

Chapter 5

Transcranial Direct Current Stimulation Modulation of Neurophysiological Functional Outcomes: Neurophysiological Principles and Rationale



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Introduction

Exploring the physiological effects of tDCS is of utmost importance for the field due to numerous reasons. First, physiological measures allow the quantification of basic effects of tDCS, and thus help to develop and tailor stimulation protocols based on parameters like magnitude, duration, and focality of effects. Second, combination of tDCS with physiological measures can help to improve mechanistic understanding of neuroplasticity of the human brain. Third, physiologically defined tDCS protocols are relevant to develop targeted and rationally based stimulation procedures for modification of psychological and behavioral processes, both in basic, but also in applied clinical studies. Nowadays, numerous neurophysiological and functional imaging tools are available which allow to monitor physiological alterations induced by tDCS in the human brain. For monitoring regional effects of tDCS of a specific target region, these include evoked potential measures, which enable monitoring of tDCS effects over sensory and motor cortices, event-related potentials, EEG, combination of transcranial magnetic stimulation (TMS) and EEG, and neuroimaging tools such as magnetic

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resonance tomography, and positron emission tomography for exploration of physiological effects also over association cortices. Some of these techniques do also allow to disentangle the effects of tDCS to afferent structures of the target area, and thus to monitor the impact of tDCS on specific neuronal populations. Adding pharmacological interventions enable to explore the impact of tDCS on specific neurotransmitters, ion channels, and receptors, or allow to disentangle the sometimes complex impact of the activity state of transmitters on tDCS effects. Depending on the specific technique, these allow monitoring of cortical excitability or activity. On the other hand, tools like functional magnetic resonance tomography and EEG allow monitoring of network effect of stimulation, by correlating activity indices of remote cerebral areas. EEG allows monitoring of associated cortical activity with high temporal, but less spatial precision, whereas fMRI enables also identification of cortico-subcortical connectivity with high spatial sensitivity. Respective studies have shown during the last years that tDCS are not restricted to a specific targeted area, but induce alterations of connectivity of distributed cerebral networks. Beyond pure physiological results at the regional and network level, combination of tDCS and cognitive or behavioral interventions with physiological monitoring might furthermore be suited to obtain information about the physiological background of task-related effects of tDCS, which is of specific relevance due to the state-dependent neuromodulatory effects of this intervention.

In this chapter, an overview about neurophysiological effects of tDCS on the human brain is given. It will cover the main fields which have been explored so far with regard to regional and network effects of tDCS, but also include emerging techniques which hold promise to reveal substantial information about tDCS-induced neuromodulation.

Regional Effects of tDCS

tDCS accomplishes its effects via electrodes positioned to affect one or more target areas. For these target areas, electrical fields are induced which are sufficiently strong to induce physiological effects at the sites of neuronal tissue, i.e. primary effects like membrane polarization, and secondary neuroplastic effects, which go along with excitability alterations and modulation of spontaneous neuronal activity. These effects under the target areas should be discerned from remote effects of tDCS on functionally connected neuronal population, which are thought to be elicited via activity alterations of the target area, but do not include respective physical polarization effects. For exploring regional physiological effects of the stimulation technique, the primary motor cortex is the most frequently used model, because it is relatively easy to access by non-invasive brain stimulation because of its surface-near position, and a couple of tools are available to explore stimulation-induced physiological effects. Physiological effects of tDCS on other cortical areas, however, have been also explored, which is relevant, because due to differences of cortical architecture, receptor distribution, and anatomical factors, it cannot be taken for granted that motor cortex tDCS effects translate one-to-one to other areas.

Motor Cortex

The majority of studies exploring physiological effects of tDCS has been conducted for the primary motor cortex. Beyond monitoring of tDCS-induced excitability alterations via transcranial magnetic stimulation (TMS) (Fig. 5.1), a couple of studies explored tDCS effects on cortical activity via functional imaging approaches such as EEG, fMRI, and PET.

Primary effects of tDCS are thought to depend on membrane polarization of the targeted neurons, causing an alteration of cortical excitability which depends on the direction of current flow in relation to neuronal orientation. Early TMS experiments support this view by showing that stimulation for a few seconds alters motor cortex excitability, as demonstrated by modulation of single pulse TMS-elicited motor evoked potentials (MEPs), a relatively unspecific parameter of cortico-spinal excitability. MEPs were enhanced by the anode positioned over the motor cortex, while cathodal tDCS resulted in an excitability diminution. In accordance with the proposed electrical field direction sensitivity of tDCS effects, in these experiments only motor cortex vs contralateral supraorbital electrode positions induced respective effects (Nitsche and Paulus 2000). In accordance with the polarization hypothesis, voltage-gated ion channel block prevented acute effects of tDCS, while pharmacological alteration of the glutamatergic system by NMDA receptor block or of the GABA-ergic system via benzodiazepines, which would affect synaptic tDCS effects, did not alter respective excitability changes (Liebetanz et al. 2002, Nitsche et al. 2003c, Nitsche et al. 2004b). Likewise, TMS double pulse stimulation protocols, which monitor synaptically driven excitability alterations were not affected by these tDCS protocols (Nitsche et al. 2005).

Secondary physiological effects of motor cortex tDCS emerge with stimulation durations for a few minutes. Similar to the acute effects, anodal stimulation enhances and cathodal tDCS reduces motor cortex excitability, as explored for single pulse TMS-elicited MEP amplitudes (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003b). These effects were accomplished with specific stimulation protocols (1 mA current intensity, 35 cm² electrode size, stimulation duration for up to 20 min in healthy young adults). Hereby, stimulation for 5 and 7 min induce relatively short lasting after-effects, while 9 min or longer tDCS prolong after-effect duration for 30–90 min. The duration of these MEP alterations is in the range of early phase long term potentiation- and depression-like plasticity (Malenka and Bear 2004). Combination of TMS with pharmacological interventions have shown that the respective excitability alterations depend on the glutamatergic system, because block of NMDA receptors with dextromethorphan abolished any after-effects of tDCS (Liebetanz et al. 2002; Nitsche et al. 2003c), whereas the NMDA receptor agonist d-cycloserine prolonged the after-effects of anodal tDCS (Nitsche et al. 2004a). Supporting evidence comes from TMS studies with double pulse stimulation TMS protocols, which show reduced intracortical inhibition, but enhanced facilitation, after anodal tDCS, but reversed effects after cathodal tDCS (Nitsche et al. 2005). For both measures, NMDA receptors are involved. Furthermore, and in accordance with the relevance of NMDA receptors for

