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# Craving Induction and Treatment Response in Transcranial Magnetic Stimulation for Tobacco Use Disorder

Dhvani D. Mehta, Matthew E. Sloan, Alexandra Sas, Clara Freeman, Tony P. George, Peter Selby, Laurie Zawertailo, Abraham Zangen, Daniel M. Blumberger, Bernard Le Foll, Scott Veldhuizen, and Victor M. Tang

## ABSTRACT

**BACKGROUND:** Repetitive transcranial magnetic stimulation (rTMS) is an emerging treatment for several mental health conditions including substance use disorders. Symptom provocation before rTMS is hypothesized to activate disease-related neurocircuitry and enhance treatment effects. For addiction, craving induction is frequently used before treatment, but its clinical utility requires further exploration. To assess whether craving induction enhances treatment outcomes, we analyzed data from the pivotal multisite trial of deep TMS (DTMS) for tobacco use disorder (TUD).

**METHODS:** A total of 262 participants were randomized to 6 weeks of active or sham DTMS and instructed to set a quit date within the first 2 weeks. Craving was assessed using a 10-point visual analog scale before and after craving induction across 18 treatment sessions. Mixed-effects models tested whether craving induction increased craving across sessions and whether its magnitude predicted end-of-trial 4-week continuous quit rate (4W-CQR).

**RESULTS:** Craving induction produced small but significant increases in craving ($b = 0.34$, 95% CI 0.18 to 0.50, $p < .05$) without evidence of habituation across sessions ($b = -0.01$, 95% CI −0.02 to 0.50, $p = .38$). Change in craving after cue induction did not significantly predict end-of-trial 4W-CQR, and there was no interaction with study arm ($p = .95$).

**CONCLUSIONS:** Craving induction reliably increased craving, although the magnitude of cue-induced craving was not associated with end-of-trial smoking cessation. This finding suggests that greater craving induction does not predict greater therapeutic effect of rTMS. Further research is needed to understand the mechanisms and clinical implications of rTMS and brain state in TUD, including potential improvements in related domains such as inhibitory control.

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Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for several difficult-to-treat psychiatric conditions, including treatment-resistant major depressive disorder (MDD) (1), obsessive-compulsive disorder (OCD) (2), and certain substance use disorders (SUDs) (3). Notably, rTMS is approved by the U.S. Food and Drug Administration (FDA) as a treatment for tobacco use disorder (TUD), the only indication for addiction. There are a range of rTMS protocols that vary by neuroanatomical target, coil type, brain state during treatment, stimulation parameters, and treatment duration, but the optimal approach remains unclear (4,5).

Symptom induction is a procedure that is thought to improve rTMS treatment response by optimizing the brain state for modulation. The underlying theory suggests that provoking symptoms activates disorder-specific neural circuits, which can then be disrupted or modified by brain stimulation (6). Evidence supporting this comes from animal models (7,8) and several clinical studies of rTMS for posttraumatic stress disorder (PTSD) and smoking cessation (9,10). Symptom provocation has also been incorporated into studies of rTMS for OCD and is part of the FDA-cleared protocol for rTMS for OCD, though these studies did not directly compare symptom induction with no induction (11,12). In the PTSD study, Isserles *et al.* (9) randomized 30 participants to receive either active or sham deep TMS (DTMS) targeting the medial prefrontal cortex (mPFC). Participants were exposed to a trauma-related script followed by a neutral script or only a neutral script. Symptom improvement was observed only in the group randomized to the trauma-related script plus active treatment. In smoking cessation, findings have been mixed. Amiaz *et al.* (13) randomized 48 smokers to either active or sham rTMS, preceded by smoking cues or neutral cues. Greater reductions in self-reported and urinary measures of nicotine consumption were found in the active treatment groups, but craving induction had no effect on either outcome. Conversely, Dinur-Klein *et al.* (10) randomized 115 smokers to





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high-frequency, low-frequency, or sham DTMS, with or without smoking cues before treatment. While there was no significant interaction between treatment and craving induction for self-reported cigarette use, the greatest reduction in nicotine dependence symptom severity scores occurred in the group receiving high-frequency DTMS with craving induction.

