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Brain Stimulation Techniques in the Treatment of Nicotine Dependence: A Review of the Literature

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Abstract

Background: Nicotine dependence accounts for significant mortality, morbidity, and socioeconomic burdens. Its use remains a significant public health concern since it is among the leading causes of mortality worldwide and is the leading cause of preventable death in developed countries. Despite the availability of approved medications to treat nicotine dependence along with cognitive-behavioral therapy, only 6% of the total number of smokers who report wanting to quit each year are successful in doing so for more than a month along with poor abstinence rates. Among alternative therapeutic approaches, attenuation of cue-elicited craving with neurostimulation techniques is a growing area of attention.

Methods: We reviewed the literature on repetitive transcranial magnetic stimulation, intermittent theta-burst stimulation and deep transcranial magnetic stimulation in the treatment of nicotine addiction.

Results: Most of these studies found that neurostimulation techniques are safe and effective in the reduction of craving to nicotine as well as in the reduction of cigarette consumption.

Conclusions: Given these promising results, future controlled studies with larger samples and optimal stimulus parameters should be designed to confirm these findings.

Keywords: Addiction; Nicotine; rTMS, dTMS; ITBS

Introduction

Nicotine dependence in particular account for significant mortality, morbidity, and socioeconomic burdens and it remains a significant public health concern. It is characterized by both tolerance and withdrawal symptoms in relation to nicotine use. In 2011, the World Health Organization [1] reported that tobacco smoking is among the leading causes of mortality worldwide and is the leading cause of preventable death in developed countries with almost 6 million deaths each year [1]. The number of individuals who smoke in developing countries continues to rise with 50% of men and 9% of women compared to 35% of men and 22% of women in developed countries [1]. More than half of cigarette smokers express a desire to quit, 72–90% of smokers attempting to quit will have relapsed by 1-year following their quit date [2,3].

Despite the availability of approved medications to treat nicotine dependence (sustained release buproprion, varenicline, nicotine chewing gum, skin patch and nasal spray inhaler and lozenges) including nicotine replacement (substitution) as well as cognitive-behavioral therapy (CBT), only 6% of the more than one billion smokers who report wanting to quit each year are successful in doing so for more than a month but with poor abstinence rates of 30% after 12 months [3]. There is thus an urgent need to develop treatments with greater efficacy. Among alternative therapeutic approaches, attenuation of cue-elicited craving with repetitive transcranial magnetic stimulation, theta-burst stimulation or deep transcranial magnetic stimulation is a growing area of attention in nicotine addiction research.

Nicotine is the principal chemical substance of tobacco smoke, resulting in addiction and can enhance glutamate transmission in cortical pyramidal neurons, can increase the levels of norepinephrine in striatal neurons, releases serotonin from the dorsal raphe neurons and activate nicotinic cholinergic receptors [4-6]. Repeated exposure to nicotine can cause long-term neural adaptations in some systems such as the activation of N-acetylcholine receptors (nAChRs) in the ventral tegmental area and increases DA levels in mesolimbic brain structures which project to reward-related brain area such as the prefrontal cortex (PFC), nucleus accumbens, amygdala and hippocampus [7]. Neuroimaging studies in nicotine dependence that have used drug-cue paradigms have shown that following acute administration of nicotine there is a reduction in global brain activity particularly of the brain reward system [8,9], increased activation in regions known to be involved in sustained attention such as the prefrontal cortex (including the dorsolateral prefrontal cortex) [9], the medial frontal, and orbitofrontal gyri, the insula, the amygdala and the thalamus [9,10], as well as increased DA concentration in the ventral striatum/nucleus accumbens. The insula is a key structure for representing the interoceptive effects of addiction [11] and could be a critical neural substrate of addiction to smoking since it has the highest density of nicotinic acetylcholine receptors in cortico-mesolimbic and in the reward system pathways [12]. The dorsolateral prefrontal cortex (DLPFC) is the most commonly reported locus of activation related to the pathogenesis of craving and it plays a critical role in working memory, in executive function, in regulating craving and in controlled response inhibition associated with cravings [13-15]. The left superior frontal gyrus is implicated in higher cognitive function such as working memory along with its inhibitory effect on cravings [13,16]. Likewise the medial frontal gyrus is associated with higher executive functioning and decision-making [17]. Responses to chronic

