A Preliminary Investigation of Two Repetitive Transcranial Magnetic Stimulation (rTMS) Strategies to Treat Cannabis Use Disorder

Study Protocol and Statistical Analysis Plan

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Protocol

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A Pilot Trial Refining the Protocol for the Use of Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Cannabis Use Disorder: Testing Two Different Treatment Locations and NeuroImaging Based Targeting.

TABLE OF CONTENTS –

SPECIFIC AIMS

Cannabis Use Disorder (CUD) is a prevalent condition[1] with substantial negative impacts on social, occupational, and health domains[2]. Further, ongoing legalization efforts may make CUD more common and impactful in the future[3]. Behavioral treatments for CUD have yielded moderate treatment effects but are not 100% effective[4], and despite some promising medications in the pipeline, a clearly effective pharmacologic agent has yet to emerge[5–12]. As such new treatment paradigms are needed for CUD.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is FDA-approved / cleared as a treatment for Major Depressive Disorder (MDD)[13–15], Obsessive Compulsive Disorder (OCD)[16], and Smoking Cessation (SC)[17]. There has been much study in the potential application of varying rTMS paradigms in the treatment of addictive disorders[18–21]—with relatively consistent clinical-behavioral effects seen when serial sessions are applied to the left dorsolateral prefrontal cortex (L-DLPFC)[22–26]. Based on this ongoing promising literature across addictive disorders our group has been developing L-DLPFC-applied rTMS as a treatment for CUD[27,28]. We recently completed a phase-2 trial which recruited N=72 treatment interested participants with CUD (mean age 30.2±9.9SD, 37.5% women) and applied 20-sessions of either active or sham rTMS as adjunctive therapy to a three session Motivational Enhancement Therapy behavioral intervention. Our preliminary results suggest a potential therapeutic effect, however prior to launching a larger phase-3 study we hope to optimize our paradigm, and also determine the feasibility and preliminary efficacy of a second promising rTMS treatment target—the ventromedial prefrontal cortex (vmPFC)—in hopes of seeing suggestions that treatment can be personalized.

Our phase-2 trial found suggestions of clinical efficacy, with those participants treated with active rTMS reporting more weeks of abstinence from cannabis following the delivery of 16-study treatments (14.86% active; 9.05% sham; RR 1.64 [0.97,2.79]) and numerically fewer days per week of cannabis use in the final two weeks of follow-up (3.67±3.09SD and 3.59±2.75SD-active; 4.67±2.50SD and 5.00±2.45SD-sham; Cohen's D at week 4 = 0.54; among completers) than those treated with sham-rTMS. Our paradigm, however, was designed to maximize feasibility and participant retention, given high levels of drop-out in early pilot work[28]. Specifically, we delivered only a total of 20-study treatments, which is a dose known to have efficacy in MDD—but lower efficacy than 36-treatments. We additionally elected to deliver treatments using a scalp-based targeting method[29] that is quickly completed, but may not target the relevant neural circuits as precisely as functionally derived targets which use functional magnetic resonance imaging (fMRI)[18,30]. Finally, there is recent data suggesting that there may be relevant variability between subjects based on which deep-brain structures are responsive to pictures of drug-cues (namely the ventral or dorsal striatum)[31–33], and that a different treatment target may be more effective at engaging the differentially dysfunctional circuitry[34,35].

In this proposed pilot trial, we subsequently hope to build on our promising results suggesting that a relatively low dose of simply-targeted L-DLPFC applied rTMS may help treatment seeking participants with CUD reduce their cannabis use—by testing the feasibility and preliminary efficacy of three refinements. The three refinements include: a) increasing the number of study-treatments delivered from 20 to 36; b) testing the ability of an fMRI task we developed (based on prior similar tasks[36,37]) to generate functional rTMS targets (which we will use for more precise targeting at two established treatment sites); and c) the preliminary comparative efficacy of applying rTMS to a second commonly targeted cortical site/circuit which may have efficacy in a different sub-type of addictions. In order to do so, we plan on recruiting N=30 treatment-interested participants with ≥moderate CUD and randomizing them to receive 36-study-treatments of rTMS applied to either the L-DLPFC or vmPFC, delivered over 6-9 weeks (two-study-treatments per visit, 18-study-treatment visits, two or three visits per week), and following them for 6-weeks. We will perform fMRI before and after study-treatment and attempt to use the pre-treatment fMRI to derive a functional rTMS target.

Aim-1 will determine the feasibility and acceptability of delivering our expanded study-treatment paradigm. We will quantify acceptibility[26], and consider our paradigm feasible if we retain >60% of our randomized sample.

Aim-2 will determine if our fMRI task is able to reliably generate a functional rTMS treatment target within the broader L-DLPFC and vmPFC structures. We will consider our task effective if the generated center of mass falls within the broader structures that we have targeted in >2/3rds of scans. We will use anatomically-derived targets[18,29] as backup should one or more participants not have a clear fMRI center of mass to target.

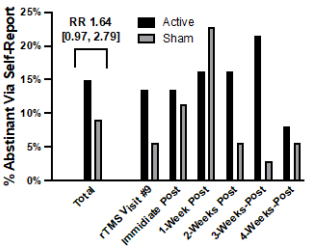
Aim-3 will determine the preliminary efficacy of the above study-treatment paradigm. We will determine whether participants treated in this pilot trial have a comparable number of weeks of abstinence and days per week of cannabis use following the delivery of 14-study-treatments, and qualitatively look at whether more dorsal or ventral striatal cue-reactivity distinguishes those who respond to L-DLPFC or vmPFC rTMS. We will also compare the results of this trial to the results of our previous Phase-2 trial.

