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Beneficial effects of cathodal transcranial direct current stimulation (tDCS) on cognitive performance

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Abstract

Transcranial brain stimulation is increasingly discussed to improve compromised and physiological cognitive functioning. Various forms of transcranial electric stimulation build on the neurophysiological effects of weak currents that are directed to brain areas to induce modulations of cortical activity. The anode-excitatory cathode-inhibitory (AeCi) physiological model of transcranial direct current stimulation (tDCS) is often expected to produce mirrored cognitive effects for stimulations of relevant cortex areas, e.g., prefrontal cortices. However, recent research indicates that cognitive performance can also be improved via cathodal tDCS. Nevertheless, considering that different cortical structures may interact with current flow in varying ways, it is not necessarily adequate to reject AeCi, to deduct a different physiological effect from cognitive outcomes, or to assume an inefficiency of cathodal tDCS in modulating higher-order cortical functions. By highlighting beneficial outcomes, we here present an alternative view on cognitive enhancements that are consistent with the concept of a predominantly inhibitory action of cathodal tDCS. Suppression of hyperactivity, dysfunctional network activity, noise filtering, and state-dependent activity tuning (homeostatic plasticity) are discussed as possible mechanisms of action. Consideration of these aspects may allow for a better understanding of the complex results of tDCS studies on the malleability of cognition and behavior.

Keywords: transcranial direct current stimulation, cognitive enhancement, cathodal tDCS, prefrontal cortex

Introduction and neurophysiology of cathodal tDCS

To achieve their goals and meet social expectations, individuals are often highly motivated to improve their cognitive abilities by means of learning, technologies, and interventions, while also trying to reduce efforts and to achieve high performance at lowest cost possible. In recent years, transcranial direct current stimulation (tDCS) has been presented and conceived frequently as an easy-to-use technology for simple upregulations of brain activity and cognitive performance. On the one side, obviously, this simple conception is ignorant of the complexity of the human brain, its involvement in solving cognitive tasks with success, and of individual differences on several neurophysiological and psychological layers. On the other side, an enhancement of neuronal activity is often assumed to automatically result in better cognitive performance. Empirically, this direct link between the quantity of neural activity and beneficial performance is not always applicable and cognitive improvements may also result from inhibitory administrations of tDCS neuromodulations. The aim of this paper is to sketch distinct mechanisms that allow for such paradoxical beneficial effects of inhibitory, cathodal tDCS on cognitive performance.

When directed through the scalp, weak electric currents can hyperpolarize or depolarize neuron populations by shifting their resting membrane potential, mostly inhibiting or facilitating the release of action potentials. In the electric fields underneath externally placed electrodes, a relatively uniformly situated majority of the neuronal population directs the hyper- or depolarizing effect of a stimulation. In sum, the dominant responses can produce behaviorally relevant inhibitory or excitatory effects, thus decreased or increased brain activity is often assumed. This physiological basis of modern tDCS methods was investigated at motor cortex regions and quantified by muscle activity triggered by (standardized) single magnetic pulses (Nitsche and Paulus 2000) and replicated with visual evoked potentials at occipital lobe (Accornero et al.

2007). Moreover, excitability changes are consistently documented to outlast the exact stimulation duration and produce after-effects in the range of hours, thus indicative of neuroplastic processes. However, a broad range of potential tDCS applications in psychiatric interventions and modulations of cognitive performance include other brain regions with different architectures, such as the prefrontal and parietal cortices. Here, a direct physiological evaluation of immediate stimulation effects is hardly possible. Moreover, inhibitory stimulations with cathodal tDCS produce ambivalent outcomes (Jacobson et al. 2012), raising the question if this method is efficient for modulating higher-order cortical functions in healthy participants (Horvath et al. 2015; see also Dedoncker et al. 2016). However, this assumption is based on empirical observations in complex behavioural tasks and does not necessarily conciliate with the neurophysiological consequences of different stimulations derived from the motor cortex.

Further complicating the inhibitory notion of cathodal tDCS is the fact that higher stimulation intensities (namely, 2 mA instead of 1 mA) over motor regions did not reduce, but rather increase cortical excitability (Batsikadze et al. 2013; Jamil et al. 2016). This behaviour is thought to reflect ceiling effects based on calcium influx, with larger postsynaptic calcium concentrations due to stronger stimulation intensities rather causing long-term potentiation than long-term depression (Lugon et al. 2015). In the following, we explicitly emphasize stimulation intensities deviating from 1 mA, which is usually administered and was shown to produce inhibitory response at motor regions.

