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Repetitive transcranial magnetic stimulation reduces cigarette consumption in schizophrenia patients

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ABSTRACT

Introduction: High-frequency repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) seemed to decrease tobacco consumption and craving in nicotine-dependent people without psychiatric disorder or otherwise healthy people. Even if the prevalence of cigarette smoking in schizophrenia patients is high and estimated to be between 45% and 88%, this technique has not been systematically studied in this indication in schizophrenia yet.
The aim of the study: The aim of this study was to test the ability of high-frequency (10 Hz) rTMS over the left DLPFC to decrease cigarette consumption in schizophrenia patients.
Methods: 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. The sham rTMS was administered using a purpose-built sham coil that was identical in appearance to the real coil and made the same noise but did not deliver a substantial stimulus. The rTMS was administered at the stimulation parameters: location (left dorsolateral prefrontal cortex: DLPFC), intensity of magnetic stimulation in % of motor threshold (110%), stimulation frequency (10 Hz), number of trains (20), single train duration (10 s), inter-train interval (30 s), and total number of stimulation sessions (21). In each stimulation session, 2000 TMS pulses were given, with a total of 42,000 pulses per treatment course. 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.
Results: 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 relevant correlations were found in the changes of ongoing negative or depressive schizophrenia symptoms and the number of cigarettes smoked.
Conclusion: High-frequency rTMS over the left DLPFC has the ability to decrease the number of cigarettes smoked in schizophrenia patients.

1. Introduction

The prevalence of cigarette smoking in schizophrenia patients is estimated between 45% and 88%, exceeding almost four times that of the normal healthy population (Wing et al., 2012a,b). The explanation may be seen in neurotransmitter alterations (nicotinic, dopaminergic, and perhaps even glutamanergic) of the brain systems in schizophrenia and social risk factors. Smoking may be also a form of self-medication to reduce the intensity of extrapyramidal adverse symptoms induced by antipsychotic medication, such as neuroleptic dysphoria, to alleviate negative symptoms of schizophrenia, or to improve some parameters of cognitive impairment, such as attention or short-term memory (Levander et al., 2007; Olincy et al., 1997; Wing et al., 2012a,b). Furthermore, schizophrenia patients extract a higher amount of nicotine per cigarette, have higher blood nicotine metabolite levels, and become more easily addicted to nicotine (Olincy et al., 1997). A plausible explanation may be found in the genetic abnormalities of nicotine receptor structures in schizophrenia (Wing et al., 2012a,b). Smoking in schizophrenia could also be due to a shared genetic vulnerability

Abbreviations: ANOVA, analysis of variance; CDSS, Calgary Depression Scale for schizophrenia; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; EMG, electromyography; ICD-10, International Classification of Diseases, revision 10; MADRS, Montgomery and Asberg Depression Scale; MINI, Mini-International Neuropsychiatric Interview; MT, motor threshold; PANSS, Positive and Negative Syndrome Scale; rTMS, repetitive transcranial magnetic stimulation.

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between nicotine dependence and schizophrenia (Chambers et al., 2001). Therefore, there is a lower rate of successful smoking cessation in schizophrenia patients than in the non-psychiatric population. While up to 42% of the healthy population succeeds in smoking cessation, in schizophrenia patients from 10.0% to 27.2% only are successful quitters (Lo et al., 2011; Wing et al., 2012a,b).

Current options for the treatment of nicotine addiction rely on the combination of several modalities. These include nicotine replacement therapy (nicotine patches or gums), varenicline (a nicotinic receptor partial agonist), bupropion (an antidepressant), and psychotherapeutic approaches. However, the treatment options for nicotine addiction can hardly be considered optimal. Schizophrenia patients have even fewer treatment options for quitting smoking due to the possible exacerbation of psychotic symptoms when non-nicotine pharmacotherapy is applied. Surprisingly some recent studies have showed that varenicline is not only effective for smoking cessation in schizophrenia and does not produce exacerbations in psychotic symptoms (Williams et al., 2012), but that psychotic, depressive, and nicotine withdrawal symptoms can be improved during varenicline treatment (Pachas et al., 2012). Despite this promising fact new innovative approaches are needed for treatment of nicotine addiction. Neuromodulation techniques may be the most promising potential treatment options, repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) in particular (Fitzgerald and Daskalakis, 2008; Wing et al., 2013).

