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Hypothesis of the optimal therapeutic effect of transcranial direct current stimulation (tDCS) for psychiatric disorders: Integration of positive cognitive tasks during the neuroplastic process

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a promising intervention for psychiatric disorders; however, little is known with regards to the optimal regime. As cognition, either spontaneously generated by patients or guided by treatment, is important in psychiatry, we have proposed a model that integrates cognition activity with the biological mechanisms of the therapeutic effect of tDCS in psychiatric disorders. We propose that the valence of the outcome of these mechanisms may be determined by the cognitive activity of the patient before or during tDCS treatment. This hypothesis implies that proper cognition activity may work in cooperation with tDCS to achieve the maximum treatment effect. Negative cognition may decrease or even reverse the positive effect of tDCS. According to this hypothesis, the performance of explicit tasks or instructions before, during, or after tDCS is important. Harm caused by misuse of home-made tDCS equipment is also addressed in this hypothesis.

Background

The therapeutic effect of transcranial direct current stimulation (tDCS), a compact and safe brain stimulation technique that employs a small current, is currently under discussion. Change in the neuronal membrane potential and increased cortical excitability are the most important biological mechanisms of tDCS [1,2], and these effects could boost ongoing endogenous neuroplasticity [3]. For instance, as the membrane resting potential is depolarized by tDCS, it becomes easier for neurons to fire an action potential, inducing subsequent tetanus-induced long-term potentiation (LTP). Therefore, tDCS paired with electrical stimulation could promote Hebbian learning [1] and bring about LTP. Meanwhile, the GABAergic system has been identified as one of the most important target sites [4]. Nevertheless, the detailed biological mechanism remains to be elucidated. It should be noted that tDCS can not only influence LTP, but also long-term depression of neurons [5]. In addition, tDCS may act upon the balance of excitation/inhibition in the cortical region [6]. Other potential mechanisms have also been presented. Animal study has indicated that tDCS causes oscillations in underlying tissue and influences functional connectivity. This effect could explain the way in which tDCS may improve the outcome of learning tasks [7].

Evidence has implied that tDCS is effective in terms of improving motor performance and the response latency and accuracy in cognitive tasks [8].

A medium to large effect was found on motor learning post-stroke [9], while medium effects on cognitive and motor performance were observed in elderly individuals [10]. However, the efficacy of treatment for other psychiatric disorders remains controversial [11]. A meta-analysis showed that the effect size of active vs. sham tDCS was small to medium for the treatment of depression [12,13]. Little is known with regards to the treatment efficacy of tDCS for schizophrenia. A meta-analysis of randomized controlled trials reported no beneficial effects on persistent hallucination [14], while a medium effect in terms of improving negative symptoms was found [15].

Hypothesis.

Considering the boosting effect of tDCS on learning [2,7], we speculated that the therapeutic effect of tDCS may not be exclusively determined by biological mechanisms. Other factors may also contribute to the therapeutic effect of tDCS, especially in the treatment of

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psychiatric disorders. Herein, we propose our hypothesis. We speculated that the most optimal therapeutic effect of tDCS in psychiatric disorders could be attained by integrating positive cognitive tasks during the neuroplastic process. Two rationales for this hypothesis are stated below.

Rationale 1. The mechanism of tDCS, neuroplasticity, may not be associated with the positive effect.

It has been established that reduced neuroplasticity could be an important etiology for mental illness [16]; however, maladaptive plasticity has been found to be related to several neuropsychiatric disorders or symptoms, such as dyskinesia [17], neuropathic pain [18,19], and dystonia [20]. It should be noted that neuroplasticity is the biological basis of negative effects. For instance, Rogan et al. demonstrated that fear conditioning could be related to neuroplasticity [21]. It was also proposed that neuroplasticity evoked by a stress event could represent an etiology of post-traumatic stress disorder [22]. In addition, neuroplasticity could be an underlying mechanism in the early stages of development of an addiction [23,24]. It was found that tDCS may induce a poor working memory performance [25,26]. An experiment showed that maladaptive plasticity could be brought about by certain tDCS montage [27]. Although the risk of unrestrained use of do-it-yourself tDCS has been addressed [28], there is little evidence in this field. Recently, a study demonstrated that a commercial tDCS headset could impair working memory [29]. Whether or not tDCS could be used to alter previously-induced plasticity is unclear. A study demonstrated that tDCS interfered with rapid training-induced plasticity [30].

