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Phase 1 Open-Label Pilot Trial of H4 Deep Repetitive Transcranial Magnetic Stimulation for Adults With Moderate-to-Severe Cannabis Use Disorder

James MacKillop, PhD, CPsych^{1,2,3} ; Carly McIntyre-Wood, MSc^{1,2}; Emily Vandehei, MSW¹; Horodjei Yaya, MSc¹; Anne-Marie Di Passa, MSc¹; Shelby Prokop-Millar, BSc^{1,2}; Allan Fein, MSc^{1,2}; Andrew Yang, MA^{1,4,5,6}; Mahmoud Elsayed, MEng^{1,2,3}; Benjamin Schwartzmann, MSc⁷; Faranak Farzan, PhD⁷; Emily MacKillop, PhD, CPsych, ABPP-CN^{1,2}; Dante Duarte, MD, PhD^{1,2}

ABSTRACT

Objectives: Cannabis use disorder (CUD) is a significant public health problem and no medical treatments have received regulatory approval to date. Deep repetitive transcranial magnetic stimulation (dTMS) provides brief powerful bursts of electromagnetic stimulation to brain networks implicated in psychiatric disorders and the Heschl (H)-4 coil, which targets the lateral prefrontal cortex and anterior insula, is approved for tobacco use disorder. This phase 1 open-label pilot study evaluated the feasibility and tolerability of H4 dTMS in conjunction with standard care for adults with moderate-to-severe CUD who were seeking treatment.

Materials and Methods: Participants received 18 sessions of H4 dTMS (three weeks of five sessions per week, one week of three sessions) in conjunction with standard care. Feasibility was operationalized as treatment completion and attainment of therapeutic dose ($\geq 90\%$ resting motor threshold). Tolerability was operationalized as adverse events. Exploratory clinical and mechanistic outcomes were 5-mg standard units of Δ^9 -tetrahydrocannabinol (THC), CUD symptoms, cravings, cannabis reinforcing value, self-efficacy, internalizing and somatic symptoms, and neuropsychological performance.

Results: Of 11 participants (64% female, CUD symptoms mean $\pm$ SD = 9.27 ± 1.10), 92% completed all dTMS treatments, of whom 91% reached therapeutic dose. Tolerability was high, with the most common adverse events being low rates (2.4%–9.2%) of headache, drowsiness, and scalp pain, primarily during the first week. No participants experienced serious adverse events. Regarding exploratory clinical outcomes, significant reductions were observed in THC consumption, CUD symptoms, cravings, cannabis reinforcing value, and depressive, anxiety, and somatic symptoms ($ps < 0.01$ – 0.001), and significant increases were observed in self-efficacy ($p < 0.001$). No significant effects on neuropsychological performance were detected.

Conclusions: These findings suggest this H4 dTMS protocol was feasible, tolerable, and associated with clinically meaningful reductions in clinical outcomes and related mechanisms, albeit in an uncontrolled design. The results support the prospect of a randomized controlled trial to test the efficacy of this novel intervention for CUD.

Clinical Trial Registration: The [Clinicaltrials.gov](https://clinicaltrials.gov) registration number for the study is NCT06114212.

Keywords: cannabis, cannabis use disorder, dTMS, neuromodulation, rTMS

Address correspondence to: James MacKillop, PhD, CPsych, Peter Boris Centre for Addictions Research, Michael G. DeGroote Centre for Medicinal Cannabis Research, Department of Psychiatry and Behavioural Neurosciences, Hamilton, Canada. Email: jmackill@mcmaster.ca

¹ Peter Boris Centre for Addictions Research, St. Joseph's Healthcare Hamilton, Hamilton, Canada;

² Michael G. DeGroote Centre for Medicinal Cannabis Research, McMaster University, Hamilton, Canada;

³ Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Canada;

⁴ Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada;

⁵ Neuron to Brain Lab, Center for Advancing Neurotechnological Innovation to Application, University Health Network, Toronto, Canada;

⁶ Division of Neurosurgery, Department of Surgery, Toronto Western Hospital, University of Toronto, Toronto, Canada; and

⁷ School of Mechatronic Systems Engineering, Simon Fraser University, Burnaby, Canada

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INTRODUCTION

Cannabis use is increasingly prevalent, and cannabis use disorder (CUD), the psychiatric diagnosis for clinically significant cannabis problems, is a substantial public health problem.^{1,2} In Canada, for example, where recreational cannabis has been legal since 2018, the lifetime prevalence of CUD is 7%,³ with approximately 5% of active consumers reporting compulsive use.⁴ Clinically, evidence supports psychologic interventions, including motivational enhancement therapy (MET), cognitive behavioral therapy, and contingency management (CM),^{5,6} but response is variable, and effect sizes are small to medium in magnitude.⁶ Several pharmacologic treatments have been explored but without consistent evidence of efficacy,^{6,7} and no medications are currently approved by national regulatory bodies.

An emerging treatment for substance use disorders (SUDs) in general⁸ and CUD in particular⁹ is neuromodulation, the stimulation of brain regions or circuits using several different approaches. These include noninvasive approaches, such as transcranial electrical stimulation, which provides weak electrical currents to the scalp to facilitate neural firing,^{10,11} and invasive approaches, such as deep brain stimulation, a neurosurgical treatment involving the implantation of electrodes in the brain for long-term direct electrical stimulation.^{12–14} Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive modality that traditionally uses figure-eight-shaped electromagnetic coils to transmit brief powerful bursts of electrical stimulation repeatedly to specific regions of the brain.

Several studies have evaluated traditional figure-eight rTMS in relation to CUD. Using a two-session (low-frequency vs high-frequency stimulation of the posterior cingulate and precuneus) cross-over design in regular cannabis users and controls, Prashad et al¹⁵ found effects on specific features of electroencephalography in response to cannabis cues but no significant effect on craving. In an early cross-over design evaluating stimulation of the left dorso-lateral prefrontal cortex (dlPFC), Sahlem et al¹⁶ found evidence of protocol feasibility but no effect on cue-elicited craving; however, only a single session of active stimulation was used. Subsequently, in a case series of 20 sessions of stimulation in conjunction with MET, Sahlem et al¹⁷ reported high dropout (six/nine), although those who completed the protocol exhibited notable reductions in cravings and cannabis use. In a much larger sham-controlled randomized controlled trial of this protocol ($n = 72$),¹⁸ active treatment was associated with more weeks of abstinence, albeit nonsignificantly ($p = 0.14$), and fewer weekly cannabis-use days during the final two weeks ($p = 0.02$), although no significant changes in craving were observed. Finally, in 19 individuals with CUD and schizophrenia/schizoaffective disorder,¹⁹ a 20-session pilot trial of stimulation of the left and right dlPFC vs sham (with both conditions also receiving CM) found evidence of feasibility, a directionally favorable reduction in grams per day (albeit not statistically significant), and a statistical trend toward reduction in craving ($p = 0.06$). Thus, the findings using traditional rTMS are highly heterogeneous and modestly supportive.