Subsequent studies have incorporated symptom provocation procedures into rTMS trials for PTSD (14,15), alcohol use disorder (16–18), and TUD (19). However, the contribution of symptom provocation procedures to treatment response remains unclear. First, trials that randomized participants to symptom induction versus no induction had small sample sizes in the symptom provocation plus active treatment groups (ranging from 9 to 16 participants), with mixed findings depending on the study and outcome analyzed (10,13). Second, numerous rTMS studies for addiction (3), OCD (20,21), and PTSD (22) produced significant improvements in active versus sham treatment arms without symptom provocation procedures. Third, for MDD, the most extensively studied rTMS indication, symptom provocation procedures are not routinely used and do not appear necessary for robust treatment response (23). Overall, this raises the question of whether symptom provocation is necessary to optimize treatment response.

To better understand the relationship between symptom provocation and rTMS treatment response, we analyzed data from the largest double-blind DTMS trial for smoking cessation ($N$ = 262) (19), which led to the FDA approval of rTMS using the H4 coil for the treatment of TUD. Our analysis aimed to evaluate the role of craving induction level in rTMS treatment response through 3 key objectives. First, we examined the efficacy of the craving induction procedure in eliciting a significant craving response across all sessions. Second, we investigated whether the magnitude of craving response induced by craving induction was associated with smoking cessation (i.e., the 4-week continuous quit rate [4W-CQR] at week 18, the study's primary outcome), comparing active versus sham treatment conditions. Third, we examined whether the absolute level of craving before rTMS treatment (rather than the change in craving produced by the induction procedure) was associated with smoking cessation, again comparing treatment arms. Based on the hypothesis that neural circuit activation via symptom provocation enhances treatment response, we hypothesized that greater craving induction would be positively associated with treatment outcomes in patients receiving active, but not sham, rTMS.

## METHODS AND MATERIALS

### Study Design

This multisite (14 sites, 2 in Israel and 12 in the United States), double-blind randomized controlled trial was conducted from August 2014 to August 2019. This study was registered on clinicaltrials.gov (NCT02126124) and the primary outcomes have been previously published (19). A total of 262 participants were randomized to either active or sham DTMS for smoking cessation in a 1:1 ratio (Table 1). Participants received 5 DTMS treatment sessions per week in the first 3 weeks of the trial followed by weekly DTMS for the last 3 weeks. Participants were asked to select a quit date within the first 2 weeks of treatment ("grace period"). DTMS was delivered bilaterally using the H4 coil (BrainsWay Ltd.), which is thought to stimulate the bilateral PFC and insula based on computational e-field models (19). Participants who were abstinent at the last treatment session (week 6) were invited for a follow-up visit at week 18 to determine 4W-CQR.

**Table 1. Demographics of Patients Randomized to Receive Active or Sham Deep Repetitive Transcranial Magnetic Stimulation**

| | Active, $n$ = 123 | Sham, $n$ = 139 | $p$ Value |
|---|---|---|---|
| Gender, Female | 48.8% | 47.5% | .834 |
| Age, Years | 45.0 ± 13.0 | 44.8 ± 13.4 | .946 |
| Age at Smoking Initiation, Years | 16.9 ± 4.0 | 17.4 ± 5.3 | .390 |
| Total Years Smoking | 27.1 ± 13.0 | 26.2 ± 13.7 | .597 |
| No. Cigarettes/Day | 18.3 ± 7.7 | 18.2 ± 7.2 | .874 |
| Desire to Quit, From 1 (Low) to 10 (High) | 8.8 ± 1.4 | 9.0 ± 1.3 | .238 |
| Tobacco Craving Questionnaire Total Score | 44.9 ± 15.8 | 42.7 ± 18.1 | .291 |
| Fagerström Test for Nicotine Dependence | 5.5 ± 2.0 | 5.3 ± 2.0 | .268 |

Values are presented as % or mean ± SD.

