REVIEW

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Transcranial direct current stimulation in the treatment of alcohol, tobacco and opioid use disorder in clinical studies

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Transcranial direct current stimulation (tDCS) is a promising research tool to address substance abuse, including alcohol, tobacco, opioid, and drug use disorders. The present literature review compared previous studies conducted with various current intensities, application regions, durations of stimulations, and different region targets of the brain. Studies based on the analyses conducted after tDCS administration in substance use disorder were promising for the use of tDCS as adjunctive therapy to reduce visible psychological and neurological symptoms of the addiction. Therefore, we aimed to provide an insight into the current state of research on tDCS as a therapeutic intervention in substance use disorders, identify gaps in the literature, and emphasize future investigation areas. Ultimately, the review sought to contribute to the understanding of the role of tDCS in addressing the complex challenges posed by substance use disorder, and its potential as a complementary or adjunctive treatment modality in addiction care. The present study identified that the left dlPFC and brain regions were effective targets for 1 mA and 2 mA tDCS current density in tobacco/nicotine use disorder. Also, the left dlPFC and 2 mA current density were identified as effective targets for tDCS in alcohol use disorder. Furthermore, left dlPFC and 2 mA current density were identified as effective targets for tDCS in opioid use disorder. Additionally, the right/left dlPFC, orbital frontal cortex, thalamus, and 2 mA current density were identified as effective targets for tDCS in other drug or substance use disorders. Animal studies demonstrated that tDCS was promising in reducing neuropathic pain, modulating neuropeptide Y activity, and reducing the redevelopment of ethanol consumption in animal models. However, further research is required to fully understand the optimal tDCS application parameters.

Key words: transcranial direct current stimulation, substance use disorder, alcohol use disorder, smoking, opioid use disorder

INTRODUCTION

Substance use disorder (SUD) is a mental health condition characterized by a pattern of problematic substance use that negatively affects an individual's life (National Institute of Mental Health, 2021). About 20.3 million people were diagnosed with a substance use disorder in 2018 according to the 2018 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2019). By 2018, there were 14.8 million alcohol use disorder and 8.1 million individuals with SUD. In certain countries, opioid abuse affected an estimated 10.3 million individuals in 2018 (Substance Abuse and Mental Health Services Administration, 2019). Opioids are the main contributor to drug overdose deaths (46,800 nationwide deaths in 2018) (Scholl et al., 2018; Substance Abuse and Mental Health Services Administration, 2019; Mahoney et al., 2020). SUD depends on various complex factors, including brain chemistry. The disease prognosis is intricate and involves multiple factors.

Intense craving, increased tolerance, and withdrawal symptoms are common symptoms in substance use disorders (Institute of Medicine (US) Committee on Op-

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portunities in Drug Abuse Research, 1996). Substances are types of drugs with possible withdrawal symptoms such as alcohol, caffeine, tobacco, nicotine like cigarette smoking, opioids, inhalants, and hallucinogens. The severity of SUD varies between mild to severe (Sayre et al., 2020). The American Psychiatric Association (DSM-V) provided clear and concise criteria for the diagnosis of substance use disorders (Pickering et al., 2011). Diagnosis is based on the presence of at least two specified symptoms within a year, accompanied with a decrease in functions (Hasin et al., 2013). Certain substance use disorder criteria, include excessive or prolonged consumption, unsuccessful attempts to quit or control, and dedication of substantial time to the acquisition, use, or disposal of the substance. Substance use disorder symptoms could include strong urge or craving to use the substance, which interferes with daily responsibilities and activities. Despite the negative consequences, the individual could continue to seek out and use the substance, even when it poses health or safety risks. Tolerance to the substance could develop, leading to withdrawal symptoms when discontinued. Cravings and tolerance are common diagnostic criteria in addiction (Hasin et al., 2013). Relapse is a common problem in addiction treatment. Quitting substances could lead to symptoms such as cognitive dysfunction, dysphoria, and anxiety, resulting in relapse (Bruijnzeel, 2016). To understand the causes of repetitive relapse behavior, the effects of substance use on the brain should be investigated (Wilcox et al., 2017).

Transcranial direct current stimulation (tDCS) is an effective and safe neuromodulation technique commonly used in the treatment of neurological disorders (Stagg et al., 2011). tDCS delivers a low electrical current through the scalp that selectively and precisely stimulates cortical areas of the brain (Nitsche et al., 2008). It was suggested that anodal stimulation promotes depolarization of neurons and cathodal hyperpolarization that suppresses the former (Yamada et al., 2021). Over the years, the clinical interest in tDCS has increased in the treatment of addiction due to its potential to modulate neural activities that affect addictive behavior (Chen et al., 2020).

In the current paper, we aimed to review tDCS applications in the treatment of alcohol, tobacco, opioid and drug use based on human and animal studies. tDCS is a promising non-invasive neuromodulation technique that entails the delivery of low electrical current to specific brain regions. Substance use disorders pose significant public health challenges globally, and there is a growing interest in the exploration of innovative treatment modalities such as tDCS.

Our review aimed to synthesize the current literature on current intensity, various brain region applications, duration of stimulation, various brain region targets, and clinical outcomes associated with tDCS interventions in substance use disorder. It could be suggested that the review of the clinical studies would elucidate the potential benefits of tDCS in the reduction of craving, cognitive function improvement, and addiction recovery (Guleken et al., 2020). Furthermore, we explored the underlying mechanisms in the effects of tDCS on neural circuits implicated in addiction.

METHODS

Literature review

The present systematic review was planned based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Liberati et al., 2009). A preliminary search was conducted in January 2022 to examine all keywords in electronic databases. The literature, title/summary/keyword search were conducted on PubMed, Scopus, Embade Registers and the Web of Science electronic databases with the terms “transcranial direct current stimulation” or “tDCS”, “smoking addiction” or “nicotine addiction” or tobacco smokers” or “smoking behavior” or nicotine consumption” or “nicotine use disorder” or “cigarette craving” or “smoking cue”, “dependence neurobiology”, “tDCS opioid” or “tDCS opioid addiction”, “tDCS alcohol” or “tDCS alcohol addiction” or “alcohol dependence” or “drinkers” or “alcohol consumption”, tDCS substance” or “tDCS substance use addiction” or “opioid dependence” or “cannabis users” or “drug and opioid” or “methamphetamine craving and users” or “cocaine use disorder” or “craving for heroin” or “craving in drug addiction” or “morphine induced response” or “cocaine dependence” to determine the previous studies in the literature. The study is limited to the selected publications between 2012 and 2023.

Selection of the studies for systematic review

The primary aim of this review was to investigate the effects of tDCS on brain structures in the studies conducted on alcohol/substance use disorder. Studies on the application of tDCS with different protocols in substance use disorders were included in the review. All human and animal studies published from 2012 on the effects of tDCS on substance use disorder were included. Initially, the replicate studies were removed. Then, the article titles and abstracts were revised, and non-English articles, studies without empirical data (reviews) and incompatible content were removed from the study data.

Inclusion criteria

Inclusion criteria are presented in the PRISMA flowchart in Fig. 1. The initial literature review included 586 papers. Then, replicate and literature reviews were removed. The papers published in peer-reviewed journals, employed tDCS, and conducted with individuals with substance use disorders were included in the study.

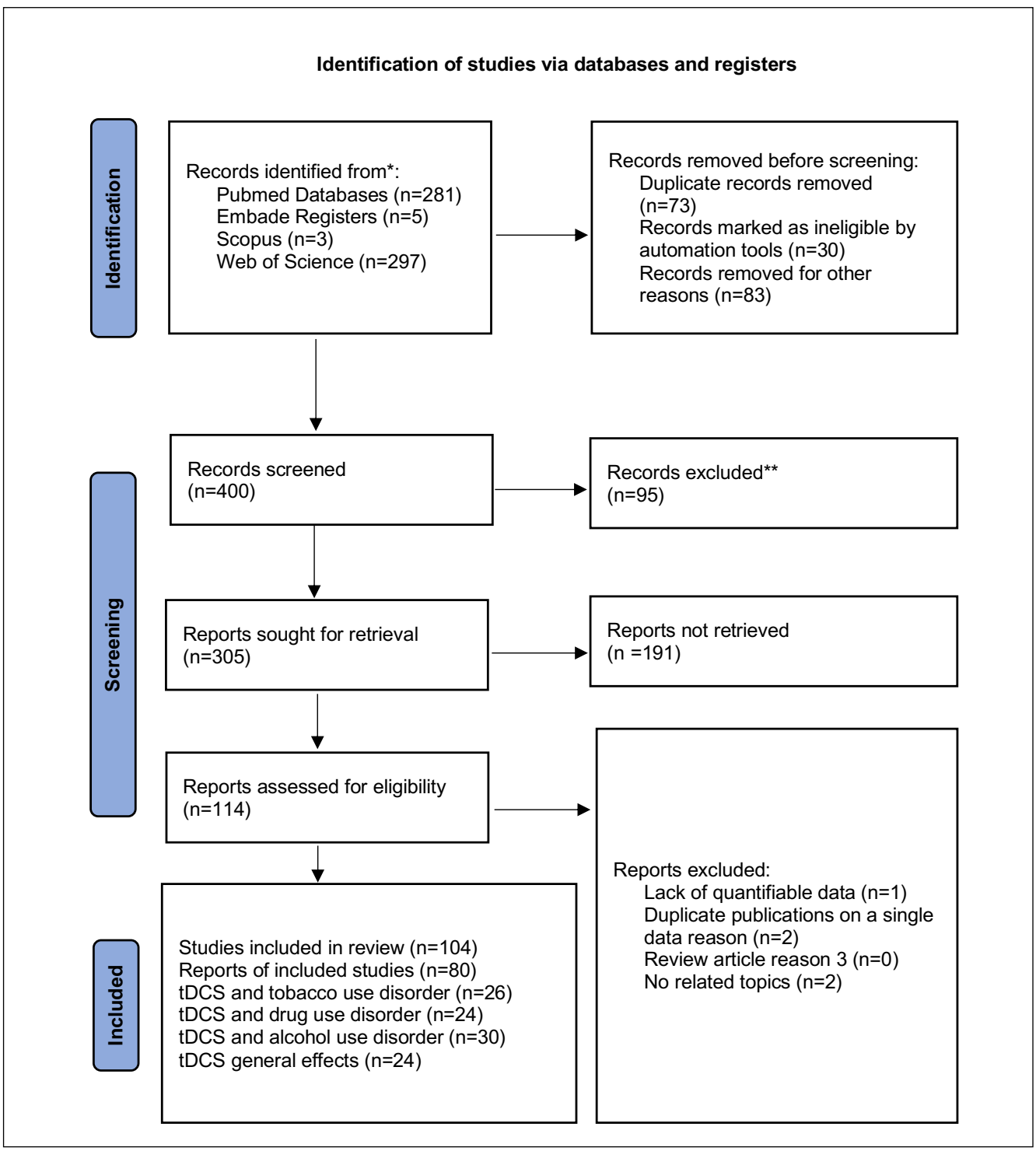

Fig. 1. PRISMA diagram.

