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Review article

Effects of repetitive transcranial magnetic stimulation on nicotine consumption and craving: A systematic review

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ABSTRACT

We performed a systematic review of the studies employing repetitive transcranial magnetic stimulation (rTMS) in subjects with smoking addiction. High-frequency (HF) rTMS over the prefrontal cortex (PFC), in particular the left dorsolateral PFC (DLPFC), might represent a save and innovative treatment tool for tobacco consumption and craving in nicotine-dependent otherwise healthy people. rTMS can be effective for this indication also in patients with schizophrenia, but the results are conflicting and sufficient evidence from large-scale trials is still lacking. Promising results have been obtained using particular techniques for brain stimulation, such as deep rTMS and theta burst stimulation. Multiple-target HF rTMS can also have a potential in smoking cessation. fMRI and EEG recordings have proven to be useful for objectively assessing the treatment effects. TMS is likely to be most effective when paired with an evidence-based self-help intervention, cognitive-behavioral interventions and nicotine replacement therapy. However, the most recent studies employed different protocols and yielded heterogeneous results, which should be replicated in further controlled studies with larger sample sizes and rigorous standards of randomization. To date, no recommendation other than that a possible efficacy of HF-rTMS of the left DLPFC can be made for alternative rTMS procedures in nicotine craving and consumption.

1. Introduction

Neuromodulatory brain stimulation techniques, such as the repetitive transcranial magnetic stimulation (rTMS), can safely modulate neural activity within specific brain regions, thus inducing changes in cortical function and behavior (Hallet, 2000, 2007; Daskalakis et al., 2006; Wagner et al., 2007).

The primary subjective and physiologic effects of smoking are known to result from the central actions of nicotine (Jarvik et al., 2000; Jones and Benowitz, 2002). Decreased function in brain reward systems during nicotine withdrawal seems to be closely related to craving, relapse, and continued nicotine consumption (Epping-Jordan et al., 1998). Especially the mesolimbic dopaminergic reward system is thought to play a pivotal role in reinforcing nicotine effects (Jarvik et al., 2000; Jones and Benowitz, 2002). rTMS delivered at high frequencies could act by mimicking the actions of nicotine on brain reward systems by blocking neuronal uptake of dopamine (Jarvik et al., 2000). Immediate, marked dopamine release after prefrontal high-frequency (HF) rTMS, as suggested by raclopride positron emission tomography (Strafella et al., 2001), may closely resemble pronounced catecholamine-releasing effects resulting from fast forms of nicotine delivery such as cigarette smoking (Benowitz, 1990). Moreover, HF rTMS can influence many neurotransmitters and biogenic amines, including arginine vasopressin2 and serotonin (5-HT) (Ben-Shachar et al., 1997), which are also altered by nicotine intake (Henningfield et al., 1995). Indeed, tobacco smoking is associated with reduction in hippocampal 5-

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Table 1
Studies on rTMS and nicotine craving in the normal polpulation: clinical and demographic characteristics of the subjects enrolled in the studies.

Studies	Nr	Age (y)	G (F/M)	Education (y)	Years smoked	Cigarettes/day	Pack/years	Attempts to quite smoke	FTND score
Eichhammer et al. (2003)	14	35.4 ± 8.9	12/2	11.2 ± 3.6	16.7 ± 10.1	16.8 ± 10	?	3.2 ± 2.6	5.1 ± 1.9
Amiaz et al. (2009)	48	SN 46.0 ± 2.8 7/6		?	26.1 ± 2.8	30 ± 2.8	42.6 ± 6.8	?	?
		SS 48.7 ± 3.5 6/3		?	30.2 ± 3.0	26 ± 2.8	42.1 ± 8.7	?	?
		RN 46.2 ± 3.1 7/7		?	25.2 ± 1.3	29 ± 2.8	38.2 ± 2.4	?	?
		RS 51.5 ± 2.6 7/5		?	32.3 ± 2.6	29 ± 2.8	49.9 ± 9.8	?	?
Chang et al. (2018)	14	43 ± 14.5	1/13	?	> 5	> 10	?	?	?
Rose et al. (2011)	15	40.7 ± 9.6	7/8	?	21.1 ± 10.7	16 ± 5.3	?	?	1.1 ± 0.3
Li et al. (2013)	14	42.6 ± 11.5	4/10	14.5 ± 1.7	20.9 ± 9.2	18.0 ± 6.3	?	?	5 ± 1.8
Sheffer et al. (2013)	66	41.3 ± 10.4	26/40	13.4 ± 2.3	?	21.23 ± 11	?	?	5.3 ± 2.0
Dieler et al. (2014)	74	a 46.7 ± 10.1	22/16	?	28 ± 11.2	21.7 ± 5.1	?	2.1 ± 1.8	5.0 ± 1.6
		s 46.3 ± 9.5	12/24	?	27.3 ± 7.5	22.9 ± 6.6	?	3.2 ± 4.6	4.7 ± 1.6
Dinur-Klein et al. (2014)	74	**0** + 51.6 ± 10.9	5/10	0/10/5 *	?	21.7 ± 9.8	37.4 ± 14.2	?	?
		0- 50.2 ± 7.5	8/8	2/12/2 *	?	31.0 ± 8.1	42.5 ± 14.0	?	?
		1 + 48.3 ± 10.8	3/4	0/5/2 *	?	24.2 ± 7.0	40.0 ± 24.2	?	?
		1- 50.1 ± 9.5	4/3	0/5/2 *	?	26.9 ± 6.6	46.0 ± 26.2	?	?
		10+ 49.9 ± 12	5/11	1/7/8 *	?	27.8 ± 8.5	41.8 ± 15.7	?	?
		10- 50.3 ± 12	4/12	1/7/8 *	?	29.7 ± 8.9	43.3 ± 20.8	?	?
Pripfl et al. (2014)	11	29.2 ± 5.5	6/5	?	> 1	> 10	?	?	3.6 ± 1.6
Trojak et al. (2015)	37	a 47.6 ± 13.5 8/10	12.5 ± 2.7	28.5 ± 11.4	?	26.7 ± 11	3.9 ± 2.1	7.8 ± 1.1	
		s 42.3 ± 12.12	9/10	13.8 ± 3.6	25.8 ± 1.3	?	26.5 ± 18.2	3.7 ± 3.0	7.7 ± 0.9
Sheffer et al. (2018)	29	a 49.5 ± 10.4	6/8	?	5–20	?	?	?	?
		s 49.7 ± 5.0	6/9						

Nr = number; *y* = years; *a* = active; *s* = sham; SN = sham-stimulated group exposed to ‘neutral’ pictures; SS = sham-stimulated group exposed to ‘smoke’ pictures; RN = real-stimulated group exposed to ‘neutral’ pictures; RS = real-stimulated group exposed to ‘smoke’ pictures; 0 + = sham with cue; 0 - = sham without cue 1 + = 1 Hz with cue; 1 – 1 Hz without cue; 10 + = 10 Hz with cue; 10 − = 10 Hz without cue; * = primary education/high-school education/academic education; FTND = Fagerström Test of Nicotine Dependence.

