Progress in Neuro-Psychopharmacology & Biological Psychiatry 49 (2014) 30–35

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Repetitive transcranial magnetic stimulation reduces cigarette consumption in schizophrenia patients

Radovan Prikryl [a,b,c,*], Libor Ustohal [a,b,c], Hana Prikrylova Kucerova [a,b,c], Tomas Kasparek [a,b,c], Jiri Jarkovsky [d], Veronika Hublova [a,b], Michaela Vrzalova [a,b,c], Eva Ceskova [a,b,c]

[a] CEITEC — Central European Institute of Technology, Masaryk University, Czech Republic
[b] Department of Psychiatry Faculty of Medicine, Masaryk University, Brno, Czech Republic
[c] Department of Psychiatry, University Hospital Brno, Czech Republic
[d] Institute for Biostatistics and Analyses of the Faculty of Medicine, Masaryk University, Brno, Czech Republic

ARTICLE INFO

Article history:
Received 23 August 2013
Received in revised form 28 October 2013
Accepted 29 October 2013
Available online 6 November 2013

Keywords:
Consumption
Dorsolateral prefrontal cortex
Schizophrenia
Smoking
Stimulation

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.

* Corresponding author at: Department of Psychiatry, University Hospital Brno, Jihlavska 20, 625 00 Brno, Czech Republic. Tel.: +420 532232055; fax: +420 532233706.
E-mail address: radovan.prikryl@post.cz (R. Prikryl).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.10.019

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),