Data collection

Study design and outcome measurements of human and animal studies were identified and entered into an Excel spreadsheet. Experimental details included the number of participants, anode and cathode placement, tDCS, current density (mA), duration of stimulation per session (minutes), simultaneous tasks during stimulation, and main findings.

Data re-coding

The variables that varied across the studies such as the number of participants, the intensity and duration of the current, and the location of the tDCS application are presented in tables.

RESULTS

Human studies: tDCS in tobacco/nicotine use disorder

Neuroplasticity refers to the remarkable brain's ability of reorganization, the development of new neural networks that adopt nerve cells to new situations (Mohammadi, 2016). Anodal transcranial direct current stimulation (tDCS) significantly improves neuronal excitability by depolarizing resting membrane potential, leading to a substantial increase in spontaneous cell firing. Conversely, cathodal tDCS reduces excitability by hyperpolarizing the resting membrane potential (Nitsche et al., 2000). Several studies investigated the changes in neuroplasticity with tDCS application in individuals with smoking disorder. Grundey et al. (2012) conducted a study with tDCS and PAS and reported that nicotine increased cognitive functions *via* neuroplasticity. A study was conducted with 24 individuals who received 1 mA tDCS. In the study, 13 minutes of anodal tDCS and 9 minutes of cathodal tDCS were applied to the participants. The MC representation area of the right abductor digiti minimi muscle and above the right orbit were stimulated. True tDCS was administered to both groups with and without nicotine disorder. It was determined that nicotine decreased out-of-focus plasticity and increased facilitating plasticity (Grundey et al., 2018). Grundey et al. (2018) aimed to investigate the effect of nicotine and calcium receptors stimulated by tDCS on focusing by changing neuroplasticity. Primary MC electrode right abductor digiti minimi muscle and contralateral supraorbital region were stimulated by 1 mA for 13 minutes. The findings demonstrated that nicotine could alter the arousal induced by anodal tDCS (Grundey et al., 2018). In another study, the effect of activation of the α4 β2 nicotinic receptor on impaired plasticity was investigated during nicotine withdrawal in smoking participants with tDCS (Batsikadze et al., 2017). 1 mA anodal tDCS for 13 minutes or cathodal tDCS was applied for 9 minutes to the primary MC. The findings demonstrated that was facilitating neuroplasticity increased (Batsikadze et al., 2017). Thus, it could be suggested that tDCS positively affects neuroplasticity in smokers.

Similar to all addictions, craving is an important research topic in cigarette addiction. Several research studied craving for smoking with tDCS and reported conflicting findings. Certain studies employed 2 mA (Xu et al., 2013; Kroczek et al., 2016; Mondino et al., 2018; Verveer et al., 2020; Müller et al., 2021; Perri & Perrotta, 2021) and 1 mA (Pripfl & Lamm, 2015) currents. Considering the application sites, tDCS were applied to ALdlPFC (Xu et al., 2013; Pripfl & Lamm, 2015; Kroczek et al., 2016; Müller et al., 2021) and anodal right (AR) dlPFC (Pripfl & Lamm, 2015; Mondino et al., 2018; Verveer et al., 2020; Perri & Perrotta, 2021). The findings revealed that active tDCS application did not lead to differences in certain studies when compared to the sham tDCS application (Xu et al., 2013; Pripfl & Lamm, 2015; Kroczek et al., 2016; Verveer et al., 2020; Müller et al., 2021). Others reported that tDCS could lead to positive outcomes in cigarette craving (Mondino et al., 2018; Perri & Perrotta, 2021). Studies on the effects of tDCS on cigarette craving demonstrated that further research should be conducted on craving.

Several tDCS studies were conducted on quitting smoking and reducing cigarette consumption. In certain studies, tDCS was applied to the right dlPFC (Fecteau et al., 2014; Mondino et al., 2018; Alghamdi et al., 2019; Verveer et al., 2020; Perri & Perrotta, 2021), while in others, it was applied to the left dlPFC (Falcone et al., 2016; Brangioni et al., 2018; Müller et al., 2021). In addition to these regions, it was applied to bilateral cathodal over both sides of frontal-parietal-temporal (FPT) and cathodal over right FPT regions (Meng et al., 2014). These studies employed 1 mA (Meng et al., 2014; Falcone et al., 2016; Brangioni et al., 2018), 2 mA (Mondino et al., 2018; Falcone et al., 2019; Verveer et al., 2020; Müller et al., 2021; Perri & Perrotta, 2021), and 1.5 mA (Alghamdi et al., 2019) currents. The findings indicated that tDCS could reduce cigarette consumption behavior (Fecteau et al., 2014; Meng et al., 2014; Alghamdi et al., 2019). However, other studies reported that tDCS had no effect on reducing cigarette consumption (Brangioni et al., 2018; Falcone et al., 2019; Mondino et al., 2018; Falcone et al., 2019; Verveer et al., 2020; Müller et al., 2021; Perri & Perrotta, 2021).

Lin et al. (2021) conducted a study on individuals with heroin addiction and smoking with the tDCS application. They recruited 30 participants who met the DSM-IV-TR criteria for opioid dependence and regularly smoked cigarettes. These subjects were randomly assigned to the active tDCS group where a constant current of 2 mA was applied for 20 minutes to the dlPFC (anode: F3, cathode: F4) or the left orbitofrontal cortex (OFC, anode: Fp1, cathode: Fp2A) or the sham control group, where the sham stimulation targeted the same areas. The preliminary analysis of the active dlPFC and OFC stimulation yielded no significant findings. Subsequent analysis pooled data from both groups. Expired carbon monoxide (CO) concentration and self-reported daily number of cigarettes smoked per day were determined, and craving was analyzed based on a visual analogue scale. Significant reductions were observed in expired CO concentration during and after tDCS treatment when compared to baseline, and no such effect was observed in sham controls. Inter-group differences were significant in various days of treatment, where the active group consistently exhibited higher reductions in CO concentration when compared to sham group. However, no significant inter-group differences were determined in the daily number of cigarettes or reduction in craving (Lin et al., 2021).

The analysis of the effects of tDCS on motivation and desire to quit smoking revealed promising findings (Brangioni et al., 2018; Hajloo et al., 2019). 1 mA (Brangioni et al., 2018) and 2 mA (Hajloo et al., 2019) anodal tDCS current was applied to the left dlPFC for 20 minutes.

Significant number of the studies focused on the impact of tDCS on charges in cognitive skills in smokers. It was reported that tDCS application reduced smoking cues associated with attention in smokers (Meng et al., 2014). Xu et al. (2013) conducted a study with 24 smokers, where they received both real and sham tDCS applications after overnight abstinence from smoking in two days. Anodal stimulation was applied to the dlPFC where the cathode was placed on the right supra-orbital area (20 minutes; 2 mA). The negative effects and cigarette craving were determined with self-report questionnaires, including the profile of mood states (POMS) and the urge to smoke (UTS) scale, respectively. Furthermore, a computerized visual target identification task was employed to evaluate attention before and after each tDCS sessions. POMS and UTS scores were compared between real and sham tDCS sessions. Correlations between changes in negative effects and nicotine dependence levels were analyzed with the Fagerström scale. Real tDCS significantly reduced the total mood disturbance POMS score and tension-anxiety, depression-dejection, and confusion-bewilderment subscale scores, which were positively correlated with nicotine dependence based on the Fagerström scale scores. These findings demonstrated that tDCS improved mood and reduced the negative affection, particularly in individuals with more severe nicotine dependence. Although there were no craving differences between real and sham tDCS groups, the findings suggested that the impact of the real tDCS was significant on the reduction of negative affection. The study demonstrated that tDCS was safe and effective in the improvement of negative affection in smokers who quit smoking for one night. However, it was noticed that there could be attentive improvements 3 months after tDCS application (Verveer et al., 2020). The application areas in these studies included left dlPFC (Xu et al., 2013), right dlPFC (Verveer et al., 2020), bilateral cathodal over both sides of the FPT, and cathodal over right of the FPT (Meng et al., 2014). Furthermore, positive findings were reported in the regulation of negative affection (Pripfl & Lamm, 2015), decision making (Fecteau et al., 2014), and cognitive regulation (Aronson et al., 2020). However, tDCS had no significant impact on executive functions (Aronson et al., 2020). The summary of these findings is presented in Table 1.

Human studies: tDCS in alcohol use disorder

tDCS device was employed in various addiction studies. Each study employed different methods to understand the efficacy of the device. These differences included changes in variables such as duration of the stimulation, applied region, and current.

Relapse is common in alcohol use disorder. Several tDCS studies were conducted on relapse prevention. 2 mA current was employed in all studies (Klauss et al., 2014; 2018; Nakamura-Palacios et al., 2016; Witkiewitz et al., 2019; Holla et al., 2020; Dubuson et al., 2021; Jitendriya et al., 2022). For relapse prevention, tDCS was applied to the left dlPFC (Nakamura-Palacios et al., 2016; den Uyl et al., 2018) and right dlPFC (Klauss et al., 2014; Witkiewitz et al., 2019; Holla et al., 2020; Dubuson et al., 2021; Jitendriya et al., 2022). The findings suggested that tDCS reduced relapse in most studies (Klauss et al., 2014; Nakamura-Palacios et al., 2016; den Uyl et al., 2018; Holla et al., 2020; Dubuson et al., 2021; Jitendriya et al., 2022). However, Witkiewitz et al. (2019) reported that active tDCS was not more effective than sham tDCS in preventing relapse based on mindfulness.

Brain regions targeted by tDCS in alcohol use disorder

Several studies were conducted on the prevention of craving in individuals with alcohol use disorder with tDCS. In studies that aimed to prevent craving, transcra-

Table 1. Human studies with tDCS in smoking disorder.

