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Efficacy of insula deep repetitive transcranial magnetic stimulation combined with varenicline for smoking cessation: A randomized, double-blind, sham controlled trial

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ABSTRACT

Background: Current smoking cessation treatments are limited in terms of efficacy, particularly with regards to long term abstinence. There is a large amount of evidence implicating the insula in nicotine addiction.
Objective: To examine the efficacy of bilateral repetitive transcranial magnetic stimulation (rTMS) directed to the insular cortex with the H11 coil, relative to sham stimulation, on smoking abstinence and smoking outcomes in smokers who are receiving standard varenicline treatment.
Methods: This randomized, double-blind, sham controlled trial recruited 42 participants who were randomized to receive either active (n = 24) or sham (n = 18) high frequency rTMS directed to the insula (4 weeks), while receiving varenicline treatment (12 weeks). The primary outcome was 7-day point prevalence abstinence at the end of 12 weeks.
Results: Smokers in the active group had significantly higher abstinence rates than those in the sham group (82.4% vs. 30.7%, p = 0.013) at the end of treatment (Week 12). Secondary outcome measures of abstinence rate at the end of rTMS treatment (Week 4), abstinence rate at 6 months, and smoking outcomes (e.g., craving, withdrawal) showed no significant differences between groups. No differences were found in adverse events reported between the groups.
Conclusion: This study provides evidence of the potential benefit of having a combined treatment for smoking cessation using insula rTMS with the H11 coil and varenicline. Maintenance rTMS sessions and continuation of varenicline for those in abstinence may induce longer-term effects and should be considered in future studies.

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1. Introduction

Tobacco is one of the biggest epidemics we face in this world and the number one cause of preventable disease and death [1]. It is estimated that there are 1.3 billion smokers worldwide. Each year there are over 8 million deaths attributed to tobacco [2]. Over 50% of smokers attempt to quit each year, but yet less than 1 out 10 successfully quit [3]. Not only is quitting difficult but remaining abstinent is also a challenge as a majority of smokers relapse. In the first year after quitting, relapse rates are over 50% depending on length of abstinence. Relapse rates are even higher for smokers with psychiatric or substance use co-morbidities [4–6]. There are currently three pharmacotherapies approved for the use of smoking cessation: bupropion, nicotine replacement therapy (NRT) and varenicline. Varenicline is currently viewed as the most effective pharmacotherapy for smoking cessation, but relapse remains an issue [6,7].

In the last decade, a large amount of evidence has implicated the insular cortex in nicotine addiction processes [8,9]. The insula is an area that is deeply embedded in the cerebral cortex, and is involved in a multitude of functions. Importantly, the insula has a central role in interoception, which is explained as the integration of body signals and external stimuli to guide behavior towards or away from said stimuli with the goal of maintaining homeostasis [10,11]. In addictions, this is important in drug seeking behavior. A seminal study reported that smokers who suffered damage to the insula were able to quit smoking immediately, with great ease and without relapse [12]. Following this study, we have reported that inactivation of the insula and modulation of the activity of this structure reduced nicotine-taking and nicotine-seeking in preclinical studies [13–15]. Now, there is an abundance of evidence that implicates the insula as a core region in addiction (see review [8,9]).

A challenge with stimulating the insula is its location and that it could not be targeted non-invasively with traditional brain stimulation techniques such as a figure-of-8 coil for repetitive transcranial magnetic stimulation (rTMS). However, now several H-coils can target deeper brain regions, such as the insula, although these coils are less focal [16]. Two previous randomized clinical trials have investigated the H4-coil for smoking cessation using a coil targeting large volumes of the prefrontal cortex (PFC) and insula bilaterally. Both trials found this to be effective in smoking cessation, which led to the FDA approval of this device for short-term smoking cessation [17,18]. However, the H4-coil stimulated both the insula and PFC and therefore it is not known if the effects are from stimulation of the insula, the PFC or both. It should be noted that a beneficial effect of insula stimulation was not found in the treatment of alcohol use disorder using the H8-coil (targets the ventrolateral PFC and partial insula) [19].

As it is now clear that multiple areas of the brain underlie addiction, we have hypothesized that engaging different mechanisms through a combination of pharmacotherapy and brain stimulation could enhance smoking cessation rates. To test this hypothesis, we conducted a randomized, double-blind, sham controlled clinical trial to assess the efficacy of a combined treatment of smoking cessation using the novel treatment of deep rTMS (using the H11-coil that primarily targets the insula bilaterally without the dorsolateral PFC) along with the currently approved pharmacotherapy, varenicline. We hypothesized that active H11 rTMS would improve abstinence rates and smoking outcomes (e.g., dependence, craving, withdrawal) in smokers who are also being treated with varenicline.

2. Materials and methods

The protocol has been previously published in detail [20].

2.1. Study design

This trial was conducted at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario. The study consisted of smokers receiving 20 daily H11 rTMS treatments (active or sham), while also receiving open label varenicline for 12 weeks. The rTMS treatment began on Day 1 and was given daily for 4 weeks (5 days/week). Once the rTMS sessions were completed, weekly follow up visits were done up until the end of varenicline treatment (i.e., 12 weeks). One last follow-up visit was done at the 6-month mark (i.e., Week 26). The trial was conducted in compliance with the protocol, Good Clinical Practice, and ISO 14155 (Clinical investigation of medical devices). The Research Ethics Board at CAMH and Health Canada approved the study procedures. The study is registered on ClinicalTrials.gov (NCT04083144).