HT (Balfour and Ridley, 2000) which may be reversed by rTMS-induced increase in hippocampal 5-HT concentrations (Ben-Shachar et al., 1997). These biological properties of HF rTMS may explain why even daily sessions of active rTMS were able to reduce cigarette smoking, while acute doses of bupropion, a norepinephrine/dopamine-reuptake inhibitor frequently used as an aid for smoking cessation, failed to reduce smoking (Cousins et al., 2001).

The findings of fMRI studies suggest that dorsolateral PFC (DLPFC) builds up value signals based on knowledge of drug availability, and support a model wherein aberrant circuitry linking DLPFC and orbitofrontal cortices may underlie addiction (Hayashi et al., 2013). The DLPFC is the most commonly reported locus of activation related to the pathogenesis of craving and plays a critical role in regulating craving and in controlled response inhibition associated with cravings (Brody et al., 2002; McBride et al., 2006). On the other hand, the DLPFC is critically involved in processing the craving of other drugs such cocaine (Garavan et al., 2000) and alcohol (George et al., 2001; Myrick et al., 2004).

We aimed to perform a systematic review of the studies employing rTMS techniques in subjects with nicotine assumption and craving. Since there is relevant literature correlating subjective craving of tobacco with objective amount of smoking (i.e. Van Den Eijnden et al., 2003; Cassidy et al., 2018), also this subjective outcome measure was included in this review.

2. Transcranial magnetic stimulation techniques

If delivered repetitively, TMS has been proven to influence cortical excitability and the metabolic activity of neurons. Indeed, the induced electrical field modulates the neural transmembrane potentials and, thereby, neural activity. The effects of rTMS depend on the intensity, frequency, and number of pulses delivered, the duration of the course, the coil location and the type of coil employed. RTMS can be applied as continuous trains of low-frequency (LF, 1 Hz) or bursts of HF (≥ 5 Hz) rTMS. In general, LF rTMS is thought to reduce, and HF rTMS is thought to enhance excitability in the targeted cortical region (Pascual-Leone et al., 1998; Fitzgerald et al., 2006). The physiological impact of rTMS and other neuromodulatory techniques involves synaptic plasticity, specifically long term potentiation and long term depression.

A r TMS protocol named theta burst stimulation (TBS) employs low intensities and has robust, long-lasting effects in normal subjects (Huang et al., 2005). Different patterns of TBS delivery produce opposite effects on synaptic efficiency of the stimulated cortex. Continuous TBS (cTBS) decreases cortical excitability, while intermittent TBS (iTBS) was shown to increase motor cortical excitability.

Standard coils used in research and the clinic for rTMS are not capable of directly stimulating deep brain regions. The Heased coil (H-coil) is likely to have the ability of deep brain stimulation without the need of increasing the intensity to extreme levels (Zangen et al., 2005)

3. Methods

A literature review was conducted using MEDLINE, accessed by Pubmed (1966 – June 2019) and EMBASE (1980 – June 2019) electronic databases. The following medical subject headings (MeSH) and free terms were searched: “transcranial magnetic stimulation”, “repetitive transcranial magnetic stimulation”, “theta burst stimulation”,“smoking”, “nicotine”, “cigarettes”, “tobacco”, “craving”, “consumption”, “addiction”, “dependence”, “abstinence”. Notably, independent variables such as nicotine consumption or craving were specifically sought.

Only original articles written in English were considered eligible for inclusion and review articles were excluded. For the selected titles full-text articles were retrieved, and reference lists of them were searched for additional publications. The principal investigators of the included studies were contacted in those cases in which useful informations were missing or incomplete. Titles and abstracts of the initially identified studies were screened independently by two review authors, in order to determine if they satisfied the selection criteria. The reviewers then assessed the methodological quality of each study and risk of bias, focusing on blinding. This search strategy yielded 17 results. After reading the full papers, one of them was excluded because no specific TMS data were reported, thereby leaving 16 studies which contributed to this review. Eleven studies were conducted on otherwise healthy subjects, the remaining 5 studies in patients with schizophrenia; the clinical and demographic characteristics of the subjects enrolled in the

Table 2
Studies on rTMS and nicotine craving in patients with schizophrenia: clinical and demographic characteristics of the patients enrolled in the studies.

Studies	Nr	A (y)	A disease (y)	G (F/M)	Education (y)	PANSS total	Years smoked	Cigarettes /day	Pack/year	Attempts to quite smoke	FTND score
Wing et al. (2012)	15	18- 60	?	?	?	≥ 70	?	?	?	?	≥ 4
Prikryl et al. (2014)	35	a 30.4 ± 6.6	3.81 ± 3.3	?	12.0 ± 1.6	48.3 ± 9.5	?	18.56 ± 6.68	19.06 ± 8.64	?	?
		s 34.6 ± 10.7	4.1 ± 5.7	?	12.2 ± 1.8	55.6 ± 7.8	?	13.42 ± 1.51	15.34 ± 2.14		
Huang et al. (2016)	37	a 40.6 ± 3.0	9.4 ± 2.2	?	10.3 ± 1.3	81.9 ± 13.5	?	22.90 ± 4.09	?	?	?
		s 39.4 ± 3.0	10.7 ± 2.4	?	9.3 ± 2.5	80.0 ± 8.0	?	22.50 ± 3.84	?	?	?
Kamp et al. (2017)	67	36.2 ± 10.5	8.4 ± 5.6	12/55	15.4 ± 5.0	83.3 ± 15.6	?	19.9 ± 9.8	?	?	?
		37.9 ± 8.9	12 ± 7.2		14.7 ± 4.3	75.5 ± 14.3	?	22.5 ± 11.2	?	?	?
Kozac et al. (2018)	13	39.5 ± 9.7	?	1/12	13.8 ± 2.1	49.8 ± 7.2	?	20.6 ± 7.8	39.5 ± 9.7	?	7.1 ± 1.5

Nr = number; A = age; y = years; G = Gender; F = female; M = male; a = active; s = sham; PANSS = Positive and Negative Syndrome Scale; FTND = Fagerström Test of Nicotine Dependence.

