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·Review·

Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation

Min-Fang Kuo, Michael A. Nitsche
Department of Clinical Neurophysiology, University Medical Center, Georg-August-University, Goettingen 37075, Germany
Corresponding author: Michael A. Nitsche. E-mail: mnitsch1@gwdg.de

The prefrontal cortex is involved in a multitude of cognitive, emotional, motivational, and social processes, so exploring its specific functions is crucial for understanding human experience and behavior. Functional imaging approaches have largely contributed to the enhancement of our understanding, but might have limitations in establishing causal relationships between physiology and the related psychological and behavioral processes. Non-invasive electrical stimulation with direct or alternating currents can help to enhance our understanding with regard to specific processes, and might provide future protocols able to improve them in case of malfunctions. We review the current state of the field, and provide an outlook for future developments.

Keywords: affective disorders; brain stimulation; frontal lobe

Introduction

The prefrontal cortex is a compartment of the human brain involved in highly diverse processes, ranging from cognition, motivation, emotion, and complex motor activity to social interactions[1-6]. Disturbances of prefrontal functions are involved in a multitude of neuropsychiatric diseases, including depression, schizophrenia, addiction, dementia, and Parkinson´s disease[7-11]. Thus understanding the complexity of prefrontal physiology is of crucial importance to understand human experience and behavior in health and disease.

Non-invasive imaging approaches, such as functional magnetic resonance tomography, positron emission tomography, and encephalographic (EEG) techniques, have largely facilitated our understanding of human prefrontal functions in the last years. These methods allow identification of cortical activity and excitability changes associated with functions. However, with these techniques it is often difficult to draw conclusions about the causal relationships between the respective processes. To this end, a combination of functional imaging and methods that modulate physiology, such as cortical excitability, activity, plasticity, and oscillations, might be helpful. If modulation of physiological processes results in functional alterations, a causal relationship can be assumed. In the last years, a couple of such stimulation protocols have become available, allowing non-invasive modulation of brain activity and excitability, and thus are principally suited to serve this aim[12-15]. In this review, we give an overview of the principal mechanisms of the tools, and their applications for the exploration of prefrontal functions.

Physiology of Transcranial Electrical Stimulation

Transcranial direct current and alternating-current stimulation (tDCS and tACS) refer to the application of relatively weak currents to the brain *via* scalp electrodes. Specifically, tDCS is the tonic application of constant direct current, and tACS refers to symmetrical oscillatory stimulation. In the case of tDCS, the resulting current flow in the brain induces a subthreshold alteration of neuronal resting membrane potentials, which alters cortical excitability and activity, dependent on the direction of current flow. In the model of the human motor cortex, anodal tDCS enhances, while cathodal tDCS reduces excitability[16-18]. Whereas the effects of brief stimulation lasting for a few seconds seem to be solely based on membrane potential changes, longer-lasting stimulation for a few minutes induces lasting changes in cortical excitability, which can be stable for about one hour or even longer. These neuroplastic after-effects are assumed to be caused by a change in the strength of glutamatergic synapses, are calcium-dependent[19,20], and thus share some similarities with long-term potentiation and depression, as found in animal studies[21].

The primary mechanism of tACS is assumed to be similar to that of tDCS, namely a sub-threshold alteration of resting membrane potential, whose direction depends on the direction of current flow. Different from tDCS, tACS has no major plasticity-inducing effect[22], although recent studies suggest that exceptions do exist[23]. Modelling and animal and human studies have shown that relatively focal AC stimulation can lead to widespread entrainment of oscillatory activity at the induced frequency[24,25]. The main effect of tACS in humans is a modulation of oscillatory frequency bands in the EEG, if these match the stimulation frequency. For instance, tACS at alpha frequency enhances activity in the visual cortex, and results in excitability alterations[26,27]. Thus the main functional effect of tACS seems to be a modulation of cortical oscillations. In this way, tACS is qualitatively different from tDCS.