Eligible participants were active smokers between 22 and 70 years of age who smoked ≥10 cigarettes daily, had been smoking for more than 1 year without abstinence periods longer than 3 months in the past year, and were motivated to quit. Exclusion criteria included smoking other forms of tobacco or other substances, use of nicotine in noncigarette forms, actively receiving medications or behavioral support to quit smoking, or failing the TMS safety screening questionnaire.

### Craving Induction and Measurement

Participants were asked to abstain from smoking for at least 2 hours before each rTMS treatment session. Craving was measured 3 times during each session using a 10-point visual analog scale (VAS). First, baseline (preinduction) craving was measured (VAS1). Then, craving induction was performed by having participants 1) imagine one of their greatest craving triggers (30 seconds; selected from a participant-specific list of 4 triggers that induce the greatest level of craving for cigarettes); 2) listen and follow a recorded script (90 seconds) instructing them to handle a cigarette (pull a cigarette out of a pack, hold it, smell it, and put it in their mouth) and lighter, but not smoke the cigarette; and 3) view cigarette smoking images for 3 minutes. The induction procedure lasted approximately 5 minutes. Craving was measured immediately after the induction (VAS2) and again following the rTMS session (VAS3).

### Other Measures and Outcomes

Cigarette consumption was measured using daily smoking diaries and the Nicotine Use Inventory. The Fagerström Test for Nicotine Dependence (FTND) (24), the Tobacco Craving Questionnaire (25), and urinary cotinine levels were collected weekly during treatment and at week 18. The primary end

point was the 4W-CQR at week 18, defined as no self-reported cigarette consumption in the past 4 weeks and urinary cotinine levels <200 ng/mL.

### Statistical Analysis

To evaluate the effectiveness of craving induction, a linear mixed-effects model was used to assess whether the induction procedure produced a significant increase in self-reported craving across all sessions and whether the magnitude of craving induction varied over time or by treatment condition. Craving magnitude (i.e., VAS score) was the dependent variable. Independent variables included induction (pre- and postinduction, coded as 0 and 1, respectively), treatment arm (sham vs. active DTMS, coded as 0 and 1, respectively), DTMS session (continuous variable), and interaction terms. Random slopes for session and random intercepts for participants accounted for within-subject variability.

To determine whether craving induction magnitude predicted smoking cessation, a logistic regression model was used with 4W-CQR at week 18 as the dependent variable. Independent variables included craving induction (i.e., postinduction minus preinduction craving [VAS2 minus VAS1] averaged across all sessions) and treatment arm, along with interaction terms. Covariates included age, gender, and baseline FTND to control for the potential confounding effects of addiction severity. Sensitivity analyses were performed using craving induction (VAS2 minus VAS1) during the first 10 sessions (the grace period) and the first session alone to account for the possibility that individuals who failed to quit early on or after the grace period might respond differently to induction procedures. If greater craving induction predicts smoking cessation outcomes in the active, but not the sham, arm (i.e., a significant interaction between treatment arm × magnitude of craving induction), it will support the hypothesis that stronger craving induction enhances neural engagement of craving-related circuits, thereby improving responsiveness to DTMS.

To explore whether absolute craving levels predicted smoking cessation, separate logistic regression models were conducted using preinduction (VAS1) and postinduction (VAS2) craving as independent variables. This investigation was guided by the rationale that absolute level of craving and circuit activation (rather than change in craving/circuit activation induced by the craving induction procedure) could be associated with quit rates. Again, if greater preinduction or postinduction craving levels predicted treatment outcomes in the active arm, it would support the hypothesis that stronger activation creates an optimized brain state for subsequent stimulation. As in the above analyses, sensitivity analyses used VAS1 and VAS2 scores from the first 10 sessions (grace period) and first session alone. Covariates included age, gender, and baseline FTND.

