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Repetitive Transcranial Magnetic Stimulation of the Dorsolateral Prefrontal Cortex Reduces Nicotine Cue Craving

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Abstract

Background—Repetitive transcranial magnetic stimulation (rTMS) can non-invasively stimulate the brain and transiently amplify or block behaviors mediated through a region. We hypothesized that a single high-frequency rTMS session over the left dorsolateral prefrontal cortex (DLPFC) would reduce cue craving for cigarettes compared to a sham TMS session.

Methods—Sixteen non-treatment seeking, nicotine-dependent participants were randomized to receive either real high-frequency rTMS (10 Hz, 100% resting motor threshold, 5 second-on, 10 second-off for 15 minutes; 3000 pulses) or active sham (eSham) TMS over the DLPFC in two visits with one week between visits. The participants received cue exposure before and after rTMS and rated their craving after each block of cue presentation.

Results—Stimulation of the left DLPFC with real, but not sham, rTMS reduced craving significantly from baseline (64.1 ± 5.9 vs. 45.7 ± 6.4 , $t = 2.69$, $p = 0.018$). When compared to neutral cue craving, the effect of real TMS on cue craving was significantly greater than the effect of sham TMS (12.5 ± 10.4 vs. -9.1 ± 10.4 ; $t = 2.07$, $p = 0.049$). More decreases in subjective craving induced by TMS correlated positively with higher Fagerström Test for Nicotine Dependence (FTND) score ($r = 0.58$, $p = 0.031$) and more cigarettes smoked per day ($r = 0.57$, $p = 0.035$).

Conclusions—One session of high frequency rTMS (10 Hz) of the left DLPFC significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants. Further studies are needed to explore the use of rTMS as an aid to smoking cessation.

Keywords

nicotine; tobacco; craving; smoking; transcranial magnetic stimulation; dorsolateral prefrontal cortex

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Introduction

Nicotine dependence remains a significant public health concern. In 2011 the World Health Organization (WHO) reported that tobacco use continues to be the leading global cause of preventable death with almost 6 million deaths each year (1). The U.S. National Health Interview Survey revealed that approximately 70% of current smokers want to quit smoking and 41% had tried to quit in the previous year. However few of these attempts were successful, with only 4.7% of current smokers able to stop smoking for at least three months (2). Despite the availability of new medications to treat nicotine dependence (3–5), only 6% of the 35 million smokers who report wanting to quit each year are successful in doing so for more than a month (6, 7).

Nicotine, like other drugs of abuse, activates the mesolimbic dopamine system, which originates in the ventral tegmental area and projects to reward-related brain area such as the prefrontal cortex (PFC), nucleus accumbens, amygdala and hippocampus (8). Decreased activity of the brain reward system during nicotine withdrawal has been associated closely with craving, relapse and continued nicotine consumption (9). The dorsolateral prefrontal cortex (DLPFC) is critically involved in processing the craving of smoking (10, 11) and other drugs such as cocaine (12) and alcohol (13, 14).

Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technology that can focally stimulate the brain of an awake individual (15, 16). Several lines of evidence suggest that repetitive TMS (rTMS) over the left DLPFC can affect processes involved in nicotine addiction. Firstly, stimulation of the DLPFC can induce release of dopamine in the caudate nucleus (17). Therefore, repeated stimulation may induce neuroadaptations in the dopaminergic system. Moreover, while administration of drugs induces an acute increase in dopamine levels, during withdrawal dopaminergic activity is reduced. Decreased dopaminergic activity has been associated with increased levels of craving and relapse (18). Therefore, it is possible that even transient increases in dopamine released by TMS may help reduce levels of craving in subjects under these withdrawal conditions (19). Secondly, the effects of brain stimulation can extend beyond the directly targeted area, including cross-hemispheric cortical and subcortical activity in remote neural networks connected to the stimulated regions (20, 21). Therefore, given the ability of TMS to modulate cortical excitability, it is possible that these stimulations are able to alter neuroadaptations and synaptic plasticity in the brain reward system. Thirdly, as we mentioned above, the PFC has been strongly implicated in drug-seeking behaviors. The DLPFC is proposed to play an executive role in controlled response inhibition through its connectivity. Therefore, it is possible that repeated DLPFC stimulation could lead to improved inhibitory control and thereby reduced levels of drug-seeking. Given these theoretical and preliminary human data, scientists have completed a few pilot studies to explore whether rTMS of the left DLPFC would reduce craving for cigarettes (22–24).