However application of rTMS in the treatment of nicotine addiction still represents an innovative research experience in comparison to its use in the treatment of depression, auditory hallucinations, or negative symptoms of schizophrenia. High-frequency rTMS applied over the left dorsolateral prefrontal cortex (DLPFC) reduced both nicotine craving and consumption in nicotine-dependent people (Amiaz et al., 2009; Brody and Cook, 2011; Eichhammer et al., 2003; Johann et al., 2003; Li et al., 2013). It has been postulated that rTMS delivered to the DLPFC affects craving/addiction through its influence on decision making (Fecteau et al., 2010) and inhibitory control (Feil and Zangen, 2010) because risky decision making and difficulty with inhibitory control are traits common to people who suffer from addiction. In addition, a possible mechanism for the effects in addiction of rTMS on frontal brain regions is that this method enhances dopamine release in mesocorticolimbic brain circuitry (Feil and Zangen, 2010), which could alleviate substance use urges by mimicking the dopamine release associated with substance use and withdrawal, thereby diminishing the need to take additional substances. Furthermore, given the ability of brain stimulation to modulate cortical excitability, it has been hypothesized that these stimulations result in neuroadaptations and changes in synaptic plasticity in the brain reward system (Fecteau et al., 2010), which could be relevant for the treatment of addiction (Brody and Cook, 2011). To date one published study also found a positive effect of rTMS on the tobacco craving reduction in schizophrenia (Wing et al., 2012a,b).

Lack of experience of rTMS application in the treatment of nicotine addiction in schizophrenia led us to design and perform the current study. The main aim was to evaluate the ability of high-frequency (10 Hz) rTMS applied over the left DLPFC to reduce the number of cigarettes smoked in schizophrenia patients. A secondary aim was focused on the possible relationship between the reduction of cigarette consumption and the change of negative or depressive symptoms of schizophrenia.

2. Methods and materials

2.1. Participants

The evaluated group included male patients who were admitted for schizophrenia to the Department of Psychiatry of the Faculty of Medicine of Masaryk University and the University Hospital in Brno, Czech Republic. Only those patients who fulfilled the criteria for schizophrenia (F20) according to the International Classification of Diseases, revision 10 (ICD-10) and who were stabilized for at least 6 weeks on the same antipsychotics, and without other psychiatric comorbidities, such as mood, anxiety, or personality disorders, were included in the study. Diagnosis was ascertained by two independent experienced psychiatrists from the medical chart review and with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Only mild intensity of positive symptoms of schizophrenia were allowed: a score of 22 or less on the sum of the 8 Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) positive symptom factor items (P1–P7 and G9 items) and no more than 2 of the items of P1 (delusions), P3 (hallucinatory behavior), P6 (suspiciousness) and G9 (unusual thought content) had a score of 4 or higher. The age of the enrolled patients ranged from 18 to 60 years and all of them smoked at least 10 cigarettes a day for the last 2 years. Patients who had cardiovascular, cerebrovascular, endocrinal, systemic autoimmune, or neurological disease (including epilepsy or abnormal EEG record), or who abused a psychoactive drug, including alcohol, who had an acute risk of suicide at screening, or had such a condition in the past were not included in the study. Absence of psychoactive drug abuse was verified by a toxicology examination of urine for cannabis, amphetamines, and opioids. Only those patients who signed an informed consent form and who had no contraindication for rTMS were admitted to the study. The study was approved by the local ethics committee and complies with the requirements of the Declaration of Helsinki.

2.2. Study design

This study was a double-blind, randomized placebo-controlled study. All patients were assigned to the active or sham (placebo) rTMS groups by software randomly determining the type of stimulation treatment (active to placebo ratio was 1:1). Both forms of rTMS treatment were performed during three consecutive weeks to total number of 15 completed procedures. The patients remained on their prescribed antipsychotic medication during the stimulation therapy. The severity of negative and depressive symptoms before and after the stimulation treatment was evaluated using the Positive and Negative Syndrome Scale (PANSS), Montgomery and Asberg Depression Scale (MADRS) and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1994; Kay et al., 1987; Montgomery and Asberg, 1979). Patients filled out forms prepared in advance to record the number of cigarettes smoked during the 7 days before the treatment started, throughout the stimulation treatment (i.e. 21 days), and again for 7 days after the treatment as a follow-up observation, especially from the 14th to 21st day after the end of the stimulation treatment. They were instructed not to restrict themselves and to smoke as they were inclined in terms of their habits and urges. The patients and raters were blind to condition of stimulation treatment. The rTMS treatments were administered by experienced staff who were aware of the patients' stimulation conditions. The evaluations of the number of cigarettes smoked, clinical status, and rTMS treatment type (i.e. active versus placebo) were carried out in a double-blind design.