Finally, all logistic regression models were repeated for secondary study outcomes (4W-CQR at week 6 and continuous abstinence through weeks 6–18) using craving data from the first 10 sessions, as they preceded the 4W-CQR period for week 6. Post-DTMS craving scores (VAS3) were not included in the analysis. Statistical significance was set at $\alpha = 0.05$, and all analyses were conducted using R (26).

## RESULTS

### Efficacy of Craving Induction

Craving induction produced statistically significant increases in craving levels from VAS1 to VAS2, with a modest main effect observed ($b$ = 0.34, 95% CI 0.18 to 0.50, $p < .001$) (Figure 1). A declining trend in overall craving scores was noted, as reflected by the main effect of session ($b$ = −0.10, 95% CI −0.13 to −0.07, $p < .001$). However, the interaction between induction and session was not statistically significant ($b$ = −0.01, 95% CI −0.02 to 0.50, $p$ = .38), suggesting that the magnitude of craving induction was consistent across all 18 treatment sessions without evidence of habituation. Moreover, there was no 3-way interaction between induction, session, and arm, meaning the induction effect did not differ between treatment condition over time and there was no significant habituation in either group. There was a significant session × arm interaction ($b$ = −0.04, 95% CI −0.08 to −0.002, $p$ = .026), such that active DTMS was associated with a greater reduction in craving over the course of the study compared with sham DTMS, which is consistent with findings from the original study (Table 2).

### Cue-Induced Craving and Smoking Cessation Outcomes

Treatment arm was a significant predictor of smoking cessation rates at week 18 (odds ratio [OR] = 2.71, 95% CI 1.14 to 7.04, $p$ = .03), with higher cessation rates in the active DTMS group, as in the original investigation (19). However, there was no main effect of craving induction on end-of-trial continuous quit rates (OR = 1.04, 95% CI 0.27 to 3.56, $p$ = .96) and no interaction between craving induction and treatment arm (OR = 0.96, 95% CI 0.23 to 4.25, $p$ = .95). Thus, while active DTMS was effective in promoting smoking cessation, there was no statistically significant association between cue-induced craving and the 4W-CQR at week 18 in either the active or the sham arm (Table 3). Similarly, sensitivity analyses using VAS scores from the first 10 sessions (OR = 0.93, 95%

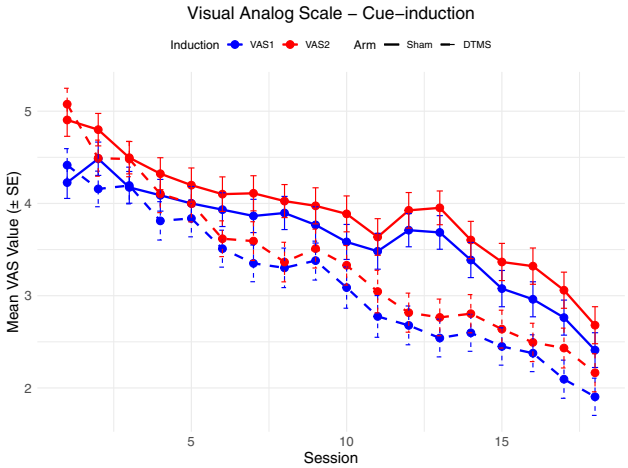


**Figure 1.** Change in preinduction (VAS1) and postinduction (VAS2) visual analog scale (VAS) scores across sessions and between treatment arm (sham vs. active deep transcranial magnetic stimulation [DTMS]).

