Combined Working Memory Training and Transcranial Magnetic Stimulation Demonstrates Low Feasibility and Potentially Worse Outcomes on Delay to Smoking and Cognitive Tasks

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Original Investigation

Combined Working Memory Training and Transcranial Magnetic Stimulation Demonstrates Low Feasibility and Potentially Worse Outcomes on Delay to Smoking and Cognitive Tasks: A Randomized 2 × 2 Factorial Design Pilot and Feasibility Study

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Abstract

Introduction: Repetitive Transcranial Magnetic Stimulation (rTMS) has shown promising results in treating several Substance Use Disorders including Tobacco Use Disorder. However, questions remain regarding how to optimize treatment outcomes. Enhancement of working memory by rTMS is a potential therapeutic mechanism. The current pilot study examined whether rTMS plus a cognitive training program could enhance the effects of rTMS on smoking behaviors using a controlled, factorial design.

Aims and Methods: We hypothesized that cognitive training plus stimulation would improve control over smoking behaviors, resulting in enhanced cognitive performance and increased latency to smoke on a delay to smoking analog task. Using a 2 × 2 factorial design, nicotine dependent smokers (n = 43) were randomized to receive 10 sessions of active (10 Hz) or sham rTMS delivered to the left dorsolateral prefrontal cortex, plus active or sham working memory training (WMT) prior to and following stimulation.

Results: Contrary to hypotheses, we observed a significant interaction effect, indicating that combining the two active interventions (rTMS+WMT) resulted in worse performance on the smoking analog task (B = −33.0, 95% CI = −64.39, −1.61, $p < .05$), compared to delivering either intervention alone. Additionally, although active rTMS (compared to sham rTMS) improved letter-sequencing performance (B = 1.23, 95% CI = 0.08–2.38, $p < .05$), and active WMT (compared to sham WMT) improved back-digit task performance (B = 1.53, 95% CI = 0.02–3.05, $p < .05$), combining interventions worsened the effect of each on a back-digit task (B = −3.01, 95% CI = −5.96, −0.052, $p < .05$).

Conclusions: These preliminary findings indicate potential iatrogenic effects of combining rTMS and this working memory training intervention and underscore the need for rigorous evaluation of substance specific conceptual frameworks when selecting future combination interventions.

Implications: Counter to hypothesis, this study found no additional benefit of adding a working memory training program to a rTMS protocol in a sample of daily smokers. The combination condition (active rTMS + active training) resulted in worse performance on a delay to smoking analog task and a measure of working memory performance compared to delivering either intervention alone. These preliminary findings inform strategies for optimizing rTMS in smokers and highlight the need for future studies to consider several key components of candidate combination interventions, including effects on regulation of substance use.

Clinical Trial Registration (if any): The trial was registered at ClinicalTrials.gov (NCT03337113).

Introduction

Neuroimaging and preclinical investigations have led to substantial advances in understanding the neural circuitry that maintains addictive behaviors. The translation of these findings to treatment for individuals with Substance Use Disorders (SUDs) has lagged but several interventions are now in early development. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation procedure that has demonstrated promise in bridging this translational gap. rTMS sends magnetic pulses through the scalp to stimulate neuronal tissue in selected brain areas, and has been shown to reduce craving for and consumption of

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several psychoactive substances, including nicotine.[1,2] rTMS represents a therapeutic modality with potential to improve upon current interventions available for tobacco use disorder (TUD), which leave as many as 70% of tobacco dependent individuals unsuccessful in their attempt to quit.[3]

rTMS now has a substantial evidence base supporting short-term efficacy in treating TUD. Clinical trials have reported significant effects of active rTMS on abstinence rates using protocols targeting prefrontal cortex regions with figure-of-eight coils[4] as well as Hesed ("H"-family) coils which have comparatively deeper field penetration and stimulate a wider portion of the cortex.[5,6] A pilot randomized trial utilizing 20 Hz rTMS figure-of-eight coil applied to the left dorsolateral prefrontal cortex (DLPFC) reported an intent-to-treat abstinence rate (confirmed via carbon monoxide <8 ppm) of 50% for active compared to 15.4% for sham rTMS at 12 weeks.[4] Recently, a large randomized controlled trial reported an intent-to-treat 18-week continuous quit rate (confirmed via urine cotinine <200 ng/ml) of 19.4% for active rTMS compared to 8.7% in sham[5] using an H4-coil to stimulate the lateral prefrontal cortex and insula.[7] These recent results in combination with the extant literature examining rTMS for smoking cessation demonstrate potential for this therapeutic modality to represent a major advance in available treatments.

Given the increasing evidence suggesting promise for rTMS in treating TUD, several methodological and conceptual questions remain regarding how to optimize its efficacy. These include identifying optimal brain regions for stimulation as well as adjunctive cognitive interventions that might improve treatment effectiveness by capitalizing on the "state" of a targeted brain region when it is stimulated (a paradigm sometimes referred to as cognitive paired association stimulation (C-PAS)[8]). Understanding the therapeutic mechanism whereby rTMS impacts TUD is important to the selection of an adjunctive cognitive intervention with potential to optimize treatment with rTMS. Regarding therapeutic mechanisms contributing to the efficacy of rTMS for TUD, two primary hypotheses have been posited: (1) increased cognitive control over smoking behavior and (2) disruption of cigarette craving.[5,9,10] Several studies have found that craving is reduced following rTMS – however, reduced cigarette consumption has been observed following rTMS even in the absence of reduced craving,[7,11] suggesting that reduced craving may not be the sole mechanism contributing to the effects of rTMS on smoking behaviors. Evidence of increased cognitive control has been observed in smokers following prefrontal rTMS,[12] and research across diverse clinical samples has demonstrated that prefrontal rTMS improves working memory,[13] that is, the cognitive process posited to support control over pre-potent incentive salience to substance use behavior.[14–16]

Several studies have included craving provocation paradigms applied directly prior to simulation.[7] The theoretical basis of this approach comes, in part, from clinical studies that suggest activation of the target circuitry by provocation may make these circuits more sensitive to modification, and that rTMS may increase plasticity – enhancing the effectiveness of a cognitive or behavioral intervention.[5,17] Results from studies examining craving provocation prior to rTMS show some promise for this approach, particularly in measures of nicotine dependence.[7] However, the craving provocation protocol preceding stimulation also included brief motivational enhancement directly following stimulation.[5] Therefore, whether observed improvements result from a disruption of the pathological circuitry (eg craving/psychiatric symptoms), or from increased effectiveness of down-regulation of craving following motivational enhancement is not well understood.