	Participants	Duration	Current Density	Anode	Cathode	Assembly Layout	Adverse Effects
Grundey et al. (2012)	n=24	13 min / 9 min	1.0 mA		AtDC / CtDCS	MC area of the right ADM / above the right orbit	NS
Reichenbach et al. (2014)	n=32						
Xu et al. (2013)	n=24	20 min	2.0 mA	F3	SOA	AL dlPFC / CRsupra-orbital area	Tingling, sleepiness & scalp burn
Fecteau et al. (2014)	n=12	30 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Trouble concentrating, headache, neck pain, sleepiness, tingling
Meng et al. (2014)	n=30	20 min	1.0 mA	T3, F3, C3, F7	T3, F3, C3, F7	1) ALFPT / CRFPT area 2) Two cathodal electrodes were placed on each side of FPT area, while two anodal electrodes were placed at the occipitallobe on respective side	Itching, tingling, mildpain, dizzines
Pripfl & Lamm (2015)	n=17	15 min	1.0 mA	F1, F3, AF1/ F2, F4, AF2	F3, F4/F3,F4	ALdlPFC / contralateral positions F3 & F4 / AR dlPFC / contralateral positions F3 & F4	Sleepiness, tingling, and itching
Falcone et al. (2016)	n=25	20 min	1.0 mA	F3	right SOA	ALdlPFC / CRsupra-orbital region	Itching, burning sensation, fatigue, nervousness, difficulty concentrating, mood change, pain, headache
Kroczek et al. (2016)	n=29	15 min	2.0 mA	F3	Fp2	Anodal dlPFC / Cathodal OFC	NS
Batsikadze et al. (2017)	n=26	13 min (AtDCS) or 9 min (CtDCS)	1.0 mA			Primary MC electrode right ADM / return electrode contralateral supraorbital region	
Yang et al. (2017)	n=32	30 min	1.0 mA	F3	F4	ALdlPFC / CRdlPFC	No significant main effect
Alghamdi et al. (2019)	n=22	20 min	1.5 mA	F3	F4	Anodal on left dlPFC / CR dlPFC	Mild headache, tingling, itching, burningsen-sation & skin redness under the area of electrodes
Brangioni et al. (2018)	n=36	20 min	1.0 mA	F3	right contralateral SOA	ALdlPFC / CRcontralateral SOA	No side effects were observed during or after the applications
Mondino et al. (2018)	n=34	20 min	2.0 mA	F4-Fp2	left occipital regions	AR dlPFC / CL occipital region	No adverse events were reported
Grundey et al. (2018)	n=12	13 min	1.0 mA	ADM	contralateral supraorbital region	Primary MC electrode right (ADM) / return electrode contralateral supraorbital region	Itching & a slight redness underneath the patch
Falcone et al. (2019)	n=106	20 min	1.0 /2.0 mA	F3	right supraorbital region	ALdlPFC / CRsupraorbital region	Discontinued tDCS during session 1 due to side effects (n=1)
Ghorbani Behnam et al. (2019)	n=170	20 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	Mild headache
Hajloo et al. (2019)	n=40	20 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	NS
Verveer et al. (2020a)	n=62	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Itching
Müller et al. (2021)	n=44	20 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	NS
Lin et al. (2021) (cigarette)	n=30	20 min	2.0 mA	F3 Fp1	F4 Fp2A	1) ALdlPFC / CRdlPFC 2) ALOFC / CROFC	NS
Perri & Perrotta (2021)	n=20	20 min	2.0 mA	F4	F3	AR dlFPC / CL dlPFC	Non significant adverse effect
Verveer et al. (2020b)	n=69	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Itching

nial direct current stimulation (tDCS) was applied to various brain areas, including to the left dlPFC (Nakamura-Palacios et al., 2012; da Silva et al., 2013; den Uyl et al., 2015; 2016; Klauss et al., 2018), the right dlPFC (Nakamura-Palacios et al., 2016; Trojak et al., 2016; Wietschorke et al., 2016; Klauss et al., 2018; Almeida-Antunes et al., 2022), dorsolateral or inferior frontal regions (Claus et al., 2019), right inferior frontal gyrus (den Uyl et al., 2015), and right inferior frontal gyrus (Brown et al., 2020).

Applied tDCS currents in alcohol use disorder

Certain studies employed 1 mA (Nakamura-Palacios et al., 2012; den Uyl et al., 2015; 2016; Wietschorke et al., 2016) and others employed 2 mA (da Silva et al., 2013; Nakamura-Palacios et al., 2016; Trojak et al., 2016; Klauss et al., 2018; Claus et al., 2019; Brown et al., 2020; Almeida-Antunes et al., 2022) tDCS currents. The study findings demonstrated that tDCS reduced craving (da Silva et al., 2013; den Uyl et al., 2015; 2016; Trojak et al., 2016; Wietschorke et al., 2016; Nakamura-Palacios et al., 2016; Trojak et al., 2016; Klauss et al., 2018; Claus et al., 2019; Brown et al., 2020; Almeida-Antunes et al., 2022). However, in some studies reported that active tDCS in craving did not produce different results from sham tDCS (den Uyl et al., 2015; Claus et al., 2019; Brown et al., 2020).

Various studies demonstrated that cognitive functions could be regulated by tDCS in individuals with alcohol use disorder. Executive function (Nakamura-Palacios et al., 2012; da Silva et al., 2013), cognitive bias (den Uyl et al., 2015; 2017), quality of life perception (Klauss et al., 2014), attention bias (den Uyl et al., 2018), decision making (Trojak et al., 2016), negative processing of alcohol-related cues (Schwippel et al., 2022), suppression of memories (Almeida-Antunes et al., 2022), and implicit relationship regulation (Schwippel et al., 2022), specific tDCS studies have been conducted. Nakamuro-Palacios et al. (2012) have found that application of anodal tDCS to the dlPFC of the individuals with alcohol use disorder improved executive function performance and increasing neural processing in frontal areas. In another study on executive functions, the findings indicated that repetitive anodal tDCS application to the left dlPFC reduced craving and depressive symptoms and improved executive functions (da Silva et al., 2013).

Klauss et al. (2014) reported that tDCS application increased quality of life perceptions. In studies on cognitive bias, the findings demonstrated that tDCS reduced alcohol cue-induced craving; however, no difference was observed between active and sham tDCS applications in cognitive bias modification training (den Uyl et al., 2016). den Uyl et al. (2017) supported the findings of another study. They reported that active tDCS and sham tDCS did not have different effects on cognitive bias. tDCS had no positive effect on attentional bias in alcohol users, while it improved decision-making (Trojak et al., 2016; den Uyl et al., 2018). Wietschorke et al. (2016), have found that participants processed alcohol-related cues more negatively after tDCS. It was also reported that repression of memories associated with alcohol could be altered in individuals with alcohol use disorder (Almeida-Antunes et al., 2022). Another study demonstrated that tDCS was not effective on regulating alcohol-related implicit relationships (Schwippel et al., 2022).

Dormal et al. (2020) tested the hypothesis that attention and inhibition abilities of the individuals with excessive alcohol use could be improved with tDCS. 1.5 mA anodal tDCS was applied to the left dlPFC region of 40 participants for 20 min. The analysis of the findings revealed no difference between behavioral outcomes in active and sham tDCS. However, it was found that tDCS could alter cognitive processes (Dormal et al., 2020).

Studies were conducted on the amount of alcohol use and impulse control in individuals with alcohol use disorder (Vanderhasselt et al., 2020) determined that sham application led to a change in reward-triggered behavioral bias and alcohol use; however, real tDCS application did not led to the same change. Almeida-Altunes et al. (2022) found that tDCS application led to a decrease in alcohol use. In another study, it was determined that tDCS improved impulse control by regulating cognitive control (Weidler et al., 2022).

Boroda et al. (2020) studied the hypothesis that tDCS application with cognitive training could have a significant effect on the increase of neuroplasticity in a study conducted with children with fetal alcohol syndrome. In the study, 2 mA of anodal tDCS was applied to the left dlPFC region of 38 children for 13 minutes. The findings revealed that the active tDCS group exhibited improvements in attention task in the performance test when compared to the sham tDCS group. However, active tDCS application did not have a different effect on working memory.

Chhabra et al. (2020) analyzed the data collected from 13 participants with alcohol use disorder in the study conducted with tDCS and individuals with several psychiatric disorders. The aim of the study was to investigate the side effects of tDCS in individuals with alcohol use disorder. 2 mA of anodal tDCS was applied to the right dlPFC region of the 13 participants for 20 minutes. The findings revealed no significant side effects except for mild itching, burning sensation and tingling (Chhabra et al., 2020). The summary of the study findings is presented in Table 2.

Table 2. Human studies with tDCS in alcohol use disorder.

Reference	Participants	Duration	Current Density	Anode	Cathode	Assembly Layout	Adverse Effects
Nakamura--Palacios et al. (2012)	n=49	10 min	1.0 mA	F3	contralateral supradeltoid region	ALdlPFC / Cathodal contralateral supradeltoid region	Itching
da Silva et al. (2013)	n=13	20 min	2.0 mA	F3	contralateral supradeltoid area	ALdlPFC / CRcontralateral supradeltoid area	Itching
Klauss et al. (2014)	n=33	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Itching, mild redness of the scalp (beneath the electrodesin patients with very white skin)
den Uyl et al. (2015)	n=48	10 min	1.0 mA	F3	contralateral supraorbital region	ALdlPFC / Cathodal contralateral supraorbital region	NS
den Uyl et al. (2016)	n=78	15 min	1.0 mA	F3	contralateral supraorbital region	ALdlPFC / Cathodal contralateral supraorbital region	Itching, less fatigue, less nausea
Nakamura--Palacios et al. (2016) (alcohol & substance)	n=22	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Itching
Trojak et al. (2016)	n=340	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Wietschorke et al. (2016)	n=30	20 min	1.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
den Uyl et al. (2017)	n=91	15 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	Itching, burning, sleepiness
den Uyl et al. (2018)	n=83	20 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	No adverse events were reported
Klauss et al. (2018)	n=45	20 min	2.0 mA	F4	F3	AR DLPFC / CL dlPFC	Tingling
Claus et al. (2019)	n=79	20 min	2.0 mA	F10	contralateral upper arm	Dorsolateral or inferior frontal regions / Cathodal con-tralateral upper arm	Itch, pain, heat, discomfort
Witkiewitz et al. (2019)	n=84	30 min	2.0 mA	F10	left upper arm	AR inferior frontal gyrus / CL upper arm	No adverse events were reported
Boroda et al. (2020)	n=38	13 min	2.0 mA	F3	Fp2	ALdlPFC / Cathodal supraorbital bone	No adverse events were reported
Brown et al. (2020)	n=68	30 min	2.0 mA	F10	left upper arm	AR right inferior frontal gyrus / CL upper arm	No adverse events were reported
Chhabra et al. (2020)	n=13	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	Burning, itching & skin rednes, scalp pain, skin redness, itching & tingling
Dormal et al. (2020)	n=40	20 min	1.5 mA	F3	Fp2	ALdlPFC / CRsupraorbital region	NS
Holla et al. (2020)	n=21	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	No adverse events were reported.
Sergiou et al. (2020)	n=50	20 min	2.0 mA	Fpz	F3, Fz, AF4, F3, F4	Anodal vmPFC / CL SOA	NS
Vanderhasselt et al. (2020)	n=45	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Dubuson et al. (2021)	n=125	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Almeida--Altunes et al. (2022)	n=90	20 min	2.0 mA	F4	contralateral supraorbital region	AR dlPFC / Cathodal contralateral supraorbital region	NS
Aman & Sharma (2022)	n=46	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Jitendriya et al. (2022)	n=22	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Schwippel et al. (2022)	n=27	30 min	1.0 mA	contralateral deltoid muscle	F3	Anodal contralateral deltoid muscle / CL dlPFC	Only mild side effects were present after sham & after cathodal SIM
Weidler et al. (2022)	n=51	20 min	1.5 mA	F4	contralateral supraorbital region	AR dlPFC / Cathodal contralateral supraorbital region	NS

Human studies: tDCS in opioid use disorder

Opioid studies with tDCS included individuals who used opioids for pain relief and those with opioid use disorder. In all studies, 2 mA of anodal tDCS was applied to various brain regions, including the knee representation of the motor strip (Borckardt et al., 2013, 2017), left dlPFC (Borckardt et al., 2017; Hamed et al., 2022), left temporal-occipital junction (Borckardt et al., 2017) and motor area M1 of the lower limb cortex (Hamed et al., 2022) of the participants with pain complaints (Borckardt et al., 2013, 2017; Hamed et al., 2022). Hamed et al. (2022) aimed to compare the effectiveness anodal tDCS application over primary M1 or left dlPFC when compared with sham, and reported that it significantly reduced pain and overall opioid consumption in spinal surgery patients. Overall morphine intake was recorded during the three postoperative days. Groups received tDCS treatment for 3 consecutive postoperative days (2 mA; 20 minutes) and assesed the pain levels. The findings suggested that that three active tDCS sessions significantly reduced postoperative morphine intake and pain level (Hamed et al., 2022).