**Table 2. Linear Mixed Model Analysis With VAS Scores as Dependent Variable and Induction, Treatment Arm[a], and Session Number as Independent Variables**

| | | 95% CI | | |
|---|---|---|---|---|
| | Estimate, *b* | Lower | Upper | *p* Value |
| Induction | 0.336 | 0.175 | 0.497 | <.001* |
| Session | −0.099 | −0.126 | −0.071 | <.001* |
| Arm | 0.058 | −0.397 | 0.513 | .782 |
| Session × Arm | −0.041 | −0.082 | −0.002 | .026* |
| Session × Induction | −0.007 | −0.022 | 0.009 | .385 |
| Arm × Induction | 0.007 | −0.231 | 0.246 | .951 |
| Session × Arm × Induction | −0.004 | −0.028 | 0.019 | .710 |

*Statistical significance at $p < .05$ level.
VAS, visual analog scale.
[a]Active and sham deep transcranial magnetic stimulation.

CI 0.26 to 3.39, $p = .91$) and session 1 alone (OR = 1.47, 95% CI 0.81 to 2.83, $p = .23$) did not find significant associations between craving induction and quit rate differentially by arm (Table S1). Findings were unchanged when the secondary study outcomes (4W-CQR at week 6 and continuous abstinence through weeks 6–18) were used as dependent variables (Table S2).

## Absolute Pre- and Postinduction Craving and Smoking Cessation Outcomes

Both higher absolute preinduction (VAS1) and postinduction (VAS2) craving was associated with reduced odds of cessation at week 18 (VAS1: OR = 0.41, 95% CI 0.24 to 0.66, $p < .01$; VAS2: OR = 0.50, 95% CI 0.31 to 0.75, $p < .01$). However, neither VAS1 nor VAS2 showed a significant interaction with treatment arm (VAS1: $p = .47$; VAS2: $p = .67$) (Table 4). Similarly, no interactions were present when analyses were restricted to the first 10 sessions alone (VAS1: $p < .84$; VAS2: $p < .98$) (Tables S3 and S4). In contrast, a significant interaction between postinduction craving and arm emerged when looking at session 1 alone ($p = .04$), such that higher craving levels predicted increased odds of cessation in the active (OR = 1.61, 95% CI 1.11 to 2.55, $p = .02$), but not the sham (OR = 1.02, 95% CI 0.76 to 1.41, $p = .88$), arm. No such effect was observed for preinduction craving at session 1 ($p = .54$). Finally, neither pre- nor postinduction craving levels predicted treatment response when the secondary study outcomes were used as dependent variables (4W-CQR at week 6 and continuous abstinence through weeks 6–18) (Tables S5 and S6).

**Table 3. Logistic Regression Analysis With 4W-CQR at Week 18 as Dependent Variable and Cue-Induced Craving[a] and Treatment Arm as Independent Variables**

| | | | 95% CI | | *z* | *p* |
|---|---|---|---|---|---|---|
| Predictor | OR | SE | Lower | Upper | Value | Value |
| Cue-Induced Craving | 1.037 | 0.651 | 0.272 | 3.558 | 0.055 | .956 |
| Arm | 2.711 | 0.460 | 1.136 | 7.044 | 2.170 | .030* |
| Cue-Induced Craving × Arm | 0.958 | 0.734 | 0.234 | 4.246 | −0.058 | .954 |
| Sham | 1.241 | 0.678 | 0.313 | 4.576 | 0.318 | .750 |
| Active | 1.074 | 0.332 | 0.553 | 2.059 | 0.216 | .829 |

OR >1 indicates increased odds of the outcome, while OR <1 indicates decreased odds.
*Statistical significance at $p < .05$ level.
4W-CQR, 4-week continuous quit rate; OR, odds ratio.
[a]Postinduction minus preinduction craving, averaged across all 18 sessions.

