



## A detailed analysis of the effect of repetitive transcranial magnetic stimulation on negative symptoms of schizophrenia: A double-blind trial

Radovan Prikryl<sup>a,b,c,\*</sup>, Libor Ustohal<sup>a,b,c</sup>, Hana Prikrylova Kucerova<sup>a,b,c</sup>, Tomas Kasperek<sup>a,b,c</sup>,  
Simona Venclikova<sup>b,c</sup>, Michaela Vrzalova<sup>a,b,c</sup>, Eva Ceskova<sup>a,b,c</sup>

<sup>a</sup> CEITEC – Central European Institute of Technology, Masaryk University, Czech Republic

<sup>b</sup> Department of Psychiatry, Faculty of Medicine Masaryk, University Brno, Czech Republic

<sup>c</sup> Department of Psychiatry, University Hospital Brno, Czech Republic

### ARTICLE INFO

#### Article history:

Received 16 February 2013

Received in revised form 9 May 2013

Accepted 2 June 2013

Available online 25 June 2013

#### Keywords:

High-frequency

Negative symptoms

Prefrontal cortex

Repetitive transcranial magnetic stimulation

rTMS

SANS

### SUMMARY

**Objective:** The aim of the study was to assess the effect of rTMS not only on the general severity of negative schizophrenia symptoms, but also particularly on their individual domains, such as affective flattening or blunting, avolition, alogia, avolition or apathy, anhedonia, and impaired attention.

**Methods:** Forty schizophrenic male patients on stable antipsychotic medication with prominent negative symptoms were included in the study. They were divided into two groups: 23 were treated with active and 17 with placebo rTMS. Both treatments were similar, but placebo rTMS was administered using a purpose-built sham coil. Stimulation was applied to the left dorsolateral prefrontal cortex (DLPFC). The stimulation frequency was 10 Hz; stimulation intensity was 110% of the individual motor threshold intensity. Each patient received 15 rTMS sessions on 15 consecutive working days (five working days “on” and two weekend days “off” design). Each daily session consisted of 20 applications of 10-second duration with 30-second intervals between sequences. The patients and raters were blind to condition of stimulation treatment.

**Results:** The active rTMS led to a statistically significantly higher reduction of the Scale for the Assessment of Negative Symptoms (SANS) total score and of all domains of negative symptoms of schizophrenia. After Bonferroni adjustments for multiple testing, the statistical significance disappeared in alogia only.

**Conclusion:** High-frequency rTMS stimulation over the left DLPFC at a high stimulation intensity with a sufficient number of applied stimulating pulses may represent an efficient augmentation of antipsychotics in alleviating the negative symptoms of schizophrenia.

© 2013 Elsevier B.V. All rights reserved.

### 1. Introduction

Negative symptoms and cognitive deficits are regarded as a part of the core symptoms of schizophrenia. In some cases, especially in the secondary negative symptoms, their severity may be in some extent improved by antipsychotics (Leclercq et al., 2006). In most cases, however, the negative symptoms remain resistant to the current options of psychopharmacology (Erhart et al., 2006). The absence of a really efficient treatment for negative symptoms appears therefore to be a major problem of schizophrenia treatment today. The presence of negative schizophrenia symptoms is closely linked to the bad prognosis and represents a potential source of significant stress factors for the patients' family and caregivers (Bow-Thomas et al., 1999; Dickerson et al., 1999; Milev et al., 2005). The severity of the negative symptoms of schizophrenia generally predicts a worse quality of life (Bow-Thomas et al., 1999), worsened social functioning (Dickerson et al., 1999),

disruptions in interpersonal relations, reduced work performance, and a generally worse effect of treatment in schizophrenia patients (Milev et al., 2005).

Brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation and/or transcranial random noise stimulation have been proved in schizophrenia neurostimulation research. However there is only sufficient experience with rTMS application in the treatment of auditory hallucinations or negative symptoms of schizophrenia. Repetitive transcranial magnetic stimulation (rTMS) is a neurostimulation method enabling brain neuronal metabolism modulation in a non-invasive way. Although the specific effect of rTMS on neurotransmission is not entirely clear, it has been proven repeatedly that high-frequency rTMS (10 to 20 Hz) increases brain excitability and low-frequency rTMS (1 Hz and low) decreases it. It has also been found that high-frequency rTMS applied over the left prefrontal cortex (PFC) increases brain perfusion, and thus the metabolism of this region, whereas low-frequency rTMS has the opposite effect (Nahas et al., 1999). Animal models showed that rTMS increases the density of *N*-methyl-*D*-aspartate (NMDA) receptors as early as after a single stimulation (Ragert et al., 2003). It can

\* Corresponding author at: CEITEC – Central European Institute of Technology, Masaryk University, Czech Republic. Tel.: +420 5 3223 2055; fax: +420 5 3223 3706.

E-mail address: [radovan.prikryl@post.cz](mailto:radovan.prikryl@post.cz) (R. Prikryl).

therefore be speculated that high-frequency rTMS over PFC may act as a potential agonist of NMDA receptors (Kole et al., 1999). Following high-frequency stimulation, up-regulation of serotonin receptors (5-HT1A and 5-HT2 subtypes) also occurs (Ben-Shachar et al., 1999). Animal and human studies have shown that high-frequency rTMS applied over the left PFC modulates the release of dopamine in the mesolimbic and mesostriatal brain pathways. A selective elevation in the dopamine levels in the dorsal striatum and the nucleus accumbens was found in animal studies (Taber and Fibiger, 1995), and in the caudate nucleus and the left putamen in humans as well (Strafella et al., 2001; Jin et al., 2006).