2.3. Active and sham rTMS treatments

The rTMS procedure commenced with the determination of the individual patient's resting motor threshold (MT) and the localization of the stimulation site. The MT was registered using electromyography (EMG) attached to the abductor pollicis brevis lat. dx muscle. The resting MT was defined as the lowest stimulation activity that caused at least 5 motor potentials with an amplitude of at least 50 mV in 10 subsequent single impulses. The proper stimulation was performed with a figure-eight stimulation coil over the left DLPFC (tangential to the midline) at a point 5 cm anterior to the scalp position at which the resting MT had been determined. The same type of stimulation coil was used for resting MT detection and stimulation treatment. The rTMS was administered at the stimulation parameters: location (left DLPFC),

intensity of magnetic stimulation in % of MT (110% of MT), stimulation frequency (10 Hz), number of trains (20), single train duration (10 s), inter-train interval (30 s), and total number of stimulation sessions (21). Thus, in each stimulation session, 2000 TMS pulses were given, with a total of 42,000 pulses per treatment course. Sham rTMS was similarly administered using a purpose-built sham coil that was identical in appearance to the real coil and made the same noise but did not deliver a substantial stimulus (Magstim Co. Ltd., UK). The clinical status and technical data of the application, including the temperature of the stimulation coil, were observed throughout the whole application. The Magstim Super Rapid stimulation device was used for the rTMS treatments, and EMG Medelec Synergy was used to evaluate the MT.

2.4. Statistical analysis

Statistical software from StatSoft, Inc. (2011), the STATISTICA (data analysis software system) version 10, was used for data analysis. Owing to the normal distribution of scores (the Shapiro–Wilk W test was used to test for normality), the data were described and processed using parametric statistics. To compare the overall effect of treatment over time for the 2 groups, repeated measures analysis of variance (ANOVA) were performed on the number of cigarettes smoked with group (active versus sham) as the between subject factor and time as the within-subject factor, significance level set at $p < 0.05$. An independent t-test was used to compare the demographics, the number of nicotine cigarettes consumed, and the clinical characteristics of the two groups, and a paired t-test was used to evaluate ongoing changes in the scales and number of nicotine cigarettes smoked. The potential relationship between the ongoing changes in the consumption of cigarettes and negative and depressive symptoms was assessed using the Pearson correlation.

3. Results

3.1. Characteristics of the evaluated group

A total of 102 patients were assessed for eligibility. The group selected for evaluation included 40 right-handed male patients. The excluded patients (N = 62) did not meet inclusion criteria (N = 45) or refused to participate (N = 17). Of the 40 selected patients, 3 patients dropped out before beginning the rTMS series because they refused to participate and 2 patients (one patient from each group) were excluded after randomization during rTMS treatments: 1 for headache (active rTMS) and 1 for failure to cooperate (sham rTMS). With the exception of 1 case of headache (completely recovered with common analgesics), no adverse events were observed during either form of stimulation. For an overview of the clinical trial, see Fig. 1. There was no difference in number of cigarettes smoked per day between the active and sham groups at baseline. The groups also did not differ in terms of demographic or clinical characteristics; see Table 1. The antipsychotic and mood-stabilizing drug profile for the active and the placebo stimulation groups (18/17), respectively, were as follows: amisulpride 1/1, aripiprazole 1/2, clozapine 1/1, clozapine + lamotrigine 1/0, haloperidol 1/0, olanzapine 4/3, olanzapine + amisulpride 1/1, olanzapine + risperidone 1/1, quetiapine 1/3, risperidone 3/2, risperidone + aripiprazole 1/0, ziprasidone 0/2 and zotepine 2/1. No difference in medication of benzodiazepines was found.