It was determined that knee representation of the motor strip and tDCS application to the left dlPFC effectively reduced the need for opioids (Borckardt et al., 2013, 2017; Hamed et al., 2022). However, another study reported that anodal tDCS application to the knee representation of the motor region did not lead to a difference in opioid requirement (Borckardt et al., 2013).

tDCS is used to prevent craving in individuals with opioid use disorder. Similar to the studies conducted with other types of addiction, different currents such as 0.5 mA (Eskandari et al., 2019), 1 mA (Meng et al., 2022), 1.5 mA (Wang et al., 2016) and 2 mA (Kooteh et al., 2020; Eskandari et al., 2021; Lin et al., 2021; Meng et al., 2022) were applied in these studies. Furthermore, tDCS was applied to various brain areas such as frontal-parietal-temporal regions (Wang et al., 2016; Lin et al., 2021), left dlPFC (Eskandari et al., 2019, 2021; Lin et al., 2021), right dlPFC (Kooteh et al., 2020; Eskandari et al., 2021), and left OFC (Lin et al., 2021). The findings demonstrated that tDCS reduced craving in individuals with opioid use disorder (Wang et al., 2016; Eskandari et al., 2019, 2021; Kooteh et al., 2020; Meng et al., 2022). However, Lin et al. (2021) reported that the impact of active and sham tDCS was not different in the reduction of craving in opioid use disorder.

The effects of tDCS on depression, anxiety and stress (Eskandari et al., 2019; Sadeghi Bimorgh et al., 2020), thoughts and fantasies of drug use (Kooteh et al., 2020) in individuals with opioid use disorder were investigated with 2 mA current (Eskandari et al., 2019; Kooteh et al., 2020; Sadeghi Bimorgh et al., 2020). The treated areas were selected as the right dlPFC (Eskandari et al., 2019; Kooteh et al., 2020; Sadeghi Bimorgh et al., 2020) and the left dlPFC (Eskandari et al., 2019). The findings showed that tDCS application is effective in reducing depression, anxiety, stress, as well as fantasy and thoughts of drug use with combined emotional therapies (Eskandari et al., 2019; Kooteh et al., 2020; Sadeghi Bimorgh et al., 2020).

Mostafavi et al. (2021) investigated the impact of bilateral tDCS application on the cognitive skills of individuals with opioid use disorder. In the study conducted with 31 participants, 2 mA of anodal tDCS was applied to the right/left dlPFC for 10-20 minutes. The findings demonstrated that skills such as planning, decision making, memory, inhibition control and cognitive flexibility skills improved after tDCS sessions. The study revealed that sham application did not lead to any changes in cognitive skills (Mostafavi et al., 2021).

Eskandari et al. (2021) investigated the effects of bilateral tDCS application on impulsive behavior in patients with opioid use disorder. 2 mA of anodal tDCS was applied to the dlPFC for 20 minutes. The findings demonstrated that real tDCS reduced impulsive behaviors (Eskandari et al., 2021).

DosSantos et al. (2014) observed that both real and sham tDCS applications led to different activation levels in m-opioid receptor neurotransmission in thalamus and prefrontal cortex (PFC). The involvement of the endogenous m-opioid system in *in vivo* global tDCS analgesia was investigated in this pilot study. The central MOR activity during tDCS *in vivo* (non-displaceable binding potential, BPND) was measured using [11C] carfentanil, a selective m-opioid receptor (MOR) radiotracer, through positron emission tomography (PET) scans - one of the main analgesic mechanisms in the brain. tDCS was administered (M1/2 mA; 20 minutes) during the PET scan. Placebo-tDCS decreased MOR BPND in the PAG, precuneus, and thalamus, indicating activation of endogenous m-opioid neurotransmission even before active tDCS. The subsequent active tDCS induced MOR activation in the PAG and precuneus, which positively correlated with the changes observed with placebo tDCS. Furthermore, active tDCS also induced MOR activation in the left prefrontal cortex. Both placebo and active tDCS led to significant changes in MOR BPND; however, only active tDCS had significant analgesic effects. The study provided preliminary evidence that the reported analgesic effects of M1 tDCS were partially associated with the recruitment of the same endogenous MOR, similar to the placebo (DosSantos et al., 2014).

Mostafavi et al. (2022) investigated the effects of bilateral tDCS application in individuals with opioid use

disorder with EEG. In the study, 2 mA of anodal tDCS was applied to the right/left dlPFC regions for 20 minutes. The findings revealed that the amplitude of slow brain waves decreased in the prefrontal, frontal, occipital, and parietal regions (Mostafavi et al., 2022). The summary of these findings is presented in Table 3.

Table 3. Human studies with tDCS in opioid use disorder.

Reference	Participants	Duration	Current Density	Anode	Cathode	Assembly Layout	Adverse Effects
Borckardt et al. (2013)	n=40	20 min	2.0 mA	C1 or C2	F4	Anodal knee representation of the motor strip / CRdlPFC	NS
DosSantos et al. (2014)	n=9	20 min	2.0 mA	M1 or C4	contralateral supraorbital region	Anodal superficial region right M1 or C4 / Cathodal contralateral supraorbital region	No major adverse events related to tDCS was reported
Wang et al. (2016)	n=20	20 min	1.5 mA	occipital lobe	FPT	Anodal occipital lobe / CR& left FPT	No side effects of tDCS were reported
Borckardt et al. (2017)	n=58	20 min	2.0 mA	C1 or C2	F4	1) Anodal knee representation of the motor / CRdlPFC	No tDCS sessions were stopped by participants or researchers due to reported intolerable discomfort, adverse events or tDCS related side effects
				F3	Fpz	2) ALdlPFC / Cathodal knee representation of the sensory cortex	
				P3	FCz	3) ALtemporal-occipital junction / Cathodal--medial-anterior--premotor-region	
Eskandari et al. (2019)	n=30	10-20 min	0.5–2 mA	F4	F3	1) AR dlPFC / CL dlPFC	NS
				F3	F4	2) ALdlPFC / CRdlPFC	
Kooteh et al. (2020)	n=54	45 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS
Sadeghi Bimorgh et al. (2020)	n=27	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	No side effects except for the redness of the SIM site
Eskandari et al. (2021)	n=31	20 min	2.0 mA	F3	F4	1) ALdlPFC / CRdlPFC	NS
				F4	F3	2) AR dlPFC / CL dlPFC	
Mostafavi et al. (2021)	n=31	10-20 min	2.0 mA	F3	F4	1) ALdlPFC / CRdlPFC	NS
				F4	F3	2) AR dlPFC / CL dlPFC	
Meng et al. (2022) (cigarette)	n=22	20 min	1.0 mA	occipital region	FPT	Anodal occipital region/ Cathodal-bilateral--frontal-parietal--temporal	NS
Mostafavi et al. (2022)	n=30	20 min	2.0 mA	F3	F4	1) ALdlPFC / CRdlPFC	NS
				F4	F3	2) AR dlPFC / CL dlPFC	
Hamed et al. (2022)	n=60	20 min	2.0 mA	M1	contralateral arm	1) Anodal M1 of the lower limbs cortex / Cathodal contralateral arm	NS
				F3	contralateral arm	2) ALdlPFC / Cathodal contralateral arm	
Taremian et al. (2019)	n=60	20 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS

Human studies: tDCS in other drug or substance use disorders

Apart from opioids, tDCS studies were conducted with various addictive substances such as methamphetamine, crack cocaine, and cannabis. Several studies were conducted to investigate the impact of tDCS on craving in individuals with substance use disorders. In these studies, 2 mA (Shahbabaie et al., 2014; Batista et al., 2015; Verveer et al., 2020; Alizadehgoradel et al., 2020; Ekhtiari et al., 2022; Patel et al., 2022) tDCS was applied to left dlPFC (Alizadehgoradel et al., 2020) and right dlPFC (Shahbabaie et al., 2014; Batista et al., 2015; Verveer et al., 2020; Ekhtiari et al., 2022; Patel et al., 2022). Although certain studies reported that tDCS reduced craving (Shahbabaie et al., 2014; Batista et al., 2015; Alizadehgoradel et al., 2020), others claimed the opposite (Verveer et al., 2020; Ekhtiari et al., 2022; Patel et al., 2022).

Several studies were conducted on the impact of tDCS on response bias, number of days substance use, and risk-taking behaviors in individuals with substance use disorders. tDCS application was conducted with 2 mA current in these studies (Patel et al., 2022; Shahbabaie et al., 2018; Verveer et al., 2020). Shahbabaie et al. (2018) applied tDCS to the right and left dlPFC in 4 combinations, and reported that tDCS application to the left dlPFC/right shoulder and left dlPFC/right dlPFC prevented response bias against drug cues. In a study that investigated the number of days of substance use, the findings revealed that tDCS did not change the number of days of substance use (Verveer et al., 2020). The findings suggested that tDCS did not lead to significant differences in risk-taking behavior in substance use (Patel et al., 2022). The summary of the study findings is presented in Table 4.

Table 4. Human studies with tDCS in substance use disorder.

