neuroplastic effects to its impact on cerebral networks. Although knowledge about the physiological effects of tDCS is still not complete, this might help to guide applications on a scientifically sound foundation.

Electrical stimulation of the brain to induce and modulate cerebral excitability and activity has a long-lasting history dating back for about few hundreds of years.[1,2] Initial approaches aimed to induce suprathreshold neuronal stimulation to generate neuronal activity and thus respective physiological, motor, or psychological effects. The breakthrough for noninvasive electrical brain stimulation in humans was in 1980, when it was shown that short-lasting, strong electrical impulses applied over the motor cortex can induce muscle twitches.[3]

Transcranial direct current stimulation (tDCS), as discussed here, qualitatively differs from those initial suprathreshold approaches. Transcranial direct current stimulation involves the subthreshold modulation of neuronal membrane potentials, stimulation that is too weak to induce neuronal activity independent from afferent input from other sources, but sufficient to alter both the excitability and spontaneous activity of neurons. Direct current (DC) stimulation in this sense was first described in the 1950s and explored in the subsequent years in animal models, but also in humans as noninvasive brain stimulation approach.[4] Probably mainly due to a paucity of tools for exploring the mechanisms of the effects of DC stimulation in humans at this time, DC stimulation in humans was nearly forgotten until the turn of the century. Awareness of DC stimulation was reawakened about 20 years ago by the publication of a handful of studies demonstrating physiological effects emerging both during stimulation and, perhaps most importantly, after stimulation, aftereffects that were shown to last for several minutes after the cessation of the intervention.[5–8] The relatively long-lasting and profound excitability aftereffects of tDCS increased the interest not only of basic neurophysiologists, but also of cognitive and behavioral neuroscientists and clinicians. As a result, over recent years, there have been numerous studies probing cognitive, behavioral, and clinical effects of tDCS.

In order to properly design studies, solid knowledge about the physiological foundation of the mechanisms of tDCS is essential. Recent studies in humans, animal, and cellular models, and also using computational modeling, have considerably increased our knowledge of the physiological underpinnings of tDCS. The aim of this review was therefore to give an overview of the main physiological mechanisms of tDCS, including effects at the microscopic, mesoscopic, and macroscopic scale, that is, cellular, regional, and whole-brain effects, to fully inform future studies of tDCS.

PHYSIOLOGICAL MECHANISMS OF tDCS: CELLULAR AND REGIONAL MECHANISMS

Acute Effects

Neurons are electrically excitable cells, and their function depends critically on the generation of action potentials. Action potentials are elicited when depolarization of the resting membrane reaches a certain potential threshold. The potential of the neuronal membrane is determined by afferent activity via electrical and chemical synapses and also by extrasynaptic substances, which activate specific ion channels and receptors. Direct current stimulation aims to directly modulate neuronal resting potentials and thus to alter the state of excitability, that is, the probability that afferent activity of a specific amplitude results in generation of an action potential. If a neuronal membrane is depolarized by a DC current, this means that less afferent activity is required to induce an action potential, and if it is hyperpolarized, neuronal excitability, and therefore spontaneous activity, is reduced. It is important to note that this mechanism of action is categorically different from suprathreshold stimulation, which elicits an action potential at an affected neuronal membrane, as it is the case for transcranial magnetic stimulation (TMS) or transcranial electric stimulation.[3]

Converging evidence exists at the whole-brain level that tDCS induces changes in cortical excitability and activity. For example, using the primary motor cortex (M1) as a model region, when the anode is placed over M1, tDCS enhances spontaneous activity and excitability. Conversely, when the cathode is placed over M1, spontaneous activity and excitability are reduced.[5,9] In the human model, these effects emerge within the first 4 seconds of stimulation, which induces no aftereffects.

However, this finding results either from recordings of multiple cells [9] or from TMS studies using motor-evoked potentials as an index of cortical excitability. This is therefore a net effect over many thousands of neurons; single neurons oriented differently in relation to the electrical field might respond in a different, even opposing, way.[10]

At the single neuron level, it is critical to be aware that an electrical current must always flow both into and out of a neuron, meaning that any given neuron is simultaneously depolarized and hyperpolarized.[11] This has important consequences for the effects of DC stimulation: the efficacy and directionality of the effects critically depend on the orientation of the neuron relative to the electrical field. When electrical current flow is perpendicular to neuronal orientation, the physiological effects of stimulation will be negligible, because antagonistic effects will take place in small neighbored membrane compartments, whereas if a current meets the long axis of a neuron, the efficacy of stimulation should be larger, because larger and more distant membrane compartments are homogeneously polarized.[12] Given that the neuronal soma and axon hillock are more sensitive than other regions of a neuron to elicit action potentials, it was suggested that the direction of polarization of these structures critically determines the directionality of DC stimulation effects,[9,13] although a contribution of apical dendrites and other structures is probable.[14] These directional effects also mean that neurons oriented at 180° to a given electrical field will be affected antagonistically by polarization. This has indeed been demonstrated.[15] It also explains why acute effects of tDCS on the motor cortex depend on the placement of the stimulation electrodes and are thus determined by the directionality of electrical current flow, with only specific electrode positions suited to induce cortical excitability alterations.[5,16]

Moreover, it was recently shown that the effects of tDCS critically depend on the orientation of the TMS coil used to elicit motor-evoked potentials,[16] suggesting that the effects of tDCS might be pathway-specific, a specificity observed in animal slice preparations.[15]

It is important to note that the change in resting membrane potentials due to tDCS at conventional intensity (1–2 mA) is relatively low; tDCS is proposed to alter neuronal membrane potential by approximately 0.2 to 0.5 mV.[17,18] Given that the resting membrane potential is approximately -70 mV, and the threshold for action potential initiation approximately -50 mV, this might at first glance seem like an insignificant change. It has been hypothesized, however, that the tDCS is effective, even given small effects on membrane potential at the single neuron level due to either amplification, caused by respective alterations of action potential generation in larger neuronal networks or modulation of action potential timing or both. Both of these mechanisms have been shown to take place in neuronal network stimulation with similar voltage changes.[19,20] It is perhaps not surprising then that most successful DC stimulation studies have been conducted in whole-brain or slice models, and respective spontaneous activity alterations have been described directly in animal models [9] and indirectly in humans via functional imaging approaches.[21–23] Studies investigating the effects of tDCS on single-neuron preparations have been much more sparse.

Converging evidence from experiments in humans suggests that the acute effects of DC stimulation are indeed driven by membrane potential alterations and not by changes of synaptic efficacy. Blocking voltage-gated ion channels, which are involved in neuronal membrane depolarization, prevents any impact of anodal tDCS on motor cortex excitability, whereas the blockade of glutamate receptors and the enhancement of [gamma]-aminobutyric acid (GABA) receptor activity had no effect on acute effects.[24] In line with these findings from pharmacological studies, TMS stimulation protocols designed to quantify changes in synaptic strength (eg, the paired pulse TMS protocol of short-interval intracortical inhibition) showed no evidence for synaptic changes during short-lasting tDCS, where no aftereffects are induced.[25]

Neuroplastic Effects

Whereas the acute effects of DC stimulation, induced by stimulation lasting few seconds, do not outlast the stimulation, longer-lasting stimulation induces aftereffects in the model of the primary motor cortex (effects on other cerebral areas will be discussed in later sections). These aftereffects can last from minutes up to more than 24 hours after the intervention, depending on the specific protocol used.[5–7,26–28] In general, the directionality of the aftereffects of tDCS is identical to that observed during stimulation: in standard protocols applied to the primary motor cortex, anodal tDCS enhances, whereas cathodal stimulation reduces, cortical excitability. Within certain limits, stronger and longer stimulation enhances the efficacy of these effects.