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nicotine exposure indicate that smoking enhances neurotransmission through cortico-basal ganglia-thalamic circuits along with structural changes in the medial frontal cortex, thalamus, insula, and anterior cingulate cortex [18,19]. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has both research and therapeutic potentials in psychiatry [20]. TMS is able to modulate cortical excitability and is used to facilitate functional brain mapping of cortical regions [21-23]. It uses a magnetic pulse of high intensity, focused in a limited area, which is administered through a coil. The extremely fast passage of electric current in the coil induces a transient, high intensity magnetic pulse that penetrates through the scalp and reaches the underlying cortex. In the targeted cortical area, the magnetic pulse generates an electric current which if of sufficient intensity induces depolarization of superficial cortical neurons and in interconnected areas beneath the coil. Repetitive TMS (rTMS) is used to induce longer lasting alterations, facilitation, or functional disruptions. In rTMS, trains of several pulses are delivered using various stimulation patterns by providing a repeated stimulation of the scalp at the same point with a frequency ranging from 1 to 20 Hz. The effects of rTMS lead to long-term changes in the functioning of the cortex which vary depending on the frequency of stimulation, resulting in inhibition or facilitation. Generally, HF rTMS (>5Hz) transiently increases cortical excitability [24,25].

The safety of TMS has been reported in a number of studies and the most recent guidelines for its use have been published in 2009 by Rossi et al., [26]. Based on existing data, rTMS appears safe when administered according to recommended guidelines, and its safety record supports its further development as a clinical treatment [27,28]. Although the neural mechanisms underlying rTMS induced reduction of tobacco craving remain elusive, rTMS over the PFC seems to have modulator effect on mesolimbic and on the dopaminergic brain reward system [29]. rTMS may modulate the neuro-adaptations in the reward system involved in nicotine to induce changes in cortical excitability [30], which could lead to changes in cortical plasticity (long-term potentiation). This implies that rTMS can induce reduction in craving and consumption of drugs of abuse as well as neuro-adaptations in the dopaminergic system leading to improved inhibitory control and reduced levels of drug-seeking behaviors [30]. High frequency (HF) rTMS of the left DLPFC as well as nicotine [31,32], have been shown to increase the availability of DA in the caudate nucleus [33], in the striatum and in the orbitofrontal cortex [34]. It is possible that the effect of rTMS treatment on cigarette consumption is mediated by its effect on striatal DA which reduces craving [35]. Moreover, while administration of drugs induces an acute increase in DA levels, during withdrawal dopaminergic activity is reduced.

Methods and Materials

Using the search terms "nicotine", "tobacco", "dependence", "smoking", "transcranial magnetic stimulation", "theta-burst stimulation" and "deep transcranial magnetic stimulation", studies published up from 1966 to June 2015 were found through Medline search. Overall 12 studies were identified that met review criteria and involved the clinical effects of repetitive transcranial magnetic stimulation, intermittent theta-burst stimulation and deep transcranial magnetic stimulation on nicotine dependence that have been published to date and that have been reviewed (Table 1) [36-41]. Nine studies involved rTMS, two involved iTBS and 1 dTMS.

Results

rTMS and nicotine addiction

In the first pilot double-blind crossover study [42] that assessed whether HF rTMS to the LDLPFC could modulate subjective tobacco craving, N=11 tobacco-dependent treatment-seeking smokers were randomly assigned to a single session of active or sham rTMS on consecutive days. The eleven subjects who were under 12-hour abstinent conditions were administered either one active or one sham session of 20 Hz rTMS over the LDLPFC at 90% of motor threshold (MT) with the following stimulus parameters: 20 trains, 2.5 sec on. Levels of tobacco craving were assessed using a 100-point visual analogue scale (VAS) both 30 minutes prior to and following the rTMS treatment. The authors were able to show that 30 minutes following the treatment after active rTMS, the level of tobacco craving was significantly reduced as compared to sham stimulation. These findings motivated further investigation on the efficacy of rTMS as a potential treatment in nicotine dependence to reduce not only the level of craving but also of smoking consumption. Treatment with a single session of HF rTMS over the LDLPFC was, therefore, found to decrease craving level for tobacco in this first pilot study, although this finding was not replicated in the study that followed.