**Table 4. Logistic Regression Analysis With 4W-CQR at Week 18 as Dependent Variable and Treatment Arm and Preinduction Craving or Postinduction Craving as Independent Variables**

| | | | 95% CI | | *z* | *p* |
|---|---|---|---|---|---|---|
| Predictor | OR | SE | Lower | Upper | Value | Value |
| Preinduction Craving (VAS1)[a] | | | | | | |
| Preinduction Craving | 0.410 | 0.261 | 0.235 | 0.661 | −3.416 | .001* |
| Preinduction Craving × Arm | 1.242 | 0.300 | 0.697 | 2.287 | 0.722 | .470 |
| Sham | 0.484 | 0.268 | 0.267 | 0.780 | −2.704 | .007* |
| Active | 0.467 | 0.207 | 0.298 | 0.678 | −3.677 | <.001[b] |
| Postinduction Craving (VAS2)[a] | | | | | | |
| Postinduction Craving | 0.495 | 0.224 | 0.307 | 0.748 | −3.136 | .002* |
| Postinduction Craving × Arm | 1.121 | 0.271 | 0.661 | 1.938 | 0.420 | .674 |
| Sham | 0.561 | 0.228 | 0.341 | 0.849 | −2.536 | .011* |
| Active | 0.525 | 0.191 | 0.347 | 0.740 | −3.374 | .001* |

OR >1 indicates increased odds of the outcome, while OR <1 indicates decreased odds.
*Statistical significance at $p < .05$ level.
4W-CQR, 4-week continuous quit rate; OR, odds ratio; VAS, visual analog scale.
[a]Averaged across all 18 sessions.

## DISCUSSION

In this secondary analysis of the pivotal multisite trial of DTMS for TUD using the H4 coil, we investigated whether the magnitude of craving induction before rTMS was associated with treatment response. While the craving induction protocol increased subjective ratings of craving, cue-induced craving before rTMS treatment was not positively associated with the end-of-trial continuous quit rate. This finding was consistent when examining the full treatment course, early sessions, and the first session alone. Importantly, analyses were adjusted for baseline FTND scores to address potential confounding effects of addiction severity. Similarly, absolute levels of pre- and postinduction craving across all sessions were negatively associated with smoking cessation outcomes in both arms. These findings do not support the hypothesis that greater symptom provocation enhances the therapeutic efficacy of rTMS.

## Implications for rTMS Protocols

Cue-exposure paradigms aim to activate addiction-related neural circuits, particularly the reward system and cognitive control centers, such as the insula and dorsolateral PFC (DLPFC). This process is presumed to create a primed state, enhancing rTMS efficacy (6). However, chronic nicotine use may lead to hyperactivation of these circuits, making further priming unnecessary. This aligns with recent findings in TUD, in which rTMS combined with smoking cues, compared to neutral cues, produced similar functional changes observed

through functional magnetic resonance imaging (fMRI) and showed no differences in craving reduction between groups (27). Importantly, the functional role of the circuits must be taken into consideration. If symptom provocation activates craving-generating/reward circuits (e.g., insula, ventral striatum), applying stimulation at this state may be counterproductive and amplify craving. In contrast, if induction primarily engages regulatory circuits (e.g., DLPFC, inferior frontal gyrus, anterior cingulate cortex [ACC]), the combination of provocation and stimulation may strengthen top-down regulation and reinforce participants' ability to exert inhibitory control over their drug-related compulsive behavior. The latter was also suggested by a previous study that combined these procedures for the treatment of OCD (11).

The inclusion of symptom provocation in rTMS protocols may also vary depending on the disorder and the associated neurocircuitry. For instance, rTMS protocols for MDD, which typically target the DLPFC, achieve substantial efficacy without symptom provocation (23), suggesting that baseline circuit dysfunction is sufficient for effective neuromodulation. Conversely, rTMS symptom provocation has shown promise in OCD and PTSD, where activation of condition-specific neurocircuitry, such as the mPFC and ACC, yielded promising preliminary results (9,11,12). For each disorder, there is a possibility of mismatch in the electrical field of stimulation in the brain induced by the rTMS coil being used and the circuits of the brain being activated through the cue procedure. This study used the H4 coil, which targets the bilateral PFC and insula. However, craving induction may activate circuits outside this field, creating a possible mismatch between the field of stimulation of the coil and craving activation. Future studies should further refine the circuits activated by symptom provocation paradigms before the selection of the rTMS coil and targeting method. For disorders in which rTMS is effective without induction, simplifying protocols could improve accessibility and reduce patient burden.