These preliminary studies demonstrate that high frequency rTMS of the left DLPFC can attenuate nicotine consumption (22, 23) and craving (22). However, one significant limitation of these two TMS studies was a questions about the validity of the sham TMS which do not cause much, if any, scalp or facial sensation (22, 23). This is a serious problem when investigators are attempting to evaluate the effects of TMS using these sham techniques because of unintended systematic differences between real and sham TMS. Taken together, the significance and duration of these effects of TMS are limited and further investigation is required to identify the appropriate stimulation parameters and targets needed with a valid sham control to further explore the utility of rTMS in smoking cessation. In this randomized, double-blind, sham-controlled crossover study, we tested whether rTMS of the left DLPFC, compared to sham stimulation, would temporarily reduce

the subjective craving triggered by exposure to smoking cues in non-treatment seeking nicotine-dependent adult smokers.

Methods and Materials

Participants

The study was approved by the Institutional Review Board of the Medical University of South Carolina (MUSC). Written informed consent was obtained from all participants. The experiment was carried out at Brain Stimulation Laboratory in the Department of Psychiatry at MUSC. Healthy, right-handed, non-treatment-seeking, nicotine-dependent smokers (10 cigarettes/day) between 21 and 60 years old were recruited through local flyers, newspaper, and internet advertisements. All study procedures were performed in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki with approval from the MUSC Institutional Review Board. Telephone screening included brief medical, substance use, and psychiatric histories completed without personal identifiers prior to scheduling the initial assessment. The Fagerström Test for Nicotine Dependence (25, 26), Questionnaire of Smoking Urges-Brief (QSU-B) (27), Minnesota Withdrawal Scale-Revised (28) and Tobacco Use History were administered. Exhaled carbon monoxide (CO) levels (10 ppm) were measured with a MicroSmokelyzer (Bedfont Scientific Ltd., Kent, United Kingdom) to confirm recent smoking before each visit. The Mini-International Neuropsychiatric Interview was completed to assess for current psychiatric and substance use disorders (29) and a physical examination assessed current physical health. Exclusion criteria included: the use of other tobacco products, current use of nicotine replacement therapy, bupropion, or varenicline, medical conditions, pregnancy, non-nicotine substance dependence or abuse, a history of psychiatric disorder and current pending charges for a violent crime. Individuals taking medications that lower the seizure threshold or with any implanted metal devices (e.g., pacemakers, metal plates, wires) were also excluded.

Experimental Design

A randomized, double-blind, sham-controlled crossover study was employed in which participants received 2 different types of brain stimulation: sham rTMS and real rTMS over the left DLPFC, with a one week interval between treatments to avoid carryover effects (see supplement 1 for details). The order of stimulation was randomized and counterbalanced across participants. The randomizations were performed with a web-based randomization generator (www.randomization.com). Participants and the investigators, except one investigator who applied the rTMS, were blinded to the treatment arm. At the baseline, demographic and smoking-habits profile data were collected. Participants were instructed to keep their regular smoking habit but not to smoke for 2 hours prior to the experiment and thus were expected to have some degree of craving and responsiveness to the cues without the potential confound of a ceiling effect from prolonged abstinence (30, 31). Craving assessments were performed before and after each stimulus experiment. (see figure 1).

Cue Presentation and Craving Measurements

Seventy scenic images (e.g. mountain), forty neutral control images (e.g. a person holds a pen) and forty cigarette smoking cue images (e.g. a person lighting a cigarette) were presented in four blocks- #1.scenic images-5 min, #2.neutral control images-1.5 min, #3.scenic images-5 min, and #4.cigarette smoking cue images-1.5 min. Pictures were obtained from Elliot Stein's lab at NIDA (32) along with updated images for contemporary salience. Immediately after viewing each block of cue images, participants completed an adapted QSU-B utilizing a computerized visual analog scale (CVAS) designed to assess craving. The ten QSU-B questions include: 1) I have a desire for a cigarette right now; 2) Nothing would be better than smoking a cigarette right now; 3) If it were possible, I

probably would smoke now; 4) I could control things better if I could smoke; 5) All I want right now is a cigarette; 6) I have an urge for a cigarette; 7) A cigarette would taste good now; 8) I would do almost anything for a cigarette now; 9) Smoking would make me less depressed; 10) I am going to smoke as soon as possible. Each question is followed by a CVAS (range 0 – 100). All the responses from the 10-question QSU-B were averaged as a single score. After 15 minutes of real or sham rTMS, participants viewed the images again and rated their cravings. At each visit, participants were blind to the rTMS condition (real or sham) and the order of sham and real TMS was randomized.

