Repetitive transcranial magnetic stimulation and treatment of negative symptoms of schizophrenia

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Abstract

One of the fundamental prerequisites of the successful schizophrenia treatment is represented by an adequately significant impact on the negative symptoms of schizophrenia. Since the present pharmacotherapy has probably reached its limit in this area, there is a logical effort to utilize other, non-pharmacological methods. One of the most promising supplements that has been for a long time verified in the clinical practice is rTMS. Most of the studies have arrived at the conclusion that rTMS is an efficient method in the treatment of negative symptoms of schizophrenia. A valuable contribution to the assessment of the rTMS application in the treatment of negative symptoms is represented by meta-analyses. The meta-analyses indicate that the effect is mild to moderate (d=0.43 to 0.68). To sum it up, there will be higher probability of the rTMS effect on negative symptoms if 10 Hz stimulating frequency and a longer stimulation period in the extent at least three, ideally four to six weeks is used.

REVIEW ARTICLE

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), which is used in psychiatry primarily for the treatment of the depressive disorder, isolated auditory hallucinations or obsessively compulsive disorder, represents a new therapeutic modality able to affect negative schizophrenia symptoms thanks to its unique ability to modulate neuronal activity of the cortical cerebral areas and neuronal circuits which are included into the pathophysiology of schizophrenia not only directly but also indirectly, by means of transsynaptic transfer (Klirova *et al.* 2008; Zaman *et al.* 2008; Anders *et al.* 2010; Havrankova *et al.* 2010).

Theoretical Grounds for rTMS Efficacy in the Treatment of Negative Schizophrenia Symptoms

Hypofrontality is expected to be a functional correlate of negative symptoms (Kim *et al.* 2000; Lui *et al.* 2010). The promising results of rTMS in the depressive disorder, when just the area of the frontal cortex is stimulated, led to the hypothesis of using this method also in the treatment of schizophrenia. Theoretical substantiation of the rTMS efficacy in the event of negative schizophrenia symptoms lies in the fact that the high-frequency rTMS shows an activating impact on the neurons of the cerebral cortex (Post *et al.* 1997). Negative

correlation between the activity of the frontal cortex and severity of negative symptoms has been repeatedly demonstrated. Another, no less important fact consists in the effect of dopamine release from the mesolimbic and mesostriatal cerebral system by high-frequency stimulation of the frontal cortex. The mesolimbic brain structures play a key role in the pathogenesis of negative schizophrenic symptoms like anhedonia or loss of interest (Heimer *et al.* 1997). By means of ^{11}C PET (positron emission tomography) Strafella has found out that high-frequency rTMS of the dorsolateral prefrontal cortex (PFC) induces release of the endogenous dopamine in the ipsilateral caudate nucleus in healthy volunteers (Strafella *et al.* 2001). The high-frequency rTMS also causes down-regulation of serotonine 5-HT_2 receptors in the frontal cortex (Ben-Shachar et al 1999). The blockade of serotonine 5-HT_2 receptors leads to a compensatory relative increase in the dopamine concentration in the PFC and is associated with the remission of negative schizophrenia symptoms. These facts are the basis of the theoretical substantiation of the efficacy of rTMS on negative symptoms of schizophrenia. Any improvement in the negative symptoms after rTMS is probably caused by the activation of mesolimbic and mesostriatal dopaminergic systems (Strafella *et al.* 2001).

AN OVERVIEW OF RTMS STUDIES RELATED TO THE TREATMENT OF NEGATIVE SCHIZOPHRENIA SYMPTOMS

The first two "pioneer" works which tried to treat schizophrenia symptoms by stimulation of prefrontal cortex were relatively small open studies. The first study assessing the rTMS effect on schizophrenia symptoms was the work of Geller (Geller *et al.* 1997). 10 patients have undergone low-frequency stimulation (0.03 Hz), each of them obtaining fifteen stimuli over the area of the right and left PFC in 30-second intervals. This has resulted in transient improvement of the mood in two patients. Feinsod treated 10 patients with schizophrenia in the open study using the low frequency stimulation of the right PFC in two one-minute daily stimulations for the period of 10 days. He managed to reach the reduction of anxiety and restlessness in 7 patients, however, he did not succeed in affecting other schizophrenia symptoms (Feinsod et al 1998).

