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Non-Invasive Brain Stimulation in Substance Use Disorders: Implications for Dissemination to Clinical Settings

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Abstract

With expanding knowledge of how neural circuitry is disrupted in substance use disorders (SUD), non-invasive brain stimulation (NIBS) techniques have emerged as potential strategies to directly modulate those neural circuits. There is some evidence supporting the two most common forms of NIBS, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), in the treatment of SUD. Yet results of recent studies have been mixed and critical methodological issues must be addressed before strong conclusions can be drawn. This review highlights recent evidence of NIBS for SUD, addressing the impact of stimulation on relevant clinical and cognitive outcomes in substance-using populations. Additionally, we aim to bring a clinical perspective to the opportunities and challenges of implementing neuromodulation in SUD treatment.

Keywords

Non-invasive brain stimulation; transcranial direct current stimulation; transcranial magnetic stimulation; substance use disorder

1. Introduction

Improving treatment outcomes for substance use disorders (SUD) continues to be a public health priority. Neurobiological theories of addiction have implicated brain networks that subserve reward, motivation, negative affect, and cognitive control in SUD initiation, maintenance, and relapse [1]. With growing knowledge of how these brain networks underlie addictive behavior, approaches to modulating brain function directly with non-invasive brain stimulation (NIBS) have received attention as a way to enhance SUD treatment.

There is some early evidence supporting the use of neuromodulation to improve the treatment of addictive disorders by enhancing top-down control within mesocorticolimbic

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Conflicts of Interest

The authors declare no conflicts of interest related to the contents of this paper.

circuits [2]. Yet this nascent field is at a critical moment when challenges and unanswered questions must be addressed if this technology is to be effectively implemented in clinical settings. This review aims to highlight current evidence and remaining methodological questions. In addition, we aim to bring a clinical perspective to the opportunities and challenges of implementing neuromodulation in SUD treatment.

2. NIBS methods

The most commonly used forms of neuromodulation are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) [3]. For both methods, it is possible to administer active (verum) stimulation designed to produce specific alterations in brain function and behavior, or to administer sham stimulation, which mimics real neuromodulation but does not deliver sufficient energy to impact brain function.

2.1 Transcranial Direct Current Stimulation.

tDCS involves the flow of weak electrical current (typically 1-2 milliamps (mA)) applied directly to the scalp, which is hypothesized to change neuronal membrane resting potentials in the underlying brain tissue. In general, tDCS enhances or inhibits ongoing neuronal activity [4], with anodal tDCS depolarizing neurons and cathodal tDCS hyperpolarizing neurons [5]. The placement of electrodes influences the polarity and amplitude of current flow at specific anatomical locations. In addition, tasks performed by individuals during tDCS may also be important [6].

2.2 Transcranial Magnetic Stimulation.

In TMS, a coil positioned next to the head sends magnetic pulses through the skull, where they generate electric currents in brain tissue through electromagnetic induction [7]. Through variation of pulse rate, TMS can be excitatory or inhibitory. Low frequency TMS (Lf-TMS; <1 Hz) and continuous theta burst neuromodulation (cTBS) have been shown to decrease brain activity, while high frequency TMS (Hf-TMS; 5-20 Hz) and intermittent TBS (iTBS) increase brain activity [8,9].

3. Review of the efficacy of NIBS on clinical outcomes

Randomized, sham-controlled trials evaluating the efficacy of tDCS and TMS have focused on a range of addictive behaviors (e.g., tobacco dependence, alcohol use disorder, cannabis use, stimulant use disorder, etc.) and outcome measures (e.g., craving, cue reactivity, relapse, etc.) that vary in terms of practical, clinical relevance. A series of reviews [10–12] and meta-analyses [13,14] show variable support for neuromodulation as a potential adjuvant treatment for addictive behaviors and no significant differences in effect by type of neuromodulation. Jansen and colleagues found a pooled standardized effect size of 0.476 (Hedge's g), which was stronger for studies stimulating the right dorsolateral prefrontal cortex (DLPFC; g=0.710) than the left DLPFC (g=0.375) [14]. Importantly, a third of studies included in this meta-analysis investigated craving for highly palatable foods, which may diminish the applicability of the results to SUD.