To our knowledge, no studies have specifically examined rTMS protocols aimed at increasing the effects of cognitive control over smoking behaviors with combination treatments as compared to rTMS alone. Thus, little is known regarding whether pairing provocation of neural circuitry associated with cognitive control and stimulation could improve therapeutic effects. Results from other non-invasive brain stimulation (ie transcranial direct stimulation) studies provide some evidence that combining stimulation and working memory training results in improved cognitive outcomes in healthy participants as well as older adults – but no evidence regarding the combination has been reported on smoking behaviors.[18,19] Working memory tasks have been shown to significantly and reliably increase activity in the DLPFC, the same brain site targeted by many rTMS studies for smoking.[20,21] Furthermore, working memory performance[16] as well as working memory related activation in the DLPFC[15] predicts subsequent relapse to smoking. Thus, development of a rTMS treatment protocol that may potentiate activity in the targeted brain region prior to stimulation or increase cognitive training performance via increased long-term potentiation,[22] resulting in the potential for improvements over standalone conditions would represent an important opportunity for targeting known executive function deficits contributing to relapse.[15,23]

The current study aimed to test the feasibility and potential for improved effects of combining a working memory training protocol with rTMS (10 Hz over left DLPFC) on smoking behaviors. Secondary aims included evaluating the effect of the combined interventions on indices of working memory. Daily smokers were randomized to one of 4 conditions within a 2 × 2 factorial design including combined active working memory training and rTMS, as well as single active and double-sham controls. We hypothesized that after 10 stimulation sessions, active rTMS and working memory training (main effects) would result in significant improvement in smoking indices and cognitive task performance as compared to the double-sham condition, and that active working memory training would significantly potentiate active rTMS so that the double-active combination condition (interaction effect) would produce significant improvements in both domains as compared to the single active conditions.

Method

Participants

This study was conducted in Providence, Rhode Island and approved by the Butler Hospital and Brown University Institutional Review Boards. Participants were recruited from the local community using print and online advertising. Eligible participants met the following inclusion criteria at the time of screening: (1) absence of medical contraindications for rTMS,[24] (2) 18–60 years of age, (3) smoked regularly for ≥1 year, (4) currently smoke ≥ 10 cigarettes daily, (5) carbon monoxide level ≥10 ppm, (6) endorse ≥ 5 (moderate) cigarette dependence (Fagerström Test for Cigarette Dependence; (FTCD),[25] (7) report no plan to quit smoking within 3-months, and (8) report no use of other nicotine products. Exclusions included: (1) met DSM-V criteria for current AUD/

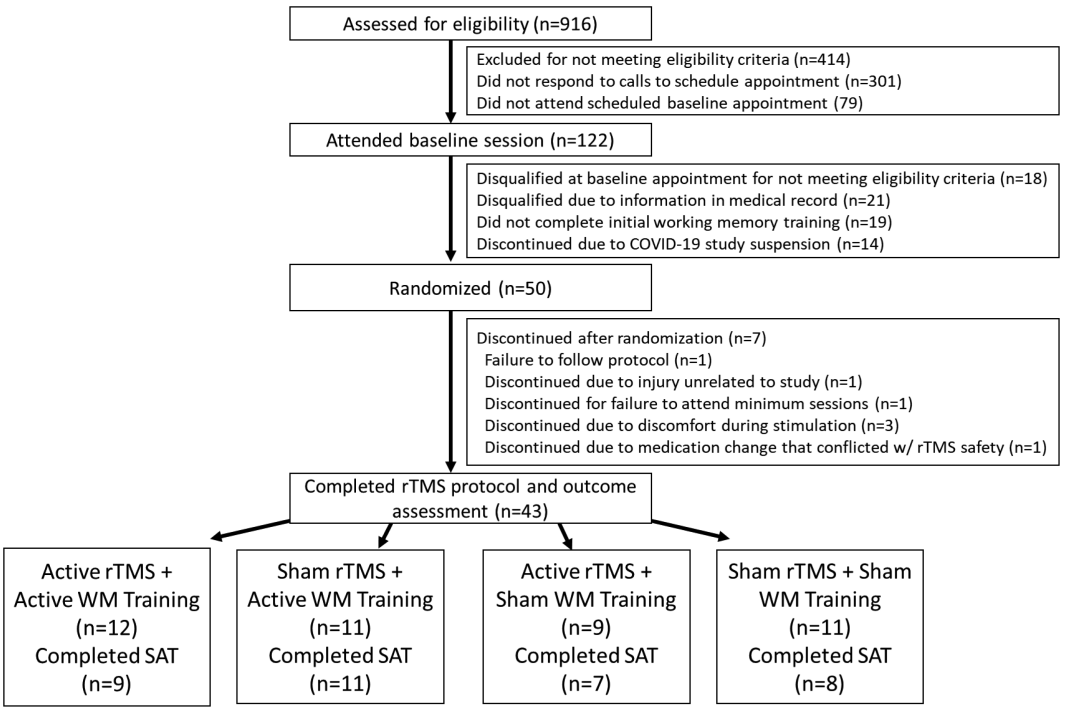
SUD as assessed by the Mini-International Neuropsychiatric Interview (MINI)[26] or medical record, (2) current diagnosis of affective disorder (major depressive disorder, bipolar disorder) or psychotic symptoms, and (3) were currently pregnant or lactating, or intended to become pregnant.

Procedure

Eligible participants were invited to participate in a baseline assessment visit, 20 days of working memory training, 10 days of rTMS sessions, and a final outcome assessment approximately 30 days after baseline. Baseline assessment included demographics, measures of smoking characteristics, psychological/psychiatric measures, and neuropsychological and behavioral economic tasks. Following the baseline assessment session, urn randomization[27] was used to ensure balance on three baseline factors: WM (assessed via n-back), cigarette dependence,[25] and age. Participants were randomized to (1) active rTMS + active working memory training ($rTMS_A$+WMT_A); (2) active rTMS + sham WMT ($rTMS_A$+WMT_S); (3) sham rTMS + active WMT ($rTMS_S$+WMT_A); and (4) sham rTMS + sham WMT ($rTMS_S$+WMT_S). During the baseline visit, participants were introduced to the WMT software and instructed on how to access and utilize the software properly from remote locations for WMT sessions occurring prior to the first rTMS session. Following the baseline assessment, participants were instructed to commence once-daily WMT sessions (five per week) for two weeks. Participants were required to complete a minimum of eight WMT sessions during this period, which were electronically logged online to verify completion. In week three, participants initiated rTMS sessions. Participants were scheduled to receive ten stimulation sessions on consecutive business days; those unable to complete a minimum of seven rTMS sessions were withdrawn. At each rTMS session, participants completed $WMT_{A/S}$ in the laboratory immediately prior to and immediately after the stimulation protocol was started. Following the final rTMS session, participants completed a final visit where baseline measures were repeated along with a laboratory-based analog of smoking lapse.[28,29] An overview of study procedures is found in Figure 1. Participants were compensated up to $540 for their participation.

