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Transcranial magnetic stimulation, deep brain stimulation, and other forms of neuromodulation for substance use disorders: Review of modalities and implications for treatment

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Abstract

Given the high prevalence of individuals diagnosed with substance use disorder, along with the elevated rate of relapse following treatment initiation, investigating novel approaches and new modalities for substance use disorder treatment is of vital importance. One such approach involves neuromodulation which has been used therapeutically for neurological and psychiatric disorders and has demonstrated positive preliminary findings for the treatment of substance use disorder. The following article provides a review of several forms of neuromodulation which warrant consideration as potential treatments for substance use disorder. PubMed, PsycINFO, Ovid MEDLINE, and Web of Science were used to identify published articles and clinicaltrials.gov was used to identify currently ongoing or planned studies. Search criteria for Brain Stimulation included the following terminology: transcranial direct current stimulation, transcranial magnetic stimulation, theta burst stimulation, deep brain stimulation, vagus nerve stimulation, trigeminal nerve stimulation, percutaneous nerve field stimulation, auricular nerve stimulation, and low intensity focused ultrasound. Search criteria for Addiction included the following terminology: addiction, substance use disorder, substance-related disorder, cocaine, methamphetamine, amphetamine, alcohol, nicotine, tobacco, smoking, marijuana, cannabis, heroin, opiates, opioids,

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Declaration of Competing Interest

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and hallucinogens. Results revealed that there are currently several forms of neuromodulation, both invasive and non-invasive, which are being investigated for the treatment of substance use disorder. Preliminary findings have demonstrated the potential of these various neuromodulation techniques in improving substance treatment outcomes by reducing those risk factors (e.g. substance craving) associated with relapse. Specifically, transcranial magnetic stimulation has shown the most promise with several well-designed studies supporting the potential for reducing substance craving. Deep brain stimulation has also shown promise, though lacks well-controlled clinical trials to support its efficacy. Transcranial direct current stimulation has also demonstrated promising results though consistently designed, randomized trials are also needed. There are several other forms of neuromodulation which have not yet been investigated clinically but warrant further investigation given their mechanisms and potential efficacy based on findings from other studied indications. In summary, given promising findings in reducing substance use and craving, neuromodulation may provide a non-pharmacological option as a potential treatment and/or treatment augmentation for substance use disorder. Further research investigating neuromodulation, both alone and in combination with already established substance use disorder treatment (e.g. medication treatment), warrants consideration.

Keywords

Neuromodulation; Substance use disorder; Transcranial magnetic stimulation; Deep brain stimulation; Focused ultrasound; Transcranial direct current stimulation; Vagus nerve stimulation; Trigeminal nerve stimulation; Percutaneous nerve field stimulation

1. Introduction

According to the 2018 National Survey on Drug Use and Health (NSDUH), approximately 20.3 million people had a substance use disorder (SUD) diagnosis in 2018 [1]. Specifically, 14.8 million people met criteria for alcohol use disorder and 8.1 million people met criteria for an illicit SUD, the most common being for marijuana (4.4 million people) and prescription pain relievers (1.7 million people). Over the past several years, the opioid epidemic has plagued our nation and it was estimated that 10.3 million people misused opioids in 2018 [1]. Opioids are the main contributor to drug overdose deaths, resulting in over 46,800 deaths nationwide in 2018 [1,2]. Further complicating matters is the elevated rate of co-occurring substance use. For example, results from a nationally representative database, which included 356 individuals with OUD, revealed that approximately 57% of individuals with OUD also met criteria for at least one other SUD. Of those co-occurring substance users, approximately 51% reported the use of cannabis, 41% reported the use of sedatives, and 31% reported the use of cocaine or other stimulants over the past year [3]. While our nation is clearly facing an opioid epidemic, we must not neglect the potential additive detriment caused by co-occurring opioid and non-opioid substance use and the aversive impact it may have on successful treatment outcomes.

Unfortunately, the number of individuals with SUD far exceeds the number of patients receiving SUD treatment. For example, of the more than 20 million individuals with SUD in 2018, only 3.7 million people received any form of SUD treatment [1]. Further complicating

matters is the high comorbidity between SUD and other psychiatric disorders. In 2018, an estimated 9.5 million adults (approximately 4% of all adults) had both mental illness and SUD in the past year, and 3.2 million adults had co-occurring *serious* mental illness and SUD [1]. Another factor impacting successful treatment is the lack of medication treatments for SUDs, other than medication for nicotine/tobacco, alcohol and opioids. This is especially critical given the rise of other substance use, such as methamphetamine, which was implicated in 35% of overdose deaths in 2017, representing over a 42% increase between 2015 and 2017 [4]. While medication has been considered an effective form of treatment in improving outcomes (abstinence, harm reduction) for those SUDs with available medication treatment, effect sizes are relatively modest for alcohol [5,6] and smoking cessation [7] and approximately 50% of those with OUD relapse to opioids and/or other substances even when receiving medication treatment [8]. For example, in a multisite, randomized trial, the rate of unsuccessful outcomes following medication treatment (using buprenorphine-naloxone) exceeded 90% and even when individuals were stabilized on medication over 12 weeks, the rate of successful outcomes was less than 50% [8]. Similarly, extended release naltrexone and buprenorphine have unacceptably high relapse rates (65% vs. 57% respectively) [9]. In addition, a recent review of extended release naltrexone, revealed that many patients never even start the treatment because of difficulty tolerating the withdrawal symptoms and those who start often discontinue [10].