Similar effects to these were described in animal experiments in the 1960s. Here, DC stimulation of the sensorimotor cortex of the rat resulted in polarity-dependent effects lasting for at least 5 hours after stimulation.9 Assuming that these aftereffects are at least similar to long-term potentiation (LTP) and depression in animal models,29 most of these effects are in the range of early-phase plasticity. Early animal experiments showed that reverberating electrical circuits do not explain these changes in excitability, as these changes remained even after electrically silencing the brain, but conversely, excitability changes were prevented by blocking protein synthesis, strongly supporting a role for synaptic changes in these aftereffects.30,31 Evidence from the primary motor cortex model in humans, as well as animal models, shows that the glutamatergic synapse seems to be at least one of the drivers of DC stimulation–induced plasticity, especially regarding *N*-methyl-D-aspartate (NMDA) receptors. Pharmacological studies show that blockade of NMDA receptors prevents tDCS-induced excitability alterations, both for anodal and cathodal tDCS, whereas NMDA receptor agonists enhance anodal tDCS-induced excitability increases.24,32 These results from pharmacological studies are in accordance with TMS studies showing enhanced intracortical facilitation and reduced inhibition after anodal tDCS, and the reverse pattern of effects for cathodal tDCS.25 Furthermore, magnetic resonance spectroscopy (MRS) studies showed reduced glutamate after cathodal and at least trend-wise enhanced glutamate after anodal tDCS.33,34

Using MRS, reductions in GABA have also been observed after both anodal 34–36 and cathodal 34 stimulation to M1. This finding is in line with TMS studies probing GABA activity alterations after tDCS.25 Thus, it seems plausible that GABA reduction gates glutamatergic plasticity regarding the aftereffects of tDCS. In line with this hypothesis, it would also make sense that a certain degree of neuronal activity is necessary for plasticity induction via tDCS because this will be required to activate NMDA receptors.37

Activation of NMDA receptors leads to an influx of calcium ions (Ca^{2+}) into the cell. Intracellular [Ca^{2+}] controls the induction of both LTP and long-term depression (LTD) in animal models; low rates of [Ca^{2+}] influx foster LTD, and high rates of [Ca^{2+}] influx lead to LTP. Furthermore, [Ca^{2+}] influx as a result of synaptic activity is a continuous variable. Therefore, between the zones of [Ca^{2+}] influx sufficient to induce either LTP or LTD, a transition zone exists, in which [Ca^{2+}] influx induces no plasticity.29,38 In humans, blocking calcium channels prevents plasticity induction by tDCS.24 In first pilot studies, stimulation that is either too long (>=25 minutes) or too strong (>=2 mA) diminishes or converts the directionality of the commonly observed tDCS effects.26,28,39 These nonlinearities of tDCS effects are presumably due to changes in [Ca^{2+}] influx into the postsynaptic cells and can be explained entirely using this model. This model might furthermore explain the brain state dependency of tDCS at least to a certain degree,40 as the initial rates of activity within a brain region and hence the initial rate of [Ca^{2+}] influx into the postsynaptic cell will be dependent on the brain state at that time.

The above gives a summary of the hypothesized major mechanisms by which plasticity is induced by tDCS. However, a number of other neurotransmitters and neuromodulators, such as dopamine, adenosine, serotonin, and acetylcholine, might be involved.37,41 For example, it has been shown that blockade of dopamine and specific adenosine receptors prevents plasticity induction due to tDCS.42,43 Indeed, modulation of activity of different groups of neuromodulators has a clear but complex impact on tDCS effects.41

Thus, taken together, as far as is currently known, tDCS induces calcium-dependent plasticity at glutamatergic synapses, which is probably gated by the reduction of GABA activity (Fig. 1). In accordance with the neuromodulatory effects of tDCS, the degree and the directionality of induced plasticity are affected in a nonlinear way not only by stimulation protocol characteristics, but also by differences in individuals and brain states. Most of this knowledge gained in humans is derived from motor cortex experimentation; however, tDCS effects have been explored also for other areas, which we will explore here.