Equipment and Materials

rTMS was delivered with a Magstim Rapid2 system using 70 mm figure-8 Air Film Coils (Magstim, Whitland, South Wales, UK). Stimulation parameters were informed with consideration for prior studies from two bodies of literature; those demonstrating protocols with the ability to increase WM capacity[13] or reduce cigarette craving/consumption at the time of study design.[10,11,30,31] Since the primary aims of the current study focused on examining potential adjunctive treatments of the effects of rTMS on smoking related behaviors, rTMS parameters with documented effects on smoking outcomes were given precedence in parameter selection. rTMS pulses were delivered at 10 Hz (100% resting motor threshold, RMT) in 5 s trains separated by 15 s intertrain intervals, for a total of 2000 pulses per session, resulting in a total stimulation protocol time of approximately 13 min. Based on consensus recommendations for targeting the left DLPFC at the time of study initiation[32] $rTMS_{A/S}$ was applied with coil placement over the standard F3 scalp location per 10/20 EEG system. An appropriately sized elastic BraiNet cap on the participant's head was used to mark the F3 location



*SAT = Smoking Analogue Task. Due to COVID-19 related research restrictions, the final 8 participants randomized could not complete the Smoking Analogue Task. Recruitment began 10/2017 and ended 2/2021, when research funds were exhausted.

Figure 1. Consort diagram. *SAT = Smoking Analog Task. Due to COVID-19 related research restrictions, the final 8 participants randomized could not complete the Smoking Analog Task. Recruitment began October 2017 and ended February 2021, when research funds were exhausted.

and then removed so the coil center could be placed directly on the scalp mark, with coil orientation 45° relative to midline. Resting Motor Threshold (RMT), defined as the energy required to elicit contralateral hand movement on ≥50% of ten trials, was assessed prior to the first rTMS session. A matching D70 Magstim Air-Film Sham Coil was used for sham stimulation. While all participants were blinded to their assigned rTMS condition, stimulation procedures were conducted by unblinded TMS research technicians who had no role in any of the study's assessment, data collection, or analysis procedures.

WMT (adapted from Houben et al.[33]) included three distinct tasks in each session: a visuospatial WM task, a backward digit span task, and a letter span task.[33,34] Difficulty level for all three WM tasks was automatically adjusted on a trial-by-trial basis for those assigned to the WMT_A condition; each task initially involved sequences comprised of three items, with the length of the sequences subsequently modified according to the participants' performance (ie +1 item in the sequence following a correct response, −1 following two incorrect responses on consecutive trials). The WM task difficulty level was not adjusted for those assigned to WMT_S; it remained at the initial level throughout each task (ie three items in each sequence). An identical protocol and software have demonstrated efficacy in increasing WM capacity in persons with addictive behavior.[33] Considering the potential disruptive effects of the rTMS protocol on WMT, sessions were completed directly prior to and directly following stimulation rather than during stimulation.

Measures

Screening measures included smoking data related to inclusion criteria and demographics, psychiatric diagnostic interview, and a series of questions evaluating safety for rTMS.[24] FTCD was used as a continuous measure of cigarette dependence.[25] Immediate ("right now") measures of smoking urge were assessed utilizing a 100-point Visual Analog Scale (VAS).[35] A variant of the Minnesota Nicotine Withdrawal Scale[36] was used to assess withdrawal symptoms, including general (past 24 h) urge to smoke, with higher scores reflecting greater levels of withdrawal/ urge. The Inventory of Depressive Symptomatology Self-Report (IDS-SR)[37] was used to quantify symptoms of depression. Participant blinding to rTMS and WMT was assessed by having participants guess their condition (ie active Transcranial Magnetic Stimulation (real stimulation) or sham Transcranial Magnetic Stimulation (no real stimulation) following completion of the final assessment session.

Primary Outcome Measures

The Delay to Smoking Analog Task (Mckee et al.[28,29]) is a behavioral choice paradigm that is sensitive to smoking medication effects, including in non-treatment seeking smokers, regardless of motivation to quit.[29,38,39] In this task participants earn monetary rewards for delaying initiation of cigarette smoking in 5-minute increments over a 50-minute period, following 3-hours of observed smoking deprivation. At the beginning of this procedure, participants were given five of their preferred brand cigarettes, a lighter, and an ashtray. Participants were told that for each 5-minute period they delayed smoking, they would earn $.50, for a maximum of $5. The primary outcome was the number of minutes that participants delayed smoking (possible range 0–50). Immediately following the delay period, all participants participated in a 60-minute ad-lib smoking period in which they were told that they could smoke as many cigarettes as they chose, but each cigarette smoked during this 60-minute period would result in a $1.00 deduction from a starting tab of $4.00. The remaining balance from each participant's "tab" was paid to the participant in the form of cash at the end of the session. Due to COVID-19 restrictions that occurred during the study, the smoking analog task could not be collected for the final 8 participants (see Figure 1 CONSORT Diagram for detail).

Working memory capacity was measured using the *National Institute of Health Examiner computerized N-back (2-back) and Dot Counting tasks*.[40] Total number of correct responses (range 0–90) on the 2-back task, and total correct responses on the Dot Counting task (range 0–27) were used for primary analysis, respectively. Working memory was also measured using the assessment version of the *Maastricht Working Memory Training program*.[33] Total score on the assessment version of the three tasks is the highest end level achieved when participants are unable to reproduce a sequence correctly on two consecutive trials. Two indices of demand on the *Cigarette Purchase Task*[41] including demand sensitivity (α; sensitivity to change in price) and elasticity ($P_{MAX;}$ point at which demand switches from inelastic to elastic) were calculated using an open source Demand Curve Analyzer,[42] with higher values representing increased demand for the monetary reinforcer. Delayed reward discounting was assessed using the *Monetary Choice Questionnaire* (MCQ[43]). Individuals made 27 hypothetical choices between smaller immediate rewards (eg $11 today) and larger delayed rewards (eg $30 in 7 days) at varying levels of hyperbolic-like discounting. Overall temporal discounting function (k) was assessed; larger values indicated steeper discounting.

