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Transcranial Magnetic Stimulation of the Dorsal Lateral Prefrontal Cortex Inhibits Medial Orbitofrontal Activity in Smokers

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Abstract

Background and Objective—Several studies have shown that repetitive transcranial magnetic stimulation (rTMS), applied to the dorsolateral prefrontal cortex (DLPFC), can reduce cue-elicited craving in smokers. Currently the mechanism of this effect is unknown. We used functional magnetic resonance imaging (fMRI) to explore the effect of a single treatment of rTMS on cortical and sub-cortical neural activity in non-treatment seeking nicotine dependent participants.

Methods—We conducted a randomized, counterbalanced, crossover trial in which participants attended two experimental visits separated by at least 1 week. On the first visit, participants received either active, or sham rTMS (10 Hz, 5 seconds-on, 10 seconds-off, 100% motor threshold, 3000 pulses) over the left DLPFC, and on the second visit they received the opposite condition (active or sham). Cue craving fMRI scans were completed before and after each rTMS session.

Results—11 non-treatment seeking nicotine dependent cigarette smokers were enrolled in the study [6 female, average age 39.7±13.2, average cigarettes per day 17.3±5.9]. Active rTMS decreased activity in the contralateral medial orbitofrontal cortex (mOFC) and ipsilateral nucleus accumbens (NAc) compared to sham rTMS.

Conclusions—This preliminary data suggests that one session of rTMS applied to the DLPFC decreases brain activity in the NAc and mOFC in smokers.

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FINANCIAL DISCLOSURES

The authors declare no conflicts of interest.

Scientific Significance—rTMS may exert its anti-craving effect by decreasing activity in the NAc and mOFC in smokers. Despite a small sample size, these findings warrant future rTMS/fMRI studies in addictions.

Keywords

nicotine dependence; TMS; fMRI; DLPFC; reward network; cue craving

INTRODUCTION

Worldwide, nearly one billion adults now smoke tobacco (1). Smoking is the most prevalent preventable cause of mortality, with approximately 5 million deaths each year (2). Quit attempts are common, however the majority of quit attempts are unsuccessful (3, 4). The reasons for relapse are multifactorial, and may include unbalanced executive control and drive-reward networks in the brain, leaving individuals vulnerable to salient cues in the environment (5, 6). The executive control network is thought to modulate activity in drive-reward networks. The executive control network consists of distributed brain regions including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and the inferior frontal cortex (7). The drive-reward network is composed of the orbitofrontal cortex (OFC), insular cortex, nucleus accumbens (NAc), and ventral tegmental area (VTA) (8).

Craving is an important behavioral driver of relapse in smokers (9). Our group and others have demonstrated that cue induced craving is related to drive-reward network activation (including the OFC and NAc) (6, 10, 11). We also reported that the prefrontal cortex was activated when participants resist the urge to smoke (6). Furthermore, previous studies have demonstrated that smoking cessation is accompanied by decreased activation of medial OFC (mOFC) during cue reactivity tasks in functional magnetic resonance imaging (fMRI) (12, 13). Given this data in composite, it has been theorized that strengthening executive control network activity and modulating drive-reward network activity may result in decreased craving, and even potentially decreased cigarette consumption (14, 15).

Transcranial magnetic stimulation (TMS) is a non-invasive means of modulating cortical and sub-cortical neural activity (16, 17). When TMS is pulsed repetitively (called repetitive TMS, or rTMS), there is an either excitatory (pulse at 5Hz), or inhibitory effect (pulse at 1Hz) (18). Excitatory rTMS delivered to the left DLPFC, which is a key cortical node in the executive control network, has been shown to modulate craving/addiction by influencing decision making (19), and inhibitory control (20). Several studies have demonstrated that rTMS applied to the left DLPFC reduces cue induced craving across addictions (21). We also reported that one session of rTMS applied to the left DLPFC reduced cue-induced craving in a cohort of nicotine dependent participants (15). However, the mechanism modulating rTMS's anti-craving effect is still poorly understood both at the behavioral (15) and neural levels (14).

