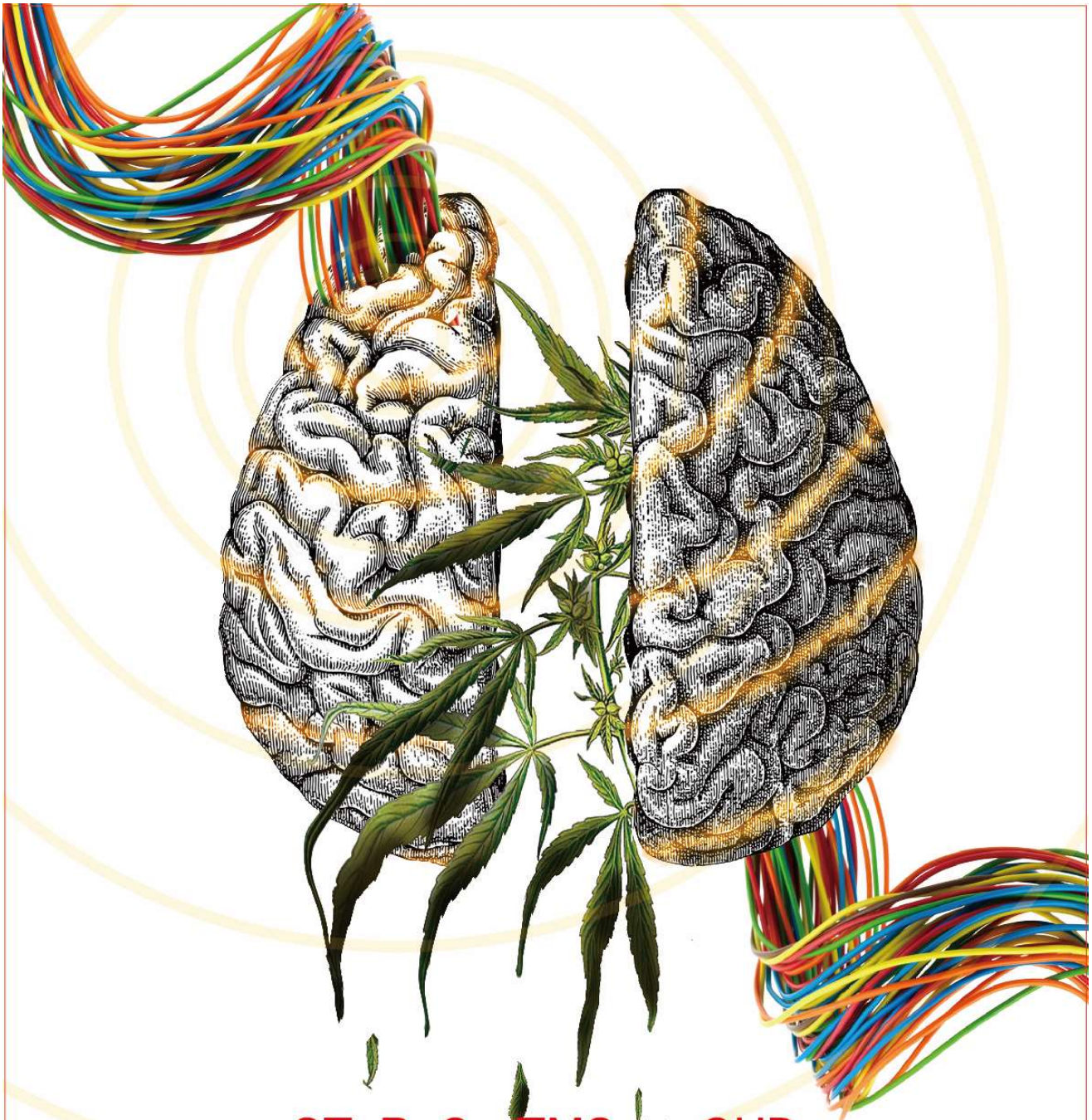

STOP-C-rTMS × CUD

精神物質(大麻)濫用至精神障礙

無創定位腦磁激療法於「大麻使用障礙症」患者的應用研究

Substance misuse To Psychiatric disorders for Cannabis
repetitive Transcranial Magnetic Stimulation for people with Cannabis Use Disorder

BDF210065 Final Research Report

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Abstract

Background

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique. Preliminary studies using rTMS targeting the dorsolateral prefrontal cortex (DLPFC) have shown therapeutic potential in treating substance use disorders. However, its clinical application for cannabis use disorder (CUD) remains underexplored.

Aims

This study aimed to evaluate the efficacy of high frequency rTMS targeting the left DLPFC in reducing cannabis craving and dependence, severity of CUD, frequency of cannabis use and abstinence in individuals with CUD. It also compared if there were similar efficacies from three different rTMS treatment schedules, ranging from two to five weeks of rTMS treatments.

Method

This interventional study employed a two-phase, three-arm, prospective, open-labelled design over a 12-month period. In the initial "active rTMS phase", each consented participant was randomized in the 1:1:1 ratio to receive 20 rTMS sessions according to three different schedules ranging from two to five weeks. Participants were then followed for a total of 12 months in the observational "maintenance phase". Outcomes including MCQ-SF, SDS, severity of DSM-5 defined CUD, frequency of cannabis use, days of abstinence from cannabis use, CPQ, BAI and BDI-II were assessed by investigators at baseline, post rTMS treatment schedules, 3rd, 6th and 12th months.

Results

Eighteen participants (12 males, mean age 25.92; 6 females, mean age 22.83) with moderate to severe CUD were randomized into six participants per groups. Every participant completed the 20 sessions of 15 Hz rTMS over the left DLPFC across 2 weeks (Group 1 with T2 schedule), 4 weeks (Group 2 with T4 schedule), or 5 weeks (Group 3 with T5 schedule). rTMS was well tolerated with no significant adverse event was reported. Across all treatment groups, rTMS significantly reduced cannabis craving, psychological dependence, severity of CUD, frequency of monthly cannabis use and problems related to cannabis use (all ps < 0.05) throughout the whole 12-month study period. No significant differences were revealed over rTMS treatment efficacy between the three different rTMS treatment schedules over time, except that rTMS treatment over 5 weeks showed a longer abstinence period at 3 months ($p < 0.05$)..

Conclusions

20-session high frequency rTMS over the left DLPFC is a well-tolerated and promising intervention for individuals with moderate to severe CUD in reducing cannabis addiction and related problems. While different rTMS treatment schedules may influence over short-term outcomes on craving and abstinence, further large-scale trials are needed to determine the optimal treatment schedules in treating CUD.