Analytic Strategy

Primary outcome variables were assessed for normality of distribution via visual inspection of scatter plots, histograms, and values of skewness and kurtosis (<3 and <7, respectively).[44] Elevated values for skewness and kurtosis necessitated log transformations for all variables reported for the Cigarette Purchase Task and Monetary Choice Questionnaire. No outliers ($z > 3.29$) were observed in primary outcome variables reported (minutes until lapse, n-back correct responses, visuospatial working memory, backward digit span task, and letter span task). Multiple regression was utilized to examine the main and interactive effects of the conditions ($rTMS_A$ vs. $rTMS_S$, WMT_A vs. WMT_S) on main outcome measures of smoking behavior and executive function. To allow estimation of main effects that account for the potential interaction between the conditions, the binary condition variables (rTMS and WMT) were centered (active = 0.5 and sham = −0.5), and interaction terms were computed from centered variables.[45] Baseline values for each repeated outcome measure were included as covariates. Sample size considerations are detailed in Supplemental Materials.

Results

See CONSORT diagram (Figure 2) for screening and recruitment results. Participants ($N = 43$) were primarily male (65.1%), 43.25 (SD = 9.4) years of age, moderately dependent

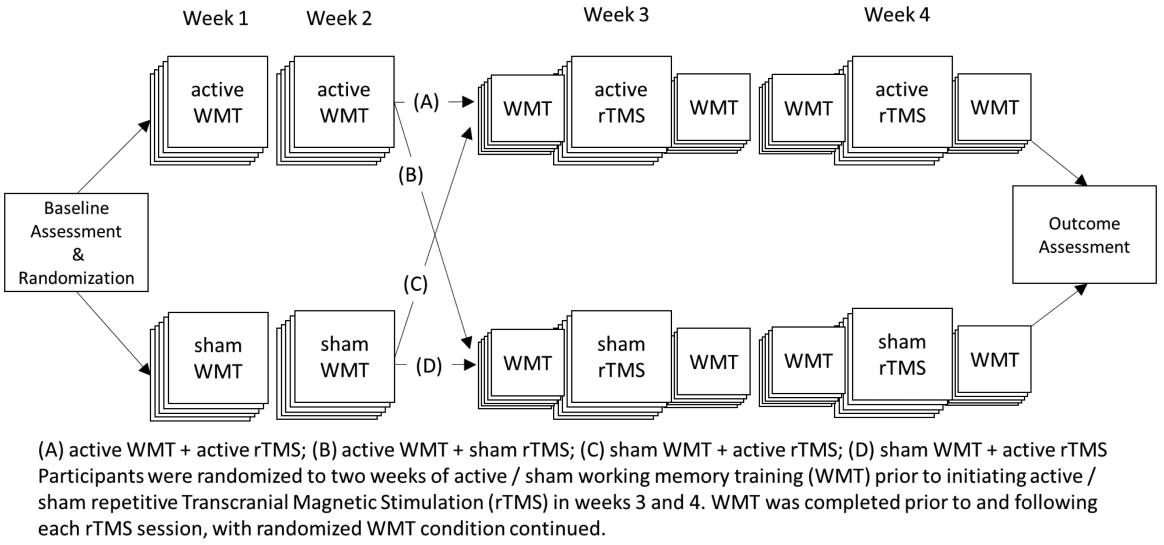


Figure 2. Schedule of study procedures. (A) active WMT + active rTMS; (B) active WMT + sham rTMS; (C) sham WMT + active rTMS; (D) sham WMT + active rTMS participants were randomized to two weeks of active/sham working memory training (WMT) prior to initiating active/sham repetitive Transcranial Magnetic Stimulation (rTMS) in weeks 3 and 4. WMT was completed prior to and following each rTMS session, with randomized WMT condition continued.

smokers (FTCD = 6.35, SD = 1.64), reporting a mean of 18.8 (SD = 7.3) cigarettes/day, and 26.4 (SD = 9.8) years of daily smoking. No significant differences were found between the four conditions on variables included in Urn randomization (age, baseline FTCD, baseline n-back score; all p's > .50). No significant differences between the four conditions were found in number of working memory training sessions completed prior to simulation (M = 9.1, SD = 0.92), number of rTMS sessions attended (M = 9.4, SD = 0.85), or in other relevant baseline characteristics (see Table 1). Participants were not able to correctly guess their stimulation condition (58.3% correct; p = .67) or WMT condition (62.5% correct; p = .19) as tested by Fischer's exact test.

Protocol Feasibility

Several factors inherent to the current study protocol affected participant dropout/final eligibility and overall protocol feasibility. Despite approximating initial enrollment goals, we observed a low rate of randomization (CONSORT Diagram Figure 2). First, the current protocol required medical record review following initial consent to confirm participant self-report and clinical interview; current psychiatric, and substance use disorder history garnered from participant's medical records resulted in 17.2% (n = 21) of the consented sample to be deemed ineligible. Second, uptake of the working memory training paradigm, which included completion of 10 sessions (8 required to continue) prior to initiation of rTMS, resulted in 22.9% (n = 19) dropout of the eligible sample following baseline assessment. Finally, although potentially uninformative to the overall feasibility of the protocol, a portion of the sample 16.9% (n = 14) was unable to complete the study due to COVID-19 research restrictions that occurred during active recruitment.

Smoking Outcome Measures

Counter to our hypotheses, there was a significant interaction effect such that the effect of either active interventions on minutes until smoking lapse was substantially worse (fewer minutes until lapse) when combined with the other (B = −33.0, 95% CI = −64.39, −1.61, p < .05), see Figure 3. The group receiving $rTMS_A$ and WMT_S demonstrated the largest mean latency until lapse (M = 38.0, SD = 18.65), however the main effect of rTMS was not statistically significant. The main effect of WMT on lapse was also nonsignificant. No significant differences in change in cigarettes per day were observed between conditions. Similarly, assessment of measures of cigarette demand on the Cigarette Purchase Task including demand sensitivity and elasticity, did not reveal significant differences between conditions.

