Study Title: A Pilot Study of Transcranial Magnetic Stimulation for Treatment of Methamphetamine Use Disorder

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Protocol and Statistical Analysis Plan

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Study Protocol

Overview

This is a pilot study to test the feasibility of a recruitment strategy and study protocol to examine the effects of transcranial magnetic stimulation (TMS) using intermittent theta burst stimulation targeting the dorsolateral prefrontal cortex (DLPFC) and continuous theta burst stimulation targeting the medial prefrontal cortex (MPFC) in people with methamphetamine use disorder (MAUD) who are engaged in psychosocial treatment. This TMS treatment is approved by the Food and Drug Administration for major depressive disorder. We will administer TMS daily for 2 weeks, followed by three times weekly for 2 weeks, and monitor depressive symptoms, anxiety, sleep, craving, quality of life, and methamphetamine use for three months. Changes in functional connectivity of brain circuits will be evaluated with magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) before and after treatment. We expect to observe changes in connectivity between the DLPFC and other regions implicated in addiction and impulsivity. Furthermore, we will evaluate if baseline differences in functional connectivity can be used to predict TMS response. Psychological tests focusing on state impulsivity and risk taking will be administered, and we expect to observe reductions in these characteristics after treatment. Participants will be randomized to receive stimulation targeting the DLPFC first or stimulation targeting the MPFC first, although all participants will receive stimulation at both sites at each treatment visit.

Primary objective

Evaluate the feasibility of a protocol to examine effects of intermittent theta burst stimulation (iTBS) to the dorsolateral prefrontal cortex (DLPFC) and continuous theta burst stimulation (cTBS) to the medial prefrontal cortex (dual target TBS) in people receiving psychosocial treatment for methamphetamine use disorder (MAUD).

Secondary Objectives

Estimate the effect size of dual target TBS on functional connectivity and impulsivity in patients with MAUD. Evaluate craving, sleep quality, depressive

symptoms, anxiety symptoms, and withdrawal symptoms during TBS treatment. Evaluate the level of continued use of methamphetamine during TBS treatment.

This pilot study will focus on our ability to engage patients with methamphetamine use disorder in TBS treatment and to complete a series of assessments over three months. We expect to observe reductions in cravings, withdrawal and related symptoms over time, and changes in anterior cingulate cortex functional connectivity from baseline to 4 weeks. Differences between subjects randomized to receive stimulation at the DLPFC and MPFC will be examined.

Significance

Methamphetamine (MA) use can cause many serious adverse health consequences and is of particular concern in Iowa. In the 2017 Treatment Episode Data Set (TEDS), 27.7% of substance use disorder treatment admissions involved MA as the primary substance, representing 7,641 admissions, second only to alcohol. Overdose deaths in Iowa involving MA roughly doubled to 91 from 2013 to 2018.(1,2) Treatment for MA use disorder (MAUD) is primarily psychosocial, rates of treatment induction and retention are poor, and relapse rates are high.(3) There is a pressing need to identify effective interventions that enhance psychosocial treatments. rTMS is a non-invasive brain stimulation technique that effectively treats major depressive disorder and is considered safe, well-tolerated, and potent. rTMS has increasingly been studied to treat addiction.(4-7) The dorsolateral prefrontal cortex (DLPFC), a brain region implicated in regulatory processes related to emotion, motivation, and craving, is a common target for rTMS. DLPFC stimulation using high frequency rTMS has reduced craving in many studies of addictive disorders, including cocaine and MA use disorders.(4) Despite these encouraging findings, no trials have reported on the efficacy for reducing MA use or preventing relapse. iTBS is a type of TMS has been studied in depression and shown to have equivalent efficacy to rTMS, and treatments can be delivered much more quickly than traditional rTMS.(8) In contrast to high-frequency rTMS and intermittent theta burst stimulation, which increase neuronal excitability, continuous theta burst stimulation (cTBS) decreases excitability. cTBS targeting the MPFC during drug cue activation reduced craving and related brain

activity in cocaine users in a sham-controlled trial evaluating the effects of a single cTBS session.(9,10) Prior work showed that rTMS to the DLPFC reduced MPFC activity in controls but not cocaine users. The findings of studies by Hanlon and colleagues supported a National Institute on Drug Abuse-funded randomized sham-controlled trial of MPFC cTBS for cocaine use disorder.(9)

Study Sites

The University of Iowa, the University of Utah, and the University of New Mexico are participating in this study.