An alternative to traditional rTMS is deep rTMS (distinguished as dTMS henceforth), which uses helmet-based Heschl coils (H-coils) that stimulate multiple regions in cortical networks implicated in psychiatric disorders and do so at a deeper level. This modality has been applied to numerous conditions, and on the basis of favorable randomized controlled trials,^{20,21} the H1 and H7 coils are cleared by Health Canada and the Food and Drug Administration (FDA) for major depressive disorder and obsessive-compulsive

disorder, respectively. For SUDs, early studies of tobacco use disorder (TUD) were highly promising,^{22,23} leading to a pivotal multisite trial that found evidence of efficacy²⁴ and led to the same regulatory bodies approving H4 dTMS for TUD. The H4 coil specifically stimulates the lateral prefrontal cortex (PFC) and the insula, both of which are implicated in smoking cessation and the pathophysiology of addiction.^{1,25,26} Most recently, combining H4 coil stimulation with varenicline was associated with robust efficacy for TUD, suggesting promise of the combined intervention.²⁷ The H4 coil, although not the H8 coil,²⁸ has also recently demonstrated benefit in the treatment of alcohol use disorder.²⁹ Taken together, these findings suggest promise of the H4 coil for CUD treatment.

As a first step toward testing dTMS for CUD, the present study undertook a pilot trial of the H4 coil in treatment-seeking adults with moderate-to-severe CUD. The primary aim was evaluating the feasibility and tolerability of the intervention, a critical role for pilot studies before proceeding to efficacy trials.³⁰ Secondary aims were to characterize changes clinical outcomes (ie, changes in standard units of tetrahydrocannabinol [THC] and CUD symptoms) and potential mechanisms to inform future efficacy trials. These candidate mechanisms were informed by the Addictions Neuroclinical Assessment (ANA) framework.³¹ Participants received an H4 dTMS regimen of 18 sessions over four weeks,²⁴ in conjunction with CM and MET.^{5,6} The dTMS regimen was adapted from the Health Canada-cleared protocol for TUD,²⁴ using the same number of sessions but consolidating a six-week schedule to four weeks to reduce burden. Adjunctive CM was included because the dTMS intervention requires high adherence, and CM is both the “gold standard” for maximizing adherence^{32,33} and has been used successfully to do so in CUD rTMS studies.¹⁹ Adjunctive MET was included because it has previously been used favorably with rTMS for CUD,¹⁷ it is available in a brief discrete format (as opposed to a more extensive behavioral treatment), and from an ethical standpoint, given that the participants were seeking treatment and the dTMS was entirely experimental, its inclusion permitted all individuals to receive at least a reasonable standard of care. A final rationale was that brief concurrent MET was considered compatible with high-quality “real-world” practice (ie, concurrent behavioral counseling in conjunction with dTMS rather than dTMS as a monotherapy).

MATERIALS AND METHODS

Study Design and Overview

This phase 1 open-label pilot trial was conducted at the Peter Boris Centre for Addictions Research, within St Joseph's Healthcare Hamilton West 5th Campus, a mental health hospital in Hamilton, Canada. The study was approved by the Hamilton Integrated Research Ethics Board (identity number = 16,698) and was registered on clinicaltrials.gov (NCT06114212). All participants provided written informed consent at study enrollment. All procedures accorded with the Declaration of Helsinki.

Participants

Participants were recruited from the greater Hamilton, Ontario area using online advertising (eg, Facebook and Instagram). The inclusion criteria were 1) aged 25 to 65 years; 2) $\geq$ four Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for CUD (moderate or higher severity); 3) cannabis use $\geq$ four days per week, with inhalation as one route of administration; 4) treatment

seeking, as assessed by a self-reported readiness of change of ≥ 5 on a 0-to-10 readiness ruler; and 5) reliable transportation with the ability to attend in-person visits. Exclusion criteria were 1) current psychotic symptoms or posttraumatic stress disorder; 2) history of schizophrenia-spectrum or bipolar disorders; 3) active suicidality or history of severe suicidality; 4) unstable management of existing mental health condition or medical condition (eg, diabetes); 5) dTMS contraindications (eg, history of seizure, pacemaker); 6) medication contraindications (eg, bupropion >300 mg/d due to seizure risk, benzodiazepine equivalent dose to lorazepam >2 mg/d); 7) past-year history of recurrent headache or migraine; 8) significant literacy, visual, or hearing problems; and 9) concurrent enrollment in another clinical trial.

Procedures

Interested individuals completed an online screening form to assess for eligibility. Those who appeared eligible were invited to complete an in-person screening, which included a review of medical history and contraindications to dTMS. If eligible, interested participants then completed a written consent form and received a brief introduction to the BrainsWay device (Jerusalem, Israel). This introduction was aimed at assessing comfort with the device and at allowing individuals an opportunity to trial the sensation of dTMS before enrolling in the study. During the introduction, individuals' motor thresholds (MTs) were first determined using established methods³⁴ using an electromyography protocol alongside the observational method, described in greater detail in the supplemental materials (Supplementary Data Method S1).

Eligible and interested individuals then enrolled in the study and provided informed consent. Initially, participants received a train of treatment (30 pulses at 10 Hz) at 50% to 60% of their MT, and on the basis of tolerability, the intensity was gradually increased to determine an acceptable intensity for 18 minutes of treatment (up to 120% of the MT). If their first treatment (T1) occurred more than a week after their in-person screening, the MT was reestablished. The complete study protocol comprised 21 in-person sessions (excluding screening) and included 18 daily dTMS treatments across four weeks. This protocol had the same dose as the cleared TUD treatment (18 sessions) but was adapted from a six-week schedule (three weeks of five sessions and three weeks of one session) to a

four-week schedule (three weeks of five sessions and one week with three sessions) to reduce participant burden. However, if participants experienced scheduling conflicts or other challenges, sessions were not terminally missed and could be rescheduled, with the expectation that the entirety of the treatment period would not exceed six weeks. A clinically meaningful treatment exposure was defined as 14 of 18 sessions (75%) over six weeks. A one-month follow-up (1MFU) was completed to assess for lasting rTMS effects. A schematic of the protocol is presented in Figure 1.

Deep rTMS Treatment

Treatments were administered using a BrainsWay dTMS system equipped with an H4 coil (BrainsWay) designed to stimulate the bilateral insular and lateral prefrontal cortices.²³ The treatment protocol was broadly consistent with the H4-coil TUD protocol that led to FDA approval: 60 rTMS trains lasting 3 seconds and comprising 30 pulses applied at 10 Hz, with 15-second intertrain intervals interspersed.²⁴ Before each of the 18 rTMS sessions, participants underwent an approximately 5-minute cue reactivity provocation. This included 1) a slideshow of cannabis images, 2) visual and tactile exposure to cannabis paraphernalia, and 3) a 2-minute audio-recorded imaginal script prompting participants to recall products, places, people, and sensory features of consuming cannabis. This multicomponent procedure was used to maximize engagement of craving-related brain networks before the brain stimulation, akin to the dTMS protocol for TUD. Rescheduling appointments for illness or unavoidable conflicts was permitted, and five participants rescheduled $\geq$ one sessions. These rescheduled visits simply extended the protocol in time. A maximum total duration of the protocol with rescheduled appointments was six weeks. The modal regimen duration, from first stimulation to 18th stimulation, was 23 days (the shortest possible duration), with the median and mean being 25 days (~one month). Participants were not required to have abstinence as a goal of treatment; acceptable goals included both reduction in use and abstinence and were permitted to fluctuate over sessions.