2.2. Participants

Participants were recruited through online advertisements, subway advertisements, newspapers, word of mouth, and through clinics at CAMH. Recruitment was done from August 2019 to June 2022; however, the study was on hold from March 2020 to April 2021 due to the COVID pandemic. Participants were screened first via telephone. Those meeting initial pre-screen criteria were invited for an in-person session to assess full inclusion and exclusion criteria (See supplementary). All participants provided written informed consent at the start of the eligibility session.

2.3. rTMS

Participants were randomized to receive either active (10 Hz) or sham rTMS targeting the insula. Randomization was done in a 1:1 ratio using simple program prepared by the device manufacturer. The deep rTMS treatment was administered using the H11-coil attached to the Brainsway 102B Model (Brainsway Ltd., Israel). Maps showing the distribution of the electric field induced by the H11-coil are presented in the supplementary material (Fig. S1). The treatment parameters for the active stimulation were 34 trains of 3 s each at 10 Hz and 30 pulses per train and an inter-train interval of 26 s (total pulses: 1020, session duration: approximately 16 min). Resting motor threshold (RMT) was determined during the first session by assessing the minimum intensity needed to induce a motor evoked potential of at least 50 μV measured from the right abductor pollicis brevis muscle in 5 out of 10 trials. Treatment was administered at 120% of RMT. During the first four sessions, titration of stimulus intensity was done to enhance tolerability. In individuals with poor tolerability, the minimum intensity was set to 110% of RMT. The sham coil was embedded in the same helmet and was designed to mimic the acoustic and scalp sensations of active treatment. Participants were given rTMS treatment for 20 sessions for four consecutive weeks (5 times/week). A target quit day was set to Day 15, such that TMS was administered for 2 weeks prior and after the target quit day.

2.4. Varenicline

All participants received open label varenicline for 12 weeks using the standard dosing schedule. Participants were given 0.5 mg tablet once daily for the first 3 days, and 0.5 mg twice a day (i.e., BID: AM and PM) for the next 4 days. Beginning at Day 8 participants were given 1 mg BID for the rest of the treatment course. Participants who could not tolerate 1 mg BID were given 0.5 mg BID. Compliance of missed doses was recorded weekly.

2.5. Outcome measures

The main outcome measure was a 7-day point prevalence abstinence at the end of 12 weeks (end of varenicline treatment). This was measured by self-report of abstinence in the past 7 days, and confirmed with serum cotinine measurement of <15 ng/ml. Several secondary outcomes were measured: 1) Fagerström Test of Nicotine Dependence

(FTND) [21]; 2) Expired carbon monoxide (CO) measurements; 3) Cigarettes per day (measured by the Timeline Followback (TLFB)) [22]; 4) Minnesota Nicotine Withdrawal Scale (MNWS) [23]; 5) Tiffany Questionnaire of Smoking Urges (T-QSU) [24]; 6) Point prevalence abstinence at end of 4 weeks (measured by self-report of abstinence for the past 7 days and confirmed with serum cotinine); 7) Prolonged abstinence from end of treatment (Week 12) to end of follow up (Week 26) (measured by self-report of continuous abstinence since the last visit (at Week 12) and confirmed with serum cotinine); 8) Prolonged abstinence with 2-week grace period at end of follow up (Week 26) (measured by self-report of continuous abstinence since Week 4 and confirmed with serum cotinine); 9) Continuous abstinence at 6 months (measured by self-report of abstinence since the target quit day (Week 2) and confirmed with serum cotinine). See Fig. 1 for overview of trial design and outcome measures and Fig. S2 for timeline of abstinence measures.

2.6. Sample size

Treatment with varenicline was anticipated to result in a 12-week abstinence point prevalence rate of 40%, based on previous results [6, 25]. To detect a clinically relevant 30% difference between the active and sham treatments with a power of 0.80 ($\alpha = 0.05$), 42 participants per study arm would be needed. However, due to this being a pilot study, the aim was to recruit n = 25 participants per study arm (power = 0.66). Attrition with smoking cessation trials was anticipated, therefore the goal was set to recruit n = 30 per arm to reach 50 completers in total.

2.7. Statistical analysis

Descriptive statistics were used to compare groups (active, sham) at baseline on clinical and demographic variables. Fisher's Exact and Mann-Whitney *U* test were used for categorical and continuous variables, respectively. Participants with missing values in the primary outcome (abstinence at 4, 12 or 26 weeks) were compared with completers on baseline characteristics, to help understand the reasons for missing values. Mixed effect logistic regression using 7-day point prevalence abstinence at 4, 12 and 26 weeks as dependent variables were adjusted to the data, with groups and categorical time as well as their interaction specified as fixed effect, and subject intercepts as random effects. For long term abstinence rates at Week 26, logistic regression was used to compare the groups. The primary hypothesis was tested using a contrast that compares abstinence at Week 12 in the logit scale. Similarly, abstinence was also compared at Week 4 and 26 as part of the secondary objectives. Other measures related to the secondary objectives (e.g., FTND, CO, TLFB) were analyzed by using one of the following models based on best AIC: random intercept model, random intercept random slope model, random intercept with diagonal covariance for residuals model or random intercept with auto-regressive of order 1 (AR1) covariance structure for the residuals model. Standardized effect sizes were calculated as partial eta-squared (η^2). All analysis were completed in SPSS Statistics (Version 29.0), except the Fisher's Exact tests and standardized effect sizes that were calculated in R Studio (Version 2022.12.0 + 353).

