

Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial

Limor Dinur-Klein, Pinhas Dannon, Aviad Hadar, Oded Rosenberg, Yiftach Roth, Moshe Kotler, and Abraham Zangen

Background: Tobacco smoking is the leading cause of preventable death in developed countries. Our previous studies in animal models and humans suggest that repeated activation of cue-induced craving networks followed by electromagnetic stimulation of the dorsal prefrontal cortex (PFC) can cause lasting reductions in drug craving and consumption. We hypothesized that disruption of these circuitries by deep transcranial magnetic stimulation (TMS) of the PFC and insula bilaterally can induce smoking cessation.

Methods: Adults ($N = 115$) who smoke at least 20 cigarettes/day and failed previous treatments were recruited from the general population. Participants were randomized to receive 13 daily sessions of high-frequency, low-frequency or sham stimulation following, or without, presentation of smoking cues. Deep TMS was administered using an H-coil version targeting the lateral PFC and insula bilaterally. Cigarette consumption was evaluated during the treatment by measuring cotinine levels in urine samples and recording participants' self-reports as a primary outcome variable. Dependence and craving were assessed using standardized questionnaires.

Results: High (but not low) frequency deep TMS treatment significantly reduced cigarette consumption and nicotine dependence. The combination of this treatment with exposure to smoking cues enhanced reduction in cigarette consumption leading to an abstinence rate of 44% at the end of the treatment and an estimated 33% 6 months following the treatment.

Conclusions: This study further implicates the lateral PFC and insula in nicotine addiction and suggests the use of deep high-frequency TMS of these regions following presentation of smoking cues as a promising treatment strategy.

Key Words: Addiction, H-coil, insula, nicotine, prefrontal cortex, smoking, TMS

Smoking is one of the most prevalent and persistent addictions in history. The World Health Organization estimates that over 6 million deaths per year are caused by tobacco and that over half a trillion dollars of economic damage are associated with tobacco use (1,2).

Addiction can be described as a persistent state in which there is diminished capacity to control compulsive drug-seeking, regardless of negative consequences (3). Most smokers identify tobacco use as harmful and express a desire to reduce or stop using it. Unfortunately, relapse rate among those who attempt quitting without assistance is hovering around 85% with the majority resuming the habit within a week (4). Numerous medications for tobacco dependence have been successful in increasing immediate abstinence rate, including nicotine replacement therapy, bupropion, and varenicline. However, long-term outcomes are relatively low, with 6 months' abstinence rate ranging between 19% and 33% (5).

The addictive effects of smoking arise primarily from the actions of nicotine on the central nervous system (6). This

psychoactive constituent of smoking tobacco stimulates the mesolimbic dopamine system, which originates in the ventral tegmental area and projects to reward-related brain areas such as the prefrontal cortex (PFC) and nucleus accumbens (7). Nicotine also alters the capacity of gamma-aminobutyric acidergic pathways to inhibit dopaminergic activity, and chronic use induces long-lasting neuroadaptations and altered cortical excitability (7). The clinical relevance of these neuroadaptations is supported by research demonstrating that decreased activity of reward-related circuitries during withdrawal correlates with levels of craving and relapse and continued nicotine consumption (8).

One tool that may potentially manipulate this circuitry is repetitive transcranial magnetic stimulation (rTMS), which can induce dopamine release and also cause lasting changes in neural excitability (9,10). Enduring changes of rTMS involve effects on task performance and cerebral blood flow and alternations of electroencephalography-evoked responses (11). rTMS has been tested as a treatment of various neuropsychiatric disorders associated with abnormal dopamine activity and altered cortical excitability (12–15). Notwithstanding the increasing reliability of rTMS as a clinical instrument, great uncertainty remains regarding the exact relationships between stimulation frequency and neuronal effects. In broad terms, low-frequency rTMS (<1 Hz) is associated with a decrease in cortical excitability, whereas high-frequency rTMS (>3 Hz) was suggested to increase excitability and facilitate neuroplasticity (10,12,13). However, several studies report that high-frequency stimulation can also increase neural inhibition, similar to the effects of electroconvulsive treatment (16,17).

Recent studies demonstrated direct effects of rTMS on cigarette consumption, general craving, and cue-induced craving (18–22). Johann *et al.* (20) and Li *et al.* (21) reported reduced

From the Beer Yaakov Mental Health Center (LD-K, PD, OR, MK), Tel Aviv University, Israel; Department of Life Science (LD-K, AH, YR, AZ), Ben-Gurion University, Beer-Sheva, Israel

Address correspondence to Abraham Zangen, Ph.D., Department of Life Sciences, Ben-Gurion University, PO Box 653, Beer-Sheva 84105, Israel; E-mail: azangen@bgu.ac.il