Craving induction may also introduce unintended challenges for the participant. Elevated cravings may evoke emotional distress and overwhelm participants' coping mechanisms (28). In particular, individuals with already elevated baseline craving may experience greater difficulty managing the physiological and behavioral responses elicited by induction. Furthermore, the individual differences in tobacco-related triggers may lead to variability in the intensity of craving responses depending on personal preferences and emotional states. This introduces uncontrolled variability both across participants and within individuals over time, potentially undermining the reliability and consistency of the intended craving induction effect. Streamlined protocols focusing on directly modulating craving-related circuits through rTMS alone may mitigate these barriers while maintaining efficacy. If craving induction is included in rTMS protocols, measuring mood and anxiety before and after induction could clarify whether these factors influence treatment outcomes. It is nevertheless important to note that repeated exposure to drug-related cues may also be beneficial by serving as exposure therapy and that rTMS may interfere with drug-related memories, as previously suggested in PTSD studies (14).

## Future Directions

Although the magnitude of craving induction was not associated with improved treatment outcomes, its reliable activation of craving symptoms offers a valuable avenue for exploring neurobiological correlates for modulation. Context-dependent neural activation may predict individual responsiveness to rTMS with greater precision than symptom scales. This parallels biomarker-driven advancements in rTMS protocols for MDD, where subgenual ACC connectivity informed individualized therapeutic targets (29). Future studies using fMRI or electroencephalography-based event-related potentials during craving induction could identify neural mechanisms of smoking cessation outcomes. Identifying specific neural signatures of craving that individualized stimulation protocols could then modify may allow for closed-loop stimulation in the future (30).

An important caveat is that the absolute craving before treatment for session 1 predicted better treatment outcome in the active, but not the sham, arm in one of our sensitivity analyses. This raises the question of whether absolute level of circuit activation could have an impact very early in treatment, but not later in treatment. This question merits further study and raises the possibility that craving induction could be used only in the first treatment sessions rather than across the whole course of treatment. However, it is important to note that only the absolute level of craving, and not the change introduced by the induction procedure, was predictive of smoking cessation in our analyses, suggesting that the induction procedure may not provide any added benefit in individuals presenting to the initial rTMS session with a high level of craving.

A possible explanation for the lack of craving induction effects on treatment response in the present study is that the procedure was not as potent as in prior studies. In the pilot trial by Dinur-Klein *et al.* (10), a precursor to the study by Zangen *et al.* (19), the investigators used a more intense and realistic smoking cue: an individual lighting up a cigarette and taking a puff in front of the participant. This approach elicited a more substantial craving induction effect ($b = 1.24$, $p < .01$) during session 1 compared with the protocol used in the current study ($b = 0.34$, $p < .01$), suggesting that it may have engaged craving-related circuits more effectively. In OCD studies, symptom provocation protocols often require a predetermined threshold of symptom exacerbation to ensure an optimal brain state before rTMS (11,12). Incorporating a similar threshold for craving induction in TUD protocols may enhance treatment efficacy, particularly given the modest induction effect observed in the present study. Future studies could explore stronger craving induction methods, such as extending the period of abstinence before treatment, to explore whether this enhances rTMS response. The wide confidence intervals in our analyses further suggest that the study may have been underpowered to detect clinically meaningful differences in craving induction.

