Review Article

Trends of Brain Stimulation Research in Substance Use Disorder: A Review of ClinicalTrials.gov Registered Trials and Their Publications

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ABSTRACT

Purpose of the Review: Brain stimulation techniques targeting neuronal pathways are evolving as a novel therapeutic option for substance use disorders. This study aims to provide an overview of the current research landscape on brain stimulation in addiction psychiatry by analyzing data from ClinicalTrials.gov. It intends to describe the global trends in these trials, highlight the findings reported in their publications, and identify the gaps and challenges to guide future research and clinical practice.

Collection and Analysis of Data: The ClinicalTrials.gov was searched on March 1, 2024, using every possible paired combination of different brain stimulation techniques (including transcranial magnetic stimulation/TMS, transcranial direct-current stimulation/tDCS, deep brain stimulation/DBS, and vagal nerve stimulation/VNS) and psychoactive substances. A total of 163 human trials were identified, and their details were extracted into a datasheet. Completed and terminated studies were searched separately for publication data. The extracted data were then analyzed using suitable descriptive statistics.

Conclusion: Most research involved TMS, tDCS, and DBS and focused on alcohol, stimulants, opioids, nicotine, and cannabis. No studies addressed sedatives, hypnotics, hallucinogens, psychedelics, and solvents. Wide variations in modulation protocols and neuroanatomical targets reflect the current lack of guidelines or consensus. Incompleteness and updating delays in the study registry raise concerns regarding registration protocols. The published trials report beneficial effects of TMS in nicotine, stimulant, and cannabis users, TMS in alcohol users, and VNS in opioid users.

Keywords: Brain stimulation, neuromodulation, substance use disorder, deaddiction, transcranial magnetic stimulation, transcranial direct current stimulation

Substance use disorders (SUDs) are a major public health problem affecting almost 6% of the global population between the ages 15 and 64 years and accountable for above 225 disability-adjusted life years per 100,000 individuals.[1,2] The negative consequences of SUDs extend beyond individual health, affecting the economy, productivity, and communities. The conventional pharmacologic prophylaxis and psychotherapies for SUDs have shown varying efficacy between studies and a relapse rate of 40 to 60%.[3] Hence, recent strides in addiction medicine have focused on understanding neurobiological underpinnings and utilizing neuromodulation for therapeutic purposes.

Addiction to psychoactive substances is widely accepted to follow a cyclical pattern characterized by increased use, withdrawal, and craving.[4] The addictive substance hijacks the reward pathway, with a surge in dopamine and glutamate in the nucleus accumbens (NAc) and the ventral tegmental area, respectively.

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This results in intense pleasure and a desire to re-experience the same, leading to bingeing or intoxication. As the drug wears off, withdrawal symptoms and negative emotions ensue by heightened activity in the amygdala, extended amygdala, and the hypothalamus-pituitary-adrenal axis, alongside an excess of endogenous opioids and stress hormones. Cravings and impulsivity (prefrontal cortex [PFC]), triggered by stress, memory (hippocampus), and cues, cause repeated use, ultimately leading to habit formation (basal ganglia).[4] Targeting these crucial brain areas employing various neuromodulation techniques has been a novel strategy for addressing SUDs, supported by two recent meta-analyses.[5,6] Also, the positive findings from the largest multi-center trial[7] led to Food and Drug Administration (FDA) approval for deep transcranial magnetic stimulation (TMS) H4 coil for smoking cessation in 2020.[8] Thus, brain stimulation for addiction psychiatry holds a promising future.

ClinicalTrials.gov is the largest clinical trial registry, launched in February 2000 by the National Library of Medicine at the National Institute of Health (NIH). As of the writing of this article, ClinicalTrials.gov lists about 0.5 million studies from over 200 countries, with 4.5 million visitors every month.[9] It is an indispensable reservoir of information for all stakeholders in the healthcare ecosystem, as it offers a publicly accessible database with tools for detailed trial characterization and analysis. Analysis of trials within a given domain may allow researchers to build on existing studies, avoid duplications, and identify gaps in current research, thereby accelerating the pace of discovery and innovations. Such comprehensive analysis also helps inform policymakers to formulate evidence-based healthcare directives and determine future funding priorities. Previous studies doing clinical trials analysis from the registry have provided helpful information in various medical fields such as nephrology,[10] infectious diseases,[11] pulmonary medicine,[12] oncology,[13] and the coronavirus pandemic.[14] Such studies have also been carried out in the areas of alcohol,[15,16] addiction,[17,18] and mental health.[19] However, no such study exists in the field of brain stimulation for SUD. We aim to review the studies registered at ClinicalTrials.gov to identify and understand the key trends and current research landscape in this field.