Keywords

Cannabis, dependence, cannabis use disorder, rTMS

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Glossary of Acronyms

ANOVA: Analysis of Variance

BAI: Beck Anxiety Inventory

BDF: Beat Drugs Fund

BDI-II: Beck Depression Inventory-II

CE: Conformité Européenne

CI: Confidence Interval

CocUD: Cocaine Use Disorder

CPQ: Cannabis Problems Questionnaire

CRDA: Central Registry of Drug Abuse

CUD: Cannabis Use Disorder

DLPFC: Dorsolateral Prefrontal Cortex

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

HA: Hospital Authority

ICD-11: International Statistical Classification on Diseases and Related Health Problems 11th Revision

M: Mean

MCQ-SF: Marijuana Craving Questionnaire – Short Form

MethUD: Methamphetamine Use Disorder

N: Number of participants

PFC: Prefrontal Cortex

PSUD: Psychoactive Substance Use Disorder

rTMS: repetitive Transcranial Magnetic Stimulation

SD: Standard Deviation

SDS: Severity of Dependence Scale

SUD: Substance Use Disorder

T2: Group 1 participants with all 20 rTMS sessions conducted in 2 weeks

T4: Group 2 participants with all 20 rTMS sessions conducted in 4 weeks

T5: Group 3 participants with all 20 rTMS sessions conducted in 5 weeks

THC: Tetrahydrocannabinol

Introduction

In Hong Kong, while the proportion of reported drug abusers using cannabis dropped from 17.0% in 2021 to 13.3% in 2024, cannabis remained as the 3rd most commonly abused psychotropic substance among all ages. In particular, among those aged <21 years, cannabis continued to be one of the most commonly abused psychotropic substances during the same surveillance period (Narcotics Division, 2024). Concerns have grown over the rising cannabis use since limited evidence was established from either psychotherapy or pharmacotherapy treatments for assisting long-term cure of cannabis use disorder (CUD) (Sherman & McRae-Clark, 2016; Chung et al., 2025). Recently, new interventions are more oriented in targeting the prefrontal cortex (PFC), where substance dependence is hypothesized to occur due to the imbalance of hyperactive emotional processing in ventral PFC and hypoactive executive control in dorsal PFC (Zhang et al., 2019). Enhancement of executive control is highlighted to reduce cue-induced craving and to minimize relapse in drug addiction due to exposure of cues, which is one of the core salient features of substance use disorder (SUD) (Ferguson & Shiffman, 2009).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that was found to be effective in reducing craving and substance consumption in SUD (Gorelick et al., 2014; Maiti et al., 2017; Zhang et al., 2019). It utilizes a fluctuating magnetic field generated by a coil placed over scalp which induces electrical currents in brain tissue and modulates neuronal firing. Therapeutic applications of rTMS had been established for treatment-resistant depression, and as an adjunctive treatment modality to medications for obsessive-compulsive disorder with the formal approvals granted by the US Food and Drug Administration (FDA) in 2008 and 2018, respectively (FDA, 2018). Combining rTMS with pharmacological treatments were also found to improve the clinical outcomes comparing to

placebo controls in Chinese populations with depression, schizophrenia, and Alzheimer's Disease (Wang et al., 2017; Wei et al., 2017; Wu et al., 2015). Recent systematic review and meta-analysis had looked more into the application of high frequency rTMS with excitatory stimulation to the dorsolateral PFC (DLPFC). The stimulation was postulated to strengthen the executive functions and cognitive control, resulting in reduced craving and addiction (Enokibara et al., 2016; Maiti et al., 2017; Zhang et al., 2019). In alcohol and nicotine use, such beneficial effects were also found to be dose-dependent, where repeated sessions (Barr et al., 2011) and number of pulses (Zhang et al., 2019) might predict the effect size from rTMS over the left DLPFC.

Long-term therapeutic effect of rTMS was suggested in people with stimulants use. In a pilot study of cocaine use disorder (CocUD), rTMS treatments over a month resulted in a significantly higher number of cocaine-free urine drug test when compared to control taking pharmacological treatment and lowered craving among cocaine abusers (Terraneo et al., 2016). A recent cohort study also demonstrated that rTMS for 11 weeks would lengthen the period to the first lapse of cocaine use to 91 days, significantly longer than the first lapse of 51 days in the control group (Madeo et al., 2020). Furthermore, trials investigating the therapeutic effects of rTMS for methamphetamine use disorder (MethUD) within the Chinese population showed a significant reduction in craving and withdrawal syndromes, and further improved abusers' cognitive function (Chen et al., 2020; Liang et al., 2018; Lin et al., 2019; Su et al., 2017). Recent studies also suggested that even 10 to 15 rTMS sessions could reduce the levels of depression and anxiety in addition to craving for CocUD and MethUD (Mansouriyeh et al., 2020; Soomro et al., 2020; Antonelli et al., 2021). In 2021, rTMS had received the approval from the Conformité Européenne (CE) of the European Union for treating psychoactive

substance use disorder (PSUD) in adults, especially for those with stimulant use to lessen their carving and relapses (MagVenture, 2021).

Nevertheless, the effect of rTMS for CUD is not well understood due to inadequate evidence available. The mechanism from rTMS on anti-craving effect through excitatory stimulation over DLPFC is not yet well-established (Gorelick et al., 2014; Sahlem et al., 2018), Sahlem and colleagues (2020) showed a large "intra-individual" effect in reducing cannabis use and spontaneous cannabis craving after 10 rTMS sessions. Prashad and colleagues (2019) also discovered that rTMS would normalize the elevated reactivity of posterior cingulate cortex/ precuneus towards external, self-relevant stimuli in cannabis users which suggested a potential heightened cue-induced attentional bias that leads to craving behaviors. Up to date, there is only one Phase 2 double-blind randomized controlled trial comparing active rTMS versus sham control in cannabis users with moderate to severe CUD that demonstrated good tolerability and therapeutic efficacy on frequency of cannabis use but not on craving (Sahlem et al., 2023) .

With the preliminary encouraging findings and therapeutic effects from rTMS as a safe treatment to cannabis abusers on DLPFC as in stimulants users, further research is needed to determine the optimal rTMS sessional schedule in treating CUD. The present pilot study therefore investigated whether multiple sessions of rTMS over DLPFC could reduce craving and its degree of severity in abusers with CUD, decrease their frequency and amount of cannabis consumed, and prolong their relapses in cannabis use. Three different rTMS treatment schedules with the same number of treatment sessions were compared in the current study as well.

Methods

Study Design

The present study employed a two-phase, three-arm, prospective, open-labelled design over a 12-month period (Figure 1). In the initial "active rTMS phase", every participant underwent 20 rTMS treatment sessions, but they were randomized to receive the sessions according to *three* different schedules:

- **Group 1** with *T2* schedule: all 20 rTMS sessions completed within *two weeks* (T2) with two treatment sessions per treatment-day for 5 consecutive days in a week;
- **Group 2** with *T4* schedule: all 20 rTMS sessions completed within *four weeks* (T4) with two treatment sessions per treatment-day for 5 consecutive days in the first week, followed by two treatment sessions per day across 5 days from second to fourth week when each treatment-session day should not be separated by more than three days; and
- **Group 3** with *T5* schedule: all 20 rTMS sessions completed within *five weeks* (T5) with two treatment sessions per treatment-day conducted across two visits per week.

The two rTMS sessions per treatment-day were separated by at least a 30-minute interval. Upon completion of rTMS in the same treatment-day, participants underwent clinical interviews and filled in self-reported questionnaires that probed various outcomes related to their cannabis use.

After the completion of their last scheduled rTMS session, participants entered the "maintenance phase" that involved only observational follow-up assessments at 3, 6, and 12 months later without further rTMS intervention.

The present study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority (HA) Hong Kong West Cluster (IRB Reference: UW 21-656). This study was also registered at the free public research website clinicaltrials.gov (NCT05292547).

Study Hypothesis

This study hypothesized that:

1. Efficacy-H_0: 20-session rTMS on DLPFC has no treatment efficacy in individuals suffering from moderate to severe DSM-5 defined CUD.
2. Treatment schedule-H_0: schedule of rTMS on DLPFC has no difference in treatment efficacy in individuals suffering from moderate to severe, DSM-5 defined CUD.