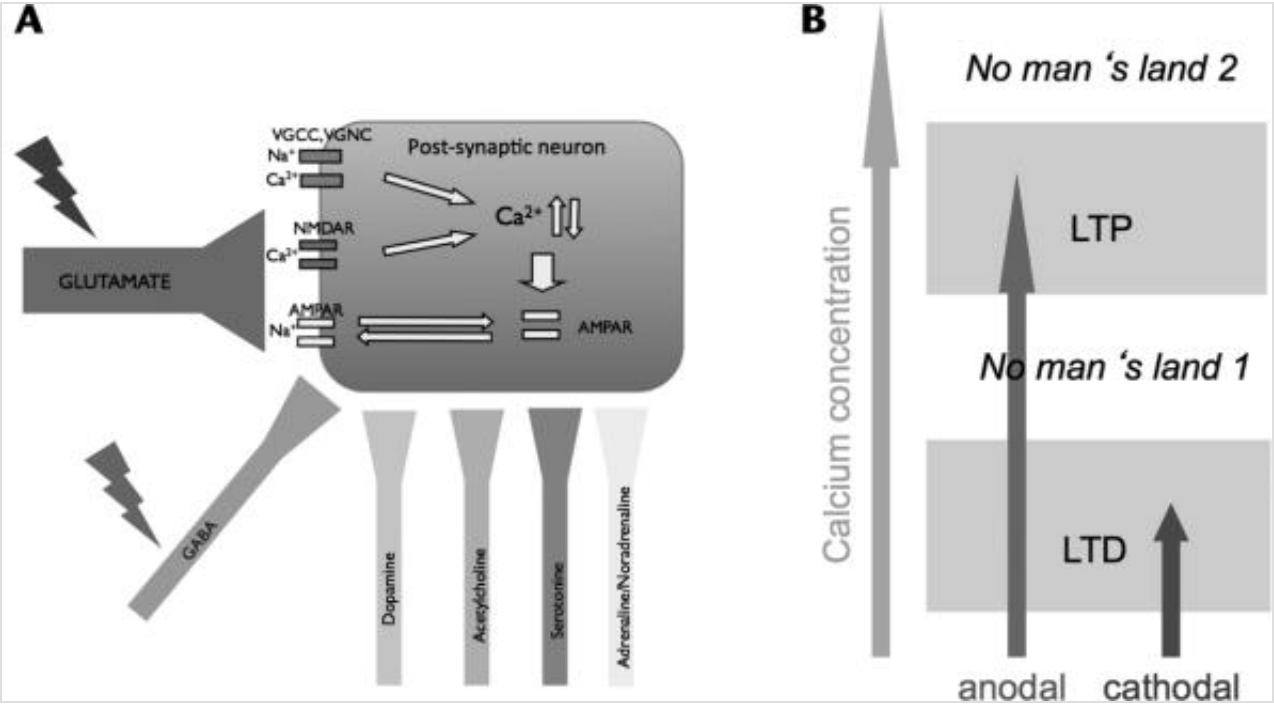

FIGURE 1. Presumed mechanism of neuroplastic effects of tDCS. A, It is assumed that tDCS induces plasticity of glutamatergic synapses and that reduction of GABA activity gates these effects. Neuromodulators such as dopamine and acetylcholine have a modulatory impact on tDCS effects. For glutamatergic synapses, by its membrane depolarizing or hyperpolarizing effects, tDCS will enhance or reduce calcium influx via NMDA receptors (NMDAR) and voltage-gated calcium channels (VGCC). Dependent on the alteration of intraneuronal calcium, enzyme cascades are activated, which insert glutamatergic AMPA receptors (AMPAR) into or remove them from the subsynaptic membrane, thus strengthening or weakening synaptic connections. B, The amount of intracellular calcium alteration determines if excitability-enhancing LTP or excitability-diminishing LTD takes place. Low intracellular calcium concentration, as presumably induced by cathodal tDCS, will result in LTD, whereas high calcium concentration, as induced by anodal tDCS, will result in LTP. Between these plasticity zones, and in case of calcium overflow, no man's lands do exist, where respective calcium concentrations do not result in clearly directed plasticity. This concept explains why intensified stimulation within certain limits results in stronger effects of stimulation, but also why specific protocols can result in a conversion of aftereffects (eg, from LTD- to LTP-like plasticity for intensified cathodal tDCS protocols 39).

REGIONAL EFFECTS OF tDCS ON NONMOTOR AREAS

During the last 2 decades, several studies have explored the impact of tDCS in the visual, somatosensory, auditory, and multisensory domains, although in our estimation approximately 80% of published tDCS studies focus on M1. It is vital to note, however, especially for more cognitive applications, that the methodologies and results from M1 studies are unlikely to be directly translatable to other cortical areas. Therefore, it is relevant to report the state of research about tDCS physiological effects on nonmotor cortex areas in its own right.

In general, most of the studies stimulating nonmotor areas targeted (i) the functional specialization of a given cortical area, for example, to examine the necessity and role of brain areas in perceptual functions in order to assess the causal link between neuronal functional specialization and perception/behavior; (ii) the flow of information between anatomically and/or functionally connected areas; or (iii) the region of interest was used as a model in order to clarify the working mechanisms of tDCS. The number of physiological tDCS studies in nonmotor areas is relatively limited; thus, the following sections will also include the effects of tDCS on elementary and complex sensory processes as a proxy (for a detailed review about prefrontal tDCS effects, refer to Sale et al,44 Wörsching et al,45 and Kuo and Nitsche 46).

Generally, tDCS has been demonstrated to alter visual, somatosensory, and auditory processing in a directionally specific manner, similar to M1. However, the effects are determined by several factors, including not only the stimulation parameters, but also the electrode positions and most importantly the type of task and the physiological state of the neuronal population before and during stimulation, the latter especially in case of task-related stimulation protocols. Pharmacological studies targeting nonmotor cortical areas during stimulation are not available; nevertheless, it is likely that the basic neuronal mechanisms of tDCS in these areas are the same as those in M1, although some area specifics might be relevant, such as the degree of dopaminergic drive.

Stimulation of the Primary Visual Cortex

It has been known for a long time that cortical areas other than M1 also undergo tDCS-induced neuroplastic changes, leading to both short- and long-term alterations of synaptic strength.47 Nevertheless, in early animal experiments, the DC effect applied, for example, over the visual cortex, was less pronounced than on M1, possibly due to the different cytoarchitecture of the cortices and different spatial orientations of the neurons.48 Human studies almost 40 years later confirmed these results, demonstrating that the tDCS aftereffects are relatively short-lasting in the visual areas compared with those of M1, using the same stimulation protocols.49,50

The reason for this difference is not simple to elucidate. Cortical areas vary with regard to factors influencing excitatory and inhibitory circuitries, and furthermore, differences in neuronal membrane properties, including receptor expression, between M1 and other cortices may also account for the altered responses to the application of tDCS. In addition to cell type and morphology, the extent to which neurons are affected by tDCS also depends on the orientation of the cells relative to the induced electric field, as discussed above. Furthermore, as well as stimulation parameters, the effects of stimulation are also strongly dependent on the functional state of the brain before or during the application, that is, whether the stimulation is given during rest or before/simultaneously with some motor or cognitive task.40

Studying the electrophysiological evidence for the efficacy of tDCS to alter excitability of the human primary visual cortex (V1), significant stimulation aftereffects were observed only on the visual-evoked potential (VEP) amplitudes evoked in response to low-contrast stimuli; when high-contrast stimuli were presented, tDCS did not modify VEP amplitudes.51 The excitability-diminishing effect of cathodal tDCS was significant immediately after and 10 minutes after the end of stimulation if the stimulation duration was sufficiently long (ie, 10–15 minutes). An increase of the N70 amplitude by anodal stimulation was significant only 10 minutes after the end of the 15-minute tDCS.51

Another study using a different visual stimulation and tDCS protocol (reference electrode over the anterior or posterior lower neck vs Cz in the previous study) reported that anodal tDCS reduced the P100 amplitude, whereas cathodal stimulation significantly increased it.52 Yet, from both studies, it is clear that the effect of tDCS depends on the contrast level of the visual stimuli; tDCS seems to have a greater effect on VEP amplitudes elicited by low-contrast stimuli than on high-contrast stimuli. Low-contrast visual stimuli recruit cortical neurons submaximally, thus allowing a more pronounced decrease or increase in neuronal recruitment by locally induced electrical stimulation. Furthermore, as it was mentioned previously, the position of the reference electrode might also play a role, resulting in antagonistic effects in both cases because of reversed electrical field orientation.

In accordance with the VEP study of Antal et al,51 tDCS elicited polarity-dependent effects on phosphene thresholds (PTs); later studies have reported that cathodal stimulation over V1 significantly increased PTs, probably due to diminished cortical excitability, whereas anodal stimulation resulted in the opposite effect,53,54 although a recent study found no effect of tDCS on PTs.55

The effectiveness of tDCS over visual areas has also been demonstrated by changes in contrast perception.49 Excitability-diminishing cathodal tDCS reduced contrast perception, whereas excitability-increasing anodal tDCS did not have any effect. In a later study, a longer stimulation duration (15 minutes) showed enhanced contrast sensitivity of central vision via anodal tDCS.50 Using a contrast discrimination task, anodal stimulation enhanced performance,56 whereas cathodal stimulation had no effect. Significant long-term effects were also observed in the central 2° to 4° of the visual field 4 weeks after 5 consecutive anodal tDCS sessions.54

Stimulation of the Primary Somatosensory and Auditory Cortex

There is also increasing evidence that tDCS modifies sensory processes other than vision, reflected by electrophysiological (somatosensory-evoked potentials [SEPs] and auditory-evoked potentials) and perceptual changes during and after stimulation. Generally, the studies conducted in the field of somatosensory or auditory processing show heterogeneous results, and for cognitive processes, the effects of stimulation depend on the kind of task under investigation.

