

Review Article

Brain Stimulation in the Treatment of Addiction

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Abstract

Drug dependence is a disorder that affects the whole subject but specially its mental health. Several brain areas involved in drug addiction have been described and the prefrontal cortex is pointed as a key structure involved in the control over drug intake behaviour. Here, we summarize the involvement of some prefrontal sites in drug abuse and we present relevant findings that point the neuromodulation of the prefrontal cortex as a promising additional tool in the treatment of addiction.

Keywords: Addiction; Drug Abuse; Brain Stimulation; Neuromodulation; Prefrontal Cortex

Abbreviations

PFC: Prefrontal Cortex;
OFC: Orbitofrontal Cortex;
ACC: Anterior Cingulate Cortex;
DLPFC: Dorsolateral Prefrontal Cortex;
tDCS: transcranial Direct Current Stimulation

Introduction

Drug dependence is known to be associated with structural and functional damage to the prefrontal cortex (PFC) culminating in the reduction of frontal activity. Besides, the PFC is critically involved in processing the craving of smoking [1,2] and drugs such as alcohol [3]; opiates [4] and cocaine [5,6]. Specifically, craving is associated with enhanced activity of this cortical area during drug cue presentation. Once PFC is broadly related to executive functions and to the brain's reward circuitry [7-9], this imbalance indicates that the cognitive ability to regulate drug-seeking behaviour is decreased, and the risk of consuming the drug increases. Reducing craving and improving cognitive functions constitute great challenges in the treatment of drug addiction and, unfortunately, pharmacological and non-pharmacological approaches have not fully addressed these issues so far.

PFC activation during the exposure of drug-related cues may be specifically related to addiction and associated with an enhanced desire for the drug [10].

Furthermore, activity enhancement of PFC areas involved in drug-related processes, including emotional responses (medial OFC and ventromedial PFC in craving), automatic behaviors (OFC in drug expectation and ACC in attention bias) and also higher-order executive responses involved in drug-related working memory (DLPFC) [11] may constitute prominent factors preceding relapses.

The mesocorticolimbic dopamine system and the nigrostriatal dopamine system both contribute to cue-induced drug seeking [12-14] and other behavioral effects of drug use, including

reward [15, 16]. Several evidences suggest that an action in dopaminergic neurons may be the mechanism responsible for the reward caused by cocaine consume, or else, the blockade in the dopamine reuptake and subsequent increase of the activity of this neurotransmitter over dopaminergic receptors may be the responsible for the “high” associated with cocaine use [17]. It is well known that some areas from the prefrontal cortex that are involved in these drug-related processes are activated when drug addicted is exposed to either the drug or some drug-cue [1,2,5,6,18-21]. Volkow et al [22] postulated that this enhanced activity of PFC could contribute to the compulsive self-administration and the lack of control (impaired inhibition) in addicted subjects and also contribute to disruptive cognitive operations that impair judgment and favor relapse [22].

Neuromodulation as an alternative therapy

Transcranial direct current stimulation (tDCS) is technically a simple method of noninvasive brain stimulation that has been used to modulate neuronal resting membrane potential leading to changes of cortical excitability and other functional parameters [23-25]. It is well established that cathodal current decreases cortical excitability and anodal current increases excitability [26-29]. The potential benefit of this neuromodulation induced by tDCS has been increasingly investigated in neuropsychiatric disorders, such as depression [30-34] and substance abuse and craving including alcohol [35,36], tobacco [37], Marijuana [38] and also foods disorders [39].

The potential use of tDCS in the treatment of drug addiction can be more explored. Assuming that tDCS has been associated with working memory enhancement and improvement in other cognitive domains [40-48], brain stimulation over dorsolateral prefrontal cortex (DLPFC) can enhance executive function, providing improved cognitive control over relapsing on drug use [49]. On the other hand, tDCS has demonstrated an important effect in the reduction of craving when applied over the DLPFC. The parameters and results of relevant literature in the field of brain stimulation, especially transcranial direct current stimulation, in the treatment of addiction are discussed below.

Discussion

Anodal tDCS over the left and right DLPFC was beneficial for reducing cue-provoked smoking craving [37]. In patients with alcohol dependence while being exposed to alcohol cues, both left anodal/right cathodal and right anodal/left cathodal significantly decreased alcohol craving compared to sham stimulation [35]. When tDCS was studied in chronic marijuana smokers, it was observed that right anodal/left cathodal tDCS over the DLPFC (the electrode montage of the present study) was significantly associated with a diminished craving for marijuana [38].