For the blood samples, the serum concentrations of nicotine, cotinine, and 3′-hydroxycotinine were quantified by LC–MS/MS using a previously reported method [26–28]. The serum ratio of 3HC (ng/mL)/COT (ng/mL) was derived as described previously [29].

3. Results

3.1. Recruitment and baseline characteristics

From August 2019 to June 2022, 612 people contacted the study. The study was put on hold by the institution as infection prevention and control measures were put in place from March 2020 to April 2021 due to the COVID pandemic. Fifty participants were enrolled, but only 42 were randomized since 8 participants were lost to follow-up before randomizing. Of the 42 randomized, 24 were randomized to active rTMS and 18 to sham rTMS. See Fig. 2 for the Consolidated Standards of Reporting Trials (CONSORT) flowchart.

The dropout rate was 26.19% (n = 11) with most participants dropping out within the first couple weeks of treatment (see Table S1 for dropout details). Of the 11 that dropped out, 8 (33.33%) were in the active group and 3 (16.67%) were in the sham group, however this difference was not statistically significant (p = 0.30). Demographic characteristics between those that completed the study (n = 31) and those that dropped out (n = 11) were compared to see if there were any differences. No significant differences were found except for the baseline CO (32.1 in dropouts vs. 21.8 in completers, p = 0.005). However, since all other smoking measures were not different and due to the small sample size, it was decided not to control for this as there was no theoretical basis for it to affect the results.

Table 1 demonstrates the demographics and baseline measures of the two treatments arms. No significant differences were found between the two groups, thus showing that the randomization was successful. On average, participants smoked 18 cigarettes per day and all participants

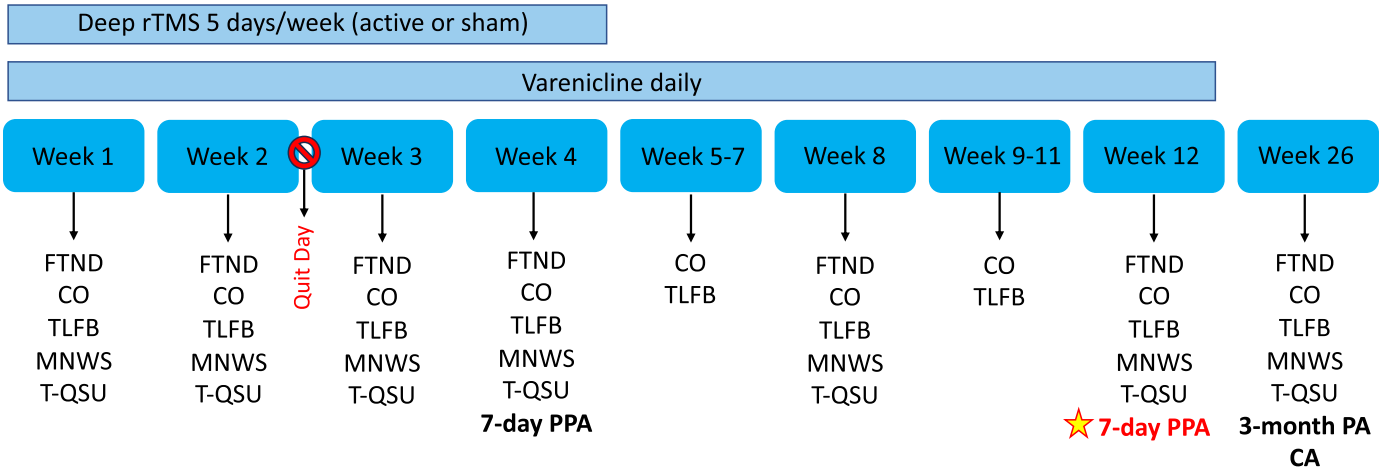

Fig. 1. Overview of trial design and outcome measures. Star indicates the primary abstinence outcome which also includes serum cotinine measurement. Bold indicates the secondary abstinence measures which also includes serum cotinine measurements. rTMS, repetitive transcranial magnetic stimulation; FTND, Fagerström Test of Nicotine Dependence; CO, Carbon monoxide; TLFB, Timeline Followback; MNWS, Minnesota Nicotine Withdrawal Scale; T-QSU, Tiffany Questionnaire of Smoking Urges; PPA, Point prevalence abstinence; PA, Prolonged abstinence; CA, Continuous abstinence. Image from Ref. [20].