Reference	Participants	Duration	Current Density	Anode	Cathode	Assembly Layout	Adverse Effects
Batista et al. (2015)	n=36	20 min	2.0 mA	F4	F3	CL dlPFC (F3) / AR dlPFC (F4)	Tingling sensation, burning sensation, tinnitus sensation, headache
Shahbabaie et al. (2014)	n=30	20 min	2.0 mA	F4	contralateral supraorbital region	AR dlPFC (F4) / Cathodal contralateral supraorbital region	Headache, vertigo, tingling, itching, dizziness, drowsiness& nausea. As for sham session, side effectswere headache, vertigo, tingling, itching, dizziness&drowsiness
Shahbabaie et al. (2018)	n=90	13 min	2.0 mA	F3	right shoulder	1) ALdlPFC (F3) / CRshoulder	Headache, vertigo, tingling, ıtching, dizziness, drowsiness, nausea
				F4	right shoulder	2) AR dlPFC (F4) / CL shoulder	
				F3	right supraorbital projection	3) ALdlPFC (F3) / CRsupraorbital ridge	
				F4	left supraorbital projection	4) AR dlPFC (F4) / Katodal left supraorbital ridge	
				F3	F4	5) ALdlPFC (F3) / Katodal right dlPFC (F4)	
Alizadehgoradel et al. (2020)	n=39	20 min	2.0 mA	F3	F4	ALdlPFC / CRdlPFC	No adverse effects were reported during & after SIM
Verveer et al. (2020c)	n=59	13 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	There were no differences between the groups (active tDCS *vs.* sham) regarding adverse effects
Ekhtiari et al. (2022)	n=60	20 min	2.0 mA	F4	Fp1	AR dlPFC / Cathodal Fp1	Headache, neck pain, scalp pain, tingling, ıtching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood change
Patel et al. (2022)	n=27	15 min	2.0 mA	F4	F3	AR dlPFC / CL dlPFC	NS

Animal studies: tDCS in alcohol/substance use disorder

Animal studies were also conducted with tDCS in alcohol use disorder. Santos et al. (2020) investigated whether tDCS would reduce neuropathic pain in alcohol withdrawal rat model. In the study conducted with 36 rats, 0.5 mA tDCS was applied for 20 minutes. The findings demonstrated that tDCS-induced analgesia delayed alcohol withdrawal (Santos et al., 2020). Santos et al. (2021) investigated the impact of tDCS on brain structure in alcohol dependence. They reported that tDCS modulated neuropeptide Y activity (Santos et al., 2020). Pedron et al. (2022) investigated which alcohol-related behavior was better modulated by tDCS administration in female mice. In the study conducted with 54 mice, 0.2 mA of tDCS was applied for 20 min. The findings evidenced that tDCS did not modulate ethanol-induced hedonic effects and behavioral sensitivity. However, tDCS reduced re-emergence of ethanol consumption by half (Pedron et al., 2022).

Anvari et al. (2019) investigated the impact of tDCS on pain response induced by different morphine intake rates. In the study conducted with 96 rats, left prefrontal 0.2 mA anodal tDCS was applied for 20 minutes. They observed that tDCS did not affect pain perception induced by various morphine doses (Anvari et al., 2019).

tDCS studies were also conducted with animals on smoking disorders. Pedron et al. (2013) investigated whether tDCS prevented nicotine addiction in mice. In the study conducted with 36 mice, 0.2 mA anodal tDCS was applied to the cranium region for 20 minutes. The findings revealed that the tDCS application performed in the animal model facilitated smoking cessation and let to a decrease in cigarette craving (Pedron et al., 2013).

It has been investigated what kind of changes tDCS can cause in executive and cognitive functions in individuals with substance use disorders. The studies were conducted with 2 mA of tDCS application to the left (Alizadehgoradel et al., 2020) and right dlPFC (Verveer et al., 2020). Alizadehgoradel et al. (2020) reported improvements in executive functions. Verveer et al. (2020) reported that tDCS had no impact on the development of cognitive functions in substance users.

In summary, the studies reviewed in the present paper recommended non-invasive brain stimulation techniques to investigate the effects of substances such as nicotine, opioids, and alcohol on the brain. The summary of the study findings is presented in Table 5.

DISCUSSION

Substance use disorder is a complex field of research due to the impact of several social, biological, and psychological factors that contribute to frequent relapses. Furthermore, the repetitive nature of substance use is also a negative factor in research. The cost of addiction treatment varies based on detoxification requirements, availability of inpatient or outpatient programs, duration of the treatment, and medication requirements, where the costs range between $1,000 and $60,000. Thus, further treatment methods have been explored to supplement pharmacological treatment and psychotherapy. Addiction studies conducted with tDCS are valuable due to the hope that tDCS could serve as an adjunct therapy.

The therapeutic effects of tDCS are believed to be induced by anodal tDCS, considered to promote long-term potentiation and depression-like plasticity (Monte-Silva et al., 2013). The glutamatergic system, which relies on NMDA receptors, is crucial for the in-

Table 5. Animal studies with tDCS in alcohol/substance use disorder.

Reference	Participants	Duration	Current Density	Anode	Cathode	Assembly Layout	Substance	Adverse Effects
Pedron et al. (2013)	n=36	20 min	0.2 mA	cranium	ventral thorax	ALfrontal cortex / Cathodal ventral thorax	Nicotine	NS
Anvari et al. (2019)	n=96	20 min	0.2 mA	left prefrontal	ventral thorax	ALprefrontal / Cathodal ventral thorax	Opioid	NS
Santos et al. (2020)	n=38	20 min	0.5 mA	parietal cortexs	SOA	Anodal the anterior & posterior regions in the mid-line between the two hemispheres of the parietal cortexs / Cathodal midpoint between the lateral angles of both eyes	Alcohol	NS
Santos et al. (2021)	n=36	20 min	0.5 mA			PFC, amigdala ve striatum	Alcohol	NS
Pedron et al. (2022)	n=54	20 min	0.2 mA	Frontal Cortex	ventral thorax	Anodal Frontal Cortex / Cathodal ventral thorax	Alcohol	NS

duction and maintenance of neuroplastic changes induced by tDCS (Paulus, 2004). Studies demonstrated that the long-term effects of tDCS on motor evoked potentials could be blocked by NMDA antagonists (Liebetanz et al., 2002). Furthermore, it was evidenced that d-cycloserine, a partial NMDA agonist, potentiates tDCS-induced excitability enhancements, providing strong evidence for the involvement of NMDA receptors in mediating tDCS effects (Nitsche et al., 2004). Also, tDCS, a non-invasive brain stimulation technique, has been demonstrated to modulate inhibitory GABAergic systems, critical in neuroplasticity regulation (Stagg et al., 2009). It was demonstrated that anodal tDCS decreases GABA concentration, indicating its involvement in neuroplastic changes, as demonstrated in magnetic resonance spectroscopy studies. Furthermore, when combined with repetitive low-frequency synaptic stimulation, anodal tDCS increases the secretion of brain-derived neurotrophic factor (BDNF), and activates tropomyosin receptor kinase B, suggesting that BDNF could mediate tDCS-induced effects (Fritsch et al., 2010). Also, tDCS significantly improves Zif268 and c-Fos expressions, two crucial proteins involved in synaptic plasticity, *via* certain mechanisms closely associated with long-term potentiation.

Primarily, significant results were reported by tDCS studies based on stimulation of the dlPFC. It could be argued that most problems associated with addiction are dlPFC-centered issues. This could be due to the fact that dlPFC is responsible for decision-making, attention, memory, impulse control, behavior and thought regulation. Thus, it could be suggested that addictive substances lead to psychological and behavioral abnormalities by affecting the dlPFC. The human and animal studies on alcohol/substance use disorder conducted with tDCS are presented in the tables. They demonstrated that the brain region where the current was applied was mainly the dlPFC. The same was true for animal experiments. Animal experiments conducted in alcohol/substance use disorder demonstrated that the activation of the frontal cortex was attempted to changed. The rationale behind the employment of various stimulating electrode polarities such as anodal tDCS or cathodal tDCS was to investigate the responses of various brain regions to stimulation, and whether they exhibit behavioral changes due to activation or inhibition after substance use.

Thus, experimental setups were designed with various electrode polarities in most studies. Furthermore, the impact of tDCS was investigated with several currents and durations of the stimulation. tDCS applications aimed to neurobiologically regulate the brain regions associated with alcohol/substance use disorder. To develop treatments for addiction and related disorders, it should be well known how neurobiological functioning occurs in brain regions. Behind the addictive property of alcohol, drugs and tobacco lies their relationship with the central nervous system. They affect several systems, including the cholinergic, dopaminergic, serotonergic, and GABAergic, leading to several functional differences. Substance use disorder, including alcohol, drug, and cigarette addiction, impacts the cholinergic system by altering acetylcholine levels, a neurotransmitter associated with learning, memory, and reward processing. Chronic substance abuse could dysregulate the cholinergic system, leading to cognitive impairments, disruption of synaptic plasticity, and heightened susceptibility to addiction-related behaviors (Gonzales et al., 2015). Also, substance abuse significantly affects the dopaminergic system, which plays a crucial role in reward processing, motivation, and learning reinforcement. Drugs, alcohol, and nicotine increase dopamine levels in the brain's reward pathway, particularly in the nucleus accumbens and the ventral tegmental area. This dopamine surge reinforces substance-seeking behavior, contributing to the development and sustenance of the addiction (Koob et al., 2016). The serotonergic system is also important and involves the neurotransmitter serotonin, which regulates mood, controls impulse and emotional states. Chronic substance use alters serotonin transmission, leading to mood disturbances, impulsivity, and dysregulated emotional responses. Serotonergic system dysfunctions contribute to the development of substance use disorders and could exacerbate comorbid mental health conditions such as depression and anxiety (Kirby et al., 2011). Furthermore, the gamma-aminobutyric acid (GABA) system, known for its inhibitory role in the brain, is affected by substance abuse, leading to alterations in neural excitability and synaptic transmission. Chronic alcohol, drug, and nicotine consumption disrupt GABAergic neurotransmission, contributing to withdrawal symptoms, tolerance, and dependence. The interplay between brain regions and neurotransmitters is crucial for the orchestration of reward-related circuitry in alcohol and other substance use (Guleken et al, 2022). Dysregulation of the GABAergic system could enhance the reinforcing effects of substances and exacerbate addictive behavior (Kalivas et al., 2009).

Furthermore, these systems could lead to addiction problem by affecting the dlPFC and other brain structures. Especially due to its capacity to affect reward mechanisms in the brain, dopamine is a crucial neurotransmitter in addiction research. The intake of the addictive substance increases dopamine activation, leading to an increase in the feelings of pleasure, motivation and reward. tDCS inhibits dopamine activation, attempting to reduce the feeling of pleasure, and

leading to the reduction of tolerance and withdrawal symptoms. Individuals could not enjoy the substance anymore; and thus, recurrence is prevented. It was suggested that tDCS could be an adjunct treatment for alcohol/substance use disorders. Addiction is still an open research field due to its complex nature. Future addiction studies that would be conducted with tDCS could focus on different brain regions to discover new regions associated with addiction. The investigation of the impact of tDCS on the brain structures of individuals with alcohol/substance use disorder is essential to understand addiction, and for the development of new treatment options.