Clearly, new modalities to treat and/or augment SUD treatment are urgently needed and investigating novel approaches is of vital importance. Specifically, non-pharmacological approaches warrant investigation especially for those substances which do not yet have medication treatments available. In addition, these approaches may provide benefit for those individuals who cannot tolerate medications due to side effects, do not have a positive response to the medication, and/or do not have access to prescribers of those medications. One such approach involves neuromodulation which has been used therapeutically for neurological and psychiatric disorders and has also been used for exploratory purposes in researching the neurocircuitry of the brain. There are various forms of neuromodulation, some which include non-invasive techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), with the primary targeted brain regions being the cortical structures of the reward neurocircuitry. Specifically, these regions include the prefrontal cortical network including the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex [11,12] which have important functions in inhibitory control, a neurobehavioral output often impaired in patients with SUDs. Reduced inhibitory control and disinhibition are also associated with relapse susceptibility [13–17]. Furthermore, the DLPFC and surrounding network are also associated with substance craving, a major clinical feature of SUD associated with poor treatment outcomes and relapse. In addition, some forms of neuromodulation, such as TMS, have demonstrated benefit in reducing symptoms of co-occurring psychiatric disorders/symptoms (e.g. depression) which may be further perpetuating and/or exacerbating an individual's SUD.

Other forms of neuromodulation involve invasive techniques, such as deep brain stimulation (DBS), which provides the ability to target subcortical structures. The primary subcortical brain target is the nucleus accumbens (NAc) which is considered the center of the reward circuitry and heavily implicated in substance use and craving [18–22]. In addition to the

prefrontal cortical network, the NAc also maintains direct and indirect involvement with several brain regions, such as the dorsal striatum, amygdala, and hippocampus, areas which are associated with emotions, self-regulation, disinhibition, insight, craving, and habit forming [19]. While not yet approved for the treatment of SUD, these forms of neuromodulation mentioned above have demonstrated promising preliminary results in reducing substance use and craving. There are additional forms of neuromodulation which have not yet been thoroughly investigated for the treatment of SUD, including focused ultrasound (FUS) and vagus (VNS) and trigeminal nerve stimulation (TNS) along with percutaneous nerve field stimulation (PNFS), the latter which has been approved for opioid withdrawal. The following article will provide a brief review of several forms of neuromodulation which are currently being investigated for SUD or warrant consideration as a potential treatment based on their targeting capabilities and findings involving other indications. A general overview of these forms of neuromodulation is displayed in Table 1 and details specific to the potential treatment of SUD can be found in Table 2.

2. Potential forms of neuromodulation for substance use disorder treatment

The number of original research publications indexed on PubMed from 1999 to 2018 which involved brain stimulation and substance use is displayed in Fig. 1. PubMed search criteria for Brain Stimulation included MESH indexing related to “transcranial direct current stimulation”, “transcranial magnetic stimulation”, “theta burst stimulation”, “deep brain stimulation”, “vagus nerve stimulation”, “trigeminal nerve stimulation”, “percutaneous nerve field stimulation”, “auricular nerve stimulation”, and “low intensity focused ultrasound.” Addiction terms included MESH indexing related to “addiction”, “substance use disorder”, “substance-related disorder”, “cocaine”, “methamphetamine”, “amphetamine”, “alcohol”, “nicotine”, “tobacco”, “smoking”, “marijuana”, “cannabis”, “benzodiazepines”, “heroin”, “opiates”, “opioids”, and “hallucinogens”. The search was limited to articles involving human subjects and original research (e.g. clinical trials, clinical or observational studies, or case reports); reviews, meta-analyses, and editorials were excluded. Of the 22,098 entries that met criteria for Brain Stimulation, and the 139,236 that met criteria for Addiction, there were 188 that met criteria for both (blue bars) and of these, 106 included a form of TMS (red bars). This highlights that as the field is growing exponentially, the variance in techniques is also changing as TMS accounted for 78% of the publications from 1999 to 2008, whereas 46% of the publications utilized techniques other than TMS from 2009 to 2019.

While Fig. 1 includes original research publications indexed on PubMed, in order to conduct a more inclusive search for this review, other electronic databases including PsycINFO, Ovid MEDLINE, and Web of Science were also included using the same search terminology mentioned above. Only those which were published in (or were translated into) English were included in the broader search. In addition, while reviews, editorials, and meta-analyses were excluded from the search referenced in Fig. 1 (in order to avoid duplication and only include those publications which contain original research), these forms of publication were included in the broader search, along with relevant references contained within those

publications. Also, for those forms of neuromodulation which lack clinical literature related to SUD (e.g. LIFU, TNS, VNS), a search of clinicaltrials.gov was performed using the terminology mentioned above to gauge current, planned, or upcoming investigations.

2.1. Transcranial magnetic stimulation (TMS)

Within interventional psychiatry, one of the most active new areas of research has been the development of TMS as a non-invasive tool to stimulate neural circuits typically involved in psychiatric disease. TMS is a non-invasive form of brain stimulation which induces a hyperpolarization or depolarization (dependent on delivered frequency as described below) of neurons through electromagnetic induction. Although a comprehensive review of studies that have demonstrated these principles of TMS is beyond the scope of this manuscript, prior behavioral, electrophysiological, and neuroimaging work in this area is well described and summarized in several review articles [23,24].