rTMS procedure

Determining resting motor threshold (rMT) and locating cortical targets: rMTs were performed via visual twitch in the contralateral (right) hand muscle at the beginning of each experiment. Before any exposure or ratings, rMT was determined using a Neuronetics® Model 3600 with a solid focal coil TMS machine (Neuronetics, Malvern, PA, USA) starting with 40% of the machine output and 0.5 Hz stimulus frequency. The coil was positioned over the area of the skull corresponding to the motor cortex, adjusted until each pulse resulted in isolated movement of the right thumb (abductor pollicis brevis – APB), and then adjusted for the lowest intensity that reliably produced thumb or hand movement. rMT was defined as the lowest output to produce thumb movement 50% of the time (33). The position of the coil used for rMT assessment was identified as the motor cortex target (M1). The standardized stimulation localization was over the left prefrontal cortex, determined by moving the TMS coil 6 cm anterior to M1 along a parasagittal line (34, 35). On the second visit, the rMT procedure was repeated and TMS coil was located the same as at visit 1.

Real rTMS procedures: Treatment was standardized at 100% resting MT, at 10 pulses per second (10 Hz) for 5 seconds, with an intertrain interval of 10 seconds. Each treatment session lasted for 15 minutes with 3000 pulses. This is a treatment dose similar to that approved by the US Food and Drug Administration (FDA) for treating depression, except that the percent MT was less, which likely made it more tolerable for participants (36).

Sham-TMS procedures: After rMT determination and the left DLPFC cortex localization, participants were fitted with two electrodes on the scalp just below the hairline. Electrodes were connected to an Epix VT® Transcutaneous Electrical Nerve Stimulation Device (Epi; St. Paul, MN, USA) with adjustable output amplitude and powered by a 9-V battery. For each participant, the electrical sham system was turned on, and a series of 1-s trains of real 10 Hz prefrontal rTMS at 100% of rMT was delivered. The electrical current of the sham system using a sham rTMS coil was titrated to a level matching participants' ratings of real rTMS in a manner that does not allow them to know which is real or sham (37). All participants underwent sham titration procedures before each experiment visit and wore the scalp electrodes in both conditions. We used 10 Hz, 5 second-on, 10 second-off for 15 minutes in both real and sham conditions. The sham-TMS scalp discomfort was matched to that of real TMS at 100% (37). During real TMS there was no current flowing through the scalp electrodes. (see supplement 1 for details).

Data Analyses

Analyses were completed with SPSS statistical software, version 20.0 (IBM corporation, Endicott, New York). A paired *t*-test was used to compare pre TMS and post TMS on smoking cue craving data to evaluate the primary hypothesis that rTMS of left DLPFC would affect the cue craving elicited by smoking cues.

The primary measure of cue craving was taken to be the contrast (difference) between smoking cues and neutral cues in the pre- to post-experiment change in subjective craving.

A two-factorial 2×2 analysis of variances (ANOVAs) (sham vs. real TMS $\times$ pre- vs. post-experiment) were performed on cigarette craving ratings. A Spearman correlation analysis was applied to the effect of rTMS on cue craving and smoking variables (cigarettes per day and FTND score).

Results

Participant characteristics

Table 1 shows the demographic information for study subjects. Sixteen non-treatment seeking participants (12 men and 4 women) signed informed consent and 14 completed the study. Two men completed the first visit (one was sham, one was real TMS), but were terminated from the study for missing their second visit. The average age of participants who completed the protocol was 42.6 years ($SD = 11.5$) and participants smoked an average of 18.1 cigarettes per day ($SD = 6.6$). Participants had been smoking for an average of 20.9 years ($SD = 9.2$) and FTND scores were moderate with an average of 5.0 ($SD = 1.8$). Exhaled CO levels were 17.7 p.p.m. ($SD = 8.8$) at the time screening, 16.9 p.p.m. ($SD = 6.2$) at the first experiment visit and 18.8 p.p.m. ($SD = 8.5$) at the second experiment visit.