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craving following a single rTMS session over the left dorsolateral PFC (DLPFC). Eichhammer *et al.* (19) in a cross-over, double-blind, placebo-controlled study demonstrated a reduction in cigarette consumption (measured 6 hours following treatment), but craving levels remained unchanged after two rTMS sessions over the left DLPFC. Amiaz *et al.* (18) found that 10 days of high-frequency rTMS over the left DLPFC reduces cigarette consumption and nicotine dependence, as well as craving provoked by smoking cues. However, this effect tended to dissipate very fast, and the reduction in cigarette consumption did not remain significant at follow-up 6 months later. Moreover, only 10% of smokers who responded to the treatment remained in full abstinence (18). Finally, Wing *et al.* (22) in a placebo-controlled study reported decrease in craving but no change in abstinence rate after a treatment that included 20 sessions of high-frequency rTMS over the bilateral DLPFC in combination with nicotine patch in heavily dependent smokers with schizophrenia. Taken together, these studies suggest that high-frequency rTMS of the DLPFC can attenuate nicotine consumption (18,19) and craving (18,20–22). However, the potency and duration of these effects are limited, and this calls for identification of the most efficacious stimulation parameters.

A possible reason for these incoherent and partial effects on nicotine consumption might be the relatively limited and shallow stimulation area targeted by the standard figure-8-shaped TMS coil, which does not induce direct stimulation of deep cortical areas (23). For example, evaluation of changes in cigarette smoking after brain damage revealed that damage to the insula is significantly more likely to induce smoking cessation than damage that spares the insula (24). This finding is consistent with the crucial role of the insula in cravings for food, cocaine, and cigarettes, as reported by several neuroimaging studies (25–27) and with the role of the insula in processes related to decision-making (28). It is thus plausible that stimulation of deeper areas of the lateral PFC, including the insula, could yield more efficacious and enduring treatment of nicotine addiction. Because some brain areas implicated in the maintenance of addiction, such as the insula, are located deeper in the brain and others receive projections from deeper cortical areas, in the present study, a deep TMS H-coil version was used (23,27–29). The H-coil version used in the present study was designed to induce a distributed and deeper electromagnetic field enabling suprathreshold intensities in both the lateral PFC and the insula. The mixed evidence regarding the laterality of these effects led us to use a bilateral stimulation approach by using a symmetric coil. Within this design, we also suggested that activation of the relevant circuitries by exposure to smoking cues prior to deep rTMS treatment (18) would enhance treatment efficacy.

Methods and Materials

This study was a prospective, double-blind, placebo-controlled, randomized clinical trial performed at Beer Yaakov Mental Health Institute, Israel (2010–2013). The study was approved by the local Institutional Review Board and the Israeli Ministry of Health.

Participants

Consenting participants were recruited by online and written media advertisements. They were screened first by a short telephone interview and then by elaborated interview (Figure S1, Tables S1 and S2 in Supplement 1). Inclusion criteria consisted

of willingness to quit smoking, daily intake of at least 20 cigarettes, failure to respond to previous antismoking treatments, and a self-report of symptoms of mild chronic obstructive pulmonary disease.

All participants were screened for neurological and other contraindications to TMS. Subjects were randomly allocated by using a computerized program, with pack years as the predefined stratification factor, to 6 experimental subgroups (Table 1) forming 3 TMS stimulation conditions (high-frequency, low-frequency, and sham) and 2 smoking cue conditions (cue, no cue).

Interim analysis was carried out midway through the recruitment process in order to determine whether one of the stimulation protocols had been less effective and subsequently to terminate recruitment to that group, in an attempt to maximize the clinical benefit to the remaining participants. This evaluation highlighted poor efficacy of low-frequency stimulation (Figure S1 and Table S3 in Supplement 1). We consequently discontinued recruitment to the 1-Hz groups.

The final analysis was performed in 115 subjects (77 completers). Participants who failed to complete at least 7 days of rTMS treatment were excluded from the main (per-protocol) analysis and had no urine measurements of cotinine changes. Dropout rates varied from 24% to 42% (Figure S1 and Table S1 in Supplement 1) but did not significantly differ among groups ($p = .3$).

In addition to the per-protocol analysis, an intention-to-treat (ITT) analysis of the primary measure (i.e., self-reported cigarette consumption, which was available for most of the subjects) was also conducted for the 115 subjects originally randomized for the study. Fifteen subjects who completed only one rTMS session and did not attend the second visit had no reports of their subsequent cigarettes consumption. For these subjects, we assumed zero change in cigarette consumption.

Deep rTMS

rTMS was administered using a Magstim Rapid² TMS (The Magstim Co. Ltd., Whitland, Carmarthenshire, United Kingdom) stimulator equipped with a unique H-shaped coil design (23,29,30). The H-coil version used in this study was the H-addiction (H-ADD) coil specifically designed to stimulate the insula and the prefrontal cortex (Figure S2 in Supplement 1 for the distribution map of the electric fields and detailed description of the device).

During each rTMS session, the optimal spot on the scalp for stimulation of the motor cortex was localized (Supplement 1), and resting motor threshold was defined. The coil was moved forward 6 cm anterior to the motor spot and aligned symmetrically (over the lateral PFC), and trains of pulses were delivered at 120% of resting motor threshold. High-frequency sessions consisted of 33 trains of 10 Hz each lasting 3 seconds, with an intertrain interval of 20 seconds. Total treatment duration was 760 seconds with 990 pulses. Low-frequency sessions consisted of 600 continuous pulses at 1 Hz.