Prevalence and Sample Size

The estimated prevalence rates for CUD range from 2.9% to 19% worldwide (Balodis et al., 2018). A recent systematic review and meta-analysis suggested the prevalence of CUD among people who used cannabis could be as high as 22% (18-26%) (Leung et al., 2020). In the United States, Compton and colleagues (2019) suggested that the prevalence rates of DSM-5 defined mild, moderate and severe CUD in adult users were 12.4%, 3.1% and 1.3%, respectively. Locally, data from Central Registry of Drug Abuse (CRDA) between 2011 and 2020 revealed that over the past 10 years, the average number of all reported cannabis abusers was 437. Thus, the estimated numbers of users having different severity of CUD are 54 (mild), 14 (moderate) and 6 (severe).

Referencing to preliminary feasibility studies using rTMS targeting heavy cannabis users or at least moderate CUD (Sahlem, 2020), and from the clinical experiences that cannabis users who sought treatment with good adherence and attendance to follow-up were usually those with moderate or severe CUD, the sample size in the current study was thus pre-determined to have 18 participants. So, six subjects were being allocated to each of the three treatment groups.

Subject Recruitment

Participants were recruited territory-widely by snowball sampling. Self-referrals, referrals from substance abuse clinic services run under HA and non-governmental organizations working in anti-drug field in Hong Kong were all allowed. All participants provided written informed consent prior to any study procedure. All study procedures adhered to the Declaration of Helsinki. Participants received HKD$250 upon finishing their rTMS session and the assessments at each rTMS session-day during the "active rTMS phase", and at each follow-up day during the "maintenance phase".

Inclusion criteria

Eligible participants were aged between 18 and 65 years and able to provide written informed consent in Chinese or English. They should also report using cannabis or marijuana as their primary substance of abuse. The primary disorder of interest was a diagnosis of CUD classified according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5). The diagnosis of CUD was ascertained by using the Structured Clinical Interview for DSM-5 Disorders: Clinician Version (SCID-5-CV) (First et al., 2016).

Exclusion criteria

Participants aged under 18 years old or those were unable to provide informed consent were excluded. Other exclusion criteria included any comorbid psychiatric diagnosis of neurodevelopmental or neurocognitive disorders classified by DSM-5 or by the International Statistical Classification of Diseases and Related Health Problems 11th Revision (ICD-11). Participants with a comorbid SUD other than cannabis were deemed ineligible if their SUD met the criteria for a moderate or severe clinical threshold, that is, any other DSM-5 SUD severity score ≥4.

To ensure safety, any psychophysiological conditions contra-indicating to receive rTMS precluded eligibility. These conditions include:

- having electronic and/or magnetic implants (e.g. pacemaker, implantable cardioverter defibrillator, cerebral shunts, cochlear implant, etc.)
- having metallic or mechanic fragments (e.g., screws, plates, stents, clips, etc.) inside body
- pregnancy
- known or history of neurological conditions (e.g., cerebral vascular accidents, epilepsy, brain tumor or space occupying lesion, etc.)
- having poorly controlled or unstable diabetes mellitus
- receiving unstable dose(s) of antipsychotics, antidepressants, benzodiazepines and/or anticonvulsants in the past 6 months

Procedures

Intervention allocation and randomization

Consented participants were randomly assigned into one of the three treatment groups in a 1:1:1 ratio by simple randomization with computer generated sequence. As no sham rTMS method was used, neither participants nor researchers were blinded to the allocation.

Intervention

Following randomization, all participants entered the "active rTMS phase" when each participant received 20 rTMS treatment sessions in total in accordance to the three treatment schedules: T2, T4 and T5.

The rTMS was delivered using the MagVenture TMS system (MagPro® X100) equipped with a Cool-B70 Bended Butterfly Coil at the Queen Mary Hospital Neuromodulation Center. Stimulation targeted to the left DLPFC was localized using the Beam F3 method (ClinicalResearcher.org, n.d.). The rTMS dosing intensity protocol adhered to the CE-approved MagVenture's TMS therapy for treating PSUD (Madeo et al., 2020; MagVenture, n.d.). rTMS was delivered at a frequency of 15 Hz. Each train consisted of 60 pulses, with a 15-second inter-train pause, for a total of 40 trains per session, amounting to 2400 pulses per session over a 13-minute stimulation period.

Outcome Measures

Primary outcomes

1. *Craving*

Cannabis craving was measured with Marijuana Craving Questionnaire – Short Form (MCQ-SF; Heishman et al., 2009). This 12-item scale captured four dimensions of craving:

compulsivity, emotionality, expectancy, and purposefulness. Each item was on a 7-point Likert scale (strongly disagree = 1 to strongly agree = 7), with total scores ranging 12 – 84. Higher scores indicated stronger craving.

2. Dependence

Psychological dependence to cannabis was measured with the self-administered, 5-item Severity of Dependence Scale (SDS; Gossop et al., 1995). SDS assessed the sense of control, anxiety, worry, desire, and difficulty with stop using cannabis. Each item anchored on a 4-point Likert scale (never = 0 to always = 3) and the total score ranged 0 – 15 with higher numbers signalling greater dependence. A total SDS score ≥ 3 reaches the clinical threshold of cannabis dependence (Chung et al., 2025).

3. Severity of CUD

Severity of DSM-5 defined CUD were assessed by SCID-5-CV. The assessment identified 11 symptoms for CUD. The more the total number of symptoms signified the greater severity of CUD: mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6 or more symptoms).

4. *Frequency of cannabis use*

Participants reported their estimated frequency of cannabis use using the BDF Drug Use Frequency Question Sets 5-6 (BDFA, Narcotics Division, n.d.-a). In order to keep the consistency of time window for the variable in the analysis, the frequency variable was transformed into *times per month* for each assessment timepoint, with a maximum of 30 times per month.

5. Abstinence from cannabis use

Participants reported their last use of cannabis on an ordinal scale ranging from today/yesterday to abstinence for more than a year. The ordinal scale was then converted into approximate days of abstinence using the midpoint as a representative value as the following: today/yesterday = 1, within two to three days = 2.5, within a week = 5, last week = 10, two weeks ago = 17.5, three weeks ago/within this month = 25, one to three months ago = 60, more than three months and within one year = 180, greater than one year = 365. Higher numbers represented longer duration of abstinence.

Secondary outcomes

1. Urine drug test

Urine drug test was administered at baseline and at each follow-up assessment to detect tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis. This was to ensure that the participants were not under the influences of substance uses other than cannabis at the time of performing the rTMS, and to correlate with the status of self-reported cannabis use. The result of the urine drug test was coded in binary format (positive = 1, negative = 0) to reflect the presence of THC.

2. Problems related to cannabis use

Cannabis use related problems were measured by the 22-item Cannabis Problems Questionnaire (CPQ; Copeland et al., 2005). Participants rated the extent to which cannabis use impacted the various domains of their life, including relationships, occupational functioning, and health. Each item was on a 4-point Likert scale (not at all = 0 to severe = 3) and the total score ranged 0 – 66 with higher numbers representing more severe cannabis-related problems.

3. Mood symptomatology

Beck Anxiety Inventory (BAI; Beck et al., 1996) and Beck Depression Inventory-II (BDI-II; Beck et al., 1996) were use to assess participant's anxiety and depression symptomatology, respectively. Both inventories are self-reported 21-item scales assessing responses on a 4-point Likert scale (not at all = 0 to severely = 3), and thus each has the total score range of 0 – 63. Higher scores indicate worse symptomatology in anxiety or depression.

Statistical Analyses

The analysis adopted the per-protocol principle to include 18 participants who completed all assigned rTMS sessions, with six participants per group. Demographic information was summarized as means and standard deviations for continuous variables and counts with percentages for categorical variables. Group differences at baseline were tested using t-tests and chi-square tests where appropriate. Linear mixed-effects models were employed to investigate the efficacy of rTMS interventions and the effect of different schedules on outcome measures. Fixed effects were specified for treatment, time, and their interaction, with adjustment for baseline outcome. Random intercepts were specified at participant level, but random slopes were not specified due to small sample sizes.