We subsequently chose to use a validated fMRI cue craving paradigm to see if a single session of rTMS would alter the blood-oxygen-level dependent (BOLD) response to active cues as compared to matched neutral cues. We performed fMRI scans before and after a

single session of rTMS applied to the left DLPFC. Our hypothesis was that rTMS would reduce brain activity in the brain regions previously implicated in cigarette smoking craving and relapse (including mOFC, NAc and ventral striatum (VS)). We additionally hypothesized that rTMS would increase cue-induced brain activity underneath the rTMS stimulation site (the DLPFC).

METHODS

Study Design

We conducted a randomized, single-blind, sham-controlled, crossover study in which participants received both active and sham rTMS over the left DLPFC, with a 1-week interval between treatments to avoid carryover effects. The order of treatment condition was randomized and counterbalanced across participants. On the first visit, participants received either active, or sham, rTMS, and on the second visit they received the alternate condition. Participants were blinded to treatment condition.

Participants

All study procedures were approved by the Medical University of South Carolina's Institutional Review Board, and were performed in accordance with the Declaration of Helsinki. Participants provided informed consent prior to study related activities. Healthy, non-treatment seeking, nicotine-dependent smokers were recruited from the community through flyers, newspaper, and internet advertisements. Participants were included if they met Diagnostic and Statistical Manual fourth edition (DSM-IV-TR) criteria for nicotine dependence, smoked 10 cigarettes/day, and were between the ages of 18 and 60. Participants were excluded if they used tobacco products other than cigarettes, currently used nicotine replacement therapy, took smoking cessation medications, took any other psychoactive medications, had any unstable medical conditions, had current or past DSM-IV-TR Axis I disorders, or were pregnant.

Baseline Assessment

Current health was confirmed through a standardized medical examination. Illicit drug use was ruled out using a urine drug screen. Recent smoking was confirmed by an exhaled carbon monoxide (CO) level (< 10 ppm), measured with a Micro-Smokelyzer (Bedfont Scientific Ltd., Kent, UK). Participants also completed a detailed tobacco use history, including the Fagerström Test for Nicotine Dependence (FTND) (22), and the Questionnaire of Smoking Urges-Brief (QSU-B) (23).

rTMS Procedure

General Procedures—Participants were instructed to maintain their regular smoking habits with the exception of not smoking for 2 hours prior to each experimental visit. This brief period of abstinence was to ensure that participants had some degree of baseline craving and responsiveness to cigarette cues without the potential confound of a ceiling effect from prolonged abstinence. Craving assessments were performed before and after each stimulus experiment. A MagPro double blinded rTMS research system (MagVenture, Denmark) was used with a Cool-B65 Butterfly Coil (a combined active and sham coil) in a

room next to an MRI scanner room. We determined the resting motor threshold (MT) of each participant at the beginning of each experimental visit prior to any exposure or ratings. MT was determined by positioning the coil over the area of the skull corresponding to the motor cortex, and adjusting the location until each pulse resulted in a movement of the right thumb. We then adjusted the amplitude of the magnetic pulse until we found the lowest intensity that reliably produced thumb or hand movements 50% of the time (24). We then determined the approximate location of the left DLPFC by moving the TMS coil 6cm anterior to the hand area of the motor cortex along a parasagittal line (15). On the second visit, we reproduced the treatment position using a MagVenture TMS repositioning cap.

Active rTMS Procedures—Treatment was standardized at 100% rMT, at 10 pulses per second (10 Hz) for 5 seconds, with an inter-train interval of 10 seconds. Each treatment session lasted for 15 minutes and delivered a total of 3000 pulses. These treatment parameters were identical to a previous investigation demonstrating that rTMS can reduce cue induced cigarette craving (15). During active stimulation, the sham stimulation electrodes were applied (as described below), but there was no electrical current flow.

