Repetitive transcranial magnetic stimulation (rTMS) administration to heavy cannabis users

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Abstract

Background—Cannabis use disorder (CUD) is a common condition with few treatments. Several studies in other substance use disorders have found that applying repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) decreases cue-elicited craving and possibly decreases use. To date, there have been no studies attempting to use rTMS in CUD.

Objectives—This study was conducted to determine if rTMS could be feasibly delivered to a group of non-treatment seeking CUD participants. Secondarily, the study aimed to estimate the effect of rTMS on craving.

Methods—In a double-blind, sham-controlled, crossover design, a single session of active or sham rTMS (Left DLPFC, 10 Hz, 110% rMT, 4000 pulses) was delivered during a validated cannabis cue paradigm. Participants crossed over to complete the other condition one week later. The feasibility and tolerability were measured by the rate of retention, and the percentage of participants able to tolerate full dose rTMS, respectively. Craving was measured using the Marijuana Craving Questionnaire (MCQ).

Results—Eighteen non-treatment seeking CUD participants were recruited from the community; 16 (three women) completed the trial (89% retained for the three study visits). All of the treatment completers tolerated rTMS at full dose without adverse effects. There was not a significant reduction in the total MCQ when participants received active rTMS as compared to sham rTMS.

Conclusion—rTMS can be safely and feasibly delivered to CUD participants, and treatment is well tolerated. A single session of rTMS applied to the DLPFC may not reduce cue-elicited craving in heavy cannabis users.

Keywords

Cannabis; marijuana; craving; transcranial magnetic stimulation; TMS

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Introduction

Cannabis Use Disorder (CUD) is a common and escalating problem in the United States (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 (3). Currently, the available treatments for CUD have low long-term success rates (4–7). There has subsequently been significant interest in the development of new treatment options for those individuals with CUD who desire to stop using.

In substance use disorders, it is theorized that there is an imbalance of executive control and reward networks. This theory posits that addiction results when normal inhibitory processes mediated by prefrontal regions, including the dorsolateral prefrontal cortex (DLPFC), are unable to control reward processes mediated by the limbic system (8–10). The DLPFC, in particular, has been implicated in the modulation of craving across substance use disorders including cocaine use disorder (11), nicotine use disorder (12), and cannabis use disorder (13).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that is able to alter cortical excitability and is an established, FDA-cleared, treatment for 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 (14), and, when multiple sessions of rTMS are delivered, there are long lasting behavioral alterations (best characterized by the long lasting antidepressant effect of rTMS (15)).

If, in fact, an imbalance of executive control and reward 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. Multiple studies have confirmed this relationship [see reviews (16–19)]. 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 top-down 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 (20), providing further strength to this relationship. Sparked by the promising literature suggesting that single sessions of pre-frontal rTMS reduce craving, two recent clinical trials demonstrated that multiple sessions of rTMS may have a more durable effect on craving and reduce drug use in nicotine use disorder (21), and cocaine use disorder (22).

If excitatory rTMS of the DLPFC has an anti-craving effect in cannabis users, then it could represent a novel treatment option for those attempting to diminish use or become abstinent from cannabis. TMS is typically a well tolerated intervention with few adverse effects (23). The major limiting factor in the initial delivery of rTMS is site discomfort (the magnetic field excites nociceptive neurons on the way through the skin and skull). Additionally, the

sham condition must match the site discomfort of active rTMS in order to be an effective blind, and is subsequently also mildly uncomfortable. Given the ambivalence common in CUD, this site discomfort may result in either dropout, or intolerance of full dose rTMS (resulting in being treated at a sub-therapeutic dose, or discontinuing treatment).

Prior to engaging in a large scale clinical trial utilizing multiple sessions of rTMS, we thought it was necessary to determine simply if rTMS can be feasibly delivered to CUD participants. Additionally, given that single sessions of rTMS have had small effects on craving in other substance use disorders, we sought to preliminarily determine the effect of rTMS on cannabis craving. We subsequently took the first step in developing this technique by determining the safety, feasibility, and preliminary effect size of a single session of rTMS in a CUD population.