In another double-blind crossover trial aimed at replicating the results of the first one [43], N=14 treatment-seeking tobacco dependent smokers were included comparing single days of active versus sham stimulation. All participants were required to abstain from smoking 12 hours before the rTMS sessions. In a randomized order, each participant received 2 active 20 Hz rTMS and 2 sham stimulation sessions over 4 consecutive days over the LDLPFC with the following stimulus parameters: stimulation intensity 90% MT, 20 trains, 2.5 sec on, 42.5 sec off. Smoking cravings were measured at baseline and 30 min after the rTMS session using a 100-point VAS. The number of cigarettes freely smoked in a 6-hour time period following treatment was also recorded. Active 20-Hz rTMS of LDLPFC reduced significantly the number of cigarettes smoked ad libitum over the 6-h time period ($p<.01$) compared with sham stimulation but levels of craving did not change significantly. Therefore, this second study by the same group demonstrated reduced smoking consumption following rTMS session but no reduction of craving unlike the first study [42].

In a randomized, double-blind, sham-controlled study, Amiaz et al., [44] evaluated the effects of HF rTMS of LDLPFC, combined with either smoking or neutral cues on cigarette consumption, dependence, and craving. N=48 chronic smokers with nicotine dependence (20-70 yrs.) motivated to quit smoking (at least 20 cigarettes/day) were randomized to active and sham stimulation groups. Each group was in turn randomized into two subgroups presented with either smoking-related or neutral pictures just before the daily rTMS intervention. Subjects underwent ten daily 10 Hz rTMS sessions applied over the LDLPFC every week-day followed by a maintenance phase for an additional month in which there were three rTMS sessions (active/sham) in the first week on alternate days followed by one session a week during the following 3 weeks. During the acute and maintenance phases the following stimulation parameters were applied: stimulation intensity of 100% MT, 20 trains per session, 5 sec on, 15 sec off with a figure-8 coil. Sham treatment was identical to active treatment, with the exception that mu-metal plates were attached to the coil in the sham condition thus blocking the magnetic field from reaching the skull. Prior to each rTMS session, participants were asked for the number of cigarettes smoked in the past 24 hours and were exposed for 5 seconds to either smoking (14 pictures: smoking-related activities) or neutral visual cues (14 pictures: non-smoking related activities) and cue-induced craving was evaluated using a VAS as well as a short version of the Tobacco Craving Questionnaire (sTCQ) [45] before and after the presentation of the smoking or the neutral cues and after rTMS

