Treating Stimulant Addiction With Repetitive Transcranial Magnetic Stimulation (rTMS)

NCT04228276

Principal Investigator: Jong H. Yoon, MD

Palo Alto VA

jong.yoon@va.gov | (650) 493-5000

April 27, 2025

Background

The under-recognition of the impact of stimulant use disorder (SUD).

NB: For the purposes of this proposal, stimulants will refer to cocaine, amphetamine, or amphetamine derivatives such as methamphetamine. While each substance may be associated with unique characteristics, this grouping is justified based on the well-documented common neurochemical mechanisms of and common clinical features shared by these agents (White & Kalivas, 1998). Consequently, there is every reason to believe that treatments will be equally effective for both cocaine and amphetamine use disorders.

SUD confers significant disability and dysfunction among veterans. In some parts of the US, SUD, and in particular methamphetamine addiction, constituted 30.6% of all substance abuse admissions (Substance Abuse and Mental Health Services Administration & Quality, 2014). Nationally, stimulant abuse is the third leading cause of substance abuse treatment facility admissions, at 12.5%, just behind alcohol and opiates (Substance Abuse and Mental Health Services Administration & Quality, 2014). The treatment of SUD is complex and resource intensive: primary methamphetamine/amphetamine admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/residential treatment (16% vs. 7%) (Substance Abuse and Mental Health Services Administration & Quality, 2014). A 2009 study by the RAND Corporation estimated that the total direct and indirect costs associated with just methamphetamine abuse alone to be over $23B dollars annually (Nicosia, 2009). SUD is accompanied by substantial adverse neurobiological, medical, psychiatric, and societal outcomes. Studies have documented that long term use of stimulants can cause neurochemical abnormalities in brain regions and circuits needed for normal functioning (Volkow, Fowler, Wang, Swanson, & Telang, 2007). SUD is associated with high rates of major psychopathology – 48.1% of individuals with SUD have psychiatric illness, most often mood and anxiety disorders, and 12.9% develop psychotic disorders (Glasner-Edwards et al., 2010). Stimulant abuse is also associated with heightened mortality rates from medical problems and suicides (Darke, 2008).

Impact of SUD on Veterans. While the available data on SUD among veterans are sparse, the studies that exist indicate that SUD impacts veterans just as much as it effects the civilian population: 1.9% of veterans suffer from SUD (Yu et al., 2003); SUD substantially increases suicide risk since *the suicide rate associated with SUD is the second highest for any substance use disorder at 95.0 suicides per 100,000 person-years* (Bohnert, Ilgen, Louzon, McCarthy, & Katz, 2017); veterans with SUD have high rates of homelessness, representing 51% of chronic homeless veterans (Cox, Malte, & Saxon, 2017). Stimulant use is associated with fewer days housed and more days homeless over time (Edens, Tsai, & Rosenheck, 2014). SUD represents a particularly complex form of substance use disorder since compared to alcohol use disorder, veterans with SUD experienced higher rates of psychiatric co-morbidity, had much higher health care utilization and experienced more complicated courses of care (Morasco, O'Neil, Duckart, & Ganzini, 2014). Recent studies have documented that past year and lifetime prevalence of SUD among veterans has been estimated to be 0.6% and 4.6% (Boden and Hoggatt, 2018). This represents the fifth most common, after alcohol, tobacco, cannabis and opioid disorders. SUD had the highest increase in prevalence between 2016-2019 (Hoggatt et al., 2023).

Critical need for new, more effective somatic treatments. Despite the tremendous public health burden, there is currently no FDA-approved or widely recognized effective medication or somatic treatment for SUD. This is not due to a lack of effort since a large number of psychotropic agents have been tested and have failed to show efficacy in controlled trials, including numerous anti-depressants, anti-psychotics and anxiolytics (Brackins, Brahm, & Kissack, 2011). A recent study has shown that the combination of naltrexone and bupropion was more effective than placebo in reducing use of methamphetamine (Trivedi et al., 2021). However, the improvements were modest, and the findings warrant replication. In this context, the mainstay of treatment has been psychosocial interventions. As reviewed by Shearer et al. (Shearer, 2007), a variety of interventions including behavioral, cognitive, psychological or supportive counseling, abstinence, and harm reduction approaches have been investigated. Overall, the effectiveness of these psychosocial interventions appears to be modest at best, with an absence of high-quality evidence for many interventions. However, the best evidence of efficacy appears to be for contingency management based

approaches (Roll et al., 2006). These conclusions are largely mirrored by a more recent review conducted by the Cochrane organization (Minozzi, Saulle, De Crescenzo, & Amato, 2016), which also concluded that contingency management represents the most promising treatment modality. Furthermore, this review noted that use of psychosocial treatments likely increases treatment participation rates. However, the relatively high treatment cost and labor intensity have been cited as potential barriers to wider implementation (Roozen et al., 2004). These data suggest that an opportunity exists for the development of new somatic treatments for SUD that may complement and act synergistically with currently available psychosocial interventions.