Sham treatment was performed using a sham coil located in the same case as the real coil and producing similar acoustic artifacts and scalp sensations but inducing only negligible electric fields in the brain (Supplement 1). Participants, operators, and raters were not aware whether an active or sham treatment was

Table 1. Treatment Groups

Frequency	Real				Sham	
	10 Hz (high)		1 Hz (low)		10 or 1 Hz	
Smoking Cue Group Name	Present 10+	Absent 10–	Present 1+	Absent 1–	Present 0+	Absent 0–

applied, as each participant received a personal magnetic card that determined which coil in the helmet would be activated (31).

Evaluation of Nicotine Consumption, Dependence, and Craving

Cigarette consumption was evaluated by subjective self-report and by measurements of cotinine levels in urine samples (32). To correct for the effect of dilution, creatinine levels were analyzed by a colorimetric assay, and a cotinine-to-creatinine (Cot/Cre) ratio was calculated (33). The Fagerström Test for Nicotine Dependence (FTND) (34) and a short version of the Tobacco Craving Questionnaire (sTCQ) (35) were used to evaluate nicotine dependence and craving, respectively.

Presentation of Smoking-related Cues

In the cue condition, each daily rTMS session was preceded by a presentation of the smoking cue, as detailed in Supplement 1.

Experimental Design

Each participant received 10 daily treatments within 2 weeks, followed by 3 nonconsecutive treatments on the following week.

Participants were instructed to abstain from smoking at least 1 hour prior to treatment. Just prior to initiation of each stimulation session, half of the participants were presented with the smoking cue. Participants were then subjected to active high, low, or sham rTMS stimulation.

Daily reports of cigarette consumption were registered, and in addition, a 6-month follow-up was conducted via structured telephone interview. Our equivalent objective measure of cigarette consumption, cotinine in urine, was taken weekly at treatments 1, 5, 10, and 13 or last treatment. All remaining relevant measurements were collected for baseline (prior to the first session) and at final treatment analysis.

Statistical Analysis

Continuous variables were compared using *t* test, analysis of covariance (ANCOVA; using baseline measures as covariates) or nonparametric equivalents. Dependent continuous variables included cotinine levels, self-reported number of cigarettes smoked, FTND score, sTCQ score, age, body mass index, and

pack years. The study hypothesis of no differences among study groups in each parameter was measured as a function of treatment and cue factors (Table S2 in Supplement 1 for detailed statistical analysis description). Effect sizes (ES) are presented as differences between means + standard error.

Significance for pairwise comparisons on all secondary outcomes, continuous or categorical, was established by the Benjamini-Hochberg method (false discovery rate = .05) to correct for multiple comparisons.

Data analysis was performed using SAS version 9.2 software (SAS Institute, Cary, North Carolina). The Pocock correction resulting from one interim analysis was used to set the alpha significance level at .025.

Results

Participant Characteristics

Table 2 presents descriptive statistics for each treatment group. No significant differences were observed at baseline among the various treatment groups.

Nicotine Consumption

Self-Reported Number of Cigarettes. The number of cigarettes smoked per day, as self-reported by the participants before the first treatment session (on the screening day) and after the last treatment session, is presented in Figure 1A. ANCOVA for the change in these values revealed a significant treatment effect, $F_{2,76} = 14.56, p < .0001$. A greater degree of reduction was found in the high-frequency groups than in the placebo groups (ES = $13.2 \pm 2.5, p < .0001$) and compared with the low-frequency groups (ES = $9.9 \pm 3.2, p = .0031$). No significant differences were observed among the low-frequency and sham groups. There was no significant effect of cue (ES = $.07 \pm 2.47, p = .97$) or cue by treatment interaction ($p = .42$). The progressive change over time in the self-reported daily number of cigarette smoked and its statistical analysis are presented in Figure 1B.

ITT analysis compared self-reported number of cigarettes smoked prior to treatment to the number reported on the last available session, per participant. A two-way ANCOVA revealed a significant effect of treatment ($F_{2,106} = 7.73, p = .0007$), such that