Cognitive Functions in the Context of Prefrontal Processing

Working Memory

The dorsolateral prefrontal cortex (DLPFC) is critically involved in working memory, as suggested by task-related activation of this area during performance[28]. In particular, the left DLPFC is relevant for verbal working memory, as explored by testing performance in an *n*-back task with excitability-enhancing anodal tDCS over the left DLPFC. In accordance with the hypothesis, tDCS improved performance, as compared to sham stimulation[29]. In a related working memory task, the beneficial effects of anodal tDCS on performance accuracy developed during stimulation, and were stable for up to 30 min after the completion of stimulation[30]. Zaehle and co-workers[31] described similar positive effects of left prefrontal anodal tDCS on response accuracy in an *n*-back working memory task, while cathodal tDCS disturbed performance. Interestingly, anodal tDCS enhanced alpha and theta activity in parallel, while cathodal tDCS had opposite effects, thus offering a plausible physiological substrate for the effects of tDCS on performance.

While the above studies report accuracy enhancements by prefrontal stimulation, other studies have reported only improvement of reaction time in related tasks[32,33], possibly due to different stimulation protocols (tDCS applied before task performance), or ceiling effects. Recent studies suggest that the specific effects also depend in a non-linear fashion on stimulation intensity[34], inter-individual anatomical and demographic differences[35–37], and task phase (learning *versus* overlearned[38]), and that left prefrontal anodal tDCS can also improve performance in other working memory tasks[39]. Given the performance-related alteration of oscillatory activity[31,40], the contribution of theta activity to working memory performance was explored in subsequent studies. Left dorsolateral prefrontal oscillatory stimulation within the theta frequency range, as well as bilateral stimulation of the DLPFC, improved working memory[40,41]. Moreover, Polania and co-workers have described task-related synchronization in the theta range in the left parietal and prefrontal areas during an *n*-back task. Testing the causal relevance of this synchronization to performance, they showed that synchronized tACS in both areas improved, but desynchronized activation impaired performance (Fig. 1). This effect is specific for the theta frequency band[40]. Therefore it can be concluded that synchronized activity in the theta frequency range between task-related activated areas is critical for working memory performance. A recent study has elucidated more closely the specific contribution of oscillatory activity in the prefrontal cortex to working memory performance, showing that decoding of oscillatory activity in the gamma frequency range allows the identification of stored information[42].

Apart from working memory, the prefrontal cortex also participates in many other cognitive processes such as attention, long-term memory, complex problem-solving, and decision-making. However, the number of studies exploring the contribution of the prefrontal cortex to these functions *via* tDCS/tACS is limited so far.