Subject Recruitment

Subjects will be recruited through advertising as well as through colleague referral and medical record review. Patients admitted to a crisis stabilization unit, inpatient unit, or partial hospitalization or intensive outpatient substance use disorder treatment program, or seen in an outpatient addiction medicine clinic, with a diagnosis of methamphetamine use disorder will be provided with information about the study by clinicians to consider participation. Initial discussions will take place in private rooms. Posters and brochures will also be located in care locations.

Inclusion/Exclusion Criteria

Inclusion criteria:

-Diagnosed with an active methamphetamine use disorder

-Is engaged in psychosocial treatment or articulates a plan to engage in psychosocial treatment for methamphetamine use disorder during the study period

-Age 18 to 60 years

-Able to consent for treatment and research participation

-English-speaking

Exclusion Criteria:

-Age less than 18 years

-Patients that are excluded during TMS assessment including: patients with epilepsy or seizure disorder, patients with implanted ferromagnetic equipment in their face or skull near the stimulation target.

-Current medical treatment with clozapine or stimulants.

-Current diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, that is deemed by research team psychiatrists not to have been drug-induced. Psychotic disorder not associated with drug use per the MINI International Neuropsychiatric Interview. Psychosis NOS, in remission, or drug-induced psychotic episodes are not exclusion criteria since these may be related to methamphetamine misuse.

-Lacks the mental capacity to provide informed consent (i.e. not able to demonstrate understanding of the risks and benefits of participation)

-Has a court appointed guardian.

-Status as a prisoner.

-Receiving treatment as an alternative to incarceration.

-Unstable medical illness.

-Current diagnosis of neurological disorder or neurocognitive disorder.

-Prior neurosurgical procedure.

-History of seizure.

-History of ECT treatment within the past three months.

-History of any previous TMS treatment within the last 12 months.

-Known inability to complete the protocol, as assessed by asking them if they are able to make it to all visits for this study without assistance.

MRI Exclusion criteria:

-Implanted device including pacemaker, coronary stent, defibrillator, or neurostimulation device that is not MRI-compatible

-Metal in body including bullets, shrapnel, metal slivers

-Claustrophobia

-Uncontrolled high blood pressure

-Atrial fibrillation

-Significant heart disease

-Hemodynamic instability

-Kidney disease

-Pregnant

Eligibility Screening Questions

- Are you receiving care for this condition (methamphetamine use disorder), or are you interested in receiving care?
- Are you less than 18 or grater than 60 years of age?
- Have you been diagnosed with epilepsy, a seizure disorder, or have you ever had a seizure?
- Have you received transcranial magnetic stimulation?
- --(If yes) Was you last TMS session within the last 3 months?
- Did have to complete the scan in more than one sitting or did you (personally) ask for the scan to stop/ to take a break?
- Have you received electroconvulsive therapy within the last three months?
- Do you have any metal implants or implanted medical devices?
- (If yes) Are they MRI safe? (no-disqualified)
- Do you have any other metal in your body, such as bullets, shrapnel, or metal slivers?
- Do you have uncontrolled high blood pressure, atrial fibrillation, other heart disease?
- Do you have another medical illness that is difficult to manage or unstable?
- Do you have kidney disease?
- Have you been diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, or another psychotic disorder?

- Have you been diagnosed with a cognitive disorder, such as mild cognitive impairment, Alzheimer's disease, or dementia?
- Are you currently pregnant or do you plan to become pregnant anytime soon?
- Are you currently taking clozapine or a prescribed stimulant such as methylphenidate (e.g. Ritalin) or dextroamphetamine (e.g. Adderall)? Stimulants are usually prescribed for attention deficit disorder.
- Are you legally required to receive treatment as an alternative to criminal prosecution or going to jail or prison?

