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Feasibility of a novel therapeutic technique transcranial direct current stimulation (tDCS) and aerobic exercise in decreasing craving and impulsivity in drug addiction and substance use disorders

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ABSTRACT Addictions and substance use disorders are among the most prevalent mental health disorders attributable globally to higher rates of death per year. Neuroimaging studies have identified the prefrontal cortex (PFC) as the primary network underlying addictive behavior. Craving and impulsivity are considered hallmarks of addiction, and are subserved by various regions on PFC. Previous studies have illustrated that tDCS can modulate craving and impulsivity in drug addiction Research has also demonstrated that acute aerobic exercise modulates drug-related cravings. The aim of this paper was to examine, in a comprehensive qualitative review the available research on the feasibility of a novel neuromodulation technique, transcranial direct current stimulation (tDCS) and physical exercise in reducing craving and impulsivity in drug dependent patients. The review has shown that physical exercise, in the form of a structured aerobic exercise and non-invasive modulation technique (tDCS) represent a potentially useful, cost free, easy employed intervention strategies for individuals with drug dependence. Neurobiological and molecular mechanisms of action of tDCS and exercise could possibly mediate the beneficial effects on craving and impulsivity. More clinical, vigorous well-designed studies are warranted in larger sample sizes, as well as examining the combined effects of tDCS and exercise, targeting nultiple regions underlying cognitive control for drug consumption.

1. INTRODUCTION

1.1 The Role of Impulsivity and Craving in Addiction

Drug addiction is a complex disease process of the brain that results from recurring drug intoxication and is modulated by genetic, developmental, environmental and experiential factors (Volkow et al., 2016). Previous research has identified impulsivity and craving (Kakko et al., 2019; Li et al., 2021) as hallmarks of addiction and substance use disorders. Impulsivity is a multi-dimensional construct, that has been conceptualized from several different research approaches, and there exist procedurally distinct measures of impulsivity and impulsive behaviors (Evenden, 1999). Impulsivity can be broadly characterized as a concept that covers a wide range actions that are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation that often result in undesirable consequences (Dalley et al., 2011)

From the neurocognitive perspective, two main forms of impulsivity have been proposed in relation to addiction. Behavioral response impulsivity ("waiting" impulsivity) and cognitive impulsivity (impulsive choice) (Verdejo-Garcia, & Albein-Urios, 2021). Response impulsivity is described as a diminished control over action cancellation and is usually assessed with Delay Discounting task (DD). Impulsive choice reflects the tendency to prefer smaller immediate rewards over larger delayed rewards and risk- taking behavior and is assessed with Stop Signal task (SSRT; Logan, 1996) and Go/NoGo paradigm.(Dalley et al., 2012). Studies have shown that drug dependent individuals, discount monetary rewards faster than abstinent users or healthy controls (MacKillop et al., 2011), and display impaired cognitive control on inhibitory Stop-Signal task (Zilverstand, et al., 2019). The prefrontal cortex (PFC) plays a crucial role in impulsivity (Dalley et al., 2011). Distinct neural networks of the PFC underlie impulsive behavior. Behavioral impulsivity relies on fronto-executive network, comprising the ventrolateral prefrontal cortex (vLPFC), dorso-lateralprefrontal-cortex (dLPFC), (Simmonds et al.,2008), anterior cingulated cortex (ACC), pre- supplementary motor area (SMA) and pre-motor cortex (Bary & Robbins, 2013), and ventral inferior frontal gyrus (vIFG) (Garavan et al.,2006); and cognitive impulsivity which is associated with rational decision making and cold cognitive functions, as well as emotional functions, relies on the ventro-medial prefrontal cortex (vMPFC), vACC and the ventral striatum (Hulvershorn et al., 2015) Similarly to the construct of impulsivity, it has been also suggested that craving plays a crucial role in the initiation, and maintenance of addictive behavior (Ekhtiari et al., 2019). Craving is defined as a pressing urgent and irrepressible desire to give in to an addiction resulting usually in a loss of control (Skinner and Aubin, 2010). Studies have identified the crucial role of the PFC in cognitive control of craving among various addictive disorders (Tanabe et al., 2019). Though a large neuronal network of the PFC is hypothesized to underlie craving, neuroimaging studies have emphasized the critical role of DLPFC in drug craving, and addictive disorders, (including alcohol) (Liu, & Yuan, 2021; Xie et al., 2022). Indeed, the DLPFC is associated in many high level executive cognitive control processes related to addiction, such as behavior monitoring and attentional and memory processes (Arnstern & Rubia, 2012; Goldstein & Volkow, 2011), presumably underlying diminished cognitive and behavioral control and a higher tendency to cue-induced relapse in alcohol or drug use.