Methods

This is a cross-sectional analysis of the interventional studies registered on ClinicalTrials.gov. Furthermore, a narrative review of the published clinical trials is provided to identify the preliminary evidence of brain stimulation therapy for substance use. A search was conducted on ClinicalTrials.gov on March 1, 2024, to locate all the registered studies on brain stimulation in SUDs. The search was done using every possible combination of addictive substances and brain stimulation techniques: Under the "condition/disease" tab, the keywords "alcohol," "cannabis," "cannabinoid," "opioid," "sedative," "hypnotic," "anxiolytic," "cocaine," "stimulant," "amphetamine," "methamphetamine," "methcathinone," "synthetic cathinone," "caffeine," "hallucinogen," "nicotine," "inhalant," "MDMA," "ketamine," "phencyclidine," "substance," "psychoactive substance," "non-psychoactive substance," and "drug" were entered one by one. For each of these search terms, under the "intervention/treatment" tab, the keywords "transcranial magnetic stimulation/TMS," "transcranial direct-current stimulation/tDCS," "deep brain stimulation/DBS," "vagal nerve stimulation/VNS," "electroconvulsive therapy/ECT," "magnetic seizure therapy/MST," and "non-invasive brain stimulation/NIBS" were used sequentially. After every search, the records were downloaded in separate comma-separated value (.csv) files, which were combined into a single editable datasheet for maximum completeness and accuracy. Duplications were identified and removed.

Only studies marked as "interventional," defined by ClinicalTrials.gov as "studies in human beings in which individuals are assigned by an investigator based on a protocol to receive specific interventions," were included in the final review. Observational studies or studies that did not focus on substance use issues (e.g., those focusing on the efficacy of repetitive TMS (rTMS) or ECT for depression in alcohol use disorder) were excluded. Two authors independently screened the studies, and discrepancies were resolved by discussing and re-extracting the relevant data. Different details of the studies were sorted into variables within the datasheet by two independent authors, and differences were resolved through discussions.

The following characteristics were of interest for our review: phase of the trial, the intervention model (single-group, parallel-group, crossover, or factorial), allocation type (randomized, non-randomized, or not applicable for single-group studies), masking (open-label, single-blind, double-blind, triple-blind, or quadruple-blind), age (children, adults, or older adults) and sex (male, female, or other) of the study population, conditions (SUD and psychiatric/medical comorbidities), intervention type (brain stimulation technique), neuro-anatomical target, recruitment status (not yet recruiting, recruiting, not recruiting, completed, withdrawn, suspended, or terminated), funding source (industrial, governmental, or others), study center (single or multi-center), and study location (country and continent).

The completed and terminated studies were further checked for publications related to them in peer-reviewed scientific journals. This was done by either of two ways: (1) following a hyperlink to the published work made available by the investigators under the "Publications" section of the Study Record on ClinicalTrials.gov or (2) searching the National Clinical Trial (NCT) identifier and/or the study title with authors' names in PubMed and Google Scholar if no link was provided. Details of the publication (such as publication date and journal metrics) were extracted and analyzed. Finally, the information from published clinical trials (sample size, sociodemographics, clinical characteristics, intervention provided, outcomes, and findings relevant to this review) were extracted and summarized to discuss the preliminary evidence of brain stimulation for substance use.

The study characteristics were summarized using descriptive statistics: categorical variables were represented as frequencies with proportions, and continuous variables were represented as mean with standard deviations. Studies reporting stimulation of more than one neuroanatomical target in their intervention protocol were counted separately for each target for a more comprehensive descriptive analysis. For the completed studies, comparisons between the published and non-published trials were conducted using suitable statistical tests: unpaired Student's *t*-test for continuous

variables and chi-square or Fisher's exact test for categorical variables. All analyses were done using IBM SPSS version 28.0.

Results

The initial searches yielded 208 potential studies, of which 11 duplicates, 18 observational studies, and 16 studies not directly addressing substance use were excluded. Finally, 163 study protocols were assessed for this review. The oldest study (NCT00901459) started in May 2009, and the most recent (NCT03981185) is expected to commence in December 2024. The number of studies has increased by 2.7 times from 2016 to the present (n = 119) compared to the previous years (n = 45). The NCT number of included study protocols is provided in **Supplementary File S1**.

Study Characteristics

The descriptive statistics of the various details of the studies are summarized in **Table 1**. Most studies were without any FDA-defined phase (n = 130, 79.8%), followed by phase 2 trials (n = 15, 9.2%). Most studies were parallel-group (n = 117, 71.8%), randomized (n = 138, 84.7%), and double-blinded (n = 46, 28.2%) clinical trials. Regarding the study population, most studies involved adults and older adults (n = 90, 55.2%) and either sex (n = 155, 95.1%). At the time of this review, 59 (36.2%) studies had a completed status, of which only 16 (26.7% of 60) had their results posted at the ClinicalTrials.gov. Among the rest, nine studies were withdrawn, and eight were terminated before their expected completion dates. The reasons reported for early terminations included suspension of product manufacturing by the supplier (NCT04971681), investigator leaving for a new job (NCT03352609), and recruitment difficulties during the coronavirus pandemic (NCT02665338 and NCT03291431). One study (NCT05401929) was suspended due to the Federal Wide Assurance imposing restrictions on human research by the New York State Psychiatric Institute in June 2023. Most of the studies were conducted at a single center (n = 131, 80.4%), with a minority were multi-centric (n = 14, 8.6%). Demographic profiling revealed that more than half of the studies were from North America (n = 88, 54.0%), followed by Asia (n = 25, 15.3%) and Europe

TABLE 1.

Characteristics of the Included Studies/Protocols in This Review.