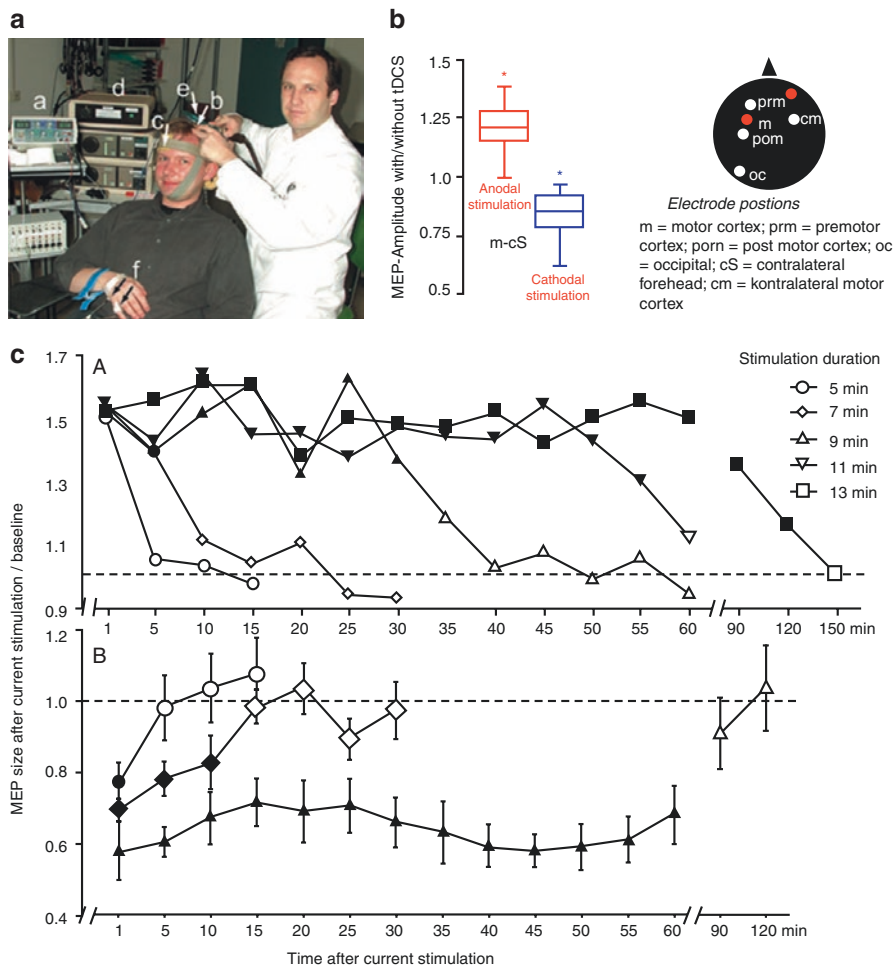


Fig. 5.1 Motor cortex TMS for monitoring tDCS-induced excitability changes. (a) shows the experimental setup. Current source is a constant current stimulator (a). The stimulator is connected with a stimulation electrode over the motor cortex (b), and a reference electrode positioned over the contralateral orbit (c). The impact of tDCS on cortical excitability is monitored by transcranial magnetic stimulation (TMS, d – stimulator, e – coil) of the representation area of the abductor digiti minimi muscle. Motor evoked potentials are recorded from this muscle via surface electromyography electrodes (f). (b) shows motor evoked potential (MEP) alterations induced by short tDCS (4 s), which induces no after-effects. (c) depicts after-effects of anodal (A) and cathodal (B) motor cortex tDCS, as monitored by baseline-standardized TMS-generated MEP amplitudes. (With permission of Klinische Neurophysiologie, J Physiol, Neurology, and Clin Neurophysiol; Nitsche et al. *Klin Neurophys* 2002, *Clin Neurophysiol* 2003, Nitsche & Paulus *J Physiol* 2000, *Neurology* 2001)

the after-effects of tDCS, which have calcium channel properties, the calcium dependence of the after-effects of tDCS is substantiated by the fact that block of voltage-gated calcium channels via flunarizin prevented the formation of excitability enhancement by anodal tDCS (Nitsche et al. 2003c). Studies combining pharmacology with TMS to explore the physiology of tDCS after effects furthermore show that dopaminergic as well as nicotinic receptor activity is required for the after effects of tDCS, since block of respective receptors or receptor hypoactivity due to nicotine withdrawal in smokers abolished after effects of tDCS (Nitsche et al. 2006; Grundey et al. 2012). With regard to the contribution of GABAergic effects, combination of tDCS with the benzodiazepine lorazepam, which enhances already active GABA receptors, did not lead to major effect differences on stimulation-induced MEP alterations (Nitsche et al. 2004b). TMS-evoked I-waves however, which are reduced by GABA activity, were enhanced by anodal and cathodal tDCS (Nitsche et al. 2005). This at first sight puzzling result is explained by a magnetic resonance spectroscopy (MRS) study, which revealed that independent from stimulation polarity tDCS reduces GABA activity (Stagg et al. 2009). Beyond the above-mentioned transmitter systems, serotonin activation has a relevant impact on tDCS-induced excitability alterations, as it enhances amplitude and duration of MEP alterations induced by anodal tDCS, whereas it converts the inhibitory effects of cathodal tDCS into inhibition (Nitsche et al. 2009; Kuo et al. 2016). Electrophysiological studies furthermore helped to define the level of action of tDCS. Comparison of tDCS-driven MEP alterations obtained via TMS, which activates corticospinal tract neurons indirectly via its impact on intracortical neurons, and high voltage transcranial electrical stimulation (TES), which directly activates corticospinal tract neurons, shows that only TMS-evoked MEPs were affected in accordance with a primary intracortical effect (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003b). This assumption is supported by a study in which spinal tract recordings were performed after tDCS, which showed a primary effect of tDCS on the amplitude of cortically evoked I-waves, and by results of two studies which demonstrated that intracortical motor cortex inhibition and facilitation were modulated by tDCS-induced excitability alterations of the premotor and posterior parietal cortex, which are both relevantly connected with the primary motor cortex (Boros et al. 2008; Rivera-Urbina et al. 2015).

All above-mentioned physiological effects were obtained with the “classic” stimulation protocols, as outlined above. For adjustment of stimulation protocols to obtain optimal physiological effects, within these limits stronger and longer stimulation increase the alteration and duration of TMS-induced MEP amplitude changes (Nitsche and Paulus 2000, 2001; Nitsche et al. 2003b). It could however be shown that too strong and long stimulation convert the direction of MEP alterations. 20 min tDCS with 2 mA resulted in an excitability enhancement after cathodal tDCS, whereas 26 min anodal tDCS with 1 mA reduced MEP amplitudes (Batsikadze et al. 2013; Monte-Silva et al. 2013). Given that tDCS effects are calcium-dependent, and that in animal experimentation low calcium increase result in LTD, and high calcium increase in LTP (Lisman 2001), it can be speculated that this shift of MEP alterations is caused by enhancing calcium concentration in case of cathodal tDCS to the LTP-inducing range, whereas in case of prolonged anodal tDCS, calcium

overflow causes counter-regulatory neuronal activities. Indeed the respective conversion of plasticity in case of anodal tDCS is abolished by calcium channel block (Monte-Silva et al. 2013). In contrast, tDCS-dependent MEP alterations can be relevantly prolonged if LTP- and LTD-like plasticity-inducing protocols are repeated within a time window critical for late phase plasticity induction in animal models, i.e. application of the second intervention within a time window of 30 min (Monte-Silva et al. 2010, 2013). Here anodal tDCS induces after effects lasting for more than 24 h after plasticity induction, and these effects are NMDA receptor dependent, because block of these receptors abolishes respective MEP alterations. Interestingly, for stimulation protocols falling short of inducing prolonged neuroplastic effects, the impact of repeated stimulation within relatively short intervals seems to be more mixed and heterogeneous (Fricke et al. 2011).

Physiological effects of tDCS are object to intra- and interindividual variability, which is not surprising given that the primary physiological effect is a slight modulation of resting membrane potentials. Wiethoff et al. (2014) found excitability enhancements following anodal tDCS in about 75% of all participants, while below 50% had lower MEP amplitudes after cathodal tDCS. Intra-individual variability seems to be lower, with about 70% of participants showing similar MEP results for an inter-session tDCS interval for up to a year (López-Alonso et al. 2015). Sources for this variability of effects might be handedness, brain state according to task performance or muscle contraction, genetic polymorphisms, or differences in availability of neurotransmitters or receptor activity, head size, and presence of neurological or psychiatric diseases, amongst others (Nitsche et al. 2006; Antal et al. 2007, 2010; Kuo et al. 2008; Hasan et al. 2011; Thirugnanasambandam et al. 2011; Grundey et al. 2012; Schade et al. 2012; Kessler et al. 2013). The relative contribution of these factors to variability of physiological tDCS effects is unknown so far. Sensitivity to TMS might have predictive value for the magnitude of MEP alterations induced at least by anodal tDCS, as shown in a retrospective analysis, where subjects displaying higher TMS sensitivity reacted stronger to tDCS (Labruna et al. 2016). If this is caused by anatomical or physiological factors, and if this means that individual intensity adjustment of tDCS based on TMS sensitivity will reduce variability is unclear at present.

Beyond tDCS-induced cortical excitability alterations, tDCS effects on human motor cortex activity were explored in a couple of studies. For oscillatory brain activity, in resting EEG motor cortex cathodal stimulation increased delta and theta activity in one study (Ardolino et al. 2005). In another study, increased power of the theta and alpha frequency bands was described after both, anodal and cathodal tDCS (Pellicciari et al. 2013). Enhanced theta and alpha power were also described in another study during anodal tDCS, while cathodal stimulation reduced delta power (Roy et al. 2014). tDCS was furthermore shown to modulate event related desynchronisation of mu rhythm polarity dependently (Matsumoto et al. 2010; Kasashima et al. 2012; Lapenta et al. 2013; Kasuga et al. 2015). For motor cortex-related blood flow alterations, which are indexing cortical activity, induced by tDCS, a PET study showed increase after anodal, and decrease after cathodal tDCS under resting conditions (Lang et al. 2005). Similar effects during stimulation were

obtained in a PET study measuring blood flow alterations during tDCS combined with motor task performance. For fMRI, BOLD measures under resting conditions showed enhancement of blood flow in the primary motor cortex after anodal tDCS in resting conditions in one study, but not in another with similar relatively short stimulation conditions (repeated stimulation for some seconds, Antal et al. 2011; Kwon et al. 2008). Zheng et al. (2011) describe blood flow enhancements during and after anodal tDCS, but reductions after cathodal tDCS for the arterial spin labeling (ASL) method, which might have superior sensitivity for detection of blood flow changes (Fig. 5.2). Task-related BOLD signal changes seem also to be somewhat heterogeneous, and might depend on stimulation parameters. Whereas Baudewig et al. (2001) did not identify tDCS-induced BOLD activity changes after 5 min tDCS in the primary motor cortex, such effects were seen in later studies, in which more extended stimulation protocols were applied (Jang et al. 2009; Stagg