To test the overall treatment effects by the fixed effects of time, the time variable was modelled as a categorical variable (i.e., "post-treatment", "3-month", "6-month", "12-month") with grand mean at pre-treatment serving as reference. "Post-treatment" referred to the finish timepoint of all rTMS sessions, which corresponded to the end of 2 weeks for T2, 4 weeks for T4, and 5 weeks for T5, respectively.

To examine group differences at each follow-up, the treatment variable was contrast-coded with T2 serving as reference: the first contrast tested whether T4 outperformed T2 and the second contrast tested whether T5 outperformed T2. Baseline outcomes were mean-centered and entered as a covariate. The significance testing for the fixed effects and interaction effects were examined with Type III ANOVA using Satterthwaite approximation. No missing data were imputed because linear mixed models provide unbiased estimates under the assumption of data missing at random. A planned logistic regression predicting rates of positive urine tests for cannabis could not be performed due to failure in model convergence caused by small sample sizes; instead, raw counts and percentages were reported. Pearson's test was performed to correlate the self-reported frequency and abstinence of cannabis use. A log-transformation was applied for days of abstinence in the regression analysis. All models converged and model diagnostics were visually inspected.

All significance tests were two-tailed with an α level of 0.05. Significant results rejected the null hypotheses.

All regressions were conducted with packages lme4 (version 1.1-35.5), lmeTest (version 3.1-3), and emmeans (version 1.10.4) for R programming language (version 4.4.1).

Results

During the study, two participants (one from Group 1 and one from Group 2) dropped out without completing all the rTMS sessions due to consent withdrawal: one from Group 1 who completed 2 rTMS sessions after one treatment-day, and one from Group 2 who completed 14 rTMS sessions after seven treatment-days. Therefore, two participants were additionally recruited to reach the targeted sample size. The final analysis included 18 participants who completed all rTMS sessions according to randomized schedules, with three balanced groups with six participants (Supplementary Materials Figure S1).

Participants also showed high fidelity for completing subsequent follow-up assessments with no differences in attendance rates across groups (Table 1). All participants tolerated rTMS well with no significant adverse events reported. The commonest side-effects were scalp discomfort (4.1%), dizziness (2.7%) and headache (1.91%) (Table 2) with no additional medical attention required.

Baseline Characteristics of the Participants

Table 3 summarized demographics, history of cannabis and other substance use, and outcome measures at baseline of the 18 participants prior to randomization. Most participants were male (66.67%), single (94.44%) and in their 20s (M = 24.89, SD = 7.97). Two-third of the participants received tertiary education (66.67%). They were having mild anxiety (M = 9.22, SD = 9.19) and moderate depressive state (M = 20.61, SD = 12.76). Half of the participants (55.56%) never registered with psychiatric services. Two of them (11.11%) who were under active psychiatric services and reported receiving regular antidepressants were from Group 3. No participant had admitted to detoxification facilities before.

All participants confirmed cannabis as their primary substance of abuse. Their average duration of cannabis use was more than five years with an average use of around 19 days per month. Many of them were smokers (88.89%) and drinkers (83.33%), and used more than one psychoactive substances in the past year (M = 1.17, SD = 0.38). LSD was the commonest other lifetime use substance among participants. Most participants (72.22%) were tested positive for cannabis on urine drug test at baseline, and the average reported abstinence period for cannabis abuse was less than two weeks. The average number of CUD symptoms as assessed by DSM-5 was 6.50 (SD = 2.26), reaching the clinical cut-off of "severe" CUD.

Overall, participants randomized to the three treatment groups were similar in terms of demographics and baseline outcome measures, except participants from Group 3 with T5 schedule reported no past LSD abuse, with lower CUD severity, and less cannabis-related problems at baseline.

Overall Treatment Effects from 20 rTMS Treatment Sessions to All 18 Participants

Primary outcomes

A significant fixed effect for time was observed for post-treatment cannabis craving as measured by MCQ-SF ($F(4, 54) = 8.75$, $p < 0.001$). There were an average reduction of 11.89 points in craving at post-treatment (95% CI = [-17.55, -6.23], $p < 0.001$), which maintained at similar magnitude at 3-month, 6-month, and 12-month follow-ups (all ps < 0.001) (Figure 2A and Supplementary Materials Table S1).

Similarly, a decrease of 1.56 points in cannabis dependence was observed at post-treatment as measured by SDS (95% CI = [-2.71, -0.40], $p = 0.009$). Such benefit maintained

at similar magnitude at all subsequent follow-up timepoints (all ps < 0.05; $F(4, 54) = 3.05$, $p = 0.024$) (Figure 2B and Supplementary Materials Table S2).

The degree of severity of DSM-5 defined CUD ($F(4, 54) = 2.59$, $p = 0.046$) also showed improvement from "severe" to "moderate" after rTMS treatment. Such improvement largely maintained at subsequent follow-up timepoints, except at the 6th month (Figure 2C and Table and Supplementary Materials Table S3).

In terms of active cannabis use, the results revealed a trend-significant decrease in monthly frequency of cannabis use ($F(4, 54) = 2.33$, $p = 0.067$). Specifically, the frequency in monthly use decreased by 5.57 times per month at post-treatment (95% CI [-10.38, -0.75], $p = 0.024$) and remained reduced at five to six times less per month at all follow-ups (all ps < 0.05) (Figure 2D and Supplementary Materials Table S4). Nevertheless, there were no significant changes in days of abstinence ($F(4, 54) = 1.01$, $P = 0.41$) observed during the study period (Figure 2E and Supplementary Materials Table S5).

Secondary outcomes

A linear decrease of positive THC urine rates was observed, from 72.22% (13/18) to 50.00% at 12-month follow-up (7/14, Table 4). The positive urine THC results corroborated to the self reported frequency of cannabis use ($r = 0.58$) and abstinence ($r = -0.60$).

Sustained reductions were also found in cannabis-related problems as measured by CPQ ($F(4, 54) = 6.31$, $p < 0.001$) (Figure 2F and Supplementary Table S6).

In contrast, the effects of rTMS on mood symptomatology were not consistent. No meaningful changes in anxiety symptomatology as measured by BAI were observed at any time ($F(4, 54) = 1.40$, $p = 0.24$) (Figure 2G and Supplementary Table S7). Although a significant fixed effect over time was observed for depression symptomatology as gauged by BDI-II ($F(4, 54) = 2.85$, $p = 0.032$), there were only transient significant reductions at the 3-month ($B = -7.65$, 95% CI = [-12.24, -3.05], $p = 0.001$) and 6-month ($B = -4.55$, 95% CI = [-9.08, -0.03], $p = 0.048$) follow-ups (Figure 2H and Supplementary Materials Table S8).

Treatment Effects from Three Different rTMS Treatment Schedules

To determine the optimal rTMS treatment schedule in treating CUD, the interaction effects between treatment and time were examined. No significant treatment by time interactions were found for any of the outcome measures (all ps > 0.05), indicating that the three treatment schedules, i.e., T2, T4 and T5, did not have systematically different response trajectories over the one-year study period. (Figure 3)

However, there were some preliminary evidence suggesting short-term differences existed between the three treatment schedules on cannabis craving and abstinence, albeit statistically significant only on abstinence. Group 2 with T4 schedule reported less cannabis craving as measured by MCQ-SF than Group 1 with T2 schedule at post-treatment (T4 × Post, $B = -13.67$, 95% CI = [-27.53, 0.19], $p = 0.053$) and such difference maintained at similar magnitude up to three months ($p = 0.058$) (Figure 3A and Supplementary Materials Table S1). Group 3 with T5 schedule reported significantly more number of days in abstinence at 3-month follow-up (T5 × Month 3; $B = 2.00$, 95%CI = [0.03, 3.98], $p = 0.047$) than Group 1 with T2 schedule, though such difference did not sustain till later study time points (Figure 3E and Supplementary Materials Table S5).