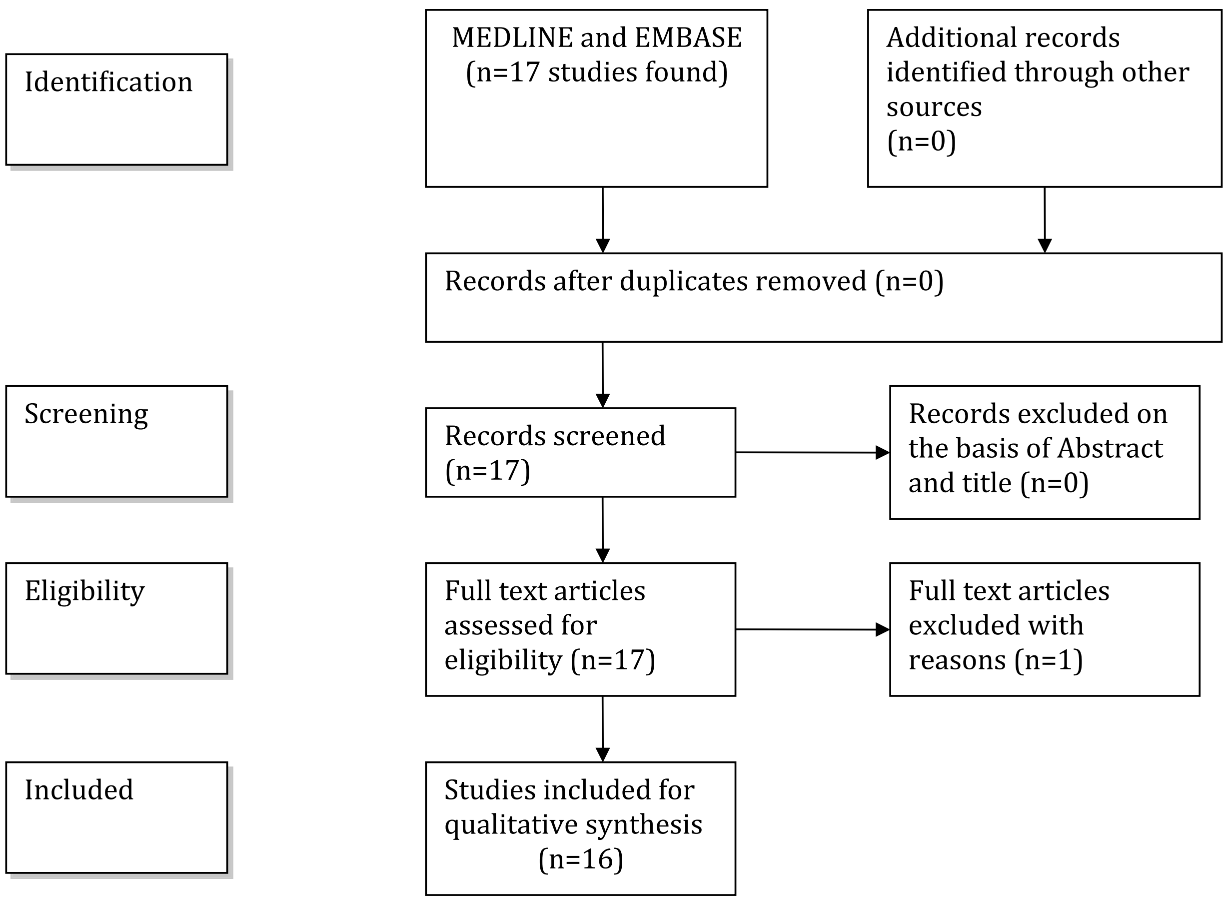

Fig. 1. Flow-chart showing the selection/inclusion process.

studies are showed in Tables 1 and 2, respectively.

A flow-chart (Fig. 1) shows the selection/inclusion process.

4. rTMS and smoking craving in the healthy population

4.1. rTMS over the dorsolateral prefrontal cortex

Acute HF rTMS of frontal brain regions has a modulatory effect on both the mesolimbic and the mesostriatal dopaminergic systems. Eichhammer and colleagues first investigated whether 20-Hz rTMS may have beneficial effects on nicotine smoking and craving. They found that active HF (20 Hz) rTMS of DLPFC reduced cigarette smoking significantly ($p < .01$) compared with sham stimulation in fourteen treatment-seeking smokers (Eichhammer et al., 2003).

In a successive randomized, double-blind, sham-controlled study, ten daily rTMS sessions over the DLPFC reduced cigarette consumption and nicotine dependence (Amiaz et al., 2009). Furthermore, rTMS treatment blocked the craving induced by daily presentation of smoking-related pictures, even if these effects tended to dissipate over time.

Also in a more recent study, one session of HF (10 Hz) rTMS of the left DLPFC significantly reduced subjective craving induced by smoking cues in nicotine-dependent participants (Li et al., 2013).

The increasing activity in the left DLPFC induced by HF rTMS can decrease cigarette consumption as well as delay discounting and decrease impulsive decision-making in a gambling task. Indeed, rTMS was able to decrease discounting of monetary gains and increased discounting of monetary losses, producing a reflection effect, normally absent in delay discounting (Sheffer et al., 2013).

Nevertheless, the neural mechanisms underlying TMS induced reduction of tobacco craving are poorly understood. Electroencephalographic (EEG) delta frequency has been associated with the activity of the dopaminergic brain reward system, which is crucial for nicotine induced effects, and decreases after nicotine administration in smokers. A combined TMS-EEG study aimed to investigate EEG delta power changes induced by HF rTMS of the DLPFC in nicotine deprived smokers and its relation to cue-induced nicotine craving (Pripfl et al., 2014).

Fourteen otherwise healthy smokers meeting ICD-10 criteria for tobacco addiction participated in this study, and were asked to abstain from smoking 6 h before the experiment. Effects of 10 Hz rTMS for verum (left DLPFC) 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 nicotine craving ($P = .046$) and EEG delta power ($P = .048$) were significantly reduced after active stimulation compared to sham stimulation across the whole post stimulation time period assessed, even if changes of craving ratings and EEG delta power did not correlate. Converging evidence suggests that relapse is associated with insufficient activation of the PFC. Delay discounting rate reflects relative activity in brain regions associated with relapse.

HF rTMS of the left DLPFC increases cortical excitability and reduces delay discounting rates, but little is known about feasibility, tolerability, and potential efficacy of this treatment for smoking cessation. To address these questions, eight sessions of 20 Hz rTMS of the DLPFC combined with an evidence-based self-help intervention have been performed in a limited double-blind randomized control trial (Sheffer et al., 2018). In this study including 29 patients, HF-rTMS of the right DLPFC was combined to the use of a standardized manual for smoking cessation and resulted in an increased abstinence rate in the active vs. sham stimulation group. Real rTMS reduced delay discounting of $100, decreased the relative risk of relapse 3-fold, increased abstinence rates, and increased uptake of the self-help intervention (Fig. 2). Clinical, feasibility, and tolerability measures were found to be favorable.