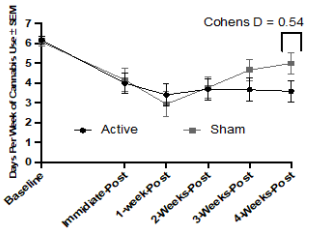
1. BACKGROUND AND SIGNIFICANCE

Cannabis Use Disorder (CUD) is a common condition with well documented adverse social, occupational, and health effects[2,38,39]. The incidence of frequent cannabis use and CUD may be increasing in the United States and worldwide[3,40] with increasing legalization and a decrease in perceived risk as potential reasons for this increase[41]. The frequency of daily cannabis use has also continually increased in prevalence in recent years in the United States—potentially further increasing the risk of an increased incidence of CUD in the future [42]. Of note, the number of people seeking treatment for CUD appears to be increasing[43], and subsequently there is likely to be an increase in demand for effective treatment in the future. Though there are promising pharmacologic treatments in the pipeline[5,6,10,44], no medication has distinguished itself as clearly effective in the treatment of CUD, and though consistently demonstrating a beneficial effect, studies testing behavioral therapies for CUD have resulted in only moderate effects to date[4]. As such, there remains a need to develop new therapeutics for CUD.

Repetitive transcranial magnetic stimulation (rTMS) works via the principles of magnetic induction and long term potentiation / depression[45–47], and is capable of focally altering circuit function in the brain[34,35,48]. Trials applying serial applications of rTMS in a variety of neuropsychiatric conditions have demonstrated that by varying the location of stimulation and the treatment paradigm it is possible to derive a therapeutic benefit in different illnesses, and rTMS is now approved / cleared by the US Food and Drug Administration for the treatment of Major Depressive Disorder (MDD)[15,49,50], Obsessive Compulsive Disorder (OCD)[16], and Smoking Cessation (SC)[17]. In line with the several indications for treatment with rTMS, there has been increasing promise that rTMS may become a therapeutic option across addictions including CUD[21]. Studies across addiction have suggested rTMS has the potential to effect behavioral aspects of addiction[25,30,51,52], engage its neurocircuitry[48,53,54], and when serial sessions of rTMS are applied have therapeutic effects. Several neurocircuit targets have emerged for study in therapeutic trials, with early promising results for the left dorsolateral prefrontal cortex (L-DLPFC)[22], the ventromedial prefrontal cortex (vmPFC)[18], the dorsomedial prefrontal cortex[19], and the anterior-insula / inferior frontal gyrus[17]—though not all trials have resulted in a beneficial effect[20].

One of the most commonly targeted cortical sites has been the L-DLPFC, which is also the most common target for MDD. Our group has since adapted the general anti-depressant treatment paradigm to treat CUD, first in non-treatment seeking participants with CUD[55], and then participants with CUD who were interested in reducing their use of cannabis[28]. Our early findings suggested that a single-session of rTMS could be feasibly applied to participants with CUD, was generally well tolerated, and may reduce the purposefulness aspect of craving[55]. In subsequent study, we found that it was infeasible to deliver daily sessions of rTMS for two-weeks in treatment interested participants with CUD, but that those participants who did attend daily sessions reported less craving and reduced cannabis use that persisted 4-weeks after receiving rTMS[28].





The findings from our preliminary work as well as therapeutic studies applying rTMS to the DLPFC of other addictive disorders[21,22,26] suggest therapeutic promise for CUD, though the need for a treatment-paradigm that differs from daily applications. Both data[56,57] and clinical experience suggest it is possible to get a therapeutic effect from rTMS even if treatments are delivered less frequently then daily, and so we completed a Phase 2 trial that randomized N=72 (mean age 30.2±9.9SD, 37.5% women) treatment-interested participants with ≥moderate CUD (8.5±1.5SD CUD criteria, 6.6±1.1SD days per week of use, 4.3±3.3SD use sessions per day) to active or sham rTMS, where study-treatments were delivered twice weekly for five-weeks. On each treatment-visit we delivered two study-treatments in the presence of cannabis-cues[58], separated by 30-minutes, for a total of 20 sessions of rTMS. We also delivered a three-session Motivational Enhancement Therapy (MET) behavioral intervention[59]. We reasoned that this lower participant burden paradigm maximized feasibility while delivering the minimum amount of rTMS needed to produce a therapeutic effect. In order to maximize future potential translation we used the original rTMS for depression treatment paradigm (10Hz, scalp-based measurement), and used a low-intensity behavioral platform. We found that the paradigm was feasible with 51 of the 72 participants completing study-treatment (28 of 37 active, 23 of 35 sham), and that those treated with active rTMS had more numeric weeks of abstinence beginning after the delivery of 16-study treatments (14.86% active; 9.05% sham; RR 1.64 [0.97,2.79]; missing data coded as non-abstinent) and numerically fewer days per week of cannabis use in the final two weeks of follow-up (3.67±3.09SD and 3.59±2.75SD-active;

4.67±2.50SD and 5.00±2.45SD-sham; Cohen's D at week 4 = 0.54; among completers) than those treated with sham-rTMS.