Anodal tDCS of the primary somatosensory cortex resulted in a significant increase of the amplitudes of parietal (P25/N33, N33/P40) and frontal (P22/N30) components of SEPs following right median nerve stimulation, for up to 60 minutes after the end of stimulation. Other components (P14/N20, N20/P25, N18/P22) were unaffected by anodal tDCS, and cathodal tDCS had no effect on SEPs.57 Another study found a significant reduction of the N20 source amplitude after cathodal tDCS, whereas there was no effect after anodal stimulation.58 For the N30 component and high-frequency oscillations, no change in source activity was observed. These seemingly contradictory results can be at least partly explained by the different stimulation and experimental protocols used, such as different electrode sizes and stimulation durations.

Studies on somatosensory perception report results compatible with the observed physiological effects. Rogalewski and colleagues 59 explored the effect of tDCS applied to C4 electroencephalogram (EEG) position, on the ability of healthy humans to discriminate between vibratory stimuli of different frequencies applied to the left ring finger. They reported reduced performance during and after cathodal tDCS, whereas anodal tDCS had no effect. In another study, anodal tDCS applied to the S1 resulted in improved spatial acuity of the contralateral index finger.60

Anodal and cathodal tDCS can furthermore modify auditory cortex reactivity. In this modality, the number of studies is more limited; however, the bidirectional polarity-dependent effects of tDCS are more consistent. Auditory-evoked potentials are differentially modulated as a function of site of stimulation.61 Whereas anodal tDCS over the temporal cortex increased auditory P50 amplitudes, cathodal tDCS over the temporoparietal cortex induced larger N1 amplitudes. In a pilot study, auditory sensory processing as indexed by the mismatch negativity (MMN) in event-related potentials was recorded before and after tDCS. Twenty-minute anodal tDCS using 2 mA over the temporal lobe increased MMN.62 In a follow-up study performed by the same group, the interacting effects of both anodal and cathodal tDCS on MMN-indexed auditory pitch discrimination were studied. In a randomized, double-blind design, MMN was assessed before and after tDCS (2 mA, 20 minutes) in 2 separate sessions, one involving sham stimulation followed by anodal stimulation and one involving cathodal stimulation followed by anodal stimulation.63 Results demonstrated that anodal tDCS over the temporal cortex increased MMN-indexed auditory detection of pitch deviance. Cathodal tDCS decreased auditory discrimination as it was expected; however, the subsequent anodal tDCS did not significantly alter MMN amplitudes.

In terms of perception, Loui et al 64 found cathodal tDCS reduced auditory pitch matching ability when stimulation was applied over the inferior frontal and superior temporal areas. In another study, anodal tDCS over the auditory cortex improved temporal processing, whereas cathodal stimulation resulted in reversed effects.65 Interestingly, multisensory perception can also be altered by tDCS of occipital and temporal areas using a sound-induced flash illusion task.66 The perceptual fission of a single flash due to multiple beeps was enhanced by anodal tDCS of the temporal and reduced by anodal tDCS of the occipital cortex. Cathodal tDCS of the same areas resulted in opposite effects.

Stimulation of Higher-Order Sensory and Multimodal Association Cortices

Several studies reported effects of tDCS when nonmotor and nonprimary visual areas were stimulated; however, again, the magnitude of these effects critically depends on the task characteristics, the state of the cortex before and during stimulation, and related physiological mechanisms. The combination of TMS and EEG was very useful to explore local and global cortical excitability modulation during and after active and sham tDCS. Using this method, a diffuse rise of cortical excitability occurred, both during and after anodal tDCS over the right PPC; an increased local mean field power in parietal and frontal clusters was observed bilaterally, whereas no difference was found in the temporal clusters.67

A number of studies have demonstrated the ability of tDCS to alter oscillatory cortical activity. Zaehle et al 68 showed that both anodal tDCS and cathodal tDCS administered over the left DLPFC were able to induce changes in working memory performance and that these changes corresponded to alterations in oscillatory theta and alpha power recorded simultaneously by EEG. Hoy et al 69 report increased performance of a 2-back working memory task following anodal tDCS over the left DLPFC in a group of schizophrenia patients, which was associated with enhanced gamma event-related synchronization in this area.

With regard to the type of the task, it is suggested that excitability-diminishing cathodal tDCS might have a "noise-reducing" effect in conditions in which distractors are introduced, whereas anodal stimulation is implied to enhance performance by increased neuronal activation in conditions without distractors. In accordance, stimulation of the motion-sensitive area V5 had distinct effects on motion perception, dependent on the specific kind of task; using a moving dot paradigm without distractors, anodal stimulation improved performance, whereas cathodal stimulation impaired it.70 In the otherwise identical task, however, with visual distractors, the effects of tDCS were reversed.

Transcranial direct current stimulation has also been shown to modify perception of more complex stimuli; Varga and colleagues 71 described a reduced face aftereffect induced by cathodal tDCS of right lateral parietotemporal areas, known to be involved in face perception. Furthermore, tDCS seems to be an efficient tool to alter visual working memory performance in healthy humans. The effects have been most extensively tested for frontal, parietal, and temporal cortex stimulation, with the aim to improve visual/sensory formation/performance. The results of these studies show that tDCS can be used in the evaluation of the contribution of specific areas to task performance and that stimulation can have a positive effect on performance. However, the effects of stimulation show strong heterogeneity, and it will be important for future studies to reproduce previous results and to explore the factors influencing the beneficial effects of stimulation to a larger degree. Anodal stimulation might have a general beneficial effect, at least in most of the studies. For example, Flöel et al 72 demonstrated that anodal tDCS over the right temporoparietal cortex improved memory consolidation in a task involving memorizing an object's location in a natural surrounding. Bolognini et al 73 explored the effects of anodal tDCS applied to the posterior parietal cortex on multisensory field exploration. Clark et al 74 explored the impact of tDCS on identification of concealed objects stimulating the right inferior frontal and right parietal areas. Anodal stimulation resulted in improved performance in a dosage-dependent manner, and performance increase was larger for naive as compared with experienced volunteers.74,75 In these studies, stimulation of the right parietal cortex improved visual exploration and orienting, when compared with sham stimulation, supporting the causal involvement of this area in visual attentional processes. The stimulation might be hemisphere dependent; Chi et al 76 applied bilateral stimulation of the anterior temporal lobes during encoding and retrieval of a visual memory task. They found an improvement in visual memory using right anodal–left cathodal stimulation, but not under reversed polarity or sham stimulation conditions.

In summary, the number of available studies assessing the effects of stimulation in nonmotor areas is still significantly fewer compared with the number of studies stimulating the motor cortex, and the results are more heterogeneous. The reasons for the relatively high variability in the nonmotor domain compared with the motor domain are far from being completely understood.77–81 In the future, more efforts should be made to enhance our understanding of the reasons behind the reported heterogeneous effects. Further studies systematically probing stimulation parameters might be needed to explore the reasons for the inconsistencies among studies. Beyond basic neuroscience research, these efforts will be relevant for the application of these stimulation techniques to neurological diseases accompanied by visual and sensory disturbances.