It has been proposed that cognitive intervention would attenuate the increased cue-induced response in the PFC during drug abstinence [11]. For example, when cocaine abusers purposefully inhibit craving when exposed to conditioned drug-cues, specific changes in brain regions that process reward and prediction of reward occur, or else, regions involved in processing conditioned responses decrease their activities. Interestingly, the increasing of the left DLPFC activity in the P3 segment under crack-related cue presentation observed in crack-cocaine users from non-stimulated group (sham-tDCS) was prevented by the cathodal tDCS applied over the left DLPFC in crack-cocaine users from real tDCS group, suggesting that cathodal tDCS over the DLPFC could be helpful to control the processing of drug-conditioned responses and subsequently the craving response [50,51]. The P3 wave is typically observed in more anterior brain areas [52] and is sensitive to general and specific arousal, contributing to attention activation and information processing [53]. The association between P3 amplitude and cue-reactivity has been described in volunteers with history of cocaine use [5,54] and other drugs [55,56]. These studies report increased craving after the presentation of drug-related cues, as well as an increased P3 amplitude. In fact, according to Volkow et al [57] “The frontal mediation of a neural circuit involved in the craving response provides a target for top-down cognitive interventions that may be therapeutically beneficial. Interventions that strengthen a weakened but still functional fronto-accumbal circuit may increase the ability of cocaine abusers to block or reduce the drug craving response” [57].

Transcranial electric activity has been shown to be associated with frontal-related cognitive changes in healthy subjects and several psychiatric conditions [40-48]. Previous study from our lab showed specific clinical and electrophysiological (as indexed by P3) effects of tDCS on patients with alcohol dependence in which we demonstrated that anodal tDCS over left DLPFC resulted in an improved cognitive function [36]. Not only transcranial, but also epidural stimulation was already used to study emotion regulation and the impact of cognitive control on neural response to visual stimuli, for instance, Hajcak et al [58] studied five patients with treatment-resistant mood disorders stereotactically implanted with stimulating paddles over DLPFC bilaterally. This study corroborated the role of DLPFC in regulating measures of neural activity that have been linked to emotional arousal and attention [58]. Though the number of studies on frontal neuromodulation has been growing in psychiatric disorders, efforts are needed to propose this technique as an effective repetitive therapy in the treatment of such conditions.

Interestingly, we have observed that the effect of anodal tDCS stimulation over the left DLPFC is restricted to the left DLPFC. Besides, when left cathodal tDCS was coupled with right anodal tDCS over the DLPFC, the effect was still restricted to the left DLPFC [50]. These facts bring the issue about inter-

hemispheric interaction which occurs via transcallosal fibers that transmit inhibitory influences between the homologous areas of both hemispheres [59]. These fibers are thought to be glutamatergic and to project onto inhibitory GABAergic interneurons [60]. This interaction had already been demonstrated for motor response after stroke through noninvasive brain stimulation over primary motor cortex (M1) [61-63]. Although neuromodulation is discussed here in the cognitive field, motor responses are also the target of several studies. In these cases, M1 receives the stimulation and the expectance is for motor rehabilitation. However, mechanisms through which the current is acting may be similar to those observed in cognitive field. The improved motor function after brain stimulation may be attributed to a suppression of interhemispheric inhibition (down-regulation of the excitability in the intact hemisphere) resulting in an improvement of the damaged function. In subjects with major depressive disorder, 1 Hz rTMS (applied to the left M1) decreased corticospinal excitability in the left hemisphere; however, it induced no significant changes in corticospinal excitability in the contralateral, right hemisphere. In this case, the authors observed a decreased interhemispheric modulation at M1 level contrary to those findings from stroke studies [64]. Knoch et al [65] used cortical stimulation over PFC and they described the asymmetric role of the PFC in decision-making showing that risk-taking behavior was induced by disruption of the right, but not the left, PFC [65]. Using concurrent tDCS over the PFC, it was demonstrated that left cathodal/right anodal decreases risk-taking behavior compared with left anodal/right cathodal or sham stimulation supporting the idea that differential modulation of DLPFC activity, increasing the right while decreasing the left, might lead to decreased risk taking behaviors [66].

Final considerations

It has to be considered that many pharmacological treatments for drug dependence are available [67-69], but these treatments have failed to successfully manage the addiction, notably for strong addictive drugs, such as crack-cocaine [70,71]. Though the importance and need of pharmacological treatments, we strongly believe that supplementary alternative tools with proved efficacy could contribute to the treatment. Reducing craving and improving cognitive functions constitute great challenges in the treatment of drug addiction and we suggest that approaches targeted for intervention on the prefrontal cortex would be of great success. Though the number of studies on brain stimulation has been growing in psychiatric disorders involving drug abuse, efforts are needed to propose this technique as an effective repetitive therapy in the treatment of such conditions.

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