Screening questions that warrant follow up if the participant answers "yes":

- Have you been diagnosed with a methamphetamine use disorder? (follow up- providers to determine if participant should have a methamphetamine use diagnosis, if not currently diagnosed)
- Are you claustrophobic or afraid of small, closed-in spaces? (follow-up- participant needs to confirm that they can handle being in an MRI machine through additional questions)
- Do you have a problem with loud noises? (follow-up- participant needs to confirm that the noises from the MRI are not too loud through additional questions)
- Have you ever had a neurosurgical procedure? (follow up- type of procedure matters)
- Have you been diagnosed with another neurological disorder?(follow-up- type of disorder matters)
- Are you able to make it to all visits for this study without assistance? Additional information: This involves a baseline visit, then visits five days a week for two weeks and three days a week for two more weeks. The visits need to take place Monday through Friday, but we can start most any day depending on what's convenient for you. There will also be follow-up visits that can be completed by phone or in person one month and two months after the other visits are completed.
    - If not, Please explain any additional services you may need to get to and from study appointments, (i.e. transportation)

Randomization

The randomization scheme was block randomization stratified by study site, with block sizes of 4 and a 1:1 ratio, designed to ensure approximate balance in the number of subjects. Subjects are randomized to receive stimulation at the DLPFC or MPFC first, although both groups receive stimulation at both sites at each visit. The subject is assigned to a group at the first TMS treatment visit.

Intervention

The study intervention is open-label dual-target theta burst stimulation delivered in sequential fashion to the DLPFC and the MPFC. The order of treatments is determined by the randomization scheme, but the treatments are otherwise identical. Treatment targeting will occur at the Beam F3 and FP1 scalp regions as defined by the 10-20 EEG system. A Magventure MagPro X100 figure-8 coil with theta burst capabilities will be used to deliver the stimulus, including intermittent theta burst stimulation to the DLPFC (2 seconds of 50-Hz triplets delivered at 5 Hz, 8 seconds intertrain interval, 600 total pulses) and continuous theta burst to the MPFC (continuous 50-Hz stimulation triplets, 600 pulses). Stimulation will be delivered at 110% of the resting motor threshold, as determined by the stimulation threshold at which single-pulse TMS stimulation over the motor cortex hand knob region can elicit visible finger movement on 3 of 5 trials, with stimulation dose adjustment for distance from target to coil as needed. Treatment sessions will consist of a single treatment protocol at each stimulation site. Sessions will occur 5 times per week for the first 2 weeks, followed by 3 sessions per week for an additional 2 weeks (16 treatment sessions total).

Study Procedures

This study lasts for a total of 12-13 weeks, and involves 19 visits. Although visits vary from 15 minutes to 5 hours, they average 45-50 minutes. The first week involves a baseline visit that will take 3-4 hours. If the subject elects to participate in the optional EEG and timing task, this will add about an hour to their first visit. Subjects will receive 4 weeks of TMS treatments, and each treatment should take about 15 minutes. The first two weeks of treatment involve 5 visits per week

where the subject receives TMS. The third and fourth weeks of treatment involve 3 visits per week where the subject receives TMS. Additional assessments are done on the last treatment day of each treatment week. These visits, including treatment time, will take about 30 minutes after the first and third weeks of treatment, 45-60 minutes after the second week of treatment, and 3-4 hours after the fourth week of treatment. If the subject elects to participate in the optional EEG and timing task, this will add about an hour to their visit after the fourth week of treatment. Follow-up phone calls lasting 45-60 minutes will take place 4 weeks and 8 weeks after the end of TMS treatment (week 9 and week 13 of the study).