Table 2. Baseline Descriptive Statistics

Measure	Study Group ^a						Statistic ^b
	0+	0–	1+	1–	10+	10–	
Number of Subjects (Male/Female)	15 (10/5)	16 (8/8)	7 (4/3)	7 (3/4)	16 (11/5)	16 (12/4)	$\chi^2_5 = 3.7 p = .59$
Mean Age \pm SD	51.6 \pm 10.9	50.2 \pm 7.5	48.3 \pm 10.8	50.1 \pm 12.1	49.9 \pm 12.0	50.3 \pm 9.3	$F_{5,76} = .11 p = .99$
Cigarettes/Day	27.1 \pm 9.8	31.0 \pm 8.1	24.1 \pm 7.0	26.9 \pm 6.6	27.8 \pm 8.5	29.7 \pm 8.9	$F_{5,76} = .85 p = .51$
Mean Pack Years \pm SD	37.4 \pm 14.2	42.5 \pm 14.0	40.0 \pm 24.2	46.0 \pm 26.2	41.8 \pm 15.7	43.3 \pm 20.8	$F_{5,76} = .3 p = .91$
Mean BMI \pm SD	29.7 \pm 4.4	26.1 \pm 5.9	26.3 \pm 5.4	26.1 \pm 3.9	25.8 \pm 5.5	27.8 \pm 5.7	$F_{5,75} = 1.18 p = .32$
Education ^c	0/10/5	2/12/2	0/5/2	0/5/2	1/7/8	1/7/8	$\chi^2_{10} = 10.19 p = .36$
Family Status ^d	3/12	4/12	1/6	3/4	5/11	5/11	$\chi^2_5 = 2.1 p = .83$
Previous Trials ^e (Median)	3	4	1	2	4	3.5	$\chi^2_5 = 8.4 p = .13$
Previous Successes ^f (Median)	1	.5	0	0	1	0	$\chi^2_5 = 2.6 p = .75$
Motivation ^g (Median)	100	100	100	95	100	100	$p = .67$

BMI, body mass index.

^a0, sham; 1, 1 Hz; 10, 10 Hz; +, with cue, –, without cue.

^bChi-square/Kruskal-Wallis/analysis of variance.

^cPrimary education/high-school education/academic education.

^dMarried/not married.

^ePrevious trials to quit in the last 10 years.

^fAbstinent for more than 1 month.

^gRange: 0–100.

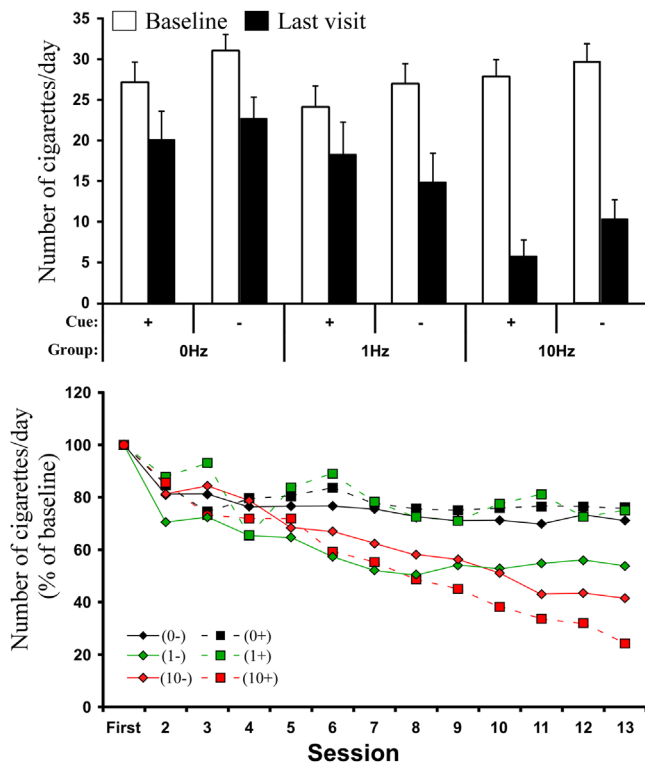


Figure 1. Treatment effects on self-reported cigarette consumption. The subjective self-reported number of cigarettes smoked by the participants prior to initiation of the treatment (on screening day) and on the last TMS session day is shown for all groups: 0+ ($n = 15$), 0– ($n = 16$), 1+ ($n = 7$), 1– ($n = 7$), 10+ ($n = 16$), 10– ($n = 16$). The upper panel presents the mean \pm SEM number of cigarettes smoked in the screening day and in the last treatment day for each group. The lower panel presents the daily change (% of baseline) in number of cigarettes smoked for each treatment session. This analysis revealed significant effects for treatment ($F_{2,70} = 5.58, p = .0057$) and for session ($F_{11,781} = 3.37, p = .0001$), as well as a significant treatment–session interaction ($F_{22,781} = 2.03, p = .0036$). No significant effects or interactions were found for cue. Pairwise comparisons revealed a significantly greater effect of the 10-Hz stimulation than of the sham stimulation from session 6 onward ($p < .05$ for sessions 6 and 7, $p < .01$ for sessions 8–10, and $p < .0001$ for sessions 11–13), whereas a greater effect of the 10-Hz stimulation than with the 1-Hz stimulation became evident from session 10 onward ($p < .05$ for session 10, $p < .01$ for sessions 11–13). No significant differences were found between the sham and 1-Hz groups in any of the sessions. TMS, transcranial magnetic stimulation.

a greater reduction in cigarette consumption was observed in the 10-Hz groups (14.45 ± 1.33) than with the sham (7.01 ± 1.46 ; $ES = 7.44 \pm 1.98, p = .0003$) and 1-Hz (8.56 ± 1.99 ; $ES = 5.89 \pm 2.39, p = .0153$) groups. No significant differences were found among the 1-Hz and sham groups ($p = .53$). In addition, no significant effect was found for cue ($p = .30$) or for treatment by cue interaction ($p = .13$).