Since relapse is common within a few days after smoking cessation, it has been hypothesized that combining the anti-craving effects of rTMS with Nicotine replacement therapy (NRT) to attenuate withdrawal symptoms could increase abstinence rates in smokers with severe nicotine dependence who quit smoking (Trojak et al., 2015). The authors applied 1-Hz rTMS of the right DLPFC in a series of thirty-seven smokers who failed to quit with the usual treatments, and were randomly assigned to two treatment groups to receive either active or sham treatment. The day after quitting smoking, each patient combined NRT (21-mg patch) with active or sham rTMS (10 sessions) over 2 weeks. Cessation support was then continued with NRT alone using lower-dose patches. Abstinence rates and self-report craving scales were used to assess the therapeutic results during the combined treatment and for up to 12 weeks after quitting. At the end of the combined treatment, there were significantly more abstinent participants in the active rTMS group than in the sham rTMS group ($P = 0.027$). The craving scales analysis revealed that active rTMS ($P = 0.011$) but not sham rTMS ($P = 0.116$) led to a significant decrease in the compulsive factor. However, no lasting rTMS effect was found.

4.2. rTMS over the superior frontal region

Craving ratings in response to smoking versus neutral cues were found to be differentially affected by HF (10 Hz) rTMS applied over the superior frontal gyrus (SFG); 2) LF (1 Hz) rTMS applied over the SFG. Craving after smoking cue presentations was increased 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 as well as the intensity of interoceptive airway sensations were also attenuated (Rose et al., 2011).

In another study, fourteen treatment-seeking smokers were offered a program involving 20 Hz rTMS, which was sequentially directed at the left DLPFC and the medial SFG (SMFC) for 10 days of rTMS treatment with a follow-up for another 25 days (Chang et al., 2018). Ten smokers completed the entire treatment program, and 90% of them did not smoke during the 25-day follow-up time. A significant smoking craving reduction and resting brain activity reduction measured by the cerebral blood flow (CBF) and brain entropy (BEN) were observed after 10 days of 20 Hz rTMS treatments compared to the baseline. These pilot findings of this pilot study are limited by the small size sample, but definitely demonstrated the high potential of multiple-target HF rTMS in smoking cessation and the utility of fMRI for objectively assessing the treatment effects.

4.3. Deep rTMS and theta burst stimulation

It has been hypothesized that deep TMS of the PFC and insula bilaterally can induce smoking cessation (Dinur-Klein et al., 2014). Deep TMS was administered using an H-coil version targeting the lateral PFC and insula bilaterally in 115 adults who smoke at least 20 cigarettes/

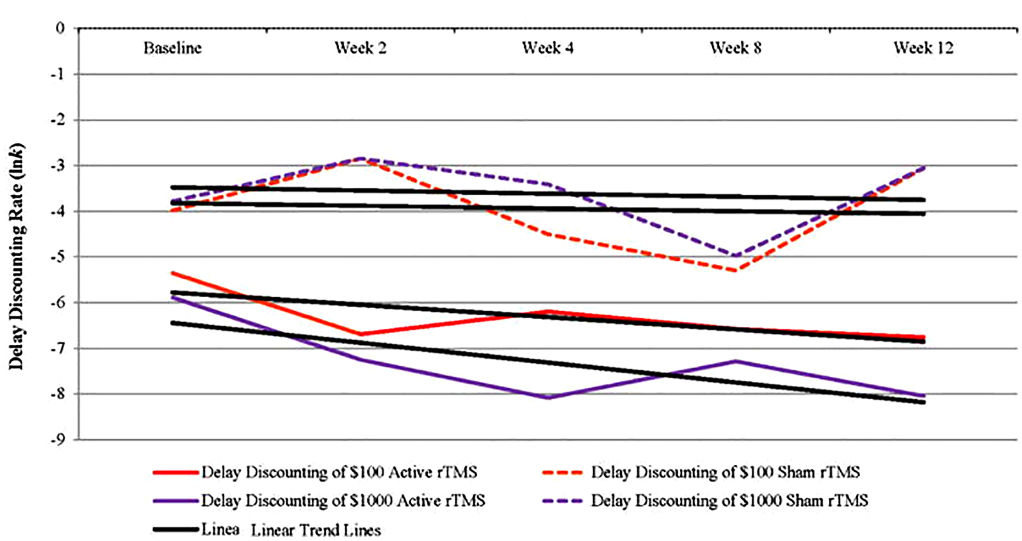

Fig. 2. Treatment effects on self-reported cigarette consumption. The subjective self-reported number of cigarettes smoked by the participants prior to initiation of the deep TMS treatment (on screening day) and on the last TMS session day is shown for all groups: 0+ ($n = 15$), 0− ($n = 16$), 1+ ($n = 7$), 1− ($n = 7$), 10+ ($n = 16$), 10− ($n = 16$). The upper panel presents the mean ± 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. Reproduced with permission from Dinur-Klein et al. (2014).