3.1 Craving following tDCS.

Several recent reviews [15–17**] and one meta-analysis [14] have concluded that tDCS interventions are associated with greater reductions in self-reported craving and cue-induced craving, as compared to sham. However, there is variability in effect sizes across trials [10], and some studies have not identified significant differences between verum tDCS and sham [18,19], nor between differing numbers of tDCS sessions [20**]. Studies evaluating objective measures of cue reactivity have also demonstrated inconsistent results, including measures of heart rate variability [21], event related potentials [18,22,23], visual attention bias [24], and emotional startle response [25].

3.2 Substance use following tDCS.

Fewer studies have evaluated actual substance use outcomes following tDCS administration, and results of extant studies are equivocal. Among cigarette smokers, anodal tDCS, thought to increase neuronal excitability, (vs. sham) has been associated with increased latency to smoking and fewer cigarettes smoked immediately following neuromodulation [26], but prolonged effects, ranging from 24 hours to four weeks following neuromodulation, on smoking have not been consistently demonstrated [26,27], Sham-controlled trials of tDCS for alcohol use disorder have found reduced risk of relapse among those receiving bilateral tDCS [28,29*], and no significant differences in alcohol use/relapse between those receiving anodal tDCS [22,30] and sham neuromodulation.

3.3. Craving following TMS.

A meta-analysis of eight randomized controlled trials that focused primarily on TMS for craving found no overall differences between verum and sham TMS, but did find a significant effect for verum Hf-TMS versus sham specifically targeting the right DLPFC (g=1.48) [13]. These authors also caution that limitations included high heterogeneity of studies and evidence of publication bias [13]. A review of TMS for cocaine use disorder found similar methodological issues, limiting firm conclusions about the effect of TMS on craving [31]. A recent study by Sauvaget and colleagues [32] using one session of Lf-TMS over right DLPFC found no effect of verum Lf-TMS versus sham in reducing craving for gambling. While there is some emerging evidence to suggest that Hf-TMS over the right DLPFC might be the most efficacious target [13], other researchers hypothesize that individualized targeting of the left DLPFC using neuroimaging may improve TMS efficacy [33].

3.4 Substance use following TMS.

There is limited evidence to suggest that TMS has a reliable impact on abstinence rates, relapse rates, or consumption outcomes [10,34]. However, some of the most recent studies with stronger research designs found that excitatory Hf-TMS over left DLPFC reduced relapse and increased abstinence among smokers compared to sham [35**]; conversely, another demonstrated that cTBS, an inhibitory procedure, over right DLPFC was associated with increased alcohol consumption [36]. Taken together, these findings suggest that upregulation of DLPFC activity is associated with greater control over substance use, while downregulation is associated with greater substance use. Similarly, Martinez and coauthors

demonstrated that multiple sessions of Hf-TMS over the medial prefrontal cortex (mPFC) decreased cocaine self-administration, as compared to Lf-TMS and sham TMS to the same sites [37].

3.5 Other clinical outcomes following NIBS.

Beyond assessment of craving and substance use, several recent studies have examined other clinically relevant outcome measures. Some trials have found promising associations between unilateral anodal and bilateral tDCS and secondary outcomes, such as reductions in depression and anxiety symptoms [19,38] and improvements in quality of life [22], but these outcomes have not been consistently evaluated, thus limiting strong conclusions. In a study of Hf-TMS over left DLPFC, individuals with methamphetamine use disorder who received verum Hf-TMS, but not sham, performed equivalently to healthy controls on an emotional attention task [39]. Hf-TMS over left DLPFC has also been shown to increase engagement with self-help treatment for tobacco compared to sham [35**].

4. Review of the efficacy of NIBS on cognitive outcomes

Predominant models of addiction involve dysregulation of prefrontal brain networks, impacting executive functioning, impulsivity, decision making, and attentional biases [40,41]. These cognitive functions are implicated in the initiation, maintenance, and relapse of SUDs, and thus are important processes to target in treatment. By modulating activity in certain prefrontal brain regions, neuromodulation techniques may be able to specifically enhance top-down control within corticostriatal circuitry [9]. However, several recent systematic reviews have concluded that, despite some promising studies, evidence as a whole is inconsistent [15,42*, 43**, 44]. Among recent studies examining the impact of neuromodulation on cognitive functioning in SUD, slightly less than half found positive effects of neuromodulation, with the remainder reporting either null or negative effects.