Discussion

Clinical Implications

The present study investigated the clinical efficacy of high-frequency rTMS applied to the left DLPFC in participants with moderate-to-severe CUD, who underwent 20 sessions of high-frequency 15 Hz rTMS delivered across three distinct schedules: 2-week, 4-week, and 5-week. Significant overall reductions were observed in all participants for both primary outcomes, including cannabis craving and dependence, severity of CUD and frequency of cannabis use, and secondary outcomes on cannabis use related problems. These desirable effects emerged as early as on post-treatment and sustained up to a 12-month follow-up period. However, the results did not indicate a statistically robust advantage favoring any one schedule over the others. Overall, it has potential application as clinical treatment in cannabis abusers with cannabis dependence.

The significant and enduring reduction in cannabis craving measured by MCQ-SF aligns well with existing evidence supporting high-frequency rTMS of the left DLPFC as effective in reducing craving across various substance use disorders, including alcohol, nicotine, cocaine, and methamphetamine use. The improvements observed in SDS measured psychological dependence, cannabis consumption and cannabis use related problems complement existing literature suggesting that excitatory rTMS enhances DLPFC-related executive control and scaffold improvements in substance use related behavioral changes (Sahlem et al., 2018, 2020, 2023; Chen et al., 2020; Belgers et al., 2022; Kan et al., 2023). However, days of abstinence from cannabis use were not significantly different after 20 sessions of rTMS treatment. It therefore highlighted the critical need to develop a more comprehensive treatment plan involving other treatment modalities, such as motivational

interviewing and motivational enhancement therapy, to enhance abstinence (Schwenker et al., 2023).

The present study also found short-term improvements in depressive symptoms but not in anxiety symptoms following rTMS treatment. Previous research indicated that rTMS targeting the left DLPFC can effectively reduce depressive symptomatology, possibly due to shared neurobiological mechanisms underlying depression and substance use disorders (Brunoni et al., 2017; Mehta et al., 2024). Nonetheless, the current beneficial effects from rTMS on CUD appeared independent to the short-term improvements in depressive state of the participants. Whereas the lack of significant improvement in anxiety symptoms may suggest a mere reflection that participants in this study only had low level of anxiety at baseline.

The absence of clear evidence favoring one rTMS treatment schedule over another is notable. Although preliminary analyses revealed subtle close-to-significant advantages for the 4-week rTMS schedule in reducing cannabis craving immediately post-treatment and significant greater benefits for the 5-week rTMS schedule in extending days of cannabis abstinence at the 3-month follow-up, these effects diminished over the 12-month period. This observation aligns with existing literature suggesting that the cumulative dose of rTMS, reflected by the total number of pulses and sessions administered, might exert greater influence on clinical outcomes than the specific distribution or frequency of sessions (Song et al., 2019; Zhang et al., 2019). Therefore, the results underscore the need for further research into both optimal “dosing” and refining session scheduling.

Study Limitations and Strengths

Several methodological limitations warrant careful consideration. Similar to other studies focusing rTMS as treatment for CUD, critical limitation was the small sample size which led to low statistical power that may obscure meaningful differences across groups with treatment schedules. Future research should prioritize larger, adequately powered double-blind, randomized, sham-controlled trials to conclusively establish the optimal scheduling of rTMS for individuals with moderate to severe CUD. Moreover, the demographic homogeneity of the sample with primarily young, tertiary educated, Asian participants may limit the generalizability of the finding to a more diverse population suffering CUD.

Several strengths that bolster the significance of this study. Notably, participant retention was high compared to previous pilot study targeting CUD populations (Sahlem et al., 2020), possibly due to the higher monetary incentives employed during subject recruitment and follow-ups. Additionally, this trial represents, to our knowledge, the first longitudinal study evaluating rTMS effects over a 12-month follow-up period within a cannabis-dependent population with moderate to severe CUD. In light of the current lack of standardized, effective treatment modalities for CUD, the sustained positive outcomes, in particular on cannabis craving, dependence and related problems documented throughout the study provide compelling preliminary evidence to support further exploration and clinical adoption of rTMS as an adjunctive treatment for CUD.

Future Directions

Future research should explore combination therapeutic strategies that integrate rTMS with cognitive-behavioral therapy or other psychotherapeutic interventions, such as motivational interviewing or motivation enhancement therapy. This recommendation is

supported by emerging evidence indicating potential synergistic effects of combined therapies, which may enhance treatment efficacy by simultaneously targeting neural circuitry implicated in craving and reinforcing behavioral coping strategies to manage substance use triggers (Dalhuisen et al., 2022; Hu et al., 2022). Such comprehensive approaches might not only optimize immediate clinical outcomes but also ensure durability of treatment effects and address the critical issue of long-term abstinence and relapse prevention.

Conclusions

The current study substantiates 20-session, high-frequency rTMS on the left DLPFC as an effective treatment modality for moderate to severe CUD. Desirable treatment outcomes including reduced cannabis craving, dependence, severity of CUD, consumption and relate problems were observed. These benefits could remain meaningful up to one year. However, despite these positive therapeutic efficacies, complete abstinence remained uncommon, and the drop in severity of CUD remained unsatisfactory after one year. Overall, this study shows that rTMS has potential application as clinical treatment in cannabis abusers with cannabis dependence.

Consequently, future research should urgently explore combined treatment approaches that integrate rTMS with psychotherapeutic interventions to maximize immediate therapeutic efficacy and facilitate long-term substantial improvement in individuals with moderate to severe CUD.

Tables

Table 1. Attendance rates at different follow-up time points of all the three treatment groups.

	Total (N = 18)	**Group 1** (N = 6)	**Group 2** (N = 6)	**Group 3** (N = 6)
Pre-treatment	18 (100.00%)	6 (100.00%)	6 (100.00%)	6 (100.00%)
Post-treatment	18 (100.00%)	6 (100.00%)	6 (100.00%)	6 (100.00%)
3-Month	15 (83.33%)	5 (83.33%)	5 (83.33%)	5 (83.33%)
6-Month	16 (88.89%)	5 (83.33%)	6 (100.00%)	5 (83.33%)
12-Month	15 (83.33%)	5 (83.33%)	5 (83.33%)	5 (83.33%)

Note. The total number of subjects completed the subsequent 3-, 6- and 12- month assessments were not equal to 18 subjects. Subjects were allowed to continue on subsequent follow-up assessments even when they missed any one of the them from 3 months onwards, provided that they had completed all the rTMS sessions and the corresponding "post-treatment" assessments. This allowed the evaluation of the longitudinal, longer-term post rTMS effects to reflect the real-world setting.

Table 2. Side-effects reported by the 18 participants who completed the 20 rTMS sessions according to randomized schedules.

Side effects reported	**Number of events** (%)
Angioedema/ urticaria	1 (0.27)
Anxiety	4 (0.11)
Dental Pain	3 (0.83)
Distractibility	2 (0.55)
Dizziness	10 (2.7)
Headache	7 (1.91)
Hypomania	0
Irritability	0
Nausea	4 (1.1)
Numbness	5 (1.38)
Scalp discomfort	15 (4.1)
Seizure	0

Note. % was calculated based on a total of 360 rTMS sessions.