Repetitive transcranial stimulation (rTMS) is a promising treatment for SUD. rTMS relies on Faraday's Law of Electromagnetic Induction and entails applying repetitive pulses of a rapidly fluctuating magnetic field, which induces an electrical current in a focal region of the brain, altering its neuronal excitability, and modulating its function. High frequency rTMS is an FDA-approved procedure for medication treatment refractory major depression. rTMS is becoming widely adopted in psychiatry and is undergoing testing for a variety of conditions, including substance abuse disorders (Spagnolo & Goldman, 2017). A limited number of controlled studies have evaluated rTMS in treating SUD, and these have shown promising results. Most studies have focused on rTMS effects on craving as a primary outcome measure. Meta-analyses have shown that high-frequency stimulation, an “activating” form of TMS (Camprodon, Martinez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Politi, Fauci, Santoro, & Smeraldi, 2008; Su et al., 2017), significantly reduces cravings (Chang et al., 2022). Moreover, the largest effect sizes have been associated with stimulation of the left DLPFC and greater effectiveness using intermittent theta burst (iTBS), specific form of high frequency stimulation (Chang et al., 2022). These findings have informed the design of our proposal, as discussed below.

These results provide convergent evidence underscoring the critical role of the left DLPFC in the psychological processes fundamental to addiction. This insight lays the groundwork for the promising treatment strategy of applying high-frequency rTMS targeting the left DLPFC, presumed to activate this key region. Notably, the only randomized control study to date that has tested whether high-frequency rTMS targeting the left DLPFC reduces stimulant use as a primary outcome measure is Terraneo et al., 2016. It found an increased duration of sobriety from stimulants in the rTMS group compared to a control group receiving standard treatment, reinforcing the potential of high-frequency rTMS of the left DLPFC as a viable approach for treating SUDs

Table 1. Outline of Design

Clinical Assessment	Randomization	Baseline	Treatment	Post-treatment		
	End of Wk 1		Wk 2-4	Wk 5	Wk 5-16, Monthly	Wk 16
Screen, In-person Evaluations, Functional Status	[active, sham] →	fMRI	Active rTMS	fMRI	Relapse Status	Functional Status
		fMRI	Sham rTMS	fMRI		

Research Design and Methods

Overview of General Design

We will utilize a randomized, double-blind, parallel-groups design. After pre-treatment assessment to confirm SUD diagnosis and characterize baseline level of use and functioning, subjects will be randomized (by computer algorithm) to either the active or sham rTMS arms. They will then receive rTMS or sham in the 2-week treatment phase, at the end of which subjects will repeat assessments to determine immediate post-treatment relapse status. In the follow-up period (3- months post treatment), we will determine the longer-term effects of rTMS by obtaining relapse status and level of functioning, along with secondary outcome measures described below.

Subjects, Screening Procedures and Randomization

General characteristics, including sex, race and ethnic origin of subjects to be recruited. Subjects with SUD between the ages of 18 and 65 will be studied. The study will be open to both men and women, regardless of race and ethnic origin.

Table 2. Inclusion and Exclusion Criteria

Exclusion Criteria	**Inclusion Criteria**
1) Pregnant or lactating female	1) Age 18-65 years
2) History of prior adverse reaction to TMS	2) SCID confirmed diagnosis of SUD
3) On medications thought to significantly lower seizure threshold, e.g. clozapine, chlorpromazine, clomipramine, and bupropion > 400mg/day	3) Last use of stimulants > 2 and < 8 weeks
4) Seizure disorder or conditions known to substantially increase risk for seizures	4) Stable medication regimen (no change in dose or agents between 2 weeks prior to the start of and throughout the treatment phase of the study)
5) Implants or medical devices incompatible with TMS	5) Stable social environment and housing to enable regular attendance at clinic visits
6) Acute or unstable chronic medical illness that would affect participation or compliance with study procedures, e.g. unstable angina	6) Stable medical health
7) Unstable psychiatric symptoms that precludes consistent participation in the study, e.g. active current suicidal intent, or plan; severe psychosis	
8) Other substance use disorder not in remission	
9) Chronic or recurring Axis I psychotic disorders	
10) For subjects participating in fMRI scans in Aim 3, presence of ferromagnetic material in their body or taking DAergic medications	