Neuropsychological and Behavioral Economic Measures

In line with poorer performance observed on the delay to smoking lapse task described above, the addition of a second active intervention (ie $rTMS_A$+WMT_A) resulted in worse performance on the Maastricht back-digit task at outcome, compared to either condition alone (B = −3.01, 95% CI = −5.96–[−0.052], p < .05), controlling for baseline performance (Figure 4). We observed a significant main effect of WMT_A compared to WMT_S on improved back-digit score (B = 1.53, 95% CI = 0.02–3.05, p < .05), and improved visuospatial scores over time in the WMT_A versus WMT_S condition that fell just over the threshold set for significance (B = 0.62, 95% CI = −0.03–1.28, p = .061). We also observed a significant main effect of $rTMS_A$, compared to $rTMS_S$, on improved performance on the Maastricht letter-sequencing task over time (B = 1.23, 95% CI = 0.08–2.38, p < .05). The effects of condition on working memory performance, assessed via the NIH Examiner 2-back and dot counting tasks were nonsignificant. Lastly, we did not observe any significant differences between conditions on measures of delay discounting, assessed via the Monetary Choice Questionnaire.

Discussion

This study is the first randomized, full factorial design to examine the feasibility, and potential efficacy of working memory training to enhance the effects of rTMS on smoking

Table 1. Participant Characteristics at Baseline

Variable	Category/ Range	% (*n*) or M (SD)					
		Total	rTMS + WMT	rTMS + sham WMT	Sham rTMS + WMT	Sham + sham	*p*
Age	21–59	43.25 (9.43)	42.50 (10.45)	44.77 (8.05)	45.72 (9.23)	40.36 (9.88)	.567
Gender	female	32.6 (14)	33 (4)	27.3 (3)	33.3 (3)	36.4 (4)	.819
Race/ethnicity	Non-Hispanic White	86.0 (37)	91.7 (11)	81.8 (9)	100 (9)	72.7 (8)	.728
	Non-Hispanic Black	4.7 (2)	0	0	9.1 (1)	9.1 (1)	
	Non-Hispanic multiracial	7.0 (3)	8.3 (1)	0	9.1 (1)	9.1 (1)	
	Hispanic White	2.3 (1)	0	0	0	9.1 (1)	
Education	12 years or less	25.6 (11)	25.0 (3)	33.3 (3)	36.4 (4)	9.1 (1)	.470
Employment	Not working	39.5 (17)	58.3 (7)	33.3 (3)	18.2 (2)	45.5 (5)	.243
Cigarettes/day	10–35	18.81 (7.30)	17.16 (7.48)	18.33 (7.93)	22.27 (8.02)	17.54 (5.41)	.336
Cigarette dependence (FTCD)	5–10	6.35 (1.64)	6.58 (1.88)	6.56 (1.66)	6.27 (1.00)	6.00 (2.00)	.802
General cigarette craving (past 24 h)	0–3	1.70 (0.88)	1.83 (1.03)	1.67 (1.00)	1.82 (.751)	1.45 (0.82)	.738
Age started smoking	5–31	13.83 (3.06)	14.25 (2.09)	14.11 (3.14)	12.63 (4.31)	14.36 (2.41)	.526
Number lifetime quit attempts	0–20	4.9 (5.02)	3.83 (3.48)	5.27 (5.53)	5.66 (6.06)	5.18 (5.51)	.849
Depression symptoms (IDS-SR)	0–54	13.00 (9.77)	13.5 (10.97)	13.78 (10.45)	13.64 (12.11)	11.18 (5.47)	.922
Working memory 2-back	0–90	68.14 (8.55)	66.58 (9.69)	71.55 (6.28)	67.45 (9.13)	67.7 (8.6)	.603
rTMS sessions attended	0–10	9.4 (0.85)	9.25 (0.86)	9.44 (0.88)	9.36 (1.0)	9.55 (0.85)	.873
WMT sessions completed	0–10	9.10 (0.92)	8.83 (0.83)	9.33 (1.0)	9.18 (.87)	9.10 (1.0)	.659

FTCD, Fagerstrom Test for Cigarette Dependence; IDS-SR, Inventory of Depressive Symptomatology Self-Report scale.

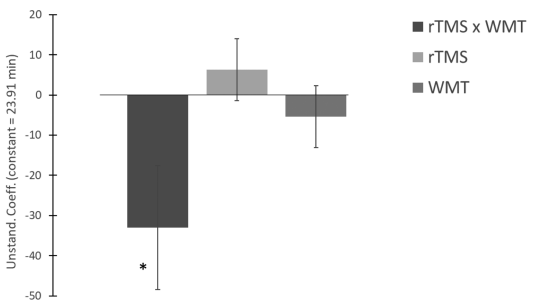


Figure 3. Minutes until smoking lapse. rTMS = active repetitive Transcranial Magnetic Stimulation. WMT = active Working Memory Training. Interaction and main effects, with the constant set to the mean of all conditions. *(interaction of rTMS × WMT, B = −33.0, 95% CI = −64.39 – [−1.61], $p < .05$).

related outcomes. We did not find evidence of added benefit from combining working memory training with a 2-week course of 10 Hz rTMS targeting the left DLPFC in dependent smokers. In fact, contrary to our hypothesis, we found the combination of active training and active rTMS (interaction effect) resulted in poorer performance (fewer minutes until lapse) on a laboratory analog of smoking lapse and one measure of working memory performance. We observed some improvements from baseline for groups that received either of the single active interventions (main effect) on measures of smoking and working memory, although not all findings met the $p < .05$ threshold for significance. Overall, our findings suggest that an aspect of the combination intervention ($rTMS_A$+WMT_A) resulted in poorer performance on smoking outcomes and working memory indices as compared to either intervention alone. These results should be interpreted with our limited sample size in mind. Support for the feasibility of our protocol is low given the high dropout rate we observed combined with the pattern of results contrary to hypotheses. Although the data should be interpreted with caution, current results indicate that there is no evidence to support promise for the feasibility or efficacy of the combined intervention protocol examined.