TMS has been FDA-approved as a treatment for major depressive disorder since 2008 and received FDA-approval for the treatment of obsessive compulsive disorder in 2018. There are now TMS clinics in all 50 states in the United States, throughout Europe, Asia, Australia, South America, and a few new clinics in Africa. While the majority of the research in TMS is focused on optimizing treatment protocols for depression, there has been an exponential growth in the application of TMS to investigate and modulate these networks in populations with SUDs including alcohol, cocaine, methamphetamine, opioid, cannabis, and tobacco use disorder [11,12,25–29]. There are four key principles of TMS that are necessary to understand before interpreting the results of current studies and designing novel interventions for alcohol and SUDs:

2.1.1. Stimulation depth—With a growing number of TMS coil designs, this is an increasingly complex question to answer. The focality of TMS is related to the shape of the coil and there is substantial body of literature devoted to computational modeling of electric field distributions associated with different coil shapes. In one of the most comprehensive papers, Deng and colleagues (2013) investigated the focality and penetration depth of 50 existing TMS coils [30]. Their computational models revealed that typical figure-of-8 coil designs affected approximately 10 cm^2 of cortical surface, circular coils affected approximately 50cm^2, and H-coil designs affected approximately 100 cm^2. Most flat figure-of-eight and circular coil designs had penetration depths from 1 to 2 cm^2, whereas the H-coil designs had consistently higher depths of 2–3 cm. The H-coil was designed to affect the neuronal pathways and fibers to deeper cortical regions in order to facilitate targeting subcortical regions (without significantly impacting the electric fields in cortical regions) [31]. While TMS was originally unable to target the deeper, subcortical structures involved in the reward circuitry, given the rich interconnectivity between the prefrontal cortex (PFC) and subcortical limbic and reward system structures [32–35], these regions are able to be indirectly impacted by the cortical stimulation, somewhat alleviating the limitation of reduced depth. However, it is well established that chronic drug use (specifically chronic alcohol use) leads to cortical atrophy [36] which suggests that a higher stimulation intensity or a bent coil may be more likely to reach the cortex of these individuals.

2.1.2. Polysynaptic transmission—Beyond the direct cortical effects of TMS, it is possible to modulate monosynaptic (and possibly polysynaptic) targets of these cortical areas. When this depolarizing current is strong enough, however, it leads to a cascade of neurotransmitter release, excitatory postsynaptic potentials, and eventually action potentials in neurons receiving monosynaptic inputs from the neurons depolarized by the TMS pulse. This has been documented using interleaved TMS/BOLD imaging wherein a single pulse of TMS induces an elevation in the BOLD signal in the vicinity of the TMS coil and in monosynaptic target regions [37,38]. In this manner, cortical pulses of TMS can be used to investigate frontal-striatal connectivity, as the dorsal and ventral striatum both receive monosynaptic inputs from the frontal cortex. The dorsal and ventral frontal-striatal circuits are topographically organized and modulate the executive control and limbic arousal aspects of the addiction and relapse cycle, respectively.

2.1.3. Frequency dependent modulation—As stated above, when single pulses of TMS are delivered in rapid succession (rTMS), it is possible to change cortical excitability and various behavioral phenomena for a relatively brief period of time (e.g. 30 min to several hours). These effects appear to be frequency dependent, wherein low frequency, continuous stimulation decreases cortical excitability wherein high frequency, intermittent stimulation leads to an increase in cortical excitability [39,40]. These LTD-like and LTP-like effects for repetitive TMS can also be achieved through theta burst stimulation (TBS). In preclinical literature, TBS is a well-known form of electrical stimulation which can induce long-term potentiation or depression of synaptic activity in a given brain region [41]. Human TBS protocols use rTMS to induce similar forms of LTP and LTD by using intermittent or continuous bursts respectively [42]. With continuous TBS (cTBS), bursts of three pulses at 50 Hz are applied at a frequency of 5 Hz at an amplitude that is typically determined by the active motor threshold. By uniting this principle with the others, it is logical to conclude that there are at least two potential neural-circuit based strategies for improving outcomes in substance users: decreasing activity in the ventral-medial, frontal-striatal circuit with LTD-like TMS or increasing activity in the dorsal-lateral, frontal-striatal circuit with LTP-like TMS. Practically speaking, an advantage of TBS is the length of the individual treatment sessions, which can be completed over 3 min, opposed to TMS, which can last approximately 40 min per session. Moreover, the reduced treatment length of TBS is not at the expense of clinical effectiveness. In a randomized, multicenter, clinical trial in patients with depression, intermittent TBS was found to be non-inferior to traditional TMS with regard to outcomes, side-effects, safety, and tolerability [43].

2.1.4. State-dependent effects—An emerging body of literature is demonstrating that behavioral priming before or during the TMS administration has a significant impact on the amplitude and possibly directionality of the TMS effects on the brain and behavior [44]. In fact, recent FDA-approval of TMS for treatment of OCD requires that the patient be exposed to a specific, anxiety-provoking stimulus during the treatment visit. The amplifying influence of cue-exposure on TMS treatment outcome was also demonstrated in a study of post-traumatic stress disorder (PTSD) [45]. A large clinical trial of TMS for smoking cessation demonstrated that the effects of TMS are amplified when an individual is exposed to a smoking cue during TMS delivery [46]. In this prospective, double-blind, sham-

controlled study, 115 regular cigarette smokers were randomized to receive 10 daily treatments of TMS. Immediately before each session, half of the participants were presented with visual smoking cues. There was reduced cigarette consumption and nicotine dependence, and the effects were greatest in the individuals that were exposed to smoking cues [46].