Study	Design	Sample	Stimulus parameters	Assessments	Results
Rose et al., [32]	Controlled rTMS superior frontal gyrus (SFG)	N=15 healthy smokers (18-50 yrs; at least 15 cigarettes/day)	Participants exposed to 1 of 3 conditions: 10 Hz rTMS to SFG; 1 Hz rTMS to SFG; and 10 Hz rTMS to motor cortex, subjects stimulated for 3 periods of 2 minutes and 30 seconds at 90% MT concurrently with presentation of smoking, control cues and smoking cigarette	Craving assessments performed before and after each stimulus presentation and cigarette smoking Craving ratings assessed by Shiffman-Jarvik questionnaire and cigarette evaluation questionnaire after smoking cue presentations	Craving ratings after smoking cue presentations were elevated in 10 Hz SFG condition, whereas craving after neutral cue presentations reduced
Johann et al., [42]	Double-blind, crossover single session of active or sham HF rTMS to LDLPFC	N=11 tobacco-dependent treatment-seeking smokers under 12-hour abstinent conditions	1 active or 1 sham session of 20 Hz rTMS over LDLPFC at 90% MT, 20 trains, 2.5 sec on	Tobacco craving assessed using 100-point VAS 30 minutes prior to and following rTMS	Active rTMS decrease craving level compared to sham stimulation
Eichhammer et al., [43]	Double-blind, crossover active or sham HF rTMS to LDLPFC	N=14 treatment-seeking tobacco dependent smokers required to abstain from smoking 12 hours before rTMS sessions and freely smoked in a 6-hour time period	2 active 20 Hz rTMS and 2 sham sessions over 4 consecutive days over LDLPFC, 90% MT, 20 trains, 2.5 sec on, 42.5 sec off.	Smoking cravings measured at baseline and 30 min after rTMS session with 100-point VAS Number of cigarettes following treatment recorded	20-Hz rTMS of LDLPFC reduced significantly N cigarettes smoked ad libitum over 6-h time period ($p<0.01$) but no reduction of craving
Amiaz et al., [44]	Single-site, randomized, double-blind, sham-controlled study HF rTMS of LDLPFC combined with smoking or neutral cues	N=48 chronic smokers with nicotine dependence (20-70 yrs, 21 m, 27 f) motivated to quit smoking (at least 20 cigarettes/day)	10 daily 10 Hz rTMS, 100% MT, 20 trains, 5 sec on, 15 sec off, figure-8 coil, LDLPFC every week-day followed by maintenance phase for additional month (3 rTMS sessions (active/sham) in 1st week on alternate days followed by 1 session per week during following 3 weeks)	Prior to each rTMS session, participants asked for number cigarettes smoked in past 24 hours and exposed for 5 sec to smoking or neutral visual cues Cue-induced craving evaluated using VAS with Tobacco Craving Questionnaire (sTCQ)	10 daily active rTMS sessions over DLPFC reduced cigarette consumption compared to sham stimulation
Li et al., [48]	Randomized, double-blind, sham-controlled, crossover single active or sham HF rTMS LDLPFC	N=16 (21-60 yrs; 12 m; 4 f) non-treatment-seeking, nicotine-dependent participants (≥ 10 cigarettes/day; 21-60 yrs)	15 min, 10 Hz, LDLPFC, 100% MT, 5-sec on, 10-sec off, 3000 pulses	Fagerstrom Questionnaire of Smoking Urges-Brief (QSU-B), Minnesota Withdrawal Scale-Revised, Tobacco Use History administered Participants exposed to cues before and after rTMS and rated craving after each block of cue presentation	Active rTMS to LDLFPC but not sham significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants from baseline ($p=0.018$)
Sheffer et al., [49]	Single-blind, within-subjects	N=47 smokers (19-55 yrs; right-handed) with no intention to quit and N=19 nonsmokers	3 sessions each of 20 Hz, 110% MT, 1 sec on, 20 sec off; 900 pulses per session; 10 Hz, 110% MT, 1 sec on, 20 sec off; or sham rTMS delivered over the LDLPFC	Tasks administered at baseline and after each stimulation session	HF rTMS of LDLPFC decreased discounting of monetary gains ($p<0.01$), but increased discounting of monetary losses ($p<0.01$), producing reflection effect Stimulation had no effect on cigarette consumption.
Wing et al., [50]	10-week, randomized, double-blind, sham-controlled active or sham bilateral rTMS HF rTMS	N=15 heavily-dependent smokers (18-60 yrs; ≥10 cigarettes/day) with schizophrenia or schizoaffective disorder	20 sessions; 5 treatments/week in weeks 1-4) bilateral 20 Hz rTMS to DLPFC, 90% MT, 25 trains, 1.5 sec on, 30 sec off, 750 pulses on each hemisphere) as adjunct to weekly group therapy and transdermal nicotine (TN; 21 mg) provided in weeks 3–9	Positive and Negative Syndrome Scale [PANSS], and adverse events assessed weekly Cravings assessed once a week immediately before and after rTMS treatment with Tiffany Questionnaire for Smoking Urges (TQSU) and withdrawal with Minnesota Nicotine Withdrawal Scale pre and post-rTMS once during each treatment wk	Active rTMS significantly reduced cravings Despite attenuation of tobacco cravings, rTMS did not increase abstinence rates

Table 1: A summary of studies on neurostimulation and nicotine dependence.