Assessment visit 1 will take place prior to TMS treatment. Information will be collected on demographics and a history of substance use and medical conditions. Subjects will be screened using the MINI International Neuropsychiatric Interview to ensure they do not have mental health conditions that should lead to exclusion. This may be conducted remotely by a psychiatrist investigator using a HIPAA compliant Zoom meeting if a psychiatrist is not available to perform the MINI on-site. The subject will complete all assessment surveys. They will also complete several psychological tests, including a Flanker task administered with an iPad, and a digitally administered delay discounting task. They will also submit a urine drug screen if there is not a recent result on file in their EHR, or one is not known to be planned for that day. Then they will complete fMRI imaging. This visit should take 3-4 hours. If the subject elects to participate in the optional EEG and timing task, this will add about an hour to this visit. If they elect to participate in this optional EEG and task, investigators will adhere electroencephalogram (EEG) leads to their scalp and then have them perform 2 blocks of the interval timing task where they estimate the passage of a specified (3 or 12 second) passage of time (~22min - 11 min blocks). The beginning of the trial is indicated by the presentation of either a 3 or a 12 on the computer screen which also indicates the duration of time the subject should estimate. During performance, we will collect electroencephalographic data from patients which will be analyzed offline.

Within a week of this visit, the subject will begin TMS treatment. TMS treatment could start as early as the same day if the subject prefers and the schedule allows.

TMS treatment using theta burst stimulation will be provided 5 days in the first week, five days in the second week, and three times per week in weeks 3 and 4. The start day will be somewhat flexible. Subjects will participate in 5 treatment sessions in each of the first two 7-day periods, and three treatment sessions in each of the third and fourth 7-day periods (treatment weeks). Theta burst stimulation can be completed in as little as 3 minutes per treatment (two sites), so these visits should take roughly 15-20 minutes total when once-weekly additional assessments are not being completed. We will measure blood pressure and pulse prior to each treatment. If systolic blood pressure exceeds 160 mmHg, diastolic blood pressure exceeds 100 mmHg, or pulse exceeds 110 beats per minute, then we will confirm this with a second measurement. If it is confirmed by a second measurement, then the treatment will be withheld, and a clinician contacted to assess the patient. Before each treatment, we will also ask the subject when they last used methamphetamine. Treatment may be withheld if it is too recent to minimize risk of adverse effects, particularly seizure. Participants will be asked to report craving using a single question before and after each treatment. Participants will only be asked to report any adverse event experiences at these visits.

On the last day of TMS in each treatment week when TMS is administered, the subject will be asked to complete additional assessments. At 1 week, 2 weeks, and 3 weeks, these will involve completion of surveys. At weeks 1 and 3 only the Brief Substance Craving Scale will be administered, while additional survey instruments will be administered after week 2. These visits will also involve reporting of the number of days in the last week in which they used methamphetamine as well as whether they remain engaged in a psychosocial treatment and what treatments (partial hospitalization, intensive outpatient, outpatient medical, outpatient psychotherapy, group therapy, other, none). If they were engaged in partial hospitalization or intensive outpatient treatment, we will ask whether they completed the planned course of treatment or stopped early.

After the last treatment in week 4, the subject will be asked to again complete all assessment instruments, provide information on substance use in the last week, complete the psychological tests, submit a urine drug screen (if there is not a recent result on file in their EHR), and complete fMRI imaging. If the subject elects

to participate in the optional EEG and timing task, this will add about an hour to this visit. If they elect to participate in this optional EEG and task, we will be adhering electroencephalogram (EEG) leads to their scalp and then have them perform 2 blocks of the interval timing task where they estimate the passage of a specified (3 or 12 second) passage of time (~22min - 11 min blocks). The beginning of the trial is indicated by the presentation of either a 3 or a 12 on the computer screen which also indicates the duration of time the subject should estimate. During performance, we will collect electroencephalographic data from patients which will be analyzed offline.

TMS treatment will end at this time. We will then plan follow-up visits at 8 weeks and 12 weeks after the start of treatment, which can be completed by phone/online or in person base on the subject's preference. At these visits subjects will complete the survey-based assessments. They will also be asked about the number of days of methamphetamine use in the last week and their current psychosocial treatment modality.

An example study schedule and full list of assessments I provided below.