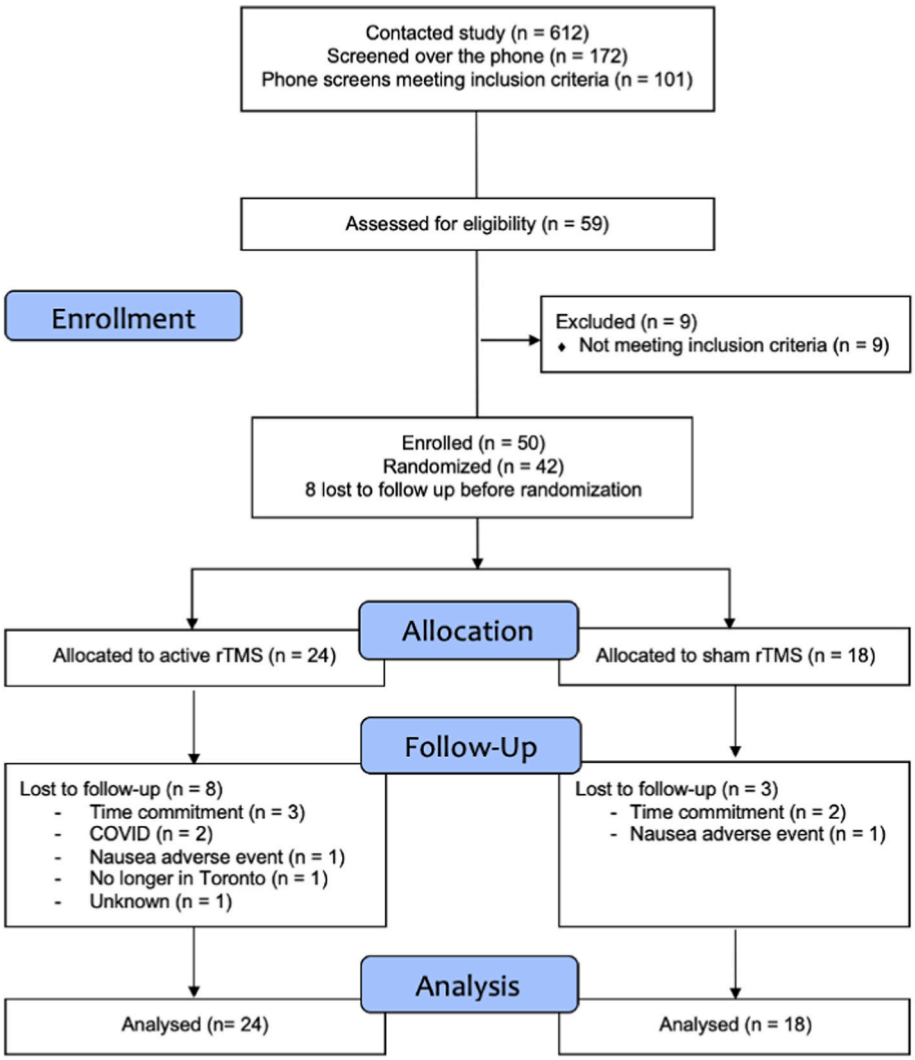

Fig. 2. Flowchart of the recruitment and enrolment according to the Consolidated Standards of Reporting Trials (CONSORT).

were highly motivated to quit based on the smoking contemplation ladder.

Participants with co-morbid psychiatric or substance use disorders were not excluded. Table 2 shows participants past year mental disorders based on the DSM-5. Due to the small sample size, anxiety disorders included social anxiety, generalized anxiety, and specific phobia; substance use disorder included stimulant and opioid use disorder; and mood disorder included major depression and persistent depression. No statistically significant differences were found between the two groups. Concomitant psychiatric medication is shown in Table S2.

3.2. Abstinence measures (Week 4, 12, 26)

Abstinence using 7-day point prevalence was measured with self-report and confirmed with serum cotinine levels at the end of weeks 4, 12 and 26. One participant reported abstinence at Week 12 and 26 and another reported abstinence at Week 12, but serum cotinine did not confirm abstinence, thus they were deemed non-abstinent. A statistically significant Time x Treatment effect between the two groups ($F(2,91) = 6.68$; $p = 0.002$) with regards to 7-day point prevalence abstinence was found (Fig. 3). The primary outcome was abstinence at Week 12 (end of varenicline treatment) which was found to be significantly higher in the active group (82.4%) compared to the sham group (30.7%) (Diff = 51.7%; 95% CI = 11.1–92.3%; $t(91) = 2.53$; $p = 0.013$). No significant difference in abstinence rates were found at Week 4 (active: 66.8%, sham: 64.8%) and Week 26 (active: 25.9%, sham: 30.7%). All three variations of long-term abstinence measures at Week 26 (i.e., prolonged and continuous abstinence) were all found to be the similar and not significant (χ^2 [1] = 0.015, $p = 0.90$).

3.3. Nicotine dependence (FTND)

There was no statistically significant Time x Treatment effect ($p = 0.98$, $\eta^2 = 0.01$). However, there was a significant Time effect ($F(7131.56) = 37.95$; $p < 0.001$, $\eta^2 = 0.67$) and a trend for a significant Treatment effect ($p = 0.071$, $\eta^2 = 0.08$). Fig. 4 demonstrates that participants dependence scores decreased over time for both groups and although differences did not reach significance, scores tended to drop lower for the active group compared to the sham group.

3.4. Craving (T-QSU)

No significant Time × Treatment effect ($p = 0.26$, $\eta^2 = 0.17$) and no significant Treatment effect ($p = 0.141$, $\eta^2 = 0.05$) were found. However, there was a significant Time effect ($F(7,45.74) = 32.14$; $p < 0.001$, $\eta^2 = 0.83$). Fig. 5 demonstrates that participants craving scores decreased over time for both groups and although differences did not reach significance, the mean score tended to drop lower for the active group compared to the sham group.

Table 1
Demographic and baseline characteristics for all randomized participants. Categorical variables are expressed as counts and percentages and p-value determined by Fisher's Exact Test. Continuous variables are presented as means with standard deviations and ranges, and p-value determined by Mann-Whitney *U* Test. No statistically significant differences were found.