REFERENCES

Alghamdi, F., Alhussien, A., Alohali, M., Alatawi, A., Almusned, T., Fecteau, S., Habib, S. S., & Bashir, S. (2019). Effect of transcranial direct current stimulation on the number of smoked cigarettes in tobacco smokers. *PLOS ONE*, *14*(2), e0212312. https://doi.org/10.1371/journal.pone.0212312

Alizadehgoradel, J., Nejati, V., Sadeghi Movahed, F., Imani, S., Taherifard, M., Mosayebi-Samani, M., Vicario, C. M., Nitsche, M. A., & Salehinejad, M. A. (2020). Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: A randomized, double-blind, parallel-group study. *Brain Stimulation*, *13*(3), 582–593. https://doi.org/10.1016/j.brs.2019.12.028

Almeida-Antunes, N., Vasconcelos, M., Crego, A., Rodrigues, R., Sampaio, A., & López-Caneda, E. (2022). Forgetting alcohol: A double-blind, randomized controlled trial investigating memory inhibition training in young binge drinkers. *Frontiers in Neuroscience*, *16*, 907. https://doi.org/10.3389/fnins.2022.914213

Aman, S., & Sharma, G. (2022). Paper Presentation: Effectiveness of tDCS in Reduction of Craving in Alcohol Dependence Syndrome. *Indian Journal of Psychiatry, 64(Suppl 3)*, S599. https://doi.org/10.4103/0019-5545.341738

Anvari, S. S., Nasehi, M., & Zarrindast, M. R. (2019). Effects of acute and subchronic anodal transcranial direct current stimulation (tDCS) on morphine-induced responses in hotplate apparatus. *Galen Medical Journal*, *8*, e1157. https://doi.org/10.31661/gmj.V8I0.1157

Aronson Fischell, S., Ross, T. J., Deng, Z. De, Salmeron, B. J., & Stein, E. A. (2020). Transcranial direct current stimulation applied to the dorsolateral and ventromedial prefrontal cortices in smokers modifies cognitive circuits implicated in the nicotine withdrawal syndrome. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(4), 448–460. https://doi.org/10.1016/j.bpsc.2019.12.020

Batista, E. K., Klauss, J., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2015). A randomized placebo-controlled trial of targeted prefrontal cortex modulation with bilateral tDCS in patients with crack-cocaine dependence. *International Journal of Neuropsychopharmacology*, *18*(12), 1–11. https://doi.org/10.1093/IJNP/PYV066

Batsikadze, G., Paulus, W., Hasan, A., Grundey, J., Kuo, M. F., & Nitsche, M. A. (2017). Compromised neuroplasticity in cigarette smokers under nicotine withdrawal is restituted by the nicotinic α4β2-receptor partial agonist varenicline. *Scientific Reports 7*(1), 1–11. https://doi.org/10.1038/s41598-017-01428-6

Borckardt, J. J., Reeves, S. T., Milliken, C., Carter, B., Epperson, T. I., Gunselman, R. J., Madan, A., Del Schutte, H., Demos, H. A., & George, M. S. (2017). Prefrontal versus motor cortex transcranial direct current stimulation (tDCS) effects on post-surgical opioid use. *Brain Stimulation*, *10*(6), 1096–1101. https://doi.org/10.1016/J.BRS.2017.09.006

Borckardt, J. J., Reeves, S. T., Robinson, S. M., May, J. T., Epperson, T. I., Gunselman, R. J., Schutte, H. Del, Demos, H. A., Madan, A., Fredrich, S., & George, M. S. (2013). Transcranial direct current stimulation (tDCS) reduces postsurgical opioid consumption in total knee arthroplasty (TKA). *Clinical Journal of Pain*, *29*(11), 925–928. https://doi.org/10.1097/AJP.0B013E31827E32BE

Boroda, E., Krueger, A. M., Bansal, P., Schumacher, M. J., Roy, A. V., Boys, C. J., Lim, K. O., & Wozniak, J. R. (2020). A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder. *Brain Stimulation*, *13*(4), 1059–1068. https://doi.org/10.1016/j.brs.2020.04.015

Brangioni, M. C. V. de S., Pereira, D. A., Thibaut, A., Fregni, F., Brasil-Neto, J. P., & Boechat-Barros, R. (2018). Effects of prefrontal transcranial direct current stimulation and motivation to quit in tobacco smokers: A randomized, sham controlled, double-blind trial. *Frontiers in Pharmacology*, *9*, 14. https://doi.org/10.3389/fphar.2018.00014

Brown, D. R., Jackson, T. C. J., Claus, E. D., Votaw, V. R., Stein, E. R., Robinson, C. S. H., Wilson, A. D., Brandt, E., Fratzke, V., Clark, V. P., & Witkiewitz, K. (2020). Decreases in the late positive potential to alcohol images among alcohol treatment seekers following mindfulness-based relapse prevention. *Alcohol and Alcoholism*, *55*(1), 78–85. https://doi.org/10.1093/alcalc/AGZ096

Bruijnzeel, A. W. (2016). Neuropeptide systems and new treatments for nicotine addiction. *Psychopharmacology 234*(9), 1419–1437. https://doi.org/10.1007/S00213-016-4513-5

Chen, J., Qin, J., He, Q., & Zou, Z. (2020). A meta-analysis of transcranial direct current stimulation on substance and food craving: What effect do modulators have? *Frontiers in Psychiatry*, 11. https://doi.org/10.3389/fpsyt.2020.00598.

Chhabra, H., Bose, A., Shivakumar, V., Agarwal, S. M., Sreeraj, V. S., Shenoy, S., Hazari, N., Dinakaran, D., Parlikar, R., Koparde, V., Ramesh, V., Biswal, J., Murugaraja, V., Gowda, S. M., Chand, P. K., Sivakumar, P. T., Kalmady, S. V., Narayanaswamy, J. C., Murthy, P., Venkatasubramanian, G. (2020). Tolerance of transcranial direct current stimulation in psychiatric disorders: An analysis of 2000+ sessions. *Psychiatry Research*, *284*, 112744. https://doi.org/10.1016/j.psychres.2020.112744

Claus, E. D., Klimaj, S. D., Chavez, R., Martinez, A. D., & Clark, V. P. (2019). A randomized trial of combined tdcs over right inferior frontal cortex and cognitive bias modification: null effects on drinking and alcohol approach bias. *Alcoholism: Clinical and Experimental Research*, *43*(7), 1591–1599. https://doi.org/10.1111/ACER.14111

da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2013). Behavioral effects of transcranial Direct Current Stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *Journal of Physiology-Paris*, *107*(6), 493–502. https://doi.org/10.1016/j.jphysparis.2013.07.003

den Uyl, T. E., Gladwin, T. E., & Wiers, R. W. (2015). Transcranial direct current stimulation, implicit alcohol associations and craving. *Biological Psychology*, *105*, 37–42. https://doi.org/10.1016/j.biopsycho.2014.12.004

den Uyl, T. E., Gladwin, T. E., & Wiers, R. W. (2016). Electrophysiological and behavioral effects of combined transcranial direct current stimulation and alcohol approach bias retraining in hazardous drinkers. *Alcoholism: Clinical and Experimental Research*, *40*(10), 2124–2133. https://doi.org/10.1111/acer.13171

den Uyl, T. E., Gladwin, T. E., Lindenmeyer, J., & Wiers, R. W. (2018). A clinical trial with combined transcranial direct current stimulation and attentional bias modification in alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research*, *42*(10), 1961–1969. https://doi.org/10.1111/acer.13841

den Uyl, T. E., Gladwin, T. E., Rinck, M., Lindenmeyer, J., & Wiers, R. W. (2017). A clinical trial with combined transcranial direct current stimulation and alcohol approach bias retraining. *Addiction Biology*, *22*(6), 1632–1640. https://doi.org/10.1111/adb.12463

Dormal, V., Lannoy, S., Bollen, Z., D'Hondt, F., & Maurage, P. (2020). Can we boost attention and inhibition in binge drinking? Electrophysiological impact of neurocognitive stimulation. *Psychopharmacology*, *237*(5), 1493–1505. https://doi.org/10.1007/S00213-020-05475-2

DosSantos, M. F., Martikainen, I. K., Nascimento, T. D., Love, T. M., DeBoer, M. D., Schambra, H. M., Bikson, M., Zubieta, J. K., & DaSilva, A. F. (2014). Building up analgesia in humans via the endogenous μ-opioid system by combining placebo and active tDCS: A Preliminary Report. *PLOS ONE*, *9*(7), e102350. https://doi.org/10.1371/journal.pone.0102350

Dubuson, M., Kornreich, C., Vanderhasselt, M. A., Baeken, C., Wyckmans, F., Dousset, C., Hanak, C., Veeser, J., Campanella, S., Chatard, A., Jaafari, N., & Noël, X. (2021). Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: A randomized placebo-controlled clinical trial. *Brain Stimulation*, *14*(6), 1531–1543. https://doi.org/10.1016/j.brs.2021.10.386

Ekhtiari, H., Soleimani, G., Kuplicki, R., Yeh, H. W., Cha, Y. H., & Paulus, M. (2022). Transcranial direct current stimulation to modulate fMRI drug cue reactivity in methamphetamine users: A randomized clinical trial. *Human Brain Mapping*, *43*(17), 5340–5357. https://doi.org/10.1002/hbm.26007

Eskandari, Z., Dadashi, M., Mostafavi, H., Armani Kia, A., & Pirzeh, R. (2019). Comparing the efficacy of anodal, cathodal, and sham transcranial direct current stimulation on brain-derived neurotrophic factor and psychological symptoms in opioid-addicted patients. *Basic and Clinical Neuroscience*, *10*(6), 641–650. https://doi.org/10.32598/BCN.10.6.1710.1

Eskandari, Z., Mostafavi, H., Hosseini, M., Mousavi, S. E., Ramazani, S., & Dadashi, M. (2021). A sham-controlled clinical trial to examine the effect of bilateral tDCS on craving, TNF-α and IL-6 expression levels, and impulsivity of males with opioid use disorder. *J Addict Dis*, *39*(3), 347–356. https://doi.org/10.1080/10550887.2021.1883208

Falcone, M., Bernardo, L., Ashare, R. L., Hamilton, R., Faseyitan, O., McKee, S. A., Loughead, J., & Lerman, C. (2016). Transcranial direct current brain stimulation increases ability to resist smoking. *Brain Stimulation*, *9*(2), 191–196. https://doi.org/10.1016/j.brs.2015.10.004

Falcone, M., Bernardo, L., Wileyto, E. P., Allenby, C., Burke, A. M., Hamilton, R., Cristancho, M., Ashare, R. L., Loughead, J., & Lerman, C. (2019). Lack of effect of transcranial direct current stimulation (tDCS) on short-term smoking cessation: Results of a randomized, sham-controlled clinical trial. *Drug and Alcohol Dependence*, *194*, 244–251. https://doi.org/10.1016/j.drugalcdep.2018.10.016

Fecteau, S., Agosta, S., Hone-Blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., & Pascual-Leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: A preliminary study. *Drug and Alcohol Dependence*, *140*, 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*, 66(2), 198–204. https://doi.org/10.1016/j.neuron.2010.03.035

Ghorbani Behnam, S., Mousavi, S. A., & Emamian, M. H. (2019). The effects of transcranial direct current stimulation compared to standard bupropion for the treatment of tobacco dependence: A randomized sham-controlled trial. *European Psychiatry, 60*, 41–48. doi:10.1016/j.eurpsy.2019.04.010

Gonzales, K., & Smith, Y. (2015). Cholinergic interneurons in the dorsal and ventral striatum: anatomical and functional considerations in normal and diseased conditions. Annals of the New York Academy of Sciences, 1349. https://doi.org/10.1111/nyas.12762.