Variables		Frequency (n = 163)	%
Study phase	Early Phase 1	7	4.3
	Phase 1	6	3.7
	Phase 1/Phase 2	2	1.2
	Phase 2	15	9.2
	Phase 2/Phase 3	1	0.6
	Phase 3	2	1.2
	Not applicable	130	79.8
Study model	Single-group	21	12.9
	Parallel-group	117	71.8
	Cross over	20	12.3
	Factorial	5	3.1
Randomization	Randomized	138	84.7
	Non-randomized	7	4.3
	Not applicable[a]	18	11.0
Masking[b]	Single	25	15.3
	Double	46	28.2
	Triple	29	17.8
	Quadruple	35	21.5
	None	25	15.3
	Unknown	3	1.8
Age of study population	Children and adults	1	0.6
	Adults	72	44.2
	Adults and older adults	90	55.2
Sex of study population	All	155	95.1
	Males	6	3.7
	Females	2	1.2
Study status	Recruiting	34	20.9
	Not recruiting[c]	8	4.9
	Not yet recruiting[d]	11	6.7
	Completed	59	36.2
	Withdrawn	9	5.5
	Suspended	1	0.6
	Terminated	8	4.9
	Unknown	33	20.2
Center	Single center	131	80.4
	Multicenter	14	8.6
	Unknown	18	11.0
Location: Continent	Asia	25	15.3
	Euro	24	14.7
	North America	88	54.0
	South America	8	4.9
	Unknown	18	11.0
Funding	NIH	5	3.1
	FED	6	3.7
	Other government	3	1.8
	Industry	3	1.8
	Other[e]	146	89.6

NIH, National Institute of Health of the United States Department of Health and Human Services; FED, Federal Government of the United States.

[a]Randomization not applicable for single-arm studies.

[b]Masking: single (participant), double (participant + care provided), triple (participant + care provided + investigator), quadruple (participant + care provided + investigator + outcomes assessor).

[c]Not recruiting: Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled.

[d]Not yet recruiting: Participants are not yet being recruited.

[e]Funded by individuals, universities, or organizations.

(*n* = 24, 14.7%). With respect to the countries, about half were from the United States (*n* = 75, 46.0%), followed by China 20 (*n* = 20, 12.3%), Canada (*n* = 10, 6.1%), France (*n* = 10, 6.1%), and Brazil (*n* = 8, 4.9%). No studies were conducted across multiple countries. The studies were funded mainly by individuals, universities, or organizations (*n* = 146, 89.6%). Only 14 (8.6%) were funded by the government, of which the Federal Government of the United States and the NIH sponsored six and five studies, respectively.

Study Focus

Table 2 summarizes the different substance use and the associated brain stimulation techniques involved in the studies. The substances that the studies focused on included mostly alcohol (*n* = 50, 30.7%), followed by stimulants (*n* = 32, 19.6%), opioids (*n* = 31, 19.0%), nicotine (*n* = 28, 17.2%), and cannabis (*n* = 17, 10.4%). Among the studies on stimulants, 18 (11.0%) focused solely on cocaine. Few studies included comorbid psychiatric conditions: schizophrenia and related disorders (*n* = 6, 3.7%), depressive disorder, anxiety disorder, post-traumatic stress disorder, and attention-deficit hyperactive disorder (each: *n* = 1, 0.6%), and comorbid medical conditions: advanced compensated liver fibrosis and multiple sclerosis (each: *n* = 1, 0.6%).

The most commonly explored brain stimulation techniques were TMS (*n* = 96, 58.9%), tDCS (*n* = 44, 27.0%), and DBS (*n* = 18, 11.0%) (**Table 2**). There was no study involving ECT that explored any direct effect on substance use (such as drug use patterns, withdrawal symptoms, abstinence rate, and craving). Two studies tested a drug (N-acetyl cysteine or yohimbine-hydrocortisone) against brain stimulation, and four others combined drugs (varenicline, Marinol/dronabinol, methylphenidate, or nicotine replacement therapy [Habitrol]) with brain stimulation. Similarly, four studies used psychotherapy as a comparator: cognitive training (*n* = 2), motivational intervention (*n* = 1), and inhibitory control techniques (*n* = 1), while eight studies augmented brain stimulation with psychotherapy: cognitive training (*n* = 4), cognitive behavioral therapy (*n* = 2), mindfulness (*n* = 1), and computerized cognitive addiction therapy (*n* = 1).

TABLE 2.

Included Studies/Protocols Stratified According to the Type of Brain Stimulation and Substance They Focused on.

Condition	TMS	tDCS	tACS	DBS	VNS	Multiple	Total	%
Alcohol	23	19	1	6	1	–	50	30.7
Opioid	14	5	–	10	1	1[a]	31	19.0
Nicotine	20	8	–	–	–	–	28	17.2
Cocaine	12	5	–	1	–	–	18	11.0
Cannabis	13	4	–	–	–	–	17	10.4
Any stimulant[b]	12	1	–	1	–	–	14	8.6
Multiple	2[c,d]	2[e,f]	–	–	–	1[g]	5	3.1
Total	96	44	1	18	2	2	163	100.0
%	58.9	27.0	0.6	11.0	1.2	1.2	100.0	-

TMS, transcranial magnetic stimulation; tDCS, transcranial direct-current stimulation; tACS, transcranial alternating current stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation.
[a]TMS, tDCS.
[b]Includes 10 studies focused only on amphetamine/methamphetamine.
[c]Alcohol, opioid, cocaine.
[d]Alcohol, cocaine.
[e]Any substance (not limited to specific few).
[f]Alcohol, stimulants.
[g]Nicotine, opioid: DBS, tDCS.