Methods

This was a randomized, double-blinded, cross-over study in which participants with CUD were exposed to a validated cannabis cue reactivity paradigm during a single session of either active or sham rTMS. Each participant then crossed over and underwent the same procedure with the opposite stimulation intervention approximately one week later (see Figure 1). Potential participants were recruited via media advertisements from the community and were compensated a total of $140 for participation in the study. All study procedures were approved by the Medical University of South Carolina's Institutional Review Board, and all procedures were performed in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to any study related procedures. Potential participants were included if they were between the ages of 18 and 65, met criteria for cannabis use disorder, and reported cannabis use on at least 20 out of the 30 days prior to enrollment. Potential participants were excluded if they had any active neurologic, psychiatric, or sleep disorder; met criteria for any other substance use disorder with the exception of nicotine use disorder; had a positive drug screen for any drug of abuse besides cannabis; were taking any medications with central nervous system activity; had a history of seizures; had metal implants above the waist; or had a history of any brain lesions.

Each participant completed three visits. On the initial visit, participants underwent a standardized evaluation that included a Mini International Neuropsychiatric Interview (MINI) (24), a Time Line Follow-Back (TLFB)(25), the Cannabis Use Disorder Identification Test-R (CUDIT-R) (26), the Inventory of Depressive Symptoms (IDS) (27), and the Pittsburgh Sleep Quality Index (PSQI)(28). Participants additionally underwent both a urine (Alere Toxicology, testing for amphetamines, benzodiazepines, cannabis, cocaine, and opiates), and saliva drug test (Confirm Biosciences, testing for amphetamines, benzodiazepines, cocaine, cannabis, and opiates) to detect the presence of cannabis and other drugs of abuse. Both the urine and saliva drug test was performed on all three visits. The urine drug screening was performed in order to confirm the recent use of cannabis, and to ensure participants had not recently used any other drugs of abuse. The saliva drug test confirmed that participants had not used any drugs for the previous 14 hours.

Over each of the next two visits, participants underwent a validated cannabis cue reactivity paradigm during a single session of either active or sham rTMS (see Figure 2, and description below). On the day of each experimental visit, participants were instructed not to use alcohol, cannabis, or any other drugs. Abstinence was verified by self-report, urine, and salivary drug testing.

Repetitive Transcranial Magnetic Stimulation (rTMS) was delivered using a Magventure Magpro ×100 TMS machine. Treatments were delivered at the EEG coordinate for F3, which was found using the Beam F3 method (29) (which closely approximates the Left DLPFC). Each rTMS treatment consisted of a total of 4000 pulses of 10 Hz stimulation (5s-on, 10s-off), at a standardized intensity of 110% of the individual's resting motor threshold (rMT), using a figure of eight coil. For tolerability, intensity was ramped up 10% of rMT every train from 60% rMT (200 pulses delivered sub 100%). Sham treatments were delivered by an electronic sham system that has been used extensively in our laboratory (30). The sham system consists of a coil that mimics the appearance and sound of rTMS, combined with a transcutaneous electrical nerve stimulator (TENS) device which produces a small electrical stimulus delivered to the scalp just below the hairline, mimicking the feeling of active rTMS (30). Both the participant and the treater were blind to the stimulation condition.

During rTMS, participants were presented both a neutral cue paradigm as well as a cannabis cue paradigm. The cue paradigm was presented during rTMS (as apposed to before or after rTMS), given that a recent study showed that rTMS had a greater antismoking effect if delivered during a smoking cue (21). The cannabis cue paradigm consisted of an auditory script and a tray of cannabis related items, and is closely adapted from (31). The auditory script consisted of an imaginal recall of a recent pleasurable cannabis experience. The physical cues consisted of a number of items associated with cannabis use such as blunt wraps, rolling papers, pipes, and a small bag containing marijuana. The small bag of cannabis also acted as an olfactory cue. The neutral cue paradigm consisted of a tray of items unassociated with drug use, such as a note pad, pencil, tea-bags, and wood chips (as an olfactory cue). The neutral auditory script asked participants to imagine a day at the beach. We elected to deliver a neutral cue paradigm in addition to an active cue paradigm as a negative control (to ensure items in general did not increase craving). We elected to deliver the neutral cue prior to the active cue on all experimental visits to reduce the variability of the protocol. The Marijuana Craving Questionnaire (MCQ) (32) was used to assess craving, and results in a total score as well as four sub-scores. In three separate studies validating two forms of the MCQ, four independent clusters of craving type were observed (32–34). The observed sub-types of craving include; 1: compulsivity, with higher levels of compulsivity indicating less ability to modulate cannabis use, 2: emotionality, with higher levels of emotionality indicating a greater desire to use cannabis to reduce withdrawal symptoms, 3: expectancy, with higher levels indicating anticipation of positive outcomes from using cannabis, and 4: purposefulness, with higher levels indicating more planning and anticipation of using cannabis for positive effects (Figure 3). Higher scores on the MCQ indicate higher levels of craving. The MCQ was administered prior to the application of rTMS, during rTMS following the neutral cue, during rTMS following the active cue, directly following rTMS, and 15 minutes after the completion of rTMS. We elected to