Attention

Excitability-enhancing tDCS of the left DLPFC has been

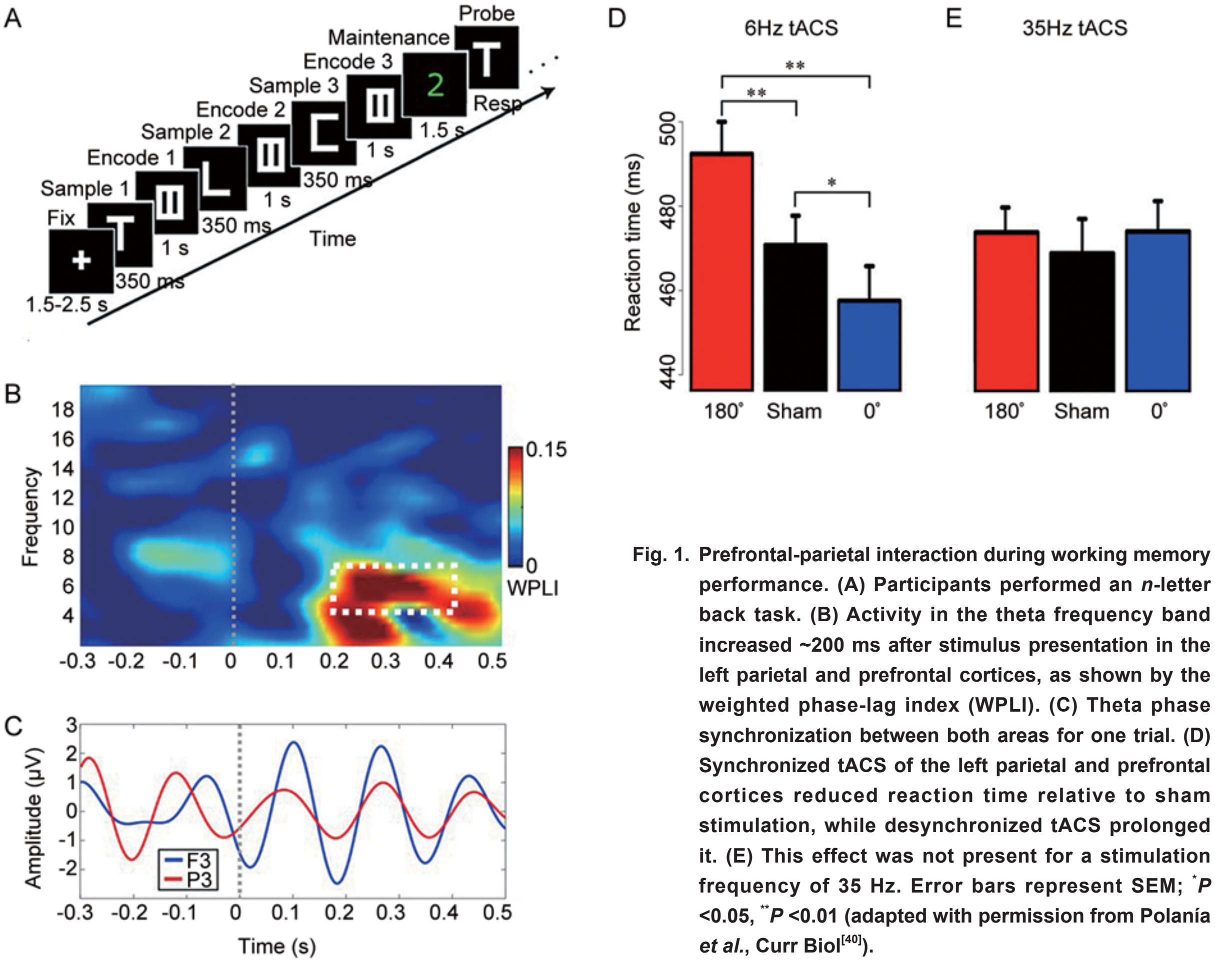

Fig. 1. Prefrontal-parietal interaction during working memory performance. (A) Participants performed an *n*-letter back task. (B) Activity in the theta frequency band increased ~200 ms after stimulus presentation in the left parietal and prefrontal cortices, as shown by the weighted phase-lag index (WPLI). (C) Theta phase synchronization between both areas for one trial. (D) Synchronized tACS of the left parietal and prefrontal cortices reduced reaction time relative to sham stimulation, while desynchronized tACS prolonged it. (E) This effect was not present for a stimulation frequency of 35 Hz. Error bars represent SEM; $^{*}P$ <0.05, $^{**}P$ <0.01 (adapted with permission from Polanía *et al.*, Curr Biol[40]).

shown to improve performance in the Stroop task[39]. Thus this area seems to be involved in attentional set-shifting. In addition, tDCS of the DLPFC seems to have beneficial effects on sustained attention[43]. A recent study showed that anodal tDCS has heterogeneous effects on set-shifting in a parametric Go/No-Go test with regard to the carrier status of the catechol-O-methyltransferase Val158Met polymorphism[44], which provides for the first time evidence for state-dependence of the effect of prefrontal activation on performance.

Long-Term Memory

With regard to long-term memory processes, Javadi and Walsh[45] have described the role of the left DLPFC in word memorization: anodal tDCS improves encoding and trend-wise recognition, whereas cathodal stimulation impairs recognition. In accord, anodal tDCS of this area improves the re-consolidation of learned verbal material[46], and improves performance when applied during word retrieval[47]. These results propose an involvement of the DLPFC in different phases of long-term memory formation and the retrieval of learned material.

Problem-Solving

Some tDCS studies have suggested an involvement of the prefrontal cortex in problem-solving. For example, Cerruti and Schlaug[48] described an improving effect of anodal tDCS of the left DLPFC on complex verbal associative thought. Another study showed that solution recognition of difficult problems is improved by anodal tDCS over the same area[49]. Interestingly, tDCS over the left DLPFC has a performance phase-specific effect in the Tower of London task, which involves strategic planning. In detail, cathodal tDCS improves task performance when applied during the early acquisition phase, probably due to its reducing effect on distractive cortical noise, whereas anodal stimulation improves performance when applied in the later stages, presumably *via* its activity-enhancing effect on task-related neuronal activity[50]. It has been suggested that prefrontal gamma activity is relevant for performance of this kind of task, and indeed tACS in the gamma frequency range seems to improve fluid intelligence[51].