The first double-blind study was the work of Klein from the year 1999, who based on his positive experience with the impact of low-frequency stimulation of the right PFC on the depressive symptomatology, tested the hypothesis whether the low-frequency rTMS applied over the area of the right PFC affects not only mood but also positive and negative schizophrenia symptoms. During the treatment, a slight improvement in the psychopathology occurred both in the placebo and in the rTMS treated group, however, no significant difference between the real and ineffective stimulation was found (Klein *et al.* 1999).

In the same year a pilot open study by Cohen *et al.* was published, trying to identify the impact of rTMS on the chronic negative symptoms. The study included 6 patients with schizophrenia with dominating negative symptoms. The left PFC was stimulated by 20 Hz frequency; the stimulation lasted 2 seconds and it was applied once in a minute for the total period of 20 minutes. Although a statistically significant decrease in the severity of negative symptoms was achieved, the clinical effect of this change was assessed as relatively low. During the stimulation also achieved was the improvement in all parameters of the applied neuropsychological tests, however, only the item of delayed visual memory reached the statistical significance. The authors explain this fact by the improvement of attention, especially the ability to keep attention. However, the neuronal activity of the PFC has not changed during the stimulation (Cohen *et al.* 1999).

In 2000, the results were published of the double-blind, placebo-controlled study including 7 schizophrenic patients in whose clinical condition the negative symptoms had been prevailing. The patients were stimulated by high-frequency (20 Hz) rTMS focused on the area of the left dorsolateral PFC. Although the real rTMS, when compared with placebo, led to the decrease in the intensity of negative schizophrenia symptoms, the results did not reach the statistic significance (Nahas *et al.* 2000).

In the same year, Rollnik published the work, whose objective was to assess the efficacy of rTMS in patients with schizophrenia in the conditions of the single-blinded, controlled study. The total of 12 patients with schizophrenia on a stabilized dose of antipsychotic drugs were included in the study. The left dorsolateral PFC was stimulated and each patient was applied 20 two-second stimulation trains within the period of twenty minutes (800 pulses in a single train, the total of 10 stimulations within the period of two weeks). The blinding in the placebo "sham" group consisted in the position of the stimulating coil (making a 45° angle with the head surface). The real rTMS led to a statistically significant reduction of the severity of schizophrenia symptoms. The fact that the intensity of schizophrenia symptoms had been reduced, leaving the symptoms of depression and anxiety unchanged, led the authors of the study to the conclusion that rTMS, applied over the PFC area of the dominant cerebral hemisphere, might show a specific antipsychotic effect (Rollnik *et al.* 2000).

Despite the positive conclusion of the Rollnik's study, the next study was published as late as in 2004. It was the double-blind study by Hajak *et al.* The priority of this work is the first use of an inefficient "sham" stimulating coil for placebo stimulation which led to the refinement of the methodological purity of the study and further reduced the possible placebo effect of rTMS. The sham stimulation coil actually gives out an equal acoustic accompaniment that may be heard by patients during the real stimulation, and therefore

it is more difficult to distinguish between efficient and inefficient stimulation. The patients were treated by high-frequency (l0 Hz) stimulation over the left PFC area, using the stimulation intensity of 110% of the MT (motor threshold) during 10 sessions. Each stimulation session included 1,000 impulses, divided into 20 five-second stimulation trains. Although in both groups the severity of psychopathology was reduced during the treatment, the reduction was more significant in the group of patients treated with real rTMS. The reduction of negative schizophrenia symptoms was not conditioned by the decrease in affective symptomatology. No significant change in the regional cerebral perfusion, related to the real/placebo stimulation, has been proved (Hajak *et al.* 2004).