Table 3. Demographic characteristics, history of cannabis and other substance use, and outcome measures of the participants at baseline.

	Total (N = 18)	**Group 1** (N = 6)	**Group 2** (N = 6)	**Group 3** (N = 6)	***p***
Male, Count (%)	12 (66.67%)	3 (50.00%)	4 (66.67%)	5 (83.33%)	.
Age, Mean (SD)	24.89 (7.97)	21.33 (1.37)	25.00 (6.75)	28.33 (11.79)	.
University undergraduate, Count (%)	12 (66.67%)	4 (66.67%)	6 (100.00%)	2 (33.33%)	.
Married, Count (%)	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	.
Forensic history, Count (%)	3 (16.67)	1 (16.67%)	1 (16.67%)	1 (16.67%)	.
Smoker, Count (%)	16 (88.89%)	5 (83.33%)	6 (100.00%)	5 (83.33%)	.
Drinker, Count (%)	15 (83.33%)	5 (83.33%)	6 (100.00%)	4 (66.67)	.
Drinking years, Mean (SD)	6.19 (4.40)	5.83 (1.60)	8.14 (5.55)	4.60 (4.10)	.
In-patient, Counts (%)	3 (16.67%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	.
Out-patient, Counts (%)	5 (27.78%)	2 (33.33%)	1 (16.67%)	2 (33.33%)	.
Detox center admission, Counts (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	.
Cannabis use (Mean [SD])					
Age of first use	18.28 (4.03)	17.17 (2.79)	18.83 (5.27)	18.83 (4.17)	.
Days since last use	2.67 (2.25)	2.00 (1.26)	3.33 (2.94)	2.67 (2.42)	.
Duration in months	65.28 (85.73)	53.14 (38.49)	56.57 (33.74)	95.83 (143.56)	.
Frequency in the past month	18.83 (11.71)	20.33 (8.89)	17.33 (14.79)	18.33 (12.78)	.
Lifetime history of other substance use (Count [%])					
Alprazolam	2 (11.11%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	.
Cocaine	3 (16.67%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	.
Ketamine	3 (16.67%)	1 (16.67%)	1 (16.67%)	1 (16.67%)	.
LSD	9 (50.00%)	5 (83.33%)	4 (66.67%)	0 (0.00%)	* T2 > T5
Magic Mushroom	4 (22.22%)	1 (16.67%)	3 (50.00%)	0 (0.00%)	.
MDMA	1 (5.56%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	.
Mescaline	3 (16.67%)	2 (33.33%)	1 (16.67%)	0 (0.00%)	.
Methaqualone	1 (5.56%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	.
Methamphetamine	2 (11.11%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	.
Methylphenidate	1 (5.56%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	.
Number of other substances used (Mean [SD])					
within a year	1.17 (0.38)	1.17 (0.41)	1.33 (0.52)	1.00 (0.00)	.
within 3 months	0.94 (0.54)	1.17 (0.41)	0.83 (0.75)	0.83 (0.41)	.
Outcome measures at baseline (Mean [SD])					
Primary outcomes					
MCQ-SF	46.33 (15.78)	37.33 (15.71)	54.50 (7.71)	47.17 (19.04)	.
SDS	6.61 (3.22)	5.33 (1.63)	7.67 (1.51)	6.83 (5.19)	.
DSM-5	6.50 (2.26)	6.17 (2.48)	8.33 (1.37)	5.00 (1.55)	* T4 > T5
Frequency of cannabis use (times per month)	18.83 (11.73)	20.33 (8.89)	17.33 (14.79)	18.83 (12.78)	.
Abstinence from cannabis use (days)	12.72 (22.01)	4.25 (4.49)	21.33 (29.99)	12.58 (23.49)	.
Secondary outcomes					
CPQ	11.17 (4.68)	11.17 (5.27)	14.17 (2.14)	8.17 (4.54)	* T4 > T5
BAI	9.22 (9.19)	7.83 (6.79)	9.83 (7.70)	10.00 (13.34)	.
BDI-II	20.61 (12.76)	18.17 (9.79)	24.00 (11.98)	19.67 (17.10)	.

Note. Asterisk (*) denotes significant group differences with Bonferroni-adjusted $p < 0.05$. LSD = Lysergic Acid Diethylamide, MDMA = 3, 4-methylenedioxymethamphetamine, N = number of participants, SD = standard deviation, T2 = Group 1 participants with all rTMS sessions conducted in 2 weeks, T4 = Group 2 participants with all rTMS sessions conducted in 4 weeks, T5 = Group 3 participants with all rTMS sessions conducted in 5 weeks

Table 4. Rates of positive urine drug tests for THC of all the three treatment groups at different follow-up timepoints.

	Total	Group 1	Group 2	Group 3
Pre-treatment	13/18 (72.22%)	4/6 (66.67%)	4/6 (66.67%)	5/6 (83.33%)
Post-treatment	13/18 (72.22%)	5/6 (83.33%)	5/6 (83.33%)	3/6 (50.00%)
Month 3	8/15 (53.33%)	3/5 (60.00%)	3/5 (60.00%)	2/5 (40.00%)
Month 6	9/16 (56.25%)	3/5 (60.00%)	3/6 (50.00%)	3/5 (60.00%)
Month 12	7/14 (50.00%)	2/5 (40.00%)	3/5 (60.00%)	2/4 (50.00%)

Note. The number of subjects in the denominator under each group referred to those who provided urine samples at the subsequent 3-, 6- and 12- month assessments, and thus the total number of subjects were not equal to 18 subjects. One subject in Group 3 attended the 12-month follow-up assessment but did not provide the urine sample. Subjects were allowed to continue on subsequent follow-up assessments and to provide their urine samples even when they missed any one of the them from 3 months onwards, provided that they had completed all the rTMS sessions and the corresponding "post-treatment" assessments. This allowed the evaluation of the longitudinal, longer-term post rTMS effects to reflect the real-world setting.

Figures

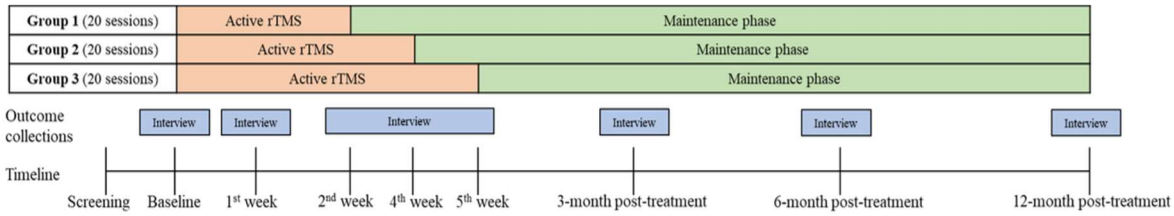

Figure 1. Schedules of rTMS sessions and follow-up assessment timepoints for the three treatment groups over the 12-month study period.