Based on evidence that working memory deficits undermine the ability to abstain from smoking and that the DLPFC is critically involved in executive function,[15,16] we expected 10 Hz rTMS to the left DLPFC combined with a working memory training protocol to positively impact smoking behaviors. Several pilot phase studies across a range of neuropsychiatric

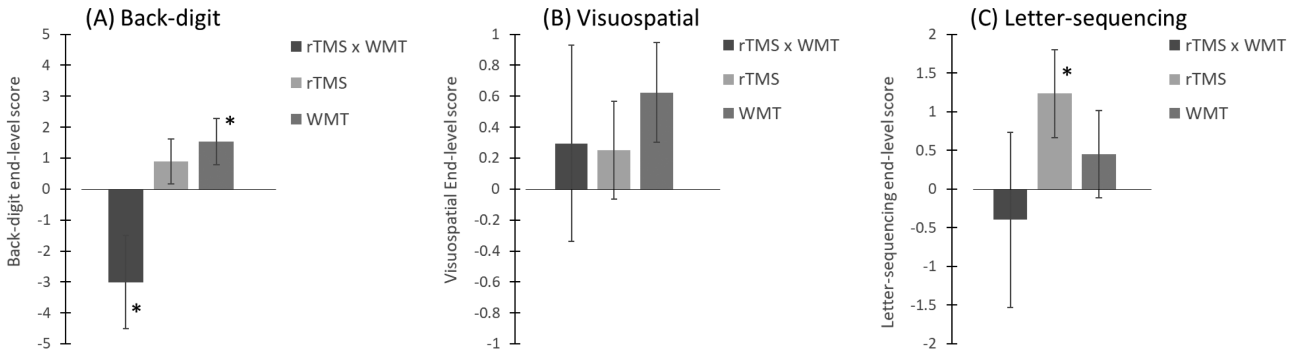


Figure 4. Cognitive performance at outcome. Interaction and main effects on (A) back-digit, (B) Visuospatial, and (C) Letter-sequencing score at outcome, controlling for baseline performance (constant set to mean of all conditions). *(A) interaction of rTMS × WMT: B = −3.01, 95% CI −5.96–(−052), $p < .05$; WMT: B = 1.53, C.I. .02–3.05, $p < .05$. *(C) rTMS: B = 1.23, C.I. .08–2.38, $p < .05$.

disorders (eg Obsessive Compulsive Disorder,[46] Posttraumatic Stress Disorder,[47] and Major Depressive Disorder[48,49]) have investigated rTMS combined with a symptom provocation or cognitive task intervention and found initial support for the combination approach. Based on the proposed circuitry underlying the disorder and target symptoms, each of these studies aimed to engage and modulate distinct neural mechanisms in order to achieve maximal therapeutic effect with its combination intervention; the engagement strategies involved both delivery of stimulation to targeted brain regions as well as activation of the targeted circuitry through some focused cognitive activity. While pilot studies of similar rTMS combination interventions have shown promising results, outcomes have been mixed when tested in subsequent, larger clinical trials.[49,50]

The largest clinical trial of rTMS for smoking to date[5] demonstrated efficacy of a protocol that used craving induction directly prior to stimulation. Zangen and colleagues posited that interference with an activated craving circuit would be a key element of the therapeutic mechanism of rTMS for addiction treatment, and results of their prior work confirmed that cue presentation conferred a modest benefit on measures of nicotine dependence when combined with active 10 Hz stimulation.[7] However, it is worth noting that the investigational treatment evaluated in this clinical trial included motivational enhancement directly following each stimulation session.[5] The intervention that proved effective for smoking behaviors was thus a combination of exposure therapy/craving induction, rTMS (broadly over prefrontal cortex and insula), and brief motivational enhancement, delivered over several weeks. Because we shared the goal of augmenting rTMS therapeutic effects on smoking behaviors through combination with a cognitive task, interpretation of our unexpected findings compels us to compare and contrast our methods with those of Zangen et al.[5]

Beyond the absence of cue-induced craving or motivational enhancement interventions in our protocol, the relatively low "dose" of rTMS we delivered (10 sessions, with stimulation intensity set at 100% relative to motor threshold) is a notable contrast to that delivered by Zangen[5] and to other clinical trials which have demonstrated efficacy of rTMS therapy, so it may be relevant to our negative outcomes. However, despite our modest sample size, we observed a pattern wherein the main effect was in the expected direction on several outcomes, leading us to conclude the stimulation dose was likely sufficiently active to influence results. Regarding effect size for the lapse task, the mean minutes to lapse for those receiving rTMS was 38.0 (SD = 16.65), which is in line with previous reports for effective smoking cessation medications (ie varenicline and bupropion) within this paradigm,[29] whereas the combination group mean minutes until lapse was 16.11 (SD = 24.21), which is in line with mean minutes to lapse for placebo conditions reported in previous studies.[29] Thus, our results suggest that cognitive training may have disrupted the effect of rTMS on delaying initiation to smoke following an abstinence period.

We can also speculate that our working memory training, which by design always ends in failure, may have yielded unanticipated distress or negative self-appraisal before or after stimulation, thus activating circuitry that undermined the potential benefits of stimulation. A similar unexpected negative effect on rTMS efficacy was observed in a depressed sample when stimulation was combined with a guided task intended to facilitate negative cognitive-emotional themes.[48] Additionally, in a recent PTSD rTMS trial, the combination of active stimulation with symptom provocation yielded poorer outcomes compared to provocation plus sham rTMS, leading the authors to speculate about whether the stimulation interfered with the therapeutic process.[50] Though we excluded individuals with current depressive disorders from enrolling, a possible role for WMT-induced emotional distress merits further scrutiny. We conducted post hoc analyses that partially assess this potential explanation in which we control for change in depressive symptoms over the course of the study (Supplemental Materials), however formal mediation tested was not conducted due to limited power in the current study.

Our results should also be interpreted within the context of the sample recruited, which was comprised of non-treatment seeking smokers; the results may have been different if the endpoint measure was obtained in smokers actively attempting to quit. Along these same lines, we did not employ other measures (eg quit rates, abstinence over long-term follow-up) that would be appropriate for a population of individuals intending to quit smoking. Additionally, given the design choice to administer WMT sessions prior to and after stimulation, rather than concurrently, the effects of the timing of the paired interventions should be considered.[19,51] Although the combined interventions resulted in poorer performance on the analog to smoking lapse task and cognitive assessments, lack of formal mediation testing precludes inferences regarding mechanisms leading to the observed

effect on smoking behavior. Post hoc analysis of the correlation between change in working memory indices and lapse task did not reveal significant effects. Other limitations of this study include methods for targeting the left DLPFC, which was not functionally defined for participants or otherwise identified with neuronavigation to guide coil placement. Several studies suggest that connectivity-guided targeting may improve rTMS treatment outcomes for depression, though this approach has not been evaluated for treating addictions.