Despite these promising findings, there are three clearly identifiable refinements that might result in a larger effect but need to be piloted before replacing aspects of the current paradigm. First, the rTMS for MDD literature consistently suggests that there is a dose-response effect for number of delivered treatments and remission rates. Early studies specifically found that 15-20 treatments of rTMS[13,60] are sufficient for an effect (remission rates of 14-18%), but that 30-treatments are more effective (24-30%)[13,61]. A similar result is found in the single addiction trial that explores dose[26], which showed that increasing the number of treatment sessions has a large effect-size on abstinence. Next, though scalp-based measurement targeting for rTMS is a valid method, and represents the clinical-backbone of targeting, an increasing body of literature suggests that anatomical and functional regions do not fully overlap[62], that treatment response in depression may be mediated by engaging sub-sections of the DLPFC connected to a deep brain structure(the sgACC)[63], and more precise targeting of this deep brain structure using functional Magnetic Resonance Imaging (fMRI) may result in a larger antidepressant effect[64–66]. Recent studies in addictions using task-based fMRI have also shown that rTMS delivered closer to an fMRI center of mass has a larger effect than when delivered further from the functional center of mass (personal correspondence related to[18,30]). We subsequently developed an fMRI task, based on these two paradigms[36,37], both of which appear to produce a strong signal in the L-DLPFC and vmPFC in response to drug cues (when one is thinking about the long-term and short-term consequences of substance use), that may provide a more precise target for rTMS. Finally, several studies have suggested that there is a progression in addiction from reward based drug use (mediated by incentive salience circuitry) to habit based drug use (mediated by habit circuitry) and can be distinguished by a shift from ventral striatal reactivity to drug cues (primary deep reward center of the brain) to dorsal striatal reactivity (primary deep habit center of the brain)[31–33]. TMS delivered to the L-DLPFC and vmPFC differentially engage the dorsal and ventral striatum respectively[34,35], and preferential ventral striatal reactivity may distinguish those who have an effect from vmPFC stimulation[67]. We subsequently plan on building upon our paradigm by increasing the number of treatment's from 20 to 36, attempting to use an fMRI task for functional targeting, and treating at two established treatment targets to determine if there is a signal in the striatal reactivity that distinguishes which might be more effective for a given individual.

2. Innovation and Public Health Impact: CUD impacts more than 14-million Americans with well-known consequences, and few treatment options[1]. As described above, rTMS has promise as a treatment for CUD, and further refinement, as proposed in this pilot trial may further its development to a point where a phase-3 efficacy trial is warranted. As such, completing the proposed trial has the potential to further develop a new treatment for CUD, and open up a new treatment to the 14-million Americans it might benefit.

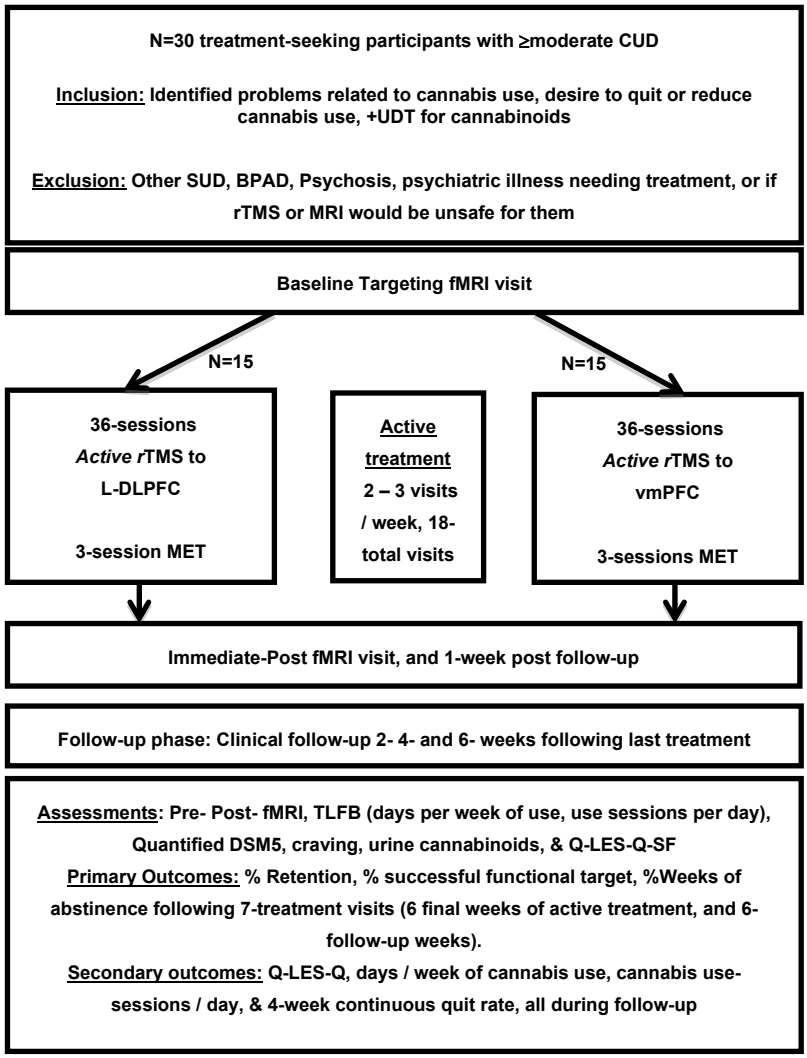
PRELIMINARY STUDIES

The study team is well experienced in rTMS[28,55], fMRI[54], and treatment trials[6] in addictive disorders. As mentioned in the body of the background and significance section, the study team has led the three trials applying L-DLPFC rTMS for cannabis use disorder[28,55,68], which have served as the justification for the present pilot trial.

3. RESEARCH DESIGN AND METHODS (including data analysis)

General Overview: The primary aims of this pilot investigation are to: a) determine whether delivering an extended course of rTMS (36 treatments instead of 20) is feasible for treatment-interested participants with CUD, b) to determine if we are able to generate an fMRI-generated target for rTMS in the L-DLPFC and vmPFC that falls within the larger anatomical structures, and to determine the preliminary efficacy / tolerability of a course of functionally-targeted rTMS in the treatment of CUD. In order to achieve these aims we plan on recruiting N=30 treatment interested participants with ≥moderate CUD from Stanford Addictions Medicine clinics (referred by providers), and also via media advertisements in the community. We will perform a phone-screen to determine preliminary eligibility, and those participants who are likely to qualify and are interested in participating in the study will undergo a comprehensive screening visit. Participants who meet enrollment criteria will then be invited to attend a baseline targeting fMRI visit where we will perform an fMRI which will generate an rTMS target. Participants will then be invited to attend a total of 18-rTMS visits (most often two or three visits per week) where we will deliver study-treatment and three sessions of MET-therapy. Finally, we will invite participants to attend four follow-up visits over the 6-weeks following their last study-treatment.