collect craving data at each of these time points given that this was an exploratory study, and it was unclear if and when rTMS would have an anti-craving effect. We extended craving analysis out to 15 minutes past treatment to see if rTMS has a delayed craving effect, and to ensure that rTMS does not result in increased craving following treatment.

Data analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data for the entire sample and across randomized order of treatment. A Wilcoxon rank sum test statistic assessed baseline differences in continuous characteristics, and differences in categorical characteristics were assessed using Fisher's exact test statistic.

Feasibility, safety, and tolerability were examined as the primary outcomes of the study. Primarily, the retention rate (feasibility), and the number of participants who reached the allotted treatment dose of 110% of motor threshold (tolerability) were assessed. Additionally, had any treatment emergent adverse events occurred, we would have compared these across the treatment condition upon which they had occurred (tolerability). Had any participants dropped out following a treatment visit, or failed to reach the allotted treatment dose, we would have additionally compared the rate of drop out and percent motor threshold dose between those receiving active or sham stimulation.

Secondarily, estimates of treatment effects on marijuana craving following the rTMS cue sessions were of interest to determine effect sizes and power estimates for larger clinical trials. To estimate treatment differences in craving after receiving active rTMS, linear mixed effects models that assessed all serially measured post-baseline time points were developed. The models tested the efficacy of active rTMS on craving responses to both the neutral and active cue (during rTMS) as well as durable effects following the rTMS procedure (immediately following, and 15 minutes post rTMS). Model-based estimates were used to construct group level pair-wise comparisons across treatment conditions at all post-baseline time points; comparisons were taken at the neutral cue, active cue, post rTMS, and at rTMS +15 minutes time points. Overall treatment effect sizes for the main effect of rTMS treatment, time, their interaction as well as the time-varying baseline craving measures taken prior to each condition were initially assessed as covariates in the model. Models additionally adjusted for active rTMS/sham rTMS order and study day. Estimated group differences and their associated 95% confidence intervals are presented. Effect sizes are calculated at each time point and presented as Cohen's d values (35). Potential baseline confounders (gender, age, depression levels, and CUDIT scores) were independently assessed in adjusted models for evidence of effect modification using appropriate interaction terms.

As this was an exploratory study, no pre-study power calculations were performed. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, US). No correction for multiple comparisons was applied to the reported results.

Results

Demographics and clinical characteristics

Eighteen total participants were enrolled in the study, and were randomized to receive either active or sham rTMS in the first experimental visit. The mean age of study participants was 26 years (SD = 17.9), 13 were men (81.3%), and 10 were Caucasian (62.5%). All participants met criteria for cannabis use disorder (MINI), and did not meet criteria for any other axis I condition, or substance use disorder. Self-reported marijuana use at study entry showed high levels of use. Participants used cannabis 23.5 (SD = 4.3) days out of the last 30 with an average of 1.3 (SD = 1.3) grams used per day (Table 1). Additionally, participants drank alcohol on average 7.4 (SD = 7.8) days out of the last 30 days [1.2 (SD = 1.3) drinks per day]. Seven participants smoked with an average of 11.7 (SD = 9.8) cigarettes per day.

Feasibility and safety

The primary aim of the current study was to assess the feasibility and tolerability of a single session of rTMS in non-treatment seeking CUD participants. The study retention rate was high with 14 of 16 (89%) participants completing the study protocol as designed (Figure 1). There were no treatment related adverse events reported in this trial. All recruited participants tolerated treatment at the fully intended dose of rTMS and had treatment related complaints. Of the two participants who withdrew from the study, one was lost to follow-up prior to the first experimental visit, and one withdrew due to a headache occurring on the day after the enrollment visit (where their motor threshold was found). The described headache was considered not likely to be related to TMS, as motor thresholds are determined using single pulse TMS only, and the event occurred on the day following the session (headaches associated with TMS typically occur directly after treatment, and are more commonly associated with rTMS).