In 2004, Holi published the double-blind, controlled study of rTMS, applied over the left PFC in the treatment of schizophrenia. The total of 22 patients with high intensity of schizophrenia symptoms were included in the study; the patients were randomized into two treatment arms, into the group of real or into the group of inefficient, i.e. placebo "sham" stimulation. The latter was reached by turning the stimulation figure-eight coil making a 90° angle with the head surface. The treatment included 10 stimulation sessions in the period of two weeks with the following stimulation parameters: twenty five-second trains followed by thirty-second intertrains, 10 Hz frequency and the intensity of stimulation of 100% of the MT. Although in both compared groups there was a statistically significant decrease in the severity of symptoms, no statistically significant difference has been found between the real and inefficient rTMS. Based on the results the authors believe that the high-frequency rTMS over the left prefrontal cortex shows rather an unspecific therapeutic effect than the direct antipsychotic effect in patients with chronic schizophrenia (Holi *et al.* 2004).

Jin stimulated 27 patients with significant negative schizophrenic symptoms daily for the period of 2 weeks bilaterally over the area of the dorsolateral PFC, using various stimulation frequencies: 8–12 Hz (so-called alpha-frequency), 3 Hz, 20 Hz or inefficient "sham" stimulation. The theoretical basis of his work was the hypothesis that the cerebral alpha frequency (8–12 Hz), detected by electroencephalography (EEG), is associated with the occurrence and severity of negative schizophrenia symptoms. Actually, as it is known from the EEG studies, the patients with schizophrenia suffer from decreased alpha activity (both spectral power and coherence), not only in the rest conditions but also during sensory/cognitive stimulations (Stevens *et al.* 1982; Colombo *et al.* 1989; Hoffman *et al.* 1991). The results of the study confirmed the hypothesis to be tested, because rTMS with the "alpha" frequency (8–13 Hz) led to a more significant remission of negative symptoms (approximately by 29.6%) in comparison with the remaining three treatment modalities (less than 9%). In addition, changes in EEG during the stimulation with the alpha frequency predicated clinical improvement. According to the authors, the identified data prove that the higher the increase of power of alpha activity over the frontal lobe, the more considerable remission of negative schizophrenia symptoms (Jin *et al.* 2005).

The effect of rTMS on negative schizophrenia symptoms and its relation to the electric activity of the brain was also the theme of the following open pilot study. The total of 10 patients with schizophrenia were included in the study. They were stimulated over the area of the left dorsolateral PFC for a period of 5 days. The stimulation frequency of 10 Hz was chosen; the stimulation session included 20 stimulating trains of 3.5 seconds, followed by 10-second intertrains. Slight improvement of negative and affective schizophrenia symptoms occurred after the treatment (reaching approximately 9% in the case of negative symptoms and about 16% in the case of affective ones; in both cases, however, reaching the statistic significance). The EEG analysis revealed the reduction of delta and beta activities frontotemporally on the right and, on the other hand, the increase of alpha activity, while temporally and parietooccipitally on the left the beta activity had been reduced. The authors suggest that despite the slight clinical improvement of negative symptoms the established changes of the EEG activity may be considered signs of improvement of negative schizophrenia symptoms after rTMS (Jandl *et al.* 2005).

Sachdev with his collaborators also treated four patients with the deficit syndrome of schizophrenia in the open study. They administered high-frequency (15 Hz) rTMS over the area of the left dorsolateral PFC during 20 sessions within the period of four weeks. A single stimulation session included 24 five-second stimulation trains. The stimulation treatment led to a statistically significant decrease in the severity of negative symptoms and improved general performance of the patients, persisting for the whole period of the subsequent one-month monitoring following the end of the stimulation (Sachdev *et al.*2005).