Cot/Cre Measurements. Comparison of the change in Cot/Cre ratio values among the treatment groups is presented in Figure 2. Two-way ANCOVA of the changes in Cot/Cre between the screening day before the first treatment and the last session revealed a significant treatment effect ($F_{2,67} = 8.77, p = .0004$). Pairwise analysis revealed higher reduction in the 10-Hz treatment compared with 1-Hz treatment ($ES = 23.2 \pm 10.3, p = .028$) and compared with the sham treatment ($ES = 32.8 \pm 8.0, p = .0002$). Nonsignificant cue effect ($F_{1,67} = 4.06, ES = 15.9 \pm 7.9, p = .048$) was found and the interaction of treatment and cue was

also nonsignificant ($F_{2,67} = .09, p = .9$). Overall, cue exposure induced a marginal reduction in nicotine consumption in all groups, and specifically, the cue exposure in the 10-Hz group tended to induce a greater reduction in nicotine consumption. The progressive change in Cot/Cre ratio over time and its statistical analysis are presented in Figure 2B.

The objective (Cot/Cre ratio) and subjective (self-reported number of cigarettes smoked) measures for nicotine consumption were altogether highly correlated ($r = .61, p < .0001$).

Treatment Responsiveness and Abstinence

Response rates, defined as the proportion of subjects in each group who reduced cigarette consumption by 50% from screening to end of treatment (Figure 3A), were higher in the 10-Hz groups than in placebo groups ($\chi^2_1 = 21.4, p < .0001$) or 1-Hz groups ($\chi^2_1 = 10.2, p = .002$). The response rates for the 1-Hz groups were not significantly different from that of the

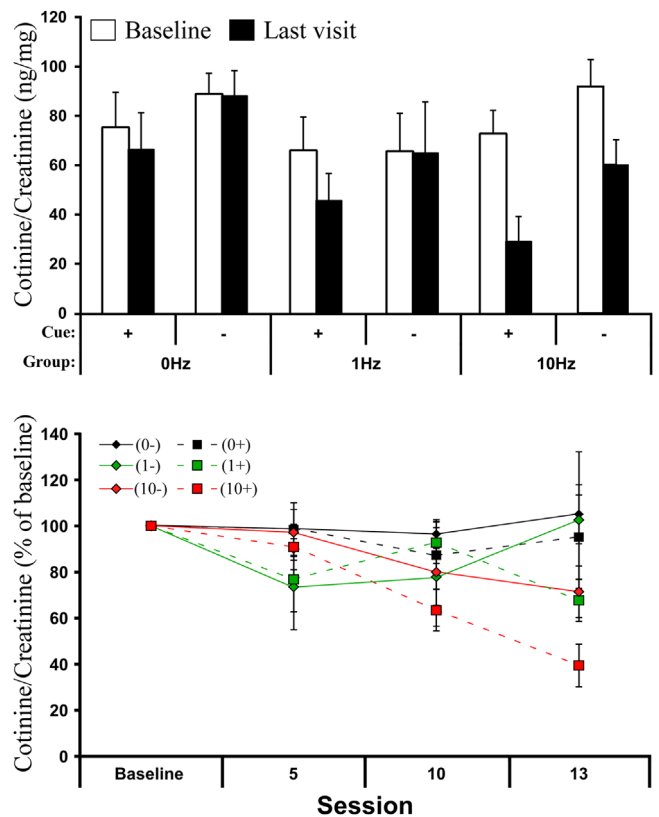


Figure 2. Treatment effects on urine cotinine levels. Cotinine and creatinine levels were measured in urine samples taken before, during, and after treatment. Data are Cot/Cre ratios to correct for dilution effects. Cotinine measurements were available for 68 subjects. Groups were: 0+ ($n = 12$); 0– ($n = 15$); 1+ ($n = 6$); 1– ($n = 6$); 10+ ($n = 15$); 10– ($n = 14$). The upper panel presents the mean Cot/Cre ratio \pm SEM for each group before and after the treatment. The lower panel presents the weekly change in Cot/Cre levels relative to the baseline measurement. This analysis revealed a significant effect for treatment ($F_{2,62} = 4.28, p = .0182$) and a significant treatment–session interaction ($F_{4,126} = 2.71, p = .0332$). No significant effects or interactions were found for cue. Pairwise comparisons revealed a significant difference between the 10-Hz group and the sham group from session 10 onward ($p < .05$ for visit 10, $p < .01$ for visit 13), whereas a significant difference between the 10-Hz group and the 1-Hz group became evident only in session 13 ($p < .05$). No significant differences between the sham and 1-Hz groups were found in any of the time points. Cot/Cre, cotinine/creatinine ratio.