Potential mechanisms for paradoxical beneficial effects of cathodal tDCS

Reduction of hyperactivity in patient groups

Whereas there indeed exist studies that confirm the negative impact of cathodal tDCS on critical cognitive functions such as cognitive control (e.g., Wolkenstein et al. 2014), response inhibition (Nieratschker et al. 2015), or working memory (Zaehle et al. 2011), there is also evidence for beneficial effects on cognitive processes. From early on, it was proposed that pathological elevations of cortical excitability in patient groups could be attenuated by cathodal inhibition and subsequently induced neuroplasticity, such as synaptic mediated after-effects (Nitsche et al. 2003b). Using a bicephalic 2 mA tDCS montage to reduce activity in the left temporo-parietal junction, linked with speech-generation, and the anode placed over the left prefrontal cortex, a hypoactive region in schizophrenia patients, auditory verbal hallucinations were markedly reduced (Brunelin et al. 2012). In another patient group with treatment-resistant obsessive compulsive disorder, a condition often linked to hyperactivity in the left orbitofrontal cortex, targeting this region with 10 sessions of 2 mA cathodal tDCS led to a significant reduction of symptoms (Bation et al. 2016). Both studies used stimulations at rest and showcase the beneficial effect of reducing hyperactivity in patient groups.

Reduction of distractive network activity in healthy participants

Similarly, certain tasks may as well profit from attenuation of disturbing neurocognitive processes. For example, a diminished internal regulation of bottom-up sensory information from reduced prefrontal activity by 1.5 mA cathodal tDCS was suggested as the mechanism to improve performance in the semantic generation of uncommon tool uses (Chrysikou et al. 2013). In our current research, we consistently observed that 1 mA cathodal tDCS can counteract implicit (potentially dysfunctional) associations substantiating the so-called SNARC effect (Schroeder et al. 2016).

Theoretically and empirically, system networks that are activated by a task can be more sensitive to the modulating effects of electric fields introduced by tDCS and could provide a more fruitful reasoning for its modulations than focal perspectives (see

Fertonani and Miniussi 2016, for elaborated discussion). For instance, in an episodic memory task, effects of stimulation were only observed with task instructions eliciting cognitive activity (Zwissler et al. 2014).

Improvement of signal-to-noise ratio

Another interesting conception of the working mechanisms underlying beneficial cathodal stimulation is that of a noise filter: By attenuating spontaneous neuron firing, goal-relevant firing may benefit from an improved signal-to-noise ratio. In different paradigms (visuomotor tracking and visual search) with stimulations over occipital and parietal areas with 1 mA and 2 mA, respectively, this focusing effect of cathodal tDCS was documented (Antal et al. 2004b; Moos et al. 2012). In a comparison of different placements with 1.5 mA, the correct target responses in a working memory task were outlined to depend on modulations below the cathode (Heinen et al. 2016). Also from prefrontal stimulations, cathodal tDCS during episodic memory encoding improved memory accuracy, whereas anodal tDCS had a detrimental effect (Zwissler et al. 2014). The noise-filter hypothesis is also consistent with the improvement of target-flanker processing from 1.5 mA prefrontal cathodal tDCS under high attentional load (O'Neil and Adamson 2012).

Homeostatic plasticity and priming

In a comparable variant of the stimulus-stimulus conflict flanker task and with a more ventrolateral cathode placement over F7, Nozari and colleagues (2014) experimentally manipulated the timings of task and 1.5 mA stimulation. They reported on a task-specific facilitatory tDCS effect only *after* 20 minutes of stimulation. Interestingly, concurrent task completion in the cathodal group produced generally increased response times only, as compared to sham, and this effect was reproduced if participants engaged in another difficult task concurrent to stimulation and before they performed on the flanker task. Advancing motor training, priming with cathodal tDCS –

thought to then reduce glutamergic activity – even further enhanced motor excitability and motor performance enhancements by subsequent online anodal tDCS (Christova et al. 2015), in line with the principles of homeostatic plasticity. Introducing further technical manipulations (different stimulation durations, pauses, and current intensities) in a visual orientation discrimination task, 1.5 mA occipital cathodal tDCS overall improved discrimination performance when applied before the task, thus suggesting regulative adaptation processes to restore brain activity following cortical depression by the cathodal stimulation (Pirulli et al. 2014).

Distant disinhibition

Lastly, effects of tDCS are not limited to the brain region under the electrode but can affect a widespread cortical and subcortical network (Bestmann et al. 2015). Modulation of distant functionally connected networks was observed in neuroimaging (Keeser et al. 2011) and even cerebellar tDCS could improve arithmetic performance by disinhibition of frontal areas (Pope and Miall 2012; see also: Plewnia et al. 2015). Thus, performance improvements might also be caused by stimulation effects on other than the targeted brain region.