3.2. Nicotine cigarette consumption: a comparison between active and sham rTMS groups

The decrease of cigarette usage was statistically significant with significant interaction between treatment type and cigarette usage

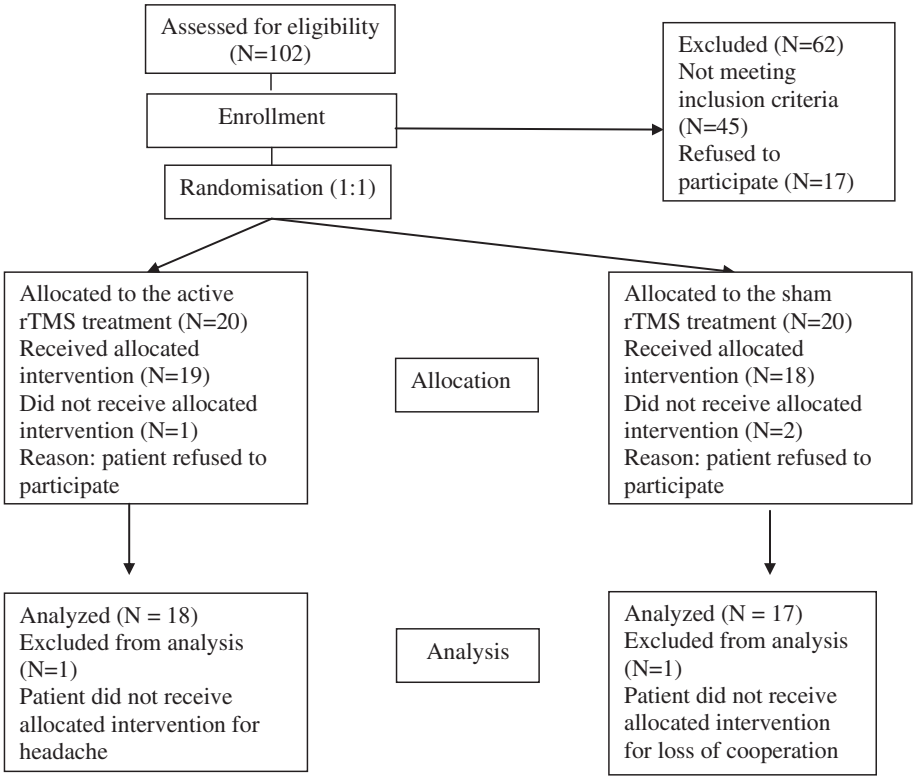

Fig. 1. Flowchart.

Table 1
Comparison of demographic and clinical data of the groups treated with active and sham rTMS.

	Active rTMS group	Sham rTMS group	Statistical analysis
N	18	17	
Demographic data			
Age (years, mean, std. dev.)	30.40 ± 6.56	34.58 ± 10.66	N.S.*
Education (years, mean, std. dev.)	12.00 ± 1.59	12.17 ± 1.80	N.S.*
Duration of schizophrenia (years, mean, std. dev.)	3.81 ± 3.35	4.13 ± 5.71	N.S.*
Diagnoses (ICD-10)			
Disorganized schizophrenia	1	2	N.S.**
Simplex schizophrenia	3	2	N.S.**
Concomitant medication			
First generation antipsychotics (yes/no)	1/17	0/17	N.S.**
Second generation antipsychotics (yes/no)	17/1	17/0	N.S.**
Anticholinergics (yes/no)	0/18	0/17	N.S.**
Mood stabilizers (yes/no)	1/17	0/17	N.S.**
Combinations (yes/no)	3/15	1/16	N.S.**
Chlorpromazine equivalent dose (mean, std. dev.)	214.16 ± 177.29	264.00 ± 148.52	N.S.*
Number of nicotine cigarettes smoked per day (mean, std. dev.)	18.56 ± 6.68	19.06 ± 8.64	N.S.*
Duration of nicotine cigarette smoking in years (mean, std. dev.)	13.42 ± 1.51	15.34 ± 2.14	N.S.*
Baseline psychopathology			
Positive subscale PANSS score (mean, std. dev.)	8.33 ± 2.14	8.31 ± 1.89	N.S.*
Negative subscale PANSS score (mean, std. dev.)	23.61 ± 4.72	20.69 ± 4.54	N.S.*
General subscale PANSS score (mean, std. dev.)	31.72 ± 6.06	31.92 ± 5.33	N.S.*
Total PANSS score (mean, std. dev.)	63.67 ± 10.84	60.92 ± 9.96	N.S.*
MADRS total (mean, std. dev.)	12.72 ± 4.36	10.62 ± 3.53	N.S.*
CDSS total (mean, std. dev.)	1.03 ± 0.82	1.14 ± 1.56	N.S.*
Post-stimulation psychopathology			
Positive subscale PANSS score (mean, std. dev.)	7.61 ± 1.15	8.00 ± 2.08	N.S.* active rTMS: N.S.*** placebo rTMS: N.S.***
Negative subscale PANSS score (mean, std. dev.)	16.61 ± 5.72	18.92 ± 2.72	N.S.* active rTMS: $p < 0.01$*** placebo rTMS: N.S.***
General subscale PANSS score (mean, std. dev.)	24.06 ± 3.81	28.69 ± 4.63	$p < 0.01$* active rTMS: $p < 0.01$*** placebo rTMS: N.S.***
Total PANSS score (mean, std. dev.)	48.28 ± 9.55	55.61 ± 7.76	$p = 0.03$* active rTMS: $p < 0.01$*** placebo rTMS: N.S.***
MADRS total (mean, std. dev.)	4.78 ± 2.88	8.46 ± 3.50	$p < 0.01$* active rTMS: $p < 0.01$*** placebo rTMS: N.S.***
CDSS total (mean, std. dev.)	0.92 ± 0.78	1.09 ± 1.51	N.S.* active rTMS: N.S.*** placebo rTMS: N.S.***