Studies involving multiple neuronal targets were counted separately for each target. Almost three-quarters of the studies targeted the PFC (*n* = 120 out of 168, 71.4%), particularly the dorsolateral PFC (dlPFC) (*n* = 90, 53.6%). The second most common neuronal target was the NAc of the reward pathway (*n* = 17, 10.1%). Most studies involving TMS and tDCS (119 out of 138) targeted the PFC, while those involving DBS (15 out of 24) focused on the NAc. **Table 3** summarizes the various neuronal targets focused by the studies.

Reporting Results and Publication

Of the 59 completed and 8 terminated studies, 23 had their results posted in the registry. The 67 studies had a pooled sample of 1,869 with an average of 55.0 (standard deviation [SD]: 57.8; range: 3–339). A total of 31 studies included 20 or more participants, with 3 studies exceeding 100.

The publications of the studies (either partial or complete) in a peer-reviewed journal could be traced online for 34 studies (32 completed and 2 terminated). These included 25 original articles (reporting the findings of the clinical trials), 5 study protocol articles, 3 letters to the editor, and 1 case series. However, the month and year of actual completion (or termination) of the study and publication in a journal could be analyzed for 25 of the 34 studies. The average time from completion to publication was approximately one year (mean: 23.9 months, SD: 15.6). The maximum duration was found to be five years for one study completed in February 2010. The 34 publications were featured in journals with an average 2022 impact factor of 5.9 (SD: 2.6, range: 2.3–11.9). Based on the 2023 SCImago Journal Ranking quartile index, 30 journals were rated as Q1 and four as Q2. For the completed trials that remained unpublished, the reasons for non-publication were not available in the public domain.

Among the 59 completed studies, a significant difference was found between the published (*n* = 25) and non-published trials (*n* = 34) with respect to the brain stimulation technique used: tDCS was more common in published trials and TMS in non-published trials (χ^2 = 4.929, *p* = 0.026). **Table 4** provides a comparative analysis between the published and non-published trials.

Published Trials

The summary of the 25 published clinical trials is provided in **Table 5**. These trials focused on alcohol (*n* = 9: five used

TABLE 3.

Included Studies/Protocols Stratified According to the Type of Brain Stimulation and Their Neuroanatomical Target.

Targets	TMS	tDCS	DBS	multiple	VNS	Total	%
dlPFC	62	28	–	–	–	90	53.6
mPFC	18	1	–	–	–	19	11.3
PFC	5	5	–	1[a]	–	11	6.5
NAc	1	–	15	1[b]	–	17	10.1
aIC	–	–	6	–	–	6	3.6
Insula	4	–	–	1[b]	–	5	3.0
ACC	4	–	–	1[b]	–	5	3.0
Cerebellum	1	1	–	–	–	2	1.2
Motor cortex	2	–	–	–	–	2	1.2
Parietal cortex	1	1	–	–	–	2	1.2
Transcutaneous[c]	–	–	–	–	2	2	1.2
Inf frontal gyrus	1	–	–	–	–	1	0.6
Sup frontal gyrus	1	–	–	–	–	1	0.6
OFC	1	–	–	–	–	1	0.6
STN	–	–	1	–	–	1	0.6
TPJ	–	1	–	–	–	1	0.6
Limbic pallidum	–	–	1	–	–	1	0.6
vStriatum	–	–	1	–	–	1	0.6
Total	101	37	24	4	2	168[d]	100

TMS, transcranial magnetic stimulation; tDCS, transcranial direct-current stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation; PFC, prefrontal cortex; dlPFC, dorsolateral PFC; mPFC, medial PFC; NAc, nucleus accumbens; aIC, anterior internal capsule; ACC, anterior cingulate cortex; Inf, inferior; Sup, superior; OFC, orbito frontal cortex; STN, subthalamic nucleus; TPJ, temperoparietal junction; vStriatum, ventral striatum.
[a]TMS, tDCS.
[b]DBS, tDCS.
[c]Site: auricular or skin over carotid triangle.
[d]Studies reporting stimulation of more than one neuroanatomical target in their intervention protocol were counted separately for each target.

TABLE 4.

Comparative Analysis of the Published and Non-published Completed Trials.