A CM protocol was used to maximize dTMS treatment adherence, as has been used in previous rTMS for CUD studies.^{18,19} The original protocol conditionally rewarded participants on the basis of weekly decreases in urinary 11-Nor- Δ^9 -THC-carboxy, an inactive metabolite of THC (week 1 = \$50; week 2 = \$50; week 3 = \$100; week 4 = \$100);

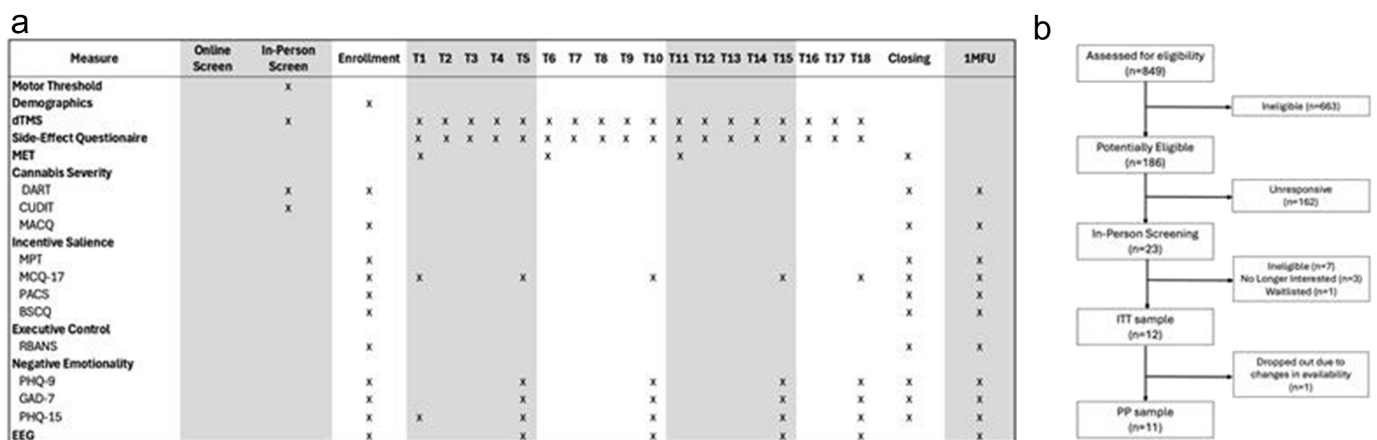


Figure 1. Study protocol (a) and Consolidated Standards of Reporting Trials diagram (b). MACQ, Marijuana Adverse Consequences Questionnaire; MCQ-17, Marijuana Craving Questionnaire 17-item. [Color figure can be viewed at www.neuromodulationjournal.org]

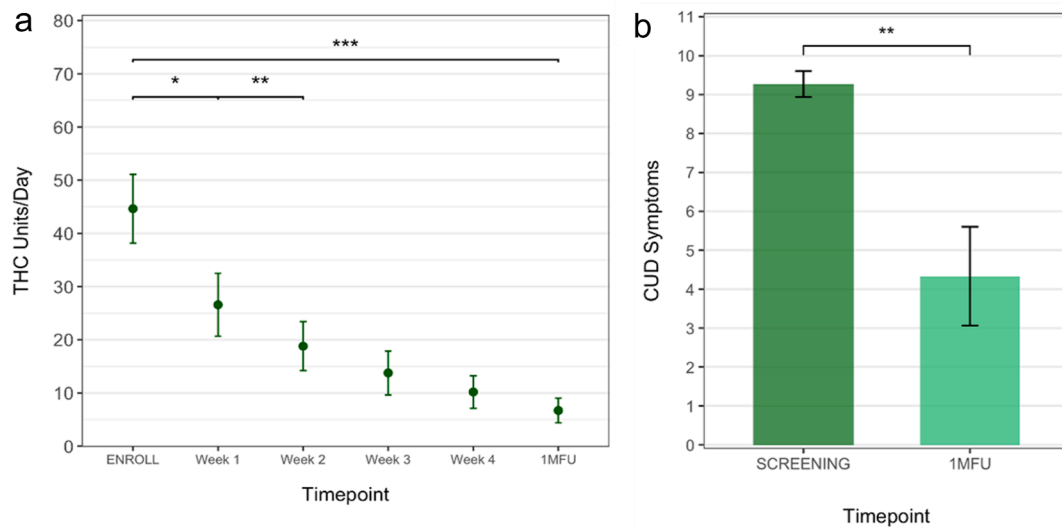


Figure 2. Within-subjects changes in clinical outcomes. a. Changes in standard units of 5 mg THC (MAEC-adjusted) at enrollment, by week, and at 1MFU. b. Changes in CUD severity at baseline and at 1MFU (days post-assessment, M [SD] = 72.9 [10.4]). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. [Color figure can be viewed at www.neuromodulationjournal.org]

however, we found that one week seemed to be too short to detect meaningful changes in THC metabolite levels. Therefore, the CM protocol was amended after the third participant to reinforce completion of all weekly dTMS treatment sessions (\$50/wk), while also reinforcing decreases in urinary THC metabolites by end of treatment, with supplemental contingencies based on overall level of metabolite reduction (one level = \$25; two levels = \$50; three levels = \$75; four levels = \$100).

Collateral Behavioral Counseling

Over the course of the 18 dTMS sessions, four visits also included MET sessions (approximately 45 minutes), consistent with previous rTMS studies^{17,18} and comprising a manualized motivational interviewing (MI) protocol adapted from previous published clinical studies.^{35,36} Structured portions included personalized feedback about cannabis motives and consequences, in addition to personal values regarding cannabis use. Semistructured portions included goal setting, developing a change plan, and executing the change plan. All sessions emphasized MI spirit, focusing on continued discussion of intrinsic motivators and person-centered goals related to reducing or terminating cannabis use. Study clinicians comprised a licensed PhD-level clinical psychologist (JM) and a licensed master's-level clinical social worker (EV). The treatment manual is available on request.

Primary Outcomes

Protocol Feasibility

To assess feasibility, overall rates of screening (ie, n screened; n enrolled/ n screened); recruitment rates and capacity (ie, n enrolled/month of recruitment); percentage of completed interventions (ie, n of treatments completed/ n possible treatments); and retention rate (ie, percentage completed of enrolled participants) were evaluated.

Treatment Tolerability

To assess the tolerability and safety of the H4 coil, the number of adverse events (AEs) and dropouts due to AEs were evaluated. The

occurrence of AEs was monitored daily using side-effect questionnaires. Specifically, participants reported any occurrences of headache, neck pain, scalp pain, drowsiness, trouble concentrating, acute mood change, or any other potential side effect. If present, participants classified symptoms as mild, moderate, or severe, and rated the likelihood that they were attributable to rTMS (1 = none; 2 = remote; 3 = possible; 4 = probable; 5 = definite). These questionnaires were administered immediately after treatments to assess for short-term AEs, and again on arrival to the subsequent treatments, to evaluate for latent or residual AEs. For this study, only AEs attributed to rTMS at a "possible" or greater level were included in the analysis.