Screening (see assessments below for further details): Participants will meet with the study team either in person (in a private office), or via Stanford Secure Zoom, and complete both self-report and clinician guided measures that will assess substance use, psychiatric history, and medical history. Participants that remain eligible after the initial series of assessments will provide a urine sample for drug screening. For females of child-bearing potential, a pregnancy test will be done prior to the drug screen. Pregnant women will not be allowed to participate. Urine testing will occur at the baseline visit in the instance of a virtual (zoom) screening visit.



fMRI Visits: Participants will undergo two fMRI scans (prior to the first rTMS treatment in a Baseline targeting visit and 1-week following their final rTMS treatment visit). 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. Prior to each fMRI, participants will be trained in each of the tasks being utilized. Each imaging session will include high resolution **T1-weighted structural images** (magnetization prepared rapid gradient echo), **Echoplanar-Imaging (EPI)** functional scans during task, and magnetic **fieldmaps** to allow geometric unwarping and cost-function masking of EPI images induced by magnetic field inhomogeneities. Total scanning time at each visit will be ≈1-hour.

Reassessment of Craving Task (ROC): We have adapted a validated fMRI[36,37] task both to target rTMS and also as an outcome measure. The ROC task is an adaptation of standard cue-reactivity (where pictures of drug cues and matched neutral images are displayed, and participants are asked to passively view the images—see example photos). The reassessment of craving task, however, differs from standard cue-reactivity in that rather than passively viewing images, participants are trained to consider the short-term consequences of using the substance in a 'Now' condition (e. g. that they will enjoy being high) or the longer-term consequences of using the substance in a 'Later' condition (e.g. I won't do well in school) on different runs of the task. Prior studies have reported strong incentive-salience (e.g. vmPFC) activation during the 'Now' runs, and strong central-executive activation (e.g. L-DLPFC) during the 'later' runs—and that activation of the central-executive circuitry mediates reduction in incentive-salience structures. We will closely adapt this validated task (which was initially validated for cigarettes), by adopting the same paradigm [where a fixation cross is jittered around 4-seconds, followed by an instructional frame for 2-seconds (either 'Now' or 'Later'), followed by a cannabis image for 6-seconds, followed by a fixation cross jittered around 3-seconds, followed by a hand-pad rating for 3-seconds] and perform half of the runs as 'Now' and half as 'Later' in a pseudorandomized order. We will use a validated cannabis-cue slide-set that is customized to the individuals most common means of marijuana use (e. g. blunt, bong, vape)[69]. We

will initially use 9-minute runs of this task and perform up to 3-total runs separated by a rest-period for the participant. We may slightly increase or decrease the duration of each run based on how many trials are needed for a consistent signal but will not exceed 12-minutes during a run without a break for the participant. We will also include neutral images (such as the pinecone or trombone pictures above) and have participants passively view them in 'Look' or 'Rest' or 'Watch' runs, and may include runs of passively viewed cannabis images in 'Look' or 'Rest' or 'Watch' runs as well. We will train participants on this task prior to each scan by having them complete the task on a computer (outside of the scanner) until they report they are reliably able to think about the short- and long- term consequences of their cannabis use during the appropriate run, and passively view the neutral or cannabis images in the 'Look' or 'Rest' or 'Watch' runs. Primary Contrast: 'Now' vs. 'Later' runs.

Standard Passive Cannabis Cue-reactivity Task: Time permitting, we may also use the validated fMRI passive cannabis cue reactivity task[70] that we used in our previous trial, or parts of this task passively in blocks of the reassessment of craving task as described above. During the passive 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. 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. 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 where participants will rate their cannabis craving, allowing the hemodynamic response from the previous block to decline before the next is presented. Primary Contrast: Cannabis images vs. Neutral images.

Emotional Responsivity Task: We may, time permitting, use a validated emotional-responsivity task to measure the negative affect / stress-hyperresponsivity associated with addiction and withdrawal. This task consisting of two brief (5min 8sec) substasks[71,72], presents images of neutral, positive (happy faces) and negative (fear, anger, disgust, sadness) emotional faces either during conscious awareness (unmasked conscious awareness, stimuli presented for 500ms with a 750ms interstimulus interval), or unconscious awareness (stimuli presented for ≈10-20ms and then masked by a neutral face for 150ms and an interstimulus interval of 1233.3ms). In both cases a total of 240 stimuli will be presented in blocks of 8 consecutive images of the same emotion, with each block repeated 5 times in a pseudorandomized order. Primary Contrasts: Negative emotion (anger, fear, sad, disgust) vs neutral (to assess emotion reactivity to negative stimuli), and positive emotion (happy) vs neutral.

GoGo/NoGo task: We may, time permitting, also use a validated GoGo/NoGo fMRI task[30,73] or[72] to test inhibitory control. In the GoGo/NoGo task participants press a button in response to common, gray-colored circles (75%) and rare yellow-colored circles (12.5%), but *inhibit* responding when seeing blue-colored "NoGo" circles (12.5%). Primary Contrast: $NoGo_{Correct}$ - $RareGo_{Correct}$. Participants will undergo a behavioral training session prior to each fMRI then practice the task off-line until achieving proficiency (<5% performance improvement over two trials).