1.2 The Potential Role of Physical Exercise in Addiction Treatment

1.2.1 Exercise and Drug craving

In general, physical exercise is characterized as a planned, organized behavior with repeated body movement that aims to maintain physical fitness. (Caspersen, Powell, & Christenson, 1985). The most common forms physical exercises include cardiovascular or aerobic type, (brisk walking, running, dancing, swimming) and mind-body exercises (Yoga, Tai - Chi and Qigong). Several recent meta analytical studies have demonstrated that exercise is a beneficial non-pharmacological treatment for addiction, SUD and alcohol use disorders (AUD) (Giesen et al., 2015; Stoutenberg et al., 2015; Patterson et al., 2022). Also, few randomized controlled pilot studies have demonstrated that exercise in the form of structured aerobic exercise is beneficial for health and fitness in alcohol use disorders (AUD) (Brown et al., 2014) and could modulate craving for alcohol (Hallgren et al., 2021), smoking (Prapavessis et al., 2016), and cannabis (Buchowski et al., 2011) in addicted patients. For instance, Buchowski et al., (2011) investigated the effects of aerobic exercise on cannabis use and cravings in cannabis dependent individuals seeking treatment. Twelve female adult marijuana addicts, aged 25 participated in the study. Participants were engaged in a 2- week exercise training program that included a total of 10 sessions of 30 minutes on a treadmill. Exercise was performed at 60–70% of maximal heart rate (HRmax). Researchers used a cued craving elicitation paradigm for craving assessment and administered a self report Marijuana Craving Questionnaire (MCQ-SF) at three time points, one week before exercise intervention, during the intervention and 2 weeks after the study ended. Results showed that during the exercise intervention and immediately post intervention cannabis use and cue induced craving were significantly reduced compared to baseline.

In another, counterbalanced cross-over design, Ussher et al., (2004) examined the acute effects of a brief moderate intensity exercise bout on alcohol urges and mood disturbances in alcohol dependent individuals. Twenty males and females (mean age 40) took part in the study. Participants were randomized to undergo either a single bout of 10 minutes of moderate intensity cycling (experimental) or a single bout of 10 minutes of a light intensity cycling (control). Alcohol urges were assessed with an Alcohol Urge Questionnaire and mood was assessed with a six-item measure of mood disturbances at five time points (for details, see Ussher et al., 2004). Results showed that relative to baseline, there was a decline in alcohol urges for the experimental condition during the exercise bout, but not at any point following exercise.