PANSS: the Positive and Negative Syndrome Scale; MADRS: Montgomery–Asberg Depression Rating Scale; CDSS: the Calgary Depression Scale for Schizophrenia.
* Independent t-test.
** Chi-square-test; paired t-test.
*** Comparison of ongoing changes in scales (post-stimulation vs. baseline psychopathology).

in time ($p < 0.001$ both for within subject changes in smoking and smoking × treatment interaction); overall statistical significance of between subjects' effect of treatment was $p = 0.067$.

3.3. Nicotine cigarette consumption in active rTMS group

Patients who underwent active rTMS smoked statistically significantly fewer cigarettes as early as the second week of the stimulation. In the course of active rTMS, the total number of cigarettes smoked decreased by 12.93% of the original number; see Table 2.

3.4. Nicotine cigarette consumption in sham rTMS group

No statistically significant change in the number of cigarettes smoked was found in the patients who underwent sham rTMS. Throughout sham rTMS, the total number of cigarettes smoked increased by 1.03% compared to the initial state; see Table 3.

3.5. Impact of changes in psychopathology on cigarette consumption during rTMS treatment

Neither the active nor sham rTMS group of schizophrenia patients showed a statistically significant correlation between the change (i.e., the initial score minus the final score divided by the initial score of a particular subscale) in schizophrenic (i.e. PANSS total score, PANSS subscales of positive, negative, and general psychopathology) or depressive symptoms (total scores in MADRS and CDSS) and the change in the number of cigarettes smoked throughout three weeks of stimulation treatment.

Table 2
Total number of cigarettes smoked and their percentage change in active rTMS group.

	Total number of cigarettes smoked		Percentage change compared to the state before rTMS (day-7 to 0)		Statistical comparison* to the state before rTMS (day-7 to 0)	
	Mean	S.D.	Mean	S.D.	t	p
Before rTMS (day-7 to 0)	18.56	6.68	–	–	–	–
After rTMS (days 1 to 7 of active stimulation)	17.51	6.14	−4.92%	8.92	2.49	0.02
After rTMS (days 8 to 14 of active stimulation)	15.94	5.33	−12.50%	16.13	3.83	<0.01
After rTMS (days 15 to 21 of active stimulation)	14.41	5.24	−21.36%	19.37	5.11	<0.01
After rTMS (days 1 to 21 of active stimulation)	15.95	5.48	−12.93%	13.80	4.28	<0.01
Follow-up (days 14 to 21 after the end of stimulation)	14.58	5.17	−21.45%	20.24	4.80	<0.01

S.D.: standard deviation.
* Paired t-test.

Table 3
Total number of cigarettes smoked and their percentage change in sham rTMS group.