Craving response

Craving to cannabis was measured using the MCQ total and subscale scores and was assessed prior to active or sham rTMS (time-varying baseline), in response to a neutral and active marijuana cue during rTMS, immediately following rTMS, and 15 minutes following the conclusion of rTMS. There were no statistically significant differences in MCQ total score between the active sham rTMS condition at baseline ($F_{1,56}$ = 0.09; = 0.769). Although there was a statistically significant increase in craving to the active cue as compared to the neutral cue under both conditions (= 4.4 ± 1.5 SEM; = 0.005), there was no differential increase between the two treatment conditions (Sham Cue Response: = 3.4 ± 1.7 vs. rTMS Cue Response: = 5.4 ± 1.7; = 0.227). There was no difference in MCQ total score between treatment conditions either during or following rTMS (Table 2). Additionally, post rTMS craving subscale measures of the emotionality, compulsion, and expectancy subscales scores were not significantly different across the two conditions (Table 2). At 15-minutes following completion of the rTMS condition, participants reported moderately lower purposefulness subscale scores following active treatment as compared sham treatment (Sham Response: = 13.7 ± 10.8 vs. rTMS Cue Response: = 12.0 ± 0.8).

Although not specifically powered to assess treatment age, gender, and severity of cannabis use (CUDIT) on the relationship between rTMS conditions and cannabis craving were investigated for potentially clinically relevant signals. No significant moderating effect on the relationship between treatment conditions and cannabis craving (MCQ total) were found in these analyses.

Efficacy of the blind

Following each experimental visit, participants were asked whether they believed they received active or sham rTMS. They were also asked how confident they were of their guess on a 5 point Likert scale with 0 = "Not confident at all", and 4 = "Almost certain". Overall 23 of 31 (74%) of the queries correctly guessed their stimulation condition with a median confidence of 1 ("somewhat confident"). Eleven out of sixteen participants (69%) correctly guessed that they received active stimulation with a median confidence of 1.5 (between "somewhat confident", and "confident"). Twelve out of fifteen (80%) correctly guessed that they received sham stimulation with a median confidence of 1 ("Somewhat confident").

Discussion

This is the first study to demonstrate that figure of eight coil rTMS can be safely and feasibly delivered to the dorsolateral prefrontal cortex of heavy cannabis users. Though the primary purpose of this study was to determine if rTMS could be feasibly delivered in this population, it also demonstrated that the application of a single session of rTMS may result in a reduction of the purposefulness aspect of cue elicited cannabis craving. These two findings taken together open the door for further study in the application of rTMS as a potential treatment for CUD.

The primary purpose of this study was to determine if rTMS was well tolerated by CUD patients. We managed to retain 89% of our enrolled participants. Furthermore, all of our participants tolerated rTMS at the full intended dose (110% of rMT), without deviation from the planned ramp of intensity, and without adverse events. As described previously, studies in participants with nicotine, alcohol, cocaine, and methamphetamine use disorders (20,22,36–45) have demonstrated that rTMS is safe and tolerable in these groups. The retention rate in other single session studies using non-treatment seekers in other addictions range from 79%–100%. Our only dropouts occurred before any treatment visit suggesting that both drop outs were non-specific to the delivery of rTMS.

With regard to cannabis craving, the observed effect size between groups was 0.23 for the MCQ-total, and 0.64 for the MCQ-Purposefulness which falls into the small to moderate categories, respectively. Our effect sizes were smaller than some recent single session investigations (37,44,45), and larger than another (42). The two most likely explanations for our smaller than anticipated effect for cue elicited craving include that there is a smaller effect of treatment in cannabis users, or that our small sample size was insufficient to detect a real change. Of interest, a statistically significant effect was seen in the Purposefulness subscale of the MCQ, which measures an individual's intention and planning to use cannabis for positive outcomes, implying that rTMS may reduce intention and planning to use cannabis. It is unclear neurobiologically why rTMS applied to the DLPFC would have a

larger effect on this aspect of craving as compared to the others. Purposefulness is related to planning and intent to use cannabis for its positive effects. Given that the DLPFC is involved in cognition and planning, DLPFC stimulation may enhance cognitive control in this area.