administration. Cigarette consumption was evaluated objectively by measuring urine cotinine levels (a metabolite of nicotine) at screening day and on days 1, 5 and 10 then at each maintenance session. Participants were also administered the Fagerström Test for Nicotine Dependence (mFTND) [46] to evaluate nicotine dependence. In order to evaluate the long-term effects of rTMS treatment on nicotine addiction a follow-up telephone survey was conducted of participants 6 months after treatment termination for all subjects who completed the 10 treatment sessions. Ten daily active rTMS sessions over the DLPFC, independent of exposure to smoking pictures, reduced subjective and objective measures of cigarette consumption and nicotine dependence. It also reduced cue-induced craving and blocked the development of general craving induced by repeated presentation of smoking-related pictures over the 10 days ($P<0.02$). Active rTMS treatment reduced cotinine levels in the urine and self-reported cigarette consumption significantly more than sham treatment. These effects dissipated after the 10 sessions and during the maintenance phase, the reduction in cigarette consumption not being significant 6 months after treatment termination thereby suggesting that longer daily treatment courses may be needed for complete cessation of smoking. Interestingly, there was a trend for lower cigarette consumption in the active rTMS-smoking picture group at 6 month follow-up. Six participants (12.5%) quit smoking completely, but four of them had used additional quitting approaches. Although a strong placebo effect was observed in most of the parameters measured, HF rTMS over the LDLPFC reduced cigarette consumption and nicotine dependence significantly compared to sham stimulation.

In a randomized, double-blind, sham-controlled crossover trial that assessed whether rTMS of the LDLPFC, compared to sham would temporarily reduce the subjective craving triggered by exposure to smoking cues in non-treatment seeking nicotine-dependent adult smokers. N=16 (21-60 yrs) healthy, right-handed, non-treatment-seeking, nicotine-dependent participants (≥ 10 cigarettes/day) were randomized to either a single active HF rTMS (15 min, 10 Hz, 100% MT, 5-sec on, 10-sec off, 3000 pulses) or sham (two electrodes on the scalp below the hairline) over the LDLPFC in two visits with 1 week between visits to avoid carryover effects. Subjects had 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. The FTND, the Questionnaire of Smoking Urges-Brief (QSU-B), and the Minnesota Withdrawal Scale-Revised [47] as well as the Tobacco Use History were administered. Participants were exposed to cues (70 scenic images; neutral: 40 control images; cigarette: 40 cigarette smoking images) before and after rTMS and rated their craving after each block of cue presentation. Active rTMS to the LDLFPC but not sham reduced craving significantly from baseline ($p=0.018$). ($p=0.027$). No significant effects were found between pre and post experiment order ($p=0.27$). Post hoc t-test showed that rTMS of the DLPFC significantly reduced the difference of subjectively rated craving (smoking cue versus neutral control) ($p=0.05$). Inversely, sham of the LDLPFC did not affect craving difference ($p=0.46$). When compared with neutral cue craving, the effect of active rTMS on cue craving was significantly greater than the effect of sham ($p=0.049$). More decreases in subjective craving induced by TMS correlated positively with higher FTND score ($p=0.031$) and more cigarettes smoked per day ($p=0.035$). This is the only study that showed that one session of 10 Hz rTMS of the LDLPFC significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants. Interestingly, greater reductions in nicotine craving following rTMS were seen in patients with higher levels of nicotine dependence [48].

In another within-subject design aimed at stimulating the superior frontal gyrus (SFG; FPz site) which supports cue-induced craving, N=15 healthy smokers (18-50 yrs; at least 15 cigarettes/day) were recruited to investigate the effects of rTMS on subjective responses to smoking versus neutral cues and to controlled presentations of cigarette smoke. On different days, participants were exposed to one of three conditions: 10 Hz rTMS targeting the SFG; 1 Hz rTMS targeting the SFG; and 10 Hz rTMS to the motor cortex (control condition). In each condition, subjects were stimulated for three periods of 2 minutes and 30 seconds at 90% MT rTMS concurrently with the presentation of smoking, control cues and smoking a cigarette. The rTMS stimulation began 20 sec before and terminated 10 sec after each stimulus presentation (or smoking period). Craving assessments were performed before and after each stimulus presentation and cigarette smoking. Compared to 1 Hz rTMS to the SFG or motor cortex, 10 Hz to the SFG resulted in increased cue-induced craving but lower craving during presentation of neutral cues. Craving ratings assessed by the Shiffman-Jarvik questionnaire and the cigarette evaluation questionnaire after smoking cue presentations were elevated in the 10 Hz SFG condition, whereas craving after neutral cue presentations was reduced. Upon smoking in the 10 Hz SFG condition, ratings of immediate craving reduction were attenuated upon smoking in the 10 Hz SFG condition. These findings support the role that the SFG plays in modulating craving reactivity and also suggest that the SFG plays a role in both excitatory and inhibitory influences on craving, consistent with the role of the prefrontal cortex in the elicitation as well as inhibition of drug-seeking behaviors. However, this study does not provide evidence for the utility of rTMS of the SFG for the treatment of tobacco addiction [32].