1.2.2 Exercise and Impulsive Behavior

In contrast to the growing body of research on efficacy of physical exercise in reducing drug craving, there has been relatively little research examining the effects of exercise on impulsivity. Most evidence on effects of exercise on impulsive behavior comes from studies on children with attention deficit hyperactivity disorder (ADHD), showing that exercise can attenuate attention deficits and inhibitory control in this population.(Chuang et al., 2015). Very few studies have investigated effects of exercise on impulsivity in healthy non addicted subjects (Chu et al., 2015; Strickland et al., 2016). For example, Chu et al., 2015, in an ERP study investigated acute aerobic exercise effects on motor response inhibition using stop-signal task. Participants were twenty-one college students, aged 19 – 24. Behavioral data showed that after exercise, participants' SSRT (stop signal reaction time) was shorter compared to the control condition, however the Go RT was not significantly different after exercise and control sessions. To the extent of my knowledge, only one recent study examined acute aerobic exercise effects enhancing inhibitory control and craving using ERP design in twenty four metamphetamine users (age 18 – 40). (Wang et al., 2016). Wang et al., (2016) employed a counterbalanced, within subject design. Aerobic exercise was performed on a stationary bicycle for 30 minutes at moderate intensity and the control condition consisted of an active reading session. The authors used a standard and MA (metamphetamine) related Go/No task. Behavioral, as well as electroeclectical data has demonstrated that exercise facilitated performance on a Go/NoGo task. Improved NoGo performance, but not Go was observed following exercise treatment compared with the control reading session suggesting acute exercise greater effects on inhibitory control which is in accordance with other studies examining healthy population and using other types of inhibitory tasks (Hillman et al., 2009).

1.3 Modulation of Drug Craving and Impulsive Behavior with Transcranial Direct Current Stimulation

1.3.1 tDCS and Drug Craving

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that modulates spontaneous neuronal network activity (Nitsche et al., 2008). DCS can potentially change addictive behavior via modulation of PFC excitability. A growing body of research has shown that tDCS over DLPFC has been found to modulate the consumption of and cravings for cigarettes (Meng et al, 2022), alcohol), tobacco (Fecteau et al., 2014), marijuana (Boggio et al., 2010) and has shown beneficial effects for modulation of addictive behavior and substance dependence (Batista et al., 2015; Hone-Blanchet et al., 2015; Shahbabaie et al., 2014). For instance, Batista et al., (2015), conducted a randomized double-blind sham-controlled study to investigate the effects of bilateral tDCS over DLPFC (left cathodal/right anodal) on carvings, in patients with crack-cocaine dependence. A total of 36 male crack-cocaine adult addicts (age 18 +) participated in the study. Seventeen participants were assigned to the active anodal tDCS condition and nineteen participants to the Sham tDCS condition.

Participants received five sessions of tDCS every other day, the current was 2mA for 20 minutes. Results showed decrease in cravings in the active tDCS condition post stimulation, compared to the Sham condition and that cravings were reduced significantly over time only in the tDCS condition. In addition, exploratory analysis showed that active and sham tDCS groups also differed in changes in anxiety scores, overall perception of quality of life, and health. In another, randomized, double blind sham - controlled crossover -study, Shahbabaie et al., (2014) investigated short-term effects of tDCS on subjective and cue induced cravings in abstinent metamphetamine users. Thirty male participants (aged 20 - 45) took part in the study. Participants were randomly allocated to receive two sessions: of either anodal tDCS or sham tDCS. During anodal tDCS the current was 2mA for 20 minutes. Participants were also administered a computerized cue-induced craving assessment task (CICT). Results showed that while active tDCS in comparison with sham stimulation led to a larger decrease of self-reported craving at rest, active stimulation of the right DLPFC compared to sham stimulation induced larger craving ratings during cue exposure.

1.3.2 tDCS and Impulsive Behavior

The current literature is currently lacking research on tDCS effects on inhibitory control and impulsive decision making in drug dependent population and stimulant drug use (but see Boggio et al.,2010), however recent small, but growing body of evidence from studies of healthy subjects has emerged, supporting the effects of tDCS on cognitive behavioral aspects of impulsivity. Though studies have targeted distinct areas of the PFC, tDCS has been proven to facilitate inhibitory control (Jacobson et al., 2011; Stramaccia et al., 2015) and modulate risky decision making (Fecteau et al., 2007; Hecht et al., 2013). For instance, in a single blind between-group design, Stramaccia et al (2015) examined the effects of a single session of tDCS over a delayed response inhibition by targeting the right inferior frontal gyrus (IFG) and rDLPFC. One hundred and fifteen undergraduate students were randomized to receive either anodal stimulation over the rIFG, cathodal stimulation over the rIFG, anodal stimulation over the rDLPFC, cathodal stimulation over the rDLPFC or sham stimulation on either rIFG or rDLPFC. tDCS session lasted 20 minutes with current delivered at 1mA. Participants performed a computerized version of a Stop Signal Reaction Task (SSRT) 15 minutes post stimulation. Results showed that anodal tDCS over the rIFG, facilitated performance on SST compared to sham tDCS. In contrast, tDCS stimulation over rDLPFC did not affect response stopping. In another study, Hecht et al., (2013) investigated tDCS effects on delay discounting task, targeting the dorso-lateral prefrontal cortex (DLPFC).Participants received three sessions of bi-frontal (right anodal/left cathodal; left anodal/right cathodal) and sham stimulation. When left DLPFC was facilitated and the rDLPFC inhibited, participants showed more preference for smaller "immediate" gains instead of the larger "delayed" rewards, compared to the sham stimulation.