Rationale 2. The valence of the outcome of these mechanisms may be determined by the cognitive activity before or during tDCS.

Changes in neural connections could be the mechanism that effects cognitive activity (either beneficial or harmful). As tDCS may enhance LTP via shifting of the membrane potential [1], it is plausible that the effect of tDCS might interact with recent cognitive activity. Although membrane potential may be modulated by tDCS, leading to change in firing rates and timing, increase in neuronal excitability, it is still needed to investigate how tDCS could enhance neuronal activity. In addition, tDCS is known as a modulator of N-methyl-D-aspartate (NMDA)-dependent plasticity, it was also found NMDA receptor could be the mediator between tDCS and LTP [31]. Thus, the role of neuronal activity on the benefit effects of tDCS should be considered. Recent basic science study [5] revealed that tDCS effects on LTP could be determined by dendritic location and endogenous source of NMDAR synaptic activity. These findings suggest that cellular tDCS effects may result in facilitated LTP in dendrites and enhance endogenous synaptic activity when tDCS is paired with training. The critical role of endogenous synaptic activity was confirmed by several human studies, as NMDA channel antagonist inhibit the tDCS effect [32]. It was found that timing might be critical to the outcome of tDCS when combining tDCS with cognitive training [33]. In a recent experiment, the effect of tDCS was enhanced when a training intervention was conducted during the tDCS session [34]. These findings may imply that the effect of tDCS is sensitive to cognitive activity near the stimulus. In a critical study, Bortoletto et al. demonstrated that the effect of tDCS, as measured by task performance and motor evoked potentials (MEPs), could be determined according to the characteristics of the combined motor task [35]. This finding indicated that tDCS may reduce or enhance learning depending on the combined task. It was also found that the cognitive demands of a memory task performed during tDCS may determine the effect on performance after stimulus [36]. Emerging evidence may support that the effect of tDCS could be moderated by combining tasks. In other words, it is not implausible that the effect of tDCS (or other NBS techniques) could be influenced or altered by cognitive activity. Further research may provide supportive evidence in relation to this issue. It was also found that tDCS may enhance the response of fear memory, which is conditioned before tDCS [37]. A study on methamphetamine craving also found a state-dependent effect of tDCS, in that tDCS reduced cravings at rest, but elevated cravings during methamphetamine-related cue exposure [38].

Therefore, we hypothesized that the most optimal therapeutic effect of tDCS in mental disorders could be attained by integrating positive cognitive tasks during the neuroplastic process. We speculated that cognitive activity induced during treatment may determine the treatment target. For example, a session of mindfulness treatment might enhance attentional monitoring and the emotional regulation system [39], and the memory system might be involved in behavioral therapy for addiction [40]. Meanwhile, tDCS may boost or support the effect, depending on the timing of the treatment and tDCS:

1. For online treatment (tDCS and treatment at the same time): tDCS may help to amplify the treatment effect.
2. For offline treatment (tDCS after treatment): tDCS may help to reconsolidate the effect.
3. For treatment after tDCS: tDCS might help to increase the level of cortical excitability and increase the effect of follow-up treatment.

Considering the biological effect of tDCS, the therapeutic effect in mental disorders could be expressed in a formula similar to the general linear model:

$$\begin{aligned} \textit{Total therapeutic effect} = {} & \textit{neuroplastic effects of tDCS} \\ & + \textit{effects of activating cognition task} \\ & + \textit{interaction of cognitive activity and tDCS} \end{aligned}$$

The positivity of *the total biological effect of tDCS*, such as cortical excitability and neuroplasticity, has been established [41,42]. *Cognition activity* is a recent activity brought about by medical intervention or self-generated by patients. As cognition activity is not constant, we suggest that salient recent cognition activity should be considered. The third term of this model, the interaction, forms the basis of the hypothesis of this study.