Cigarette smokers and substance users have been observed to discount the value of delayed outcomes more steeply than non-users. In a single-blind, within-subjects design, N=47 smokers (19-55 yrs; right-handed) with no intention to quit and N=19 nonsmokers underwent three sessions each of 20 Hz (110% MT, 1 sec on, 20 sec off; 900 pulses per session) 10 Hz (110% MT, 1 sec on, 20 sec off), sham rTMS delivered over the LDLPFC. Smokers were required to smoke at least 10 cigarettes per day and have no plans to quit smoking in the next 30 days. Tasks were administered at baseline and after each stimulation session. Smokers were provided with two packs of cigarettes after each session and they were required to smoke one cigarette immediately before beginning session. Afterwards, smokers were invited to repeat each condition after 24 hours of abstinence. HF rTMS of the LDLPFC decreased discounting of monetary gains ($p<0.01$), but increased discounting of monetary losses ($p<0.01$), producing a reflection effect, normally absent in delay discounting. However, stimulation had no effect on cigarette consumption. HF rTMS seems to be most effective when paired with CBT. Hence HF rTMS to the LDLPFC led to lower discounting rates and to a decrease in impulsive decision-making. Hence HF rTMS to the LDLPFC led to lower discounting rates and to a decrease in impulsive decision-making [49].

A sham-controlled study investigated EEG delta power changes induced by HF rTMS of the LDLPFC and its relation to cue-induced nicotine craving in N=14 healthy smokers meeting criteria for tobacco addiction and nicotine deprived smokers. Participants had to abstain from smoking 6 h before the experiment. Effects of 10 Hz rTMS for active and sham (vertex) stimulations on cue-induced nicotine craving and resting state EEG delta power were assessed before and three times within 40 min after rTMS. Both craving ($P=0.046$) and EEG delta power ($P=0.048$) were significantly lower after active stimulation compared to sham stimulation across the whole post stimulation time period assessed. HF rTMS applied to the LDLPFC reduced nicotine craving in short-term abstinent smokers [29].

rTMS in nicotine addiction among schizophrenia patients

The prevalence of cigarette smoking is higher in schizophrenia (45-88%) than in the general population. People with schizophrenia possess multiple vulnerability factors for tobacco addiction [50]. For example, smokers with schizophrenia crave cigarettes more than control smokers [51]. Although pharmacological and behavioral interventions have demonstrated efficacy in schizophrenia, quit rates remain low [50].