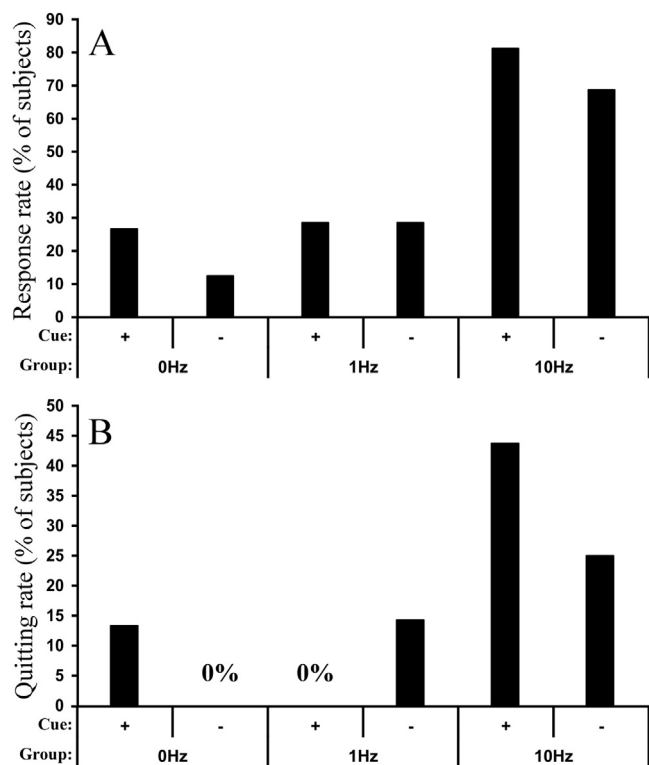


Figure 3. Response and abstinence rates at the end of treatment. Response (**A**) for each subject was defined if cigarette consumption (according to the self-reported number of cigarettes smoked/day) was reduced by at least 50% in the last treatment session relative to that on the screening day just prior to the initiation of treatment. Abstinence (**B**) for each subject was defined based on the self-reported measure (complete abstinence) which was corroborated by the objective cotinine test (undetected in the last urine sample). 0+ ($n = 15$), 0- ($n = 16$), 1+ ($n = 7$), 1- ($n = 7$), 10+ ($n = 16$), 10- ($n = 16$).

placebo group ($\chi^2_1 = .45$, $p = .49$). No significant effect of cue was observed ($\chi^2_1 = 1.2$, $p = .26$).

Abstinence rates at the end of treatment were based on self-reports confirmed by cotinine measurements (Figure 3B). Abstinence rates were significantly greater in the 10+ and 10- groups (43.75%, 25%) than in the placebo groups (13.3%, 0%, respectively; $\chi^2_1 = 6.1$, $p = .039$). The differences among the 1-Hz groups (0%, 14.3%, respectively) were marginally significant ($\chi^2_1 = 3.66$, $p = .075$). Abstinence rates for the 1-Hz groups did not statistically differ from those of the placebo groups ($\chi^2_1 = .005$, $p = .94$). Exposure to cue just prior to each treatment session did not induce a statistically significant effect ($\chi^2_1 = 1.6$, $p = .2$).

Nicotine Dependence (FTND)

Changes in FTND scores from the first to the last session (Figure 4) were analyzed by ANCOVA, revealing a significant treatment effect ($F_{2,73} = 4.34$, $p = .017$). Pairwise analysis showed greater reductions in the 10-Hz groups than in the 1-Hz groups ($p = .045$) or the sham groups ($p = .0144$). No significant effect of cue was found ($F_{1,73} = .66$, $p = .41$). However, there was a significant treatment by cue interaction ($F_{2,73} = 3.77$, $p = .028$), suggesting a selective effect of cue in the high-frequency treatment group. This interaction was further broken down, revealing greater reduction in the 10+ group than in the 0+ ($ES = 2.02 \pm .65$, $p = .0106$), 0- ($ES = 2.51 \pm .67$, $p = .0044$), 1+ ($ES = 2.73 \pm .81$, $p = .0066$), and 10- ($ES = 1.85 \pm .64$, $p = .0143$) groups. In

contrast, the 10-, 1+, and 1- groups were not statistically different from either the 0+ or 0- group. The 10- group was not statistically different from either the 1+ or 1- group.

General Craving (sTCQ)

Changes in sTCQ scores from the first to the last session were analyzed by ANCOVA, revealing no significant treatment or cue effects. However, the treatment by cue interaction was marginally significant ($F_{2,73} = 2.5$, $p = .08$). Pairwise statistics revealed no significant group differences for sTCQ scores.

Abstinence and Consumption 6 Months After Treatment Completion

A total of 69 participants completed follow-up evaluation of self-reported daily consumption of cigarettes. Five participants were excluded from analysis due to enrolment in another treatment during this period. Two-way ANCOVA revealed a significant effect of treatment ($F_{2,62} = 5.71$, $p = .006$). Pairwise comparisons revealed that the reduction in cigarette consumption in the 10-Hz groups (11.68 ± 2.25) was significantly greater than that in the sham groups ($.35 \pm 2.49$; $ES = 11.33 \pm 3.35$, $p = .0026$) but not compared to those in the 1-Hz groups (6.57 ± 3.53 ; $ES = 5.11 \pm 4.18$, $p = .1533$). The sham and 1-Hz groups were not significantly different from each other ($p = .159$). No significant effect of cue ($F = .04$, $p = .84$) and no significant treatment by cue interaction were found ($F = 1.19$, $p = .31$).