Figure 1: Example Study Schedule

Study Week	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**
1	First visit: determine eligibility to continue, questionnaires, psychological testing, urine drug screen if needed, MRI, optional EEG **(3-5 hours)**				
1	TMS	TMS	TMS	TMS	TMS, questionnaires, urine sample if needed **(about 30 minutes)**
2	TMS	TMS	TMS	TMS	TMS, questionnaires, urine sample if needed **(45-60 minutes)**
3	TMS		TMS		TMS, questionnaires, urine sample if needed **(about 30 minutes)**
4	TMS		TMS		TMS, questionnaires psychological testing, urine sample if needed, MRI, optional EEG **(3-5 hours)**
8	One follow-up visit or phone call to complete questionnaires **(45-60 minutes)**				
12	One follow-up visit or phone call to complete questionnaires **(45-60 minutes)**				

Figure 2: Schedule of study assessments by visit

Measure	**Time to complete (minutes)**	**First Visit**	**Last TMS day week 1**	**Last TMS day week 2**	**Last TMS day week 3**	**Last TMS day week 4**	**Week 8**	**Week 12**

Interview Questions								
Personal information, medical history, substance use history	20	x						
Report substance use and current treatment	2	x	x	x	x	x	x	x
Urine drug screen (if needed)	10	x	x	x	x	x		
Mini International Neuropsychiatric Interview	20	x						
Written Questionnaires								
Brief Substance Craving Scale	5	x	x	x	x	x	x	x
Assessment of Recovery Capital	5-10	x				x	x	x
Brief Addiction Monitor	10	x				x	x	x
Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form	5	x		x		x	x	x
Patient Health Questionnaire	3	x		x		x	x	x
Generalized Anxiety Disorder 7-item scale	2	x		x		x	x	x
Positive and Negative Affect Scale	5-10	x		x		x	x	x
Pittsburgh Sleep Quality Index	5-10	x		x		x	x	x
Big Five Inventory-2	5-15	x						
UPPS-P Impulsive Behavior Scale	15	x				x		
Difficulties in Emotion Regulation Scale-Short-Form	5	x				x		
Monetary Choice Questionnaire	5	x				x		
Psychological Testing								
Flanker Inhibitory Control and Attention	3-5	x				x		
Imaging								
MRI	60-90	x				x		
EEG and Timing Task (optional)	60	x				x		

Procedures for contacting subjects lost to follow-up

The subject will be called or texted (per their preference) up to 5 times after each loss to follow-up with two days between contacts and messages left to contact the research assistant if voice messaging is available. If the subject provided a secondary contact person that individual will be called up to three times with two days between calls and voice messages left if available, starting after the third failed attempt to contact the subject. We will inform that person that we are trying to reach the study subject about a research study and the subject said they might be able to help us find them, without disclosing the details of the study or the subject's health conditions. If the secondary contact is reached, they will be asked if they know the whereabouts of the person, if they could reach out to them, and for new contact information if that has changed. If the secondary contact provides information saying that the person cannot be reached for a particular reason, then this will be documented in the record. If the subject is said to be deceased, then the secondary contact will be asked if they know the circumstances of the death.

Expected Risks of Participation

TMS Risks

Transcranial magnetic stimulation is a non-invasive method of brain stimulation that relies on electromagnetic induction using an insulated coil placed over the left prefrontal cortex. The coil generates brief magnetic pulses, which pass easily and painlessly through the skull and into the brain. The pulses generated are of the same type and strength as those generated by magnetic resonance imaging (MRI) machines. When these pulses are administered in rapid succession, it is referred to as "repetitive TMS" or "rTMS", which can produce longer lasting changes in brain activity. During the treatment, the patient may experience light-headedness, tapping, tingling, itching, headaches, or muscle twitching while the magnetic coil is turned on. However, TMS has been proven safe in major depressive disorder and the treatment team will be using an FDA-approved protocol for DLPFC iTBS. We will also be using a cTBS protocol that has been previously studied by Hanlon et al, who did not note meaningful differences in adverse effects. Because the TMS device produces a loud click with each pulse, the subject will wear earplugs during treatment to minimize discomfort. The most serious known risk of TMS is the production of a seizure. To minimize this risk, all

subjects with a history of epilepsy or epileptogenic intracranial lesions will be excluded from the study; any subjects that are deemed inappropriate for TMS treatment by the physician who administers TMS will also be excluded from the study.