According to this formula, it is plausible that performance of a negative cognitive activity during tDCS might cancel out or even reverse the supposed therapeutic effect. For instance, patients with MDD who are not taking medication or undergoing other interventions might self-generate negative thinking during the session. Considering the prevalence of the placebo effect in the treatment of mental disorders [43], the therapeutic effect of tDCS monotherapy might be a summation of the tDCS effect and the placebo effect boosted by tDCS.

Evaluation of the hypothesis

Several previous studies of healthy subjects may have provided supportive evidence for our hypothesis [35,36]. A recent study indicated that concurrent tDCS could enhance motor learning among children [44]. In addition, a case report stated that add-on cognitive behavioral therapy (CBT) enlarged the effect of tDCS initiated prior to the CBT [45]. A similar effect was replicated in a randomized trial, indicating that cognition control training boosted the antidepressant effect of tDCS [46]. In an interesting reported phenomenon, tDCS and classical extinction could be combined to decrease the avoidance tendency [47]. Several trials demonstrated better effects of tDCS (or other similar techniques) when combined with cognitive-related interventions, which also supported this hypothesis [48,49]. A meta-analysis confirmed that working memory training is enhanced when accompanied by tDCS [50]. In order to test this hypothesis, systematic manipulation of the nature of the task that is combined with tDCS is needed.

Discussion

This hypothesis may help to explain why tDCS might be more reliable in enhancing motor task performance than when used for the

treatment of psychiatric disorders, and may provide a concept that integrates biological and cognitive interventions in this promising treatment technology. Several implications can be drawn from this hypothesis. First, an appropriate intervention combined with tDCS is crucial to enhance the treatment efficacy. Second, performance of an explicit task or instruction before, during, or after tDCS is important. In patients with a tendency to generate negative cognition (such as those suffering from depression) during tDCS, avoidance of adverse online effects (maladaptive thinking during the tDCS session) is important. Third, considering the feasibility of home-made tDCS equipment, the adverse effects of utilizing such equipment without medical advice should be addressed [28]. The hypothesis may not be limited to tDCS, but may also apply to other non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) or other transcranial current stimulation (tCS) methods. Considering that tDCS can be performed using a compact and potentially wearable device, addressing this hypothesis for tDCS is urgent.

The clinical implication of this hypothesis is still unclear. Although herein we hypothesized an optimal regime for cognitive manipulation, clinical application should be conducted with care. The hypothesis we have proposed may be very useful for the treatment of some mental disorders in which problematic cognition, or beliefs, may play an important role. For example, cognition errors combined with depression could be a treatment target of psychotherapy with tDCS. As cognitive distortion is also related to altered prefrontal function [51], combining tDCS with cognitive training might be a useful tool. Our hypothesis could increase our insight into the proper use of tDCS. For example, repetitive negative thinking (RNT), which is uncontrolled, excessive, negative thinking, might be a characteristic of anxiety. Applying tDCS in cases of patients with anxiety without proper cognitive treatment before or during tDCS could be dangerous, as tDCS might boost the harmful effect of RNT [52]. Also, our hypothesis may imply that some positive symptoms (i.e., hallucinations) in schizophrenia might not be readily treated by tCDS if no appropriate intervention or cognitive training is applied. Attention should be paid to the unexpected interaction between positive symptoms and tDCS in patients with schizophrenia.

This paper focused on the interaction between cognition activity and tDCS, which is a critical issue in the treatment of mental disorders. Whether this effect is important in terms of other targets, such as motor performance, is as yet unclear. In addition, other fundamental factors, such as dosage, may also alter or even reverse the effect of tDCS [53]. The formula we have proposed is a theoretical one. The purpose of this model was to initiate intuitive thinking to enhance our understanding of the effect of tDCS on psychiatric disorders. The prediction power of this model is limited in terms of quantitative analysis.

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Conflict of interest declaration

We declare that we have no conflicts of interest.

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