Continuous abstinence rates (i.e., quitters who remained non-smokers for at least 6 months [Figure 5]) were greater in the 10+ and 10- groups (33% and 23%, respectively) than in the 0+ and 0- groups (9% and 0%, respectively) with marginal significance ($p = .06$). On the other hand, abstinence rates in the 1+ and 1- groups (0% and 14%, respectively) were not different from those in the sham controls. Although it was nonsignificant, we observed a trend toward higher abstinence rates in the 10+ group than in the 10- group (Figure 5).

Discussion

This study examined effects of multiple treatment sessions with deep rTMS over the lateral PFC and insula, using either high- or low-frequency pulses, on cigarette dependence, craving, and consumption.

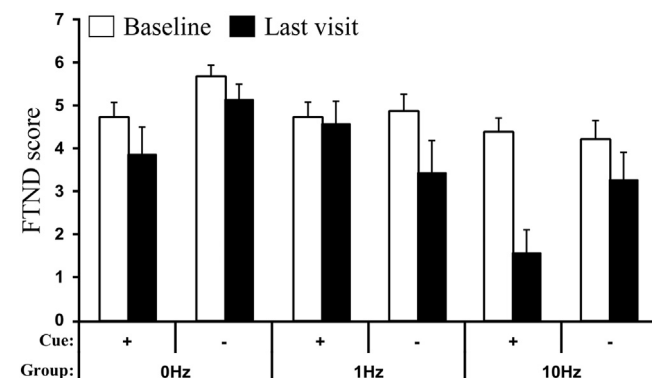


Figure 4. Treatment effects on nicotine dependence. The FTND questionnaire scores before and after the treatment are presented as the group mean FTND score \pm SEM. 0+ ($n = 15$), 0- ($n = 16$), 1+ ($n = 7$), 1- ($n = 7$), 10+ ($n = 16$), 10- ($n = 16$). FTND, Fagerström Test for Nicotine Dependence.

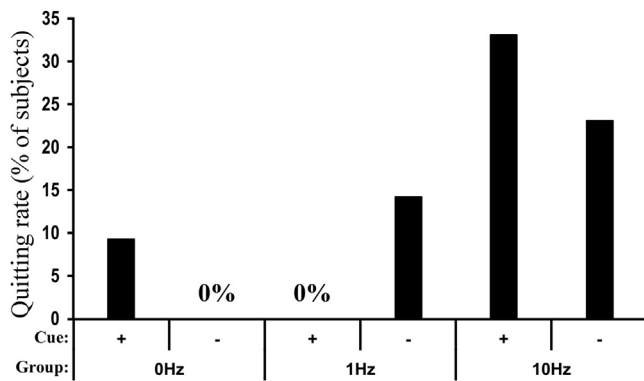


Figure 5. Abstinence rates after 6 months. Rates were calculated for all groups by using subjective self-reported number of cigarettes 6 months after the last treatment session. Groups were 0+ ($n = 11$); 0- ($n = 13$); 1+ ($n = 5$); 1- ($n = 7$); 10+ ($n = 15$); 10- ($n = 13$).

To the best of our knowledge, this is the first large scale clinical trial of rTMS in the treatment of smoking addiction that demonstrates a decrease in cigarette consumption with an indication for an enduring smoking cessation effect. The current study extends our earlier study showing effect of 10 daily sessions of high-frequency stimulation with standard TMS on nicotine dependence and consumption (18). The earlier study showed reduction in cigarette consumption which was not accompanied by significant quitting rates, and the effect dissipated within 6 months (18). There are several possible explanations for the differences between the two studies. First, the deep TMS coil used in the current study could affect more relevant addiction-related neural networks than those affected by the standard figure-8-shaped coil used in the earlier study. The H-ADD coil used in the present study targets deeper PFC areas including the insula, which may be a key region where neuroadaptations can cause effective and sustainable changes in addiction-related reward circuitries (36). Furthermore, the electromagnetic field of the H-ADD coil spreads bilaterally in contrast to the unilateral stimulation induced by standard coils. The bilateral stimulation simultaneously may have enhanced the desired behavioral change in risk taking, associated with chronic smoking (37).