Factors		Published *n* (%)/$\bar{x}$ (SD)	Non-published *n* (%)/$\bar{x}$ (SD)	Statistics[a] (P value)
Sample size		49.1 (27.1)	69.1 (106.7)	.917 (.363)
Brain stimulation	tDCS	13 (54.2)	9 (26.5)	4.584 (.032)
	TMS	11 (45.8)	25 (73.5)	
Substance use	Alcohol/nicotine	17 (68.0)	20 (58.8)	.519 (.471)
	Other	8 (32.0)	14 (41.2)	
Masking[b]	Double or more	20 (83.3)	22 (64.7)	2.682 (.145)
	Single or none	4 (16.7)	12 (35.3)	
Study model	Cross-over or factorial	4 (16.0)	7 (20.6)	.738 (.745)
	Single- or parallel-group	21 (84.0)	27 (79.4)	
Study location[c]	United States	12 (48.0)	17 (54.8)	.259 (.611)
	Other	13 (52.0)	14 (45.2)	
Center[c]	Single-center	24 (96.0)	28 (93.3)	1.698 (.999)
	Multi-center	1 (4.0)	2 (6.7)	

n, frequency; %, percentage; $\bar{x}$, group mean; SD, standard deviation; tDCS, transcutaneous direct current stimulation; TMS, transcranial magnetic stimulation.
Total counts: completed studies (*n* = 59, 100%), published trials (*n* = 25, 42.4%), and non-published trials (*n* = 34, 57.6%).
[a]Unpaired Student's *t*-test (for continuous variable) or chi-square/Fisher's exact test (for categorial variables), *P* value ≤ .05 is significant.
[b]One published trial with masking not reported (not included in the analysis).
[c]Four non-published trials with location and center not reported (not included in the analysis).

tDCS[20–24] and four used TMS[25–28]), nicotine (*n* = 8: four each for tDCS[29–32] and TMS[33–36]), stimulants (*n* = 6: three each for tDCS[37–39] and TMS[26,40,41]), opioid (*n* = 2: both used tDCS[42,43]), and cannabis (*n* = 1, using TMS[44]). The trial by Kearney-Ramos et al. (2018) (NCT02939352) included both nicotine and stimulant use and provided their respective findings separately.[26] Majority were double-blinded randomized controlled trials (db-RCTs) (*n* = 16), with a sample size ≥20 (*n* = 21), involving both genders (*n* = 22) of mean age ≥30 years (*n* = 21). The outcomes included craving (*n* = 8), reduction in drug use (*n* = 7), abstinence or relapse rates (*n* = 3), cognitive performance (*n* = 2), cue-induced neuronal reactivity (*n* = 2), treatment adherence (*n* = 1), emotion regulation (*n* = 1), and withdrawal symptoms (*n* = 1).

Significantly, better abstinence was reported with tDCS with exciting current to right dlPFC versus sham stimulation in two RCTs.[20,24] Another db-RCT reported a nearly significant reduction of craving with tDCS versus sham targeting dlPFC.[21] Furthermore, a recent db-RCT noted that treatment adherence and tDCS significantly predicted post-treatment craving scores. However, a db-RCT involving tDCS targeting the inferior frontal gyrus found no significant effects on alcohol approach bias or drinking outcomes compared to sham stimulation. One single-blind RCT (sb-RCT) found a significant reduction in craving with high-frequency repetitive TMS (hf rTMS) to dlPFC of either hemisphere.[25] Significant reduction in craving was also reported with multiple sessions of deep TMS to midline cortical areas.[28] Conversely, two sb-RCTs reported no significant positive effects with TMS compared to sham.[26,27] As with alcohol, evidence for right anodal/left cathodal tDCS to dlPFC was mixed with two RCTs showing a significant reduction in daily cigarette consumption and craving,[30,31] while two RCTs showed no significant effects compared to sham stimulation.[29,32] Conversely, a significant decrease in smoking craving was found with hf rTMS targeting superior frontal gyrus,[33] dlPFC,[34,35] and dorsomedial PFC.[36] Two db-RCTs exploring right anodal/left cathodal tDCS to dlPFC in cocaine addiction found no significant

TABLE 5.

Summary of the Published Clinical Trials Included in This Review.