N-Back / CPT tasks: We may, time-permitting, also use validated tasks of working memory / executive function via the *N*-Back or CPT task[74]. In the *N*-Back task participants will be presented a series of letters and will be asked to press a trigger every-time the same letter is presented a certain number-back (i.e. 0 back, 1 back, and 2 back). Primary Contrast: 2-back vs. 0-back. Participants will undergo a behavioral training session prior to each fMRI then practice the task off-line until achieving proficiency (<5% performance improvement over two trials).

rTMS Sessions: We will deliver **rTMS** via a MagPro X100 or R30 double-blinded rTMS research device (MagVenture, Denmark) with a Cool-B65 coil equipped with a Localite Neuronavigation System (Sankt Augustin, Germany). We will use a standard resting motor threshold (rMT) determination to determine the TMS dose[75]. Treatment will be delivered at 120% rMT. The rTMS strategies differ in terms of the two different target circuits. In addictions there are suggestions that the incentive-salience circuitry is over-engaged in response to the substance in question and the central executive circuitry is under-engaged. Subsequently, the delivered stimulus pattern will differ by target. In one group of participants we will attempt to strengthen central-executive circuitry in response to cannabis cues by applying 'excitatory' 10Hz stimulation (5s-on,10s-off), 3000 pulses

per study-treatment—in a similar fashion to our phase-2 study. Stimulation will be delivered to the portion of the L-DLPFC that most activates during the 'Later' run of the ROC fMRI task. If there are any participants who do not generate such a target we will deliver stimuli to an anatomical location for the L-DLPFC such as[22,26,29]. In the other group we will attempt to reduce incentive-salience circuitry activation to cannabis cues using 'inhibitory' 1Hz stimulation. To match treatment-time we will deliver 900 pulses per study-treatment. Stimulation will be delivered to the area of the vmPFC that most activates during the 'Now' run of the ROC task or the passive cue-reactivity task[70]. If there are any participants who do not generate such a target we will deliver stimuli to an anatomical location for the vmPFC such as[18].

Prior to each session of rTMS we will present physical cannabis cues and play a brief induction script instructing participants to think of their last pleasurable cannabis use session[76], similar to what we did in our prior Phase-2 trial. Following each study-treatment we will remind participants of the downside of using cannabis as they report to us similar to[17]. We chose to administer cannabis cues prior to rTMS treatments given data suggesting that doing so increases rTMS's efficacy[58], and remind participants of the downside of using cannabis after treatment due to its use in the recent positive pivotal trial for smoking cessation[20].

A total of 36 study-treatments will be delivered as two study-treatments each study-treatment-visit separated by approximately 45-minutes. Study-treatments will be delivered in as little time as four-weeks (2 study-treatments each day, five treatment-days per week, 18-study-treatment-visits), but will be most often delivered over six to nine-weeks (two to three study-treatment-visits each week, two rTMS-sessions each study-treatment-visit). We have adapted a flexible study-treatment delivery paradigm given clinical data that consistently reports that the total number of rTMS-treatments delivered is more important than the number of treatments delivered per week[56,77], that rigid treatment delivery paradigms reduce the feasibility of rTMS[28] delivery in CUD, and that even highly accelerated rTMS paradigms are safe, tolerable, and efficacious[64–66]. In addition to the pre-specified urine drug testing paradigm in this study, 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.

Behavioral Platform: We will use a three-session version of Brief Marijuana Dependence Counseling (BMDC) for our behavioral platform (similar to our last study), and will follow the protocol outlined in the manual published by NIDA[59]. 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 screening visit. The PFRs will be used by the clinician to facilitate discussion in the three MET sessions, which will occur most often on rTMS-study-treatment visits 1, 5, and 10. Discussions will center around 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 may audio-tape sessions for review and fidelity ratings.

Follow-up: There will be follow up visits one (where the post-fMRI will be completed), two, four, and six weeks after study-treatment completion. Participants will be asked about cannabis use, symptoms of CUD, craving, withdrawal, and may undergo behavioral cognitive tests (delayed discounting, *n*-back, CPT, GoGo/NoGo).

Cross-Over: Those participants who complete the trial above with one of the treatment targets who meet entry criteria following the last follow-up visit may be considered for re-enrollment for the second treatment-target. The experiment will be completed in an identical fashion including all visits, assessments, and remuneration.

Recruitment and Participant Population:

Recruitment: Participants will be recruited through, a) media advertisements (such as Craigslist and facebook), b) using Trialfacts, a professional recruitment agency (similar to our last trial), and c) via referrals from addictions medicine clinics. Ads will recruit heavy cannabis users who are interested in quitting or substantially reducing their use of cannabis. Participants will undergo a phone screen to ensure they meet basic eligibility criteria (see included phone screen), and those who do will be invited for a full screening visit.

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 65. **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 UDT for cannabis during their enrollment visit (confirming they are regular users). **6)** The investigative team must believe each participant is a good study-candidate.

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 that have changed in the past 6-weeks. **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. **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 180 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: Behavioral data will be managed using REDCap and all data entry will take place directly in REDCap. We will use e-consents through Adobe sign, and these documents will be uploaded into REDCap. There will however be emergency paper backups of the database should it 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. Video and Audio recordings will be uploaded to Stanford Medicine Box, as will be backup copies of MRI files.

