A Preliminary Investigation of Pre-Frontal Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Cannabis Use Disorder

Study Protocol and Statistical Analysis Plan

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Protocol

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Study Title: **A Preliminary Investigation of Pre-Frontal repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Cannabis Use Disorder.**

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A. SPECIFIC AIMS

Specific Aims:

Cannabis use disorder (CUD) is a common and escalating problem in the U.S. with few validated treatment options. The prevalence of CUD in the U.S. has more than doubled in the past decade(1). Consistent with a high prevalence, there is also a high demand for treatment, with more than one million CUD patients seeking treatment in 2014 alone (2). There is currently no standard of care intervention or FDA-approved medication with demonstrated efficacy in this population; subsequently, providers are left with few options to offer treatment seekers.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is FDA-approved as a treatment for major depressive disorder. rTMS is also actively being pursued as a treatment for substance use disorders. In substance use disordered populations, the use of rTMS has garnered significant attention as an innovative tool to decrease craving [see reviews: (3-6)]. Several studies that employed a single rTMS session demonstrated that applying excitatory rTMS to the DLPFC can decrease cue-induced craving in nicotine, cocaine, and alcohol use disordered populations. As expected, single session studies have only resulted in small temporary reductions in craving; however, these promising data have led to preliminary clinical trials using multiple sessions of rTMS in alcohol(7), nicotine(8) and cocaine(9) use disorders. The largest such clinical trial (n=130 smokers) demonstrated that 13 sessions of DLPFC rTMS resulted in six month tobacco abstinence rates of 33%(8). This encouraging single site study is now being tested for replication in larger multisite studies.

To date there has been limited work examining the effect of rTMS on aspects of CUD. Drawing from the published literature suggesting that excitatory rTMS applied to the DLPFC can reduce craving, the candidate and mentorship team recently completed a preliminary sham-controlled crossover study in cannabis use disordered individuals. The trial suggested that rTMS is safe and well-tolerated, and that a single session of rTMS *acutely* decreases cannabis cue-induced craving. The promising results from our single session trial parallel the single session results found in nicotine and cocaine use disordered populations which subsequently translated into positive multiple session clinical trials(8, 9). As such, it follows that a trial utilizing multiple sessions of rTMS in cannabis use disordered patients may yield positive results.

The overarching goal of this proposal is to investigate if a course of excitatory DLPFC rTMS results in reduced cannabis cue-induced craving in treatment seeking individuals with CUD (Aim1). Additionally, we seek to explore the mechanistic underpinnings of any observed effect by collecting functional magnetic resonance imaging (fMRI) data during cannabis cue-administration before and after the treatment course (Aim 2). These aims will be addressed through a double-blind, randomized, sham-controlled study in which 72 treatment seeking cannabis use disordered participants (36/group) will be given 20 sessions of either *Active* or *Sham* excitatory rTMS applied to the DLPFC. rTMS will be delivered in an accelerated fashion as quickly as in two-weeks, but most often over five-weeks (2 sessions each day, 10 treatment-days). rTMS will be applied in conjunction with a validated three-session Motivational Enhancement Therapy (MET) behavioral intervention.

Aim 1: Determine if a course of excitatory rTMS applied to the DLPFC results in reduced cue-induced craving. We hypothesize that as compared to participants receiving sham rTMS, participants receiving active rTMS will have a reduced level of cannabis cue-induced craving following their final rTMS session as compared to prior to their first rTMS session. We will measure self-reported cannabis craving during a validated cannabis cue-reactivity paradigm, and define cue-induced craving as change in self-reported craving from pre-to-post cue administration.

Aim 2: Determine if a course of excitatory rTMS applied to the DLPFC reduces cue-reactivity in reward network structures during a validated fMRI paradigm. We hypothesize that as compared to participants receiving *sham rTMS*, participants receiving *active rTMS* will have a reduced percent signal change in BOLD response in reward structures during a validated cue-reactivity fMRI paradigm following their final rTMS session as compared to prior to their first rTMS session.

Exploratory Aim: Determine if participants receiving active rTMS have a higher rate of abstinence following treatment as compared to participants receiving sham rTMS. We hypothesize that participants receiving *active rTMS* will be more likely to be abstinent over the final two-weeks of the study period than participants receiving *sham rTMS*. We will define abstinence as no self-reported cannabis use over the final two weeks of the study, and a ratio of four week to two-week creatinine corrected urine THCCOOH of < 0.5 (10-12).

B. BACKGROUND AND SIGNIFICANCE

Cannabis Use Disorder (CUD) is a common and escalating problem in the United States. The prevalence of CUD more than doubled between 2001-2002 and 2012-2013 (1). Coinciding with the high prevalence of CUD, there has been a high demand for treatment. According to SAMHSA, in 2014 over one million individuals sought treatment for CUD(2). In recent years it has become increasingly clear that those desiring to quit cannabis are rarely able to do so on their own and suffer from a clear withdrawal syndrome(13). Currently available treatments have low long-term success rates(14-17)**.** There has subsequently been significant interest in the development of new treatment options for those individuals with CUD who desire to stop using.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is able to alter cortical excitability and is FDA-approved to treat Major Depressive Disorder. Magnetic fields pass unimpeded through the scalp, skull and meninges, and can directly excite cortical areas. High frequency rTMS (greater than 5 pulses per second) increases cortical excitability(18). Single sessions of rTMS induce temporary changes; however, multiple sessions can induce more long-term changes.

The dorsolateral prefrontal cortex (DLPFC) is a key node in the executive control network. Current and historical evidence suggests that in major depressive disorder there is an imbalance of so called cognitive control (exerted by the executive control network) over deeper limbic regions(19). rTMS applied over the DLPFC likely exerts its anti-depressant effect by acting to re-regulating these dysfunctional cortical-limbic circuits(20). Single sessions of rTMS have little effect on depression; however, multiple sessions of rTMS have been demonstrated to be an effective (21, 22) and durable (23, 24) antidepressant treatment. Further, although single daily-sessions given over a period of four to six weeks are often utilized, there have been studies supporting the efficacy of accelerated treatment courses of rTMS, where multiple sessions are given each day over a shorter period of time(25-27). The advantages of accelerated treatment paradigms include more rapid delivery of treatment (with more rapid improvement) and fewer needed visits, thus likely enhancing compliance and reducing dropouts.

In substance use disorders there is mounting evidence that there is an imbalance of neural activity between the executive control network and the reward network. As the executive control network is thought to have a modulatory effect on the reward network (28), this imbalance may play a key role in the inability of those with substance use disorders to modulate drug craving and use (28-34). If in fact an imbalance of these two networks results in craving, then it would follow that either the application of excitatory rTMS to the executive control network or inhibitory rTMS to the reward network would result in decreased craving. More than 20 studies have confirmed this relationship [see reviews:(3-6)]. The majority of these studies applied single sessions of excitatory stimulation to the DLPFC, with the idea that this type of stimulation can result in enhanced executive control network modulation of the reward network, resulting in less reactivity to drug cues. Of note, another study demonstrated that inhibitory rTMS applied to the DLPFC resulted in increased craving(35), providing further strength to this relationship.

Sparked by the promising literature suggesting that single sessions of prefrontal rTMS reduces craving, two recent clinical trials demonstrated that multiple sessions of rTMS may have a more durable effect on craving and reduce drug use(8, 9). The largest trial (n=130 smokers) demonstrated that 13 sessions of excitatory DLPFC stimulation resulted in six-month tobacco abstinence rates of 33%(8). The second clinical trial demonstrated that 8 sessions of DLPFC rTMS decreased cocaine craving, and resulted in one-month abstinence rates of 69% (9).

Imaging studies using cannabis cue reactivity (32-34) and cognitive tasks (36, 37) demonstrate that there is likely the same neural imbalance between executive control and reward networks in CUD. Drawing on the apparent shared neural dysfunction between CUD and other SUDs, and the promise of rTMS as a potential treatment for SUDs, our group recently completed a small trial to determine if a single session of DLPFC rTMS was safe and well tolerated in a group of CUD participants. Our preliminary data demonstrated that rTMS was safe and well tolerated, and suggests a reduction in cue induced craving. However, as expected, the effect on craving with a single session of pre-frontal rTMS was small.