Author date [NCT No.]	Blinding	N (M/F)	Age: mean (SD)	Intervention	Target	Outcomes	Findings
Alcohol use disorder							
Klauss et al., 2014 [NCT01330394]	Double	33 (M+F)	Active: 44.0 (7.8) Sham: 45.5 (8.9)	tDCS (2 mA, 35 cm^2, 13 min) or Sham: 2 sessions/day for 5 days	Anode: right dlPFC Cathode: left dlPFC	Relapse: abstinent rate	At 6 months follow-up, 50% of tDCS group and 11.8% of Sham group were abstinent: intergroup difference in survival was significant ($p = 0.021$).
Klauss et al., 2019 [NCT02091284]	Double	45 (M+F)	Active: 46.3 (12.0) Sham: 43.5 (10.2)	tDCS (2 mA, 35 cm^2, 20 min) or sham: alternate day sessions × 10 sessions	Anode: right dlPFC Cathode: left dlPFC	Craving: OCDS 5-item	Nearly significant ($p = 0.056$) intergroup difference in the reduction of craving favoring tDCS vs. Sham (effect size: 0.58).
Claus et al., 2019 [NCT02045108]	Double	79 (M+F)	24.5 (2.7)	2 (verum vs. sham CBM) × 2 (verum vs. sham tDCS) factorial design; 4 sessions of CBM/tDCS	Anode: right inferior frontal gyrus	DDD, pHDD	No reduction of alcohol approach bias with CBM/tDCS/both. No significant change in DDD or pHDD with CBM/tDCS/both.
Dubuson et al., 2021 [NCT03447054]	Single	125 (M+F)	47.12 (9.95)	2 (verum vs. sham tDCS) × 2 (alcohol cue vs. neutral ICT) factorial design; tDCS: 5 sessions, 2 mA, 20 min	Anode: right dlPFC Cathode: left dlPFC	Relapse: abstinent rate	At 2 weeks follow-up, better abstinence rate with tDCS vs. sham (79.7% (95% CI = 69.8–89.6) vs. 60.7% (95% CI = 48.3–73.1); $p = 0.02$)
Gibson et al., 2022 [NCT02861807]	Double	84 (M+F)	52.3 (13.0)	tDCS vs. sham with concomitant MBRP	–	Craving: PACS	Interaction between treatment adherence and tDCS condition significantly predicted post-treatment craving.
Mishra et al., 2015 [NCT01093716]	Single	20 (M+F)	Right: 37.10 (10.48), Left: 43.20 (9.74)	hf rTMS (figure-8 coil, 10 Hz, 110% rMT, 4.9-sec on, 15-sec off; 1,000 pulses), 1 session/day × 10 days	Right/left dlPFC	Craving: ACQ-NOW	Significant craving reduction with rTMS in both groups. No intergroup differences in craving reduction.
Kearney-Ramos et al., 2018 [NCT02939353]	Single	24 (M+F)	26.8 (5.6)	cTBS (figure-8 coil, 3 pulse bursts at 5 Hz, 110% rMT, 15 pulses/sec; 1,800 pulses/train; 2 trains; 60-sec intertrain interval) or sham	Left vmPFC	Craving: self-reported	No significant change in craving between the groups.
Jansen et al., 2019 [NCT02557815]	Single	75 (M+F)	AUD: 41.64 (8.63) HC: 43.75 (10.90)	hf rTMS (10 Hz, 110% rMT, 65-sec trains) vs. sham: 2 sessions	Right dlPFC	Craving: AUQ	No significant intergroup differences in craving.
Harel et al., 2022 [NCT02691390]	Double	51 (M+F)	Active: 43.7 (8.7) Sham: 42.5 (9.8)	dTMS (H7 coil) or sham: 15 sessions in 3 weeks, then 5 sessions in 3 months	Midline fronto-cortical areas, including mPFC and ACC	pHDD, PACS	Reduced pHDD in active vs. sham group (2.9 ± 0.8% vs. 10.6 ± 1.9%; $p = 0.037$). Significantly reduced PACS score at end point in active vs. sham group.
Nicotine use disorder							
Xu et al., 2013 [NCT01567982]	Single	24 (M+F)	45 (7.6)	tDCS (2 mA, 35 cm^2, 20 min) or sham: 2 sessions at ≥2 days interval	Anode: left dlPFC Cathode: right supraorbital region	Craving: UTS	No significant intergroup difference in craving
Brangioni et al., 2018 [NCT02146014]	Double	36 (M+F)	45 (11)	tDCS (1 mA, 35 cm^2, 20 min) or sham: 1 session for 5 days, motivation to quit (in all patients)	Anode: left dlPFC Cathode: right supraorbital region	Cigarettes smoked per day	tDCS caused significantly reduced daily cigarette consumption; effect was modified by motivation to quit.
Mondino et al., 2018 [NCT01288183]	Double	29 (M+F)	Active: 41.2 (9.1) Sham: 40.8 (9.4)	tDCS (2 mA, 35 cm^2, 20 min) or sham: 2 sessions/day for 5 days	Anode: right dlPFC Cathode: left occipital region	Cigarettes smoked per day, craving	Significantly fewer cigarettes/day smoked in tDCS vs. sham group. Significant reduction in craving with tDCS vs. sham.
Verveer et al., 2020 [NCT03027687]	Double	71 (M+F)	22.3 (4.7)	tDCS (2 mA, 35 cm^2, 13 min) or sham: 2 sessions for 3 days in 1 week	Anode: right dlPFC Cathode: left dlPFC	Cigarettes/day, craving	No significant intergroup differences in daily cigarette consumption and craving.
Rose et al., 2011 [NCT00901459]	–	15 (M+F)	40.7 (9.56)	1) hf (10 Hz) rTMS at SFG; 2) lf (1 Hz) rTMS at SFG, and 3) lf (1 Hz) rTMS at motor cortex (control)	Active: SFG Control: Motor cortex	Craving: SJQ (brief)	Craving was elevated and reduced with smoking and neutral cues, respectively, in 10 Hz SFG condition.