2. DISCUSSION

Drug addiction and substance dependence is a complex process that involves several stages (initiation, intoxication, withdrawal and relapse), and multiple mechanisms (cognitive, emotional and neurobiological) may underlie addiction. Craving and Impulsivity are both complex constructs governed by personality motivational, behavioral, cognitive , neural and molecular mechanisms. I have shown that a short bout of aerobic exercise and non invasive neuromodulation with tDCS over the PFC, enhanced cognitive control, reduced craving and drug intake and modulate risky decision making. One possible explanation for the observed positive effects found in the cited above literature, could be well accounted for by neurobiological and molecular mechanisms. Firstly, it is crucial to note that drug of abuse and aerobic exercise share common neurobiological mechanisms, activating similar reward pathways in the brain (Lynch et al., 2010). Thus, since aerobic exercise, just as drugs results in rewarding stimuli, it could well be a healthy efficient substitute for drug dependent individuals seeking reward. Several neuroimaging studies have identified the role of neurotransmitters in craving and impulsive behavior, such as disrupted functioning of brain 5-HT (serotonin), reduced D2/D3 receptors in the dopaminergic reward systems (Volkow et al., 2014), over flow of GABA glutamate and NMDA receptors (Addolorato et al., 2015; Moeller et al., 2016; Shin, et al., 2016) and noradrenaline pathways (Solecki et al., 2018). Physical exercise increase the concentration of neurotransmitters dopamine and serotonin in the brain (Meeussen et al., 1995) and decreases glutamate in the striatum, which may protect against overstimulation of GABA glutamatergic receptors following chronic drug exposure (Guezennec et al., 1998). As regards to tDCS, anodal tDCS over DLPFC (left cathode/right anode electrode) and modulation of rIFG resulted in reduced craving and impulsive behavior (inhibitory control). In the scientific literature, findings emphasize the role of the PFC in addictive behavior, specifically the critical involvement of DLPFC. (citation). Addictive behavior is associated with reduced activation in right DLPFC, thus tDCS, via its primary neurophysiological mechanism of action, modulation of neuronal exitability (Nitsche & Paulus, 2000) was able to enhance activity in right DLPFC and reduce activation in left DLPFC. In addition tDCS, also interacts with several neurotransmitters systems (dopamine and serotonin) (Kuo et al., 2014) and the electrical current is able to modify synaptic strength at NMDA receptors and alter GABA glutamate activity (Staag et al., 2009).

3. FUTURE DIRECTIONS

In the future, more clinical well controlled studies are needed, with larger sample size extending integration of physical exercise into clinical settings. Moreover, studies should expend intervention period to examine long-term effects of exercise and tDCS on complete drug abstinence, as well as to investigate thoroughly their neurobiological, physiological and molecular mechanisms of action.

4. CONCLUSION

A single bout and short term aerobic exercise intervention, and anodal tDCS over DLPFC and rIFG, as stand alone interventions have shown to be effective, non-pharmacological and non invasive intervention strategies in changing human behavior resulting and reducing drug related craving, enhance cognitive control and decision making, and decrease impulsive behavior in drug addicted patients.

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