Results from this study underscore the importance of carefully controlled examination of stimulation plus contextual manipulation. It is possible that the effect of adjunctive therapies (eg those focused on activating cognitive control vs. craving provocation) on smoking outcomes may be differentially affected by the target site (DLPFC vs. lateral prefrontal and insular cortices). Thus, pairs of adjunctive therapies and stimulation sites should be examined with outcome assessments including craving and control over craving. Moreover, the current study relied on two key assumptions from the extant literature supporting the use of a WM protocol, (1) that the training would result in activation within brain regions key to cognitive control over smoking behavior, and/or (2) that the cognitive training would transfer to observed behavioral changes in control over smoking behavior. Our findings cast doubt upon these assumptions. Specifically, we did not observe any evidence of WMT transfer to other measures of cognitive function beyond the assessment versions of the training tasks. Future research aimed at optimizing the effect of rTMS on control processes may benefit from targeting substance specific behaviors[52–54] rather than cognitive processes believed to underly those behaviors. Paradigms in which participants are trained to effectively regulate control process in relation to substance specific cues (eg cigarettes)[52,53] may engage processes that are more clinically meaningful than the general WMT paradigm examined in the current study. This may be achieved through identifying brain regions activated during a cognitive control over craving task and stimulating based on the identified functional activations on an individual basis. This would first require demonstrating that a reliable target for cognitive control over craving could be identified within individuals and establishing when stimulation should be paired with the cognitive task (before, during, after, or throughout).[19,51] Lastly, studies fully powered to examine mediators of the effect of rTMS on smoking outcomes will provide critical information on target selection.

In conclusion, working memory training directly prior to and directly following 10 Hz rTMS to the DLPFC did not improve measures of smoking behavior or cognitive performance, and resulted in poorer performance as compared to single active conditions in a sample of daily smokers. Additionally, elements of the protocol, perhaps most importantly, the requirement to complete a potentially burdensome WMT paradigm prior to stimulation, resulted in significant dropout. Given the sample size limitations of the current study, and result on power to detect effects, the lack of significant effect on secondary outcomes examined should be interpreted with caution. However, we interpret the direction of significant effects observed, and some consistency in patterns for the double active condition, to indicate that the current protocol examined is unlikely to be feasible or efficacious for optimizing rTMS in smoking cessation. Recommendations for future research examining adjuncts with potential to improve rTMS effects include (1) utilizing paradigms more proximal to smoking behaviors rather than underlying cognitive processes proposed to support the behaviors, (2) considering timing effects of the adjunct in relation to stimulation, (3) considering whether the rTMS protocol is capable of directly stimulating the brain region hypothesized to be activated by the adjunct, and (4) identifying the feasibility of targeting rTMS individually based on activations caused by the adjunctive therapy.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

The authors have no conflicts of interest or financial relationships relevant to disclose.

Author Contributions

WVL: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review & editing; Funding acquisition. NSP: Conceptualization; Investigation; Methodology; Formal Analysis; Writing - review & editing. CWK: Conceptualization, Investigation; Methodology; Analysis supervision; Writing - review & editing. KH: Software development and data collection. Writing - review & editing. ET: Conceptualization, Data curation; Project administration; Resources; Writing - review & editing. LLC: Conceptualization; Investigation; Methodology, Supervision; Writing - original draft; Writing - review & editing.

Data Availability

Data reported in this manuscript can be made available upon reasonable request to the corresponding author.

References

1. Hauer L, Scarano GI, Brigo F, *et al*. Effects of repetitive transcranial magnetic stimulation on nicotine consumption and craving: a systematic review. *Psychiatry Res*. 2019;281:112562.
2. Ekhtiari H, Tavakoli H, Addolorato G, *et al*. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. *Neurosci Biobehav Rev*. 2019;104:118–140.