Li et al., 2013 [NCT01690130]	Double	16 (M+F)	42.6 (11.5)	hf rTMS (10Hz, 100% rMT, 5-sec on, 10-sec off for 15 min; 3000 pulses) or Sham: 2 stimulations 1 week apart	Left dlPFC	QSU-B	Reduced craving score from baseline with hf rTMS vs. sham (64.1 ± 5.9 vs. 45.7 ± 6.4, t = 2.69, p = 0.018). Greater effect on neutral cue craving for hf rTMS vs. sham (12.5 ± 10.4 vs. −9.1 ± 10.4; t = 2.07, p = 0.049)
Li et al., 2020 [NCT02401672]	Double	42 (M+F)	Active: 41.19 (11.8) Sham: 44.12 (9.1)	hf rTMS (10Hz, 100% rMT, 5-sec on, 10-sec off for 15 min; 3,000 pulses) or sham: 10 daily sessions over 2 weeks	Left dlPFC	Cigarettes smoked per day, quit rate	Significantly fewer cigarettes/day smoked in rTMS vs. sham group. rTMS group more likely to quit (23.81% vs. 0%, OR 11.67, 90% CI, 0.96–141.32, X^2 = 4.66, p = 0.031)
Du et al., 2024: Study II [NCT03281629]	Double	30 (M+F)	Active: 44.3 (11.8) Sham: 41.9 (12.8)	hf rTMS (figure-8 coil, 10 Hz, ≥100 V/m, 4-sec on, 26-sec off for ~15 min; 1,200 pulses) vs. sham: 20 sessions over ~4 weeks	Left dmPFC	Smoking severity: FTND	Nicotine addiction severity showed decreasing trends after week 3 and 4 ($p \leq 0.05$) with rTMS vs. sham. rTMS over target area predicted reduction in cigarette/day (R = −0.56, p = 0.025) and morning smoking severity (R = −0.59, p = 0.016)
Stimulant use disorder							
Conti et al., 2014 [NCT01337297]	–	13	30 (7)	tDCS (1 mA, 35 cm², 10 min) or sham	Anode: right dlPFC Cathode: left dlPFC	ACC response to drug cues	Post-visual drug cues, decreased ACC with tDCS and increased ACC activity with sham
Klauss et al., 2018 [NCT02091167]	Double	35 (M+F)	Active: 35.1 (8.2) sham: 35.0 (9.6)	tDCS (2 mA, 35 cm², 20 min) or sham: alternate day sessions for 10 sessions	Anode: right dlPFC Cathode: left dlPFC	Craving	No significant intergroup difference in the reduction of craving.
Verveer et al., 2020 [NCT03025321]	Double	59 (M+F)	Active: 37.6 (10.7) Sham: 41.9 (9.7)	tDCS (2 mA, 35 cm², 13 min) or sham: 2 sessions/day for 5 days	Anode: right dlPFC Cathode: left dlPFC	Relapse at 90-day follow-up, craving, inhibitory control (Go-NoGo test)	No significant intergroup difference in relapse, craving, or cognitive functions.
Su et al., 2017[a] [NCT02713815]	Double	30 (M)	Active: 31.85 (5.25) Sham: 32.84 (4.79)	hf rTMS (figure-8 coil, 10 Hz, 80% rMT, 5-sec on, 15-sec off for 8 min; 1,200 pulses) vs. sham: 1 session/day for 5 days	Left dlPFC	Craving	At study end-point, rTMS group showed significant reduction in cue-induced craving from baseline scores.
Kearney-Ramos et al., 2018 [NCT02939352]	Single	25 (M+F)	41.6 (9.0)	cTBS (figure-8 coil, 3 pulse bursts at 5 Hz, 110% rMT, 15 pulses/sec; 1,800 pulses/train; 2 trains; 60-sec intertrain interval) or sham	Left vmPFC	Self-reported craving	Post hoc analysis: reduced craving from baseline with cTBS vs. sham (t = −3.18, p = 0.004)
Lolli et al., 2021 [NCT03607591]	Double	62 (M+F)	–	hf rTMS (15 Hz, 100% rMT, 15-sec off, 2,400 pulses, 13 min) or sham	Left dlPFC	Abstinence: cocaine lapse in twice-weekly urine test, craving	33% of rTMS group vs. 14.8% of sham group tested negative in urine (p < 0.03, OR: 2.88, CI:0.9–10). Significant reduction in cocaine-related cues mediated craving with rTMS vs. sham.
Opioid use disorder							
Gazi et al., 2022 [NCT04556552]	Double	21 (M+F)	Active: 37.5 (11.4) Sham: 33.27 (10.2)	tcVNS vs. sham	–	Subjective opioid withdrawal, opioid craving	Reduced subjective opioid withdrawal with tcVNS vs. sham (p = 0.047). No significant inter-group difference in craving.
Aksu et al., 2024 [NCT05568251]	Triple	38 (M+F)	Active: 34.0 (13.0) Sham: 30.0 (13.0)	tDCS (2 mA, 35 cm², 20 min) or sham: single session with concomitant CT	Anode: right dlPFC Cathode: left dlPFC	Cognitive tasks	Greater improvements in decision-making under ambiguity (p = 0.016), set shifting and alternating fluency with tDCS vs. sham.
Cannabis use disorder							
Johnstone et al., 2022 [NCT03189810]	–	–	–	hf rTMS (20 Hz) vs sham: weekly 5 times for 4 weeks	Bilateral dlPFC	Drug use	Better baseline performance in sustained attention, delayed discounting, and complex planning tasks moderated the cannabis use reduction in the active group.