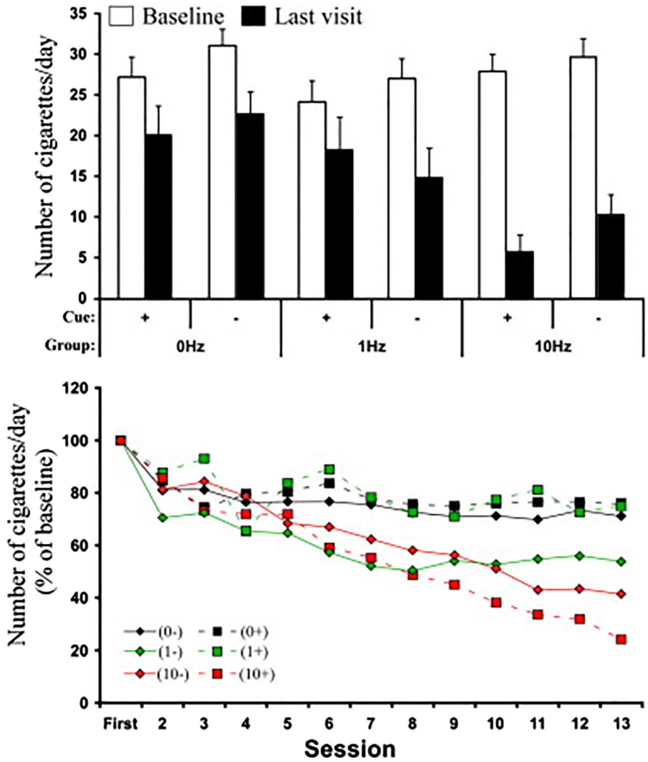

Fig. 3. Differences in delay discounting rates throughout the study by condition. Participants in the active condition (20 Hz rTMS of the DLPFC) demonstrated decreases in delay discounting rates not evident among participants in the sham condition. No differences in delay discounting rates were found at baseline ($100: F (1,25) = 2.78, *p* = .11; $1000: F (1,25) = 3.55, *p* = .07); however, significant differences emerged at the end of the two week stimulation period ($100: F (1,22) = 12.34, *p* < .01; $1000: F (1,22) = 6.66, *p* = .02). For the $100 magnitude, the significant difference between conditions was not maintained 4 weeks (F (1,23) = 1.17, *p* = .29), 8 weeks (F (1,22) = 0.59, *p* = .45, and 12 weeks (F (1,21) = 3.73, *p* = .07) after the quit date. For the $1000 magnitude, the significant difference between conditions was maintained 4 weeks (F (1,23) = 7.70, *p* = .01) and 12 weeks F (1,21) = 10.79, *p* < .01) after the quit date, but not 8 weeks after the quit date (F (1,22) = 1.48, *p* < .24). Reproduced with permission from Sheffer et al. (2018).

day and failed previous treatments were recruited from the general population, and were randomized to receive 13 daily sessions of HF, LF or sham stimulation 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. Dependence and craving were assessed using standardized questionnaires. HF and LF 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 (Fig. 3). This study further highlights the role of the lateral PFC and insula in nicotine addiction and suggests the use of deep HF TMS of these regions following presentation of smoking cues as a promising treatment strategy.

Dieler at al investigated whether 4 sessions of iTBS as add-on treatment to cognitive-behavioral therapy (CBT) reduces nicotine craving and improves long-term abstinence (at 3, 6 and 12 months) (Dieler et al., 2014) Smokers were randomly assigned to a treatment (*n* = 38) or a sham group (*n* = 36). Although the authors failed to find reduced craving, the results showed higher abstinence rates in the treatment group at 3 months. However, at 6 and 12 months, abstinence rates did not differ significantly, but results at 12 months have to be interpreted cautiously due to significant differences in the dropout rates between the two groups at this time point.

5. rTMS and nicotine craving in patients with schizophrenia

The prevalence of cigarette smoking in patients with schizophrenia is higher than in the general population and estimated to lie between 45% and 88%. The high rates of cigarette smoking and smoking cessation failure in schizophrenia patients is thought to be related to prefrontal cortical dysfunction, abnormalities in several neurotransmitter systems (nicotinic, dopaminergic, glutamatergic), and social risk factors. rTMS technique has been systematically studied in this indication also in patients with schizophrenia. Wing and colleague first reported that treatment with rTMS significantly reduced craving in a small number of smokers with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (Wing et al., 2012). However, despite attenuation of tobacco cravings, rTMS did not increase abstinence rates.

Prikryl also aimed to test the ability of HF (10 Hz) rTMS over the left DLPFC to decrease cigarette consumption in schizophrenia patients (Prikryl et al., 2014). The study included 35 male schizophrenia patients on stable antipsychotic medication. The patients were divided into two groups: the first (18 patients) were actively stimulated and the second (17 patients) underwent sham (placebo) stimulation. All patients noted the number of cigarettes smoked in the 7 days before treatment, during the whole stimulation treatment (21 days), and again for a 7-day period after treatment. Cigarette consumption was statistically significantly lower in the actively stimulated patients than in the sham rTMS group as early as the first week of stimulation. No statistically significant correlations were observed in the changes of ongoing negative or depressive schizophrenia symptoms and the number of cigarettes smoked.

Huang et al. (2016) also investigate the effects of HF (10 Hz) rTMS on the amount of cigarette smoking in 37 patients with schizophrenia (Huang et al., 2016). The patients were randomly divided into a treatment group (*n* = 19), which received rTMS on the left DLPFC, and a control group (*n* = 18), which received placebo treatment. Assessments using the Positive and Negative Syndrome Scale (PANSS), Wisconsin Card Sorting Test (WCST), and Montgomery Asberg Depression Rating Scale (MADRS) were applied before and after treatment. Compared to the control group, the number of cigarettes smoked in the treatment group showed a statistically significant reduction in the first week after treatment, whereas there was no significant correlation between the scores on PANSS, WCST and MADRS and the number of cigarettes smoked before and after treatment in both groups. Therefore, HF rTMS to bilateral DLPFC seems to be able to suppress tobacco craving also in smokers with schizophrenia.

However, in another study, 10 Hz rTMS applied over the left DLPFC 5 days per week for 3 weeks failed to reduce the number of cigarettes smoked daily of schizophrenia patients with predominantly negative symptoms (Kamp et al., 2017).

The aim of a more recent study was to determine effects of rTMS for tobacco craving and cognition using a short-term (3-day) human laboratory paradigm (Kozac et al., 2018).

Bilateral active HF (20 Hz) versus sham rTMS stimulation was administered in a counterbalanced, double-blind, cross-over design to thirteen smokers with schizophrenia and fourteen non-psychiatric smoking controls. All subjects were studied at baseline (smoking satiated), after 16 h of smoking abstinence, and after smoking reinstatement. Primary outcome measures included nicotine craving, withdrawal and cognition. Overnight abstinence produced a significant increase in tobacco craving and withdrawal, and impaired verbal memory and visuospatial working memory in both diagnostic groups; these effects were reversed by smoking reinstatement. However, active rTMS did not modify this pattern of results. Moreover, active versus sham rTMS had no significant effects on cognitive outcomes, and was not associated with significant adverse events. These findings suggest

Table 3
Technical aspects and principal findings in the studies on otherwise normal subjects and patients with schizophrenia.