Statistical Analysis: The primary outcomes for this study are generally qualitative in nature and will serve as pilot data to power a larger trial if indicated. We will subsequently not perform formal hypothesis testing. We will, however, generate proportions of success for retention (Aim1) and fMRI target generation of our ROC-task for both vmPFC and L-DLPFC (Aim2). We will further calculate effect sizes for clinical, behavioral, and fMRI outcomes (Aim3), and compare them qualitatively to the results of our phase-2 trial (where we have complete data for N=28 participants who received anatomically targeted L-DLPFC stimulation and 23 participants who received sham stimulation)—assuming we find this paradigm to be feasible, and our functional-targeting development successful, we believe we will have a sufficient sample size to compare effect sizes between the two open-label conditions, our prior active condition, and our prior sham condition—acknowledging that the comparison will be imperfect with this trial being open-label, and the previous trial being double-blind. 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 our proposed treatment paradigm is feasible, that we can generate functionally derived rTMS targets, and that our new, refined, protocol has suggestions of improved efficacy relative to our lower burden/complexity paradigm. We reasoned that we must be able to retain approximately 60% of the study sample to design a reasonable Phase-3 trial with an expanded number of treatments (10% lower retention rate than our Phase-2 trial), and that we must be able to generate functional targets for 2/3rds of participants to justify the increased complexity of the paradigm. Finally, assuming a 60% retention rate, we reasoned we would need at least 9-participants per cell to generate a meaningful effect size (Aim3, weeks of abstinence and days per week of cannabis use in the 12-weeks following the delivery of 14-study treatments) with which to judge whether the new paradigm is an improvement relative to the old paradigm.

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 one of the study clinicians, most often Dr. Sahlem (a licensed and board-certified psychiatrist) and appropriate referral will be made. Participants will be considered dropouts if they do not come back to treatment after receiving three phone calls.

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; 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

a. Participant description and compensation

Targeted/Planned Enrollment Table
Total Planned Enrollment 30 (Randomized)

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	3	5
Not Hispanic or Latino	9	16	25
Ethnic Category: Total of All Subjects*	30		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	3	4	7
White	4	9	13
Other / More than one race	2	4	6
Racial Categories: Total of All Subjects*	11	19	30

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 as well as our recently completed phase-2 trial.

Compensation and Retention: Participants will be compensated based upon attending visits as well as given additional compensation using a Prize-Based Contingency Management (PB-CM) paradigm[78–82]. Participants who attend all visits as scheduled will receive $[redacted] for visit attendance, and up to an additional $[redacted] for PB-CM (see below for a further description of each type of compensation).

For visit attendance, participants will be compensated $[redacted] for the screening visit, $[redacted] for each fMRI visits (two-fMRI visits), $[redacted] for each rTMS/BMDC visits (18 rTMS-visits), $[redacted] for attending the two-week follow-up visit, $[redacted] for attending the four-week follow-up visit, and $[redacted] for attending the 6-week follow-up visit—for a total of $[redacted].

Prize-Based Contingency Management (PB-CM) will be used to reinforce visit attendance. In PB-CM participants pick a pre-specified number of numbered-chips out of a bowl. Each number corresponds to a dollar amount—in this case 250 chips will be used (230 chips will be worth $[redacted] 18 chips will be worth $[redacted] one chip will be worth $[redacted] and one chip will be worth $[redacted] Participants will be given a chip pick for attending the initial MRI visit, and then every other visit that is attended on time and without rescheduling, the number of chips will escalate by 1. If a participant misses a scheduled visit or attends more than 10-minutes late the number of chip-picks reset to 1 and again escalate by a chip-pick every-other visit. The amount of compensation based on PB-CM, will by definition vary to some degree between participants, but fall within a predictable range. The average value of a chip is (230*$[redacted] + 18*$[redacted] + 1*$[redacted] + 1*$[redacted] / 250 total chips is = $[redacted] per chip). Using the escalation paradigm described above, participants who attend all visits as scheduled will receive 144 chip picks. Participants who attend all visits as scheduled will subsequently be compensated a minimum of $[redacted] a mean / median (since chips are picked at random) of 144*$[redacted] = $[redacted], and we will cap PB-CM total compensation at $[redacted] We used this strategy successfully in our prior Phase-2 trial (with fewer visits) and found the mean value of each chip pick was $[redacted].
The total estimated direct time commitment for the study is approximately 38.5 hours (not accounting for travel time), and so participants receiving the expected amount of PB-CM compensation will be compensated approximately $[redacted] per hour—when including travel time and cost of travel we believe this is a reasonable amount of compensation and is not likely to be coercively high.

b. Sources of Materials

Assessments:

Data collection:

Research Procedures Table

	Screening Visit	Baseline fMRI Visit	rTMS Visits	Post- Tx fMRI Visit	Follow-up Visits
Screening and Enrollment Eligibility					
Quick Structured Interview for the DSM-5 (Quick-SCID-5)[83], Medical, Surgical, Social, Family, and Medication History	X				
Brief Counseling for Marijuana Dependance Questionairres[59]: A series of measures used to complete the personal feedback form of the Motivational Enhancement Therapy behavioral intervention including the Marijuana Problem Scale, the Reasons for Quitting Questionnaire and the Self-Efficacy Questionnaire	X				
Urine Pregnancy Test (bHCG) for participants of childbearing potential	X				
Study Procedures:					
MRI-Procedures:		X		X	
Repetitive Transcranial Magnetic Stimulation (rTMS) study-treatments			X		
Brief Counseling for Marijuana Dependance sessions:		X	~5 & ~10		
Clinical Substance Use Measures:					
Craving Scale (CS)[84]: Validated brief measure of sub-acute craving (past 24-hours), that has predicted future use of	X	X	X	X	X