Secondary Outcomes

Cannabis Use

Cannabis consumption was quantified continuously through the timeline follow-back interview.³⁷ Route of consumption was collected to permit the incorporation of a method of administration efficiency constant (MAEC), which considered THC loss on the basis of the administration method. The MAEC estimates were used based on Budney et al,³⁸ who defined the following average efficiency values based on laboratory studies: 30% for smoking flower or concentrates,^{39–41} 50% for vaping flower,^{40–43} and 50% for vaping concentrates.^{42–44} For all products, the mean of the advertised THC range was used in calculations. For instance, if a product was marked as 20% to 24% THC, 22% was used in calculations. In select cases, participants were unable to recall the exact THC potency of the dried flower, and a provincial average of 22% was supplemented.⁴⁵ For standardization, reported cannabis consumption was converted to milligrams of THC. For those smoking dried flower or concentrates through combustion, the gram amount was first converted to THC milligrams using the amount in grams and the THC concentration (eg, 2 g of 25% THC = 2 g $\times$ 250 mg/g = 500 mg crude THC). Crude THC was then corrected for route of administration using the appropriate MAEC (eg, 500 mg crude THC $\times$ 0.30 [MAEC] = 150 mg MAEC-adjusted THC). For those vaping concentrates, a hit was quantified as 12 mg of

cannabis (eg, 10 hits = 10 hits $\times$ 12 mg/hit = 120 mg^{38,44,46}). The amount was then multiplied by THC concentration to calculate crude THC (eg, 120 mg $\times$ 0.42 mg/mg = 50.4 mg), and crude THC was then corrected using MAEC. MAEC-adjusted THC milligrams were converted to standard THC units by dividing by total MAEC-corrected THC milligrams by 5 mg, an amount previously recommended on the basis of physiologic response, ecologic data, and existing policy (eg, packing limits for retail cannabis).^{47,48} To enable standardized calculations across participants, weekly consumption averages from the timeline follow-back interview³⁷ were derived exclusively from active treatment days. Variability in the weekday of initial treatment necessitated the exclusion of intervening weekends to avoid temporal inconsistencies in consumption metrics. Enrollment consumption was calculated as the mean intake over the seven days preceding the enrollment visit; 1MFU consumption was calculated as the mean intake across the 28 days preceding the follow-up visit. Although total THC in milligrams was calculated, the primary consumption outcome measure was standard units of THC for ease of interpretation; the two measures yield identical test statistics.

CUD Severity

CUD was assessed at screening and 1MFU using the Diagnostic Assessment Research Tool (DART), a validated, semistructured diagnostic interview that evaluates for the 11 DSM-5 diagnostic criteria.⁴⁹ The DART was not administered at the end of treatment because the time interval was too short (symptoms are assessed over the past three months). At 1MFU, the interview was oriented toward the period since treatment commenced, and the duration of time between interviews ranged from 61 to 92 days ($M = 72.9$; $SD = 10.4$).

Motivational Mechanisms

To assess changes in the addictive mechanisms of CUD, we broadly followed the ANA framework, which characterizes addiction motivation through three domains: 1) incentive salience, 2) executive function, and 3) negative emotionality.^{31,50} A list of assessments and frequency of administration is presented in Figure 1.

Incentive salience was assessed using several validated measures. Cannabis craving was measured using the 17-item Marijuana Craving Questionnaire,⁵¹ which characterizes craving into four domains: 1) Compulsivity (ie, lack of control); 2) Emotionality (ie, mood or withdrawal relief); 3) Expectations (ie, anticipation of positive outcomes); 4) Purposefulness (ie, intention for positive outcomes); and an adaptation of the Penn Alcohol Cravings Questionnaire (PACS)-Cannabis wherein references to “alcohol” were replaced with “cannabis.”⁵² Cannabis craving also was assessed in vivo during the brief provocation preceding each TMS treatment (Supplementary Data Method S2 for a complete overview). Briefly, participants were asked to rate cannabis craving, urge, and want from 0 to 100 using a participant-led PsychoPy paradigm. Ratings were prompted four times: 1) Preprovocation (before any cannabis stimuli), 2) Postimage (after viewing cannabis images), 3) Postparaphernalia (after visual and tactile exposure to cannabis paraphernalia), and 4) Postimaginal Script (after listening to an imaginal script). Because cannabis craving, urge, and want ratings were very highly correlated ($rs > 0.87$), ratings were averaged to create a composite in vivo cannabis craving rating.⁵³ Conversely, confidence to resist urges to use cannabis was assessed using the Brief Situational Confidence Questionnaire for

Cannabis (BSCQ-C).⁵⁴ The last incentive salience indices were the reinforcing value of cannabis as assessed using a marijuana purchase task (MPT).⁴⁵ The task asked participants to report how many grams of their usual cannabis product they would purchase over a week at 20 ascending prices, ranging from \$0/g to \$60/g. MPT responses were processed into four demand metrics: 1) intensity (consumption at \$0/g); 2) inelasticity (ie, insensitivity to price increases); 3) O_{max} (ie, maximum weekly expenditure); and 4) breakpoint (ie, \$/g that suppresses consumption). Task details are in McIntyre et al,⁵⁵ and an overview of quality control and processing^{56,57} is presented in Supplementary Data Method S3.

Executive function was principally assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)⁵⁸ and was administered by trained research staff supervised by a board-certified clinical neuropsychologist (EM). The battery included 12 subtests that were processed into five cognitive domains based on the manual’s normative information. All scores were converted to standard scores ($M = 100$, $SD = 15$). Index scores included immediate memory, visuospatial/construction, attention, language, delayed memory, and a total score representing overall cognition. To minimize practice effects, a unique version of the RBANS was used at each time point (Enrollment = B, Closing = A, 1MFU = C). A secondary measure of brain function was resting state brain activity, assessed using dry electroencephalography (EEG) through CGX Quick-20r (CGX Systems, San Diego, CA). This measure was collected for exploratory purposes to establish the feasibility of collecting neural mechanistic indicator, but EEG outcomes fall beyond the scope of the manuscript.

Negative emotionality was assessed through several validated self-report tools. Depression symptoms were assessed using the nine-item Patient Health Questionnaire (PHQ)-9, which has been validated for individuals with SUDs⁵⁹; somatic symptoms were assessed using the 15-item PHQ⁶⁰; and generalized anxiety disorder was assessed using the Generalized Anxiety Disorder 7-item (GAD-7⁶¹).

Statistical Analyses

Feasibility outcomes are reported using raw absolute values and percentages. Tolerability (reported AEs) was assessed on an intention-to-treat (ITT) basis using χ^2 tests. Changes in cannabis use severity and consumption, incentive salience, executive function, and negative emotionality were assessed on a per-protocol (PP) basis using repeated measures analysis of variance (rmANOVA). Specifically, rmANOVAs were completed using both end-of-treatment (EOT) (T18 or Closing) and 1MFU as end points, to assess both immediate and lasting effects of rTMS, with a Greenhouse-Geisser correction if the assumption of sphericity was violated. For cue reactivity, the session, provocation stage, and their interaction over time were evaluated. Statistical analyses were completed using IBM SPSS (v30) and R (v4.3.3; packages: ggpubr, tidyr, dplyr, ggplot2, rstatix), with a statistical significance level set at $p < 0.05$. For the changes in clinical and mechanistic outcomes, although many tests were run, no type 1 error rate correction was used because as a pilot study, the priorities were observing evidence of clinical signal, estimating a credible range of effect sizes, and identifying which mechanistic measures were most sensitive to changes in cannabis use.

RESULTS

Feasibility

Between March 2024 and February 2025, 12 participants were enrolled (Fig. 1), with an average of 1.1 participants per month.