It should be noted that this study was designed to determine feasibility and safety of rTMS rather than to determine clinical efficacy. In order to observe a clinical effect using rTMS in the treatment of major depressive disorder, multiple sessions of treatment are required (commonly 20 or more) (46). A similar phenomenon has been observed in alcohol use disorder, where one study failed to find an anti-craving effect after delivering a single session of rTMS (42), but other studies have found a robust, stable anti-craving effect after delivering multiple sessions (38,47). Studies delivering more than one session of rTMS in larger groups of CUD participants will be needed in order to definitively determine if rTMS has an anti-craving effect in this population.

The results of this pilot study should be interpreted in light of several limitations. First, our sample size was relatively small, though within the range of sample sizes found in other single session investigations. Despite our relatively small sample, we managed to retain nearly 90% of those who enrolled, and each enrolled participant was able to tolerate 110% of motor threshold stimulation without any adverse events. Our high retention rate, and the fact that our participants tolerated a therapeutic dose of stimulation, thus demonstrates that it is possible to recruit and retain CUD participants. It is subsequently likely that it is possible to implement larger, more definitive trials using rTMS. Second, participants managed to correctly guess their condition nearly 69% of the time. This high rate of correctly guessing the treatment condition may suggest that our sham system was ineffective in this study. Though inadequate blinding may have contributed to our craving results, the primary aim of our study (to determine feasibility and tolerability) would not be influenced by an ineffective blind. In future studies, using a parallel design may result in a more effective blind, as there would be less of a direct comparison of active and sham sensations. The blinding system used in this study is more effective when patients are not crossed over and just receive one form of either active or sham stimulation. In order to achieve full blinding in crossover studies, one must titrate and match the painfulness of the sham stimulation (48), and should be considered in future crossover trials.

Our findings taken in composite suggest that DLPFC rTMS can be feasibly delivered to CUD participants. Additionally we found that the anti-craving effects found in other substance use disorders may be replicated in CUD. Though our findings are not definitive, they support future studies in this population.

Acknowledgments

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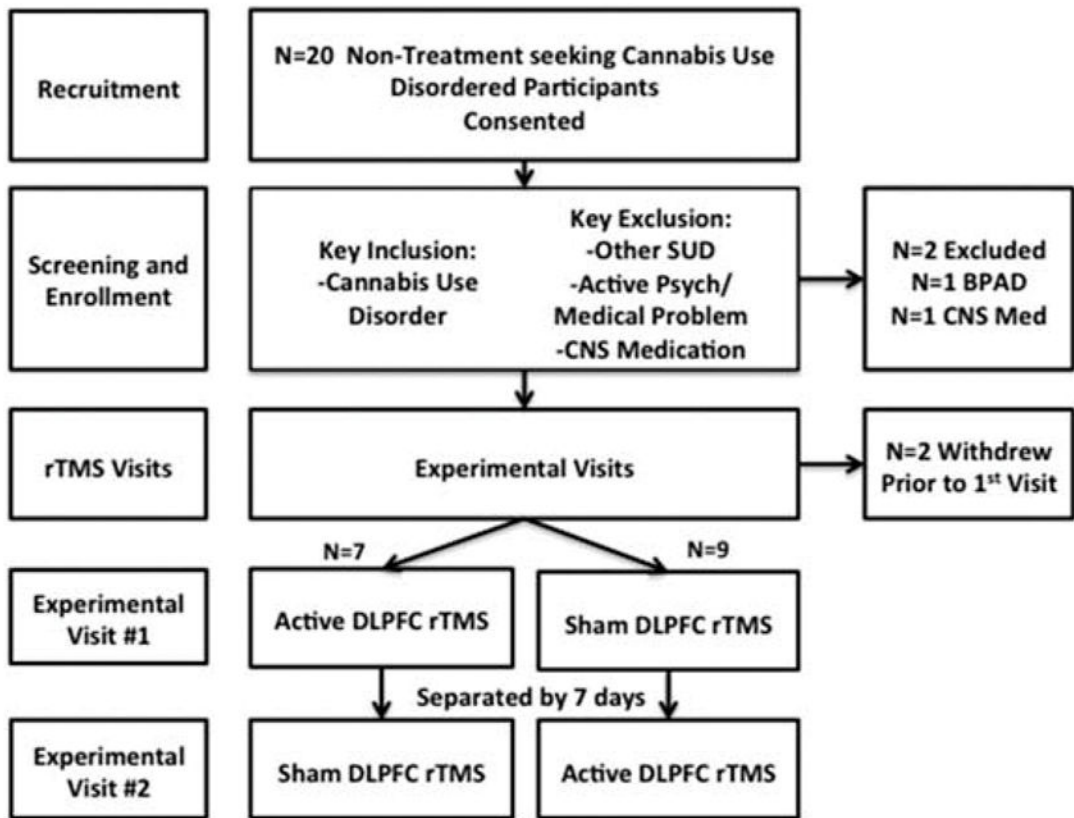
Figure 1.
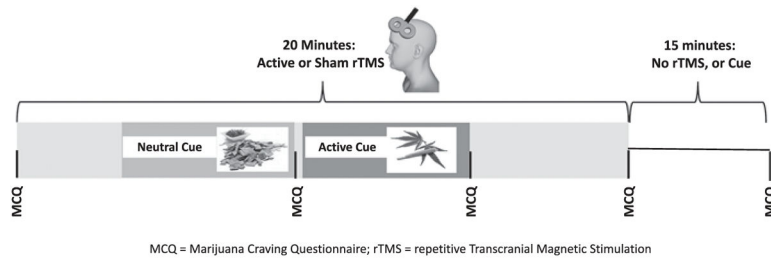Enrollment flow chart and study design.