substance in Alcohol, stimulants, and opioids.					
The Marijuana Craving Questionnaire (MCQ)[85]: Validated measure of immediate cannabis craving, for use at MRI visits.		X	X	X	
Time Line Follow Back (TLFB)[86]: Calendar-based instrument designed to assess substance use.	X	X	X	X	X
Diagnostic criteria for Cannabis Use Disorder from the Structured Interview for the DSM-5[87], and additional quantifying questions via the Repeatable Clinician-Administered Diagnostic Interview for Substance Use Disorders (CADiSUDS)—recently developed by our team. *With participant permission we may videotape administrations of the CADiSUDS for QA, training, and dissemination purposes.	X	X	#8 only	X	X
Urine Drug Testing with creatinine corrected cannabinoid levels	X	X	#16 only	X	X
Cannabis Withdrawal Scale (CWS)[88]: Validated questionnaire that measures symptoms of cannabis withdrawal.	X	X	X	X	X
Participant Burden, Quality of Life, and Function / Functional Improvement:					
Marijuana Problem Scale (MPS)[59]	X			X	X
Q-LES-Q-SF[89]: Brief measure of quality of life and the Work Productivity and Activity Impairment (WPAI-SF) scale[90]	X	X	Weekly	X	X
Perceived Research Burden Assessment[91]			Final Visit		X
Cognitive Tasks and Relevant Covarying Symptoms:					
Delayed Discounting Task: Participants choose between receiving hypothetical money / cannabis immediately or more money / cannabis if they wait longer. Determine whether participants favor smaller immediate rewards or larger delayed rewards.		X	#8 only	X	X
Behavioral GoGo-NoGo Task / *n*-back / CPT: Behavioral version of the fMRI tasks described above. We may collect these, time permitting		X	#8 only	X	X
We will measure relevant covarying symptoms including sleep[92], depression[93,94], ADHD, impulsivity[95] and anxiety[96]. If there is question as to whether there is sufficient symptomatology in depression or anxiety to require separate treatment, we may perform the more extensive clinician rated measures[97,98].	X	X	#8 only	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. We will recruit a total of thirty cannabis use disordered participants from the community and randomize them to receive DLPFC or vmPFC study-treatment.

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).

6) The investigative team must believe each participant is a good study-candidate.

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 that have changed in the past 6-weeks.

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.

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 180 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 recruit from: a) social media platforms such as facebook or youtube and through media advertising platforms such as craigslist; b) we will work with addictions medicine clinics such as the Stanford Dual-Diagnosis clinic to recruit appropriate and interested clinical patients with CUD. Participants meeting with study-team members remotely will be asked to find a private location, and those meeting with study-team members in person will do so in a private office. After referral we will first schedule a phone call to briefly describe the study to potential participants and then will ask basic screening questions to those who are interested. Those participants who meet basic inclusion/exclusion criteria based on the phone screen will be scheduled for either in-person or e- screening visits through Stanford's secure Zoom account. First, participants will meet with study-team members to go through a second level of screening. During the second level 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 and 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 the second level of screening will meet with one of the clinically trained study team-members, most often the PD, for a final level of screening. During the final level of screening participants will first review a full consent document. 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 clinically trained study team-members, 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. Participants will then undergo the remainder of the screening items with the clinically-trained study-team member, and 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, interviews with study personnel, and potentially audio and video recordings of those interviews. Additional information will be obtained from the Stanford Epic chart if the participant has one. All behavioral data will be directly input into REDCap which is a secure, password protected web-based data collection system. With participant permission, we may video-record some parts of the interviews (for quality assurance, educational, and dissemination purposes), and may audio-record therapy sessions for later review for fidelity. In the instances of these recordings we will store data in secure Stanford Medicine Box folders. We will also record digital calendars for the Timeline Follow-Back which will also be stored in secure Stanford Medicine Box folders. Urine samples will be delivered to the Stanford laboratory labeled only by participant ID, age, and gender. The Stanford laboratory will process the urine samples and send them to the MUSC laboratory (contract submitted and approved), who will deliver results via secure email. MRI data will be kept in secure Stanford servers and backed up in Stanford Medicine Box.

d. Potential Risks and Risk Mitigation Strategies:

Potential risks of rTMS: TMS and rTMS (repeated trains of TMS) has been in use for decades, and high-frequency rTMS (10Hz) has been FDA-approved for depression and in common clinical use since 2008[50]. One-Hz stimulation has also been a common stimulation pattern used both experimentally and clinically[61,99]. There is subsequently extensive safety data on a number of paradigms including the 1-Hz and 10-Hz paradigms which we are proposing to use in this investigation. The 1Hz paradigm we are using has been applied in a number of investigations in depression[61] and addictions[100]. The 10Hz paradigm we are using is nearly identical to the FDA-approved protocol and the one we used in our prior work in CUD[27,28,68]. A summary of the safety data for TMS and recommendations for the safe application of TMS are summarized in the following two comprehensive papers[101,102]. Both papers conclude that TMS can be safely applied to both healthy volunteers and clinical populations with little risk when appropriately excluding higher risk populations. The most substantial risk associated with rTMS is seizure (approximately 1: 30,000 treatments in high-frequency rTMS such as 10Hz)[103] and presumably lower in low frequency, 'inhibitory' rTMS (such as 1Hz)[102]. Myriad investigations have applied rTMS to the L-DLPFC or vmPFC[18,48,48,52,104,105], and there is no data suggesting any additional safety concerns beyond the standard low risk of seizure. Applying rTMS to the prefrontal cortex in general appears to be safe and well tolerated. Various paradigms have now applied stimulation to all areas of the brain anterior to the motor cortex without additional safety concerns[15–17,106]. Increasing the number of pulses delivered in a session of rTMS, or the number of total sessions of rTMS may increase efficacy, but does not appear to negatively effect safety, indeed a number of investigations have safely applied many more pulses per session, per day, and per course than we plan on applying in this investigation[66,107]. Even investigation of serial applications of rTMS over a number of years has not provided any indication of ill effect[108]. Please see below for a description of the major (and minor) risks associated with TMS as well as how we plan on mitigating these risks.

Risk of Seizure: As mentioned above, the most serious risk associated with the use of rTMS is seizure. Since the adoption and widespread use of standard safety guidelines in 1997[109], 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). 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 minimize 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 such as 10Hz and 1Hz stimulation), 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, those with medical history suggestive of increased seizure risk, 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 sufficient to stop the seizure (all TMS related seizures have been self-limited to this point), and there does not appear to be an increased risk of subsequent seizures.