NETWORK-LEVEL EFFECTS

As discussed previously, the effects of tDCS applied to a single brain region on cortical excitability and neurophysiological changes within that brain region have been relatively well studied, particularly for the motor system. However, it is now increasingly well understood that brain regions do not act in isolation, and rather, many functions of the brain are underpinned by functional networks, which include multiple anatomically distant but functionally interconnected regions.

Here, we will concentrate largely on the motor network, as the majority of tDCS studies performed have used M1 as a target, but will include evidence from other regions as appropriate.

The Task-Activated Motor Network

The motor network consists of a number of anatomical regions, including the primary motor cortices bilaterally, premotor cortices, supplementary motor area, and some more frontal and parietal cortical areas. In many imaging studies, only the cortical areas are routinely considered; it is, however, important to highlight that the motor network will also include subcortical regions including the thalamus and basal ganglia, as well as the cerebellum.

The motor network can be investigated by using functional magnetic resonance imaging (fMRI) to investigate brain regions that are active during performance of a motor task. Direct comparisons between studies of functional changes during task performance are difficult because of the variety in tasks performed, stimulation parameters, and analysis methods.

However, some overall conclusions can be drawn. The aftereffects of tDCS on brain activity in response to a task are not limited to the stimulated region; rather, they may be seen across the whole motor network. Whereas some studies have seen only marginal effects [82,83] of tDCS, a number of studies have demonstrated a significant increase in activity within closely functionally connected regions within the stimulated hemisphere in response to anodal tDCS.[84–88] Cathodal tDCS, conversely, has been relatively less studied but has been demonstrated to increase activity within the contralateral M1.[88,89] This consistent finding has been suggested to reflect a reduction in the interhemispheric inhibition exerted on the contralateral M1 by the reduction in excitability in the M1 ipsilateral to stimulation.

Transcranial direct current stimulation has also consistently been shown to modulate functional connectivity between regions within the motor network active during the motor task. One early study demonstrated no change in functional connectivity with anodal tDCS but a significant increase in task-related functional connectivity with cathodal tDCS during a serial reaction time task within the motor network.[88]

It is possible to perform network connectivity analyses using techniques other than fMRI. An EEG study using a graph theory approach showed a significant increase in functional connectivity between M1 and the premotor and sensorimotor of the stimulated hemisphere during activity in the gamma (60–90 Hz) band after anodal tDCS.[90]

The Resting-State Motor Network

Using a task in fMRI raises inherent problems, not least that the fMRI signal is directly related to behavior, and therefore the changes in fMRI activity directly caused by an intervention such as tDCS, which changes response times or learning rates, cannot be easily disentangled from fMRI activity changes resulting from a change in behavior. One way to remove the effects of behavioral difference is to study functional connectivity in the resting state. Here, subjects are placed at rest in the MRI scanner, and fMRI data are acquired in the absence of a task. When analyzed, a number of so-called “Resting State Networks” are visible across the brain, the majority of which are highly anatomically similar to the task-related functional networks described above. Of particular interest, perhaps, is the default mode network (DMN) which is consistently observed in resting fMRI studies and is comprised of a network of brain regions that show task-negative rather than task-positive activity in response to a range of tasks. Although questions remain as to the physiological basis of these networks, the use of resting state fMRI has increased exponentially over the last decade as the benefits of ease of acquisition and sensitivity of the measures have become evident.

As with task-related analysis above, a plethora of analysis approaches have been used to analyze the effects of tDCS on resting connectivity making comparison between studies difficult. However, tDCS has been shown to have significant effects on resting functional connectivity. Resting state network analysis approaches have shown a significant increase in network strength after anodal tDCS 36,91 and an increase in functional connectivity both between key motor network nodes and in default mode network strength after cathodal tDCS.92

Other studies have used other analysis approaches. Using a graph theory approach, local and distant M1 connectivity was explored in a series of studies. Anodal tDCS enhanced long-distance functional connectivity of M1.93 Further work suggested an increase in connectivity between M1 and closely functionally connected regions such as the premotor cortex,94 and further that anodal tDCS increased coupling between the left (stimulated) M1 and the ipsilateral thalamus.95 Eigenvector centrality analysis also showed a pattern of increased connectivity after M1 anodal tDCS in parietal and frontal regions known to be functionally connected to M1,96 although a subsequent study using a seed-based analysis showed only marginal changes,97 and a study using a correlational approach showed a decrease in functional connectivity after anodal tDCS.82

There have been fewer studies examining the resting effects of cathodal tDCS to M1. Cathodal tDCS boosted local M1 connectedness,93 and a further study showed decreases between the M1 and contralateral putamen after cathodal tDCS.95 Outside the motor network, blood flow changes resultant from tDCS to the left DLPFC have been studied using arterial spin labeling. This study showed complex widespread perfusion changes, both during and after both anodal and cathodal tDCS.22

Physiological Mechanisms Underpinning Network-Level Changes

As described in the preceding section, while there is evidence that tDCS has significant effects not only on the directly stimulated brain region but also on functionally connected regions, it is difficult to form a coherent from the patterns described above. At least in part this is due to the different analysis approaches used to study resting connectivity. However, by understanding the physiological mechanisms that underpin network-level functional connectivity, it may be that we can at least present a coherent hypothesis to be tested in further studies.

Both animal models and computational approaches have suggested that changes in the low-frequency long-range network connectivity patterns observed as resting state networks are reflected in modulation of local, higher-frequency activity, particularly in the gamma frequency band.98 Gamma frequency activity is driven, at least in part, by local inhibitory activity,99,100 suggesting an overarching hypothesis. Local M1 GABA concentration as assessed by MRS has been shown to predict functional network strength,36,91 and decreasing local GABA via tDCS leads to an increase in network strength.36 It may be, therefore, that gamma oscillatory activity is the physiological mechanism to explain these findings; tDCS decreases local GABA, which in turn increases local firing rates, leading to an increase in local synaptic plasticity. This decrease in GABA and increase in firing rates lead to an increase in local gamma-band oscillatory activity, which will then lead to an increase in functional connectivity in highly connected regions. Although speculative, this hypothesis is supported by the finding that anodal tDCS specifically leads to an increase in functional coupling with closely connected regions in the gamma band 90 and that tDCS leads to an increase in gamma activity, as assessed by magnetoencephalography (MEG).101

CONCLUSIONS

Transcranial direct current stimulation is showing increasing promise as a tool for neuroscientific research and as a potential adjunct therapy for a range of neurological and psychiatric conditions. However, until its underlying physiological mechanisms are understood, it is likely that its potential will be inherently limited. Here, we have reviewed the current understanding of the cellular, synaptic, and network-level effects of tDCS, concentrating primarily on the motor network, but including nonmotor regions as well.