20 Minutes:
Active or Sham rTMS

15 minutes:
No rTMS, or Cue

Neutral Cue

Active Cue

MCQ   MCQ   MCQ   MCQ   MCQ

MCQ = Marijuana Craving Questionnaire; rTMS = repetitive Transcranial Magnetic Stimulation

Figure 2.
Treatment visit protocol. This figure represents the time course of each of the experimental visits.
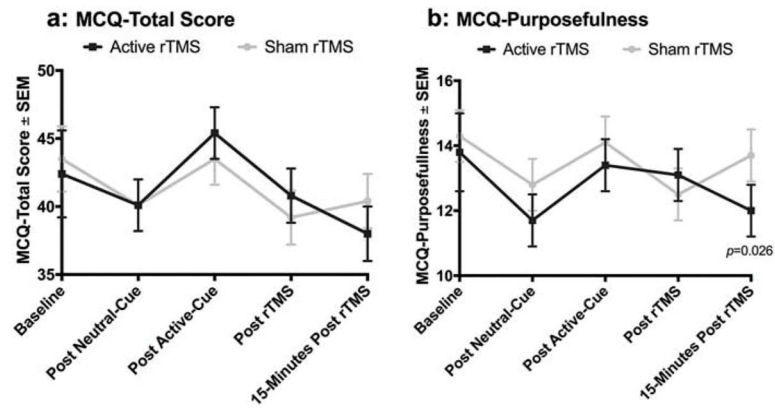
Figure 3.

3a) Marijuana Craving Questionnaire (MCQ) total score; and 3b) Marijuana Craving Questionnaire (MCQ) purposefulness score. Error bars denote S.E.M. This figure denotes the course of cue induced craving. Baseline refers to craving measured prior to any cue presentation, or rTMS. Post neutral-cue refers to craving following a neutral cue presentation during rTMS, post active-cue refers to craving following an active cannabis cue presentation during rTMS, post rTMS refers to craving following the cessation of rTMS, and 15-minutes post rTMS refers to craving 15 minutes following the cessation of rTMS.

Table 1

Demographics and clinical characteristics at study baseline.

	Overall	First randomized treatment		
		Sham first N = 7	rTMS first N = 9	P-Value
Age	26.0 ± 7.9	24.6 ± 3.7	27.2 ± 10.1	0.952
Male gender	81.3 (13)	85.7 (6)	77.9 (7)	0.999
Caucasian	62.5 (10)	42.8 (3)	77.8 (7)	0.302
Age at regular MJ use	18.1 ± 2.6	18.7 ± 3.1	17.6 ± 2.1	0.301
MJ smoked per day (grams)	1.3 ± 1.3	1.4 ± 1.5	1.3 ± 1.1	0.835
MJ days smoked (past 30)	23.5 ± 4.3	22.0 ± 3.7	24.7 ± 4.5	0.094
CUDIT score	17.1 ± 6.1	14.9 ± 5.4	18.9 ± 6.4	0.279
CUDIT score > 12	68.8 (11)	57.1 (4)	77.8 (7)	0.596
IDS-SR	10.3 ± 10.0	12.9 ± 10.8	8.3 ± 9.6	0.204

Table 2

Craving as measured by the Marijuana Craving Questionnaire (MCQ).