A complete review of the existing literature on TMS applied to SUDs can be found in recent review articles [47,48]. Most of the rTMS studies to date have applied an LTP-inducing form of TMS to the DLPFC in an effort to decrease craving [17]. This area has an important role in executive and inhibitory control, often impaired in patients with SUDs, and disinhibition is also associated with relapse [13–17]. At the current time, it is not entirely clear why increasing activity in the DLPFC (an element in the executive control network) would decrease craving (a function typically ascribed to the ventral medial PFC and ventral subcortical areas). A recent study, however, demonstrated that, within healthy controls, there was a reciprocal relationship between DLPFC stimulation and subsequent attenuation of Brodmann 10 in the MPFC, but this was not present in cocaine users [49]. These data build upon studies in patients with depression [39,50] and provide a biological mechanism through which DLPFC may be effective at attenuating craving. An alternative TMS treatment strategy that has shown promise is the application of LTD-like TMS directly to the ventral MPFC [51,52].

As described above, the largest TMS study in addiction to date was performed by Dinur-Klein and colleagues (2014) [46] wherein they demonstrated that TMS delivered to the left DLPFC reduced cigarette consumption for 3 months. There are now over 20 published manuscripts evaluating TMS as a method to decrease smoking and smoking related behaviors. There are also several relatively large published trials which have evaluated TMS as a tool to decrease alcohol [53] and cocaine use [54]. There is only one published study on the use of rTMS for opioid use disorder, which demonstrated that a single session of rTMS to the left DLPFC reduced cue-induced craving [55], however, given the ongoing opioid crisis in many parts of the world, this area of research maintains positive momentum as a potential treatment for OUD.

In summary, there is currently a growing body of literature which suggests it is possible to induce circuit-specific and frequency dependent effects on dopamine, glucose, and neural activity (measured through functional neuroimaging) through the administration of rTMS. The conceptual framework for designing TMS treatment strategies in alcohol and substance use research is well described in a recent consensus paper published by over 50 scientists in this area [48]. This form of neuromodulation is actively being investigated as a new therapeutic agent in a number of clinical trials in individuals with cocaine, nicotine, alcohol, and methamphetamine use disorders. That being said, the optimal cortical location to target in substance users is unclear and many of the current investigations in SUD are based on the parameters used for depression rather than evidence from addiction literature. Fortunately, there are decades of functional neuroimaging research in cocaine users that can serve as “maps” for optimal TMS target selection. By harnessing the knowledge we have acquired from functional neuroimaging studies, it may be possible to develop TMS as an evidence-based, translationally-grounded therapeutic treatment for SUD.

2.2. Focused ultrasound (FUS)

Transcranial focused ultrasound (FUS) is a non-invasive technique which has the capability to precisely target subcortical brain structures and modulate neural circuitry [56,57]. There are two major modalities of FUS: High Intensity Focused Ultrasound (HIFU) and Low Intensity Focused Ultrasound (LIFU). HIFU creates permanent lesions through coagulation of cellular proteins and thermal ablation [58] and is FDA approved for the treatment of tremor associated with Parkinson's disease [59] and essential tremor [60,61]. HIFU is also emerging as a viable treatment option for chronic pain [62] and the effects of HIFU treatment in pain reduction are relative rapid (within a day of sonication) in patients refractory to treatment with more traditional methods, exhibiting benefit one year after treatment. In addition, patients treated with HIFU also evidenced marked reductions in opioid intake following the sonication of painful lesions [63].

Unlike the permanent lesions/ablation caused by HIFU, LIFU is considered an emerging form of non-invasive neuromodulation as it creates reversible functional lesions that produce no pathological changes on histological examination [58]. While the primary mechanism behind HIFU is rapid heating of targeted tissue for ablation, LIFU is delivered in a pulse mode with less intensity which minimizes the probability of tissue heating or damage. LIFU is unique among neuromodulatory methods in that it not only has exceptional spatial resolution [64–66] but also has the capability of targeting deeper, subcortical structures [67]. In a recent study conducted in patients with Alzheimer's disease, the application of LIFU, coupled with injected microbubbles, transiently opened the blood brain barrier in a targeted, noninvasive, safe, and reversible manner [68]. This demonstrates the potential application for targeted neuromodulation and/or medication delivery for those therapies which would otherwise be unable to cross the blood brain barrier [56].

Given the known cognitive dysfunction present in individuals with SUD, LIFU also has the potential to possibly remediate these cognitive deficits. For example, fMRI findings following LIFU sonication of the human primary visual cortex demonstrated that the sonication effects expanded to remote areas in the brain outside of the primary visual circuits. Specifically, LIFU increased neural activity at the level of brain networks involved in higher-order visual and cognitive processing, regions which included the frontal-temporal-parietal areas and cerebellum (the attention networks involved in cognitive processing) and the parahippocampal gyrus and thalamus (the memory/navigation/recognition networks) [69]. While, to the best of our knowledge, LIFU as a potential treatment for SUD has not yet been investigated, this form of neuromodulation warrants consideration. For example, LIFU has the potential to provide results of greater magnitude than other forms of neuromodulation given the exceptional spatial resolution and ability to target deeper, subcortical structures such as the NAc.