Sham-rTMS Procedures—Participants were fitted with two electrodes on the scalp just below the hairline. Electrodes were connected to a transcutaneous electrical nerve stimulator (TENS) on the TMS coil. For each participant, the electrical sham stimulation was delivered under a sham coil which looks and sounds like the active coil, but does not produce magnetic stimulation. Prior to each visit (both active and sham), we matched the electrical output of the TENS stimulator to mimic the sensation of active stimulation. This identical sham procedure has been used extensively in our laboratory and has been demonstrated to be indistinguishable from active stimulation (25).

Presentation of Smoking-Related Cue during rTMS

One previous rTMS study suggested that using a provocation with a smoking cue during treatment resulted in a larger effect than rTMS without a concurrent cue (26). We subsequently presented smoking cues during both the active and sham rTMS sessions. The smoking cues consisted of a house made smoking cue video, and a series of smoking related images. The smoking related images included the heads and mouths of people smoking, hands holding a cigarette, and cigarettes in ashtrays or in a pack. Cue effectiveness was measured before and after each rTMS session using a visual analog scale (VAS) (0–10, 0 indicated no craving, and 10 indicating extreme craving).

MRI Scanning Procedures

fMRI Data Acquisition—Structural and functional MRIs were performed directly before and after each rTMS session with an approximate delay of 10 minutes (described in more detail below). Functional scanning was performed using a 3 Tesla MRI (Trio, Siemens Medical, Erlangen, Germany). Each fMRI scan was acquired using a standard multi-slice single-shot gradient echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2.2 secs, echo time (TE) = 35 ms, 64×64 matrix, parallel imaging factor of 2, $3 \times 3 \times 3$ mm voxels, 328 volumes, 36 ascending transverse slices with approximate anterior commissure-posterior commissure (AC-PC) alignment. After each

volume was acquired, it was automatically exported in DICOM format from the MRI scanner computer to a separate computer for in-scan processing.

Cue Presentation and Craving Measurements in the Scanner—Visual stimuli were adapted from previous smoking cue fMRI studies conducted by our group (6), and were presented in a block design using standardized pictures. The pictures consisted of, people smoking or engaged in matched neutral activities, and objects related to smoking (cigarettes, ashtrays, etc.) or matched neutral objects (pencils, dishes, etc.). Pictures were obtained from Elliot Stein's lab at NIDA (27), along with updated images for contemporary salience. A 12-minute sequence for stimuli presentation consisted of eight, 90-second epochs presented after participants briefly handled and smelled their preferred brand of cigarette. Each epoch consisted of three, 30-second blocks (24-second cue induction immediately followed by a 6-second self-rating period). The three, 30-second blocks were randomized by one of three cue induction stimuli (cigarette smoking, neutral control, or cross-hair rest). The total time can be calculated as 8 epochs of (3 blocks, 30-seconds each), or 8×90 -seconds totaling 720-seconds (12 minutes). The 24-second cue induction stimuli contained 5 individual pictures, displayed for 4.8 seconds each. The 6-second self-rating of craving asked subjects to use a hand-pad fitted on to the right hand to rate their craving on a 1–5 scale. In order to control for time and order effects across participants, the order of individual pictures, blocks, and epochs were randomly presented (Figure 1).

fMRI Data Analysis

Individual fMRI Data Analysis—MR scans were transferred into ANALYZE format with MRICron (<http://people.cas.sc.edu/rorden/mricron/index.html>) and then further processed in Matlab 7.3 (Mathworks, Sherborn, MA) with Statistical Parametric Mapping software 8 (SPM8, The Wellcome Department of Cognitive Neurology, London, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). All volumes were realigned to the first volume. After realignment, for all subjects, movement across the 12 minutes (328 time points) was less than 0.5 mm in 3 axes and less than 0.5 degree in 3 orientations. The images were normalized stereotactically into a standard space with a resolution of 3 mm^3 voxels using the averaged functional EPI image – the Montreal Neurological Institute (MNI) EPI template in SPM8. Subsequently, the data were smoothed with an anisotropic 8 mm^3 Gaussian kernel and high-pass filtered (cut-off period=128s). In a first level of statistical analysis, using a boxcar function convolved with the modeled hemodynamic response function as the basic function for the general linear model (28), we obtained contrast-maps of the difference between task and neutral for each subject. The six head movement parameters were included as confounds.