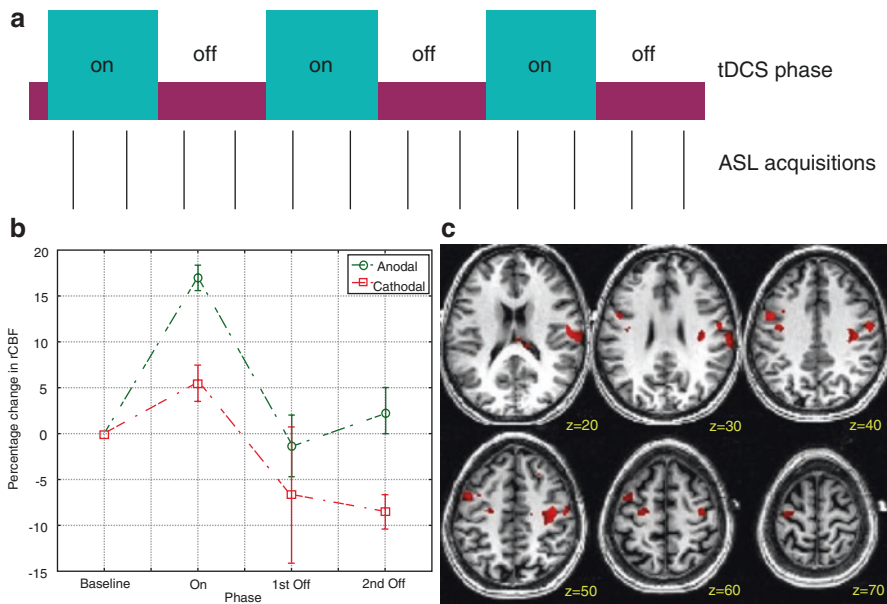


Fig. 5.2 Blood flow alterations induced by motor cortex tDCS. In this study, arterial spin labeling (ASL) was used to explore cerebral blood flow changes induced by anodal and cathodal tDCS. (a) shows interleaved tDCS-off and tDCS-on design while acquiring ASL images, where two ASL images were acquired at each on phase and two ASL images were acquired at each off phase, beginning with a baseline consisting of three ASL acquisitions. (b) shows the average changes in rCBF (normalized to zero) for the first OFF-ON-OFF of anodal and cathodal stimulation across all subjects. The description *1st off* and *2nd OFF* refers to the two acquisitions after the end of the stimulation and reflects the trend in rCBF after the stimulation has been turned off. (c) displays the averaged distribution of CBF response across the entire brain space correlated with the timecourse obtained from the VOI under the electrode for the anodal condition. Significant correlations ($p < 0.001$, uncorrected at the group level) were overlaid onto a single spatially standardized brain (Zheng et al. 2011, with permission by the authors, and Neuroimage)

et al. 2009; Kwon and Jang 2011). Thus taken together, beyond polarity-dependent cortical excitability changes, tDCS results in similar effects on cortical activity, as shown by EEG, PET, and fMRI studies.

The study results described so far were conducted with the “classic” electrode arrangement with relatively large target electrodes positioned over the hand area of the primary motor cortex. This stimulation procedure elicits relatively diffuse effects, affecting different movement representations relatively unspecifically (Nitsche et al. 2007), and might tackle also adjacent areas, such as the premotor cortex (Boros et al. 2008), although at least under task performance conditions, physiological specificity of tDCS effects might be determined also by synergistic effects on task-related activations (Polanía et al. 2011b). The focality of stimulation can be enhanced by reducing the size of the target electrode, and adjusting stimulation intensity accordingly to keep current density constant (Nitsche et al. 2007). Reduction of the motor cortex electrode size in this study limited MEP alterations during and after tDCS to a hand muscle representation covered by the small electrode, but left an adjacent hand muscle representation not covered by the electrode unaffected. Another electrode arrangement which was developed for more focal stimulation is so-called high-definition (HD) tDCS. Here, a central relatively small target electrode is surrounded by 4 return electrodes (Edwards et al. 2013). The efficacy of this electrode arrangement to induce MEP alterations is similar to the classic electrode arrangement (Kuo et al. 2013). Enhanced focality of this electrode arrangement is suggested by modelling approaches, but physiological evidence for respective higher focality of stimulation effects is limited (Edwards et al. 2013).

The majority of motor cortex physiological tDCS studies was so far conducted for small hand muscles. The respective motor cortical sub-field has the advantage that it is situated relatively superficially, and thus easy to be influenced by non-invasive brain stimulation. Moreover, sophisticated TMS protocols do exist for this area which allow monitoring of specific cortical subsystems, such as intracortical inhibition, facilitation, I-wave facilitation, amongst others, which are not in each case similarly well established for other motor cortex regions. However, tDCS exerts physiological effects also on other sub-compartments of the primary motor cortex. Only a limited amount of studies is available for physiological effects of stimulation of proximal muscles of the upper limb is available. It was however shown that anodal tDCS of the motor cortex representation enhances the activation of the contralateral biceps brachii muscle significantly, as shown by surface electromyography (Krishnan et al. 2014). For TMS-elicited MEP alterations in this muscle at rest, however, no significant effects of anodal tDCS were described (Mccambridge et al. 2015). Similarly, cathodal tDCS of the biceps brachii representation has not been shown to alter MEP amplitudes so far, however, it was suggested to suppress ipsilateral projections to propriospinal neurons of the proximal upper limb (Bradnam et al. 2011). Interestingly, in the same study cathodal tDCS suppressed MEP in a contralateral distal hand muscle. This pattern of results argues against missing efficacy of this specific stimulation protocol. The relatively minor plasticity effects of tDCS on proximal upper limb muscles might be caused by relatively low proneness of these

muscles to undergo neuroplastic changes. Alternatively, differences in orientation or position of these neurons might require adjusted stimulation protocols. For the pharyngeal motor cortex, initial evidence is available that anodal tDCS enhances, whereas cathodal tDCS reduces respective MEP amplitudes (Jefferson et al. 2009). For physiological effects of tDCS on lower extremity muscles, an MEP enhancement was described in the resting and pre-contracted anterior tibial muscle after anodal tDCS, while cathodal stimulation over the primary motor cortex had no effect (Jeffery et al. 2007). In accordance, anodal, but not cathodal tDCS improved maximal pinch force (Tanaka et al. 2009). BOLD fMRI results were showing no direct effects on the stimulated primary motor cortex in another study, but indicative for increased activity of the ipsilateral sma and decreased activity of contralateral primary motor cortex, as compared to sham stimulation (Kim et al. 2012). Thus so far no protocols are available which reduce leg motor cortex excitability, whereas the physiological impact of anodal tDCS on lower extremities movement representations seem to be similar to those of hand muscle representation stimulation. Similar to proximal muscles of the upper extremity, limited effects might be caused by a minor propensity for plasticity in lower extremities, different neuronal orientations, or also caused by the larger electrode to brain distance, as compared to the motor cortex hand area.

Taken together, for motor cortex tDCS numerous studies are available which favour a polarity-dependent effect on cortical excitability and activity. Whereas the primary effect of tDCS seems to depend on subthreshold membrane polarization, after effects involve modification of the strength of glutamatergic synapses, and reduced GABAergic activity. The neuromodulatory effects of tDCS imply that beyond specific limits of stimulation intensity and duration, the impact of tDCS on cortical excitability converts its direction. Less studies are available which explore the effect of tDCS on cortical activity via functional imaging tools, and respective results are less clear-cut. Physiological mechanisms of action have been best clarified for hand muscle representations, but effects are also obtained for other motor cortex areas. Especially for these protocols, studies which systematically explore protocol parameters suited to induce optimal effects are missing.

Sensory Cortices

Somatosensory Cortex

Effects of tDCS on neurophysiological function of the somatosensory cortex can be evaluated by means of changes in the somatosensory evoked potentials (SEPs) or somatosensory evoked magnetic fields (SEFs), changes in brain's hemodynamic response, or at the behavioral level by effects on measures of somatosensory perception (Dieckhöfer et al. 2006; Sugawara et al. 2015; Kojima et al. 2015; Wang et al. 2015; Grundmann et al. 2011; Rehmann et al. 2016; Song et al. 2011; and others).