Studies	TMS target	rTMS parameters	Nr of sessions	Outcome measures/Assessment	Principal effects
Normal population					
Eichhammer et al. (2003)	L DLPFC	20 Hz, 90% RMT, 20 trains 2.5 s on, 42.5 s off 1000 pulses/sess, 14 min	4	Smoking craving 100-points VAS at baseline and 30 min	a rTMS ↓ nr cigarettes smoking over 6-h time period but no reduction in craving
Amiaz et al. (2009)	L DLPFC	10 Hz, 100% RMT, 20 trains 5 s on, 42.5 s off 1000 pulses/sess, 14 min	10	Exposure to smoking or neutral cues VAS with sTCQ 100; urine cotinine levels; telephone survey	a rTMS ↓ cigarette consumption and craving (independent to exposure to smoking pictures)
Rose et al. (2011)	SFG	10 Hz and 1 Hz to SFG, 10 Hz	1	Craving rating by Shiffman-Jarvik	a rTMS ↑ craving during presentation of neutral cues
	M1	To M1, 90% RMT, 3 periods of 2 min and 30 s		questionnaire and cigarette evaluation questionnaire after cue presentation	Craving ratings after smoking cue presentation ↑ in 10 Hz SPG condition versus 1 Hz or M1 conditions
Li et al. (2013)	L DLPFC	10 Hz, 100% RMT, 20 trains 5 s on, 10 s off 3.000 pulses/sess	1	FTND, QSU-B, MWS-R; exposure to smoking and neutral cues before an rTMS; craving rates	a RTMS ↓ subjective craving induced by smoking cues in nicotine-dependent participants from baseline
Sheffer et al. (2013)	L DLPFC	20 Hz, 110% RMT, 1 s on, 20 s off 900 pulses/sess	3	Smokers required to smoke 1 cigarette before sessions + after 24 h abstinence	a rTMS ↓ discontinuing monetary gains, ↑ discounting monetary losses, had no effects on cigarette consumption
Dieler et al. (2014)	R DLPFC	iTBS, 80% RMT, 3 pulses every 200 msec for 2 s at 50 Hz, 600 pulses	4	FTND before, all other questionnairs before and after tt, QSU Add-on to CBT	a rTMS ↑ abstinence rates at 3 mo No differences at 6 −12 mo
Dinur Klein et al. (2014)	H-coil	10 Hz, 110% RMT, 33 trains 3 s on, 20 s off 760 s, 990 pulses/session	13	Cotinine levels in urine samples and subjects self-reports, FTND, sTCQ to evaluate dependence/craving	dTMS ↓ cigarette consumption, nicotine dependence Combination tt with smoking cigarettes cues enhanced ↓ in cigarette consumption
Pripfl et al. (2014)	L DLPFC	10 Hz, 90% RMT, 24 trains 5 s on, 25 s off 11.6 min, 1200 pulses	1	Effects on cue induced nicotine craving and resting state EEG delta power before and 3 times within	a rTMS ↓ EEG delta power, and nicotine craving in short-term abstinent smokers
Trojak et al. (2015)	r DLPFC	1 Hz, 120% RMT, 6 trains 60 s on, 30 s off 360 pulses/session	10	Craving assesses with VAS, QSU, self reporting scales, and abstinence rates for up 12 w; Add-on to NRT	a RTMS results in ↓ level of craving and more abstinent subjects; ↓ self-reported compulsive behaviors related to craving
Chang et al. (2018)	L DLPFC	20 Hz, 90% RMT	10	CO level, withdrawal and craving	a rTMS ↑ smoking cessation rate, ↓ BEN in the PFC-
	L SMFC	50 pulses for 2.5 s on, 28 s off		scales, neuroimaging data	insula, ↓ CBF in the right hemisphere
Sheffer et al. (2018)	L DLPFC	20 Hz, 110% RMT 45 trains of 1 s, 20 s off 900 pulses/session	8	FTND, MNWS, ARME, PSS-4, PANAS CES-D, STAI, BIS, delay discounting, FF booklet content uptake, CO level	a rTMS ↓ delay discounting of $ 100 and $ 1000, the risk of relapse 3-fold, increased abstinence rates and ↑ uptake of self-help intervention
Schizophrenia					
Wing et al. (2012)	DLPFC Bil	20 Hz, 90% RMT, 20 trains 1.5 s on, 30 s off 750 pulses/ each hemisphere	20	PANSS, craving assessed with TSQU, withdrawal assessed with MNWS pre- and post-rTMS	a rTMS ↓ tobacco craving, but did not ↑abstinence rates
Prikryl et al. (2014)	L DLPFC	10 Hz, 110% RMT, 20 trains 10 s on, 30 s off 2000 pulses/session	21	PANNS, MADRS, CDSS before and after stimulation	a rTMS ↓ cigarette consumption as early as 1st w tt
Huang et al. (2016)	L DLPFC	10 Hz, 110% RMT, 10 s on, 30 s off 2000 pulse/session	21	PANNS, MADRS, WCST,	a rTMS ↓ nr of cigarettes smoked. No correlation between PANNS, MADRS, WCST and nr. of cigarettes smoked
Kamp et al. (2017)	LDLPFC	10 Hz, 110% RMT, 20 trains 50 pulses/train, 30 s off, 1000 pulse	15	Nr of cigarettes smoked daily PANNS	No changes in the nr of smoked cigarettes
Kozac et al. (2018)	DLPFC Bil	20 Hz, 25 trains 30 pulses/train, 30 s off	6	TQSU, MNWS, SDRT, HVLT	No modifications in tobacco craving and withdrawal No cognitive impairments

Nr = number; L = left; R = right; Hz = Herz; RMT = Resting Motor Threshold; sec = second; min = minute; h = hour; w = week; mo = month; a = active; s = sham; DLPFC = dorsolateral prefrontal cortex; SFG = superior frontal gyrus; M1 = primary motor cortex; ↑ = increases; ↓ = decreases; VAS = Visual Analogue Scale; sTCQ = short version of the Tobacco Craving Questionnaire; *FTND = Fagerström Test for Nicotine Dependence; QSU = Questionnaire of Smoking Urges; QSU-B = Questionnaire of Smoking Urges-Brief; MNWS = Minnesota Nicotine Withdrawal Scale; MWS-R = Minnesota Withdrawal Scale Revised; CBT = cognitive-behavioral therapy; NRT = nicotine replacement therapy; ARME = Abstinence-Related Motivational Engagement; PSS-4 = Perceived Stress Scale-4; PANAS = Positive and Negative Affect Schedule; CES-D = Center for Epidemiologic Studies Depression Scale; STAI = State-Trait Anxiety Inventory; BIS = Barratt Impulsiveness Scale-11; FF= Forever Free; TQSU* = Tiffany Questionnaire for Smoking Urges; SDRT = Spatial Delayed Response Task; HVLT = Hopkins Verbal Learning Task; PANSS = Positive and Negative Syndrome Scale; MADRS = Montgomery and Asberg Depression Scale; CDSS = Calgary Depression Scale for Schizophrenia; WCST = Wisconsin Card Sorting Test; CO = carbon monoxide; tt = treatment; BEN = brain entropy; CBF = cerebral blood flow.

that short-term rTMS administration may not be sufficient enough to modify cognition, craving, and withdrawal outcomes in smokers with schizophrenia. Longer-term, controlled treatment studies examining effects of rTMS on smoking behaviors and cognition in schizophrenia are thus warranted.