MRI Risks

A metal object flying through the air toward the magnet and hitting the subject comprises the greatest risk associated with MRI.

-There is a minimal risk to the subject's hearing.

-There is a risk that we will discover an abnormality or disease in the subject, which would otherwise not be found. This risk can increase the psychologically-induced stress associated with participating in this study.

-Although there are no known risks associated with limited exposure to magnetic fields, we cannot rule out the possibility that in the future some risks may be discovered.

Emotional Risks

-When answering questions about emotionally-charged topics such as depressive symptoms and substance use, there is a risk of triggering negative thoughts or emotions in the participant. Similarly, the subject may experience some stress when performing psychological tests. However, there is no evidence to suggest that asking these questions could make the specific symptoms or disease state worse.

EEG

There are no risks, although patients will be required to have gel applied in their hair and the surface of their skin may be mildly scratched by the EEG gel applicator. These risks will be mitigated by asking for feedback from the patient frequently and adjusting procedure as needed to minimize discomfort.

Other Risks

Loss of confidentiality is a risk. This has potential legal consequences since the study involves questions about illegal drug use and urine drug screens. There is also a risk of boredom or cognitive fatigue, particularly from the lengthier visits

involving surveys, neurocognitive testing, and imaging at first visit and at the end of the treatment course.

Procedures to Minimize Risks

Minimizing psychological risks:

A psychiatrist will be conducting the initial evaluation of the patient to determine appropriateness for treatment. Psychiatrists are trained on how to manage responses that demonstrate concern for imminent danger to self or others. The study will take place in a safe research environment and if the subject reports any current suicidal thoughts, a physician will be available to assist the patient and the patient will be sent for immediate psychiatric care at the appropriate level of medical and psychiatric attention needed based on the physician's clinical judgment. Patients will also have access to the 24-hour nurses number for emergent psychiatric needs. This number will be called if there is concern for imminent suicidality or concern for safety, and the physician overseeing treatment will arrange for urgent patient transport to the emergency room for psychiatric stabilization. If a subject expresses suicidal ideation or intent to a research assistant or other non-psychiatrist during study participation, a psychiatrist investigator will be paged to respond.

Minimizing the risks of TMS:

TMS will be administered by combining an FDA-approved protocol and a protocol that has been previously studied with no notable differences in adverse effects, and will be overseen by a psychiatrist in the clinical TMS service in the standard fashion.

We will measure blood pressure and pulse prior to each treatment. If systolic blood pressure exceeds 160 mmHg, diastolic blood pressure exceeds 100 mmHg, or pulse exceeds 110 beats per minute, then we will confirm this with a second measurement. If it is confirmed by a second measurement then the treatment will be withheld and a clinician contacted to assess the subject and their potential need for acute medical care. We will also ask the person when they last used methamphetamine, and withhold treatment if we believe they may still be intoxicated with methamphetamine.

Minimizing the risks of MRI:

To reduce the risk of a metal object flying through the air and hitting the subject, technologist or nearby person, we require that all people involved with the study remove all metal from their clothing, pockets and body prior to entering the scan room. No metal objects will be brought into the magnet room while the subject is inside the room. In addition, the door to the room remains closed throughout the entire study so that no one accidentally takes a ferrous metal object into the scan room. We also have a ferromagnetic detector for the research suite. The metal detector will work in tandem with our MRI screening sheet to ensure no metal is accidentally overlooked and taken into the scan room.

-Subjects will be given either ear plugs or headphones to reduce the risk of hearing damage.

-In the event that an abnormal finding is suspected, a radiologist trained in reading the examination will be consulted. If it is felt that the subject needs to be notified in order to seek out further medical advice, a physician will then contact the subject to discuss the issue.