	Total number of cigarettes smoked		Percentage change compared to the state before rTMS (day-7 to 0)		Statistical comparison* to the state before rTMS (day-7 to 0)	
	Mean	S.D.	Mean	S.D.	t	p
Before rTMS (day-7 to 0)	19.06	8.64	–	–	–	–
After rTMS (days 1 to 7 of sham stimulation)	19.77	11.10	+1.83%	22.37	−0.47	0.64
After rTMS (days 8 to 14 of sham stimulation)	19.83	10.65	+2.28%	18.96	−0.60	0.56
After rTMS (days 15 to 21 of sham stimulation)	19.25	9.64	+1.00%	9.52	−0.35	0.73
After rTMS (days 1 to 21 of sham stimulation)	19.61	10.35	+1.03%	16.31	−0.51	0.62
Follow-up (days 14 to 21 after the end of stimulation)	19.35	9.58	+0.17%	0.09	−0.56	0.59

S.D.: standard deviation.
* Paired t-test.

4. Discussion

The primary aim of our study was to determine the potential of high-frequency (10 Hz) rTMS applied over the left DLPFC to reduce the consumption of cigarettes in schizophrenia patients. Our results show that active rTMS had a trend to reduce the consumption of cigarettes in schizophrenia patients compared to sham rTMS. The number of cigarettes smoked decreased by almost 13% in patients treated with active rTMS during a three-week stimulation therapy and this reduction reached a statistical significance level. In contrast, the consumption of cigarettes remained practically unchanged in patients treated with sham rTMS. Furthermore, the effect of rTMS on the reduction of the number of cigarettes smoked was already observed after the first week of stimulation. This corresponds to a recent finding that the anti-craving effect of rTMS appears after only one stimulation session (Li et al., 2013). The follow-up observation after the end of rTMS treatment proved that the positive effect of rTMS on the reduction of the number of cigarettes smoked lasts at least three weeks after the end of rTMS.

The results are similar to the conclusions of previous study which reported the positive effect of high-frequency rTMS on tobacco craving in schizophrenic patients (Wing et al., 2012a,b). Our study however measured nicotine consumption and had larger sample size (35 versus 15). The rTMS parameters were also different. While we stimulated the left DLPFC at 10 Hz frequency, Wing's study used bilateral prefrontal stimulation at 20 Hz (Wing et al., 2012a,b).

High-frequency rTMS over the left DLPFC has a repeatedly confirmed antidepressant effect (Dell'Osso et al., 2011) and also probably, with some caution regarding to the last published schizophrenia trials conclusions, especially 10 Hz frequency stimulation directed on the left DLPFC, alleviates the severity of negative symptoms of schizophrenia (Dlabac-de Lange et al., 2010; Freitas et al., 2009). While the effect of rTMS on negative schizophrenia symptoms is independent of its effect on the depressive symptoms in schizophrenia patients (Hajak et al., 2009), the anti-craving effect of rTMS has not yet been researched in this sense. Our findings suggest the rTMS efficacy in reducing the number of cigarettes smoked is independent of its effect on the change in either depressive or negative symptoms of schizophrenia. Therefore, we may conclude that the anti-craving and anti-consumption effect of high-frequency rTMS may be relatively specific and not only secondary to rTMS efficacy on schizophrenic symptoms. This corresponds well with the positive effect of rTMS on nicotine craving in healthy persons (Amiaz et al., 2009; Brody and Cook, 2011; Eichhammer et al., 2003; Johann et al., 2003; Li et al., 2013). Similarly, the concordant decrease in the number of cigarettes smoked in patients with schizophrenia stimulated at various frequencies (10 Hz and 20 Hz) may suggest other neurobiological impacts of rTMS than that in the treatment of negative symptoms of schizophrenia, in which the stimulation at 20 Hz is considered to be less effective than 10 Hz (Dlabac-de Lange et al., 2010).

Our study has two main limitations. The first it is difficult to generalize our findings to the whole population as only men were included in the study. However, no sex differences in the effects of rTMS have been described before (Matheson et al., 2010). Then we used only self-evaluated questionnaires to record the number of cigarettes smoked, however no objective scales to measure tobacco craving nor measures of breath carbon monoxide (CO) were employed. While craving is often not assessed in clinical trials, the participants in our study were non-treatment seeking, so these scales would have been good to have in addition to the number of cigarettes that were being smoked.

In spite of the deficiencies, this is the first study trying to evaluate the anti-nicotine cigarette consumption effect of rTMS and its relation to the change in negative or depressive symptoms in schizophrenia patients. We may conclude that high-frequency rTMS applied over the left DLPFC has the potential to decrease the number of cigarettes smoked in schizophrenia patients, an effect that lasts at least three weeks after the end of rTMS treatment. The effect is independent of change in negative or depressive symptoms of schizophrenia.

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