----- PLEASE PLACE TABLE 1 ABOUT HERE-----

Need for polarity-specific psychological models

Nevertheless, it is premature (and not supported by the literature in general) to assume that anodal tDCS produces opposite, detrimental effects in these tasks or even includes the same working mechanisms. Although desirable for the correct identification of theoretical and computational models, further empirical validations of the presented mechanisms are challenged by the involvement of task- and state-dependent brain activity that may interact differentially with direct currents dependent

on their direction. The apparent oppositeness of neuromodulation underneath cathodes and anodes is further also subject to partially different physiological mechanisms: At the least, AeCi polarity effects of tDCS are not symmetrical and appear to be more effective underneath anode or cathode, dependent on the domain and paradigm under study (Antal et al. 2004a; Jacobson et al. 2012). In motor cortex stimulations, tDCS often demonstrates sustained shifts of excitability in- and decreases exceeding a stimulation duration for 1h or more. Especially the neuroplastic after-effects of cathodal tDCS were found to depend on modulation of glutamatergic interneurons, whereas anodal tDCS seems additionally to rely on GABAergic synapses (Stagg and Nitsche 2011). A blockage of voltage-dependent sodium channels can only nullify immediate anodal, but not cathodal tDCS effects on motor cortex excitability, whereas NMDA receptors are generally involved in after-effects of both anodal and cathodal tDCS (Nitsche et al. 2003a).

Individual differences

Moreover, distinct neurochemical dependencies can predict stimulation effects in groups with different neurotransmitter distributions, e.g., due to a specific genetic profile. For instance, in a group of genotyped individuals, an impairment of response inhibition by cathodal tDCS was entirely driven by Val/Val homozygous COMT allele carriers, which demonstrates a dependency of optimal performance on prefrontal dopamine signalling (Nieratschker et al. 2015). Thus, such non-linear interactions may account for the observation that further enhancements by tDCS can deteriorate performances (Plewnia et al. 2013; Schroeder et al. 2015). In addition to the influence of the genetic makeup on stimulation effects, a dimensional conception of interacting factors has to consider cortical and skull structure, personality, and baseline performance. Electric field modelling of individual MRI data confirmed that the current

strength at a targeted region was related to tDCS behavioural effects, but also showcased notable variability in stimulation response for different head and cortex structures (Kim et al. 2014). Furthermore, current density and direction are potentially susceptible to practically relevant differences in hair thickness and saline saturation, sweat, pressure by rubber bands, and other (unexplored) montage variations (Horvath et al. 2014).

Exceeding these rather directly relevant individual characteristics, there are also indirect modulations of stimulation effects. Not only baseline performance may predict stimulation successes (Heinen et al. 2016), but unrelated cognitions and emotions can also alter the direction of a neuromodulation, as research with groups of math-anxious and math-leveraged individuals demonstrated (Sarkar et al. 2014). Here, performance improvements and impairments in high- and low-math anxiety groups were documented from the identical prefrontal anodal tDCS configuration when solving simple arithmetic decisions. A recent study on psychopathic personality traits essentially cross-validated this principle with prefrontal cathodal tDCS by showing that particularly individuals high in Cold-Heartedness improved in a response inhibition task (Weidacker et al. 2016).

What effect could different cortical structures have on tDCS effectivity? Certainly this question should be elaborated on in much greater detail, but we wish to formulate a few speculations. One instructive idea could be drawn from the observation that prefrontal TMS with the identical stimulus intensity led to smaller EEG responses than motor TMS (Kähkönen et al. 2004), which has not been tested with tDCS, to the best of our knowledge. However, different prefrontal tDCS intensities may not produce linear and systematic modulations of behavioural or even neural responses (Faehling and Plewnia 2016). Further considerations were raised by Jacobson and colleagues (2012) by pointing to network involvements in cognitive tasks, their noisy measurements, and

contralateral compensation processes, which together rightfully constrain direct comparisons between effective task handlings and externally induced effector movements in TMS-MEP measurements. Finally, cytoarchitecture and receptor density can vary notably between functionally different cortical areas, e.g., motor and multimodal association cortices (Zilles et al. 2002).

Further reducing the apparent AeCi dichotomy, development of more focal stimulation electrodes (e.g., concentric electrodes or HD-tDCS) or multicortical placements (bilateral, bicortical) could profit from refinement of current flow neural polarization effects. Recent studies have already motivated the concurrent up- and downregulation of respective brain areas with standard configurations (e.g., Bation et al. 2016) or with concentric montages, which appear feasible and effective in modulating response inhibition (Hogeveen et al. 2016). By turning necessary return electrodes into pragmatic co-generators of a more focal current field, concentric montages may also reduce the current lack of standardization and motivate theory-guided stimulation approaches.

Conclusion

We here described beneficial effects of cathodal tDCS on cognitive functions and their assumed rationales (cf. Table 1). There is currently no direct neurophysiological or computational confirmation of these mechanisms. In addition, the majority of studies investigating cathodal placements do neither find positive nor negative evidence (Jacobson et al. 2012). Future research should explore interactions between the described mechanisms that may have additive or neutralizing relevance for different behaviours, and could result in unwanted cognitive side effects. The acknowledgement of cathode placements as active contribution to successful enhancements with tDCS, paired with (individualized) network-function definitions and specification of electrical

parameters, will help us avoid diffuse stimulation effects and provide new options for an effective, targeted and knowledge driven modulation of cognitive and behavioural functions.

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