Group Data Analysis—For comparisons between treatment (active vs sham) and time (pre vs post), subject-specific contrasts of smoking minus neutral were entered into a 2×2 factorial design model to measure the effect of treatment, time and, treatment $\times$ time interaction on BOLD activity. Post hoc analysis included within-treatment comparison of before and after treatment (active and sham). All group maps were thresholded at $p = 0.005$, uncorrected and cluster analyses were performed with a spatial extent threshold of 5 voxels.

Region of Interest (ROI) Analysis—To specifically test the effect of treatment (active vs sham) in executive control brain regions (the left DLPFC) and, drive-reward brain regions (mOFC and NAc), we performed ROI analysis in the 3 regions. We created masks for the left DLPFC, the right mOFC and the left NAc with WFU_PickAtlas 3.0.5 (<http://fmri.wfubmc.edu/software/pickatlas>) and then calculated the beta values from ROI masks for each individual data (smoking vs neutral).

General Data Analyses

Analyses were completed with SPSS statistical software, version 20.0 (IBM, Endicott, New York). The primary behavioral measure of cue craving was taken to be the contrast (difference) between active and sham rTMS in the pre- to post experiment change in subjective craving. A two factor mixed model (treatment: active vs sham) and (time: pre- vs post) were performed on cigarette-craving ratings. A partial correlation analysis was applied to the hand-pad craving rating and beta values from ROIs. We powered this study based on the effect size generated in a previous study measuring the fMRI effect of a single session of rTMS measured in healthy controls (29). With a two tailed test and within subject design, 9 subjects achieve a power of 0.9. According to a conservative attrition rate of 10%, we enrolled 10 participants to have sample power to detect a significant difference in the effects of rTMS.

RESULTS

Participant Characteristics

Eleven non-treatment seeking participants (6 female) signed informed consent, and 10 participants completed the study. One participant was terminated from the study for missing his second appointment. Demographic characteristics and smoking history are listed in Table 1. The only reported side effect was the report of mild site discomfort at the start of stimulation by all participants. The discomfort was mild and transient and equal across the sham and active sessions. Such site discomfort is common with the initiation of rTMS.

Effect of rTMS on Cue-induced Brain Activity

Within-treatment (pre to post)—active TMS reduced brain activity in the right mOFC (18, 29, -11; $t = 7.29$, cluster of 54 voxels) (Figure 2B) and left NAc (-6, 8, -8; $t = 3.73$, cluster of 11 voxels) (Figure 2A).

The beta values from the right mOFC and the left NAc were analyzed with a mixed model of treatment (sham vs active) and time (pre vs post). The results of right mOFC showed a significant interaction between TMS treatment condition and scan time ($F_{1, 36} = 6.05$, $p = 0.019$) (Figure 2D). The results of NAc showed a significant interaction between treatment condition and scan time ($F_{1, 36} = 7.96$, $p = 0.008$) (Figure 2C). Post hoc analysis demonstrated that active rTMS significantly reduced BOLD beta values in the NAc (0.14 ± 0.09 vs -0.38 ± 0.13 , $t = 3.34$, $p = 0.004$) and mOFC (0.13 ± 0.09 vs -0.22 ± 0.10 , $t = 5.30$, $p < 0.001$, Figure 2C and 2D). No significant change in NAc (0.02 ± 0.08 vs 0.07 ± 0.11 , $t = -0.92$, $p = 0.37$) or mOFC (-0.03 ± 0.08 vs 0.11 ± 0.12 , $t = -0.40$, $p = 0.69$) was found before or after sham treatment.