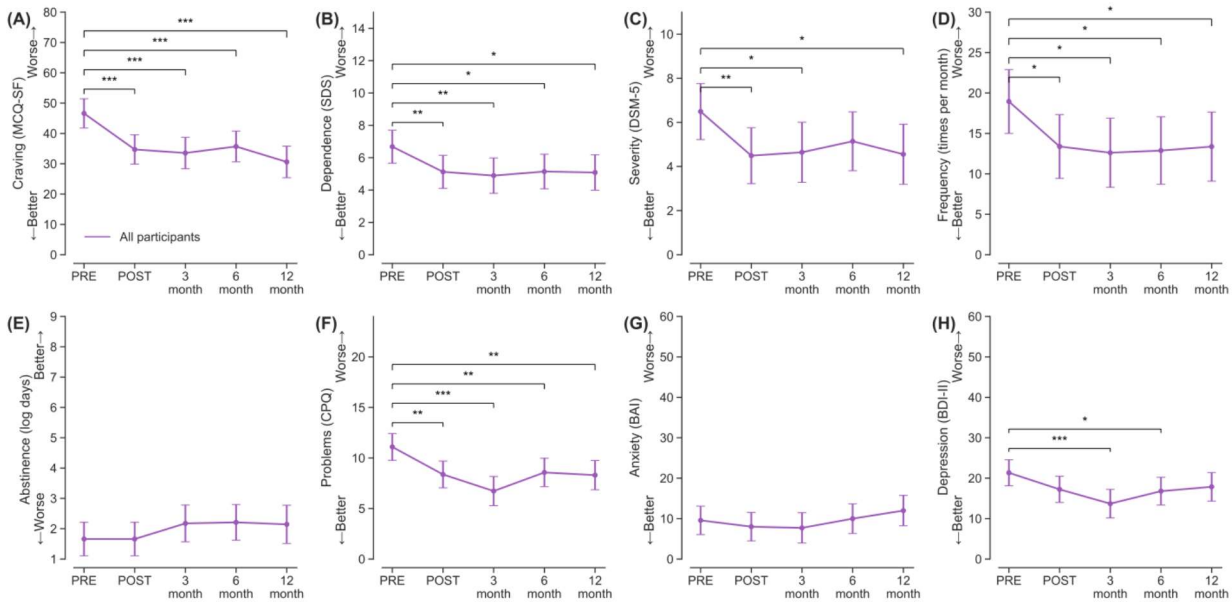

Figure 2. Estimated marginal means for the overall treatment effects from 20 rTMS treatment sessions over time for all 18 participants.

Note. Asterisk (*) denotes significant group differences with *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$.

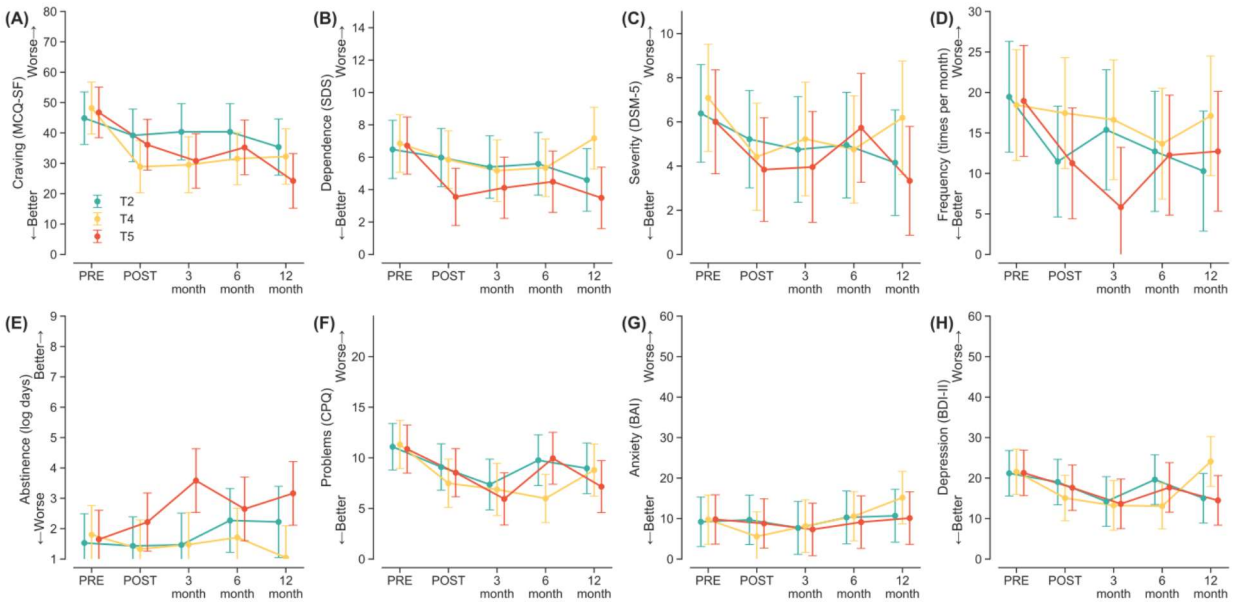

Figure 3. Estimated marginal means by treatment groups with three different rTMS schedules over time.

Note. T2 = Group 1 participants with all rTMS sessions conducted in 2 weeks, T4 = Group 2 participants with all rTMS sessions conducted in 4 weeks, T5 = Group 3 participants with all rTMS sessions conducted in 5 weeks.

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Supplementary Materials

Table S1. Results for linear mixed-effects model for cannabis craving (MCQ-SF).

Predictors	Estimates	CI	P
(Intercept)	9.02	-2.87 – 20.91	0.135
Baseline	0.81	0.57 – 1.04	**<0.001**
T4 (– T2)	3.34	-9.07 – 15.75	0.593
T5 (– T2)	1.91	-10.05 – 13.87	0.750
Post (– Pre)	-11.89	-17.55 – -6.23	**<0.001**
Month 3 (– Pre)	-13.06	-19.05 – -7.08	**<0.001**
Month 6 (– Pre)	-10.90	-16.78 – -5.02	**<0.001**
Month 12 (– Pre)	-16.00	-21.99 – -10.02	**<0.001**
T4 × Post	-13.67	-27.53 – 0.19	0.053
T5 × Post	-5.00	-18.86 – 8.86	0.474
T4 × Month 3	-14.19	-28.86 – 0.47	0.058
T5 × Month 3	-11.50	-26.16 – 3.17	0.122
T4 × Month 6	-12.17	-26.45 – 2.11	0.094
T5 × Month 6	-7.05	-21.72 – 7.63	0.341
T4 × Month 12	-6.47	-21.14 – 8.19	0.381
T5 × Month 12	-13.05	-27.72 – 1.63	0.080

Table S2. Results for linear mixed-effects model for cannabis dependence (SDS).

Predictors	Estimates	CI	P
(Intercept)	1.04	-0.83 – 2.91	0.269
Baseline	0.84	0.60 – 1.08	**<0.001**
T4 (– T2)	0.37	-2.17 – 2.91	0.773
T5 (– T2)	0.24	-2.26 – 2.74	0.851
Post (– Pre)	-1.56	-2.71 – -0.40	**0.009**
Month 3 (– Pre)	-1.79	-3.02 – -0.56	**0.005**
Month 6 (– Pre)	-1.54	-2.74 – -0.33	**0.013**
Month 12 (– Pre)	-1.60	-2.82 – -0.37	**0.011**
T4 × Post	-0.50	-3.34 – 2.34	0.726
T5 × Post	-2.67	-5.50 – 0.17	0.065
T4 × Month 3	-0.59	-3.59 – 2.41	0.695
T5 × Month 3	-1.52	-4.52 – 1.49	0.317
T4 × Month 6	-0.61	-3.54 – 2.31	0.677
T5 × Month 6	-1.34	-4.35 – 1.67	0.376
T4 × Month 12	2.21	-0.79 – 5.21	0.146
T5 × Month 12	-1.34	-4.35 – 1.67	0.376

Table S3. Results for linear mixed-effects model for severity of cannabis use disorder (DSM-5).