SEPs represent electrical potentials generated in sensory pathways at peripheral, spinal, subcortical and cortical levels, elicited by electrical stimulation of a peripheral nerve (usually the median or posterior tibial nerves). A comprehensive overview of SEP components, normal waveforms and clinical interpretations can be found in Mauguiere (1999). SEP evaluations often include low-frequency SEP components, such as N20, P20, P22, N30, P35, or P60; neuroanatomical studies suggest that generator sources for these components are located cortically, including area 1,2 (component P60) or 3b (N20) of the primary sensory cortex (S1) or in the motor cortex (e.g. component P35). Further, SEP evaluations may also include high-frequency oscillations (HFOs; ~600 Hz) which are believed to be at least partially generated by postsynaptic activities in S1 as well as by subcortical generators, such as presynaptic terminals of thalamo-cortical pathways to S1 (Curio et al. 1994, 1997; Curio 2000; Dieckhöfer et al. 2006). Some SEP evaluations employ a paired-pulse paradigm, which typically involves evaluation of the N20 (N20-P25) component after stimulation of the median nerve with two stimuli delivered in a short interval (~30 ms), and is based on the premise that the resulting second N20 response shows a reduction in its amplitude when compared to the first pulse (Ragert et al. 2004a). The strength of the paired-pulse suppression depends on the interstimulus interval, but – contrary to the single-pulse SEP response -- shows only weak dependence on stimulus intensity; only the N20-P25 component shows some intensity effects. Here higher intensities result in stronger paired-pulse suppression (Ragert et al. 2004b). The paired-pulse suppression is believed to arise from inhibition generated by intracortical networks and it has been used as a marker of cortical excitability.

Evidence up to date indicates that tDCS delivered over the somatosensory cortex exerts different effects on low- and high-frequency SEPs, and the effects depend on tDCS modality. Nine minutes of cathodal tDCS at 1 mA applied to the somatosensory cortex in healthy subjects (Dieckhöfer et al. 2006) resulted in a long-lasting reduction of the low-frequency N20 SEP component after contralateral median nerve stimulation (Fig. 5.3). This finding corroborates evidence for an inhibitory effect of cathodal tDCS on the excitability of the human cortex (Nitsche and Paulus 2000). Accordingly, application of cathodal tDCS to the somatosensory cortex has been shown to have similar effect on paired-pulse suppression of SEPs (Rehmann et al. 2016), reduces tactile acuity (Rogalewski et al. 2004), and also resulted in decreased amplitudes of laser-evoked potentials (LEPs) and decreased pain perception in experimentally induced pain (Antal et al. 2008).

Application of anodal tDCS over S1 in Dieckhofer's study (Dieckhöfer et al. 2006) had no significant effects on low-frequency SEPs. Notably, when applied over the *sensorimotor* cortex, anodal tDCS resulted in increased amplitudes of P25/N33, N33/P40 and P22/N30 in another study (Matsunaga 2004). Anodal tDCS over S1 had no effects on LEPs, or pain perception (Antal et al. 2008). As for tactile acuity, anodal tDCS over S1 had no effect if applied for 10 min (Rogalewski et al. 2004), but an increase in tactile acuity was observed after an extended (20 min) stimulation (Ragert et al. 2008a, b), and anodal tDCS delivered over S1 also had an

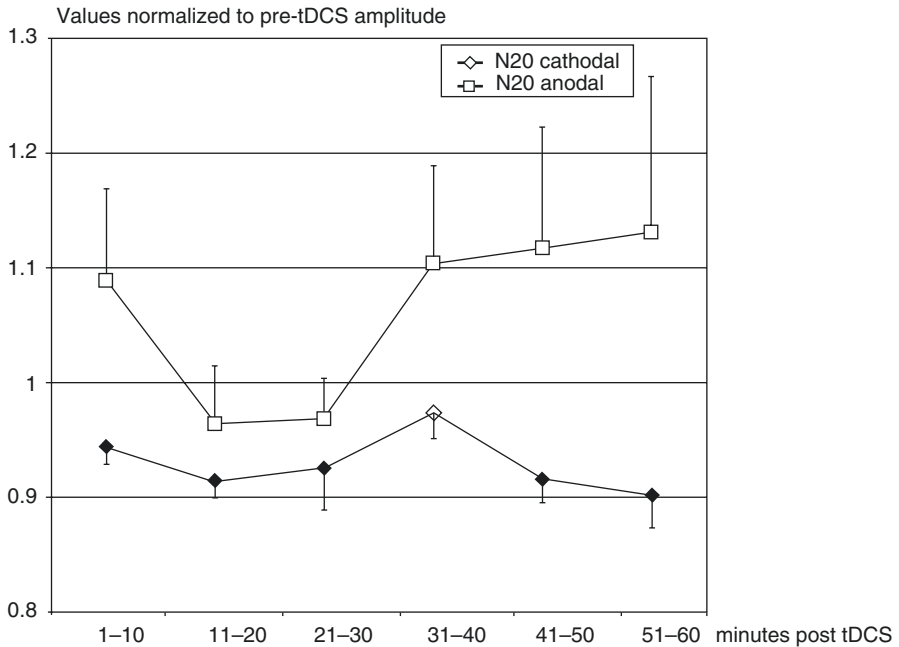


Fig. 5.3 After-effects of anodal and cathodal tDCS on somatosensory-evoked potentials. Time course changes in N20 amplitude evoked by stimulation of the contralateral median nerve following 9 min polarization with 1 mA DC current. Filled symbols indicate significant differences between SEP amplitudes after polarization and baseline. Error bars indicate standard error of means (From Dieckhöfer et al. 2006, Fig. 3, with permission)

excitatory effect on paired-pulse suppression of SEPs in a paired-pulse paradigm study (Rehmann et al. 2016).

For the high frequency SEP component (600 Hz oscillations, HFOs), no effects from anodal or cathodal tDCS over S1 were observed (Dieckhöfer et al. 2006). This finding is in accordance with evidence that the generators of HFOs are localized subcortically and therefore distant from the local effects of tDCS.

Some evidence of tDCS effects on the somatosensory cortex originates from studies employing evaluation of somatosensory evoked magnetic fields (SEFs). Evaluations of SEFs following median nerve stimulation focused on three main components: N20, P35 and P60 (Huttunen et al. 2006; Sugawara et al. 2015). In a study by Suguwara et al. (2015), anodal tDCS (15 min at 1 mA; electrodes 35 cm²) over the somatosensory cortex had a significant effect on somatosensory evoked magnetic fields, increasing the source strength of P60. As noted above, it is believed that the generator for this component is located within areas 1 and 2 (Huttunen et al. 2006; and others). The component P35, which is believed origin from the motor cortex (Kawamura et al. 1996), was unchanged. Notably, the source strength of both components increased, if tDCS was delivered over the motor cortex.

Accordingly, tDCS delivered over the motor association cortex has been shown to induce plastic changes in the ipsilateral primary motor as well as somatosensory cortices (Kirimoto et al. 2011).

In summary, existing studies indicate that tDCS effects on neurophysiological activity of the somatosensory cortex depend on multiple factors including tDCS modality, such as anodal or cathodal tDCS, tDCS-targeted area, including its location (cortical or subcortical) of the neural generators of the response.

Visual Cortex

In the visual system, polarity-specific tDCS effects were demonstrated, too.

Anodal tDCS enhances excitability of the visual cortex. In a study by Sczesny-Kaiser et al. (2016), real or sham tDCS were applied in healthy subjects over V1 in a randomized, double-blinded design over four consecutive days. Excitability parameters were measured by analyzing paired stimulation-elicited visual-evoked potentials (ps-VEP) and by measuring phosphene thresholds before and after a stimulation period of 4 days. Compared with sham-tDCS, anodal tDCS resulted in increased ps-VEP ratios (Fig. 5.4) and reduced phosphene thresholds (Sczesny-Kaiser et al. 2016). Decreased phosphene thresholds after anodal tDCS over the occipital cortex have been also observed by Antal et al. (2003a, b). However, anodal tDCS over the visual cortex did not result in significant changes of contrast perception thresholds (Antal et al. 2001), possibly due to a ceiling effect.

Cathodal tDCS has been shown to increase thresholds for moving as well as stationary phosphenes in studies by Antal et al. (2003a, b), but had no effects on phosphene thresholds or VEPs in a study by Sczesny-Kaiser et al. (2016). Further, Accornero et al. (2007) evaluated changes in amplitudes and latencies of VEP component P100 (VEP-P100) in healthy subjects after anodal and cathodal tDCS applied for 3 and 10 min at 1 mA, with an extracephalic position of the return electrode (Accornero et al. 2007). In this study, anodal tDCS resulted in reduced VEP-P100 amplitude, whereas cathodal polarization significantly increased the amplitude, and no significant changes were observed in the VEP-P100 latencies.