It is evident that, whereas the basic physiological effects of tDCS to M1 are well understood and well replicated, the task of translating these to other cortical regions and inferring complex cognitive effects from the known basic physiological changes still largely remains incomplete. There may be many reasons for this, but not least the near-infinite parameter space within which brain stimulation operates. Electrode position and size, current intensity and duration, target site, and neural state during stimulation will all likely have a significant influence on the cortical effects induced by tDCS.

Moreover, tDCS effects have been shown to be interindividually, as well as intraindividually, variable,45,102,103 although the amount of variability differs between studies 26 and is a shared feature of noninvasive brain stimulation tools in general.104 This variability is also a probable reason for heterogeneous replication rates between studies. Different sources of variability, which include intrinsic features of neuromodulatory interventions, such as state dependency, and also dependency of intervention effects from neurotransmitter and receptor distribution and cortical architecture, including brain folding,105 contribute to a greater or lesser extent. Methodological aspects, such as sample size, applied methods, and methodological rigor, may also play a role. These and other factors should be taken into account for planning and conduction of experiments in the field of neuromodulation. Multimodal approaches might be relevant to enhance our understanding about the mechanisms and effects of respective interventions to a larger degree.106

The question then might be: How can we progress with our exploration of tDCS as a putative therapeutic intervention? Modeling approaches may present a useful method by which to narrow the likely options to be explored, although these may have their own limitations. Further study of the mechanisms underpinning commonly used tDCS montages, both within and outside the motor system, will help to narrow our field of exploration, and it is vital that the physiological effects of a given set of parameters are not simply assumed but rather tested directly. By summarizing our current understanding of the field, we hope that this chapter will provide readers with a framework in which to directly test the physiological changes induced by their proposed stimulation approach, as a first step to assessing its potential clinical utility. In this way, the significant potential of tDCS may be realized in both neuroscientific and clinical applications.

REFERENCES

1. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clin Neurophysiol*. 2003;114:589–595. [Context Link]

2. Guleyupoglu B, Schestatsky P, Edwards D, et al. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. *J Neurosci Methods*. 2013;219:297–311. Bibliographic Links | [Context Link]

3. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature*. 1980;285:227. Bibliographic Links | [Context Link]

4. Nitsche MA, Liebetanz D, Antal A, et al. Modulation of cortical excitability by weak direct current stimulation —technical, safety and functional aspects. *Suppl Clin Neurophysiol*. 2003;56:255–276. Bibliographic Links | [Context Link]

5. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527:633–639. Bibliographic Links | [Context Link]

6. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. 2001;57:1899–1901. Ovid Full Text | Bibliographic Links | [Context Link]

7. Nitsche MA, Nitsche MS, Klein CC, et al. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin Neurophysiol*. 2003;114:600–604. [Context Link]

8. Priori A, Berardelli A, Rona S, et al. Polarization of the human motor cortex through the scalp. *Neuroreport*. 1998;9:2257–2260. Ovid Full Text | Bibliographic Links | [Context Link]

9. Bindman LJ, Lippold O, Redfearn J. 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*. 1964;172:369–382. [Context Link]

10. Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol*. 1965;28:166–185. Bibliographic Links | [Context Link]

11. Bikson M, Inoue M, Akiyama H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol*. 2004;557:175–190. Bibliographic Links | [Context Link]

12. Jefferys J. Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. *J Physiol*. 1981;319:143–152. Bibliographic Links | [Context Link]

13. Radman T, Su Y, An JH, et al. Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects. *J Neurosci*. 2007;27:3030–3036. Bibliographic Links | [Context Link]

14. Rahman A, Reato D, Arlotti M, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J Physiol*. 2013;591:2563–2578. Bibliographic Links | [Context Link]

15. Kabakov AY, Muller PA, Pascual-Leone A, et al. Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *J Neurophysiol*. 2012;107:1881–1889. Bibliographic Links | [Context Link]

16. Rawji V, Ciocca M, Zacharia A, et al. tDCS changes in motor excitability are specific to orientation of current flow. *Brain Stimul*. 2018;11:289–298. Bibliographic Links | [Context Link]

17. Opitz A, Falchier A, Yan CG, et al. Spatiotemporal structure of intracranial electric fields induced by transcranial electric stimulation in humans and nonhuman primates. *Sci Rep*. 2016;6:31236. Bibliographic Links | [Context Link]

18. Radman T, Ramos RL, Brumberg JC, et al. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimul*. 2009;2:215–228. Bibliographic Links | [Context Link]

19. Anastassiou CA, Montgomery SM, Barahona M, et al. The effect of spatially inhomogeneous extracellular electric fields on neurons. *J Neurosci*. 2010;30:1925–1936. Bibliographic Links | [Context Link]

20. Carandini M, Ferster D. Membrane potential and firing rate in cat primary visual cortex. *J Neurosci*. 2000;20:470–484. Bibliographic Links | [Context Link]

21. Lang N, Siebner HR, Ward NS, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci*. 2005;22:495–504. [Context Link]

22. Stagg CJ, Lin RL, Mezue M, et al. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. *J Neurosci*. 2013;33:11425–11431. Bibliographic Links | [Context Link]

23. Zheng X, Alsop DC, Schlaug G. Effects of transcranial direct current stimulation (tDCS) on human regional cerebral blood flow. *Neuroimage*. 2011;58:26–33. Bibliographic Links | [Context Link]

24. Nitsche MA, Fricke K, Henschke U, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol*. 2003;553:293–301. [Context Link]

25. Nitsche MA, Seeber A, Frommann K, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol*. 2005;568:291–303. Bibliographic Links | [Context Link]

26. Jamil A, Batsikadze G, Kuo HI, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *J Physiol*. 2017;595:1273–1288. Bibliographic Links | [Context Link]

27. Monte-Silva K, Kuo MF, Liebetanz D, et al. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). *J Neurophysiol*. 2010;103:1735–1740. [Context Link]

28. Monte-Silva K, Kuo MF, Hessenthaler S, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul*. 2013;6:424–432. Bibliographic Links | [Context Link]

29. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron*. 2004;44:5–21. Bibliographic Links | [Context Link]

30. Gartside IB. Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: role of protein synthesis. *Nature*. 1968;220:383–384. Bibliographic Links | [Context Link]

31. Gartside IB. Mechanisms of sustained increases of firing rate of neurons in the rat cerebral cortex after polarization: reverberating circuits or modification of synaptic conductance? *Nature*. 1968;220:382–383. Bibliographic Links | [Context Link]

32. Nitsche MA, Jaussi W, Liebetanz D, et al. Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology*. 2004;29:1573–1578. Bibliographic Links | [Context Link]

33. Clark VP, Coffman BA, Trumbo MC, et al. Transcranial direct current stimulation (tDCS) produces localized and specific alterations in neurochemistry: a ^{1}H magnetic resonance spectroscopy study. *Neurosci Lett*. 2011;500:67–71. Bibliographic Links | [Context Link]

34. Stagg CJ, Best JG, Stephenson MC, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J Neurosci*. 2009;29:5202–5206. Bibliographic Links | [Context Link]

35. Stagg CJ, Bestmann S, Constantinescu AO, et al. Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. *J Physiol*. 2011;589:5845–5855. Bibliographic Links | [Context Link]