Cue exposure paradigm validity and reliability

Pre-experiment (sham TMS) cue exposure assessment: The craving rating following smoking cue exposure was significantly higher than after the neutral control cue rating (63.0 ± 4.8 vs 56.2 ± 4.9 , $t = 4.1$, $df = 13$, $p = 0.001$). The craving ratings following smoking cues were also significantly higher than those following the scenic images rating. Neutral control cue craving ratings were not different from ratings following the scenic image cues.

Pre-experiment (real TMS) cue exposure assessment: Smoking cue craving ratings were significantly higher than following the neutral control cues (64.1 ± 5.9 vs. 57.6 ± 5.5 , $t = 2.5$, $df = 13$, $p = 0.026$). Smoking cue craving ratings were also significantly higher than scenic images cue ratings. Neutral control cue craving ratings were not different from ratings following the scenic image cue. (additional analyses in supplement 1).

Effects of rTMS on absolute subjective nicotine cue craving

Comparison of participant subjective smoking craving rating pre and post experiment showed that real or active TMS significantly reduced subjective cue cravings (64.1 ± 5.9 vs. 45.7 ± 6.4 , $t = 2.692$, $n = 14$, $p = 0.018$), whereas sham stimulation did not affect subjective cue rating (63.0 ± 4.8 vs 52.4 ± 6.3 , $t = 1.82$, $n = 14$, $p = 0.092$). (see Figure 2).

Different effects of rTMS on nicotine cues and neutral control cues

The difference in craving after smoking cue versus neutral cue exposure was used for the secondary analysis. We defined the difference of craving after smoking cues versus neutral control cues = $100 * (\text{smoking cue craving rating} - \text{neutral control cue craving rating}) / (\text{neutral control cue craving rating})$.

Factorial 2×2 factorial ANOVA revealed a significant main treatment (sham vs real TMS) effect ($F = 5.17$, $df = 1, 52$, $p = 0.027$). No significant effects were found between pre and post experiment order ($F = 1.27$, $df = 1, 52$, $p = 0.265$). No significant two way interaction “treatment $\times$ pre-post experiment” was found ($F = 3.32$, $df = 1, 52$, $p = 0.074$). Post hoc t -test showed that rTMS of the DLPFC significantly reduced the difference of subjectively rated craving (smoking cue versus neutral control) (12.5 ± 10.4 vs. -9.1 ± 10.4 ; $t = 2.07$, $df = 28$, $p = 0.049$). Inversely, sham TMS of the DLPFC did not affect craving difference (15.2 ± 9.1 vs. 20.7 ± 9.1 ; $t = 0.612$, $df = 28$, $p = 0.459$). (see Figure 3).

Correlations between the effects of rTMS and FTND score and cigarette per day

We used the percent change of smoking cue craving before and after rTMS to correlate with clinical variables including FTND score and cigarettes smoked per day, both of which are measures of nicotine dependence. The correlational analyses showed that the effect of rTMS on cue craving was positively correlated with FTND ($n = 14$, $r = 0.58$, $p = 0.031$) and cigarette per day ($n = 14$, $r = 0.566$, $p = 0.035$). (see Figure 4). That is, greater reductions in nicotine craving following TMS were seen in the patients with higher levels of nicotine dependence.

Safety

The only adverse events were that some participants experienced mild discomfort at the start of stimulation. Two participants dropped out because of scheduling conflicts.

Discussion

This study found that a lab-based paradigm of smoking-related cue exposure produced reliable increases in subjective craving to smoke. With this background, high-frequency rTMS over the left DLPFC for 15 minutes, compared to sham stimulation, significantly reduced cue-induced cravings to smoke. Across the group, the reduction in cue-induced craving was positively correlated with level of nicotine dependence. That is, more TMS induced craving reductions were seen in those with higher levels of nicotine use.