Predictors	Estimates	CI	P
(Intercept)	2.11	-1.59 – 5.81	0.258
Baseline	0.68	0.14 – 1.21	**0.014**
T4 (– T2)	0.70	-2.59 – 4.00	0.671
T5 (– T2)	-0.38	-3.53 – 2.77	0.811
Post (– Pre)	-2.00	-3.44 – -0.56	**0.007**
Month 3 (– Pre)	-1.85	-3.38 – -0.32	**0.019**
Month 6 (– Pre)	-1.35	-2.85 – 0.15	0.078
Month 12 (– Pre)	-1.94	-3.47 – -0.41	**0.014**
T4 × Post	-1.50	-5.04 – 2.04	0.400
T5 × Post	-1.00	-4.54 – 2.54	0.574
T4 × Month 3	-0.23	-3.98 – 3.52	0.904
T5 × Month 3	-0.41	-4.16 – 3.33	0.826
T4 × Month 6	-0.90	-4.55 – 2.75	0.625
T5 × Month 6	1.16	-2.60 – 4.92	0.540
T4 × Month 12	1.34	-2.41 – 5.09	0.479
T5 × Month 12	-0.44	-4.20 – 3.32	0.816

Table S4. Results for linear mixed-effects model for frequency of use (in times per month).

Predictors	Estimates	CI	P
(Intercept)	6.41	0.63 – 12.18	**0.030**
Baseline	0.66	0.44 – 0.88	**<0.001**
T4 (– T2)	-1.02	-10.68 – 8.64	0.833
T5 (– T2)	-0.51	-10.15 – 9.13	0.916
Post (– Pre)	-5.57	-10.38 – -0.75	**0.024**
Month 3 (– Pre)	-6.34	-11.42 – -1.25	**0.015**
Month 6 (– Pre)	-6.07	-11.07 – -1.07	**0.018**
Month 12 (– Pre)	-5.58	-10.67 – -0.49	**0.032**
T4 × Post	7.00	-4.79 – 18.79	0.240
T5 × Post	0.30	-11.49 – 12.09	0.960
T4 × Month 3	2.26	-10.21 – 14.73	0.718
T5 × Month 3	-9.05	-21.52 – 3.42	0.152
T4 × Month 6	1.96	-10.18 – 14.11	0.748
T5 × Month 6	0.05	-12.43 – 12.53	0.994
T4 × Month 12	7.84	-4.64 – 20.32	0.214
T5 × Month 12	2.95	-9.53 – 15.43	0.638

Table S5. Results for linear mixed-effects model for abstinence (in log-transformed days).

Predictors	Estimates	CI	P
(Intercept)	0.69	0.02 – 1.35	**0.044**
Baseline	0.59	0.37 – 0.81	**<0.001**
T4 (– T2)	0.27	-1.09 – 1.63	0.691
T5 (– T2)	0.12	-1.24 – 1.47	0.863
Post (– Pre)	-0.00	-0.77 – 0.77	0.999
Month 3 (– Pre)	0.52	-0.29 – 1.32	0.207
Month 6 (– Pre)	0.55	-0.24 – 1.34	0.171
Month 12 (– Pre)	0.48	-0.34 – 1.31	0.246
T4 × Post	-0.38	-2.26 – 1.50	0.691
T5 × Post	0.67	-1.21 – 2.55	0.481
T4 × Month 3	-0.26	-2.23 – 1.72	0.794
T5 × Month 3	2.00	0.03 – 3.98	**0.047**
T4 × Month 6	-0.83	-2.76 – 1.10	0.392
T5 × Month 6	0.26	-1.71 – 2.24	0.792
T4 × Month 12	-1.45	-3.49 – 0.60	0.162
T5 × Month 12	0.82	-1.22 – 2.87	0.424

Table S6. Results for linear mixed-effects model for cannabis problem (CPQ).

Predictors	Estimates	CI	P
(Intercept)	0.85	-1.79 – 3.49	0.522
Baseline	0.92	0.72 – 1.13	**<0.001**
T4 (– T2)	0.23	-3.07 – 3.53	0.891
T5 (– T2)	-0.23	-3.53 – 3.07	0.891
Post (– Pre)	-2.72	-4.42 – -1.02	**0.002**
Month 3 (– Pre)	-4.37	-6.16 – -2.57	**<0.001**
Month 6 (– Pre)	-2.52	-4.29 – -0.76	**0.006**
Month 12 (– Pre)	-2.79	-4.58 – -1.00	**0.003**
T4 × Post	-1.83	-6.00 – 2.33	0.382
T5 × Post	-0.33	-4.50 – 3.83	0.873
T4 × Month 3	-0.72	-5.11 – 3.68	0.746
T5 × Month 3	-1.19	-5.59 – 3.20	0.589
T4 × Month 6	-4.00	-8.29 – 0.28	0.066
T5 × Month 6	0.42	-3.98 – 4.82	0.850
T4 × Month 12	-0.40	-4.80 – 4.00	0.856
T5 × Month 12	-1.58	-5.98 – 2.82	0.475

Table S7. Results for linear mixed-effects model for anxiety symptomatology (BAI).

Predictors	Estimates	CI	P
(Intercept)	2.55	-1.83 – 6.92	0.249
Baseline	0.72	0.44 – 1.01	**<0.001**
T4 (– T2)	0.55	-7.98 – 9.09	0.898
T5 (– T2)	0.60	-7.94 – 9.14	0.889
Post (– Pre)	-1.56	-5.31 – 2.20	0.411
Month 3 (– Pre)	-1.86	-5.84 – 2.12	0.354
Month 6 (– Pre)	0.42	-3.49 – 4.33	0.830
Month 12 (– Pre)	2.42	-1.56 – 6.40	0.229
T4 × Post	-4.67	-13.87 – 4.53	0.315
T5 × Post	-1.50	-10.70 – 7.70	0.746
T4 × Month 3	-0.10	-9.85 – 9.66	0.984
T5 × Month 3	-0.97	-10.73 – 8.78	0.843
T4 × Month 6	-0.26	-9.75 – 9.23	0.956
T5 × Month 6	-1.76	-11.53 – 8.00	0.720
T4 × Month 12	3.93	-5.82 – 13.69	0.423
T5 × Month 12	-1.16	-10.93 – 8.60	0.813

Table S8. Results for linear mixed-effects model for depression symptomatology (BDI-II).

Predictors	Estimates	CI	P
(Intercept)	1.33	-3.02 – 5.68	0.544
Baseline	0.94	0.79 – 1.08	**<0.001**
T4 (– T2)	0.38	-7.58 – 8.33	0.925
T5 (– T2)	0.10	-7.82 – 8.01	0.981
Post (– Pre)	-4.11	-8.48 – 0.25	0.064
Month 3 (– Pre)	-7.65	-12.24 – -3.05	**0.001**
Month 6 (– Pre)	-4.55	-9.08 – -0.03	**0.048**
Month 12 (– Pre)	-3.48	-8.08 – 1.12	0.136
T4 × Post	-4.33	-15.03 – 6.36	0.421
T5 × Post	-1.50	-12.19 – 9.19	0.780
T4 × Month 3	-1.36	-12.62 – 9.89	0.810
T5 × Month 3	-0.68	-11.93 – 10.58	0.905
T4 × Month 6	-6.93	-17.91 – 4.05	0.212
T5 × Month 6	-2.03	-13.28 – 9.23	0.720
T4 × Month 12	8.70	-2.55 – 19.96	0.127
T5 × Month 12	-0.63	-11.88 – 10.63	0.912

Figure S1. CONSORT flow diagram (n = number of participant).