Decision-Making

Prefrontal areas also seem to be involved in decision-making. Bilateral activity modulation of the DLPFC by tDCS reduces risky behavior in a decision task, most probably by altering bihemispheric activity balance, because unilateral stimulation has no effect[52]. In a related task, however, only anodal right/cathodal left stimulation improved performance[53], which is compatible with a risk-avoiding impact of right prefrontal activity. In older participants however, the same electrode arrangement results in more risky behavior, which is possibly caused by age-dependent differences in prefrontal information-processing[54]. The results of a related study conducted by Pripfl and co-workers[55] show different effects of tDCS in risky decision-making dependent on the inclusion of emotional content and smoking state, which hints at the impact of task characteristics and personality factors on information-processing in the prefrontal cortex. In another risk-taking task, however, the same electrode arrangement did not modulate risky behavior, but enhanced confidence in the decision, which shows that evaluative aspects of a decision are also under prefrontal control[56].

Social Cognition

The prefrontal cortex is also involved in social cognitive processes. Knoch and co-workers[57] have explored the importance of the right DLPFC for performance in the ultimatum game. In this game, a fixed monetary reward has to be split between two participants, one of whom (the proposer) proposes how to split the amount of money, and the other (the responder) can accept or reject the offer. If the responder accepts the offer, he/she gets the money as proposed; if not, he/she gets nothing. The conflicting aspects involved in decision-making are the perception of unfairness and economic self-interest. In line with the hypothesis that the right DLPFC is associated with social decision-making, especially with regard to emotion-based control processes, cathodal stimulation of the right prefrontal cortex, which is involved in the generation of negative emotions, increases the acceptance rate of unfair offers. Recently, the role of the right prefrontal cortex in decision-making was explored in a similar game from the perspective of the proposing participant[58]. The results showed that anodal tDCS of this area improves norm-compliant behavior, but cathodal stimulation selectively reduces it when unfair behavior is expected to be punished by a human counterpart. Interestingly, these behavioral changes are not accompanied by related changes in the rating of fairness, or expected punishment. In addition, these effects are substantially weaker in a non-social scenario version of the game, in which the counterpart is a computer, showing that these effects are specific for social norm-compliant behavior.

Taken together, the results of these studies underscore the role of the prefrontal cortex in a multitude of cognitive functions. So far, the DLPFC has been chosen most often as the target of stimulation, probably because it is relatively easily accessed by non-invasive brain stimulation and has been closely associated with many cognitive processes by functional imaging methods. Exactly how stimulation alters prefrontal information processing has not been explored in much detail so far, maybe with the exception of working memory, and is an important future endeavor. Interestingly, some studies have reported that identical stimulation protocols have distinct effects depending on demographic and personality factors, as well as task characteristics. Given the complex anatomy, physiology, and pharmacology of this brain area, this is not surprising. Closer identification of the contributions of these factors might help to unravel the mechanisms of prefrontal information processing in greater detail in future studies.

Emotional Processes

It is well established that the prefrontal cortex is part of the neuronal networks involved in mood and emotion processing. In healthy individuals, the ventromedial and inferior-medial prefrontal cortex seems to be prominently involved in self-referenced affective state[59,60], whereas the DLPFC is more important for processing stimuli without self-referential emotional content, e.g. faces or visual scenes[61-63]. However, this distinction seems to be gradual and might reflect the fact that the medial prefrontal cortex is generally more heavily involved in emotional, and the lateral prefrontal cortex in cognitive processing, but both functional properties substantially overlap[60]. In addition, a hemispherical difference in the processing of positive and negative emotional content has been described. Happy mood and positive emotional stimuli induce predominant left DLPFC activity[62,64,65]. Accordingly, lesions of the left prefrontal cortex by stroke, tumors, or epilepsy are often accompanied by depression, while lesions of the right prefrontal cortex are associated with elated mood[66-68]. Also, clinical depression is associated with left DLPFC hypoactivity, while activity of the right prefrontal cortex might be increased[69].