-Exposure to magnetic fields and radiofrequency fields will be kept to a minimum by setting a cutoff time of any study of 90 minutes in the magnet.

-Subjects will be given a squeeze ball while in the MRI scanner to alert the investigators to stop the study.

Minimizing emotional risks:

During completion of surveys, testing, and other study procedures, participants who express distress or discomfort will be given options of continuing, suspending trying again at a later time, or withdrawing from the study. If a subject is able to complete most but not all assessments, and the assessments are not required to confirm eligibility for the study (e.g. the MINI to confirm diagnoses), then subjects may be allowed to continue in the study without completing all assessments. Investigator discretion will be used to determine if the subject is still contributing adequate data to help inform how outcomes change with TMS treatment.

Minimizing EEG risks:

The risk of scratching will be mitigated by asking for feedback from the patient frequently and adjusting procedure as needed to minimize discomfort.

Minimizing other risks:

Data will be encrypted and protected and deidentified. All research data will be stored in a secure REDCap database.

A member of the research team will give instructions on how to provide a urine sample. Participants may take a break at any time.

Data Collection and Protection of Privacy

No more data than required will be collected. All research data will be stored in a secure REDCap database, with the exception of MRI, EEG, and timing task data that will be stored on secure research drives. Only research team members will have access to this information. Study procedures will take place in secure private settings to prevent disclosure of personal health information. We will use a shared REDCap database with collaborating sites, but only investigators at specific sites will have access to identifiers for subjects from their site (such as name and address).

All survey instruments and other data collection forms will be collected on an iPad through REDCap and stored in a secure REDCap database. For follow-up visits completed by phone, the research assistant may use a computer to enter data into REDCap. Data from fMRI and neuropsychological tests not completed in REDCap will be linked to the study ID and contain no other identifiers. Neuropsychological test results will be uploaded to REDCap after completion. EEG and timing task data will be stored on a secure research drive and stored with a study ID and no other identifiers. A special computer will be used for analysis of fMRI data, and all software will be protected with encrypted strong passwords. Electronic records will be kept on a secure research drive which will only be accessible to the research team by password encryption. All patient-identifying information will be stored behind UIHC Firewalls on REDCap. Name, contact information, medical record number, secondary contact person information, and the linked study identifier will be stored in a separate REDCap database from the other data to help prevent accidental disclosure and unnecessary downloads of identifiable information. The REDCap database with survey responses and other data for analysis will use this linked study ID to identify the subject. The REDCap surveys that were submitted as attachments will autopopulate with the study ID each time the surveys are deployed.

Paper copies of consent forms, and the MINI International Neuropsychiatric Interview with only a linked study ID, will be stored in a locked file cabinet in private office.

Subjects will collect urine samples using standard methods and provide them to a research team member who will perform a dipstick urine drug screen. The urine sample will be discarded appropriately after the testing is complete.

Potential Benefits to Society

Treatment for methamphetamine use disorder is primarily psychosocial, and outcomes are suboptimal. No other treatments for methamphetamine use disorder have been proven safe and effective. If TMS treatment proves feasible in this study and we see improvements in symptoms, substance use, and functional connectivity then this study will justify a randomized controlled trial to evaluate the efficacy and safety of TMS for methamphetamine use disorder. If effective, this could prove to be a breakthrough in treatment options for methamphetamine use disorder.

Statistical Analysis Plan

Sample Size Justification

This is a pilot study without an untreated control group so will not be able to establish that the treatment is causal in improving outcomes. The overarching goal is to evaluate the ability to recruit and retain subjects, establish safety of the intervention in this population, evaluate target engagement of TMS using fMRI, and to determine the extent to which patient symptoms and substance use appear to improve during participation in treatment. We anticipate approximately 20 subjects, which should be adequate to statistically detect clinically meaningful changes in symptoms and other outcome measures, depending on attrition. We will randomize order of treatments to gather preliminary data on any differences, but do not anticipate power to detect significant differences in effect by order of treatment with this sample size.