Into his double-blind, fictitious stimulation-controlled, randomized study, Novak included 18 patients with the diagnosis of schizophrenia with prevailing negative symptoms. The patients were stimulated with high frequency (20 Hz) over the area of the left dorsolateral PFC for a period of two weeks. The placebo stimulation was reached by positioning the stimulating coil, making a 90° angle with the surface of the head, which ruled out the real stimulation. The intensity of stimulation was set to 90% of the MT, a single stimulation session included 40 2.5-second stimulation trains with thirty-second intertrains. During the single stimulation the patients obtained 2,000 impulses, the total number of session was 10 within the period of two weeks. However, neither the clinically relevant effect of the high frequency rTMS in the treatment of negative symptoms of schizophrenia nor any impact on cognitive functions has been proved (Novak *et al.* 2006).

In 2007, the double-blind study was published, whose objective was to show the impact of high frequency rTMS, applied over the area of the left PFC, with the total number of 15 stimulation sessions, using the maximum stimulating intensity on the alleviation of the intensity of negative schizophrenia symptoms. The stimulation itself was targeted at the left dorsolateral PFC, using the 10 Hz frequency with stimulating intensity of 110% of individual MT. Every patient was stimulated 15 times on workdays of three consecutive weeks. Each stimulation session included 15 applications of 10-second train followed by 30-second interval of intertrain. The real stimulation treatment led to a statistically significant decrease in the intensity of negative schizophrenia symptoms. The authors ascribe the rate of reduction of the negative symptoms intensity, which they consider clinically significant, to the number of 15 stimulation sessions, which was, with the exception of the pilot Sachdev work (Sachdev *et al.* 2005), the highest number of stimulation sessions in the studies dealing with this issue (Prikryl *et al.* 2007).

In the same year the results were published of the double-blind study assessing the effect of high frequency rTMS on not only negative but also positive schizophrenia symptoms. The real treatment was characterised by the following stimulation parameters: 10Hz frequency, the left PFC being the area of stimulation, the treatment consisting of 10 stimulation sessions with the length of the train of 4.9 s and that of the intertrain 30 s, repeated 20 times during a single 20-minute session, the intensity of the stimulation being defined to 110% of the individual MT. The real stimulation treatment led to a significantly more substantial alleviation of the severity of negative symptoms compared to the placebo stimulation. The severity of positive symptoms remained equal regardless of the stimulation type (Goyal *et al.* 2007).

In 2007 the work was also published whose aim was to assess not only the rTMS impact on negative schizophrenia symptoms but also to evaluate the effect of rTMS on mood, cognitive functions or quality of life (Mogg *et al.* 2007). The study was also enriched by a two-week monitoring after the end of the stimulation treatment. The real treatment was characterized by high-frequency 10Hz stimulation, pointed at the left PFC, with the intensity of 110% of the individual MT. It included 10 sessions in the working days during two consecutive weeks. At each stimulation session 2,000 pulses were applied in 20 trains of 10 second duration with 50 second intertrains. In total 20,000 stimulation pulses were applied. The most important result of the study consisted in the finding that no statistically significant difference had been found between the impact of the real and of placebo rTMS on the negative schizophrenia symptoms. Since the age is considered one of the possible negative indicators of the rTMS treatment efficacy (Kozel *et al.* 2000), the effect of the age was taken into account in the final analysis, however, even in that case no significant efficacy of rTMS on negative symptoms was found. The same negative results were also found in relation to the quality of life, depression, anxiety or cognitive functions. However, there are certain limits of the study: small sample of patients and related risk of false negative results (Mogg *et al.* 2007).