Some tDCS studies have been performed to disentangle the causal contribution of the prefrontal cortex to the experience of emotion, and emotion-related information processing in healthy humans. From their results, tDCS of the DLPFC does not modify mood in healthy individuals[70,71]. With regard to information-processing that includes emotional content, however, the DLPFC seems to be involved. tDCS of the left DLPFC and the right frontopolar cortex improves identification of faces displaying non-neutral mimics independent of stimulation polarity, as compared to sham stimulation (Fig. 2)[70]. Moreover, emotionally aversive faces are rated less unpleasant with anodal stimulation of the left DLPFC[72]. The same stimulation protocol also reduces the emotional valence of negative pictures[73,74]. In the latter studies, this was associated with higher beta and lower alpha EEG activity, and introversion was positively associated with the efficacy of stimulation. For positive affective stimuli, anodal stimulation of the left DLPFC also improves reaction times, and increases the amplitude of relevant event-related potentials[75]. Beyond perceptual and evaluative emotion-associated information processing, the DLPFC seems also to be involved in emotion regulation. In a task in which the participants are instructed to downregulate or upregulate emotional responses to the presentation of negative or neutral pictures, anodal tDCS of the right DLPFC improves the amount of intended emotion regulation[76]. Finally, anodal tDCS over the right DLPFC combined with left frontopolar cathodal tDCS applied in the re-consolidation phase of a fear-conditioning paradigm improves fear memories, which is in accord with an involvement of the prefrontal cortices in fear memory consolidation[77].

In general, the results of these studies support the assumption that prefrontal areas are involved in the processing of emotional information at different levels of complexity, ranging from perception to memory. Further, some pilot studies suggest that relevant alterations are associated with physiological changes in event-related potentials and EEG activity. Most of the studies have been performed with regard to the contribution of the DLPFC. For ventromedial and frontobasal areas that might be more closely associated with emotion generation, no studies are available so far. While this might be due to the fact that these areas are less accessible to non-invasive brain stimulation techniques, this might nevertheless be an important future endeavor.

Concluding Remarks

The prefrontal cortex has been implicated in a multitude of psychological processes, including cognition and emotion. Since functional imaging and EEG approaches are in many cases not well-suited to establishing causal connections between physiological and psychological processes, brain stimulation is a potentially attractive approach to drawing conclusions. tDCS and tACS have been introduced to modulate task-dependent cortical activity and excitability changes. Indeed, many studies in healthy humans have shown that both tools can be used to modulate psychological functions and physiological processes. While the results of these studies have improved our knowledge of prefrontal functions, many questions are still unanswered, and these should be topics for future studies.

Most stimulation protocols so far have explored the functions of the DLPFC, most probably because it is relatively easy to access. The functions of other areas such as the ventromedial or orbitofrontal cortices in emotional processes are also worth studying. Modelling approaches might offer options to tackle these areas more selectively[78]. A related potential shortcoming is the use of relatively large electrodes, and bipolar electrode montages, which limit the specificity of stimulation effects. Also, advanced stimulation protocols, e.g. using smaller stimulation electrodes, large return electrodes, or multiple electrode approaches, might be helpful[79,80]. Moreover, combining measures of task performance with physiological outcome parameters *via*