36. Bachtiar V, Near J, Johansen-Berg H, et al. Modulation of GABA and resting state functional connectivity by transcranial direct current stimulation. *Elife*. 2015;4:e08789. [Context Link]

37. Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*. 2010;66:198–204. [Context Link]

38. Lisman JE. Three Ca^{2+} levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. *J Physiol*. 2001;532:285. Bibliographic Links | [Context Link]

39. Batsikadze G, Moliadze V, Paulus W, et al. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol*. 2013;591:1987–2000. [Context Link]

40. Antal A, Terney D, Poreisz C, et al. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *Eur J Neurosci*. 2007;26:2687–2691. [Context Link]

41. Nitsche MA, Müller-Dahlhaus F, Paulus W, et al. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. *J Physiol*. 2012;590:4641–4662. Bibliographic Links | [Context Link]

42. Márquez-Ruiz J, Leal-Campanario R, Sánchez-Campusano R, et al. Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proc Natl Acad Sci U S A*. 2012;109:6710–6715. Bibliographic Links | [Context Link]

43. Nitsche MA, Lampe C, Antal A, et al. Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *Eur J Neurosci*. 2006;23:1651–1657. [Context Link]

44. Sale MV, Mattingley JB, Zalesky A, et al. Imaging human brain networks to improve the clinical efficacy of non-invasive brain stimulation. *Neurosci Biobehav Rev*. 2015;57:187–198. Bibliographic Links | [Context Link]

45. Wörsching J, Padberg F, Ertl-Wagner B, et al. Imaging transcranial direct current stimulation (tDCS) of the prefrontal cortex—correlation or causality in stimulation-mediated effects? *Neurosci Biobehav Rev*. 2016;69:333–356. Bibliographic Links | [Context Link]

46. Kuo MF, Nitsche MA. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. *Neurosci Bull*. 2015;31:198–206. Bibliographic Links | [Context Link]

47. Sherman SM, Spear PD. Organization of visual pathways in normal and visually deprived cats. *Physiol Rev*. 1982;62:738–855. Bibliographic Links | [Context Link]

48. Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical D-C currents on cortical neuronal activity. *Exp Neurol*. 1962;5:436–452. Bibliographic Links | [Context Link]

49. Antal A, Nitsche M, Paulus W. External modulation of visual perception in humans. *Neuroreport*. 2001;12:3553–3555. Ovid Full Text | Bibliographic Links | [Context Link]

50. Kraft A, Kehrer S, Hagendorf H, et al. Hemifield effects of spatial attention in early human visual cortex. *Eur J Neurosci*. 2011;33:2349–2358. [Context Link]

51. Antal A, Kincses TZ, Nitsche MA, et al. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Invest Ophthalmol Vis Sci*. 2004;45:702–707. Bibliographic Links | [Context Link]

52. Accornero N, Li Voti P, La Riccia M, et al. Visual evoked potentials modulation during direct current cortical polarization. *Exp Brain Res*. 2007;178:261–266. Bibliographic Links | [Context Link]

53. Antal A, Kincses T, Nitsche M, et al. Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Exp Brain Res*. 2003;150:375–378. Bibliographic Links | [Context Link]

54. Behrens JR, Kraft A, Irlbacher K, et al. Long-lasting enhancement of visual perception with repetitive noninvasive transcranial direct current stimulation. *Front Cell Neurosci*. 2017;11:238. [Context Link]

55. Brückner S, Kammer T. No modulation of visual cortex excitability by transcranial direct current stimulation. *PLoS One*. 2016;11:e0167697. Bibliographic Links | [Context Link]

56. Olma MC, Kraft A, Roehmel J, et al. Excitability changes in the visual cortex quantified with signal detection analysis. *Restor Neurol Neurosci*. 2011;29:453–461. Bibliographic Links | [Context Link]

57. Matsunaga K, Nitsche MA, Tsuji S, et al. Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol*. 2004;115:456–460. Bibliographic Links | [Context Link]

58. Dieckhöfer A, Waberski TD, Nitsche M, et al. Transcranial direct current stimulation applied over the somatosensory cortex—differential effect on low and high frequency SEPs. *Clin Neurophysiol*. 2006;117:2221–2227. Bibliographic Links | [Context Link]

59. Rogalewski A, Breitenstein C, Nitsche MA, et al. Transcranial direct current stimulation disrupts tactile perception. *Eur J Neurosci*. 2004;20:313–316. [Context Link]

60. Ragert P, Vandermeeren Y, Camus M, et al. Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clin Neurophysiol*. 2008;119:805–811. [Context Link]

61. Zaehle T, Beretta M, Jäncke L, et al. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Exp Brain Res*. 2011;215:135–140. Bibliographic Links | [Context Link]

62. Impey D, Knott V. Effect of transcranial direct current stimulation (tDCS) on MMN-indexed auditory discrimination: a pilot study. *J Neural Transm (Vienna)*. 2015;122:1175–85. Bibliographic Links | [Context Link]

63. Impey D, de la Salle S, Knott V. Assessment of anodal and cathodal transcranial direct current stimulation (tDCS) on MMN-indexed auditory sensory processing. *Brain Cogn*. 2016;105:46–54. Bibliographic Links | [Context Link]

64. Loui P, Hohmann A, Schlaug G. Inducing disorders in pitch perception and production: a reverse-engineering approach. *Proc Meet Acoust*. 2010;9:50002. [Context Link]

65. Ladeira A, Fregni F, Campanhã C, et al. Polarity-dependent transcranial direct current stimulation effects on central auditory processing. *PLoS One*. 2011;6:e25399. Bibliographic Links | [Context Link]

66. Bolognini N, Rossetti A, Casati C, et al. Neuromodulation of multisensory perception: a tDCS study of the sound-induced flash illusion. *Neuropsychologia*. 2011;49:231–237. Bibliographic Links | [Context Link]

67. Romero Lauro LJ, Rosanova M, Mattavelli G, et al. TDCS increases cortical excitability: direct evidence from TMS-EEG. *Cortex*. 2014;58:99–111. Bibliographic Links | [Context Link]

68. Zaehle T, Sandmann P, Thorne JD, et al. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. *BMC Neurosci*. 2011;12:2. Bibliographic Links | [Context Link]

69. Hoy KE, Bailey NW, Arnold SL, et al. The effect of transcranial direct current stimulation on gamma activity and working memory in schizophrenia. *Psychiatry Res*. 2015;228:191–196. Bibliographic Links | [Context Link]

70. Antal A, Nitsche M, Kruse W, et al. Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *J Cogn Neurosci*. 2004;16:521–527. Bibliographic Links | [Context Link]

71. Varga ET, Elif K, Antal A, et al. Cathodal transcranial direct current stimulation over the parietal cortex modifies facial gender adaptation. *Ideggyogy Sz*. 2007;60:474–479. Bibliographic Links | [Context Link]

72. Flöel A, Suttorp W, Kohl O, et al. Non-invasive brain stimulation improves object-location learning in the elderly. *Neurobiol Aging*. 2012;33:1682–1689. Bibliographic Links | [Context Link]