In sum, studies across substance use disorders suggest that dysfunction of the executive control network and reward network are associated with drug cue-reactivity across SUDs including CUD. Excitatory rTMS applied to the DLPFC (a key node in the executive control network) can reduce craving across SUDs, and has translated to two recent positive clinical trials. We have successfully applied rTMS to a CUD population with promising early results. The next logical step in the development of this novel treatment for CUD is to determine the effects of a course of treatment in a treatment seeking CUD population.

Public Health Impact: *rTMS could provide a much needed treatment for those seeking to quit cannabis and result in the improvement of many lives. rTMS, assuming positive effectiveness and safety for addictions, has major potential public health value. There is a large network of TMS providers worldwide, with rapidly expanding numbers. rTMS is subsequently widely clinically available with decreasing costs.*

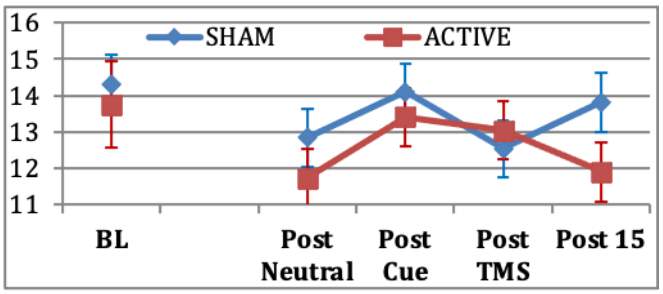
C. PRELIMINARY STUDIES

1: This proposals primary mentor, Dr.McRae-Clark, and her group has been one of the leaders in the field of interventional clinical trials in CUD. Since 2009 they have performed four large clinical trials (38-41) in treatment seeking individuals with CUD that would have likely met our inclusion criteria. Her research program has a well established recruitment network in place and they have consistently exceeded recruitment goals.

2: Mentor, Dr.George, and his colleagues have had success in delivering courses of rTMS to addictions populations. In nicotine use disordered participants, the group was able to deliver 10 daily rTMS treatments with a retention rate of 92% (36/39 participants) with all participants receiving 10 treatments in three-weeks or less. In alcohol use disordered participants, the group has been able to deliver 10 daily rTMS treatments to 5/5 participants, with all participants receiving 10 treatments in three-weeks or less.

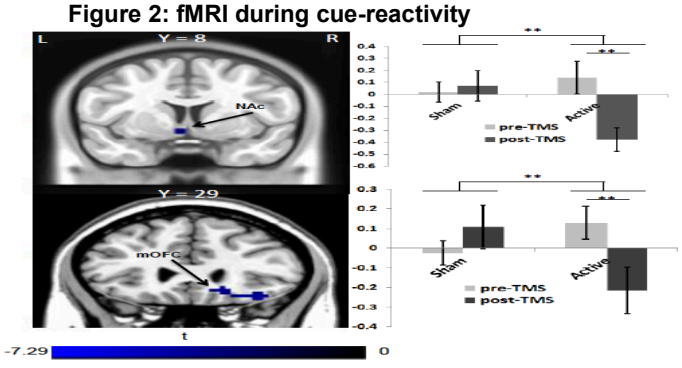
3: The candidate recently completed a single-blind, sham-controlled crossover study demonstrating TMS is safe and well tolerated in a group of individuals with CUD. Additionally, a single session of rTMS *acutely* decreased self-reported cannabis craving. This small trial demonstrated that our group is able to feasibly deliver rTMS to this population. Further, reductions were seen with active rTMS administration in the purposefulness subscale of the Marijuana Craving Questionnaire (T=2.5, DF=43, *p*=0.016, Figure 1).

Figure 1: MCQ purposefulness subscale ± SEM



4: We also completed a double-blind, sham-controlled, crossover-trial in nicotine use disordered participants. A single treatment of either active or sham rTMS was applied between fMRI scans. Compared to sham rTMS, active rTMS applied to the DLPFC resulted in a decrease in reward network activation and an increase in executive control network activation in response to smoking cues (Figure 2). (mean

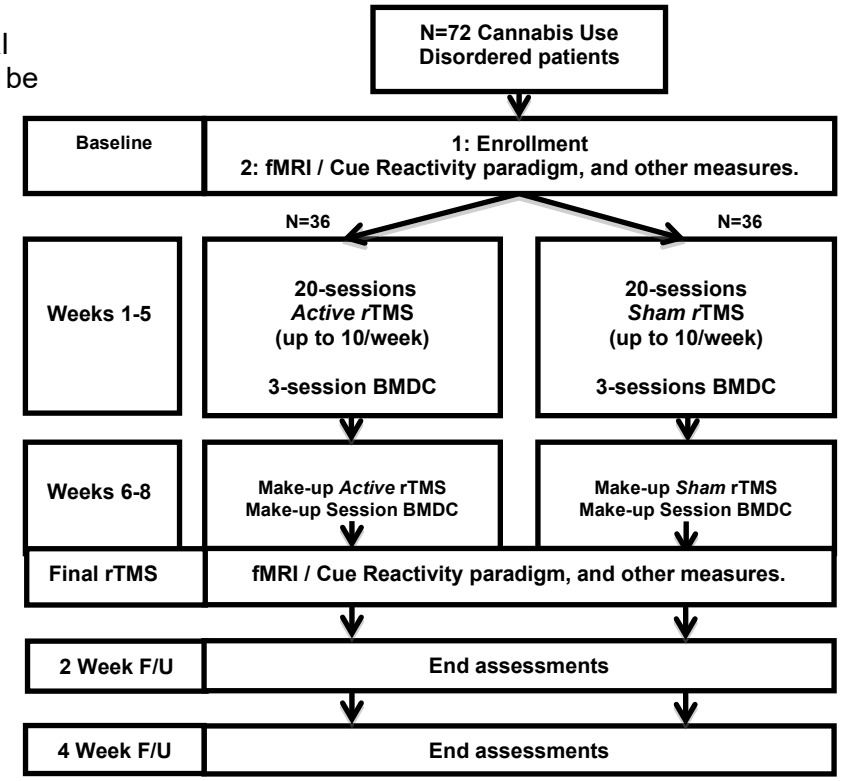
Figure 2: fMRI during cue-reactivity



BOLD signal changes between groups from pre-post, left NAc (-6, 8, -8) (top) and right mOFC (18, 29, -11) (bottom). N = 10, * p<.05, **p<.01,)

D. RESEARCH DESIGN AND METHODS (including data analysis)

General Overview (Figure 3): The primary aims are to determine the efficacy of 20 sessions of DLPFC rTMS in decreasing cannabis cue-induced craving (Aim 1) and cue reactivity in a validated fMRI paradigm (Aim 2). The aims of the study will be accomplished by performing a double-blind, randomized, sham controlled clinical trial with two arms. Individuals with CUD will be recruited from the community. All participants will receive a three-week behavioral intervention and adjunctively undergo a course of either *active* or *sham* rTMS during that time. Post-treatment outcomes will be assessed at two- and four- weeks following completion of the rTMS course.



Screening: Participants will meet with study personnel either in person, or via Stanford Secure Zoom, and complete assessments about substance use, psychiatric and medical history. Eligible participants will complete questionnaires and provide a urine sample for drug screening. For females, a pregnancy test will be done prior to the drug screen. Pregnant women will not be allowed to participate.

rTMS Sessions: rTMS will be delivered via a MagPro double blinded rTMS Research System (MagVenture, Denmark) with a Cool-B65 Butterfly Coil (a combined active and sham coil). We will use a standard resting motor threshold (rMT) determination to determine the TMS dose (42). Treatment will be delivered at 120% rMT. Each active rTMS study-treatment will consist of a total of 4000 pulses of 10Hz stimulation (5s-on,10s-off). Treatments will be delivered at the EEG coordinate for F3 (which approximates the left DLPFC), and will be found using the Beam-F3 method (43). This is a treatment paradigm that has been used extensively in other trials (25, 44-46). Sham sessions will be delivered using an electronic sham system consisting of a coil that mimics the appearance and sound of rTMS, combined with a TENS device which produces a small electric shock mimicking the feeling of active rTMS. This type of sham has been demonstrated to be indistinguishable from active rTMS, has been well tolerated in (21, 25), and successfully used in other clinical trials(47, 48).

