Neuromodulation for Addiction by Transcranial Direct Current Stimulation: Opportunities and Challenges

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Key Words

Neuromodulation · Neuroengineering · Transcranial direct current stimulation

Abstract

The field of neuromodulation encompasses a wide spectrum of interventional technologies that modify the pathological activity within the nervous system to achieve a therapeutic effect. Therapy, including transcranial direct current stimulation, has shown promising results across a range of neurological and neuropsychiatric disorders. This article reviews the state-of-the-art of neuromodulation for addiction and discusses the opportunities and challenges available for clinicians and researchers interested in advancing the neuromodulation therapy. A neuromodulation-based approach for addiction has the advantage that the effects might be immediate and selective to the dysfunction. If an alteration in the mechanisms of brain plasticity indeed represents the proximal cause for nicotine-associated cognitive decline and is a critical contributor to the early pathogenesis of addiction, novel interventions that forestall the development of symptoms might be possible.

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Introduction

Addiction is a neuropsychiatric disorder that is characterized by compulsive seeking behavior to rewarding stimuli in spite of its adverse consequences, which is associated with an increase in extracellular dopamine concentration. Such behavioral sensitization produces a persistent hyper-responsive state induced by different types of substances such as tobacco, alcohol, food, and addictive drugs. The neurobiological correlates of addiction is known to be related to several areas in the mesocorticolimbic network including the nucleus accumbens, and the ventral tegmental area with the dopaminergic transmission in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and anterior cingulate cortex [1, 2].

Among them, addiction to tobacco, for example, kills one person prematurely every 6 s. One in 2 long-term smokers, largely in low and middle-income countries, will die from tobacco addiction [3, 4]. This epidemic reflects the highly addictive nature of tobacco, especially nicotine, its principal addicting component. Despite the criticality, appropriate treatments for nicotine addiction

Fig. 1. A graphical illustration of transcranial direct stimulation mechanism. How the direction of the electric field determines neuronal polarization in compartment-specific fashion (Quantitative Neurophysiology with Applied Electric Fields).

are yet to be discovered; also, favorable outputs of accepted treatments have not been significant in the long run. Craving and substance abuse are highly variable and dependent on environmental influences, and an individualized intervention might be critical for successful therapy. Different brain areas involved in different dimensions of this illness and different chemical substances present in processes involved in substance abuse complicate the execution of therapeutic interventions.

Even though pharmacological treatments for addiction have had promising outcomes, their nonspecific effects on different receptors and the impossibility of local intervention in targeted areas in the brain, have slowed their advancement in the treatment of addiction. Greater insight into the malfunction of neural networks associated with cognitive control and in smokers could provide valuable information to understand the low success rates for giving up smoking. Such findings must be rooted in a better understanding of the neurobiological underpinnings of the addiction disorder and require careful translation into large patient populations.

Neuromodulation is a rapidly growing field of study, encompassing a wide spectrum of implantable and non-invasive technology-based approaches for the treatment of neurological and neuropsychiatric disorders. Neuromodulation refers to interfacing and intervening with the nervous system through various sources of energy such as ultrasound, electric and magnetic pulses with the goal of long-term activation, inhibition, modification, and/or regulation of neural activity [5].

Transcranial direct current stimulation (tDCS) has been used in the clinical field to treat movement disorders

(Parkinson's disease, dystonia, tremor), Tourette syndrome, obsessive-compulsive disorder, depression, tinnitus, sensory disabilities, bladder control, epilepsy, headache, chronic pain, spasticity, stroke, minimally conscious state, and spinal cord injury [6]. With these successes, there is tremendous impetus to refine existing technologies and develop new approaches to modulate the nervous system for existing and emerging indications for addiction.

It is also important to acknowledge at the outset that there is no single mechanism by which all neuromodulation therapies act. The short- and long-term effects of neuromodulation depend on the clinical disorder, patient's anatomy and co-morbidities, neural pathway(s) targeted, modality of stimulation, duration of stimulation, and applied stimulation settings, which can range in terms of amplitude and polarity of the underlying neural activity. The nervous system is a dynamic entity and the application of neuromodulation can depend on plasticity and brain state. The field of neuromodulation is poised to see explosive growth over the next decade.

Non-invasive brain stimulation (NIBS) is a technique for modulating brain activity using various transmitting energy source such as electromagnetic fields or ultrasonic wave through skull non-invasively. tDCS is a NIBS technique in which 2 spongy electrodes, an anode and a cathode, are placed on the scalp after being soaked in saline solution. A current generator is connected to the 2 electrodes, and it delivers a low intensity electrical current, thereby polarizing membrane potential of neurons in the stimulated area. Current that flows from the cathode to the anode has an inhibitory effect on the