Between-treatment (Active vs Sham, pre to post stimulation)—In the contrast of smoking cues vs neutral cues from pre to post stimulation, participants treated with active rTMS had a significant stimulation-induced reduction in activation in the mOFC and the interconnected anterior cingulate cortex ($-6, 28, -3$; $t = 4.14$, cluster of 63 voxels).

Effect of TMS on the Site of Stimulation (Left DLPFC): Using a mask created from the left DLPFC, factor design imaging analysis showed an interaction between treatment type (sham vs active) and scan time (pre vs post) [(sham pre (0.10 ± 0.13) vs post (-0.13 ± 0.06); active pre (-0.14 ± 0.09) vs post (0.11 ± 0.09)] $F_{1, 36} = 6.01$, $p = 0.019$). Post hoc: paired t-test showed that active rTMS increased BOLD signal in the left DLPFC ($t = 2.45$, $n = 10$, $p = 0.037$). There was no significant difference between pre to post sham beta value ($t = -0.07$, $n = 10$, $p = 0.95$).

Correlation between Cue Craving and Brain Activity: We performed a partial correlation analysis between hand pad ratings of craving in the scanner and beta value from ROIs (left DLPFC, right mOFC and left NAc), controlling for treatment and time. Results showed that craving ratings were significantly correlated with mOFC activation ($r = 0.42$, $p = 0.008$). We also performed partial correlation within active and sham rTMS respectively (controlling time). The results showed that a significant correlation was only found during sham rTMS ($r = 0.51$, $p = 0.025$). However, the majority of the effect was driven by a single observation, and if that observation is removed from the analysis the correlation is no longer significant ($r = 0.28$, $p = 0.25$). No significant correlation was found during active rTMS ($r = 0.23$, $p = 0.343$) (Figure 3).

Behavioral Data

Self-Reported Craving—No statistically significant difference was found between the two pre TMS craving visual analog scale ratings ($t = 1.45$, $p = 0.182$). A two-way ANCOVA did not show a statistically significant difference between active TMS (Pre 6.75 ± 2.32 vs post 6.35 ± 2.40) and sham TMS (Pre 5.35 ± 2.43 vs post TMS 6.45 ± 2.08 , $F_{1, 36} = 0.79$, $p = 0.38$). No significant interaction of treatment condition (active vs sham) and time (pre vs post) was found ($F_{1, 9} = 4.36$, $p = 0.067$). When percent change was used to calculate pre to post craving, active rTMS produced a statistically significant reduction of cue craving as compared to sham rTMS (3.89 ± 6.98 vs -37.54 ± 15.84 ; $t = 2.49$, $p = 0.034$).

Self-reported Craving in the MRI Scanner—A three-way mixed model analysis revealed significant differences between smoking cues (3.19 ± 0.91), neutral cues (2.55 ± 0.96), and rest (2.67 ± 0.93) ($F_{2, 108} = 8.59$, $p < 0.001$); however, neither treatment effects [sham (2.89 ± 0.77); active (2.72 ± 0.84)], nor time effects [pre-treatment (2.92 ± 0.88); post-treatment (2.73 ± 0.71)] were found to be statistically significant.

DISCUSSION

Our findings demonstrate that one session of 10Hz rTMS applied to the left DLPFC significantly decreased BOLD activation in the left NAc and right mOFC during cigarette cues in nicotine dependent individuals. To the best of our knowledge, this is the first report demonstrating that a single session of high-frequency rTMS of the DLPFC can cause

decreased activation in drive-reward regions in smokers. Although no significant activity was found in the left DLPFC (underneath the coil) in whole brain analysis, ROI analysis of the left DLPFC showed a significant interaction of rTMS treatment (sham vs active) and time (pre vs post) in this area.