2.3. Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is a surgical procedure in which bipolar electrodes are placed into specific brain regions and stimulated through implanted pulse generators [70]. Stimulation parameters are programmable and depend on targeted brain region, disorder, and patient response. DBS is an FDA approved treatment for patients with Parkinson's disease,

essential tremor, dystonia and OCD (under a Humanitarian Device Exemption [HDE]), and most recently, treatment refractory epilepsy. Several clinical investigations have explored the utility of DBS to treat a range of neurobehavioral disorders including OCD, depression, Tourette's disease, eating disorders, traumatic brain injury, and Alzheimer's disease [71–86]. DBS for pain reduction has demonstrated favorable results when other methods, such as medications have not been successful. Various chronic pain conditions which respond to DBS include failed back surgery syndrome, phantom limb pain, and peripheral neuropathic pain with a higher response rate for those with nociceptive pain compared to neuropathic pain [87].

DBS has not been investigated extensively in addiction, though there have been reports of the potential utility of this form of treatment. In humans, case studies have reported that stimulation to the ventral striatum/nucleus accumbens (NAc) reduced the consumption of substances of abuse, such as alcohol, nicotine, and heroin [14]. In one report, an individual who underwent the NAc DBS procedure abstained from heroin use during active DBS for the first 2.5 years and remained drug free for 3.5 years following DBS removal without relapse at a 6-year follow-up. Notable improvements of the subjects' memory, IQ, and emotional status were also observed [88]. In a separate case study, two individuals with treatment refractory heroin use disorder achieved complete heroin abstinence at 2-year follow-up with the exception of one single incident of heroin consumption in the weeks following surgery. These individuals reported that their isolated use was solely motivated by "mere curiosity" yet was not reinforcing and did not reinstate chronic heroin use [89]. In a study of five participants with treatment-resistant alcohol use disorder who received DBS of the NAc, all reported a complete absence of craving for alcohol up to 8 years following DBS implantation; two patients remained abstinent for several years, and three showed a marked reduction of alcohol consumption [90]. Another case study reported that DBS of the NAc reduced symptoms related to OCD, which may serve as additional support given the compulsive nature of some drug-taking behavior [73,91–93]. Interestingly, one of these studies found that DBS targeting the NAc resulted in an unintended and "effortless" smoking cessation [94].

2.4. Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive form of neuromodulation where low-amplitude direct currents are applied directly to the scalp via electrodes. tDCS can be applied unihemispherically or bihemispherically, targeting dual stimulation to two parallel brain regions [95,96]. Anodal tDCS involves the depolarization of neurons, subsequently increasing cortical excitability, while cathodal tDCS involves the hyperpolarization of neurons, subsequently decreasing cortical excitability [97]. Currently, tDCS is not FDA approved for any indications though trials have demonstrated potential efficacy in the treatment of depression [98], anxiety [99], and other psychiatric disorders [100]. While there have been inconsistent findings related to the efficacy of tDCS for the treatment of SUD [101], further investigation is warranted with particular emphasis on methodological approaches and long term outcomes. For example, while the inconsistency and variability noted in previous studies can be due to several factors, varying study designs (e.g. duration, length, intensity, and location target of treatment) are likely a primary factor

contributing to these discrepancies. For example, given that 20 or more tDCS sessions have been found necessary to achieve clinically significant changes, the reduced number of tDCS sessions delivered in some studies likely contributes to those reports which noted a lack of or non-significant effect of the treatment [102]. Also, many studies provide insufficient power due to small sample sizes [103,104]. Regardless, tDCS continues to be explored for the treatment of psychiatric disorders and novel approaches are being used to increase efficacy, for example, the combination of tDCS stimulation with cognitive tasks [105].

There remains potential applicability of tDCS in treating SUD and the therapeutic effects are conceptualized as secondary to a disruption of the reward networks between the prefrontal regions [105]. While there has been inconsistency noted in the results of tDCS for SUD, methodological limitations, such as those noted above, may have contributed to those negative findings. Regardless, some studies have demonstrated positive findings even after shorter durations of treatment. Anodal tDCS to both the right and left DLPFC has been shown to reduce cue-induced nicotine craving and smoking behavior [106,107]. In addition, when used in combination, both left cathodal/right anodal and left anodal/right cathodal reduced alcohol craving when compared to sham tDCS [108]. Anodal tDCS targeting the left DLPFC reduced cue-induced alcohol craving and emotional symptoms (e.g. anxiety, depression) when compared to sham; however, this form of treatment was associated with a trend toward greater relapse in treatment seeking individuals [109]. In cocaine users, five sessions of tDCS to the DLPFC (left cathodal/right anodal) significantly reduced cocaine craving when compared to sham [110]. In cannabis users, right anodal/left cathodal applied to the DLPFC reduced cannabis craving compared to sham stimulation [111]. Also, given the known cognitive deficits associated with SUD, tDCS may also be a mechanism for improving cognitive dysfunction as studies have demonstrated that tDCS can modify behavior, improve learning, and improve inhibition [96,112,113].

2.5. Vagus nerve stimulation, percutaneous nerve field stimulation, and trigeminal nerve stimulation

Stimulating afferent sensory nerves, nerve fibers in the spinal cord, autonomous nerves, and/or cranial nerves, are additional potential methods for modulating brain networks. For example, transcutaneous nerve stimulation and spinal cord stimulation are methods to treat pain [114]. Vagus nerve stimulation (VNS) is a neuromodulation therapy that is FDA approved as adjunctive therapy for the treatment of epileptic seizures in patients that are refractory to antiepileptic medications. VNS is also FDA approved for the adjunctive long-term treatment of chronic or recurrent depression in patients suffering from major depressive episodes that are refractory to antidepressant treatments. The VNS system is indicated for use in stimulating the left vagus nerve in the neck area inside the carotid sheath and involves the placement of a percutaneous cuff electrode that delivers electric pulses generated by an implantable pulse generator [115]. More recently, transcutaneous VNS has been investigated for a variety of indications, including epilepsy [116] and an external transcutaneous VNS system is approved for the treatment of migraine and cluster headache [117]. The mechanism of action of VNS has not been fully elucidated but is thought to involve connections to the brainstem resulting in brain network changes, including modulation of cortical excitability and induction of synaptic plasticity [118].