	Active (n = 24)	Sham (n = 18)	P-value
Age, mean (SD)	43.8 (12.5)	46.2 (12.9)	0.47
Sex, n (%)			
Male	20 (83.3)	10 (55.6)	0.084
Female	4 (16.7)	8 (44.4)	
Education Level, n (%)			
Less than grade 8	1 (4.2)	1 (5.6)	0.065
Highschool	8 (33.3)	1 (5.6)	
College/University/Grad School	15 (62.5)	16 (88.9)	
Education Years, mean (SD)	14.8 (3.6)	14.5 (2.8)	0.49
Race, n (%)			
Asian	2 (8.3)	0 (0)	0.17
Black or African American	0 (0)	3 (16.7)	
White	19 (29.2)	13 (72.2)	
More than one race	3 (12.5)	2 (11.1)	
Employment Status, n (%)			
Employed	15 (62.5)	11 (61.1)	1
Unemployed	6 (25.0)	5 (27.8)	
Retired	3 (12.5)	2 (11.1)	
Housing, n (%)			
House	7 (29.2)	7 (38.9)	0.57
Apartment	15 (62.5)	11 (61.1)	
Condo	2 (8.3)	0 (0)	
Income, n (%)			
<19,999	7 (29.2)	2 (11.1)	0.45
20,000–49,999	9 (37.5)	10 (55.6)	
50,000–74,999	4 (16.7)	4 (22.2)	
>75,000	4 (16.7)	2 (11.1)	
Marital Status, n (%)			
Married/Common Law	6 (25.0)	5 (27.8)	1
Separated/Divorced/Annulled	6 (25.0)	4 (22.2)	
Never Married	12 (50.0)	9 (50.0)	
FTND (max 10), mean (SD)	5.6 (1.5)	6.3 (1.4)	0.16
MMSE (max 30), mean (SD)	28.5 (1.5)	28.4 (1.5)	0.95
Smoking Contemplation Ladder (max 10), mean (SD)	9 [1]	9 [1]	0.12
CO Measurement (ppm), mean (SD)	24.7 (13.9)	24.3 (11.3)	0.74
Cigarettes/day, mean (SD)	16.9 (5.3)	19.4 (7.8)	0.45
Alcoholic Drinks/day, mean (SD)	1.1 (1.7)	1.3 (1.6)	0.39
Nicotine Metabolite Ratio, mean (SD)	0.50 (0.30)	0.55 (0.22)	0.36

Table 2
Recent (within past year) diagnosis of mental disorders of all randomized participants. P-value found using Fisher's Exact Test. No statistically significant differences were found.

	Active (n = 24)	Sham (n = 18)	P-value
Anxiety Disorder, n (%)	4 (16.7)	3 (16.7)	1
Cannabis Use Disorder, n (%)	4 (16.7)	1 (5.6)	0.37
Attention-Deficit/Hyperactivity Disorder, n (%)	3 (12.5)	2 (11.1)	1
Alcohol Use Disorder, n (%)	2 (8.3)	2 (11.1)	1
Substance Use Disorder, n (%)	3 (12.5)	0 (0)	0.25
Mood Disorder, n (%)	1 (4.2)	1 (5.6)	1
Obsessive Compulsive Disorder, n (%)	0 (0)	1 (5.6)	0.43
Post-Traumatic Stress Disorder, n (%)	1 (4.2)	0 (0)	1
Schizophrenia Disorder, n (%)	0 (0)	1 (5.6)	0.43

3.5. Withdrawal (MNWS)

No significant Time × Treatment effect ($p = 0.24$, $\eta^2 = 0.07$) and no significant Treatment effect ($p = 0.98$, $\eta^2 < 0.001$) were found. However, a significant Time effect ($F(7127.85) = 5.51$; $p < 0.001$, $\eta^2 = 0.23$) was seen. Fig. 6 shows that withdrawal symptoms peak at Week 2 for both groups. Withdrawal continuously decreases after Week 2 for the active group, whereas in the sham group a slow increase after Week 4 was observed.

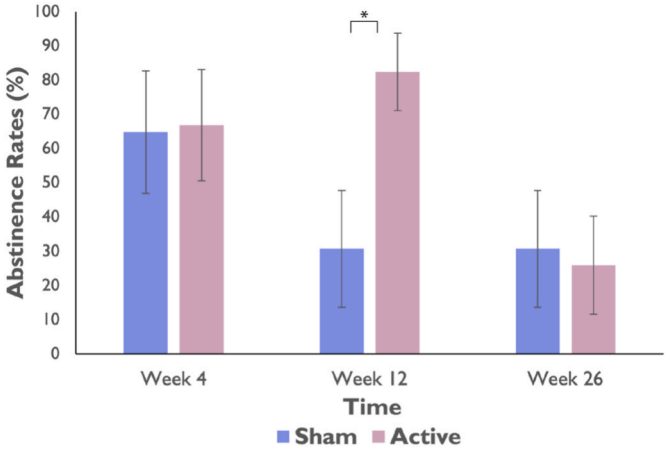

Fig. 3. Abstinence rates at Week 4, 12, and 26. Abstinence was measured by 7-day point-prevalence abstinence. All measures were confirmed with plasma cotinine. Bars represent (±) standard error. Group sample sizes: Week 4 (n = 18 active, n = 16 sham), Week 12 (n = 17 active, n = 15 sham), and Week 26 (n = 16 active, n = 15 sham). * Indicates statistical significance $p < 0.05$.