To the best of our knowledge, this is the first demonstration that a single session of high frequency rTMS of the DLPFC can significantly reduce cigarette craving induced by cue exposure. This is partially consistent with prior findings by Amiaz and colleagues (22), who reported that rTMS (100% rMT, 10 Hz, 20 train/day, total 1000 pulses) of the DLPFC reduced cigarette craving and consumption. However, although they found a reduction of craving after ten treatment sessions they did not find an immediate craving effect after one session of TMS. In another study, Eichhammer and colleagues (23) showed a significant reduction in the number of cigarettes smoked after active rTMS (90% rMT, 20 Hz, 20 train, 1000 pulses/day); however, craving levels did not change. One possible explanation to explain how this study differs from these others is differences in the rTMS protocol used. Compared to the previous studies, we employed more stimulation pulses, a different stimulation location and an affordable eSham system. Both the Amiaz and Eichhammer studies used 1000 pulse per session while this study utilized 3000 pulses; both prior studies used a 5 cm rule for prefrontal location determination, while the current study used 6 cm rule. A meta-analysis (38) and a prospective clinical trial (39) suggest that use of greater numbers of rTMS stimulations is more effective in depression treatment. In addition, one study suggested that the 5 cm rule resulted in 30% of depressed participants being treated over the supplementary motor area rather than the prefrontal cortex (40). Two retrospective analyses of clinical trials in which brain imaging was performed to document the coil location have independently confirmed that an anterior and lateral coil position is associated with a better clinical response to active but not sham TMS (35). In a recent study, Rose and colleagues reported that 10 Hz rTMS over the superior frontal gyrus increased smoking cue craving, whereas craving after neutral cue presentation was reduced (24). In sum, perhaps the most logical explanation for the reduction in craving in the present study as compared to prior studies did not is that the increased pulse per session TMS protocol and 6 cm rule for prefrontal location produced a more robust and immediate rTMS effect on cue-elicited craving.

The mechanism of action of rTMS with regard to cue-elicited craving in nicotine dependence is likely multifaceted. One possible explanations is the fact that rTMS increases

the availability of striatal dopamine (17, 41), which reduces craving (42). Because both nicotine (43, 44) and acute high frequency rTMS of the DLPFC induce dopamine release in the caudate nucleus (17) and striatum (45), it is possible that the effect of rTMS treatment on cigarette consumption is mediated by its effect on striatal dopamine. Even transient elevations in dopamine secretion may be helpful to subjects experiencing nicotine withdrawal. Alternatively, rTMS might alter the neuroadaptations in the reward system that mediates nicotine addiction. This could be accounted for by rTMS effects on cortical excitability (46) which, in turn, activate synaptic plasticity mechanisms such as long-term potentiation (47). Another possible explanation is that rTMS can mediate the potentiation of γ -aminobutyric acid (GABA_B) receptor (48). By contrast, rTMS has previously been shown to activate pyramidal neurons transsynaptically, with direct activation of GABAergic interneurons, translating into potentiation of GABA_B receptor-mediated inhibitory neurotransmission. It appears, therefore, that potentiation of GABA_B receptor mechanisms in nicotine dependence may be another therapeutic target through rTMS (49). This is supported by a previous finding of rTMS that showed rTMS reduced cue smoking cue in patients with schizophrenia (50). Furthermore, previous studies combining TMS and functional Magnetic Resonance Imaging (fMRI) done by our group have confirmed that rTMS of the DLPFC induces brain activation in sub-cortical regions (20, 51, 52) linked with appetitive drive. These TMS/fMRI findings provide evidence to support that rTMS of the DLPFC causes brain function change in sub-cortical regions including reward system. In addition, the DLPFC has been implicated in tobacco dependence and addictive behavior in general (30). The region is associated with such functions as decision making, behavioral inhibition, and repetitive behavior. High frequency rTMS of the DLPFC may affect craving through its influence on decision making (53) and inhibitory control (54) as risky decision making and difficulty with inhibitory control are traits common to people who suffer from addiction. Finally, another potential mechanism is that stimulation of the DLPFC might mimic craving-related processes and thus reduce the necessity to initiate reward-related behavior (23). McBride and colleagues proposed that the DLPFC 'integrates information about internal state (craving, withdrawal) motivation, expectancy, and cues, and uses this information in the regulation and planning of drug-seeking or drug-avoiding behavior' (11). Taken together, these studies indicate that prefrontal rTMS might increase the availability of striatal dopamine (17), modulate sub-cortical region function (20, 51, 55) and influence inhibitory control (54), all of which could contribute to reduction in the level of craving (56).

In the present study, another interesting finding was that the reduction in cue-induced craving from rTMS was positively correlated with the number of cigarettes smoked per day and higher FTND score. FTND scores and cigarettes per day are widely used as measures of dependence. Smokers who smoke only a few cigarettes per day are more likely to quit and maintain abstinence as compared to smokers who smoke a large number of cigarettes per day (57, 58). Studies have been less consistent regarding the ability of FTND scores to predict smoking cessation (59–61) and it has been criticized as being more measure of physical tolerance than of the attributes (e.g. psychosocial) that may contribute to nicotine dependence (62). However, in the present study, we first found that the reduction in cue-induced craving following stimulation of the left DLPFC was positively correlated to FTND score and cigarettes per day. This suggests that rTMS of the left DLPFC might affect smoking-cue craving more effectively in heavy smokers than in light ones. Taken together, these results might have important clinical implications for smoking reduction or cessation treatment. If rTMS could be used to induce a prolonged decrease in reactivity to smoking cues or decrease the reinforcing value of smoking in heavy smokers, there might be a unique therapeutic benefit in this difficult to treat population.