Time window of last stimulant use at study entry. Subjects will be recruited whose last use of stimulants is greater than 2 weeks but less than 8 weeks. The former will ensure that study participation occurs after subjects fully complete stimulant detoxification and withdrawal, which may preclude reliable participation in the study and confound hypothesis testing. The upper limit of 8 weeks is intended to maximize the likelihood of detecting a treatment effect. It is clear from the investigators' clinical experience that the first eight weeks following drug use cessation includes the highest risk period for relapse, and therefore, is also the period for a treatment to have the greatest impact on lowering relapse rates. The date of last use will be ascertained using the Timeline Followback (TLFB) method described below.

Screening procedures

Initial telephone interview. Potential participants identified by clinical staff will be given a brief description of study procedures and research goals. Interested subjects will provide verbal consent to be contacted by research staff, who will conduct a telephone screen to determine initial study eligibility as well as to provide basic study information. Subjects passing the telephone screen and providing written consent for study participation will proceed to an in-person clinical assessment. Table 2 summarizes the inclusion and exclusion criteria for this study.

Discussion of inclusion/exclusion issues. The inclusion/exclusion criteria have been derived based on two principles: safety vis-à-vis experimental procedures (rTMS), and limiting major confound.

rTMS and seizures. Although the actual incidence of seizure during rTMS is thought to be "very low" (Rossi et al., 2021), with estimates of 0.31 per 10,000 sessions and 0.71 per 1000 patients (Taylor et al., 2021), seizures, nonetheless remains the single most significant safety concern. This concern is particularly relevant for a study of users of stimulants since these agents are well known to lower seizure threshold. However, a review of the literature shows that high frequency rTMS has been well-tolerated in rTMS treatment studies of SUD. In the several publications involving over 100 subjects with SUD, no cases of seizures or any other significant adverse events have been reported (Bolloni et al., 2016; Camprodon et al., 2007; Politi et al., 2008; Rapinesi et al., 2016; Su et al., 2017; Terraneo et al., 2016). Nonetheless, we will institute procedures to minimize the possibility of seizures in our subjects. These procedures can be found in the Human Subjects section. These include administering a urine toxicology test just prior to the start of treatment and at least one additional test at a randomly chosen time point during the treatment phase. Most antipsychotics and antidepressants are thought to lower seizure threshold (Bolloni et al., 2016; Camprodon et al., 2007; Politi et al., 2008; Rapinesi et al., 2016; Su et al., 2017; Terraneo et al., 2016) prompting questions about the safety of administering rTMS to individuals taking these medications. However, the best available evidence suggests that these agents likely do not significantly increase the risk of rTMS-induced seizures. A review of various psychoactive agents, including antidepressants and antipsychotics (Ziemann, 2004), revealed that these agents in general do not affect motor threshold, which can be taken as a proxy measure for an agent's effect on cortical excitability, and hence a mediator of seizure potential. However, due to the particularly higher seizure risks associated with clozapine, chlorpromazine, and clomipramine (Pisani et al., 2002), as well as with high dose of bupropion (>400mg/day), we will exclude subjects taking these agents.

Psychiatric co-morbidity. Co-morbidity is common among veterans and a complicated consideration for research studies involving veterans and substance use disorders. From a practicality and future implementation robustness perspective, it would not be advisable to impose overly stringent exclusionary criteria for co-morbidity. However, from a scientific perspective, it would be prudent at this early stage of testing of rTMS efficacy, to impose some limitations on the extent co-morbidity, which may lead to Type II error. These considerations informed the decision to exclude psychotic disorders, such as schizophrenia and bipolar disorder. This study will not exclude major depression, PTSD, and other anxiety disorders. As a practical matter, given the high prevalence of these disorder among veterans, a useful treatment for this population would have to be effective with these co-morbid conditions. Furthermore, they contribute to substance abuse and in turn it becomes a significant barrier to receiving mental health treatment within the VA. Thus, the demonstration that rTMS can treat SUD with co-morbid disorders would further enhance the appeal of this treatment.