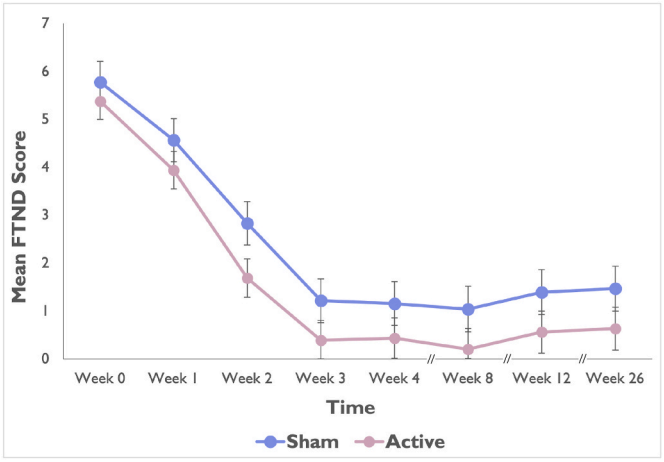

Fig. 4. FTND (nicotine dependence) scores at various weekly follow ups. Bars represent (±) standard error. Group sample size: week 0 (n = 24 active, n = 18 sham), week 1 (n = 21 active, n = 16 sham), week 2 (n = 20 active, n = 16 sham), week 3 (n = 19 active, n = 16 sham), week 4 (n = 18 active, n = 16 sham), week 8 (n = 17 active, n = 14 sham), week 12 (n = 17 active, n = 15 sham), week 26 (n = 16 active, n = 15 sham). Week 0 represents the score recorded at the first study visit.

3.6. Cigarette consumption

The number of cigarettes smoked were recorded daily using the TLFB during treatment. At the 6 month follow up, a 7-day TLFB was collected. No significant Time x Treatment effect ($p = 0.98$, $\eta^2 = 0.02$) and no significant Treatment effect ($p = 0.91$, $\eta^2 < 0.001$) were found. However, a significant Time effect ($F(12, 230.08) = 37.43$; $p < 0.001$, $\eta^2 = 0.66$) was found. Fig. 7 shows both groups decreased the number of cigarettes smoked after Week 2 (target quit day). The active group appears to remain constant thereafter up until Week 26, whereas the sham group slowly starts to increase after Week 7.

CO was measured at every visit. No significant Time × Treatment effect ($p = 0.76$, $\eta^2 = 0.16$) and no significant Treatment effect ($p = 0.63$, $\eta^2 = 0.0061$) were found. However, a significant Time effect (F

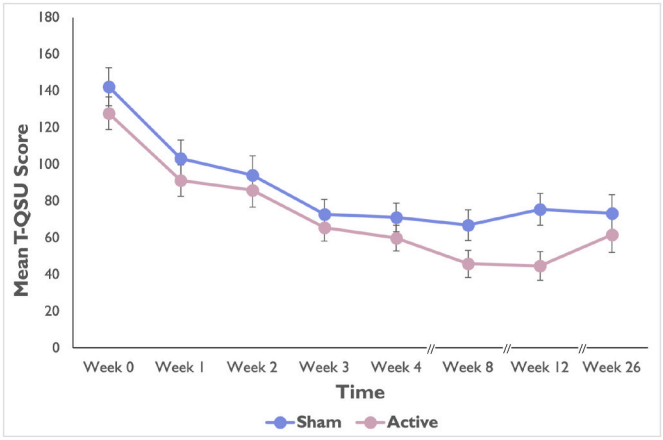

Fig. 5. T-QSU (craving) scores at various weekly follow ups. Bars represent (±) standard error. Group sample size: week 0 (n = 24 active, n = 18 sham), week 1 (n = 21 active, n = 16 sham), week 2 (n = 20 active, n = 16 sham), week 3 (n = 19 active, n = 16 sham), week 4 (n = 18 active, n = 16 sham), week 8 (n = 17 active, n = 14 sham), week 12 (n = 17 active, n = 15 sham), week 26 (n = 16 active, n = 15 sham). Week 0 represents the score recorded at the first study visit.

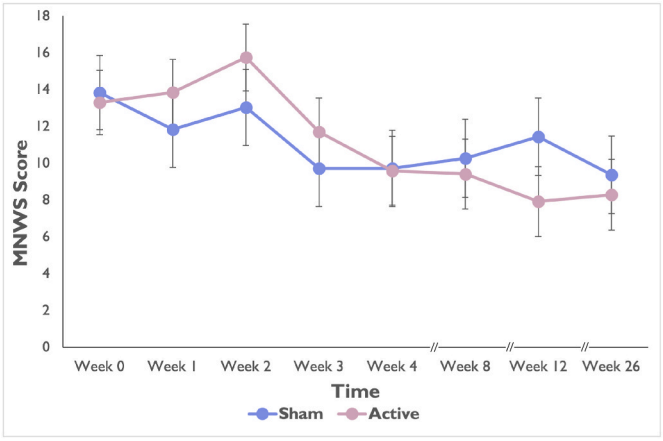

Fig. 6. MNWS (withdrawal) scores at various weekly follow ups. Bars represent (±) standard error. Group sample size: week 0 (n = 24 active, n = 18 sham), week 1 (n = 21 active, n = 16 sham), week 2 (n = 20 active, n = 16 sham), week 3 (n = 19 active, n = 16 sham), week 4 (n = 18 active, n = 16 sham), week 8 (n = 17 active, n = 14 sham), week 12 (n = 17 active, n = 15 sham), week 26 (n = 16 active, n = 15 sham). Week 0 represents the score recorded at the first study visit.