One strategy for reducing relapse in addiction is to promote self-regulation by extinguishing responses to drug-associated environmental stimuli. VNS inhibits heroin-seeking behavior induced by heroin priming or heroin-associated cues in rats [119] and also reduces cocaine seeking and alters plasticity in the extinction network in rats [120]. The data suggests that VNS reduces reinstatement by the facilitation of extinction. Connections between the PFC and the basolateral amygdala may contribute to the beneficial effects observed. Translation of these pre-clinical findings suggest that VNS for the treatment of SUD warrants investigation in humans. To the best of our knowledge, no human clinical trials involving VNS for the treatment of addiction have been published to date nor listed on the clinical trials listing site Clinicaltrials.gov.

Minimally invasive and non-invasive auricular nerve stimulation has been studied extensively in several indications including depression, epilepsy, stroke and other neurological disorders [121]. The auricular nerve is a branch of the vagus nerve and transcutaneous auricular vagus nerve stimulation (taVNS) is thought to mediate its effect via afferent pathways to brain. A recent meta-analysis revealed the taVNS reduced Hamilton Depression Rating scale ratings and self-reported depression when compared to sham intervention [122]. Previous findings have also demonstrated that taVNS produces changes in resting-state functional connectivity distributed throughout several neural networks involved in addiction, including the default mode, salience, and executive networks [123]. As such, exploring taVNS for the treatment of SUD warrants consideration.

A specific form of auricular nerve stimulation is also referred to as Percutaneous Nerve Field Stimulation (PNFS) which involves branches of the Cranial Nerves V, VII, IX and X and the occipital nerves. PNFS is an FDA approved therapy as an aid to reduce the symptoms of opioid withdrawal [124]. This therapy involves the placement of a percutaneous nerve field stimulator, a multi-pin wire harness percutaneous electrode arran and a pen light for use in the transillumination technique that aids in the positioning of the percutaneous electrodes. The FDA clearance was based on a single-arm, open label, multi-center retrospective study of 73 patients measuring reduction in Clinical Opioid Withdrawal Score (COWS) where the mean COWS score was reduced by 62.7% twenty minutes after initiation of therapy. Five days following treatment, 33 patients returned to clinic and the mean withdrawal score reduction was 97.1% [125]. While these results are promising, this trial was not controlled and conducted retrospectively, therefore, prospective and controlled clinical trials should be conducted to establish efficacy.

Trigeminal Nerve Stimulation (TNS) has recently been approved for the treatment of attention deficit and hyperactivity disorder (ADHD). An external TNS System, is indicated for patients ages 7 to12 years old who are not currently taking prescription ADHD medication [126]. In a clinical trial, ADHD-RS total scores showed significant group-by-time interactions. CGI-Improvement scores also favored active treatment [127]. TNS has been studied in a variety of disorders including pain [128], epilepsy [129], and depression [130]. While not yet investigated for the treatment of SUD, the non-invasive TNS warrants consideration.

3. Discussion

Given the high prevalence of individuals diagnosed with SUD, along with the elevated rate of attrition and relapse following treatment initiation, investigating novel approaches and new modalities to treat and/or augment SUD treatment is of vital importance. Both invasive and non-invasive methods of neuromodulation have shown promise in the treatment of psychiatric disorders including SUD. There are notable differences when considering these different methods of neuromodulation discussed above as potential treatments for SUD. An obvious difference is the non-invasive nature of some forms, such as TMS, tDCS, and LIFU versus the invasive nature of DBS and nerve stimulation (e.g. VNS). While non-invasive methods are generally preferable for numerous reasons, there are limitations to consider. For example, non-invasive techniques, such as TMS and tDCS, have low spatial resolution, lack specificity, and are limited to superficial target points preventing the application to deeper subcortical targets such as the NAc.

Differences between these non-invasive forms are also present as tDCS has poor spatial and temporal resolution, whereas TMS has higher focality and temporal resolution (milliseconds) and is less sensitive to anatomical differences (e.g. skull thickness). DBS overcomes these limitations through deep, subcortical targeting with greater precision; however, requires an invasive brain surgery and implantation of hardware, which often require replacement of pulse generator (battery), and associated complications of the implanted hardware. While not yet investigated for SUD, LIFU has the potential to overcome these limitations above by utilizing a preferred non-invasive approach though having the capability to precisely target relatively smaller, subcortical brain regions. In addition to LIFU, there are other methods of neuromodulation not previously mentioned which have not yet been thoroughly investigated for SUD. For example, brain photobiomodulation (PBM) therapy, which uses red to near-infrared light, is an innovative treatment for a wide range of neurological and psychological conditions including depression and anxiety [131,132] and there is also preclinical evidence of improvement in cognitive decline [133,134]. While the literature related to PDM for SUD is limited, laser irradiation to auricular acupoints of patients with alcohol use disorder reduced depression and symptoms accompanying alcohol withdrawal [135].