Co-morbid use of other substances. Stimulant use is often accompanied by the use of other substances, such as alcohol or opiates. While a common set of psychological and neurobiological systems may be involved across all substances of abuse, each class of substances also likely has unique effects, which could confound efforts to determine rTMS efficacy for SUD. Thus, it would be prudent to place some limits on co-morbid substance use for participants of this study. On the other hand, overly stringent exclusion of concurrent or history of use of other substances would overly tax our ability to recruit subjects for this study, with unclear benefit, given the current lack of data indicating whether co-morbid substance use in fact represents a significant confound. These considerations have led us to 1) not exclude individuals who have co-morbid use disorder in remission or meeting mild level of severity, 2) exclude individuals continuing to use other substances meeting DSM-5 use disorder criteria at moderate or severe levels of severity. In cases where there is on-going use of a substance not meeting criteria for a use disorder, we will carefully document amount of use so that we can conduct exploratory moderator analyses to determine its impact on rTMS effectiveness.

Psychotropic medications. We will document all psychoactive medications taken by our subjects during study participation so that we can conduct post-hoc moderator analysis of their impact on treatment efficacy. For subjects participating in Aim 3, we will exclude veterans taking DAergic medications, such as bupropion. This is because DA is well known to strongly modulate reward processing in subcortical circuits of interest in this study. Hence, DAergic medications are likely to confound measurements of reward associated activity. A review of our pilot study indicates that this exclusion criteria would affect ~10% of subjects.

Pre-treatment, in-person assessment

Diagnostic assessment. Inclusion and exclusion criteria, outlined in Table 2, will be reviewed in person. A doctoral or a master level clinician trained to administer the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID) will conduct interviews to confirm the diagnosis of SUD, severe, and the presence of psychiatric co-morbidity.

Severity of stimulant use. The quantification of stimulant use with a common metric is notoriously difficult due to the wide variability in purity and content of stimulants across samples, diversity in method of administration and street value/cost between communities. Consequently, the number of days of use within a time window may be the most reliable and straightforward quantification method for stimulant use. We will use the Timeline Followback (TLFB) method for this purpose (https://www.nova.edu/timeline/index.html). This method has been demonstrated to be highly reliable with a variety of substances of abuse, including stimulants (Robinson et al., 2014). We will quantify the number of days of use within a 60-day period prior to the start of the relapse period in which participation occurred. We will conduct exploratory analyses with this information to investigate the possibility that severity of stimulant use moderates rTMS treatment effects. We will also estimate use severity of other substances with the using the TLFB to explore the possibility that use of other substances moderates rTMS treatment effects.

Functional status. To quantify the functional impact of SUD and changes resulting from treatment, we will utilize the Addiction Severity Index (ASI). It is an instrument specifically developed to assesses the impact of substance use disorders on several domains of function, including medical, employment/support status, legal, family/social, and psychological. It is one of the best validated and commonly used scale for research into the problems associated with substance abuse (Amin-Esmaeili et al., 2024; McLellan et al., 2010; Miguel et al., 2021). Consequently, the ASI will facilitate the integration and comparison of results from this proposal to findings in the literature. To supplement this measure, we will also apply the Community Integration Questionnaire (CIQ) (Dijkers, 1997) as an additional measure of functional change. The CIQ will complement the ASI since it is broader and more general assessment of everyday functioning in the community. Both assessments will be administered two times: pre-treatment and 3 months after completion of the last treatment session.

Randomization of subject treatment assignments, drop-outs and subject flow. We will use a modification of the Efron procedure (Efron, 1971) developed by Dr. Helena Kraemer (H. Kraemer, C., 1981) to randomize

participants and to assure comparable stimulant use severity between groups at baseline. Subjects screened out during baseline (prior to randomization) will be replaced. After randomization, dropouts will not be replaced but will be retained in the statistical modeling, i.e. their data will be retained in these analyses because they are equivalent to intention to treat analyses. This minimizes loss of power and bias caused by dropouts.

Treatment Phase

rTMS stimulation parameters

2.a.3.d. Post-Treatment Phase

2.a.3.d.1. Assessment of relapse

The primary outcome measure will be rate of relapse within a three-month period following rTMS treatment completion. Relapse within the 3-month period following treatment will be determined using the Timeline Followback (TLFB) method. Subjects will be contacted monthly to review the prior months use history if any. We will supplement this assessment with a review of electronic medical records to look for evidence of relapse, such as progress notes from clinical staff and urine toxicology results. Relapse is defined as any use of a stimulant. Frequent testing occurs for veterans enrolled in ATS at the Palo Alto VA Medical Center, where most subjects will be recruited and will continue to be seen in their treatment programs.

Secondary outcome measures will be: 1) duration of sobriety following end of treatment phase; 2) change in level of craving (assessed by 10-point Likert scale) at end of treatment phase and three month follow up compared to baseline; 3) amount of stimulant use quantified as number of days of use of stimulants normalized by baseline values.

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