Auditory Cortex

Very few tDCS studies have focused on tDCS modulation of sensory processing in the auditory cortex (Vines et al. 2006; Mathys et al. 2010; Chen et al. 2014a, b; Impey and Knott, 2015; Impey et al. 2016). The available studies mostly employed event-related potentials (ERPs) as an objective neural measure of information processing pertaining to early pre-attentive auditory processes such as sensory gating indexed by the ERP component P50, sensory discrimination indexed by the mismatch negativity (MMN) component, or novelty detection indexed by P3a; as well

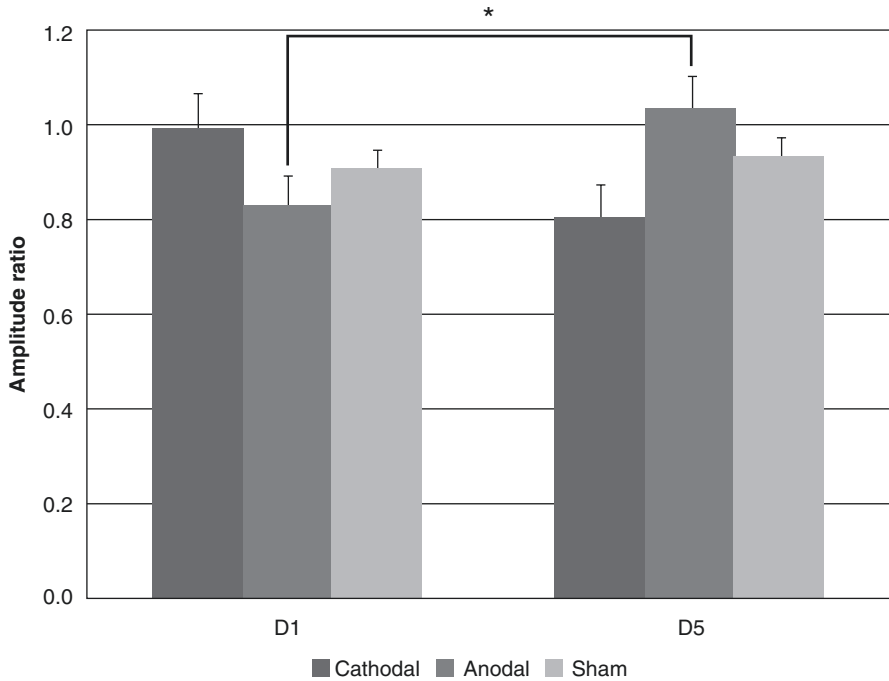


Fig. 5.4 Effects of DCS on paired-stimulation VEP (psVEP). Mean amplitude ratios of all three groups on day 1 (D1) and day 5 (D5) are plotted. *significance level, $p < 0.017$. Error bars indicate standard error of the mean (From Sczesny-Kaiser et al. 2016, Fig. 5, with permission)

as to assess higher order auditory processes, such as attentional allocation and processing speed indexed by P3b (Impey et al. 2016).

Early findings by Zaehle and colleagues (Zaehle et al. 2011) indicate that anodal tDCS over the auditory cortex increases amplitudes of the auditory P50, whereas cathodal tDCS over the primary and secondary auditory cortex (Vines et al. 2006; Mathys et al. 2010) resulted in decreased pitch discrimination and pitch memory performance. Further, pilot findings by Impey and Knott (2015) and a subsequent study by Impey et al. (2016) have suggested that an application of anodal tDCS over the temporal lobe in healthy subjects can increase auditory discrimination indexed by MMN, and that this modulation is baseline-dependent: anodal tDCS over the temporal cortex improved MMN-indexed auditory discrimination, compared to sham stimulation, particularly in individuals with relatively low sensory discrimination performance. In contrast, reduced MMN amplitudes with cathodal tDCS, compared to baseline assessment were obtained particularly in individuals with relatively high level task performance. These studies point toward the importance of the use of neurophysiological markers stratified by the baseline response when examining tDCS modulatory impact on cerebral functions.

Association Areas

Association areas are defined as cortical regions which receive projections from specific primary sensory or motor cortices. In addition, multimodal association areas receive sensory input from different sensory modalities and various specific association areas and play a crucial role in multisensory integration. The posterior multimodal association area relates to bodily spatial awareness, as well as to reading, naming, and emotional components of speech. The anterior association area together with the limbic association area is involved in multimodal integration of past experience and processes of conditioning. Previous research employing rTMS indicates that modulation of multisensory integration, such as an integration of the proprioceptive, somatosensory and visual input, is possible (Tsakiris et al. 2008; Azanon and Haggard 2009). Accordingly, at the behavioral level tDCS has been shown to alter multisensory input, such as visuomotor coordination (Antal et al. 2004; Kwon et al. 2015) or visuomotor learning (Antal et al. 2004b; Shah et al. 2013), as well as processes pertaining to various cognitive domains, including risk taking behavior, planning ability, or behavioral inhibition. Further, in a study by Lapenta et al. (2014), tDCS has been shown to modulate inhibitory control as indexed by ERPs, and at the behavioral level reduced food consumption. In this study, active tDCS over the dorsolateral prefrontal cortex (anode right/cathode left) reduced the frontal N2 component and increased the P3 component of responses to No-go stimuli, as compared to sham, and these physiological effects were paralleled by reduced food craving and caloric intake. Increased No-go P3d amplitudes are in general interpreted as indicators that increased cognitive resources are recruited to achieve inhibition (Albert et al. 2010; Yang et al. 2009; Pfefferbaum et al. 1985; and others). In the study by Campanella et al. (2017) tDCS over the right inferior frontal cortex (rIFC, a neural substrate crucial for inhibitory control), but not sham stimulation, resulted in reduced P3d amplitudes in a Go/No-go task, indicating that boosting rIFC may specifically enhance inhibitory skills by decreasing the neural activity needed to correctly inhibit the response. Modulatory effects of tDCS on P3 ERP components have also been observed in other studies. A study by Conti et al. (2014) examined the effects of DLPFC modulation by single and repetitive tDCS on prefrontal visual P3 ERP components under neutral and drug cue exposition in crack-cocaine addicted subjects. Significant differences were found in P3-related parameters when comparing group of stimulation (active vs. sham tDCS) and number of sessions (single vs. repetitive tDCS). Specifically, P3 amplitudes in the left DLPFC after a single active tDCS application increased during neutral cues and decreased during crack-related cues, while opposite effects were observed in the sham group. Furthermore, significant increases of P3 DLPFC activity under both, neutral and crack-related cues (Fig. 5.5) were obtained bilaterally after five tDCS applications on five alternated days as compared to activity measured before the first tDCS application. When compared to the effects of a single dose, the multiple tDCS application increased P3 amplitudes not only in the DLPFC, but also in a wider array of prefrontal areas, including presumably the frontopolar cortex,