During each session of rTMS we will present physical cannabis cues (49). We chose to administer cannabis cues during rTMS as it may enhance the clinical efficacy of rTMS in SUD populations (8). Before the first, and after the last rTMS treatment we will present a full cannabis cue paradigm. The cannabis cue paradigm consists of an auditory script, a tray of cannabis related items, and an olfactory cue. The auditory script consists of an imaginal recall of a recent pleasurable cannabis experience. The physical cues consist of a number of items associated with cannabis use such as a blunt wrap, rolling papers, pipes, a small bag containing fake marijuana, a water bong, rolled fake joints, etc.). The olfactory cannabis cue consists of an essential oil of cannabis.

A total of 20 study-treatments will be delivered as two study-treatments each treatment-day separated by 30-minutes. Study-treatments will be delivered in as little time as two weeks (2 study-treatments each day, five

treatment-days per week), but will be most often delivered over 5-weeks (2-study treatment days each week, two rTMS-sessions each treatment day). Urine drug tests will be done at visits 1, 5, and 10 and at both follow-up visits. Urine drug tests may be done at additional visits at the investigator's discretion based on concerns of drug or alcohol use that may reduce the safety of study-treatment.

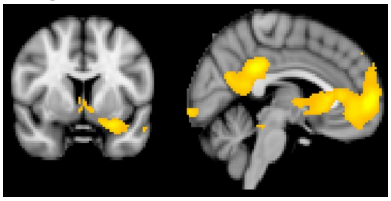
fMRI Paradigm: Participants will undergo two fMRI scans (prior to the first rTMS treatment and prior to the final rTMS treatment). Participants will be instructed to abstain from cannabis and alcohol for 24 hours prior to scanning to avoid acute intoxication during procedures and will be asked to provide a saliva sample to verify abstinence from recent cannabis use through use of SalivaConfirm® testing (Confirm Biosciences, Inc.). Pre- and post-fMRI state craving measures will be collected. Each imaging session will include a structural and cue reactivity task scan and lasts approximately 20-40 minutes total.

T1-weighted structural: A high-resolution anatomical scan (magnetization prepared rapid gradient echo) will be acquired, to allow subsequent registration to functional images and region-of-interest (ROI) definition (parameters: repetition/echo time (TR/TE)= 1900/2.26 ms; flip angle (FA)= 9°; field of view (FOV)= 256 mm^2; voxel size= 1 mm^2; 192 contiguous 1-mm-thick slices).

The Cannabis Cue Reactivity (CR) Task. We will use a validated fMRI cannabis cue reactivity task (50). During the cannabis CR task, we will show participants pseudo-randomly interspersed images of cannabis (i.e., cannabis plant, cannabis-related paraphernalia) and neutral (e.g., pinecone, trumpet) images, visual control images (i.e., blurred images), and a fixation cross (Figure 4). The cannabis stimuli are matched by color, hue, and complexity. Blurred images and the fixation crossed trials are used as contrasts to evaluate attention and non-cannabis specific effects. The task reliably elicits a response in reward regions, including the bilateral medial prefrontal, striatum, anterior cingulate, subcallosal, precuneus, and posterior cingulate cortex in heavy cannabis-users (Figure 5). Stimuli are presented in six 120-s epochs, each consisting of four 24-s blocks of an image type (one block each of cannabis, non-cannabis control, and fixation). Each block is followed by a 6-s washout period, allowing the hemodynamic response from the previous block to decline before the next is presented. A 12-m gradient-echo EPI sequence will be acquired (parameters: repetition/echo time (TR/TE)= 2200/35 ms; flip angle (FA)=90°; field of view (FOV)= 220 x 220 mm; voxel size= 3.00 x 3.00 mm; 37 contiguous 3-mm-thick slices). A magnetic **fieldmap** will also be acquired to allow geometric unwarping and cost-function masking of EPI images induced by magnetic field inhomogeneities. The main contrast of interest for analyses will be activation during the cannabis vs. neutral trials.

Figure 4

Figure 5



Use of this paradigm elicits: Robust activation in reward regions including the medial prefrontal cortex and anterior cingulate in cannabis, compared to neutral, stimuli in heavy cannabis users.

Behavioral Platform: We will use the three-session version of Brief Marijuana Dependence Counseling BMDC (51) for our behavioral platform, and will follow the protocol outlined in the manual published by NIDA (52). Briefly, we will generate personalized feedback reports (PFRs) by collecting the following measures: Marijuana Use Summary Sheet, Self-Efficacy Questionnaire, Marijuana Problem Scale, and Reasons for Quitting Questionnaire during the baseline visit. These PFRs are used by the clinician to facilitate discussion in the three MET sessions, which will occur most often at treatment visits 2, 4, and 10, regarding participants' frequency of cannabis use, concerns related to use, possible reasons for changing use, high risk use situations, and short and long-term goals related to reduction of use. To ensure our behavioral platform is delivered with fidelity, we will audio-tape sessions for review and fidelity ratings. The audiotapes will be reviewed and assessed for fidelity utilizing techniques developed in the Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency (MIASTEP) manual (53).

Follow-up: There will be follow up visits 2-weeks and 4-weeks after treatment completion. Participants will be asked about cannabis use and urine drug tests will be performed.

Open label extension: Those participants not achieving abstinence following the four-week follow-up visit, who are interested, will be offered 20 additional treatments of rTMS in an open label fashion. Treatments will

be delivered in the same fashion as above, however only active treatment will be given (there will be no possibility of sham treatment). Craving, and other data may be collected in the same fashion as during the primary experiment.

Recruitment and Participant Population:

Recruitment: Participants will be recruited through media advertisements (such as Craigslist and facebook) using trialfacts, a professional study-recruitment agency. Ads will recruit heavy cannabis users who are interested in quitting. Participants will undergo a phone screen to ensure they meet basic eligibility criteria (See included phone screen).

Participant Population:

Inclusion Criteria: 1) Participants must be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments. **2)** Participants must be between the ages of 18 and 60. **3)** Participants must meet DSM-5 criteria for at least moderate Cannabis Use Disorder, with use of at least 20 / last 28 days. **4)** Participants must express a desire to reduce cannabis use or quit. **5)** Participants must have a positive UDS for cannabis during their enrollment visit (confirming they are regular users).

Exclusion Criteria: 1) Participants must not be pregnant or breastfeeding. **2)** Participants must not meet moderate or severe use disorder of any other substance with the exception of Tobacco Use Disorder. **3)** Participants must not be regularly taking any medications that have central nervous system effects. **4)** Participants must not have a history of/or current psychotic disorder or bipolar disorder. **5)** Participants must not have any other Axis I condition requiring current treatment and must have a $HRSD_{24}$ ≤10 indicating no clinically relevant depressive symptoms. **6)** Participants must not have a history of dementia or other cognitive impairment. **7)** Participants must not have active suicidal ideation or a suicide attempt within the past 90 days. **8)** Participants must not have any contraindications to receiving rTMS or MRI (e.g. metal implanted above the head, history of seizure, any known brain lesion). **9)** Participants must not have any unstable general medical conditions.

DATA MANAGEMENT AND STATISTICAL ANALYSIS: Data will be managed using REDCap and all data entry will take place directly in REDCap. The only required paper items will be the paper calendar for the Timeline Follow-Back, consent and HIPAA documents. There will however be emergency paper backups of the database should the database be unavailable for any reason. If data is collected on paper, the information will be immediately transferred to the REDCap database, and the paper record will be safe-shredded.