Grundey, J., Barlay, J., Batsikadze, G., Kuo, M. F., Paulus, W., & Nitsche, M. (2018). Nicotine modulates human brain plasticity via calcium-dependent mechanisms. *The Journal of Physiology*, *596*(22), 5429–5441. https://doi.org/10.1113/JP276502

Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A. C., Lang, N., Paulus, W., & Nitsche, M. A. (2012). Neuroplasticity in cigarette smokers is altered under withdrawal and partially restituted by nicotine exposition. The Journal of neuroscience, 32(12), 4156–4162. https://doi.org/10.1523/JNEUROSCI.3660-11.2012

Guleken, Z., & Uzbay, T. (2022). Neurobiological and neuropharmacological aspects of food addiction. *Neuroscience and Biobehavioral Reviews*, 139, 104760. https://doi.org/10.1016/j.neubiorev.2022.104760

Guleken, Z., Eskikurt, G., & Karamürsel, S. (2020). Investigation of the effects of transcranial direct current stimulation and neurofeedback by continuous performance test. *Neuroscience letters*, *716*, 134648. https://doi.org/10.1016/j.neulet.2019.134648

Hajloo, N., Pouresmali, A., Goradel, J. A., & Mowlaie, M. (2019). The effects of transcranial direct current stimulation of dorsolateral prefrontal cortex on reduction of craving in daily and social smokers. *Iranian Journal of Psychiatry*, *14*(4), 291–296. https://doi.org/10.18502/IJPS.V14I4.1979

Hamed, R., Khedr, E. M., Haridy, N. A., Mohamed, K. O., & Elsawy, S. (2022). Effects of transcranial direct current stimulation in pain and opioid consumption after spine surgery. *European Journal of Pain*, *26*(7), 1594–1604. https://doi.org/10.1002/EJP.1985

Hasin, D. S., O'Brien, C. P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W. M., Crowley, T., Ling, W., Petry, N. M., Schuckit, M., & Grant, B. F. (2013). DSM-5 criteria for substance use disorders: Recommendations and rationale. *American Journal of Psychiatry*, *170*(8), 834–851. https://doi.org/10.1176/appi.ajp.2013.12060782

Holla, B., Biswal, J., Ramesh, V., Shivakumar, V., Bharath, R. D., Benegal, V., Venkatasubramanian, G., Chand, P. K., & Murthy, P. (2020). Effect of prefrontal tDCS on resting brain fMRI graph measures in Alcohol Use Disorders: A randomized, double-blind, sham-controlled study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *102*, 109950. https://doi.org/10.1016/j.pnpbp.2020.109950

Institute of Medicine (US) Committee on Opportunities in Drug Abuse Research. (1996). Pathways of addiction: Opportunities in drug abuse research. *Pathways of Addiction*. https://doi.org/10.17226/5297

Jitendriya, B., B, H., V, S., PK, C., P, M., G, V., V, B., & RD, Bharath. (2022). Effect of transcranial direct current stimulation on relapse of alcohol. *Indian Journal of Psychiatry*, *64*(Suppl 3), S629. https://doi.org/10.4103/0019-5545.341837

Kalivas, P. (2009). The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*, *10*, 561-572. https://doi.org/10.1038/nrn2515.

Kirby, L., Zeeb, F., & Winstanley, C. (2011). Contributions of serotonin in addiction vulnerability. Neuropharmacology, 61, 421–432. https://doi.org/10.1016/j.neuropharm.2011.03.022.

Klauss, J., Anders, Q. S., Felippe, L. V., Nitsche, M. A., & Nakamura-Palacios, E. M. (2018). Multiple sessions of transcranial direct current stimulation (tDCS) reduced craving and relapses for alcohol use: A randomized placebo-controlled trial in alcohol use disorder. *Frontiers in Pharmacology*, *9*, 716. https://doi.org/10.3389/FPHAR.2018.00716

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., Correia Santos, G. D. A., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *International Journal of Neuropsychopharmacology*, *17*(11), 1793–1803. https://doi.org/10.1017/S1461145714000984

Koob, G., & Volkow, N. (2016). Neurobiology of addiction: a neurocircuitry analysis.. The lancet. Psychiatry, 3 8, 760-73 . https://doi.org/10.1016/S2215-0366(16)00104-8.

Kooteh, B. R., Dolatshahi, B., Nosratabadi, M., Bakhshani, N. M., Mahdavi, A., & Hakami, M. C. (2020). Combination therapy and opioids: effectiveness of transcranial direct-current stimulation (tDCS) and emotion regulation training in reducing current drug craving. *Maedica*, *15*(1), 53–60. https://doi.org/10.26574/MAEDICA.2020.15.1.53

Kroczek, A. M., Häußinger, F. B., Rohe, T., Schneider, S., Plewnia, C., Batra, A., Fallgatter, A. J., & Ehlis, A. C. (2016). Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure. *Drug and Alcohol Dependence*, *168*, 123–127. https://doi.org/10.1016/J.DRUGALCDEP.2016.09.006

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*, *339*. https://doi.org/10.1136/BMJ.B2700

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain: a journal of neurology*, *125*(Pt 10), 2238–2247. https://doi.org/10.1093/brain/awf238

Lin, S. H., Chen, P. S., Chen, K. C., Chang, W. H., Wang, T. Y., & Yang, Y. K. (2021). Transcranial direct current stimulation (tDCS) may reduce the expired CO concentration among opioid users who smoke cigarettes: a randomized sham-controlled study. *Psychiatry Research*, *299*, 113874. https://doi.org/10.1016/J.PSYCHRES.2021.113874

Mahoney, J. J., Hanlon, C. A., Marshalek, P. J., Rezai, A. R., & Krinke, L. (2020). Transcranial magnetic stimulation, deep brain stimulation, and other forms of neuromodulation for substance use disorders: Review of modalities and implications for treatment. *Journal of the Neurological Sciences*, *418*, 117149. https://doi.org/10.1016/J.JNS.2020.117149

Meng, Z., Li, Q., Ma, Y., & Liu, C. (2022). Transcranial direct current stimulation of the frontal-parietal-temporal brain areas reduces cigarette consumption in abstinent heroin users. *Journal of Psychiatric Research*, *152*, 321–325. https://doi.org/10.1016/J.JPSYCHIRES.2022.06.045

Meng, Z., Liu, C., Yu, C., & Ma, Y. (2014). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates smoking behavior. *Journal of Psychiatric Research*, *54*(1), 19–25. https://doi.org/10.1016/J.JPSYCHIRES.2014.03.007

Mohammadi, A. (2016) Induction of Neuroplasticity by Transcranial Direct Current Stimulation. *J Biomed Phys Eng*. 6(4): 205-208. PMID: 28144588; PMCID: PMC5219570.

Mondino, M., Luck, D., Grot, S., Januel, D., Suaud-Chagny, M. F., Poulet, E., & Brunelin, J. (2018). Effects of repeated transcranial direct current stimulation on smoking, craving and brain reactivity to smoking cues. *Scientific Reports 2018 8: 1*, *8*(1), 1–11. https://doi.org/10.1038/s41598-018-27057-1

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation*, 6(3), 424–432. https://doi.org/10.1016/j.brs.2012.04.011

Mostafavi, H., Dadashi, M., Armani Kia, A., Ahmadi, D., Pirzeh, R., & Eskandari, Z. (2021). The effect of bilateral tDCS over dorsolateral prefrontal cortex on the cognitive abilities of men with opioid use disorder under methadone therapy: A sham-controlled clinical trial. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, *57*(1), 1–8. https://doi.org/10.1186/S41983-021-00401-5

Mostafavi, H., Dadashi, M., Faridi, A., Kazemzadeh, F., & Eskandari, Z. (2022). Using bilateral tdcs to modulate eeg amplitude and coherence of men with opioid use disorder under methadone therapy: A sham-controlled clinical trial. *Clinical EEG and Neuroscience*, *53*(3), 184–195. https://doi.org/10.1177/15500594211022100

Müller, T., Shevchenko, Y., Gerhardt, S., Kiefer, F., & Vollstädt-Klein, S. (2021). The influence of perceived stress and self-control on efficacy of repeated transcranial direct current stimulation in non-treatment-seeking smokers. *Drug and Alcohol Dependence*, *226*, 108861. https://doi.org/10.1016/j.drugalcdep.2021.108861

Nakamura-Palacios, E. M., De Almeida Benevides, M. C., Da Penha Zago-Gomes, M., De Oliveira, R. W. D., De Vasconcellos, V. F., De Castro, L. N. P., Da Silva, M. C., Ramos, P. A., & Fregni, F. (2012). Auditory event-related potentials (P3) and cognitive changes induced by frontal direct current stimulation in alcoholics according to Lesch alcoholism typology. *International Journal of Neuropsychopharmacology*, *15*(5), 601–616. https://doi.org/10.1017/S1461145711001040

Nakamura-Palacios, E. M., Lopes, I. B. C., Souza, R. A., Klauss, J., Batista, E. K., Conti, C. L., Moscon, J. A., & de Souza, R. S. M. (2016). Ventral medial prefrontal cortex (vmPFC) as a target of the dorsolateral prefrontal modulation by transcranial direct current stimulation (tDCS) in drug addiction. *Journal of Neural Transmission*, *123*(10), 1179–1194. https://doi.org/10.1007/S00702-016-1559-9

National Institute of Mental Health. (2021). *NIMH » Substance Use and Co-Occurring Mental Disorders*. https://www.nimh.nih.gov/health/topics/substance-use-and-mental-health

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(Pt 3), 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M., Cohen, L., Wassermann, E., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P., Fregni, F., & Pascual-Leone, Á. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, 1, 206-223. https://doi.org/10.1016/j.brs.2008.06.004

Nitsche, M., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Consolidation of human motor cortical neuroplasticity by d-cycloserine. *Neuropsychopharmacology*, 29, 1573-1578. https://doi.org/10.1038/sj.npp.1300517

Patel, H., Naish, K., Soreni, N., & Amlung, M. (2022). The effects of a single transcranial direct current stimulation session on impulsivity and risk among a sample of adult recreational cannabis users. *Frontiers in Human Neuroscience*, *16*, 9. https://doi.org/10.3389/fnhum.2022.758285

Paulus W. (2004). Outlasting excitability shifts induced by direct current stimulation of the human brain. *Supplements to Clinical Neurophysiology*, *57*, 708–714. https://doi.org/10.1016/s1567-424x(09)70411-8