4.1 Risk decision making following tDCS.

Risk-taking has been the most frequently tested cognitive domain among studies evaluating NIBS for SUD. Some studies using anodal tDCS over left DLPFC have found reductions in risky decision making on the Balloon Analogue Risk Task [45] and Cold Columbia Card Task [46]. However, others found that left DLPFC anodal tDCS led to riskier decisions among heavy marijuana users, but not healthy controls [47], and fewer safe decisions among cocaine users [45]. Regulating risky decision making, particularly when reward is at stake, is critically important for reducing relapse and these potential negative findings should be carefully considered before widespread implementation.

4.2 Other cognitive outcomes following NIBS.

Additional cognitive domains have been studied as potential targets for neuromodulation, predominantly with mixed findings. Studies using Hf-TMS over left DLPFC have found modest support in improving response inhibition [48] and delay discounting [35**]. Studies have found no effect of anodal tDCS [19] or Hf-TMS on various measures of attention, with the exception of a reduction on intra-individual reaction time variability on a Go/No-Go task [49]. One recent study examining the effect of Hf-TMS in methamphetamine users found

positive effects on social cognition and verbal learning/memory tasks [50]. Presently, the majority of studies on neuromodulation and batteries of general executive functioning have found no statistically significant effect of neuromodulation in alcohol users [22,28].

5. Challenges and inconsistencies

Differences in methodology might explain inconsistent findings, including variability in: (1) duration of treatment (ranging from 10 to 30 minutes; e.g., [51]), (2) number of treatment sessions (ranging from one to ten sessions; e.g., [29*,51]), (3) time between treatment sessions (ranging from 24 hours to one week; e.g., [22,23]), (4) tasks completed during NIBS (neuromodulation at rest, during cue reactivity task, during cognitive bias modification intervention; e.g., [19,30]), (5) tDCS montage (cathodal vs. anodal, bilateral vs. unilateral DLFPC; e.g., [22,28]), (6) TMS target (left or right DLPFC, e.g., [13]), (7) within- vs. between-subjects designs (e.g., [19,38]), and (8) use as standalone intervention or in combination with evidence supported treatments [35**]. Few comparison studies have been conducted to optimize neuromodulation protocols.

Furthermore, study design considerations include small sample sizes, lack of double-blind, sham control groups, lack of follow-ups, and reliance on self-report craving scales rather than measures of behavior (e.g., substance use) [31] to assess outcomes. More recent studies have attempted to address some of these issues, and have emphasized an individualized precision medicine approach [33,52], the inclusion of sham controls, investigations of neural mechanisms of action [53,54], and examinations of how baseline differences might impact outcomes [55].

Prior to implementation of NIBS in treatment settings, important clinical issues must be considered. Neuromodulation effects might have limited generalizability to individuals seeking treatment for SUD. As with most clinical trials, individuals are excluded with treatment contraindications (e.g., epilepsy, neuropsychiatric medications, etc.) and co-occurring psychiatric disorders, which might represent a majority of individuals in SUD treatment [29*]. Trials have also been characterized by substantial differences in populations enrolled vis-à-vis treatment-seeking status (ranging from non-treatment-seekers to patients in residential programs; e.g., [26,28]), duration of abstinence, and severity of substance use. It is unknown if any of these characteristics influence outcomes. Finally, many trials have examined acute (e.g., same-day; [18]) changes in craving and have employed single-item measures of craving. Future studies employing a wider range of reliable and valid outcome measures, including multimodal measures of craving, negative affect, quality of life, neurocognition, and verified substance use, are needed to assess the clinical significance of NIBS effects prior to implementation.

6. Conclusions

NIBS techniques have great appeal as a relatively simple way to enhance disrupted brain circuits in addiction. Despite methodological inconsistencies across studies that prevent firm conclusions, preliminary evidence exists and more research is currently in progress. The field must continue to grapple with the complexities of addictive disorders and the dynamic

neural systems supporting addictive behavior in order to understand how, for whom, and in what contexts neuromodulation may improve outcomes for SUDs.

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