We hypothesized that rTMS applied to the left DLPFC might reduce cue-induced responses in drive-reward network structures. In support of our hypothesis, our data demonstrated that active rTMS reduced cue-elicited brain activity in the mOFC and NAc compared with sham rTMS. Varenicline is a first-line treatment option for smoking cessation, and has been investigated using similar cue-reactivity imaging protocols as the one utilized in this study (30). The use of varenicline has been associated with reductions of smoking cue-elicited VS and mOFC activity in treatment-seeking (12), and non-treatment seeking (31) smokers. Additionally, our current findings are consistent with other studies demonstrating that reduced cue-induced craving is associated with a reduction in cue-induced activation of drive-reward and prefrontal brain regions (12, 13). Our findings subsequently may suggest that rTMS reduced cue induced craving through decreasing drive-reward circuits including mOFC and NAc.

The prefrontal cortex has been implicated in the control and regulation of drug-seeking behavior (32, 33). The DLPFC is strongly implicated in controlled response inhibition, and high-frequency stimulation of the DLPFC can modulate activation of the OFC and ACC via descending lateral pathways (20, 26). Our findings demonstrate that rTMS applied to the left DLPFC resulted in increased activity in the DLPFC (consistent with our findings in depression (34). The findings were also consistent with previous findings that rTMS of the left DLPFC decreased delay discounting rates and showed more conservative risky decision-making (35). Therefore, it is plausible that one of the mediating mechanisms of our findings is increased DLPFC/executive control activity, leads to enhanced inhibitory control of drive-reward related brain regions (NAc and mOFC).

Several limitations should be noted in the interpretation of the present study. The small sample size may have led to Type II errors, however, as we used a within subject design, participants served as their own control for both imaging and subjective craving outcomes reducing the likelihood of such an error. The second potential limitation is that participants were non-treatment-seeking smokers, and findings may not generalize to treatment-seeking smokers. The third potential concern involves the lack of anatomic specificity concerning stimulation location, however, compared with previous studies, we did improve accuracy in determining the TMS location by using a method which reliably targets the DLPFC (15). The third potential limitation of our study was the lack of a blind for the investigator. This may have resulted in investigator bias, however this limitation was mitigated by standard procedures, and MRI analysis. The final possible limitation is the variability of pre-treatment MRI scans, however 2×2 full factorial analysis showed a significant interaction of treatment and time which mitigates this limitation.

In summary, using fMRI, we provide preliminary evidence for a rational basis for the apparent anti-craving effect of rTMS applied to the left DLPFC in smokers. Our results

support the hypothesis that an imbalance in drive-reward and executive control circuitry is critical for craving and relapse in nicotine dependence.

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Figure 1.
Cigarette smoking cue-induced fMRI paradigm

Figure 2.

One session of rTMS of 3000 pulse over the left DLPFC reduced brain activity in nucleus accumbens (A) and medial orbitofrontal cortex (B). The bar graph shows the mean BOLD signals (beta value ± SE), left NAc (-6, 8, -8) (C) and right mOFC (18, 29, -11) (D). N = 10, * $p < .05$, ** $p < .01$

Figure 3.

Correlation plot between handpad craving rating and beta value in medial orbitofrontal cortex. Dashed line: the relationship of craving rating and beta value in mOFC ($r = .51$, $p = .025$) in pooled pre and post sham treatment. Solid line: the relationship of craving rating and beta value in mOFC in pooled pre and post active treatment ($r = .23$, $p = .343$).

Table 1

Participant Characteristic

Characteristic	Value
Age, mean (SD), y	39.7 (13.2)
Gender (M/F)	4/6
Education years, mean (SD), y	13.6 (2.4)
Years smoked, mean (SD), y	22.8 (9.8)
FTND score, mean (SD)	5.2 (1.8)
Cigarette per day, mean (SD)	17.3 (5.9)
CO level at sham rTMS visit, mean (SD)	12.7 (4.6)
CO level at active rTMS visit, mean (SD)	13.1 (8.3)