Pedron, S., Dumontoy, S., González-Marín, M. del C., Coune, F., Van Schuerbeek, A., Haffen, E., Naassila, M., & Van Waes, V. (2022). Transcranial direct current stimulation (tDCS) reduces motivation to drink ethanol and reacquisition of ethanol self-administration in female mice. *Scientific Reports 12*(1), 1–12. https://doi.org/10.1038/s41598-021-03940-2

Pedron, S., Monnin, J., Haffen, E., Sechter, D., & Van Waes, V. (2013). Repeated transcranial direct current stimulation prevents abnormal behaviors associated with abstinence from chronic nicotine consumption. *Neuropsychopharmacology 2014 39: 4*, *39*(4), 981–988. https://doi.org/10.1038/npp.2013.298

Perri, R. L., & Perrotta, D. (2021). Transcranial direct current stimulation of the prefrontal cortex reduces cigarette craving in not motivated to quit smokers: A randomized, sham-controlled study. *Addictive Behaviors*, *120*, 106956. https://doi.org/10.1016/j.addbeh.2021.106956

Pickering, R. P., Goldstein, R. B., Hasin, D. S., Blanco, C., Smith, S. M., Huang, B., Pulay, A. J., Ruan, W. J., Saha, T. D., Stinson, F. S., Dawson, D. A., Chou, S. P., & Grant, B. F. (2011). Temporal relationships between overweight and obesity and DSM-IV substance use, mood, and anxiety disorders: Results from a prospective study, the national epidemiologic survey on alcohol and related conditions. *Journal of Clinical Psychiatry*, *72*(11), 1494–1502. https://doi.org/10.4088/JCP.10m06077gry

Pripfl, J., & Lamm, C. (2015). Focused transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex modulates specific domains of self-regulation. *Neuroscience Research*, *91*, 41–47. https://doi.org/10.1016/j.neures.2014.09.007

Reichenbach, N., Karch, S., Klemme, J., Keeser, D., Ludwig, H., Zeren, A., Paolini, M., Blautzik, J., Pogarell, O., Padberg, F., & Rüther, T. (2014). EPA-1578 – Modifications of human brain activity due to transcranial direct current stimulation (tdcs) in patients with nicotine dependence. *European Psychiatry, 29*, 1. https://doi.org/10.1016/s0924-9338(14)78734-6

Sadeghi Bimorgh, M., Omidi, A., Ghoreishi, F. S., Rezaei Ardani, A., Ghaderi, A., & Banafshe, H. R. (2020). The effect of transcranial direct current stimulation on relapse, anxiety, and depression in patients with opioid dependence under methadone maintenance treatment: A pilot study. *Frontiers in Pharmacology*, *11*, 401. https://doi.org/10.3389/fphar.2020.00401

Santos, D. S., Lopes, B. C., Medeiros, L. F., Assumpção, J. A. F., de Souza, A., Salvi, A. A., da Silva, L. S., Fregni, F., Caumo, W., & Torres, I. L. S. (2020).

Transcranial direct current stimulation (tDCS) induces analgesia in rats with neuropathic pain and alcohol abstinence. *Neurochemical Research*, *45*(11), 2653–2663. https://doi.org/10.1007/S11064-020-03116-W

Santos, D. S., Medeiros, L. F., Stein, D. J., De Macedo, I. C., Da Silva Rios, D. E., De Oliveira, C., Toledo, R. S., Fregni, F., Caumo, W., & Torres, I. L. S. (2021). Bimodal transcranial direct current stimulation reduces alcohol consumption and induces long-term neurochemical changes in rats with neuropathic pain. *Neuroscience Letters*, *759*, 136014. https://doi.org/10.1016/j.neulet.2021.136014

Sayre, M., Lapham, G. T., Lee, A. K., Oliver, M., Bobb, J. F., Caldeiro, R. M., & Bradley, K. A. (2020). Routine assessment of symptoms of substance use disorders in primary care: Prevalence and severity of reported symptoms. *Journal of General Internal Medicine*, *35*(4), 1111–1119. https://doi.org/10.1007/s11606-020-05650-3

Scholl, L., Seth, P., Kariisa, M., Wilson, N., & Baldwin, G. (2018). Drug and opioid-involved overdose deaths – United States, 2013–2017. *MMWR. Morbidity and Mortality Weekly Report*, *67*(5152). https://doi.org/10.15585/mmwr.MM675152E1

Schwippel, T., Schroeder, P. A., Hasan, A., & Plewnia, C. (2022). Implicit measures of alcohol approach and drinking identity in alcohol use disorder: A preregistered double-blind randomized trial with cathodal transcranial direct current stimulation (tDCS). *Addiction Biology*, *27*(4), e13180. https://doi.org/10.1111/adb.13180

Sergiou, C. S., Woods, A. J., Franken, I., & van Dongen, J. (2020). Transcranial direct current stimulation (tDCS) as an intervention to improve empathic abilities and reduce violent behavior in forensic offenders: study protocol for a randomized controlled trial. *Trials, 21(1)*, 263. https://doi.org/10.1186/s13063-020-4074-0

Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., Fregni, F., & Ekhtiari, H. (2014). State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *International Journal of Neuropsychopharmacology*, *17*(10), 1591–1598. https://doi.org/10.1017/S1461145714000686

Shahbabaie, A., Hatami, J., Farhoudian, A., Ekhtiari, H., Khatibi, A., & Nitsche, M. A. (2018). Optimizing electrode montages of transcranial direct current stimulation for attentional bias modification in early abstinent methamphetamine users. *Frontiers in Pharmacology*, *9*(AUG), 907. https://doi.org/10.3389/fphar.2018.00907

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist*, *17*(1), 37–53. https://doi.org/10.1177/1073858410386614

Stagg, C., Best, J., Stephenson, M., O'Shea, J., Wylezinska, M., Kincses, Z., Morris, P., Matthews, P., & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of Neuroscience*, 29, 5202–5206. https://doi.org/10.1523/jneurosci.4432-08.2009

Substance Abuse and Mental Health Services Administration. (2019). *Results from the 2018 National Survey on Drug Use and Health: Detailed tables*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/

Taremian, F., Nazari, S., Moradveisi, L., & Moloodi, R. (2019). Transcranial Direct Current Stimulation on Opium Craving, Depression, and Anxiety: A Preliminary Study. *The journal of ECT, 35(3)*, 201–206. https://doi.org/10.1097/YCT.0000000000000568

Trojak, B., Soudry-Faure, A., Abello, N., Carpentier, M., Jonval, L., Allard, C., Sabsevari, F., Blaise, E., Ponavoy, E., Bonin, B., Meille, V., & Chauvet-Gelinier, J. C. (2016). Efficacy of transcranial direct current stimulation (tDCS) in reducing consumption in patients with alcohol use disorders: Study protocol for a randomized controlled trial. *Trials*, *17*(1), 1–8. https://doi.org/10.1186/S13063-016-1363-8

Vanderhasselt, M. A., Allaert, J., De Raedt, R., Baeken, C., Krebs, R. M., & Herremans, S. (2020). Bifrontal tDCS applied to the dorsolateral prefrontal cortex in heavy drinkers: Influence on reward-triggered approach bias and alcohol consumption. *Brain and Cognition*, *138*, 105512. https://doi.org/10.1016/j.bandc.2019.105512

Verveer, I., Remmerswaal, D., Jongerling, J., Van Der Veen, F. M., & Franken, I. H. A. (2020). No effect of repetitive tDCS on daily smoking behaviour in light smokers: A placebo controlled EMA study. *PLOS ONE*, *15*(5), e0233414. https://doi.org/10.1371/journal.pone.0233414

Verveer, I., Remmerswaal, D., van der Veen, F. M., & Franken, I. H. A. (2020). Long-term tDCS effects on neurophysiological measures of cognitive control in tobacco smokers. *Biological Psychology*, *156*, 107962. https://doi.org/10.1016/j.biopsycho.2020.107962

Verveer, I., van der Veen, F. M., Shahbabaie, A., Remmerswaal, D., & Franken, I. H. A. (2020). Multi-session electrical neuromodulation effects on craving, relapse and cognitive functions in cocaine use disorder: A randomized, sham-controlled tDCS study. *Drug and Alcohol Dependence*, *217*, 108429. https://doi.org/10.1016/j.drugalcdep.2020.108429

Wang, Y., Shen, Y., Cao, X., Shan, C., Pan, J., He, H., Ma, Y., & Yuan, T. F. (2016). Transcranial direct current stimulation of the frontal-parietal-temporal area attenuates cue-induced craving for heroin. *Journal of Psychiatric Research*, *79*, 1–3. https://doi.org/10.1016/j.jpsychires.2016.04.001

Weidler, C., Habel, U., Wallheinke, P., Wagels, L., Hofhansel, L., Ling, S., Blendy, J. A., & Clemens, B. (2022). Consequences of prefrontal tDCS on inhibitory control and reactive aggression. *Social Cognitive and Affective Neuroscience*, *17*(1), 120–130. https://doi.org/10.1093/scan/NSAA158

Wietschorke, K., Lippold, J., Jacob, C., Polak, T., & Herrmann, M. J. (2016). Transcranial direct current stimulation of the prefrontal cortex reduces cue-reactivity in alcohol-dependent patients. *Journal of Neural Transmission*, *123*(10), 1173–1178. https://doi.org/10.1007/S00702-016-1541-6

Wilcox, C. E., Calhoun, V. D., Rachakonda, S., Claus, E. D., Littlewood, R. A., Mickey, J., Arenella, P. B., & Hutchison, K. E. (2017). Functional network connectivity predicts treatment outcome during treatment of nicotine use disorder. *Psychiatry Research: Neuroimaging*, *265*, 45–53. https://doi.org/10.1016/j.pscychresns.2017.04.011

Witkiewitz, K., Stein, E. R., Votaw, V. R., Wilson, A. D., Roos, C. R., Gallegos, S. J., Clark, V. P., & Claus, E. D. (2019). Mindfulness-based relapse prevention and transcranial direct current stimulation to reduce heavy drinking: A double-blind sham-controlled randomized trial. *Alcoholism: Clinical and Experimental Research*, *43*(6), 1296–1307. https://doi.org/10.1111/ACER.14053

Xu, J., Fregni, F., Brody, A. L., & Rahman, A. S. (2013). Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers. *Frontiers in Psychiatry*, *4*(SEP), 112. https://doi.org/10.3389/fpsyt.2013.00112

Yamada, Y., & Sumiyoshi, T. (2021). Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. *Frontiers in human neuroscience*, *15*, 631838. https://doi.org/10.3389/fnhum.2021.631838.

Yang, L. Z., Shi, B., Li, H., Zhang, W., Liu, Y., Wang, H., Zhou, Y., Wang, Y., Lv, W., Ji, X., Hudak, J., Zhou, Y., Fallgatter, A. J., & Zhang, X. (2017). Electrical stimulation reduces smokers' craving by modulating the coupling between dorsal lateral prefrontal cortex and parahippocampal gyrus. *Social cognitive and affective neuroscience, 12(8)*, 1296–1302. https://doi.org/10.1093/scan/nsx055