Screening and enrollment rates by source are listed in [Supplementary Data Table S1](#). Of those, 11 participants (91.7%) completed all 18 TMS treatments, with one voluntarily withdrawing after eight treatments. This participant did not report any moderate or severe side effects to TMS but believed they could no longer commit to treatments owing to family demands. The final PP sample thus comprised 11 individuals with a mean age of 32 years and a modest overrepresentation of women (63.4%; [Table 1](#)).

Sample characteristics ([Table 1](#)) indicated, on average, participants endorsed 9.27 ± 1.10 CUD symptoms at baseline, with all reporting ≥ 6 CUD symptoms, meaning that although the eligibility criteria were for moderate-to-severe CUD, all participants had severe CUD.⁶² The primary method of consumption was combusted dried flower (54.6%, 6/11), combusted concentrates (18.2%, 2/11) (eg, shatter, resin), vaporized concentrates (18.2%, 2/11), and vaporized dried flower (9.1%, 1/11). Most individuals (54.6%; 6/11) used a single consumption modality, but 36.4% (4/11) reported using two modalities, and 9.1% (1/11) reported using three modalities.

Overall, the study had high retention (> 90%), with an ITT dropout rate of 8.3% (1/12). As noted above, this individual did not experience AEs; instead, they could no longer commit owing to familial obligations. Intervention completion rates were similarly high, with 95.4% completed in the ITT sample and 100% completed in the PP sample. Two participants became nonresponsive after treatment was complete and were considered lost to follow-up (82% PP retention, 75% overall retention). The final follow-up occurred in April 2025.

Tolerability and Safety of the dTMS Treatment Protocol

Overall, treatments were well-tolerated by participants. In the PP sample ($n = 11$), 100% of participants completed the full 18 treatments, with 90.9% reaching a therapeutic dose ($\geq 90\%$ rMT) and 18.2% reaching a maximal dose ($\geq 90\%$ rMT) by the end of treatment ([Supplementary Data Table S2](#) presents a detailed breakdown). AEs (side effects) are in [Table 2](#) and [Supplementary Data Figure S1](#). Across all dTMS treatments in the ITT sample, acute headache was the most reported AE, with 17 occurrences across the 206 total treatments (8.3%). Of note, rates of AEs differed by week ($\chi^2 = 19.63$, $p < 0.001$), with the highest prevalence in week 1. Overall, acute AEs were more commonly reported than residual

($\chi^2 = 8.76$, $p = 0.003$). Although not assessed within our side-effect questionnaire, instances of mild-to-moderate teeth chattering (19 events) and/or facial muscle contraction (15 events) also were recorded during treatment ([Supplementary Data Table S3](#)). In these cases, mouthguards were provided to participants. Depending on the severity, the helmet position was shifted slightly, or intensity was reduced to relieve the muscular contractions.

Secondary Outcomes

Cannabis Consumption and CUD Severity

The rmANOVA of MAEC-adjusted milligrams of THC across the treatment period revealed a significant, large effect of time from T1 to EOT ($h_p^2 = 0.31$) and to 1MFU ($h_p^2 = 0.31$) ([Table 3](#)), reflecting a decrease in consumption. As shown in [Figure 2](#), standard units of THC decreased by approximately 78% to 87%, representing an average reduction from approximately 45 units at enrollment to approximately ten at EOT and six at 1MFU. CUD symptoms also decreased significantly over the treatment protocol ([Fig. 2](#) and [Table 3](#)), from approximately nine symptoms at enrollment to approximately four at 1MFU. From severe CUD at the onset of the study, 73% transitioned to moderate or mild severity, including 33.3% (three/nine) reaching remission status by 1MFU. Past seven-day cannabis use frequency was notably but not statistically significantly reduced at the EOT ($p = 0.067$) and 1MFU ($p = 0.092$).

Motivational Mechanisms

All measures of incentive salience revealed significant decreases over the treatment protocol ([Table 3](#)). Post hoc t -tests revealed the largest craving reductions to be within the first week of treatment; this was significant across all domains apart from emotionality. The PACS-C, which was assessed at enrollment, closing, and 1MFU, also displayed a significant decrease in craving over time ([Fig. 3](#) and [Table 3](#)). For cue reactivity, there was a significant main effect of time ($F(17,170) = 10.54$, $p < 0.0001$, $\eta_p^2 = 0.51$), provocation stage ($F(1.14, 11.37) = 9.27$, $p < 0.0001$, $\eta_p^2 = 0.48$), and the interaction ($F(51,510) = 2.01$, $p < 0.0001$, $\eta_p^2 = 0.17$). As shown in [Figure 3](#), these changes reflected a progressive global decrease in craving over sessions but also a reduction in within-session cue reactivity time. Consistent with reduced incentive salience, the BSCQ revealed a significant increase in

Table 1. PP and ITT Participant Demographics and Cannabis Use Characteristics at Baseline.

Variable	PP sample ($n = 11$)*	ITT sample ($n = 12$)*
Demographics		
Age	32.36 [4.61]	33.75 [6.51]
Sex	63.6% female	58.3% female
Race	81.8% White	83.3% White
Income (CAD)	\$45,000–\$60,000	\$45,000–\$60,000
Education level	Some college/university	Some college/university
Employment	Part-time	Part-time
Cannabis involvement		
CUD Sxs, total	9.27 [1.10]	9.08 [1.24]
CUDIT, total	25.67 [2.69]	25.67 [2.69]
THC mg/d—d 0 [†]	237.03 [106.29]	223.17 [112.14]
THC units/d—d 0 [†]	47.41 [21.26]	44.63 [22.42]
Past 7 d cannabis	7 [0.00]	7 [0.00]
CAD, Canadian Dollar; CUDIT, Cannabis Use Disorder Identification Test; Sxs, symptoms.		
*M (SD)/median/%.		
[†] MAEC-corrected.		

Table 2. Acute (Postsession) and Residual (Next Day) AEs Reported by Week Within the ITT Sample.

AE		Wk 1			Wk 2			Wk 3			Wk 4			Total protocol		
		<i>n</i>	<i>T</i>	<i>I</i>	<i>n</i>	<i>T</i>	<i>I</i>	<i>n</i>	<i>T</i>	<i>I</i>	<i>n</i>	<i>T</i>	<i>I</i>	<i>n</i>	<i>T</i>	<i>I</i>
Headache	Acute	7	60	11.7%	3	58	5.2%	5	55	9.1%	2	33	6.1%	17	206	8.3%
	Residual	3	60	5.0%	1	57	1.8%	1	55	1.8%	0	33	0.0%	5	205	2.4%
Neck pain	Acute	1	60	1.7%	0	58	0.0%	1	55	1.8%	1	33	3.0%	3	206	1.5%
	Residual	0	60	0.0%	0	57	0.0%	0	55	0.0%	0	33	0.0%	0	205	0.0%
Scalp pain	Acute	3	60	5.0%	0	58	0.0%	2	55	3.6%	0	33	0.0%	5	206	2.4%
	Residual	0	60	0.0%	0	57	0.0%	0	55	0.0%	0	33	0.0%	0	205	0.0%
Drowsy	Acute	5	60	8.3%	1	58	1.7%	2	55	3.6%	0	33	0.0%	8	206	3.9%
	Residual	5	60	8.3%	0	57	0.0%	1	55	1.8%	0	33	0.0%	6	205	2.9%
Concentration	Acute	0	60	0.0%	0	58	0.0%	0	55	0.0%	0	33	0.0%	0	206	0.0%
	Residual	2	60	3.3%	0	57	0.0%	0	55	0.0%	0	33	0.0%	2	205	1.0%
Mood change	Acute	0	60	0.0%	0	58	0.0%	0	55	0.0%	0	33	0.0%	0	206	0.0%
	Residual	0	60	0.0%	0	57	0.0%	0	55	0.0%	0	33	0.0%	0	205	0.0%
All	Acute	16	360	4.4%	4	348	1.1%	10	330	3.0%	3	198	1.5%	33	1236	2.7%
	Residual	10	360	2.8%	1	342	0.3%	2	330	0.6%	0	198	0.0%	13	1230	1.1%

For "All" category, the numbers of AEs and opportunities for AEs were summed to create a combined numerator and denominator. One participant dropped out of the study after completing eight treatments, only completing eight acute side-effect questionnaires and seven residual side-effect questionnaires. Acute questionnaires were administered immediately after treatment. Residual questionnaires were administered before the following treatment (24 hours later for same week appointments, or 36 hours for Friday appointments).