Outcomes

Primary outcomes:

1. Retention in the Study: Measured from Baseline to 12 weeks
2. Retention in Psychosocial Treatment: Measured from Baseline to 18 days (self-reported)

Secondary outcomes (used all available data points as specified in figure 2):

1. Functional Connectivity of the Dorsolateral Prefrontal Cortex and Anterior Insula—change from baseline to 4 weeks. Measured by correlation of region activity over MRI time series data, averaged for left and right hemisphere.
2. Functional Connectivity Dorsolateral Prefrontal Cortex and Anterior Cingulate Cortex—change from baseline to 4 weeks. Measured by correlation of region activity over MRI time series data, averaged for left and right hemisphere.
3. Functional Connectivity of the Medial Prefrontal Cortex and Ventral Striatum—change from baseline to 4 weeks. Measured by correlation of region activity over MRI time series data, averaged for left and right hemisphere.
4. Kirby Delay Discounting Questionnaire, 27 Item

5. Number of Days of Methamphetamine Use in the Past Week
6. Urine Drug Screen Positive for Stimulant
7. Brief Substance Craving Scale
8. Brief Addiction Monitor—Use Subscale
9. Brief Addiction Monitor—Risk Factors Subscale
10. Brief Addiction Monitor—Protective Factors Subscale
11. Brief Addiction Monitor—Satisfaction with Progress Toward Achieving Recovery Goals (question 17)
12. Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form
13. Patient Health Questionnaire--8 Item Scale
14. Generalized Anxiety Disorder 7-item Scale
15. Assessment of Recovery Capital
16. Positive and Negative Affect Scale—Positive Affect Score
17. Positive and Negative Affect Scale—Negative Affect Score
18. Pittsburgh Sleep Quality Index
19. Difficulties in Emotion Regulation Scale--Short Form
20. UPPS-P Impulsive Behavior Scale, 59-item Revised Version

Safety outcomes

Adverse events are reported at each TMS treatment visit, or if otherwise volunteered by subject.

Populations to be analyzed

Intention to treat: Subjects will be analyzed in the groups they were randomized to. However, only complete data will be used, and subjects were discontinued from the study if they missed more than 4 TMS treatments.

Analyses

Descriptive statistics will be examined for demographic and other variables, overall and by intervention group.

For other analyses, a fixed time will be assigned for each study visit, which approximates the time at which the visit would have occurred on a typical study schedule.

Primary outcomes

The primary analysis will compare intervention groups (DLPFC first or MPFC first) on time to discontinuation in the study and time to discontinuation of psychosocial treatment. The latter is defined as a participant indicating they are no longer in or seeking treatment. All subjects were in treatment or planning treatment at baseline, as an inclusion criterion. Time retained in the study or treatment will be described using Kaplan-Meier curves, and intervention groups will be compared using log-rank tests.

Secondary outcomes

Most secondary outcomes will be examined using linear mixed models. These allow for estimation of within group change over time as well as between group differences in change over time. Group by continuous time interaction terms will be the primary test of hypotheses for differences between groups. For outcomes measured at only two time points (baseline and week 4), if sample size is not adequate or mixed models do not converge, changes from baseline to the second measure will be calculated. Wilcoxon-rank sum tests or t-tests comparing differences in changes from baseline to week 4 will be used to compare groups, as appropriate based on the data distribution. A generalized estimating equations model clustered on subject with a logit link, with empirical standard error estimates, will be used to analyze the outcome of positive urine drug screens for stimulants, as this is binary, and this approach does not assume a correlation structure. The primary analysis of this outcome will still use a group by continuous time interaction to examine whether the odds of a positive urine drug screen decreases over time in each group, and whether any reduction over time differs between groups.

Missing data

As this is a pilot study with a small sample size, and dropout is expected, analyses will use all available data as feasible for randomized subjects who received at least one treatment, irrespective of the number of data points collected. For changes in functional connectivity as measured by MRI, only subjects with both baseline and 4-week assessments will be included. No imputation of data will be performed.

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