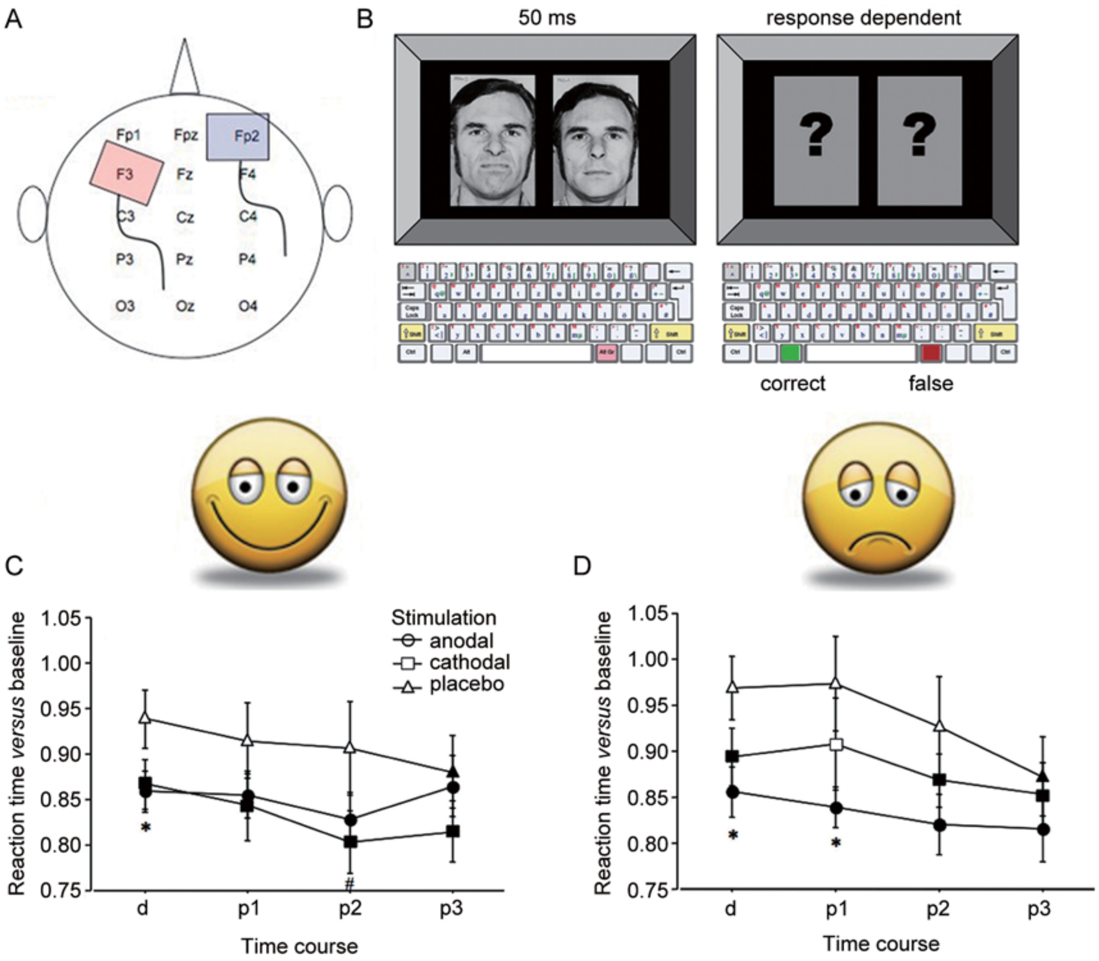

Fig. 2. Alteration of emotion-based information-processing by prefrontal tDCS. (A) tDCS was applied to the left dorsolateral prefrontal and right frontopolar cortex. Polarity refers to the dorsolateral prefrontal electrode. Participants had to identify the position of a non-neutral facial emotional expression as rapidly as possible, and press the appropriate key repetitively before, during, and after anodal, cathodal, or sham tDCS (B). For positive (C), and negative (D) facial expressions, reaction times became faster during the course of the experiment, thus indicating learning of the task in all stimulation and emotional conditions. Under both real stimulation conditions and for both facial expressions, reaction time reductions became significantly faster than with placebo stimulation. For anodal tDCS, positive emotional facial expressions were identified faster than with placebo stimulation during and after tDCS. For emotionally negative facial expressions, anodal tDCS improved perception only during tDCS as compared to placebo stimulation. A minor effect can be seen for cathodal tDCS compared to placebo stimulation (p2 only). Filled symbols: significant reaction time differences relative to baseline values; asterisks: significant differences between anodal tDCS and placebo tDCS; hash symbols: significant differences between cathodal and placebo tDCS for a given time point (paired, two-tailed *t*-tests, $P < 0.05$). Vertical bars indicate standard error of the mean. d, during; p1, immediately and 5 min; p2, 10 and 20 min; p3, 30 and 60 min after tDCS. Adapted with permission from Nitsche *et al.*, Front Psychiatry[70].

simultaneous EEG, ERP, or functional imaging approaches, which is now technically possible, will further enhance our understanding of psychological-physiological interactions. In this connection, functional connectivity approaches might be especially helpful, since the respective psychological functions, and the effects of electrical stimulation, alter network functions[40,81]. An emerging topic might be the elucidation of the foundation of inter-individual differences with regard to the efficacy of transcranial electric stimulation. Here, initial efforts have been made to explore trait- and state-dependency of the effects.

With regard to application aspects, it should be kept in mind that the studies referred to in this review were not intended to induce maximally strong effects, but aimed to explore the contribution of certain cortical areas to psychological processes. So far, it is unknown to what degree tES can alter psychological functions. Likewise, the impact of tES on performance in a certain laboratory task does not necessarily imply that the same effects are achieved in everyday life, and – maybe more important – whether these effects would be meaningful. This applies also to clinical applications, where pathological changes of cortical excitability, activity, and pharmacology might alter the impact of brain stimulation as compared to healthy humans.

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