I, incidence ($[n/T]$; *n*, number of TMS-related AEs; *T*, total number of treatment sessions (opportunities for an AE to occur)).

confidence to resist cannabis cravings from enrollment to EOT and 1MFU (Fig. 4 and Table 3). Results on the MPT revealed prototypic demand curves, and significant decreases in cannabis reinforcing value were present from enrollment to EOT and 1MFU across all metrics (Fig. 3 and Table 3).

In terms of executive function (RBANS), at enrollment, participants indicated average cognitive function across domains, and rmANOVAs revealed no significant effect of time (Table 3).

For negative emotionality, all three outcomes significantly improved across the study. At study onset, participants exhibited moderate depressive symptoms, but there was a large effect of time, reflecting a significant reduction of depressive symptoms from study onset to EOT, a reduction that was sustained into 1MFU (Table 3), with final scores predominantly falling below the PHQ-9 depression screening cut-off threshold (Supplementary Data Fig. S2). Symptoms of anxiety, as assessed by the GAD-7, also showed significant decreases by EOT and into 1MFU (Table 3), with a reduction from, on average, mild-to-moderate anxiety at baseline to below the clinical cutoff (Supplementary Data Fig. S2). Similar reductions were observed for the severity of somatic symptoms (Table 3 and Supplementary Data Fig. S2).

DISCUSSION

The primary aims of this pilot study were to evaluate the feasibility and tolerability of an H4 dTMS treatment protocol for CUD. Feasibility was determined to be high as far as the intended number of participants was ascertained from the local community and almost all those who started the protocol were retained to completion. Two participants completed treatment but did not complete the 1MFU, although the level of retention remained at an acceptable level. The tolerability of the intervention was high as far as the AEs observed were of relatively low frequency, low severity, and principally at the beginning of treatment. Consistent with previous dTMS studies, the most common side effects were acute

headache and drowsiness, both of which were typically rated as mild. Teeth chattering was observed in a small number of participants but was not associated with discontinuation and was managed through dose titration and/or mouthguards. Taken together, feasibility and tolerability of the treatment were determined to be high.

The study's secondary aims were to evaluate changes in cannabis use and motivational mechanisms, acknowledging that the absence of a control group and use of a standard care treatment platform meant changes could not be exclusively attributed to dTMS. Including these outcomes was also a part of protocol feasibility testing, given these measures (or similar ones) would be used in larger-scale future trials. For these outcomes, participants exhibited statistically significant large magnitude reductions in standard units of THC and significant reductions in CUD symptoms, with a directional decrease in days per week of cannabis use. The smaller magnitude decreases in frequency may be attributable to the measure being coarser than the other two and most patients identifying a substantial reduction cannabis consumption and harms, not complete abstinence from cannabis, as their preferred outcome. Concurrently, significant changes in motivational mechanisms were observed, including decreases in cannabis cravings, all indices of cannabis reinforcing value, and depressive, anxiety, and somatic symptoms, in addition to significant increases in self-efficacy. Neurocognitive performance over the protocol suggested minimal adverse cognitive side effects of the dTMS. Collectively, acknowledging this was an open-label pilot trial, participants exhibited a highly favorable clinical response to the treatment protocol.

In the larger context, these clinical findings are generally more favorable than previous studies of traditional (figure-eight) rTMS^{15–19} although it is a small literature comprising highly heterogeneous studies, making direct comparisons challenging. Nonetheless, the high retention and tolerability, and favorable within-person changes suggest the H4 dTMS coil has substantial promise. The more favorable outcomes are putatively due to the H4 coil stimulating the anterior insula and lateral PFC, two key nodes in the pathophysiology of addiction.^{1,25,26} An important

Table 3. Results From rmANOVAs Evaluating the Effects of Time on Measures of Incentive Saliency, Executive Function, and Negative Emotionality From Initial Assessment to EOT and Subsequent Follow-up in the PP Sample.

Measure	EOT ^{†††}			1MFU [†]		
	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2
Cannabis consumption						
1. THC units (5 mg) [‡]	4.44	<0.0001 [§]	0.31	1. 4.76	<0.0001 [¶]	0.37
2. CUD Sxs	–	–	–	2. 18.49	0.002	0.67
3. cannabis frequency	4.23	0.067	0.30	3. 2.79	0.092	0.26
ANA: incentive saliency						
4. MCQ—total	24.62	<0.0001 ^{*,##}	0.71	4. 17.01	<0.0001 ^{*,***}	0.68
5. MCQ—compulsivity	21.02	<0.0001 [#]	0.68	5. 16.98	<0.0001 ^{**}	0.68
6. MCQ—emotionality	5.02	<0.001 ^{††}	0.33	6. 4.47	0.016 [*]	0.36
7. MCQ—expectations	8.41	<0.001 ^{*,††}	0.46	7. 5.91	0.006 [*]	0.43
8. MCQ—purposefulness	17.07	<0.0001 ^{*,§§}	0.63	8. 11.78	<0.0001 ^{¶¶}	0.60
9. PACS C—total	16.82	0.002	0.63	9. 14.12	<0.0001 ^{†††}	0.64
10. MPT—intensity	21.04	0.001	0.70	10. 19.49	0.001 [*]	0.71
11. MPT—inelasticity	20.64	0.001	0.70	11. 10.84	0.001	0.58
12. MPT—O _{max}	21.24	0.001	0.70	12. 11.51	<0.001 ^{†††}	0.59
13. MPT—breakpoint	15.78	0.003	0.64	13. 6.66	0.008	0.45
14. BSCQ	33.23	<0.001 ^{§§§}	0.77	14. 16.53	<0.0001 ^{¶¶¶}	0.67
ANA: executive function (neuropsychologic performance)						
15. immediate memory	0.94	0.355	0.09	15. 2.24	0.139	0.22
16. visuospatial/construction	1.50	0.249	0.13	16. 2.16	0.148	0.21
17. attention	0.32	0.586	0.03	17. 0.61	0.555	0.07
18. language	1.17	0.306	0.10	18. 1.35	0.286	0.15
19. delayed memory	2.81	0.125	0.22	19. 1.11	0.353	0.12
20. total scaled	3.56	0.088	0.26	20. 2.56	0.109	0.24
ANA: negative emotionality						
21. PHQ-9	13.02	<0.001 ^{*,###}	0.57	21. 12.85	<0.0001 ^{****}	0.62
22. PHQ-15	6.41	0.009 [*]	0.39	22. 7.11	<0.0001 ^{††††}	0.47
23. GAD-7	5.73	0.005 [*]	0.36	23. 5.90	0.005 [*]	0.42

One participant was excluded from the EOT MPT analysis owing to quality control.