The lack of effect on craving may appear inconsistent with several earlier studies demonstrating a transient effect of rTMS on nicotine craving (20,22). Li *et al.* (21) showed a significant reduction in cue-induced craving following a single intensive session of rTMS, and similar findings on general craving were reported using 2 (20), 5 (22), and 10 (18) treatments of high-frequency stimulation. Critically, our subjects were instructed to refrain from smoking at least 1 hour prior to treatment, whereas in these earlier studies, participants did not smoke for consecutive 12 or 2 hours, respectively, prior to each treatment (18,19,21). Previous studies have shown that tobacco deprivation enhances craving according to self-reports (38) and that the sTCQ is sufficiently sensitive to detect overnight tobacco deprivation (35). We thus hold that our 1-hour instruction has facilitated a scenario in which nonresponsive subjects smoked their last cigarette an hour before filling out the questionnaire, whereas responsive subjects (as a result of effective treatment) were most probably deprived for a few hours or days prior to taking the sTCQ. Consequently, the time elapsed from the last cigarette consumed to the test was unequally distributed between high-frequency groups and the remaining groups.

Despite this unintended inflated craving in the high-frequency groups, there was a nonsignificant tendency for reduction in general craving.

The present study also suggests an advantage for using a provocation with real-life smoking cue exposure just prior to the high-frequency stimulation treatment. Specifically, the exposure to smoking cue seemed to reduce nicotine dependence, as measured by the FTND. This finding expands the scope of a previous study in posttraumatic stress disorder patients (31), in whom provocation with brief exposure to the traumatic memory cue just prior to the TMS treatment alleviated symptoms and physiological responses to the traumatic memory, whereas a TMS protocol per se (without prior provocation) was not effective. This leads to the idea that rTMS interferes with the reactivated labile memory traces (39), namely the cue-induced craving or inhibitory control circuitry. It has been previously shown that disrupting reconsolidation of drug-related memories (by pharmacological means) reduced cocaine-seeking behavior in animal models (40,41) and attenuated reactivity to *in vivo* smoking cues in humans (42). Nevertheless, the differences between the group that received the cue exposure and the group that did not receive the cue exposure were not significant in most outcome measures. We therefore consider that the effect of cue exposure is more variable than the effect of stimulation frequency. Future studies with larger samples would assist in concluding whether cue exposure is a necessary part of rTMS smoking cessation protocols.

Numerous mechanisms may account for the pronounced therapeutic effects produced in the high-frequency stimulation group. First, prefrontal circuitry has been strongly implicated in the control and regulation of drug-seeking behavior (12,43). The DLPFC is strongly implicated in controlled response inhibition, and high-frequency stimulation of the DLPFC can induce neuro-modulations in the orbitofrontal cortex and anterior cingulate cortex (also implicated in inhibitory control) via descending lateral pathways. Indeed, several studies indicate that such stimulation can directly enhance response inhibition capacity and thereby alter habits (44–47). Thus, we propose that neuro-modulations induced to the prefrontal cortex reinforced participants' ability (who all came to the study with motivation to quit smoking) to exert inhibitory control over the compulsive desire to smoke. Therefore, it is plausible that one of the mediating mechanisms is increased inhibitory control. Second, as mentioned above, rTMS following smoking cue exposure may disrupt circuits associated with craving (21). The effects of deep TMS influence cross-hemispheric cortical and subcortical activity including the insula and neuroanatomically connected brain regions. Indeed, the insula has been previously named "the hidden island of addiction" (28), and repeated session may induce long-lasting synaptic plasticity within this region. Such neuroplastic changes during an ongoing attempt to withdraw the addiction may alter circuits responsible for the maintenance of addiction. Finally, chronic drug use repeatedly activates dopaminergic reward-related pathways (48), whereas withdrawal is associated with attenuated dopaminergic activity, which induces craving and relapse (49–51). Hence, given that both human and animal studies indicate that PFC stimulation can induce dopamine release in the mesolimbic and mesostriatal pathways, it is plausible that the transient stimulus-induced increase in dopaminergic activity "mimics" the effect of the nicotine on the mesolimbic pathway while participants are not smoking. Speculatively, our treatment may facilitate dissociation between the actual consumption of nicotine and the activation of dopaminergic rewarding pathways. In order to establish the exact role of each of these potential

mechanisms and the interplay between them, future research should use simultaneous imaging and stimulation techniques (52,53).

We note several important limitations of the current study. First, the exact time window between each treatment and the last cigarette smoked has not been controlled for in this design. This might have masked the effect of our treatment on craving levels as explained above. Second, dropout rates in this study were high and tended to be higher in both active stimulation groups. This tendency of our sample may be the result of greater probability of mild adverse reactions in these groups (Table S2). However we emphasize that there were no significant differences in dropouts among groups and that our per-protocol and ITT analyses pointed to similar trends. Furthermore, smoking cessation treatment generally exhibits low adherence to treatment, and the current treatment is consistent with this trend. Finally, we did not obtain objective measurements of cigarette consumption (cotinine in urine) in our 6-month follow-up. Instead, we conducted a telephone interview with treatment completers. Despite the overall strong correlation in our sample between self-reported consumption and the measure of cotinine in urine, future studies should verify follow-up cigarette consumption by using biological samples.

In conclusion, this study indicates that deep high-frequency rTMS of the lateral PFC and insula, especially when applied following presentation of smoking cue, reduces nicotine addiction with high and long lasting abstinence rates in treatment resistant smokers. Future studies should determine whether this promising technique may become an established smoking cessation treatment.

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