It is also possible that the utility of symptom provocation may rely less on the magnitude of craving induction and more on activating a particular brain state before stimulation independent of subjective intensity. Cue-exposure paradigms are intended to engage addiction-related neural circuits to potentially increase their responsiveness to stimulation, rather than to directly diminish cue-induced craving. As such, the absence of a correlation between the magnitude of reported craving and clinical outcome may not undermine its utility. Furthermore, the VAS3 data (craving scores after rTMS

treatment session) measure interaction between the provoked craving and the stimulation, and rTMS may still interact with the patient's craving state even if it is at low-intensity level. In the original trial, the authors reported that the reduction in craving from rTMS (VAS3 minus VAS2) in the first treatment visit, was associated with eventual quitting in the active, but not the sham, group (19). In a recent meta-analysis, researchers found that, while symptom provocation was not significantly associated with better response to TMS in nicotine dependence, active TMS combined with provocation yielded stronger effect sizes than TMS without it (31). Overall, symptom provocation may have clinical utility in the context of rTMS for TUD; however, its inclusion may require further optimization.

### Limitations

A key limitation of this study is the absence of a neutral cue group, limiting our ability to draw definitive conclusions about the role of craving induction in rTMS efficacy. Future studies should directly compare induction and noninduction conditions in a sham-controlled rTMS trial to clarify these effects. Additionally, participants in the current study were asked to refrain from smoking for at least 2 hours before each visit, potentially introducing withdrawal effects that could have influenced the efficacy of the craving induction protocol. Moreover, this study excluded individuals with concurrent psychiatric disorders, including other SUDs, and individuals using nicotine in forms other than cigarettes, limiting generalizability. Our analyses largely converged, though one sensitivity analysis showed an association between session 1 postinduction craving and treatment response. As these sensitivity analyses were not corrected for multiple comparisons, this finding may be spurious.

### Conclusions

This secondary analysis addressed the efficacy and habituation to craving induction in DTMS for TUD and whether the magnitude of cue-induced craving can predict treatment efficacy. Although craving induction before stimulation reliably increased craving levels, it was not associated with improved smoking cessation outcomes. These findings challenge the hypothesis that greater craving induction enhances the therapeutic effect of rTMS. Future studies should directly compare rTMS with and without symptom provocation. Additionally, research should test alternative rTMS protocols, such as using craving reduction instead of induction or by better matching activated circuits with the regions targeted by the rTMS coil. Given the recent breakthrough finding that rTMS for TUD is safe and effective, the field must now optimize this treatment approach to reduce the burden of tobacco-related diseases.

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AZ is the inventor of the DTMS coils and holds a financial interest in BrainsWay Ltd., the company that manufactures these coils. He is also the first author of the original investigation on DTMS for nicotine cessation, which serves as the basis for the present secondary analysis. BLF has received a DTMS coil from BrainsWay Ltd. for use in a research study. DMB has received research funding and in-kind equipment support from BrainsWay Ltd. for an investigator-initiated study and has served as site principal investigator for 3 sponsor-initiated studies supported by BrainsWay Ltd. All other authors report no biomedical financial interests or potential conflicts of interest.

## ARTICLE INFORMATION

From the Addictions Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (DDM, MES, AS, TPG, PS, LZ, BLF, SV, VMT); Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (DDM, MES, AS, TPG, PS, DMB, BLF, VMT); Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (MES, TPG, PS, DMB, BLF, VMT); Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada (MES, LZ, BLF); Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (MES, TPG, PS, LZ, DMB, BLF, SV, VMT); Department of Psychological Clinical Science, University of Toronto Scarborough, Toronto, Ontario, Canada (MES); Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (MES, PS, LZ, BLF, SV, VMT); Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut (CF); Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada (PS, BLF, SV); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (PS, BLF); Department of Life Sciences and the Zelman Center for Neuroscience, Ben Gurion University, Be'er Sheva, Israel (AZ); Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, Ontario, Canada (DMB); and Waypoint Research Institute, Waypoint Centre for Mental Health Care, Penetanguishene, Ontario, Canada (BLF).

DDM and MES contributed equally to this work.

Address correspondence to Victor M. Tang, M.D., M.Sc., at victor.tang@camh.ca.

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