73. Bolognini N, Fregni F, Casati C, et al. Brain polarization of parietal cortex augments training-induced improvement of visual exploratory and attentional skills. *Brain Res*. 2010;1349:76–89. Bibliographic Links | [Context Link]

74. Clark VP, Coffman BA, Mayer AR, et al. TDCS guided using fMRI significantly accelerates learning to identify concealed objects. *Neuroimage*. 2012;59:117–128. Bibliographic Links | [Context Link]

75. Bullard LM, Browning ES, Clark VP, et al. Transcranial direct current stimulation's effect on novice versus experienced learning. *Exp Brain Res*. 2011;213:9–14. Bibliographic Links | [Context Link]

76. Chi RP, Fregni F, Snyder AW. Visual memory improved by non-invasive brain stimulation. *Brain Res*. 2010;1353:168–175. Bibliographic Links | [Context Link]

77. Buch ER, Santarnecchi E, Antal A, et al. Effects of tDCS on motor learning and memory formation: a consensus and critical position paper. *Clin Neurophysiol*. 2017;128:589–603. Bibliographic Links | [Context Link]

78. Kim JH, Kim DW, Chang WH, et al. Inconsistent outcomes of transcranial direct current stimulation (tDCS) may be originated from the anatomical differences among individuals: a simulation study using individual MRI data. *Conf Proc IEEE Eng Med Biol Soc*. 2013;2013:823–825. Bibliographic Links | [Context Link]

79. Laakso I, Tanaka S, Koyama S, et al. Inter-subject variability in electric fields of motor cortical tDCS. *Brain Stimul*. 2015;8:906–913. Bibliographic Links | [Context Link]

80. Madhavan S, Sriraman A, Freels S. Reliability and variability of tDCS induced changes in the lower limb motor cortex. *Brain Sci*. 2016;6:E26. [Context Link]

81. Worsching J, Padberg F, Helbich K, et al. Test-retest reliability of prefrontal transcranial direct current stimulation (tDCS) effects on functional MRI connectivity in healthy subjects. *Neuroimage*. 2017;155:187–201. Bibliographic Links | [Context Link]

82. Alon G, Roys SR, Gullapalli RP, et al. Non-invasive electrical stimulation of the brain (ESB) modifies the resting-state network connectivity of the primary motor cortex: a proof of concept fMRI study. *Brain Res*. 2011;1403:37–44. Bibliographic Links | [Context Link]

83. Antal A, Polanía R, Schmidt-Samoa C, et al. Transcranial direct current stimulation over the primary motor cortex during fMRI. *Neuroimage*. 2011;55:590–596. Bibliographic Links | [Context Link]

84. Jang SH, Ahn SH, Byun WM. The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. *Neurosci Lett*. 2009;460:117–120. Bibliographic Links | [Context Link]

85. Kwon YH, Jang SH. The enhanced cortical activation induced by transcranial direct current stimulation during hand movements. *Neurosci Lett*. 2011;492:105–108. Bibliographic Links | [Context Link]

86. Kwon YH, Ko MH, Ahn SH, et al. Primary motor cortex activation by transcranial direct current stimulation in the human brain. *Neurosci Lett*. 2008;435:56–59. Bibliographic Links | [Context Link]

87. Lindenberg R, Nachtigall L, Meinzer M, et al. Differential effects of dual and unihemispheric motor cortex stimulation in older adults. *J Neurosci*. 2013;33:9176–9183. Bibliographic Links | [Context Link]

88. Stagg CJ, O'Shea J, Kincses ZT, et al. Modulation of movement-associated cortical activation by transcranial direct current stimulation. *Eur J Neurosci*. 2009;30:1412–1423. [Context Link]

89. Stagg CJ, Bachtiar V, O'Shea J, et al. Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke. *Brain*. 2012;135:276–284. Bibliographic Links | [Context Link]

90. Polanía R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum Brain Mapp*. 2011;32:1236–1249. Bibliographic Links | [Context Link]

91. Stagg CJ, Bachtiar V, Amadi U, et al. Local GABA concentration is related to network-level resting functional connectivity. *Elife*. 2014;3:e01465. [Context Link]

92. Amadi U, Ilie AS, Johansen-Berg H, et al. Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. *Neuroimage*. 2014;88:155–161. Bibliographic Links | [Context Link]

93. Polanía R, Paulus W, Nitsche MA. Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation. *PLoS ONE*. 2012;7:e30971. Bibliographic Links | [Context Link]

94. Polanía R, Paulus W, Antal A, et al. Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage*. 2011;54:2287–2296. Bibliographic Links | [Context Link]

95. Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp*. 2012;33:2499–2508. Bibliographic Links | [Context Link]

96. Sehm B, Schafer A, Kipping J, et al. Dynamic modulation of intrinsic functional connectivity by transcranial direct current stimulation. *J Neurophysiol*. 2012;108:3253–3263. Bibliographic Links | [Context Link]

97. Sehm B, Kipping J, Schäfer A, et al. A comparison between uni- and bilateral tDCS effects on functional connectivity of the human motor cortex. *Front Hum Neurosci*. 2013;7:183. [Context Link]

98. Cabral J, Hugues E, Sporns O, et al. Role of local network oscillations in resting-state functional connectivity. *Neuroimage*. 2011;57:130–139. Bibliographic Links | [Context Link]

99. Hall SD, Stanford IM, Yamawaki N, et al. The role of GABAergic modulation in motor function related neuronal network activity. *Neuroimage*. 2011;56:1506–1510. Bibliographic Links | [Context Link]

100. Nowak M, Hinson E, van Ede F, et al. Driving human motor cortical oscillations leads to behaviorally relevant changes in local GABAA inhibition: a tACS-TMS Study. *J Neurosci*. 2017;37:4481–4492. Bibliographic Links | [Context Link]

101. Venkatakrishnan A, Contreras-Vidal JL, Sandrini M, et al. Independent component analysis of resting brain activity reveals transient modulation of local cortical processing by transcranial direct current stimulation. *Conf*

Proc IEEE Eng Med Biol Soc. 2011;2011:8102–8105. Bibliographic Links | [Context Link]

102. Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. *Brain Stimul*. 2015;8:1130–1137. Bibliographic Links | [Context Link]

103. Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimul*. 2014;7:468–475. Bibliographic Links | [Context Link]

104. López-Alonso V, Cheeran B, Río-Rodríguez D, et al. Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul*. 2014;7:372–380. Bibliographic Links | [Context Link]

105. Reato D, Rahman A, Bikson M, et al. Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. *Front Hum Neurosci*. 2013;7:687. [Context Link]

106. Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci*. 2018;21:174–187. Bibliographic Links | [Context Link]

Key Words: functional connectivity; neuroplasticity; noninvasive brain stimulation

IMAGE GALLERY

Select All

Export Selected to PowerPoint

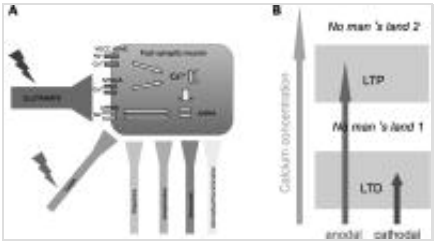

Figure 1

Back to Top