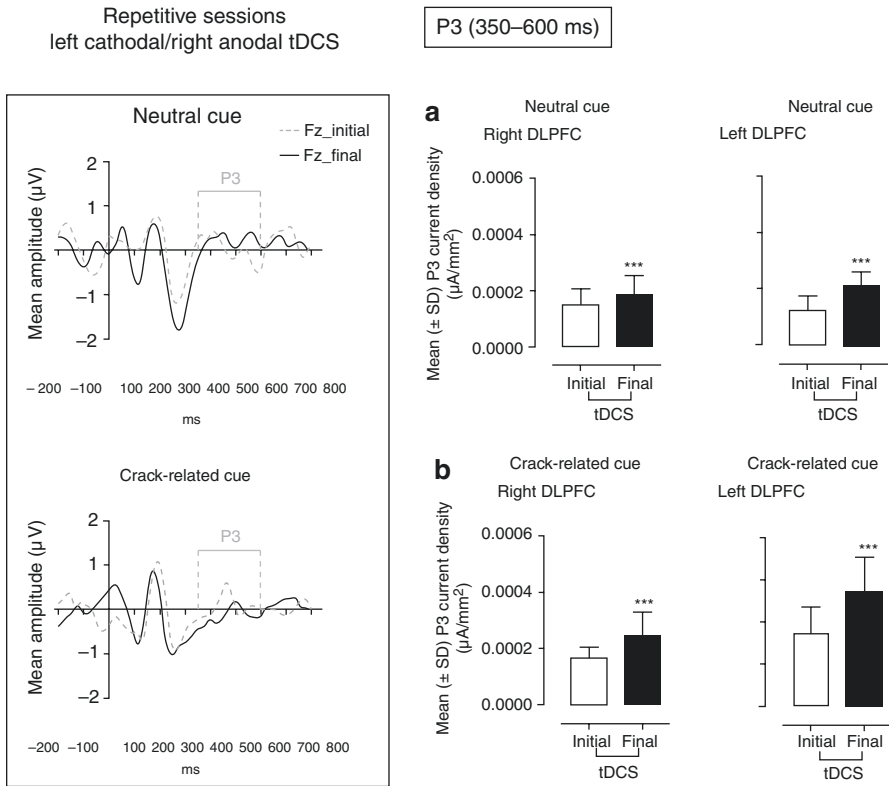


Fig. 5.5 Event Related Potentials (ERPs) evoked by neutral or crack-related visual stimuli at baseline (initial) and after five (final) applications of bilateral (left cathodal/right anodal) transcranial Direct Current Stimulation (tDCS, 2 mA, 35 cm², for 20 min) in crack-cocaine addicts at frontal site (Fz) Fz (according to 10–20 EEG international system). Current density in the P3 segment (350–600 ms) elicited by neutral (a) or crack-related (b) cue presentation in the right and left Dorsolateral Prefrontal Cortex (DLPFC) at the baseline (initial) and at the end of five sessions (final) of bilateral tDCS (n = 6) over the DLPFC ***p < 0.0001 (Wilcoxon signed rank test when comparing initial vs. final). (From Conti et al. 2014, Fig. 4, with permission)

orbitofrontal cortex and anterior cingulate cortex, when subjects were visualizing crack-related cues. These effects may reflect rescuing of prefrontal cognitive control that might have clinical potential for addiction management (Conti et al. 2014). Another study (Faehling and Plewnia 2016) focused on tDCS modulation of cognitive control upon negative emotional distraction. In this study, healthy subjects performed working memory tasks with neutral or emotionally loaded distraction during sham or real tDCS at intensities of 0.5–1.5 mA, with the anode placed over the left DLPFC, and the cathode over the right deltoid muscle. The late positive potential (LLP) – an ERP that indexes attention allocation, was recorded during tDCS/sham. The results show that in the sham group a valence-specific increase of the early portion of the LPP (eLPP, 250–500 ms) was associated with less emotional distraction,

and tDCS had an intensity-related effect on this correlation. The later part of LLP (iLLP, 500–1000 ms) correlated with reaction time regardless of valence, while a general effect of tDCS on LLPs was not detected. These findings support the notion that the changes of eLPP reflect effective compensation for behavioral distraction by negative stimuli and thus points toward a neuronal mechanism for effective control of the emotional bias.

Overall, the findings up to date indicate that tDCS can impact on activity of neuronal networks of brain association areas and can modulate outcomes at both neurophysiological and behavioral levels.

Network Effects: Functional Imaging

A large body of research suggests that goal-directed behavior depends on an efficient integration of neural activity where several connected but widely distributed areas linking whole brain regions, cell populations, and individual cortical neurons, closely interact to generate an action or choice. In a typical goal-directed choice scenario, we must first process incoming sensory signals, then recognize the alternatives for choice, compute their values and the difference between them, followed by a mapping of these computations to locations in space and finally execute the appropriate action (Rangel et al. 2008; Rangel and Hare 2010; Polanía et al. 2014, 2015; Grueschow et al. 2015). But the question is: How can the brain achieve such a fast and efficient integration of information in a quickly changing environment? Synchronized neural activity in the brain appears to be a fundamental mechanism for such cognitive processes requiring an efficient large-scale integration of distributed neural activity, supporting both neural communication and plasticity (Polanía et al. 2012a, b; Siegel et al. 2012).

Based on the physiological effects observed in primary motor and other cortices described in the previous sections of this chapter, it can be speculated that tDCS could be used as tool to modulate more complex cognitive functions involving the type of goal-directed choice described above that are predominant in our everyday life. This also suggests that tDCS could potentially be used to resolve whether certain brain regions are indeed causally involved in specific behaviors based on, for instance, neuroimaging studies which are limited by their correlative nature. For example, based on prior neuroimaging work implicating the frontopolar cortex (FPC) in exploratory reward learning behavior (Daw et al. 2006), it was investigated whether upregulating and downregulating neuronal excitability with anodal or cathodal tDCS it is possible to show that the FPC is indeed causally involved for this type of complex behavior (Raja et al. 2015). The investigators found that that applying different types of tDCS (anodal or cathodal) over FPC indeed causes participants to explore more or less in uncertain environments, thus establishing a causal role for the FPC in regulating both exploration and exploitation behavior in humans.

Beyond behavior at the level of individual decisions, many of the proposed links between social decision making (and social learning) also come from neuroimaging studies in healthy participants and thus rely on correlations between task parameters and brain activity, thus once more raising the question of whether the observed neural responses are merely correlated with the observed behavior in social settings or whether they play a causal part. Based on a prior neuroimaging study implicating activity in the lateral prefrontal cortex (LPFC) in compliance with social norms (Spitzer et al. 2007), it was investigated in a subsequent tDCS study whereas this brain region is indeed implicated in this type of complex social behavior (Ruff et al. 2013). The investigators showed that LPFC is indeed involved in both voluntary and sanction-induced norm compliance (Fig. 5.6). Interestingly, both types of compliance could be changed by varying the neural excitability of this brain region with anodal or cathodal tDCS, but they were affected in opposite ways. Thus, once more using tDCS as a tool to test the link between activity and in this case complex social behaviors, the results of this study revealed that LPFC is a key biological prerequisite for social norm compliance, a socially important aspect of human behavior.

Despite the fact that in the above-mentioned examples tDCS was used to resolve whether certain brain regions are indeed causally involved in specific behaviors, the effects underlying these tDCS-induced modulations in the human brain, which are afterwards reflected in modulations of behavior, remain incompletely understood. For instance, from these studies (Ruff et al. 2013; Raja et al. 2015) it is unknown whether the observed effects on behavior are due to tDCS-induced alterations of activity underneath the electrode, and if it is the case, it is unknown what type of alterations are induced by the stimulation. On the other hand it could be hypothesized that one important aspect of the tDCS-induced functional effects could be attributed to learning- or task-related synaptic connections. Hereby, tDCS-induced effects might modulate functional connectivity between segregated cortical areas in the task under study.

Electrophysiological and neuroimaging methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have been used as tools to noninvasively acquire information regarding the neural activity of the brain with their respective spatial-temporal advantages and dis-advantages. In the last decade, these methods have been used as powerful tools to study the architecture of human brain functional networks at the large scale level both during rest (Keeser et al. 2011; Polanía et al. 2011b; Peña-Gómez et al. 2012), and also during the planning and execution of goal-directed actions (Antal et al. 2011; Saiote et al. 2013). Hence, the use of methods such as EEG and fMRI combined with noninvasive brain stimulation might be an appropriate starting point to elucidate the impact of tDCS-induced neuroplasticity on human brain functional networks on how these are linked to the observed changes in behavior.

In the following sections we provide insights on how different imaging and statistical methods can be used to track for tDCS-induced brain network effects in humans. We start by using the primary motor cortex as an example region, where