Neuromodulation technologies have the potential to play a valuable role in assisting patients in several phases of recovery and preventing relapse. For example, while neuromodulation may be helpful during the initial phase of treatment, if symptoms (e.g. craving) begin to re-emerge after sustained abstinence, maintenance therapy should be considered as this form of therapy (specifically TMS) has demonstrated benefit in other populations when symptoms, such as depression, re-emerge after a period of remission. During the early stages of SUD treatment, one of the primary goals is to maintain patient engagement, prevent attrition or discharge against medical advice, and begin to foster the adaptation of coping mechanisms rather than substance use for dealing with distress. Emotional symptoms, substance craving, psychosocial distress, cognitive difficulties, and sleep dysfunction are some of the many inner-related factors and comorbidities which contribute to treatment drop out and relapse further supporting neuromodulation as a stand-alone or adjunctive treatment for SUD given the demonstrated effectiveness in treating these comorbidities.

One of the primary factors contributing to relapse is substance craving [136,137] and, mechanistically, one conceptualization is that neuromodulation may be effective in extinguishing the learned response to the reinforcing effects of substances, related cues, or other triggers. That being said, while findings have suggested that various forms of neuromodulation can reduce or suppress craving, prior literature has stated that the reduction of craving is necessary but not sufficient for achieving and maintaining abstinence from an addictive substance or behavior [138]. Given that a majority of the research investigating neuromodulation for SUD has involved Phase I studies with the primary outcome of craving, future research should also focus on the outcome of direct clinical relevance – actual substance use. The exception to this includes studies of nicotine/tobacco which have demonstrated that neuromodulation (e.g. TMS, tDCS) can reduce both craving as well as smoking behavior and/or tobacco use [139].

Other factors which detrimentally impact treatment outcomes and contribute to treatment attrition and relapse include depression, anhedonia, hopelessness, reduced interest/motivation, and anxiety. As mentioned previously, there is a very high comorbidity between SUD and other psychiatric disorders [1] and differentiating whether these symptoms are resultant from or exacerbated by ongoing substance use or whether they precipitated substance use is often challenging. Regardless of whether psychiatric symptoms predated substance use or are secondary to ongoing substance use, patients remain at increased risk of relapse if these symptoms and diagnoses are not appropriately managed. Given that TMS is FDA approved for the treatment of depression and has also been utilized to treat anxiety, it is certainly plausible that implementing this form of neuromodulation for the treatment of SUD will also reduce these co-occurring symptoms which interfere with successful treatment. In other words, treating these symptoms in parallel may lead to improved treatment adherence and engagement and better patient experiences overall, subsequently leading to improved outcomes (sustained abstinence). Additionally, if one assumes the same degree of treatment resistance to SUD treatment that is found across other psychiatric conditions, it is equally likely that several failed medication trials will have similar diminishing returns. While controlled substances are commonly utilized in psychiatry for a variety of co-occurring conditions, these medications (e.g. sedatives, stimulants) may have unfavorable risk-benefit profiles for those with SUD. As such, given the limited pharmacotherapeutic options, non-pharmacological interventions such as neuromodulation warrant consideration, especially in those treatment resistant individuals.

While neuromodulation alone has demonstrated positive effects in reducing substance use and those risk factors associated with relapse, perhaps the best approach would be to evaluate the effectiveness of neuromodulation as an adjunctive treatment to already established behavioral and/or pharmacological treatments for SUD (rather than as a stand-alone treatment). For example, by using neuromodulation to improve the altered reward circuitry in those with SUD, those individuals will then be more likely to comply and engage in with other forms of SUD treatment thus resulting in a higher probability of remaining abstinent. The importance of investigating neuromodulation in combination with behavioral and/or medication treatments has been acknowledged previously [138,140], though the literature integrating neuromodulation with psychosocial and pharmacological interventions is currently lacking. Recent case studies however have described the potential usefulness for

combining neuromodulation with comprehensive SUD treatment [141,142]. For example, a case report was recently published investigating TMS in combination with comprehensive SUD treatment which included buprenorphine/naloxone, individual and group therapy, and attendance of social support groups (e.g. AA/NA) within the community. In this case, an individual with treatment refractory cocaine and heroin use disorder demonstrated ~60–82% reductions in craving for these substances following seven sessions of TMS. This individual also remained entirely abstinent from all substances and was fully engaged in his comprehensive SUD treatment for approximately one month following the final TMS session, a considerable improvement as he had previously only been to sustain abstinence for no longer than a few days prior to receiving the TMS treatment [141]. In a separate case report involving DBS of the nucleus accumbens/ventral capsule for polysubstance use disorder, an individual with treatment refractory benzodiazepine and opioid use disorder demonstrated complete abstinence, significant decreases in craving, and remained fully engaged in comprehensive SUD treatment at 12 and 24 week outpatient assessments [142]. While the findings from these cases must be replicated in a larger cohort of individuals in randomized, controlled trials, these results are promising in the potential utility of neuromodulation as an adjunctive strategy to augment comprehensive SUD treatment.

4. Conclusions

Investigating novel modalities for the treatment of SUD treatment is of vital importance given the high prevalence of individuals diagnosed with SUD in combination with the elevated rate of attrition and relapse following treatment initiation. Neuromodulation warrants consideration as a potential treatment given promising findings in reducing substance use and craving in individuals with SUD. Currently, there are several forms of neuromodulation, both invasive and non-invasive, which are being investigated for the treatment of SUD. Further research investigating neuromodulation, both alone and in combination with already established behavioral and medication treatment, warrants consideration in those seeking treatment for SUD. While neuromodulation has demonstrated some promising results thusfar for the treatment of SUD, more extensive clinical data, subsequent regulatory approvals, and more favorable medical coverage policies will be needed in order to successfully implement this form of treatment to overcome the current substance use crisis our nation is facing.