Statistical Analysis: Baseline demographic and clinical measures will be compared across treatment groups using standard statistical methods (i.e., categorical variables compared using Pearson chi square test of independence; continuous variables compared using univariate ANOVAs). Characteristics that display imbalance at the baseline measure, association with the dependent variable, or are known to be predictive of cue induced craving, reactivity, or cannabis-use outcomes will be assessed for inclusion as covariates in the final models. To test our primary hypothesis that a full course of active excitatory rTMS will reduce cue induced craving as compared to sham rTMS (Aim 1), generalized linear mixed effects models will be constructed to estimate treatment group differences in craving scores. Overall statistical significance for the effects of treatment group, time, and their interaction will be assessed using a likelihood ratio test that compares the final model, to a model consisting of an intercept term alone. The hypothesis that those receiving active rTMS will have decreased craving will be tested using model-based estimates to construct group level comparisons across all the planned time points. Normality of residuals will be tested for these models and when found in error, appropriate transformations or non-parametric methods will be conducted. For Aim 2 (evaluating the impact of rTMS on cannabis CR), BOLD response during the cannabis cue vs. neutral cue trials will be the primary contrast of interest to test hypotheses. Where significant differences are observed, parameter estimates from task-based models, from each ROI will be extracted and relations with clinical endpoints examined. For our exploratory Aim: The primary analysis will involve preliminarily investigating the efficacy of active rTMS, compared to sham rTMS in increasing the proportion of cannabis abstinent participants during the final two weeks of study treatment (four-week follow-up). A combination of self-reported abstinence from

marijuana during the final two study weeks (via Timeline Follow-Back) as well as a ratio of the creatinine corrected UCTs at the four week follow-up visit divided by the creatinine corrected UCT from the two week follow-up of <0.5 (used in (10-12)) should be sufficient to assign abstinence (yes/no) and assess the overall treatment effect. Logistic regression models will be used to assess end of study abstinence proportions across treatment assignments. Primary analysis models will be reported both unadjusted and adjusted for significant clinical covariates (determined as associated with abstinence from the baseline analysis as well as known clinical confounders). All statistical analysis will be conducted using SAS/STAT version 9.4 (SAS Institute Inc. 2015. SAS® 9.4 Statements: Reference, Fourth Edition. Cary, NC: SAS Institute Inc.).

Missing Data and Attrition. Missing data in longitudinal studies can be a problematic feature but can be mitigated through study design considerations. In order to minimize missing data and study attrition, study simplification and enhanced communication between study staff and participants will be emphasized. We will make every effort to prevent attrition (e.g., phone/text visit reminders, participation compensation, reinforcing adherence to the study protocol at each visit). In addition, in keeping with the Intent to Treat Principle, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who fail to adhere to randomized assignment or stop participating in the study assigned intervention.

Sample Size Justification: The primary focus of this study is to show evidence, with sufficient strength, that treatment with active rTMS will result in decreased cue induced craving (Aim 1), and decreased BOLD response in reward network structures during a cue-reactivity fMRI paradigm (Aim 2) in CUD participants treated with either active or sham rTMS. For Aim 1: Within subject craving measures tend to be highly correlated when measured closely in time and thus we assume a conservative ICC of ρ=0.75 (previous CUD studies range ρ=0.60-0.75) with a standard deviation of ≈ 12.2. We intend to detect a clinically meaningful craving score difference between the two treatment groups of 8.5 (Cohen's d=8.5/12.2≈0.7). This is a conservative estimate given that recent multi-session rTMS treatment trials have yielded larger effect sizes on craving (d=0.98 (7) in alcohol users, and d=0.84 (9) in cocaine users). In the proposed study we will measure increased craving (via MCQ total score) following the presentation of a validated cannabis cue paradigm both before and after a treatment course of rTMS. Under the assumption of independent observations, a total sample size of 32 participants equally allocated to each treatment assignments will provide 80% power with a type 1 error rate of 5% to detect the stated effect size of 0.7. However, the effective sample size in a repeated measures data setting is reduced when assuming an ICC of 0.75. The number of participants per group required is therefore estimated to be n=27. Additionally, we need to adjust for study attrition between randomization and the 4-week follow up visit. Assuming an attrition rate of up to 25%, a sample size of **36 participants randomized to each treatment group** (**n=72 total**) will provide adequate power to detect the primary aim effect size of d=0.7 between those receiving active and sham rTMS. For Aim 2: In a within subjects investigation of nicotine use disordered participants undergoing a single session of rTMS, there was a significant effect on BOLD response to smoking cues (see figure 2, Preliminary Studies section). If we assume that, as with previous study of cue induced BOLD reactivity in smokers using rTMS, our effects are of medium to large size (e.g. d=0.7-0.8) with alpha =5% (2-tailed), a sample of **36 randomized participants in each group will result in greater than 80% power for detecting effects of treatment on CR-BOLD response**. In sum, we are confident that the proposed randomized sample size of 72 participants will be sufficient to test Aims 1 and 2. For our exploratory Aim, our recent, non-contingency management based medication trials for cannabis cessation have shown varying placebo abstinence rates (defined as ≤50 ng/ml THCCOOH UCT) at the end of study (EOS) treatment (5-15%) (38, 39, 41). Since we are only hoping to provide preliminary data to power a more definitive study, our sample is not designed to sufficiently answer this question definitively. Despite this fact we will still have power to detect a large effect on abstinence. An rTMS abstinence rate of at least 30% greater than placebo at the end of study treatment under the most conservative conditions, at a 10% placebo abstinence rate, a randomized sample size of 36 participants in each treatment group will provide 80% power with a type 1 error of 5% to detect this difference at the end of this pilot study.

Relapse, Drop-Out and Clinical Deterioration: Every effort will be made to re-engage participants who miss appointments. Clinical deterioration, such as exacerbation of psychiatric or substance use disorder, will be assessed on a case-by-case basis by Dr. Sahlem and appropriate referral will be made. Participants will be considered dropouts if they do not come back to treatment after receiving three phone calls. A last observation carried forward will be used for each outcome in participants who formally withdraw from the study or stop participating.

Strategies to ensure a robust and unbiased approach: The proposed study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of treatment condition; the use of a validated sham control; blinding; use of validated laboratory and interview/self-report measures and methods; explicit hypotheses and corresponding planned statistical analyses; power estimates; planned handling of retention/attrition and missing data; and careful consideration of potential confounds. All experimental details are reported in a detailed and fully transparent manner to support replication.

Consideration of gender as a biological variable: Though this trial is not powered to detect gender differences, we will perform our analysis using gender as a potential covariate, and should there be a potential gender difference found, we will be able to use that data to power a larger trial.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

Targeted/Planned Enrollment Table
Total Planned Enrollment 72 (Randomized)

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	1	3	4
Not Hispanic or Latino	4	4	68
Ethnic Category: Total of All Subjects*	72		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	8	17	25
White	12	30	42
Racial Categories: Total of All Subjects*	22	45	72

We will attempt to recruit all potential participants from the community. We will not exclude anyone based on gender, ethnicity, or race. The above estimated enrollment numbers are based on our experience with this clinical population. We have randomized a total of 43 participants at MUSC, and so plan on randomizing an additional 28 participants at Stanford. Assuming two participants will be lost to follow-up between an enrollment visit and randomization visit, we plan on enrolling a total of 30 additional participants at Stanford to randomize 28.

Compensation and Retention: Participants will be compensated based upon attending visits as well as given additional compensation using a contingency management paradigm. Participants will be given $40 for their baseline visit. Participants will then be compensated $25 for each rTMS/BMDC visit they attend during the acute treatment phase (10 visits), $80 for attending the two-week follow-up visit, and $100 for attending the four-week follow-up visit. Additionally, “fishbowl” contingency management will be used (an average of $175, a minimum of $78, and a maximum of $350) for participants who attend all appointments in order). For “fishbowl” contingency management, participants who present at their scheduled visits will receive chances to draw from a bowl containing 250 chips that are assigned a certain value (230 chips denote $1, 18 chips denote $10, one chip denotes $50, and one chip denotes $100). Participants will start with one draw on the first TMS visit and the number of token picks will increase by 1 for every scheduled visit attended including follow up visits. If participants miss a scheduled visit, then token picks will start back at 1 token, and the process repeats. If completing all visits and assessments, participants could potentially receive a total of $645. Participants will be

compensated at the end of each visit, and thus will receive pro-rated compensation as they complete the study.