Table 3 summarizes the most important technical aspects, the assessments and the principal findings of all the reviewed studies.

6. Discussion

The studies reviewed here have illustrated that some regions of the PFC, in particular the DLPFC and the SFG, play a significant role in craving for cigarettes. HF rTMS of the human PFC has been shown to induce dopamine release in the nucleus cuadatus (Strafella et al., 2001), and effectively stimulates dopamine release in the mesolimbisìc dopaminergic strctures, including the ventral tegmentum, the nucleus accumbens and parts of the PFC, which is involved in the perception of reward and craving (Grace, 2000; Reuter et al., 2005; Spyraki et al., 1983). It has been suggested that excitatory rTMS over DLPFC may be useful in disorders related to subcortical dopamine dysfunction, such as addiction. Moreover, stimulation of the DLPFC can affect cue-induced craving. Indeed, rTMS over the left DLPFC inhibits craving induced by the presence of appetitive food (Uher et al., 2005).

On the other hand, the DLPFC is involved in decision-making (Di Chiara, 2000; Krain et al., 1996), attentional control (Diggs et al., 2013), and inhibitory control (Pripfl et al., 2013). All these processes are typically impaired in people who suffer from addiction.

The decision-processes can be modulated by rTMS (Mitchell, 2004). Because addiction is associated with increased impulsivity and risk-taking leading to altered decision-making processes (Knoch et al., 2006), rTMS of the DLPFC might alter these processes in nicotine addicts leading to reduced impulsivity and enhance inhibitory control, which can lead to a decreased consumption of cigarettes.

Some studies (of Class II/III) reported beneficial effects of HF rTMS (10–20 Hz) of the left DLPFC on cigarette craving and cigarette consumption as well as nicotine dependence. From these results, a level C of evidence (possible effect) was proposed for HF-rTMS of the left DLPFC in the treatment of nicotine craving and consumption.

These findings support the Competing Neurobehavioral Decisions Systems (CNDS) model (Bickel et al., 2007, 2012, 2014; Koffarnus et al., 2013) suggesting that increased activity in the left DLPFC can improve the ability to control the urge to smoke and maintain abstinence.

Changes in EEG delta activity produced by HF rTMS applied to the left DLPFC indicate that the TMS effects are mediated by the reward signaling dopaminergic brain system, which is thought to play a prominent, even if probably not exclusive, role in this stimulation- induced behavioral modulation, making this method a promising smoking cessation treatment candidate.

A more recent sham-controlled study was based on a protocol of focal HF-rTMS, but delivered to the right DLPFC and not the left DLPFC (Sheffer et al., 2018). Sheffer et al. (2013) demonstrated that combining 20 Hz rTMS of the right DLPFC with an evidence-based self-help intervention is feasible, well-tolerated, and potentially efficacious.

Trojak and co-workers also applied LF-rTMS to the right DLPFC and found reduced craving and more abstinent patients in the active vs. sham stimulation group (31). The novel finding of this study was that 1-Hz rTMS combined with NRT improved the success rate of abstinence in smokers during tobacco cessation. This result can be explained by the stimulation-induced reduction in compulsivity.

The results of some studies support the view that the SFG also plays a role in both excitatory and inhibitory influences on craving. These findings are consistent with those of previous experimental studies demonstrating the role of the PFC in the elicitation and inhibition of drug-seeking behaviors, as well as with previous fMRI studies showing activation in responses to smoking cues versus neutral cues in the SFG.

ITBS is an rTMS protocol that is delivered at lower intensities and shorter intervals, improving its tolerability and safety in comparison to conventional rTMS protocols (Huang et al., 2005). Dieler et al. first provided evidence for a beneficial effect of additional iTBS on intermediate nicotine abstinence. Indeed, CBT for smoking cessation might benefit from add-on treatment with iTBS, i.e. a higher abstinence rate was observed in the real as compared to the sham group, at 3 months after the end of therapy. The low number of iTBS sessions might have prevented longer effect, and more lasting effects might be achieved by iTBS maintenance sessions. Notably, changes in craving did not differ between groups, indicating that craving as not a substantial mediator between iTBS and abstinence in our study. It can be hypothesized that different neurobiological processes are triggered in the two protocols, which influence addictive behavior.

A possible reason for these above illustrated somewhat incoherent and incomplete effects on nicotine consumption and craving 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 (Zangen et al., 2005). 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 (Naqvi et al., 2007). It is thus plausible that stimulation of deeper areas of the lateral PFC, including the insula, by means of the H-coil could yield more efficacious and enduring treatment of nicotine addiction. Indeed, a randomized, double-blind, sham-controlled trial design demonstrated that 10 Hz deep TMS using H-coil methods administered bilaterally to the DLPFC and insular cortex was found to reduce short-term biochemically verified cigarette consumption and nicotine dependence levels and increase short-term and long-term smoking abstinence rates (Dinur Klein et al., 2014). Given the more invasive nature of deep rTMS and associated level of tolerability, it could represent a feasible treatment for nicotine and other drugs addiction.

Smoking cessation with rTMS may be related to the potentiation of PFC–mediated cognition. Although smoking has been associated with both enhanced and reduced cognitive functions, TMS and neuroimaging studies have demonstrated reduced GABA levels in the motor and PFC of nicotine-dependent individuals. Reduced GABA levels may explain the severe cognitive deficits observed with heavier smokers and account for the high smoking rates among patients with schizophrenia.

The response to rTMS could be related to working memory (WM) improvement. Indeed, rTMS has been shown to normalize GABAergic-mediated gamma (30–50 Hz) oscillations depending on baseline activity and to improve WM accuracy among patients with schizophrenia (Barr et al., 2013). It is possible that WM may represent a neurophysiologic index for predicting smoking cessation success and an indication that rTMS exerts its effects through the modulation of neuroplasticity. These questions need to be carefully evaluated in future trials.

HF rTMS over the left DLPFC has the ability to decrease the number of cigarettes smoked in schizophrenia patients. However, the findings of the most recent study of smokers with schizophrenia suggest that acute (3 day) administration of rTMS is insufficient to ameliorate such abstinence-induced effects on craving, withdrawal and cognition in these subjects (Kozac et al., 2018). Therefore, longer-term, controlled treatment studies examining effects of rTMS on smoking behaviors and cognition in schizophrenia are warranted.