(13,45.66) = 12.03; $p < 0.001$, $\eta^2 = 0.77$) was observed.

3.7. Treatment compliance and blinding

No difference was found in varenicline and rTMS compliance between the two groups (see supplementary). Participants in the active group were more likely to be accurate at guessing their treatment arm at Visit 1 (p = 0.0022), but they were not more likely to be accurate at Visit 11 (p = 0.31) (see Table S3).

3.8. Adverse events

A total of 29 different adverse events (AEs) were reported throughout the study (see Table S4). Out of the 29 types of events reported, 17 of them were reported only once. No adverse events were considered serious. No significant differences were found in any of the adverse

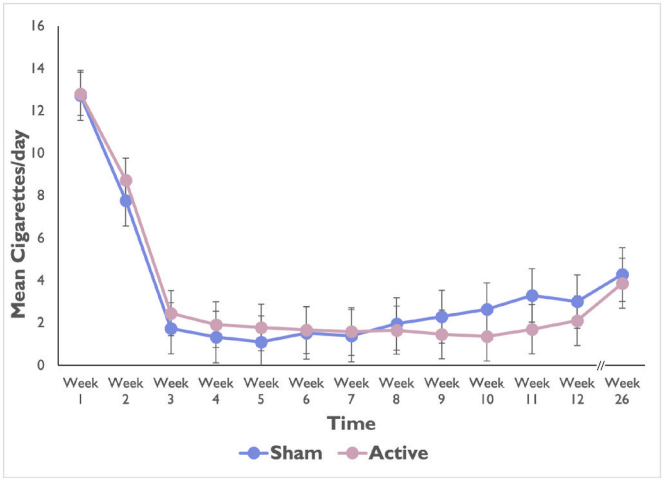

Fig. 7. Average cigarettes smoked per day across various weeks. Bars represent (±) standard error. Group sample size: week 1 (n = 24 active, n = 18 sham), week 2–3 (n = 20 active, n = 16 sham), week 4 (n = 19 active, n = 16 sham), week 5–7 (n = 18 active, n = 16 sham), week 8 (n = 17 active, n = 16 sham), week 9–12 (n = 17 active, n = 15 sham), week 26 (n = 16 active, n = 15 sham).

events between the active and sham group. The most reported events were nausea (33.3% active vs. 16.7% sham), headache (16.7% active vs. 33.3% sham), and vivid dreams (16.7% active vs. 11.1% sham).

4. Discussion

This trial aimed to investigate the efficacy and effect of H11 rTMS targeting the insula combined with varenicline treatment on abstinence rates and other smoking outcomes such as cravings, withdrawal, and dependence. To our knowledge, this is the first trial investigating the combined treatment of varenicline along with a H11 rTMS coil targeting the bilateral insula for smoking cessation.

The primary outcome measure was abstinence at the end of 12 weeks, defined by a 7-day point prevalence abstinence and confirmed with serum cotinine. Abstinence rates were significantly higher in the active group compared to the sham group. In fact, abstinence rates at the primary timepoint (12 weeks) were more than 2.5 times higher in the active group compared to sham. Given that this is the first study to use the H11-coil and combine it with varenicline, it is difficult to compare the results with other studies. However, two previous smoking cessation studies using the H4-coil can be used, where one found an abstinence rate of 44% after 3 weeks of daily treatment [17] and the other found an abstinence rate of 25.3% at end of treatment (i.e., 6 weeks) [18]. However, unlike the present study, these previous studies did not include psychiatric patients and did not include varenicline or other treatments. In terms of varenicline, the best comparison for the present study is the EAGLES trial, since it included over 8000 participants and half of which had a psychiatric disorder, which is more in line with our cohort. That trial found that varenicline abstinence rate at Week 12 was 33.5% [6]. We found a similar abstinence rate for the sham group at Week 12. Interestingly, the abstinence rates in both groups in the present study were very high (>60%) at Week 4. Yet, for the active group the abstinence rate was 82.4% at Week 12, while for the sham group it was only 30.7%, which demonstrates that the combined treatment seemed to have a positive additive effect in this cohort of patients. Others have investigated the efficacy of combining pharmacotherapies for smoking cessation. For example, combining varenicline with NRT appears to increase smoking cessation rates compared to treatment alone [30] and treatment with both varenicline and bupropion has also been seen to have more success by some [31], but that is also debatable based on others who found more mild effects [32].

We found that the abstinence rates remained high until Week 12,

therefore it is maintained up to 2 months after the completion of rTMS. However, rates dropped substantially from Week 12–26 in the active group, which shows that the additive effect seen in Week 12 seems to not be maintained over time. Studies do show that smokers are at their most vulnerable for relapse within the first year of quitting [33]. This information is important because it can help with future studies to find the best rTMS protocol. This is an area that is not well studied, and researchers have used different protocols. For example, this study had 20 daily rTMS sessions over the course of 1 month (5 sessions/week), whereas Dinur-Klein et al. (2014) [17] had 10 daily sessions for 2 weeks followed by 3 nonconsecutive treatments the following week and Zangen et al. (2021) [18] had 15 daily sessions for 3 weeks followed by 1 weekly session for 3 weeks. All three studies also had different treatment parameters such as number of pulses administered. Although the latter two studies used a coil targeting the insula and PFC, it still demonstrates the variability in treatments. The finding that abstinence rates dropped between the end of treatment at Week 12 to Week 26 might allude to the fact that there is vulnerability during that time and perhaps a longer treatment with maintenance rTMS sessions may help.