There will be no additional compensation for those choosing to receive open label treatment following the experiment.

b. Sources of Materials

Assessments:

Data collection:

Schedule of visits and assessments and Data Collection:

	Assessment domain	Screen	Baseline	Final rTMS Visit	2-week F/U	4-week F/U
Screening and Enrollment Eligibility:						
MINI International Neuropsychiatric Interview (MINI) for the DSM-5 (54): Structured interview to determine DSM-5 based psychiatric conditions.	**Psychiatric history**	**X**				
Urine Pregnancy Test (bHCG)	**Pregnancy status**	**X**				
Hamilton Rating Scale for Depression 24-Item ($HRSD_{24}$)(55): Clinician administered measure of depressive symptoms.	**Depressive symptoms**	**X**		**X**	**X**	**X**
The Cannabis Use Disorder Identification Test-R (CUDIT-R)(56): Validated measure assessing severity of disordered cannabis use.	**Severity of Cannabis Use**	**X**				
Cannabis Cue-Induced Craving (Aim 1): Primary outcome: Change in MCQ score during cannabis cue paradigm. **Secondary outcome:** Average weekly change in MCQ assessed during each TMS treatment session.						
The Marijuana Craving Questionnaire (MCQ) (57): Validated measure of cannabis craving. **Collected before and after each cannabis cue exposure.**	**Provoked Cannabis Craving**		**X**	**X**	**X**	**X**
Activation of Reward Structures (Aim 2): Primary outcome: Percent signal change in BOLD response during cue-reactivity fMRI paradigm.						
Substance Use Outcomes (Exploratory Aim): Primary outcome: Number of participants who are abstinent by TLFB for the last 2 weeks of the study with a ratio of four-week to two-week creatinine corrected urine THCCOOH of <0.5. The THCCOOH ratio is able to accurately predict no new cannabis use (10-12). **Secondary outcomes:** change in a) creatinine corrected cannabis level (ng/ml) and; b) subjective use measured by TLFB (number of days used per week and number of cannabis use sessions per week).						
Time Line Follow Back (TLFB) (58): Calendar-based instrument designed to assess substance use.	**Self-Reported Substance Use**	**X**	**X**	**X**	**X**	**X**
Urine Drug Test with Creatinine Corrected Cannabis Level (Collected on the 1st, 5th and 10th rTMS visit, and at follow-up visits)	**Objective Substance use**	**X**	**X**	**X**	**X**	**X**

Delayed Discounting Task (67): Participants choose between receiving hypothetical money immediately or more money if they wait longer.	**Cognitive Control**		**X**	**X**		
Cannabis Withdrawal Scale (59): Validated questionnaire that looks at symptoms of withdrawal.	**Cannabis Withdrawal**		**X**	**X**	**X**	**X**

PROTECTION OF HUMAN PARTICIPANTS

1. PARTICIPANT CHARACTERISTICS AND RISK MITIGATION STRATEGIES

Admission into the study is open to men and women and to all racial and ethnic groups whose age is between 18-65. We will recruit a total of seventy-two cannabis use disordered participants from the community and randomize them to receive either active or sham rTMS.

a. General Inclusion / Exclusion Criteria

Inclusion Criteria:

1) Participants must be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.

2) Participants must be between the ages of 18 and 60.

3) Participants must meet DSM-5 criteria for at least moderate Cannabis Use Disorder, with use of at least 20 out of the last 28 days.

4) Participants must express a desire to reduce cannabis use or quit.

5) Participants must have a positive UDS for cannabis during their enrollment visit (confirming they are regular users).

Exclusion Criteria:

1) Participants must not be pregnant or breastfeeding.

2) Participants must not meet moderate or severe use disorder of any other substance with the exception of tobacco.

3) Participants must not be on any medications that have central nervous system effects.

4) Participants must not have a history of/or current psychotic disorder or bipolar disorder.

5) Participants must not have any other Axis I condition requiring current treatment and must have a $HRSD_{24}$ ≤10 indicating no clinically relevant depressive symptoms.

6) Participants must not have a history of Dementia or other cognitive impairment.

7) Participants must not have active suicidal ideation, or a suicide attempt within the past 90 days.

8) Participants must not have any contraindications to receiving rTMS or MRI (e.g. metal implanted above the head, history of seizure, any known brain lesion).

9) Participants must not have any unstable general medical conditions.

b. Recruitment and Informed Consent

We will use two primary recruitment methods to recruit from the community. We will work with trialfacts, a third-party study recruitment company, to advertise on social media platforms. We will perform a basic phone

screen for interested participants who are either referred from trialfacts, or are referred by Stanford clinicians. Those participants who meet basic inclusion/exclusion criteria based on the phone screen will be scheduled for either an in-person visit or an e-visit through Stanford's secure Zoom account. During the e-visit, participants will undergo a second level of screening with a research specialist. That meeting may occur directly after the phone screen, or immediately prior to the full enrollment visit. During that screening visit participants will be given a screening consent to review, and if interested will go through it with a qualified study team member. If understanding all of the risks of benefits of proceeding with a screening visit, the research staff will collect information in order to determine preliminary eligibility. Those participants who remain eligible after this level of screening will meet with one of the study physicians, most often the PD, who will review a full consent document. Participants completing this visit remotely will be asked to find a private location, and those coming in person will be given an informed consent document to review in a private office. The informed consent form includes a detailed description of the study procedures, along with statements regarding participants' rights to withdraw from the procedure at any time without consequences. After the participant reviews the informed consent document, one of the study physicians, most often the PD, will cover all of the key elements of informed consent with the participant and ensure they have an understanding of the RBA of participating in this study. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent. We will check the Stanford epic chart for all participants who have an MRN and will create an MRN for all those participants who do not.

c. Sources of Materials

Research material obtained from individual participants includes urine samples, fMRI-data, questionnaires, and interviews with study personnel. Additional information will be obtained from the Stanford Epic chart if the patient has one. All behavioral data will be directly input into REDCap which is a secure, password protected web-based data collection system. The only written research material will be the calendar from the Timeline Follow-Back. This paper record will be stored in a locked filing cabinet in an office at 401 Quarry Road that is locked when it is not in use. Urine samples will be delivered to the Stanford laboratory labeled only by participant ID, age, and gender. They will process the urine sample and send to the MUSC laboratory (contract submitted and approved), who will deliver results via secure email. MRI data will be kept in secure Stanford servers.

d. Potential Risks and Risk Mitigation Strategies:

Potential risks of rTMS: The use of high frequency rTMS has been FDA approved for the treatment of major depressive disorder since 2008. Our stimulation parameters (4000 pulses, 10Hz, 5-Seconds on 10-Seconds off) are nearly identical to the FDA approved protocol (3000 pulses, 10Hz, 4-Seconds On, 8-Seconds off), and have been used safely in many investigations including those in depression(25), pain(45), and addictions(46, 60). We chose to use the slightly longer train duration of 5-seconds rather than 4-seconds due to its demonstrated safety and efficacy in many trials including our preliminary single session trial with cannabis users. We chose to increase the number of pulses in each treatment from 3,000 to 4,000 pulses, as we wanted to ensure we gave an adequate dose of rTMS. The common clinical dose of rTMS in depression is 36 treatments with 3000 pulses per treatment, for a total of 108,000 pulses(23). We will deliver a total of 20 study-treatments with 4,000 pulses per treatment, for a total of 80,000 pulses. We subsequently will be giving a lower total dose to each participant than is commonly given to patients being treated for depression. We may deliver our twenty treatments in as few as two weeks which also differs from the standard FDA approved protocol (treatment may be accelerated). Accelerated treatment paradigms have been safely delivered in both depression(25-27, 61), and addictions (62, 63) populations without any clear adverse effect.

Risk of Seizure: The most serious risk associated with the use of rTMS is seizure. Since the adoption and widespread use of standard safety guidelines in 1997 (64), there have only been a few documented seizures. The risk of seizure has been estimated to be less than 1:30,000 treatments, (or less than 1:1000 courses of treatment), which is lower than the risk of seizure associated with pharmacologic antidepressants(65). The risk of seizure is related to the various stimulation parameters (intensity, frequency, train duration), location of

application, pre-existing risk of seizure, and substance/medication factors. In order to mitigate the risk of seizure we will carefully individualize the intensity of stimulus (by performing a resting motor threshold determination), treat using standard treatment protocols (used safely in other studies), and exclude potential participants at higher risk of seizure (those with a past history of seizures, those with known CNS lesions, those in withdrawal from alcohol or benzodiazepines etc). Neither cannabis use or withdrawal are known to increase the risk of seizure, and subsequently we do not believe concurrent use of cannabis, or early abstinence from regular cannabis use will result in any increased risk of seizure. In the very rare event rTMS causes a seizure, removing the coil is typically sufficient to stop the seizure, and there is no increased risk of subsequent seizures.