Prefrontal hypometabolism, altered NMDA and serotonin receptor functions are considered to be involved in the pathophysiology of negative symptoms of schizophrenia. There is a strong correlation between prefrontal hypometabolism and severity of negative symptoms of schizophrenia (Andreasen et al., 1992). The positive impact of rTMS on negative symptoms can be therefore seen in the ability to restore prefrontal hypometabolism and affect glutamate and serotonin brain neurotransmission in a positive way (Kole et al., 1999; Dlabac-de Lange et al., 2010). Improvement of negative symptoms after rTMS is also possibly caused by the activation of mesolimbic and mesostriatal dopaminergic systems (Strafella et al., 2001).

Although a number of double-blind studies proved a statistically significant decrease in the intensity of the negative schizophrenia symptoms when current antipsychotic treatment was augmented with rTMS, the actual clinical significance of this procedure is disputed by a number of authors (Matheson et al., 2010). The same conclusion was also essentially reached by two meta-analyses. The first meta-analysis reviewed eight double-blind studies and found that rTMS had a mild to moderate ( $d = 0.58$ ) effect size on alleviating the negative symptoms of schizophrenia (Freitas et al., 2009). The other meta-analysis evaluated nine double-blind studies with more than two hundred enrolled patients (Dlabac-de Lange et al., 2010). When studies with any high-frequency stimulation of the left PFC were evaluated, the effect size of the treatment was low ( $d = 0.43$ ); when the analysis included only studies with a 10 Hz frequency, the effect size of the treatment was intermediate ( $d = 0.63$ ).

Published studies of the rTMS application in the treatment of negative symptoms of schizophrenia are burdened with a number of methodological issues and drawbacks, in both the stimulation parameters (the accuracy of the focus of the stimulating coil, the number of stimulating pulses administered, the total number of stimulation sessions, the conditions for blinding, etc.) and the own evaluation of the character of the negative symptoms. No study has presented a detailed analysis of which domains of the negative symptoms are actually influenced by rTMS. The main clusters of negative symptoms include affective flattening or blunting, alogia, avolition or apathy, anhedonia, and impaired attention (Andreasen, 1982). The results of the studies conducted only indicate a change in the general severity of negative symptoms, without any detailed analysis of the influence of rTMS on the particular items of negative symptoms. Only Barr's study directly reported no therapeutic effect of bilateral high-frequency rTMS on negative schizophrenia symptoms subclassified as primary or deficit (e.g. anhedonia and blunted affect) and secondary or nondeficit (e.g. avolition) symptoms (Barr et al., 2012). This is surprising, especially since antipsychotics can also influence the individual domains of negative symptoms in different ways. Clozapine, for instance, has been proven to be most effective in anhedonia (Buchanan et al., 1998), while olanzapine influences all the negative symptoms except anhedonia and social withdrawal (Tollefson et al., 1997).

The lack of a factor analysis of the effect of rTMS on the particular clusters of negative schizophrenia symptoms led us to design a double-blind, sham stimulation-controlled study. The main aim of the study was to assess the efficacy of rTMS not only on the general severity of the negative symptoms but also especially on their individual domains, such as affective flattening or blunting, alogia, avolition or

apathy, anhedonia, and impaired attention. We tested the hypothesis of whether the active rTMS treatment is more effective in the reduction of overall severity including particular clusters of the negative symptoms of schizophrenia compared to the placebo stimulation.

## 2. Methods

### 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 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 diagnostic research criteria, who were stabilized for at least last 6 weeks on the same antipsychotics, and who had significant negative symptoms 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). The age of the enrolled patients ranged from 18 to 60 years. Patients who had a neurological disease (including epilepsy or abnormal EEG record), a cardiovascular, cerebrovascular, endocrinal, or systemic autoimmune disease, psychoactive drug abuse including alcohol, or acute risk of suicide at screening, or who had such a condition in the past were not included in the study. Absence of psychoactive drug abuse was verified using the 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 included in 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

All patients were randomly assigned to the active and/or placebo rTMS groups based on a software randomly determining type of stimulation treatment (active to placebo relation was 5:4). Both forms of rTMS treatment were performed on workdays, i.e. five times a week, until fifteen procedures were completed (three weeks in total). The patients remained on their prescribed antipsychotic medication during the stimulation therapy. The severity of negative symptoms before and after the stimulation treatment was evaluated using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). The SANS contains 30 particular items divided into 5 symptomatological domains: 1) affective flattening and/or blunting, 2) alogia, 3) avolition and/or apathy, 4) anhedonia, and 5) impaired attention. The severity of the individual SANS items was assessed using six grades of intensity: 0 – absence, 1 – questionable, 2 – mild but definitely present, 3 – moderate, 4 – marked, and 5 – severe. The severity of positive symptoms of schizophrenia before and after the treatment was evaluated using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Potential affective symptomatology was evaluated before and after the treatment using the Montgomery–Asberg Depression Rating Scale (MADRS) and the Calgary Depression Scale for Schizophrenia (CDSS) (Montgomery and Asberg, 1979; Addington et al., 1990). 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 patients were advised that they would receive either active or the placebo-controlled sham rTMS; however, the specifics regarding the difference between the stimulations were not described. After stimulation course patients were asked about their best guess of the treatment they received.

Download English Version:

<https://daneshyari.com/en/article/6825986>

Download Persian Version:

<https://daneshyari.com/article/6825986>

[Daneshyari.com](https://daneshyari.com)