MCQ, Marijuana Craving Questionnaire; O_{max}, maximum weekly expenditure; PACS C, Penn Alcohol Craving Scale—Cannabis Adaptation; Sxs, symptoms.

*Greenhouse-Geiser correction due to lack of sphericity.

[†]*n* = 9.

[‡]MAEC-corrected.

[§]*p* = 1.50E-7.

[¶]*p* = 3.30E-8.

[#]*p* = 2.97E-11.

^{**}*p* = 2.11E-10.

^{††}*p* = 8.41E-4.

^{†††}*p* = 6.90E-4.

^{§§}*p* = 1.20E-5.

^{¶¶}*p* = 4.49E-8.

^{###}*p* = 1.77E-6.

^{††††}*p* = 2.92E-4.

^{†††††}*p* = 8.01E-4.

^{§§§}*p* = 1.80E-4.

^{¶¶¶}*p* = 1.28E-4.

^{###}*p* = 2.71E-4.

^{****}*p* = 1.43E-8.

^{†††††}*p* = 4.47E-6.

^{††††††}*n* = 11.

^{***}*p* = 2.58E-5, and place this before the ††† table footnote.

nuance is that more recent work suggests the H4 electrical field affects anterior cingulate⁶³ or dorsomedial PFC,⁶⁴ although these also are regions implicated in addiction. Notably, these results are comparable with the early H4 dTMS studies of TUD^{22,23} and suggest the need for a similar proof-of-concept randomized controlled

trial to test the benefits of dTMS directly in comparison with a sham stimulation control condition.

Several limitations pertain to the present findings. As noted, first, caution must be applied to the conclusions drawn because this was an initial pilot study to test feasibility and tolerability

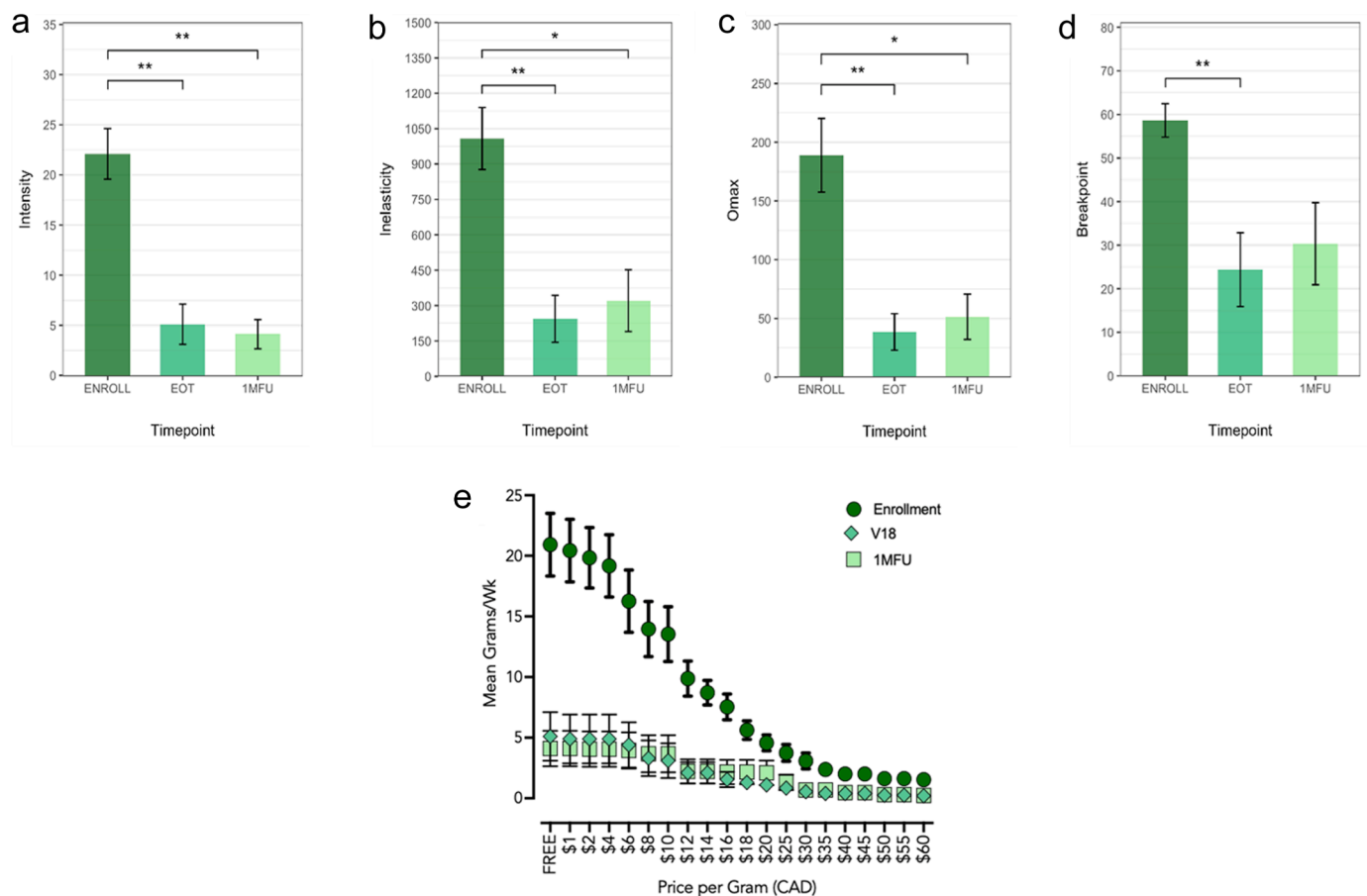


Figure 3. Changes in reinforcing value of cannabis as assessed by an MPT. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. CAD, Canadian dollars. [Color figure can be viewed at www.neuromodulationjournal.org]

and did so in a relatively small sample. Second, although the 18 sessions of dTMS constituted the most substantial aspect of treatment, all participants also received MET and CM, meaning clinical benefits of dTMS cannot be isolated from those effects. This is mitigated somewhat because previous studies have also combined neuromodulation with MET and CM for treating CUD,^{17–19} and, independently of rTMS, these interventions are associated with positive therapeutic benefits but at small-to-medium effect sizes,⁶ which is considerably smaller than the effects observed in this trial. Nonetheless, the effects observed can only be interpreted as pertaining to the overall multicomponent dTMS treatment protocol, and in addition to including a sham control condition, separating dTMS from these components may be warranted in future studies. Related, reductions in cue-elicited craving were substantial but also were consistent with behavioral extinction training independent of augmentation,^{65,66} and the extent to which dTMS per se accelerated this process cannot be inferred. There is some conjecture about the necessity of the cue provocation in dTMS treatment, and rigorous evaluation of whether dTMS augments extinction and this mechanism contributes to its clinical efficacy is warranted in future studies; the present pilot study is too small to address this question robustly. Finally, it also should be noted that the protocol was similar to the Health Canada and FDA-cleared TUD

protocol but not identical, adapting a six-week schedule to a four-week schedule to reduce patient burden.