Risk of site discomfort and headache: Two relatively common risks associated with the use of rTMS include the risk of mild transient site discomfort during treatment (most patients), and the risk of post treatment headache (Approximately 5%). Both of these potential side effects are typically mild. In terms of mitigating site discomfort, we will slowly ramp up stimulation intensity during the first three sessions. In our experience both clinically and experimentally, ramping initial sessions results in improved tolerability of treatment. Additionally, due to the anti-pain effect of rTMS participants rapidly adjust to stimulation. In the unusual circumstance that a headache is caused by rTMS, over the counter analgesics are typically sufficient to alleviate the headaches, and we will forewarn participants of the possibility of headache and the effectiveness of over the counter analgesics.

Potential hearing loss: The discharge of the TMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to rTMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Foam earplugs can protect against these changes and will be worn during rTMS sessions.

Safety in the case of pregnancy: This protocol will exclude pregnant women. Pregnancy status will be confirmed during the baseline visit with a urine pregnancy test, and we will only include participants if they are willing to use an effective form of birth control.

Potential Risks of MRI: The risk from magnetic resonance imaging (MRI) is low. No radiation or x-rays are used in making pictures of the brain during MRI. Participants cannot have an MRI scan if they have metal in the skull, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. The major potential risks are primarily for those individuals who have metallic implants, or pacemakers. These individuals will be excluded from the study. Other potential hazards of MRI scanning include: collision hazards, noise, body temperature changes, helium, and nitrogen hazards. The MRI facility is tested regularly by internal and external safety monitoring teams. These risks are minimal, and within FDA guidelines. We will guard against scanning anyone with implanted metal by screening all potential participants thoroughly. Although the MRI scanner is open on both ends, some people become anxious when entering the MRI scanner due to the feeling of being enclosed. We will exclude those participants who report claustrophobia, and immediately remove participants undergoing scans if they feel uncomfortable. There is a theoretical risk of harm to an unborn child and consequently all women of child-bearing potential will be given a urine pregnancy test prior to the scanning procedures, and all women of childbearing age must be on a reliable form of contraception.

Potential risks of cue Induced craving paradigm: Drug cues are known to increase craving, and subsequently the use of a cannabis cue paradigm will likely temporarily increase craving for cannabis(49). We will mitigate the risk of increased craving in two ways. First, our cannabis cues will all be given while participants are closely monitored by study staff, eliminating the possibility of participants immediately going to use cannabis. Second, we will continually assess craving using the Marijuana Craving Questionnaire until participants are within 20% of baseline craving. We will ask them to stay until they have reached this threshold of craving in order to reduce the chances of them leaving the appointment and immediately using cannabis. Should participants have elevated craving beyond 1-hour post cue exposure we would have one of the study physicians meet with the patient and provide counseling to prevent possible excess use.

Risks of Motivational Enhancement Therapy (MET): Motivational enhancement therapy is well tolerated, and rarely associated with adverse effects (owing to its supportive, non-judgmental approach). Nonetheless, it is possible that participants will feel distressed while discussing sensitive topics. We mitigate this risk by having

a trained therapist deliver MET—most often the PD. The study-therapist will be trained on techniques to reduce any distress experienced by the participant.

Safety plan for suicidal or decompensated participants: Should any patient report suicidality on the Hamilton Depression scale, the MINI, or in any other manor, the PD or covering physician will evaluate the participant and make any appropriate referral.

2. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECT AND OTHERS

All participants will receive a 3-session behavioral intervention with demonstrated efficacy in the treatment of Cannabis Use Disorder (Brief Marijuana Dependence Counseling). This treatment will be provided at no charge. Participants will also have the ability to receive study-rTMS, which may reduce their craving for cannabis or help them reduce their cannabis use. In addition to the potential direct benefits of participation in this study, participants will also help investigators understand the utility of rTMS as a potential treatment for Cannabis Use Disorder.

3. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information that can improve treatment for future patients with Cannabis and other substance use disorders.

4. RISK BENEFIT ASSESSMENT FOR THE PROPOSED RESEARCH

All of the procedures we will perform as part of this trial are low-risk, and each said risk has been minimized. Each participant will receive a standard of care behavioral treatment for Cannabis Use Disorder, and a promising candidate-treatment. We subsequently believe that the risk-benefit ratio is favorable for each individual participant. We also believe the data obtained in this trial has the potential to benefit society by developing this candidate-treatment.

5. DATA AND SAFETY MONITORING PLAN *This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html). A detailed DSMP will be developed and approved by NIH program staff prior to study initiation.*

a. Summary of the Protocol.

This application proposes to investigate the effects of rTMS on craving and cannabis use in Cannabis Use Disordered participants. The primary outcomes of interest are cannabis cue induced craving (Aim 1), and cue reactivity in reward network areas (Aim 2). Inclusion/exclusion criteria are outlined above. Power calculations and sample sizes are in the Data Analysis Plan section above.

b. Trial Management.

The study will be managed from the Brain Stimulation Lab within the Department of Psychiatry and Behavioral Sciences at Stanford University. The target population is described above in the inclusion/exclusion criteria.

c. Data Management and Analysis.

Data will be entered by research team-members directly into REDCap, and fMRI data will be kept on secure Stanford servers.

d. Quality Assurance.

We will conduct quarterly data audits. Confidentiality protections are outlined above.

e. Regulatory Issues.

Potential conflicts of interest will be reported using the NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented,

and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research specialist will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research specialist will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

f. Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a medical treatment that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect OR
- Requires intervention to prevent one of the above outcomes.

g. Documentation and Reporting.

AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Review of Adverse Events: Adverse events (AEs) will be assessed at each visit by study personnel. The type of AE, severity of AE, and the relationship to the application of rTMS will be recorded. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) rules. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research team will notify the Stanford Institutional Review Board (IRB) within 24 hours.

Other adverse events will be reported to the Stanford IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the Stanford IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

h. Trial Safety.

The potential risks and benefits and methods to minimize these risks are outlined above. The research team will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Study procedures will follow the FDA’s Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Dr.Sahlem.

An interim analysis is not planned at this time.

i. DSM Plan Administration.

Dr. Sahlem will be responsible for monitoring the study and will participate in weekly study team meetings.

j. DSM Board.

A Data Safety and Monitoring Board will be formed to monitor both the rate and severity of adverse events. This panel will include an expert in addictions clinical-trials (Keven Gray MD), an expert in brain stimulation (Baron Short MD MSCR), an expert in neuroimaging (Lindsay Squeglia PhD), and a biostatistician with expertise in addictions clinical trials (Nathaniel Baker MS). The DSM Board will meet twice-yearly while the study is recruiting.

6. CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

F. REFERENCES/LITERATURE CITATIONS

1. Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, Jung J, Pickering RP, Ruan WJ, Smith SM, Huang B, Grant BF. Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. JAMA psychiatry. 2015:1. doi: 10.1001/jamapsychiatry.2015.1858.
2. SAMHSA. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration, 2015 [Internet]. 2017.
3. Bellamoli E, Manganotti P, Schwartz RP, Rimondo C, Gomma M, Serpelloni G. rTMS in the treatment of drug addiction: an update about human studies. Behavioural neurology. 2014;2014:815215. doi: 10.1155/2014/815215. PubMed PMID: 24803733; PMCID: 4006612.
4. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Annals of the New York Academy of Sciences. 2014;1327:79-93. doi: 10.1111/nyas.12479. PubMed PMID: 25069523; PMCID: 4206564.
5. Wing VC, Barr MS, Wass CE, Lipsman N, Lozano AM, Daskalakis ZJ, George TP. Brain stimulation methods to treat tobacco addiction. Brain stimulation. 2013;6(3):221-30. doi: 10.1016/j.brs.2012.06.008. PubMed PMID: 22809824.
6. Barr MS, Farzan F, Wing VC, George TP, Fitzgerald PB, Daskalakis ZJ. Repetitive transcranial magnetic stimulation and drug addiction. International review of psychiatry. 2011;23(5):454-66. doi: 10.3109/09540261.2011.618827. PubMed PMID: 22200135.
7. Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. Addiction. 2010;105(1):49-55. doi: 10.1111/j.1360-0443.2009.02777.x. PubMed PMID: 20078462.
8. Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, Zangen A. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biological psychiatry. 2014;76(9):742-9. doi: 10.1016/j.biopsych.2014.05.020. PubMed PMID: 25038985.
9. Terraneoa AL, Lorenzo; Saladinie, Marina; Ermanie,Mario; Boncib, Antonello; Gallimbertia, Luigi. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. European Neuropsychopharmacology. 2015. doi: 10.1016/j.euroneuro.2015.11.011.
10. Huestis MA, Cone EJ. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. Journal of analytical toxicology. 1998;22(6):445-54. PubMed PMID: 9788519.
11. Smith ML, Barnes AJ, Huestis MA. Identifying new cannabis use with urine creatinine-normalized THCCOOH concentrations and time intervals between specimen collections. Journal of analytical toxicology. 2009;33(4):185-9. PubMed PMID: 19470219; PMCID: PMC3159564.
12. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, Buffkins K, Kyle M, Adusumalli M, Begovic A, Rao S. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012;37(7):1689-98. doi: 10.1038/npp.2012.14. PubMed PMID: 22373942; PMCID: 3358737.
13. Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. Journal of substance abuse treatment. 2008;35(4):362-8. doi: 10.1016/j.jsat.2008.01.002. PubMed PMID: 18342479.
14. Vandrey R, Haney M. Pharmacotherapy for cannabis dependence: how close are we? CNS Drugs. 2009;23(7):543-53. doi: 10.2165/00023210-200923070-00001. PubMed PMID: 19552483; PMCID: PMC2729499.
15. Nordstrom BR, Levin FR. Treatment of cannabis use disorders: a review of the literature. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2007;16(5):331-42. doi: 10.1080/10550490701525665. PubMed PMID: 17882603.
16. Kadden RM, Litt MD, Kabela-Cormier E, Petry NM. Abstinence rates following behavioral treatments for marijuana dependence. Addictive behaviors. 2007;32(6):1220-36. doi: 10.1016/j.addbeh.2006.08.009. PubMed PMID: 16996224; PMCID: PMC1903379.

17. Compton WM, Pringle B. Services research on adolescent drug treatment. Commentary on "The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials". Journal of substance abuse treatment. 2004;27(3):195-6. doi: 10.1016/j.jsat.2004.07.003. PubMed PMID: 15501372.
18. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society. 1998;15(4):333-43. PubMed PMID: 9736467.
19. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. The Journal of neuropsychiatry and clinical neurosciences. 1997;9(3):471-81. doi: 10.1176/jnp.9.3.471. PubMed PMID: 9276848.
20. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biological psychiatry. 2004;55(9):882-90. doi: 10.1016/j.biopsych.2004.01.017. PubMed PMID: 15110731.
21. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE, 3rd, Schwartz T, Sackeim HA. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Archives of general psychiatry. 2010;67(5):507-16. doi: 10.1001/archgenpsychiatry.2010.46. PubMed PMID: 20439832.
22. McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, Avery D, Anderson BS, Nahas Z, Zarkowski P, Sackeim HA, George MS. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. Depression and anxiety. 2011;28(11):973-80. doi: 10.1002/da.20885. PubMed PMID: 21898711.
23. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, Brock DG, Bonneh-Barkay D, Cook IA, Lanocha K, Solvason HB, Demitrack MA. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation for Patients With Pharmacoresistant Major Depressive Disorder. The Journal of clinical psychiatry. 2014. doi: 10.4088/JCP.13m08977.
24. Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, Tendler A, Daskalakis ZJ, Winston JL, Dannon P, Hafez HM, Reti IM, Morales OG, Schlaepfer TE, Hollander E, Berman JA, Husain MM, Sofer U, Stein A, Adler S, Deutsch L, Deutsch F, Roth Y, George MS, Zangen A. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World psychiatry : official journal of the World Psychiatric Association. 2015;14(1):64-73. doi: 10.1002/wps.20199. PubMed PMID: 25655160.
25. George MS, Raman R, Benedek DM, Pelic CG, Grammer GG, Stokes KT, Schmidt M, Spiegel C, Dealmeida N, Beaver KL, Borckardt JJ, Sun X, Jain S, Stein MB. A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain stimulation. 2014;7(3):421-31. doi: 10.1016/j.brs.2014.03.006. PubMed PMID: 24731434.
26. Holtzheimer PE, 3rd, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, Epstein CM. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depression and anxiety. 2010;27(10):960-3. doi: 10.1002/da.20731. PubMed PMID: 20734360; PMCID: PMC3020591.
27. Baeken C, Vanderhasselt MA, Remue J, Herremans S, Vanderbruggen N, Zeeuws D, Santermans L, De Raedt R. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. Journal of affective disorders. 2013;151(2):625-31. doi: 10.1016/j.jad.2013.07.008. PubMed PMID: 23896317.
28. Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(33):14811-6. doi: 10.1073/pnas.1007779107. PubMed PMID: 20679212; PMCID: 2930456.
29. Hanlon CA, Dowdle LT, Austelle CW, DeVries W, Mithoefer O, Badran BW, George MS. What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. Brain research. 2015. doi: 10.1016/j.brainres.2015.02.053. PubMed PMID: 25770818.
30. Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. Resting state functional connectivity in addiction: Lessons learned and a road ahead. NeuroImage. 2012;62(4):2281-95. doi: 10.1016/j.neuroimage.2012.01.117. PubMed PMID: 22326834; PMCID: 3401637.
31. Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. NeuroImage. 2010;49(3):2536-43. doi: 10.1016/j.neuroimage.2009.10.088. PubMed PMID: 19913102; PMCID: 2818484.
32. Charboneau EJ, Dietrich MS, Park S, Cao A, Watkins TJ, Blackford JU, Benningfield MM, Martin PR, Buchowski MS, Cowan RL. Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: preliminary results. Psychiatry research. 2013;214(2):122-31. doi: 10.1016/j.pscychresns.2013.06.005. PubMed PMID: 24035535; PMCID: 3904759.
33. Cousijn J, Goudriaan AE, Ridderinkhof KR, van den Brink W, Veltman DJ, Wiers RW. Neural responses associated with cue-reactivity in frequent cannabis users. Addiction biology. 2013;18(3):570-80. doi: 10.1111/j.1369-1600.2011.00417.x. PubMed PMID: 22264344.