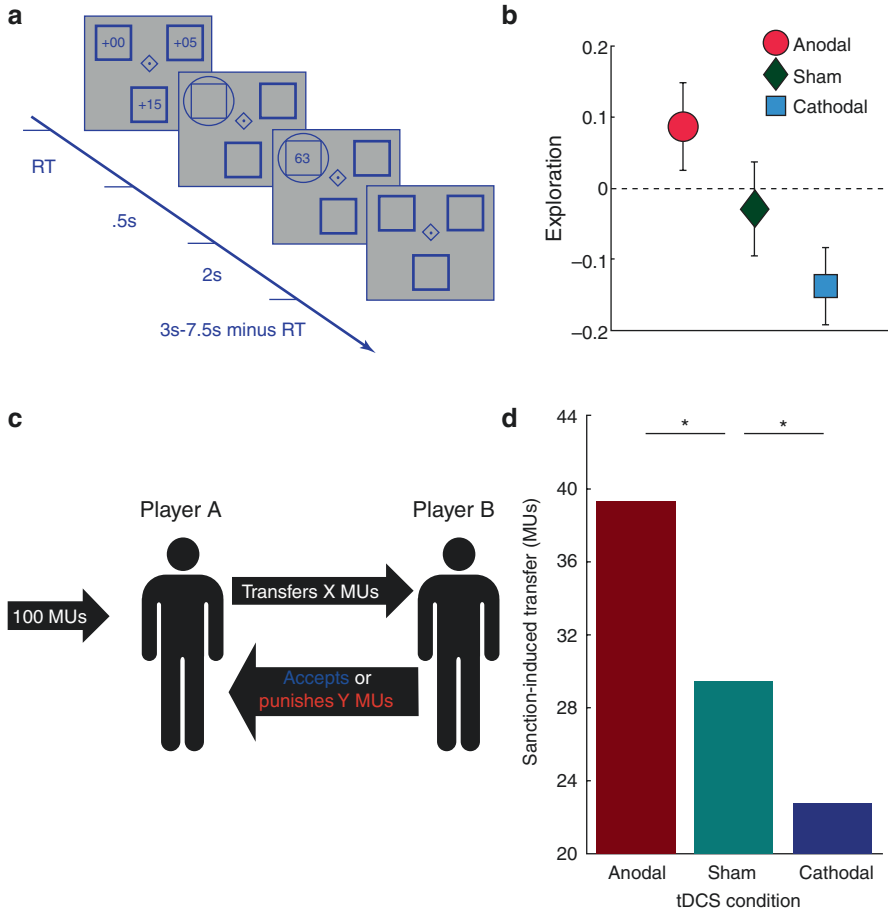


Fig. 5.6 (a) Brief description of the Bandit (Explore/Exploit) Task: Participants selected among three virtual slot machines (squares) whose payout values drifted independently and randomly across trials. The randomly-varying monetary rewards required participants to continuously learn about the slot machines payout values to maximize their monetary payoffs. At the start of each trial, participants saw three bonuses (numbers in first screen) that had to be added to the slot machine's underlying payout value to determine the total reward. After participants made their choice (circle), the total reward was displayed (last screen). The Degree of exploration on each trial was defined as the amount of monetary reward the participant was willing to give up by not selecting the highest-paying option and instead explore. (b) Effects of tDCS on Explore/Exploit behavior: Anodal stimulation over the FPC led to an increase in exploration, whereas cathodal stimulation decreased exploration, relative to inactive sham stimulation that left exploration unaffected. (c) Brief description of the norm compliance task: Both players (a and b) receive 25 initial monetary units (MUs). Player a is given an additional 100 MUs that she can share with player B by sending a transfer X (in multiples of 10 MUs). In a subsequent decision stage, Player B can either accept X or invest Y MUs from her initial endowment to punish player A and therefore reducing A's payoff by $5 \times Y$ MUs. Player A is aware of this possible sanction; any increase in transfers for punishment relative to baseline rounds therefore measures sanction-induced norm compliance. (d) Effects of tDCS on norm compliance: Higher values indicate that the punishment threat led to a larger adjustment of transfers toward the fairness norm of an equal split, thus, suggesting that anodal tDCS over the rLPFC enhances fairness in the presence of sanction-induced norms, whereas cathodal tDCS induces the opposite effect

the tDCS-induced effects on brain networks have been more systematically studied relative to other brain areas and cognitive tasks, and then we complement this knowledge with more recent studies attempting to investigate tDCS-induced effects on higher cognitive functions and their associated brain networks.

tDCS-induced Global Network Effects

Characterization of complex human brain networks has been of increasing interest in the recent years using graph theory as a mathematical approach (Bullmore and Sporns 2009). This approach allows examining the functional connectivity architecture of the brain, which provides information regarding its organization linked to the capability of integration and transfer of information within and between different regions. Using this computational methodology in combination with EEG, it was investigated whether tDCS-induced excitability changes are expressed in modifications of the functional cortical architecture in humans when anodal tDCS was applied over the primary motor cortex (M1) during the execution of a simple motor task (Polanía et al. 2011a). The authors found a prominent increase in synchronization of regions involved in motor task performance in the gamma band (between 60 and 90 Hz) but also enhanced synchronization between the primary motor area, premotor and sensorimotor areas. Based on these results, it is tempting to speculate that tDCS-related increases of functional synchronization when applied over M1 is relevant for the beneficial effects of anodal tDCS on motor learning observed in a large number of reports in the past decade (Nitsche et al. 2003a; Reis et al. 2009). Based on this evidence, it is well possible to hypothesize that an important aspect of the beneficial effect of excitatory anodal tDCS might be that it enhances strengthening of dynamical task-related synaptic connections.

In a second study, the same authors aimed to explore whether tDCS-induced functional connectivity changes can be identified by a voxel-based graph theoretical approach in BOLD fMRI (Polanía et al. 2011b), thus exploiting the high spatial resolution offered by this non-invasive imaging technique (however, this time during resting state fMRI measurements). The graph theoretical analysis revealed once more a reconfiguration of the functional brain networks: Anodal stimulation over M1 combined with cathodal stimulation over the contralateral fronto-polar cortex during rest induces a global decrease in the long distance topological functional coupling of the left M1 with the rest of the brain. In other words, the number of direct functional connections from the left M1 to topologically distant brain areas significantly decreased. Interestingly, this result was accompanied by an increase of the functional coupling between M1 and neighbored topological regions such as the left premotor, and left parietal cortex, which is in line with the results found in the initial EEG study (Polanía et al. 2011a). Extending the previously postulated hypothesis (that anodal stimulation over M1 enhances strengthening of dynamical task-related synaptic connections (Polanía et al. 2011a)), the results of the resting

state fMRI study suggest that excitatory anodal stimulation over M1 preconditions the task-related cortical motor areas by enhancing functional coupling within these cortical regions.

Beyond the effects on M1, tDCS in combination with fMRI has been recently used to understand the brain mechanisms underlying more complex behaviors. One such behavior crucial in many aspects of interactions with the environment is inhibitory control, which reflects the ability to suppress proponent responses. Neuroimaging studies have implicated a network of regions that together form the “stopping network” that supports the processes involved in inhibitory control. This network includes the pre-supplementary motor area (preSMA) as a key player in the implementation of inhibitory control of motor actions, which actively interacts with other brain regions such as the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), and posterior parietal cortex (PPC) (Ray Li et al. 2006). Based on this evidence, researchers used tDCS in combination with fMRI to investigate the potential causal role of preSMA on inhibitory control (Yu, Tseng et al. 2015). In line with their hypothesis, investigators found that applying anodal tDCS over the preSMA leads to a significant improvement of inhibitory control in healthy participants. Interestingly, these behavioral improvements were accompanied by an increased activation in the preSMA following anodal DCS as opposed to the sham condition when stopping processes occurred. Additionally, a subsequent connectivity analysis revealed increased coupling with the ventro-medial prefrontal cortex (vmPFC), a region relatively remote with respect to the preSMA, but the only region whose activation difference was predictive of the individual improvement in behavioral performance. Hence, the results of this study further support the notion that the neural mechanisms behind the short and rapid behavioral improvement brought forth by tDCS may be quite different from, yet functionally connected to, the region/network targeted by the stimulation also in more complex cognitive functions.

tDCS-induced Local Network Effects

Coming back to tDCS-induced effects on M1 connectivity, it is also well possible that induced network effects also take place at the level of local circuits. Following this idea, researchers investigated the hypothesis that the relatively long-lasting synaptic modification induced by tDCS over M1 results in the alteration of associations among populations within M1 neurons which may be reflected in a change of its intrinsic functional architecture (Polanía et al. 2012c). This hypothesis is based on the fact that the intrinsic horizontal neuronal connections within M1 have been found to exhibit short-term and long-term plasticity, which is a strong substrate for learning-related map reorganization (Iezzi et al. 2011; Sanes 2000). Such a

tDCS-generated alteration of intrinsic connectivity might help to explain the previously reported impact of tDCS on motor learning (Nitsche et al. 2003c; Reis et al. 2009). Thus, in this study the authors based their graph theory analysis focused on resting-state BOLD fMRI measurements within the M1. For anodal tDCS, the authors did not find any region where the connectivity degree significantly increased or decreased, however they found that nodes belonging to a cluster around the arm/hand region of M1 (located at approximately the center of the tDCS electrode) communicate more efficiently with the rest of the M1 network. This pattern of results suggests that the increase in efficient connections does not depend on an increase in the total number of functional connections, but is rather due to an efficient reorganization of the functional network. These results therefore provide important evidence indicating that the promotion of LTP-like plasticity induced by anodal tDCS (Fritsch et al. 2010) might be related to an efficient reorganization of the functional architecture of M1.