Clinically, it bears mentioning that most participants did not initially seek abstinence so much as a substantial reduction in consumption and cannabis-related harms, and most substantially reduced cannabis consumption but did not eliminate use. Similarly, although most participants exhibited substantial decreases in cannabis use, not all participants experienced response to the treatment; evaluation of individual participant data suggests approximately 20% of participants did not have a response. Subsets of responders and nonresponders have been documented in previous rTMS trials,^{67–69} and are typical in psychiatry,^{70,71} suggesting a priority in future trials should not only be testing efficacy but predicting prognosis. Similarly, given some ambiguity about the brain regions preferentially stimulated by the H4 coil, it will be critical for future studies to illuminate the brain mechanisms of therapeutic benefit,^{63,64} as has been explored in the recent alcohol use disorder trials.^{28,29} Finally, a modest sex imbalance was present and warrants consideration for future studies.

Acknowledging these considerations, the present pilot study nonetheless provides evidence of the feasibility and tolerability of a protocol testing H4 dTMS for CUD. Moreover, although the single-arm open-label design prevents specific attribution of

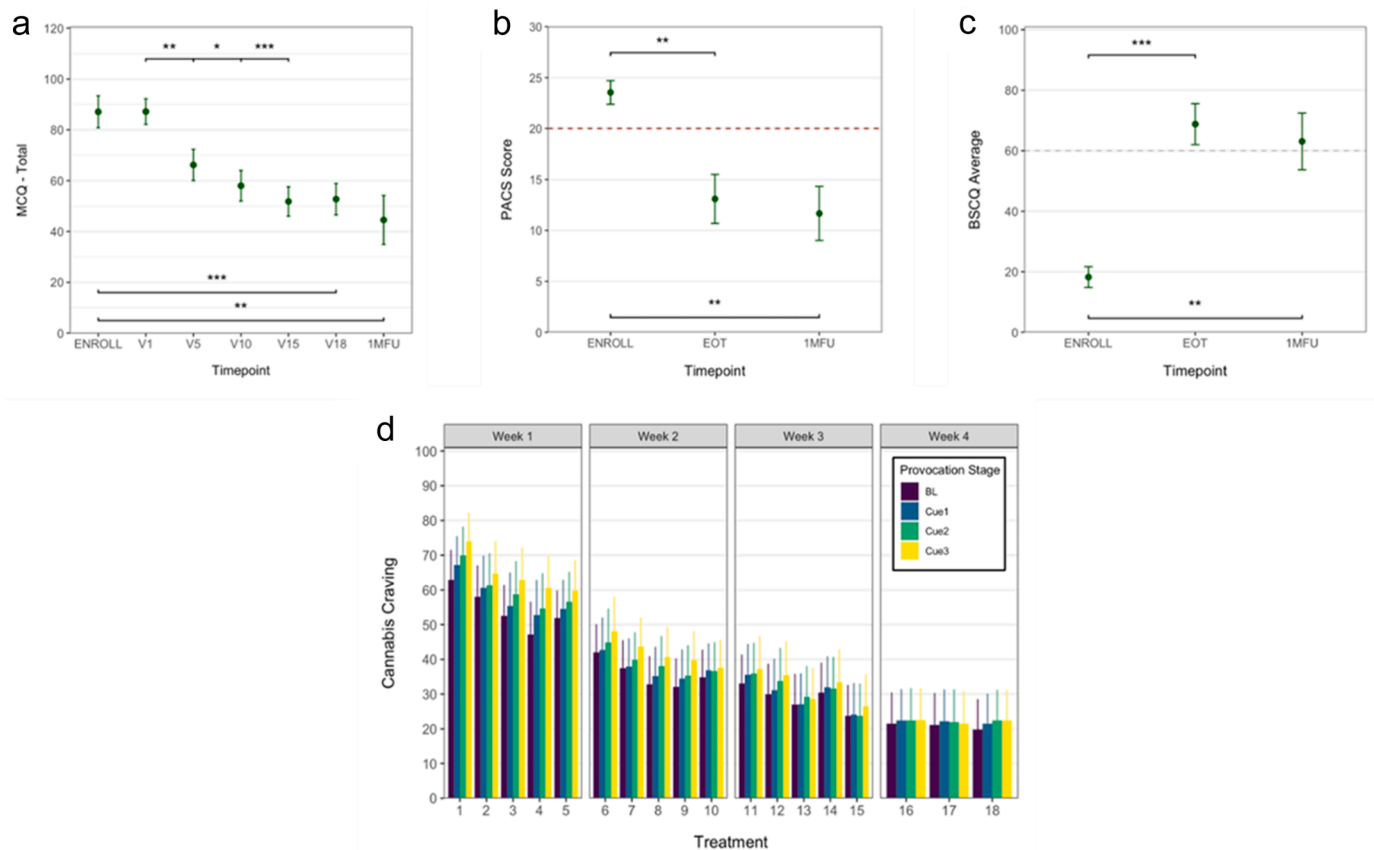


Figure 4. Changes in incentive salience measures over the study protocol; self-efficacy falls within scope by reflecting perceived ability to resist cravings. a. MCQ. b. Cannabis adaptation of the PACS. c. BSCQ (self-efficacy). d. Cue-elicited craving during the pre-dTMS cue exposure provocation. Dotted lines reflect clinically relevant cutoffs. Significant changes are indicated between intermediate visits (above) and across the entire protocol (bottom). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. MCQ, Marijuana Craving Questionnaire. [Color figure can be viewed at www.neuromodulationjournal.org]

benefit to the dTMS, the changes in clinical and mechanistic outcomes in the study were very favorable. In terms of future directions, these findings suggest H4 dTMS is a promising novel treatment for CUD and support the prospects of a formal randomized controlled proof-of-concept trial testing its efficacy. If supported, multisite trials will ultimately be necessary to determine whether H4 dTMS warrants regulatory clearance as an effective treatment for CUD.

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Authorship Statements

James MacKillop, Emily MacKillop, and Dante Duarte designed the study, with important methodological contributions from Carly McIntyre-Wood, Emily Vandehei, Benjamin Schwartzmann, and Faranak Farzan. Carly McIntyre-Wood, Emily Vandehei, Anne-Marie DiPassa, Shelby Prokop-Millar, Allan Fein, Andrew Yang, and Mahmoud Elsayed contributed to patient recruitment, data collection, and data processing. Principal data analysis and visualization were conducted by Carly McIntyre-Wood and James

MacKillop. All authors contributed to data interpretation. James MacKillop and Carly McIntyre-Wood prepared the manuscript draft, with all authors providing editorial feedback and important intellectual input. All authors approved the final version of the manuscript.

Conflict of Interest

James MacKillop reports financial support was provided by Canada Research Chairs Program; and reports his status as a principal and senior scientist in Beam Diagnostics, Inc, which has no relevance to the subject matter and provided no products or services in the research reported. The remaining authors reported no conflict of interest.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at <https://doi.org/10.1016/j.neurom.2026.01.003>.

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COMMENT

There are relatively few studies testing TMS for CUD. This is an important study that combines TMS with psychotherapy (MET) and behavioral intervention (CM) to show significant reductions in cannabis use, craving, and its rewarding value. This is an exciting step forward for the field as we continue to develop and optimize TMS for cannabis use.

Heather Burrell Ward, MD
Nashville TN, USA