NCT No., National Clinical Trial number; N, sample size; (M/F), participant's gender; SD, standard deviation (in brackets); tDCS, transcranial direct current stimulation; CBM, cognitive bias modification; ICT, inhibitory control training; MBRP, mindfulness based relapse prevention; hf rTMS, high-frequency repetitive transcranial magnetic stimulation; dTMS, deep TMS; cTBS, continuous theta-burst stimulation; tcVNS, transcutaneous vagus nerve stimulation; CT, cognitive therapy; SFG, superior frontal gyrus; dlPFC, dorsolateral prefrontal cortex; vmPFC, ventero-medial PFC; mPFC, medial PFC; ACC, anterior cingulate cortex; SFG, superior frontal gyrus; DDD, drinks per drinking day; pHDD, percent heavy drinking days; OCDS, Obsessive-Compulsive Drinking Scale; PACS, Penn Alcohol Craving Scale; ACQ, Alcohol Craving Questionnaire; AUQ, Alcohol Urge Questionnaire; UTS, Urge to Smoke Scale; SJQ, Shiffman-Jarvik questionnaire, QSU-B, Questionnaire of Smoking Urges-Brief; FTND, Fagerstrom test for nicotine dependence.

[a]Methamphetamine use (rest in the group focused on cocaine use).

effect on craving compared to sham stimulation. Instead, one small trial reported decreased cortical response to visual drug cues with tDCS.[38] Two RCTs involving hf rTMS to left dlPFC found a significant reduction in drug-induced craving versus sham stimulation. Similarly, a post hoc analysis of an sb-RCT involving continuous theta-bursts TMS to ventromedial PFC found craving reduction at the baseline.[26] In a db-RCT, transcutaneous VNS showed a reduction in opioid withdrawal symptoms but had no significant impact on craving compared to sham treatment.[42] A triple-blind RCT demonstrated improved decision-making under ambiguity and cognitive flexibility among opioid users with tDCS compared to sham.[43] In a recent trial with cannabis users, baseline cognitive task performance influenced the reduction in cannabis use in the active arm receiving hf rTMS to bilateral dlPFC.[44]

Discussion

Our analysis found a leap in the last 10 years of studies investigating brain stimulation for substance use problems. The majority were single-center, double-blinded, randomized parallel-group clinical trials involving adults and older adults of either sex. Most were located in the United States and China. Despite this geographical spread, government funding only accounted for less than 10% of the total. Most research involved TMS, tDCS, and DBS (among brain stimulation techniques) and alcohol, opioids, nicotine, cocaine, and cannabis (among SUDs). No studies were found on sedatives, hypnotics, hallucinogens, or inhalants. The most common neuronal targets were the PFC, particularly the dlPFC (crucial for decision-making, impulse control, and inhibiting cravings) and the NAc (crucial for reward processing and negative withdrawal effect).[4,45] This aligns with the current understanding of addiction neurobiology—the three-stage cycle and associated brain areas.[4] However, the lack of specific details and considerable variability in the neuromodulation protocols made it difficult to conduct meaningful analysis using the registry data. This reflected the lack of clear guidelines and consensus regarding neuromodulation protocols.

Nevertheless, few conclusions may be drawn regarding the evidence of brain stimulation from the findings of the published trials. Administration of tDCS to the dlPFC in alcohol users has demonstrated a reduction in drinking and craving. However, results were inconsistent or negative for nicotine and stimulant use, respectively. Promising outcomes were seen with rTMS in nicotine, stimulant, and cannabis users, while mixed results were reported in alcohol users. This may allude to differences in the modulation protocols and target areas across the studies. Encouraging results were seen with VNS in opioid use disorder.

Notably, the published trials predominantly appeared in high-impact journals ranking in the top quartile of their respective fields within a year of completion. The journal quality can be used as a proxy marker of the novelty, importance, and influence of these studies in addiction psychiatry. Furthermore, it guarantees the credibility and visibility of these studies. Most studies focused on changes in drug use, craving, and abstinence rates with the interventions.

Our findings also found several "areas of focus" for future research. There is a scope to explore a broader range of psychoactive substances, including sedatives, inhalants, and psychedelics. Also, increased government funding is crucial for more comprehensive research to aid breakthroughs. Additionally, the issues of incomplete registration and delayed updates in the registry raise ethical concerns, necessitating stricter regulation of the registration procedures. Finally, future studies with a multi-center, cross-country design involving larger samples may be conducted.

This review has a few limitations. First, studies around the world that were not registered on ClinicalTrials.gov were yet to be included in the analysis. This might explain the high representation of studies from the United States and the absence of studies from Australia. Also, clinical trial registration and reporting became mandatory in 2007 and 2008, respectively. The earliest study in this review dates back to 2009, suggesting the possibility of omission of any previous research. Studies missed by our search terms and those that are non-interventional or not in English have also been left out. Second, delays between trial completion and data reporting on the registry can impact the information available for review. The quality and completeness of the data may also vary and are subject to regular updates by the researchers. Additionally, some published studies may have been overlooked due to the non-systematic nature of this review.

Conclusion

The growing research has mainly focused on TMS, tDCS, and DBS for alcohol, stimulants, opioids, nicotine, and cannabis. Several challenges and gaps have been highlighted, including heterogeneous study designs, varied neuromodulation targets and protocols, limited public funding, and issues regarding registration and publication of results. A precise understanding of the specific neurocircuitry functions and standardization of the modulation protocols can help improve the comparability of studies in the future. Targeting the underlying neurocircuitry for treating SUDs appears promising, although future reviews may explore the efficacy, safety, retention rates, and feasibility of these treatment modalities.

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