The rTMS was relatively well tolerated even though our stimulation pulse numbers were much greater than previous studies. The only adverse events reported were that some participant felt uncomfortable at the start of stimulation. The absence of adverse effects suggests that similar parameters might be acceptable and tolerated in future clinical trials (63).

There are several limitations to this study. The small sample size may have led to type II errors. However, the participants served as their own control for subjective craving when these cravings were measured on separate visits. Additionally, the current cue craving paradigm has a high validity and reliability. In addition, we did not measure cigarette consumption during the experiment day. However, previous studies of non-treatment seeking smokers have shown a positive correlation between dependence and craving in response to smoking-related cues, suggesting that heavier smokers are more cue reactive (64, 65). Another potential limitation is the lack of anatomical specificity concerning stimulation location. However, compared to previous studies, we did improve accuracy in determining the TMS location by using the 6 cm rule which is more likely to result in stimulation over the left DLPFC and not the supplemental motor area (SMA). In addition, participants were non-treatment-seeking smokers and findings may not generalize to other populations, such as treatment seeking smokers or restrained smokers. Finally, although this study preliminarily demonstrated that rTMS of the left DLPFC temporarily reduced cue-induced craving to smoke, the results do not necessarily imply that rTMS might be effective in helping smoking cessation. The reduction of craving might be only temporary. To induce longer lasting effects, several daily sessions of rTMS would need to be applied as is done in using TMS to treat depression (66–68). Thus, the next step of the investigation of the role of rTMS in smoking craving is the study of consecutive sessions of rTMS to explore whether craving reduction might translate to smoking cessation in treatment-seeking smokers.

In conclusion, the results of this preliminary study demonstrate that rTMS of the left DLPFC can temporarily suppress cue-induced smoking craving. This finding extends the results of previous studies and opens the way for further exploration of the use of brain stimulation techniques in smoking cessation treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Diagram showing the stimulation and assessments that were performed during this study

Figure 2.

Effects of rTMS of DLPFC on subjective nicotine craving provoked by smoking cue. ((Mean $\pm$ SEM) (* $n = 14$, $t = 2.692$, $p = 0.018$)) Note, DLPFC = dorsal lateral prefrontal cortex, Note, * $p < 0.05$

Figure 3.

Comparison of the smoking cue-induced craving rating to the neutral cue-induced craving rating between sham and real rTMS. (Mean $\pm$ SEM; Y axis = $100 \times (\text{smoking cue craving rating} - \text{neutral control cue craving rating}) / \text{neutral control cue craving rating}$). Factorial 2×2 factorial ANOVA revealed a significant main treatment (sham vs real TMS) effect ($F=5.17$, $df=1, 52$, $p=0.027$). Post hoc t -test showed that rTMS of the DLPFC significantly reduced subjectively rated craving difference (smoking cue versus neutral control) (12.5 ± 10.4 vs. -9.1 ± 10.4 ; $t=2.07$, $df=28$, $p=0.049$). Note, * $p < 0.05$

Figure 4. Association between the rTMS effect of cue craving and level of nicotine dependence. A. Correlation between effects of rTMS and FTND score ($n=14$, $r = 0.575$, $p = 0.031$); B. correlation between effects of rTMS and cigarette-day ($n=14$, $r = 0.566$, $p = 0.035$) Note, FTND = Fagerstrom Test for Nicotine Dependence

Table 1

Characteristics of Participants

Characteristic	Value
Age, mean (SD), y	42.6 (11.5)
Gender (M/F)	10/4
Education years, mean (SD), y	14.5 (1.7)
Years smoked, mean (SD), y	20.9 (9.3)
FTND score, mean (SD)	5.0 (1.8)
Cigarette per day, mean (SD)	18.0 (6.3)
CO level at 1 st visit, mean (SD)	16.9 (6.2)
CO level at 2 nd visit, mean (SD)	18.8 (8.5)

Abbreviation: SD = Standard Deviation; FTND = Fagerstrom Test for Nicotine Dependence; CO = Carbon Monoxide