3. Ebbert JO, Hatsukami DK, Croghan IT, *et al.* Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *J Am Med Assoc*. 2014;311(2):155–163.
4. Sheffer CE, Bickel WK, Brandon TH, *et al.* Preventing relapse to smoking with transcranial magnetic stimulation: feasibility and potential efficacy. *Drug Alcohol Depend*. 2018;182:8–18.
5. Zangen A, Moshe H, Martinez D, *et al.* Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. *World Psychiatry*. 2021;20(3):397–404.
6. Lu M, Ueno S. Comparison of the induced fields using different coil configurations during deep transcranial magnetic stimulation. *PLoS One*. 2017;12(6):e0178422.
7. Dinur-Klein L, Dannon P, Hadar A, *et al.* Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. *Biol Psychiatry*. 2014;76(9):742–749.
8. Sathappan AV, Luber BM, Lisanby SH. The Dynamic Duo: combining noninvasive brain stimulation with cognitive interventions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;89:347–360.
9. Barr MS, George TP. Deep repetitive transcranial magnetic stimulation for smoking cessation: is going deeper better? *Biol Psychiatry*. 2014;76(9):678–680.
10. Amiaz R, Levy D, Vainiger D, Grunhaus L, Zangen A. Repeated high-frequency transcranial magnetic stimulation over the dorsolateral prefrontal cortex reduces cigarette craving and consumption. *Addiction*. 2009;104(4):653–660.
11. Eichhammer P, Johann M, Kharraz A, *et al.* High-frequency repetitive transcranial magnetic stimulation decreases cigarette smoking. *J Clin Psychiatry*. 2003;64(8):951–953.
12. Li X, Sahlem GL, Badran BW, *et al.* Transcranial magnetic stimulation of the dorsal lateral prefrontal cortex inhibits medial orbitofrontal activity in smokers. *Am J Addict*. 2017;26(8):788–794.
13. Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn*. 2014;86:1–9.
14. Bickel WK, Miller ML, Yi R, *et al.* Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. *Drug Alcohol Depend*. 2007;90(Supplement 1):S85–S91.
15. Loughead J, Wileyto EP, Ruparel K, *et al.* Working memory-related neural activity predicts future smoking relapse. *Neuropsychopharmacology*. 2015;40(6):1131–1120.
16. Patterson F, Jepson C, Loughead J, *et al.* Working memory deficits predict short-term smoking resumption following brief abstinence. *Drug Alcohol Depend*. 2010;106(1):61–64.
17. Tendler A, Sisko E, Barnea-Ygael N, Zangen A, Storch EA. A method to provoke obsessive compulsive symptoms for basic research and clinical interventions. *Front Psychiatry*. 2019;10:814.
18. Nissim NR, O'Shea A, Indahlastari A, *et al.* Effects of transcranial direct current stimulation paired with cognitive training on functional connectivity of the working memory network in older adults. *Front Aging Neurosci*. 2019;11(340):1–11.
19. Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Exp Brain Res*. 2014;232(10):3345–3351.
20. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005;25(1):46–59.
21. Ungerleider LG, Courtney SM, Haxby JV. A neural system for human visual working memory. *Proc Natl Acad Sci*. 1998;95(3):883–890.
22. Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. *Front Hum Neurosci*. 2015;9:1–14.
23. Xu J, Mendrek A, Cohen MS, *et al.* Brain activity in cigarette smokers performing a working memory task: effect of smoking abstinence. *Biol Psychiatry*. 2005;58(15):143–150.
24. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;120(12):2008–2039.
25. Fagerström KO. Determinants of tobacco use and renaming the FTND to the Fagerströöm Test for Cigarette Dependence. *Nicotine Tob Res*. 2012;14(1):75–78.
26. Sheehan DV, Lecrubier Y, Sheehan KH, *et al.* The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*. 1997;12(5):232–241.
27. Stout RL, Wirtz PW, Carbonari JP, Del Boca FK. Ensuring balanced distribution of prognostic factors in treatment outcome research. *J Stud Alcohol Suppl*. 1994;(12):70–75.
28. McKee SA, Krishnan-Sarin S, Shi J, Mase T, O'Malley SS. Modeling the effect of alcohol on smoking lapse behavior. *Psychopharmacology (Berl.)* 2006;189(2):201–210.
29. McKee SA, Weinberger AH, Shi J, Tetrault J, Coppola S. Developing and validating a human laboratory model to screen medications for smoking cessation. *Nicotine Tob Res*. 2012;14(11):1362–1371.
30. Barr MS, Farzan F, Rajji TK, *et al.* Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. *Biol Psychiatry*. 2013;73(6):510–517.
31. Abdelrahman AA, Noaman M, Fawzy M, *et al.* A double-blind randomized clinical trial of high frequency rTMS over the DLPFC on nicotine dependence, anxiety and depression. *Sci Rep*. 2021;11(1):1640.
32. McClintock SM, Reti IM, Carpenter LL, *et al.* Consensus recommendations for the clinical application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of depression. *J Clin Psychiatry*. 2018;79(1):35–48.
33. Houben K, Wiers RW, Jansen A. Getting a grip on drinking behavior training working memory to reduce alcohol abuse. *Psychol Sci*. 2011;22(7):968–975.
34. Klingberg T. Training and plasticity of working memory. *Trends Cogn Sci*. 2010;14(7):317–324.
35. Day AM, Kahler CW, Metrik J, *et al.* Working memory moderates the association between smoking urge and smoking lapse behavior after alcohol administration in a laboratory analogue task. *Nicotine Tob Res*. 2015;17(9):1173–1177.
36. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*. 1986;43(3):2890294.
37. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.
38. Perkins KA, Stitzer M, Lerman C. Medication screening for smoking cessation: a proposal for new methodologies. *Psychopharmacology (Berl.)* 2006;184(3–4):628–636.
39. McKee SA. Developing human laboratory models of smoking lapse behavior for medication screening. *Addict Biol*. 2009;14(1):99–107.
40. Kramer JH, Mungas D, Possin KL, *et al.* NIH EXAMINER: conceptualization and development of an executive function battery. *J Int Neuropsychol Soc*. 2014;20(1):11–19.
41. MacKillop J, Murphy JG, Ray LA, *et al.* Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers. *Exp Clin Psychopharmacol*. 2008;16(1):57–65.
42. Gilroy SP, Kaplan BA, Reed DD, Koffarnus MN, Hantula DA. The Demand Curve Analyzer: behavioral economic software for applied research. *J Exp Anal Behav*. 2018;110(3):553–568.
43. Kirby KN, MarakoviĆ NN. Delay-discounting probabilistic rewards: rates decrease as amounts increase. *Psychon Bull Rev*. 1996;3(1):100–104.
44. Field A. *Discovering Statistics Using IBM SPSS Statistics*. London, England: Sage; 2013.
45. Kraemer HC, Blasey CM. Centring in regression analyses: a strategy to prevent errors in statistical inference. *Int J Methods Psychiatr Res*. 2004;13(3):141–151.
46. Carmi L, Tendler A, Bystritsky A, *et al.* Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. *Am J Psychiatry*. 2019;176(11):931–938.
47. Isserles M, Shalev AY, Roth Y, *et al.* Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure

procedure in post-traumatic stress disorder--a pilot study. *Brain Stimul*. 2013;6(3):377–383.
48. Isserles M, Rosenberg O, Dannon P, *et al*. Cognitive-emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome. *J Affect Disord*. 2011;128(3):235–242.
49. Sabbagh M, Sadowsky C, Tousi B, *et al*. Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. *Alzheimers Dement*. 2020;16(4):641–650.
50. Isserles M, Tendler A, Roth Y, *et al*. Deep transcranial magnetic stimulation combined with brief exposure for posttraumatic stress disorder: a prospective multisite randomized trial. *Biol Psychiatry*. 2021;90(10):721–728.
51. Friehs MA, Frings C. Offline beats online: transcranial direct current stimulation timing influences on working memory. *Neuroreport*. 2019;30(12):795–799.
52. Kober H, Kross EF, Mischel W, Hart CL, Ochsner KN. Regulation of craving by cognitive strategies in cigarette smokers. *Drug Alcohol Depend*. 2010;106(1):52–55.
53. Kober H, Mende-Siedlecki P, Kross EF, *et al*. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci USA*. 2010;107(33):14811–14816.
54. Dubuson M, Kornreich C, Vanderhasselt MA, *et al*. Transcranial direct current stimulation combined with alcohol cue inhibitory control training reduces the risk of early alcohol relapse: A randomized placebo-controlled clinical trial. *Brain Stimul*. 2021;14(6):1531–1543.