Outcome	Treatment condition		Treatment Difference	Effect Size[†]
	Sham rTMS	Active rTMS		
Baseline craving prior to rTMS [*]				
MCQ Total Score	43.5 (37.4,49.6)	41.9 (35.8,47.9)	−1.7 (−6.6,3.3)	0.15
Emotionality	10.4 (8.0,12.7)	10.1 (7.7,12.4)	−0.3 (−2.1,1.5)	0.08
Purposefulness	14.3 (12.1,16.6)	13.6 (11.4,15.9)	−0.7 (−3.2,1.8)	0.17
Compulsion	5.0 (3.8,6.3)	4.7 (3.4,5.9)	−0.4 (−1.5,0.7)	0.16
Expectancy	13.7 (11.6,15.9)	13.5 (11.4,15.6)	−0.2 (−2.0,1.6)	0.05
Analytic model results [**]				
Neutral cue during rTMS				
MCQ Total Score	40.1 (36.2,44.0)	40.1 (36.2,43.9)	0.0 (−3.2,3.2)	0.00
Emotionality	9.7 (8.2,11.2)	10.2 (8.7,11.7)	0.5 (−1.0,2.0)	0.16
Purposefulness	12.8 (11.2,14.4)	11.7 (10.2,13.3)	−1.1 (−2.5,0.4)	0.38
Compulsion	5.0 (4.0,6.0)	5.5 (4.5,6.5)	0.5 (−0.3,1.4)	0.31
Expectancy	12.7 (11.4,13.9)	12.4 (11.2,13.7)	−0.2 (−1.6,1.1)	0.08
Active cue during rTMS				
MCQ Total Score	43.5 (39.6,47.3)	45.4 (41.6,49.3)	2.0 (−1.8,5.7)	0.27
Emotionality	10.5 (9.0,12.0)	11.3 (9.8,12.8)	0.8 (−0.7,2.2)	0.27
Purposefulness	14.1 (12.5,15.7)	13.4 (11.9,15.0)	−0.6 (−2.1,0.8)	0.22
Compulsion	6.0 (5.0,7.0)	6.9 (5.9,7.9)	0.9 (0.0,1.7)	0.49
Expectancy	13.0 (11.7,14.2)	13.7 (12.4,14.9)	0.7 (−0.6,2.2)	0.26
Immediately following rTMS				
MCQ Total Score	39.2 (35.3,43.1)	40.9 (37.0,44.7)	1.7 (−2.1,5.4)	0.22
Emotionality	9.2 (7.7,10.7)	9.6 (8.1,11.1)	0.4 (−1.2,1.9)	0.12
Purposefulness	12.5 (10.9,14.1)	13.1 (11.5,14.6)	0.6 (−0.9,2.0)	0.19
Compulsion	5.4 (4.4,6.4)	5.4 (4.4,6.4)	0.0 (−0.8,0.9)	0.03
Expectancy	12.2 (10.9,13.4)	12.6 (11.4,14.0)	0.5 (−0.9,1.8)	0.17
15 Minutes following rTMS				
MCQ total score	40.4 (36.5,44.3)	38.6 (34.7,42.5)	−1.8 (−5.6,2.1)	0.23
Emotionality	9.5 (8.0,11.0)	9.0 (7.5,10.5)	−0.5 (−2.1,1.0)	0.17
Purposefulness	13.7 (12.1,15.3)	12.0 (10.4,13.6)	−1.7 (−3.2, −0.2)	0.63
Compulsion	5.4 (4.3,6.4)	4.8 (3.8,5.8)	−0.6 (−1.5,0.4)	0.31
Expectancy	11.9 (10.6,13.2)	12.7 (11.4,14.0)	0.8 (−0.6,2.2)	0.28

Note.

[*]
Baseline results are adjusted for rTMS treatment, study day, and treatment order.

[**]
Results obtained from the analytic models are adjusted for the main effect of rTMS treatment, time, their interaction, study day, treatment order, as well as the time-varying baseline craving measures taken prior to each condition.