To elucidate the mechanism of the rTMS effects on cue-elicited craving and cigarette consumption, individual variability in the location of peak cortical activity during cue-elicited craving has been assessed in a functional magnetic resonance imaging (fMRI) study (Hanlon et al., 2012). When viewing nicotine cues all 26 participants had at least one cluster of significant PFC activity ($p < .05$, cluster corrected). Only 62% had peak activity in the medial PFC cluster; in 15% of the participants peak activity was located in either the left lateral PFC or left insula cluster, while peak activity in the remaining 23% was dispersed throughout the PFC. There is considerable individual variability in the location of the cue-elicited 'hot spot' as

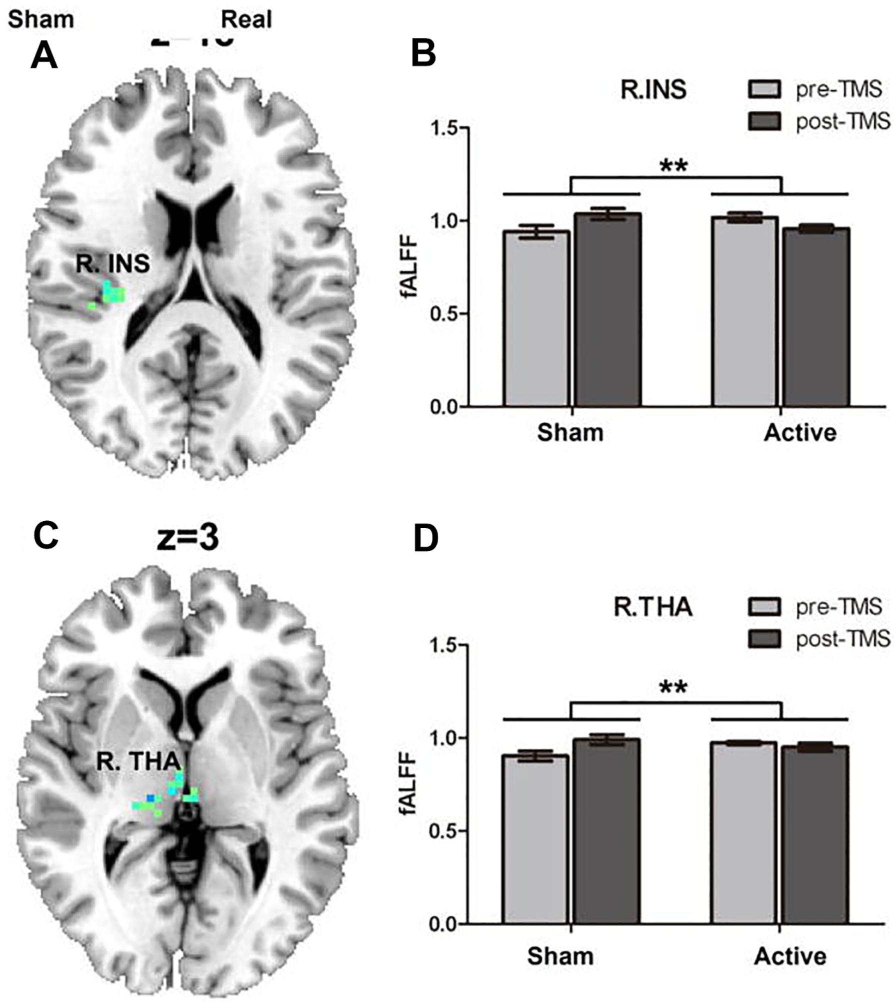

Fig. 4. One session of rTMS of 3000 pulse over the left dorsolateral preforntal cortex reduced brain activity in **(A)** right insula ($p < .05$, AlphaSim corrected); **(B)** The bar graph shows the mean fractional amplitude of low frequency fluctuation (fALFF) of insula (33, −24, 18); **(C)** right thalamus ($p < .05$, AlphaSim corrected); **(D)** The bar graph shows the mean fALFF of right thalamus (15, −24, 3). * $p < .05$, ** $p < .01$. Reproduced with permission from Li et al. (2017).

measured by BOLD activity. Men appear to have a more uniform location of peak BOLD response to cues than women. Consequently, acquiring individual functional imaging data may be advantageous for either tailoring treatment to the individual or filtering participants before enrollment in treatment.

In another study, resting-state fMRI (rsfMRI) has been used to test the effects of rTMS in a group of non treatment seeking smokers (Li et al., 2017). A session of rTMS can reduce activity in the right insula and right thalamus as measured by fractional amplitude of low frequency fluctuation (fALFF). The data also demonstrates that rTMS can reduce resting state functional connectivity between the left DLPFC and the medial orbitofrontal cortex (Fig. 4).

Future studies need to investigate potential laterality differences in the application of rTMS or iTBS.

Limitations of some illustrated pilot studies include a small number of participants and consequent limits on detecting differences, inflexible scheduling procedures, and short-term follow-up. In some pilot studies certain aspects, such as objective abstinence (CO levels), number of cigarettes smoked per day/week by relapsers, or use of nicotine replacement products, have not been systematically assessed.

An additional limitation was that craving responses were in some studies smaller overall in the rTMS sessions than at the screening session. This diminution of response magnitude might have reflected habituation to the smoking cues or distracting effects of the rTMS apparatus or procedure. Furthermore, identifying brain location by skull-based location methods is imprecise, and future studies should use magnetic resonance imaging-based identification of brain regions to be targeted by rTMS.

The modulation of prefrontal structures or neural circuits that involve these structures could be assumed, but this needs to be confirmed in systematic neurobiological studies.

Unlike reduced craving following rTMS of the right DLPFC (Sheffer et al., 2018), the expected processes could not be shown after iTBS. It may be that different neurobiological processes are triggered in the two protocols, which influence addictive behavior; this question, however, will have to be addressed in more basic research studies.

Some studies using rTMS to examine the effects on smoking craving did either not use any cues to induce craving (Eichhammer et al., 2003), or used them only during stimulation (Rose et al., 2011) and for pre-stimulation craving induction (Li et al., 2013; Wing et al., 2012), respectively, but not for post stimulation craving assessment, which was performed using a single question based VAS (Amiaz et al., 2009) or tobacco craving questionnaires (Rose et al., 2011).

One limitation of this review is the use of a subjective outcome, namely craving, in many of the included studies.

In conclusion, the available studies showed heterogenous protocols and resulting data, which should be replicated in further controlled studies with larger sample sizes, rigorous blinding procedures and standards of randomization (Rachid, 2016). Therefore, no new recommendation other than that previously proposed for level C evidence (possible efficacy) of HF-rTMS of the left DLPFC (Lefaucheur et al., 2014) can be made for all these rTMS procedures in cigarette craving and consumption.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112562.

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