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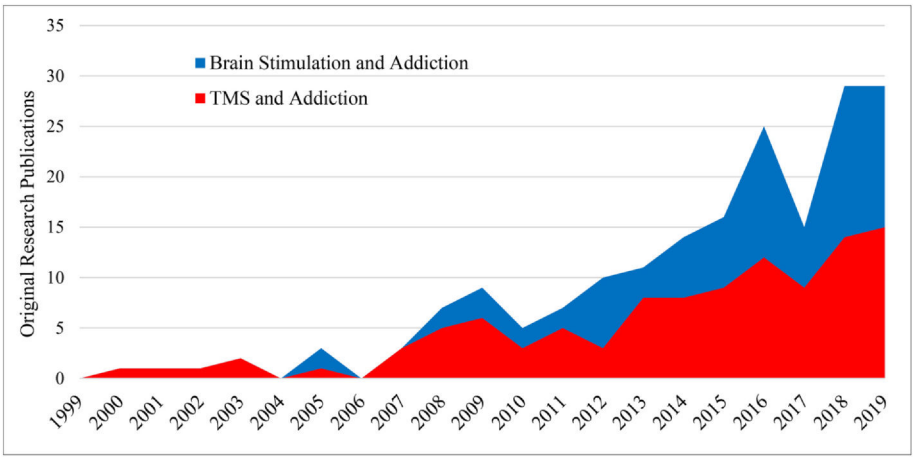

Fig. 1.

20 years of Research on Human Brain Stimulation in Addiction-Related Disorders.

Table 1

General overview of potential forms of neuromodulation for the treatment of SUD.

Neuromodulatory technique	Invasive/Non-invasive	Target depth	Focal	FDA approved indications	Adverse events	Patient acceptability
Transcranial Magnetic Stimulation (TMS)	Non-Invasive	Cortical	No	Depression, OCD	Temporary pain, muscle twitch, very low seizure risk	Some forms (rTMS) require daily visits to a clinic for several weeks (though continuous theta burst stimulation treatment requires less treatment frequency/length).
Low Intensity Focused Ultrasound (LIFU)	Non-Invasive	Subcortical	Yes	Parkinson's, Essential Tremor,	Limited, theoretical risk of ICH	Perceived as non-invasive by patients
Deep Brain Stimulation (DBS)	Highly Invasive	Subcortical	Yes	Parkinson's, Essential Tremor, Dystonia, Epilepsy, OCD	Brain implant related side effects: pain, intracerebral hemorrhage, infection	Patient's concern regarding brain implant and managing an implanted device
Transcranial Direct Current Stimulation (tDCS)	Non-Invasive	Cortical	No	None	Few side effects	Patients can self-manage at home
Vagus Nerve Stimulation (VNS)	Invasive (Implantable VNS)	Direct Nerve Stimulation	Yes	Depression, Epilepsy	Difficulty swallowing, vocal changes, shortness of breath	Patient's concern regarding implant and managing an implanted device
Auricular Nerve Stimulator/ Percutaneous Nerve Field Stimulation (PNFS)	Minimally Invasive/ Non-Invasive	Direct Nerve Stimulation	No	Symptoms of Opioid withdrawal	Bleeding, pain, dermatitis	Minimally invasive wearable device, viewed as more acceptable by patients
Trigeminal Nerve Stimulation (TNS)	Non-invasive (eTNS)	Direct Nerve Stimulation	Yes	Pediatric ADHD	Drowsiness, increased appetite, sleep dysfunction, teeth clenching, headache, fatigue	Viewed as more acceptable due to non-invasiveness

Table 2

Applicability of neuromodulation for the treatment of SUD.

Neuromodulatory technique[1]	SUD research	Region of interest or brain target	Evidence level
Transcranial Magnetic Stimulation (TMS)	Alcohol, cocaine, methamphetamine, opioid, cannabis, nicotine	DLPFC, Medial Prefrontal cortex, ACC	Multiple clinical trials, associated with reductions in substance craving and use
Low Intensity Focused Ultrasound (LIFU)	None	NAc	No published pre-clinical or clinical investigations
Deep Brain Stimulation (DBS)	Alcohol, heroin, nicotine	NAc	Multiple case reports, pre-clinical data, associated with reductions in substance craving and use
Transcranial Direct Current Stimulation (tDCS)	Alcohol, cocaine, cannabis, nicotine	DLPFC	Multiple clinical trials, associated with reductions in substance craving and use though inconsistent evidence for efficacy, likely due to varying study designs
Vagus Nerve Stimulation (VNS)	Pre-clinical only	Vagus nerve	Changes in cortical excitability, extinguishing responses to drug-associated environmental stimuli
Auricular Nerve Stimulation/Percutaneous Nerve Field Stimulation (PNFS)	Opioid Withdrawal	Percutaneous Nerve Field	One open label trial
Trigeminal Nerve Stimulation (TNS)	None	Trigeminal Nerve	No published pre-clinical or clinical investigations

[1]None of the above mentioned methods of neuromodulation have received FDA approval for SUD (with the exception of PNFS which received De novo 510(k) clearance for SUD) and none have been approved for insurance reimbursement.