Risk of site discomfort, headache, and fatigue (see the AE table from our recently completed phase-2 trial): Three relatively common risks associated with the use of rTMS include the risk of mild transient site discomfort during treatment (most patients), the risk of mild, transient, post treatment headache (27% of our phase-2 trial participants reported at least one headache) and the risk of post-treatment fatigue (approximately 16% of our phase-2 trial participants reported fatigue on at least one day). All three of these potential side effects are typically mild. In terms of mitigating site discomfort, we will slowly ramp up stimulation intensity at a rate each participant can tolerate. 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. Should an rTMS associated headache occur, over the counter analgesics are typically sufficient to alleviate it, and we will forewarn participants of the possibility of headache and the effectiveness of over-the-counter analgesics. TMS associated fatigue is typically mild and transient. We will warn participants about the possibility they may have fatigue after treatments and educate them that the fatigue is self-limited.

Table 2: This table represents the collected Adverse Events between groups in our recently completed Phase2 trial.

	Total Sample, N, and (% of ITT sample—total / 72)	Active condition, N, and (% of ITT sample—total / 37)	Sham condition, N, and (% of ITT sample—total / 35)	Significance (Chi-square, or Fishers Exact)
# of participants with Any Adverse Events (%)	23 (31.9%)	16 (43.2%)	7 (20.0%)	*p*=0.035
Total number of Adverse events	30	19	11	*p*=0.047
Headache (%)	14 (19.4%)	10 (27.0%)	4 (11.4%)	*ns*
Fatigue (%)	9 (12.5%)	6 (16.2%)	3 (8.6%)	*ns*
Eye Twitch	1 (1.4%)	1 (2.7%)	0 (0)	ns
Jaw Pain	1 (1.4%)	1 (2.7%)	0 (0)	ns
Persistent site discomfort	1 (1.4%)	1 (2.7%)	0 (0)	ns
Insomnia	1 (1.4%)	0 (0)	1 (2.9%)	ns
Irritability / mood swings	1 (1.4%)	0 (0)	1 (2.9%)	ns
Hand numbness	1 (1.4%)	0 (0)	1 (2.9%)	ns
Increased anxiety	1 (1.4%)	0 (0)	1 (2.9%)	ns

Potential changes in auditory thresholds: The discharge of the TMS coil generates a high-energy click that may temporarily shift auditory temporarily thresholds (there has also been a single case of longer term shifting of auditory thresholds when ear protection was not used). Foam earplugs have proven effective at protecting 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: Participants will undergo a total of two MRI's in this investigation each with a duration of approximately 60-minutes. MRI is thought to be a low-risk procedure[110,111]. The risks associated with MRI include the risk of injury if a participant enters the MRI bore with implanted ferromagnetic metal or an implanted device. Additionally, there is the potential for psychological distress in participants with severe claustrophobia. We will protect against these risks by rigorously screening participants and excluding those who have implanted metal / devices and those that are claustrophobic and unable to tolerate a "mock-scan". Participants will be assessed for safety and claustrophobia via clinician assessment, and if needed will undergo a "mock-scan" which mimics the experience of MRI without actual scanning. MRI is likely safe in the case of pregnancy, however, as mentioned above, pregnant women will not be enrolled in this study.

Safety of targeting methodology: As stated above, studies have applied serial sessions of rTMS to much of the cortex including all of the cortex anterior to the motor strip. There has been no suggestion that any treatment location is unsafe, and particularly within the confines of the larger L-DLPFC or vmPFC structures we will be targeting. Most of the existent clinical trials in addiction have used anatomical targeting, and so it is possible that the functional targeting that we are piloting might be less effective than the anatomical targeting that has so far been used. As described in the background and significance section, more precise functional targeting may have an advantage over anatomical targeting in terms of engaging the target circuitry, and that this may result in increased efficacy[18,30,63]. We subsequently believe our targeting method will result in increased efficacy, though we will carefully monitor participant response, and will be able to compare the results of our functionally targeted rTMS to the results of our anatomically targeted Phase-2 results.

Potential risks of cue Induced craving paradigms prior to rTMS treatments and during MRI: Prior to each session of rTMS we will perform an in-vivo cannabis provocation using a shortened version of this standardized paradigm[76]. In the cue-paradigm participants will listen to a brief induction script asking them to remember a time they used cannabis, and will then be presented with cannabis related items (e.g. a vape pen, fake joints, etc.). The use of in-vivo drug cues appear to enhance the efficacy of rTMS[58], and has become a commonly employed approach prior to delivering rTMS[17,22]. Additionally, our MRI paradigms include exposure to cannabis related images. The risk associated with presenting cannabis cues is that exposure to these cues are likely to result in transiently increased craving. Our approach to this likely increased craving is as follows. Increased craving in this instance is likely to follow a predictable time-course, return to baseline within an hour (a shorter period than the visit duration)[76], and will likely be of lower magnitude compared to "real-life" cues participants will encounter in their life. We will continually assess craving and will use a "talk-down" strategy to reduce excessive craving should it occur. Study staff will stay with each participant until their craving has returned to baseline levels. In the unlikely event that the individual has prolonged cue-induced craving, one of the study physicians will provide an appropriate referral.

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 has been, or 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 depression measures, the Quick-SCID, or in any other manor, the PD or covering clinician 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 assist them reduce their use of cannabis or quit using cannabis. 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 further.

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 further refine a promising rTMS treatment paradigm for cannabis use disorder by increasing the dose of rTMS, adding in functional targeting, and testing the efficacy of a second treatment target.

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 / video / audio data will be kept on secure Stanford servers.

d. Quality Assurance.

We will conduct twice yearly data audits prior to DSMB meetings. 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 clinician, 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, an expert in brain stimulation, and an expert in neuroimaging. 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

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