In a different study, researchers used a type of brain scan called magnetic resonance spectroscopy (MRS) to gain insights into the neuro-chemical mechanisms by which tDCS induces its effects at the level of local circuits (Stagg et al. 2009). The levels of a chemical called GABA (a neurotransmitter molecule that inhibits the activity of nerve cells) were measured in the primary motor cortex before and after healthy participants received tDCS over M1. The results revealed that anodal stimulation leads to a significant decrease in the GABA concentration in the cortex. In contrast, inhibitory, cathodal stimulation leads to a significant decrease in glutamate, with a correlated decrease in GABA. Crucially, this finding is in line with the hypothesis that LTP-like plasticity within the neocortex is critically dependent on GABA modulation (Trepel and Racine 2000), thus further supporting the notion of tDCS being capable of inducing LTP-like plasticity alterations in local neural circuits.

Using this knowledge, in a recent study investigators used tDCS as a mean to test the theoretical proposal that cognitive function is tightly related to the maintenance of detailed cortical balance, where synaptic inputs received by cortical neurons is balanced such that excitatory and inhibitory currents are precisely matched and stable firing preserved (Okun and Lampl 2008; Haider and McCormick 2009). This hypothesis was tested using an associative learning task in humans where the prediction is that when stimuli are paired together, their neuronal activity patterns should exhibit representational overlap at the local circuit level, a consequence of the increase in strength of mediating excitatory connections (Barron et al. 2016). To assess the consequences of cortical rebalancing, the investigators used fMRI to track changes in representational overlap of the learned associations over time, before combining this approach with anodal tDCS in order to induce a local reduction in cortical GABA. In an extremely fascinating finding, the investigators showed that cortical memories can be re-exposed by reduction in local GABA concentrations, induced via tDCS. Interestingly, the extent to which the memory is re-

expressed occurs in proportion to the tDCS-induced GABA reduction. Thus, this finding provides a clear example into how tDCS in combination with different neuroimaging modalities (MRS and fMRI) can be used to reveal the neural mechanisms of rather complex cognitive processes at the level of local neural circuits in healthy humans.

tDCS-induced Cortico-Subcortical Network Effects

Many of the tDCS-induced effects when the stimulation is applied over M1 can be readily explained by the effect of tDCS within the primary motor cortex (Nitsche and Paulus 2000; Stagg et al. 2009; Polanía et al. 2012c) and also due to alterations of task-related cortical connectivity of motor areas by enhancing functional coupling within these cortical regions (Polanía et al. 2011a; Stagg et al. 2014). However, some other functional effects of tDCS are more compatible with an additional alteration of subcortical areas. For instance, it has been shown that tDCS over M1 induces changes in thermal and mechanical sensory percepts and produces long lasting pain relief in chronic pain patients (Fenton et al. 2009). These effects have been attributed to suppression of thalamic sensory pathways following motor cortex stimulation. Additionally, motor cortex tDCS improves gait and bradykinesia in patients suffering from Parkinson's disease (PD) (Benninger et al. 2010), which might be caused by tDCS-induced alterations of basal ganglia function. The results of these studies suggest that cortico-striato-thalamo-cortical circuits might be modulated by transcranial cortical stimulation. Thus based on this evidence, it could be hypothesized that anodal tDCS over M1 would increase the functional connectivity between striatal and thalamic regions and cortical regions associated with motor function. Once more based on resting-state fMRI measurements, it was found that anodal tDCS over left M1 enhanced functional connectivity between the left primary motor cortex and the ipsilateral thalamus (Polanía et al. 2012d). Additionally, functional connectivity of the caudate nucleus, which receives afferents from the cortex and the thalamus, with associative areas such as the superior parietal cortex was enhanced. In line with these findings, in another work it was shown that tDCS over the primary sensori-motor cortex in anaesthetized animals not only affects cortical neurons, but also facilitates activation of neurons in subcortical motor systems (Bolzoni et al. 2013). In addition, it was shown that this subcortical facilitation greatly outlasts (by more than 1 h) the period of transcranial polarization. These studies carried out both in humans and animals provide new evidence of plasticity at subcortical levels, the mechanisms for which remain to be investigated. These findings are of great interest for clinical translational applications considering that anodal stimulation over the motor cortex has been shown to improve gait and bradykinesia in patients suffering from PD (Benninger et al. 2010), where it was speculated whether thalamic activity could be theoretically modulated by cortical

stimulation. The results of the above mentioned studies are indeed in favor for connectivity-driven indirect effects of tDCS on thalamic function.

Beyond the effects on M1, tDCS in combination with fMRI has been recently used to understand the brain mechanisms underlying more complex behaviors involving higher cognitive functions, which most likely also actively involve the action of subcortical brain circuits. One such behavior which has received considerable attention in the last few years, is value-based decision-making, sometimes also known as economic decision-making (Krajbich and Dean 2015). Compelling evidence has shown that making decisions based on subjective values involve a large network of regions including cortical areas such as the ventromedial prefrontal cortex (vmPFC) and dopaminergic subcortical structures such as the ventral striatum (VS), substantia nigra (SN) and ventral tegmental area (VTA) that in turn project to numerous cortical areas in the brain including the vmPFC (Williams and Goldman-Rakic 1991; Clithero and Rangel 2013). Using tDCS applied over the frontopolar cortex combined with fMRI, a group of researchers investigated whereas vmPFC causally supports choices based on subjective preferences in a task where healthy participants had to make attractiveness ratings of a series of faces while being scanned with fMRI before and after receiving tDCS over the FPC (Chib et al. 2013). In line with their hypotheses, following anodal stimulation of vmPFC, participants found the presented faces significantly more attractive. The fMRI analyses revealed that activity in the vmPFC was correlated with attractiveness ratings for all participants both before and after stimulation, however, with no specific effects induced by the stimulation. However, in a subsequent interaction analysis in order to test for the specific effects of tDCS, the investigators found that, following stimulation, activity in the ventral midbrain was more positively correlated with attractiveness ratings. In a subsequent connectivity analysis, the investigators examined the network effects of VMPFC stimulation on other brain regions with special interest in regions encompassing the ventral midbrain dopaminergic areas. Strikingly, they found that the same ventral midbrain region found in the interaction analysis was more functionally coupled with activity in the vmPFC following stimulation. Thus, providing crucial evidence that functional connectivity between vmPFC and ventral midbrain is enhanced by anodal tDCS applied over the vmPFC. The results of this work have once more implications for clinical applications. Given that midbrain regions such as SN/VTA neurons lie deep within the brain, the primary means of influencing them in neuro-pathologies affecting midbrain dopaminergic structures have been with systematic pharmacological interventions, however, it precludes from region-specific interventions (Miyamoto et al. 2012). Alternatives, when the pharmacological interventions fail to deliver the desired effects, include the implantation of deep brain stimulators (Mayberg et al. 2005), however, at the expense of invasive and high risk surgical procedures. As shown by the above-mentioned example study (Chib et al. 2013), networks of interconnected brain areas can be stimulated with tDCS to influence deep brain regions, thus making tDCS a promising tool to noninvasively modulate subcortical activity and functions that may be disrupted in neuropsychiatric disorders.

Conclusions

The studies presented in this section provide important evidence that long-lasting synaptic modifications induced by tDCS, which result in behavioral improvements, might include an alteration of associations among populations of neurons involved in the respective task-relevant functional networks. These series of studies have important clinical implications given that functional connectivity loss and alterations have been observed in many neurological diseases such as stroke (Wang et al. 2010), Alzheimer's disease (AD) (Stam et al. 2007), Schizophrenia (Zhou et al. 2007), among many others (Van Den Heuvel and Pol 2010). Thus the combination of tDCS, non-invasive brain imaging techniques and computational methods provide a new and promising platform to track for functional recovery and to correlate these changes with behavioral improvements in both health and disease.

Concluding Remarks

Insight into neurophysiological effects of tDCS on targeted neuronal populations as well as on complex cerebral networks provides the crucial foundation for advancing both research and clinical applications of tDCS. Quantification of tDCS effects using advanced neurophysiological and functional imaging tools represent an important stepping stone towards the development of parameter-tailored stimulation protocols in order to improve mechanistic understanding of neuroplasticity of the human brain, to elucidate the link between changes in cerebral activity and modification of functional and behavioral outcomes, as well as to facilitate the development of physiologically justified tDCS treatment protocols for clinical applications in neurorehabilitation, psychiatry or pain management. Despite enormous progress in mapping and understanding tDCS effects in recent years, many questions remain unanswered or only poorly understood. Among them stands out the gap in understanding the sources of inter-individual and intra-individual variability in tDCS effects at the molecular, cellular, systemic and functional/behavioral level. Regardless, tDCS bears great potential for modulation of neurophysiological outcomes in health and disease.

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