34. Goldman M, Szucs-Reed RP, Jagannathan K, Ehrman RN, Wang Z, Li Y, Suh JJ, Kampman K, O'Brien CP, Childress AR, Franklin TR. Reward-related brain response and craving correlates of marijuana cue exposure: a preliminary study in treatment-seeking marijuana-dependent subjects. Journal of addiction medicine. 2013;7(1):8-16. doi: 10.1097/ADM.0b013e318273863a. PubMed PMID: 23188041; PMCID: 3567235.
35. Li X, Malcolm RJ, Huebner K, Hanlon CA, Taylor JJ, Brady KT, George MS, See RE. Low frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex transiently increases cue-induced craving for methamphetamine: a preliminary study. Drug and alcohol dependence. 2013;133(2):641-6. doi: 10.1016/j.drugalcdep.2013.08.012. PubMed PMID: 24028801; PMCID: 4196687.
36. Kober H, DeVito EE, DeLeone CM, Carroll KM, Potenza MN. Cannabis abstinence during treatment and one-year follow-up: relationship to neural activity in men. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2014;39(10):2288-98. doi: 10.1038/npp.2014.82. PubMed PMID: 24705568; PMCID: 4138744.
37. Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. NeuroImage. 2005;26(2):480-92. doi: 10.1016/j.neuroimage.2005.02.012. PubMed PMID: 15907305.
38. McRae-Clark AL, Baker NL, Gray KM, Killeen TK, Wagner AM, Brady KT, DeVane CL, Norton J. Buspirone treatment of cannabis dependence: A randomized, placebo-controlled trial. Drug and alcohol dependence. 2015;156:29-37. doi: 10.1016/j.drugalcdep.2015.08.013. PubMed PMID: 26386827; PMCID: PMC4633378.
39. McRae-Clark AL, Baker NL, Gray KM, Killeen T, Hartwell KJ, Simonian SJ. Vilazodone for cannabis dependence: A randomized, controlled pilot trial. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2016;25(1):69-75. doi: 10.1111/ajad.12324. PubMed PMID: 26685701.
40. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, McRae-Clark AL, Brady KT. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. The American journal of psychiatry. 2012;169(8):805-12. doi: 10.1176/appi.ajp.2012.12010055. PubMed PMID: 22706327; PMCID: 3410961.
41. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, Wahlquist AE, Simpson SA, Brady KT. A placebo-controlled trial of buspirone for the treatment of marijuana dependence. Drug and alcohol dependence. 2009;105(1-2):132-8. doi: 10.1016/j.drugalcdep.2009.06.022. PubMed PMID: 19699593; PMCID: PMC2789590.
42. Borckardt JJ, Nahas Z, Koola J, George MS. Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. The journal of ECT. 2006;22(3):169-75. doi: 10.1097/01.yct.0000235923.52741.72. PubMed PMID: 16957531.
43. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain stimulation. 2009;2(1):50-4. doi: 10.1016/j.brs.2008.09.006. PubMed PMID: 20539835; PMCID: 2882797.
44. Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, Nahas Z, Byrne KT, Morgan K, George MS. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: a replication study. Brain stimulation. 2008;1(2):122-7. doi: 10.1016/j.brs.2008.04.002. PubMed PMID: 19759838; PMCID: 2744083.
45. Short EB, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, George MS. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. Pain. 2011;152(11):2477-84. doi: 10.1016/j.pain.2011.05.033. PubMed PMID: 21764215; PMCID: 3199360.
46. Li X, Hartwell KJ, Owens M, Lematty T, Borckardt JJ, Hanlon CA, Brady KT, George MS. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. Biological psychiatry. 2013;73(8):714-20. doi: 10.1016/j.biopsych.2013.01.003. PubMed PMID: 23485014; PMCID: 3615051.
47. Borckardt JJ, Walker J, Branham RK, Rydin-Gray S, Hunter C, Beeson H, Reeves ST, Madan A, Sackeim H, George MS. Development and evaluation of a portable sham transcranial magnetic stimulation system. Brain stimulation. 2008;1(1):52-9. doi: 10.1016/j.brs.2007.09.003. PubMed PMID: 19424444; PMCID: 2677803.
48. Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, Long J, Sackeim HA, George MS. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: Does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? Brain stimulation. 2008;1(1):44-51. doi: 10.1016/j.brs.2007.08.006. PubMed PMID: 19424459; PMCID: 2678025.
49. McRae-Clark AL, Carter RE, Price KL, Baker NL, Thomas S, Saladin ME, Giarla K, Nicholas K, Brady KT. Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. Psychopharmacology. 2011;218(1):49-58. doi: 10.1007/s00213-011-2376-3. PubMed PMID: 21710170; PMCID: 3209966.
50. Meredith LR, Schacht, J. P., Henderson, S., & Squeglia, L. M., editor. Development of fMRI visual marijuana cue reactivity task for regular adolescent marijuana users. Poster presented at the Darby Children's Research Institute and Pediatric Research Day; 2016, March; Charleston, SC.
51. Marijuana Treatment Project Research G. Brief treatments for cannabis dependence: findings from a randomized multisite trial. Journal of consulting and clinical psychology. 2004;72(3):455-66. doi: 10.1037/0022-006X.72.3.455. PubMed PMID: 15279529.

52. Steinberg KLR, R.A.; Carroll, K.M.; McRee, B.; Babor, T.F.; Miller, M.; Kadden, R.; Duresky, D.; and Stephens,, R. Brief Counseling for Marijuana Dependence: A Manual for Treating Adults. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration; 2005.
53. Martino S, Ball, S.A., Gallon, S.L., Hall, D., Garcia, M., Ceperich, S., Farentinos, C., Hamilton, J., and Hausotter, W. Motivational Interviewing Assessment: Supervisory Tools for Enhancing Proficiency. Salem, OR: Northwest Frontier Addiction Technology Transfer Center, Oregon Health and Science University; 2006.
54. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57. PubMed PMID: 9881538.
55. Hamilton M. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry. 1960;23:56-62. PubMed PMID: 14399272; PMCID: 495331.
56. Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, Sellman JD. An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). Drug and alcohol dependence. 2010;110(1-2):137-43. doi: 10.1016/j.drugalcdep.2010.02.017. PubMed PMID: 20347232.
57. Heishman SJ, Evans RJ, Singleton EG, Levin KH, Copersino ML, Gorelick DA. Reliability and validity of a short form of the Marijuana Craving Questionnaire. Drug and alcohol dependence. 2009;102(1-3):35-40. doi: 10.1016/j.drugalcdep.2008.12.010. PubMed PMID: 19217724; PMCID: 2694410.
58. Sobell LC aSM. Timeline Follow-Back. Measuring Alcohol Consumption1992. p. 41-72.
59. Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. Drug and alcohol dependence. 2011;119(1-2):123-9. Epub 2011/07/05. doi: 10.1016/j.drugalcdep.2011.06.003. PubMed PMID: 21724338.
60. Breedlove JL, A; Back, SE; Borckardt, JJ; Taylor, JJ; Badran, BW; Sahlem, GL; Rostami, R; Brady, KT; George, MS; and Hanlon, CA., editor. 10 Hz rTMS May Reduce Pain and Craving in Prescription Opiate Dependent Individuals: a pilot study. Annual Meeting of the Society of Biological Psychiatry; May 14th-16th, 2015; Toronto, On.
61. McGirr A, Van den Eynde F, Tovar-Perdomo S, Fleck MP, Berlim MT. Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: an open label trial. Journal of affective disorders. 2015;173:216-20. doi: 10.1016/j.jad.2014.10.068. PubMed PMID: 25462419.
62. Herremans SC, De Raedt R, Van Schuerbeek P, Marinazzo D, Matthys F, De Mey J, Baeken C. Accelerated HF-rTMS Protocol has a Rate-Dependent Effect on dACC Activation in Alcohol-Dependent Patients: An Open-Label Feasibility Study. Alcoholism, clinical and experimental research. 2016;40(1):196-205. doi: 10.1111/acer.12937. PubMed PMID: 26727534.
63. Herremans SC, Van Schuerbeek P, De Raedt R, Matthys F, Buyl R, De Mey J, Baeken C. The Impact of Accelerated Right Prefrontal High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) on Cue-Reactivity: An fMRI Study on Craving in Recently Detoxified Alcohol-Dependent Patients. PloS one. 2015;10(8):e0136182. doi: 10.1371/journal.pone.0136182. PubMed PMID: 26295336; PMCID: PMC4546410.
64. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and clinical neurophysiology. 1998;108(1):1-16. Epub 1998/02/25. PubMed PMID: 9474057.
65. Janicak P, Dokucu ME. Transcranial magnetic stimulation for the treatment of major depression. Neuropsychiatric disease and treatment. 2015:1549. doi: 10.2147/ndt.s67477.

65. Heckathorn, D.D. (1997). Respondent-driven sampling: A new approach to the study of hidden populations. *Social Problems, 44*(2), 174-199.
66. Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Strong DR, Brown RA. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). Journal of experimental psychology Applied. 2002;8(2):75-84. PubMed PMID: 12075692.
67. Johnson, M. W., Bickel, W. K., Baker, F., Moore, B. A., Badger, G. J., & Budney, A. J. (2010). Delay Discounting in Current and Former Marijuana-Dependent Individuals. Experimental and Clinical Psychopharmacology, 18(1), 99–107. http://doi.org/10.1037/a0018333