With regards to the secondary outcomes of dependence, craving, withdrawal and smoking measures, no significant differences between the active and sham group were found. However, all measures were markedly reduced compared to baseline and the trends all favored the active group. It is not the first time where abstinence rates are significantly different between treatment groups, but dependence, withdrawal and craving measures are not. The previous smoking cessation H4 rTMS trials found similar results [17,18]. Furthermore, all participants were receiving varenicline and that alone has been shown to help with withdrawal and craving [34], thus making it more difficult to detect a difference between the groups. In addition, participants were not given instructions to refrain from smoking before a session and no information was collected regarding last cigarette smoked prior to the assessments, thereby making it difficult to control for differences that may have occurred due to those factors. Participants were also not presented with smoking cues prior to rTMS treatment, which was used in the prior H4 rTMS smoking cessation trials [17,18]. However, evidence showing the efficacy of cue presentation is not strong [17].

Another important finding from this study is that no significant difference in adverse events between the active and sham group were found. Therefore, the combination of the two treatments did not pose an increased risk of adverse events. Furthermore, the main adverse events are known effects of varenicline [35] and/or rTMS [17,18]. This shows that even with a more inclusive sample of smokers with psychiatric and substance use co-morbidity, no additional safety risks accrued.

One important consideration is the fact that even though this coil is designed to target the insula, it may not be the only region affected by stimulation due to the decreased focality seen in H-coils and due to the possibility of secondary activations occurring [36]. The primary site of activation may cause neurotransmitter release or back propagation of action potentials that leads to secondary activations [37]. These activations may not be limited to the networks associated with the primary target [38]. Studies with both brain stimulation and imaging have demonstrated these activation [39]. Thus, it cannot be certain that all the effects were attributable to the insula. Furthermore, it is not entirely known why the beneficial effects stem from high frequency rather than low frequency stimulation. There is a divergence between different lines of evidence, with preclinical studies showing the benefits of lesioning or inhibiting the insula [12], but clinical trial data showing that high frequency groups have greater improvement in smoking abstinence [17,18]. In addition, although previously it was thought that low frequency stimulation leads to inhibition and high frequency stimulation to facilitation, recent research has shown that it is not always the case [40]. Therefore, future studies should combine rTMS with brain imaging as this can provide valuable insights as to what might be occurring during H11 rTMS.

This study is not without limitations. First, the sample size was small and the power was low, which could be the reason why no differences were found in the secondary outcome measures. In addition, the sample consisted of mainly males, which is consistent with the fact that there are more male smokers [41]. Even though this was a randomized study, and no significant differences were found at baseline between the two groups with regards to sex, there are known sex differences in this field (e.g., smoking behaviors, nicotine metabolism) [42–44]. In addition, females during periods of high estrogen have been found to be more sensitive to the effects of rTMS [45]. Future studies should aim to consider sex in their recruitment and analysis. In terms of dropouts, the rates tended to be higher in the active group than the sham group. However, this was not statistically significant and based on the reasons provided from the participants, it did not seem like the deep rTMS treatment was a contributing factor. When comparing dropout rates to other trials, we show similar if not better rates [6,17,18]. Lastly, we did not assess the TMS operators blindness, which should be something considered in future studies.

5. Conclusion

In conclusion, this is the first trial to investigate the combined treatment H11 rTMS to the insula with varenicline in smokers motivated to quit. A beneficial effect of the active rTMS on abstinence rate at the end of varenicline treatment was seen, thus demonstrating that smokers may benefit from a combined treatment. Nonetheless, this was a pilot study so results should be interpreted with caution. This study provides promising data that encourages further exploration into combination treatments with rTMS and pharmacotherapy for smoking cessation. Future research should include large-scale trials with a focus on establishing the best rTMS protocol with combined varenicline for smoking cessation.

Author Contribution

Christine Ibrahim: Methodology, Formal analysis, Investigation, Data curation, Writing- original draft, Visualization, Writing - review & editing; Victor M. Tang: Investigation, Writing - Review & Editing; Daniel M. Blumberger: Conceptualization, Methodology, Investigation, Funding acquisition, Writing - review & editing; Saima Malik: Conceptualization, Methodology, Funding acquisition, Writing - review & editing; Rachel F. Tyndale: Resources, Formal analysis, Writing - review & editing; Alisson P. Trevizol: Investigation, Writing - review & editing; Mera S. Barr: Conceptualization, Methodology, Funding acquisition, Writing - review & editing; Zafiris J. Daskalakis: Conceptualization, Methodology, Funding acquisition, Writing - review & editing; Abraham Zangen: Conceptualization, Methodology, Writing - review & editing; Bernard Le Foll: Conceptualization, Methodology, Investigation, Supervision, Project administration, Funding acquisition, Writing - review & editing.

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Declaration of competing interest

BLF has obtained funding from Pfizer Inc. (GRAND Awards, including salary support) for investigator-initiated projects. BLF has obtained funding from Indivior for a clinical trial sponsored by Indivior. BLF has in-kind donations of cannabis products from Aurora Cannabis Enterprises Inc. and study medication donations from Pfizer Inc. (varenicline for smoking cessation) and Bioprojet Pharma. He was also provided a coil for a Transcranial magnetic stimulation (TMS) study from Brainsway. BLF has obtained industry funding from Canopy Growth Corporation (through research grants handled by the Centre for

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.10.002.

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