Wing et al., [50] examined the efficacy of HF rTMS for smoking cessation in treatment-seeking individuals with schizophrenia or schizoaffective disorder. The authors completed a 10-week, randomized, double-blind, sham-controlled trial of rTMS (20 sessions; 5 treatments/week in weeks 1-4) as an adjunct to weekly group therapy and transdermal nicotine (TN; 21 mg) provided in weeks 3–9 in 15 heavily-dependent smokers (18-60 yrs; ≥10 cigarettes/day) with schizophrenia or schizoaffective disorder. The subjects were motivated to quit within the next month and the target quit date was set at the start of week 3. Subjects were randomly assigned to receive active (N=6) or sham (N=9) rTMS. Bilateral 20 Hz rTMS was administered to the DLPFC at 90% MT for 25 trains (1.5 sec on, 30 sec off, 750 pulses on each hemisphere). Sham stimulation was administered in the single-wing tilt position. Smoking (self-report and breath carbon monoxide [CO] levels), psychiatric measures (Positive and Negative Syndrome Scale [PANSS]), and adverse events were assessed weekly. Cravings were assessed once a week immediately before and after rTMS treatment with the Tiffany Questionnaire for Smoking Urges (TQSU)[52] and withdrawal using the Minnesota Nicotine Withdrawal Scale [52,53], were assessed pre and post-rTMS once during each treatment week. Pre- and post-rTMS data collected in week 1 showed that treatment with active rTMS significantly reduced cravings. rTMS did not alter craving in weeks 2–4. While there was a robust increase in craving following the rTMS session in the sham group, post-treatment cravings in the active group were the same or lower than the pre-treatment assessment. rTMS did not alter craving at weeks 2-4. Smoking consumption was unchanged. Despite attenuation of tobacco cravings, rTMS did not increase abstinence rates. This was a small study resulting in modest power to detect differences between active and sham rTMS groups and evaluation of rTMS's effects after week 1 was limited by provision of behavioral and pharmacological interventions to both groups. As short-term smoking abstinence did not increase craving in these weeks, data obtained in week 1 provides the most sensitive measurement of rTMS effects on craving. This study represents the first evaluation of rTMS in smokers with schizophrenia.

Another study assessed the effects of 10 Hz rTMS over the LDLPFC in decreasing cigarette consumption in schizophrenia patients and included N=35 schizophrenia patients on stable antipsychotic medication who were randomized into one of two groups, N=18 patients were actively stimulated and N=17 patients underwent sham stimulation. The sham rTMS was administered using a purpose-built sham coil that was identical in appearance to the real coil with the same noise but without delivering a substantial stimulus. The following stimulus parameters were applied: 10 Hz, intensity of stimulation 110% MT (110%), 20 trains, 10 sec on, 30 sec off, 21 sessions, 2000 pulses per session. Patients counted the number of cigarettes smoked in the 7 days before treatment, during the whole phase of treatment (21 days), and again for 7 days after treatment. Cigarette consumption was statistically significantly lower in the active group than in the sham rTMS group as early as the first week of stimulation. The authors concluded that HF rTMS over the LDLPFC tends to decrease the number of cigarettes smoked in schizophrenia patients [53].

Other neurostimulation techniques and nicotine dependence

Intermittent theta-burst stimulation (iTBS) has been shown to generally facilitate corticospinal excitability in the human primary motor cortex and it may induce long term potentiation (LTP) similarly to animal models. In a double-blind sham-controlled cross-over study conducted with 10 healthy subjects, Swayne et al., [54] delivered iTBS 60 min after subjects took either 4 mg nicotine or placebo lozenges, and motor-evoked potentials (MEPs) were then recorded for 40 min after the end of stimulation. The effects of iTBS were found to be enhanced and prolonged by nicotine.

Dieler et al., [55] randomized n=74 smokers to either 4 sessions of active iTBS (n=38) or sham (n=36) as add-on treatment to CBT to investigate whether it reduced nicotine craving and improved long-term abstinence (at 3, 6 and 12 months). iTBS was administered with the following stimulus parameters (80% individual MT and at 60% MT for sham with the coil tilted by 45°, 3 pulses of stimulation, repeated every 200 ms for 2 sec at 50 Hz, trains were repeated every 10 sec, with 600 pulses for a total duration of 190 sec). Stimulation was administered before or after CBT meetings. No reduced craving was observed, however the authors showed higher abstinence rates in the active group at 3 months. At 6 and 12 months abstinence rates did not differ significantly. At 12 months, there were significant differences in the dropout rates between the two groups. There was evidence for a beneficial effect of additional iTBS on intermediate nicotine abstinence. More lasting effects might have been achieved by iTBS maintenance sessions in analogy to the treatment of depression. In conclusion, the results of this preliminary study demonstrate that rTMS of the left DLPFC can temporarily suppress cue-induced smoking craving.

