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

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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

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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 month 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 Rapid^2 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

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