stimulated area, while current that flows from the anode to the cathode is typically excitatory (fig. 1). The excitatory and inhibitory potentials tDCS can regulate are of great importance in clinical applications [7–9]. Over the past decade, tDCS has emerged as a non-invasive tool to modulate the excitability of the cortex. tDCS is typically applied with a current intensity of 0.5–2 mA for a period of 10–20 min per session [10–12]. There is also strong evidence that increasing the current density and duration of stimulation can lead to more significant and longer lasting effects on cortical activity. However, it is important to maintain relatively weak currents to retain subthreshold effects of tDCS on cortical excitability, and avoid safety concerns with higher levels of electricity. Recent advancements in the neuroscience research-related brain oscillation [13] and its functional significance, the modulation of frequency-dependent brain oscillation by transcranial alternating current stimulation (tACS) have become more significant [9, 14]. tACS enhanced the possibility of using it in the clinical field by controlling stimulation strength and frequency [15, 16]. During tACS, a sinusoidal electrical current at a specific frequency is applied to the subject through electrodes placed on the scalp. This technique may give us valuable information about the potential roles of neural oscillations by manipulating them with simultaneously measuring the effect and behavior. However, measuring its physiological effects is still a challenge due to the difficulty to tease out the stimulation noise [14].

Several studies have also attempted to reduce impulsive and risk-taking behaviors in healthy populations using tDCS [17–19]. Individuals with substance abuse problems generally exhibit increased impulsivity and risk-taking behavior when compared to controls, due to deficits in top-down cognitive control. Bilateral stimulation of the DLPFC was shown to elicit a significant decrease in ambiguous risk-taking behavior in healthy human subjects [20] and a decrease in impulsivity on a non-ambiguous risk task [21]. The principal target for such studies is the DLPFC based on prior rTMS, which shows that modulation of this area results in a decrease in nicotine, cocaine and also food craving [22], and neuroimaging studies show that the activity in this area is significantly associated with drug craving (alcohol: [23], cocaine: [24], nicotine: [25], heroin: [26]).

This means that these interventions may result in lower drug-seeking behavior. Moreover, there are some studies showing that drug craving is correlated to the level of impulsivity [17, 27] and that when there is a cue as-

sociated with a drug such as images of the drug or people using drug, this creates a response in the mesolimbic pathways generating an increase in DLPFC activity that, in part, may be responsible for the drug-seeking behavior. 'It would follow that if the activity of DLPFC is modulated externally by tDCS, this might block this cascade of events due to the competition with the input coming from tDCS that can ultimately decrease the signal to noise in the neural system associated with reward'. Whether DLPFC stimulation in addiction is influenced based on the mechanism associated with cognitive control of craving [9, 17], decreased attentional bias [18, 19], or control of the impulsivity through mesocorticolimbic dopaminergic pathway still remains illusive and needs to be explained further.

Nevertheless, we have come to believe that tDCS might be a reasonable alternative therapeutic treatment for addiction. The device to deliver tDCS is simple, can cost less than US\$10,000 and can be manufactured locally. The equipment is fully reusable and utilizes one standard battery that can last several weeks. Furthermore, this treatment is easy to administer, and can be applied by technicians following appropriate instruction and training. Although further studies evaluating this method are warranted, tDCS might help to improve mental health in areas with poor resources [8].

Though tDCS are noninvasive by nature, tDCS technique is associated with potential risks that require certain precautions. If, however, the experienced investigator follows the appropriate guidelines and recommendations, it can be applied safely with minimal adverse effects [8, 9].

Given the extensive health technologies available, it is often difficult for developing countries to decide which emerging technologies are best suited for their own needs with their current resources. In the long run, maintaining the lifestyle of neurologically impaired individuals can be extremely costly and time-consuming.

Although the majority of tDCS studies to date have focused on behavioral effects, several groups have begun to assess the neurophysiological effects of tDCS in greater detail through the use of noninvasive functional imaging methods.

Functional MRI has also been used to assess the effects of transcranial electrical stimulation in both animal models and humans [28]. Multiple studies in humans indicate that tDCS is able to induce local, polarity-dependent effects on the fMRI BOLD signal and significant changes in resting state functional connectivity [29].

Conclusion

Despite many advances in tDCS research, there are still a number of technical challenges. First, the optimal tDCS stimulation configurations and protocols for different cortical regions need to be established. Second, variations in electrode design beyond the traditional large sponge electrodes may improve the focality of tDCS. Third, electrode positioning and underlying cortical anatomy play a significant role in determining current flow and distribution during tDCS. The existing body of tDCS literature reveals large variations in subject-specific effects of stimulation, even within a particular cortical region. Though current approaches generally utilize the international 10–20 EEG system for positioning tDCS electrodes, future work will benefit from the use of subject-specific computational models based on anatomical MRI and FEM/BEM for targeting tDCS.

Functional neuroimaging of tDCS also faces significant challenges. Currently, there have been very few attempts to simultaneously record EEG during tDCS stimulation. The majority of tDCS-EEG studies have collected

EEG only before and after a period of tDCS stimulation. In summary, tDCS have gained immense popularity due to their effects on modulating cortical activity and, consequently cognitive performance. However, the neurophysiology underlying such neuroplastic changes is less understood.

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Authors' Contributions

S.B. designed, prepared and wrote the final draft. W.-K.Y. read and approved final draft and revised manuscript.

Disclosure Statements

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