In a randomized, sham-controlled study, N=115 smokers who (at least 20 cigarettes/day) and failed previous treatments were randomized to receive 13 daily sessions of either HF, LF or sham stimulation with deep TMS (dTMS; H-coil) targeting the lateral PFC and insula bilaterally following or without presentation of smoking cues. Cigarette consumption was evaluated during the treatment by measuring cotinine levels in urine samples and recording participants' self-reports as a primary outcome variable. High (but not low) frequency dTMS 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. This study further implicates the lateral PFC and insula in nicotine addiction and suggests the use of HF dTMS of these regions following presentation of smoking cues as a promising treatment strategy [56].

Discussion and Conclusion

In this review, we were able to retrieve twelve studies, 9 of which investigated the effect of HF rTMS over the LDLPFC and the SFG (1 study) on nicotine craving and dependence. In a pilot study [42], treatment with a single session of HF rTMS over the LDLPFC was shown to decrease craving level for tobacco whereas in a second study by the same group [43], active 20-Hz rTMS of the LDLPFC reduced significantly the number of cigarettes smoked ad libitum over the 6-h time period ($p<0.1$) compared with sham stimulation although levels of craving did not change significantly. In a third study, ten daily active HF rTMS sessions over the DLPFC, independent of exposure to smoking pictures, reduced subjective and objective measures of cigarette consumption and nicotine dependence significantly compared to sham stimulation, also reduced cue-induced craving and blocked the

development of general craving induced by repeated presentation of smoking-related pictures over the 10 days (P<0.02). In another study [48], HF rTMS of the DLPFC significantly reduced cue craving in comparison to sham (p=0.049). Greater reductions in nicotine craving following rTMS were seen in patients with higher levels of nicotine dependence [48]. Rose et al., [32] found that compared to 1 Hz rTMS to the SFG or motor cortex, 10 Hz to the SFG resulted in increased cue-induced craving but lower craving during presentation of neutral cues. Upon smoking in the 10 Hz SFG condition, ratings of immediate craving reduction were also attenuated upon smoking in the 10 Hz SFG condition. In a first study that included smokers with schizophrenia [50], treatment with active rTMS significantly reduced cravings, smoking consumption was unchanged. Also, HF rTMS over the LDLPFC tends to decrease the number of cigarettes smoked in schizophrenia patients [53]. The effects of iTBS can be enhanced and prolonged by nicotine and these results are consistent with animal models demonstrating nicotinic modulation of facilitatory plasticity [38]. In another study [54], there was evidence for a beneficial effect of additional iTBS on intermediate nicotine abstinence. More lasting effects might have been achieved by iTBS maintenance sessions in analogy to the treatment of depression. Also, in the only study that applied dTMS for the treatment of nicotine dependence [56], high (but not low) frequency dTMS significantly reduced cigarette consumption. The combination of dTMS 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. Overall, the results of this preliminary study demonstrate that rTMS of the left DLPFC can temporarily suppress cue-induced cravings. Overall, the majority of the studies that assessed the therapeutic potential of HF rTMS, iTBS and HF dTMS of the LDLPFC or the SFG found that these techniques can reduce intermittently nicotine craving and number of cigarette consumed mostly after exposure to smoking-related cues. These studies are limited in number and in sample sizes and also have methodological limitations because they are exploratory in nature. Although several studies demonstrated that rTMS of the LDLPFC temporarily reduced impulsivity, cue-induced craving and cigarette consumption through its influence on decision making [57] and inhibitory control [58] as well as dependence (but no increase in abstinence rates) but the results do not necessarily imply that rTMS is effective in helping smoking cessation. None of these studies demonstrated complete abstinence from substance use and few studies [43] evaluated craving in the natural environment of the patients. Currently, the best level of evidence of the effectiveness of rTMS is in the treatment of nicotine dependence showing reduction in craving, consumption, and dependence meaning level B recommendation as probably effective in the treatment of nicotine addiction. Despite the somewhat promising results of research in this area which is limited with scanty data, future research involving randomized, sham-controlled population samples with adequate statistical power should identify the optimal parameters of stimulation in rTMS studies for the most effective and safe treatment of drug addiction, possibly in combination with CBT would produce a positive clinical outcome [55]. Several daily sessions of rTMS sessions will have to be included if possible with longer follow-up studies to induce longer lasting effects.

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