Up to now published works are based on the main theoretical assumption that only the left PFC is included into the pathophysiology of negative schizophrenia symptoms (Klemm *et al.* 1996). Despite that the disturbed activation of the PFC related to negative schizophrenia symptoms is also shown in the right cerebral hemisphere (Wolkin *et al.* 1992) or bilaterally (Sabri *et al.* 1997). Therefore Fitzgerald proposed the study, in which he tried to verify the effect of the bilateral PFC stimulation for the treatment of negative schizophrenia symptoms (Fitzgerald *et al.* 2008). The stimulation frequency of 10 Hz was used; during a single stimulation session 20 trains of 5-second length were applied with intertrains lasting 25 seconds. In total 1,000 pulses were administered to each cerebral hemispheres. First the left and immediately after that the right PFC were stimulated. The results indicate that no statistically significant differences have been found between the real and placebo rTMSs both in the change of psychopathology and in cognitive functions (Fitzgerald *et al.* 2008).

In his work, Schneider verified the hypothesis that only high frequency stimulation of the PFC may be efficient in the reduction of negative symptoms. Therefore he proposed to form three investigation groups, each consisting of 17 patients; the first of them was to be treated by 10 Hz stimulation (1,000 pulses daily, the total of 20,000 pulses), the second using the 1 Hz stimulation (100 pulses daily, the total of 2,000 pulses) and the third using the placebo stimulation for the period of 4 weeks (20 stimulation sessions). The stimulation was targeted at the left PFC with the intensity of 110% of the MT, the lengths of the train and intertrain being 5 seconds and 15 seconds, respectively. Placebo conditions were provided by the placebo "sham" coil. In the group treated by 10Hz rTMS a statistically significant decrease occurred in the severity of negative symptoms; such reduction did not occur in any other group. Also, if mutually compared, the high-frequency stimulated patients showed a statistically more significant reduction of negative symptoms then those of the two compared groups (Schneider *et al.* 2008).

META-ANALYSES OF THE RTMS STUDIES IN THE TREATMENT OF NEGATIVE SCHIZOPHRENIA SYMPTOMS

The efficacy of rTMS use in influencing the negative schizophrenia symptoms was, on the basis of so far published double blind studies also verified by means of two meta-analyses.

The first of them was published in 2009 (Freitas *et al.* 2009); in the area of assessment of rTMS efficacy on negative schizophrenia symptoms the total of 19 stud-

ies were analysed. The high frequency stimulation of the left PFC was used in 13 studies, 10 of them using the PANSS/SANS scale for the assessment of negative symptoms intensity changes. The statistical analysis finally included 8 studies because only in those studies average values and standard deviations had been available. The analysis indicated that the effect size corresponds to the value of 0.58, which represents mild to moderate effect of rTMS on the alleviation of negative schizophrenia symptoms. For comparison, the efficacy of rTMS in the treatment of isolated auditory hallucinations in the same meta-analysis was assessed as significantly higher (effect size 1.28). The results also indicate that the intensity of negative symptoms is considerably reduced if uncontrolled studies are included. However, if only controlled works are included in the analyses, the final therapeutic effect is lower. This reflects the presence of the placebo effect of rTMS, which is projected to the final result, especially in the open studies. The main conclusion of the meta-analysis therefore is that in patients treated by real stimulation there occurred only a statistically insignificant influence of the negative schizophrenia symptoms when compared to the placebo stimulation. Therefore, the hitherto used stimulation parameters do not seem to be sufficiently efficient. The explanation of the low effect of rTMS in this indication may also consist in the fact that the number of studies analysed was relatively low and, in addition, two works with positive results (Hajak *et al.* 2004; Jin *et al.* 2006) had been excluded due to insufficiently statistically supported data. Especially the Jin's study showed very promising results on the large population of patients, however, it was necessary to use the individualized alpha (8–13 Hz) frequency for successful treatment of negative schizophrenia symptoms.

The second meta-analysis published this year has concentrated only on verification of the rTMS efficacy in the treatment of negative schizophrenia symptoms (Dlabac-de Lange *et al.* 2010). Although 16 studies dealing with this theme had been found, due to methodological drawbacks or repeated publication of identical results only 9 of them were included in the final statistical analysis. Generally, the efficacy of rTMS was assessed on 213 patients (198 with schizophrenia and 15 with schizoaffective disorder). Upon the evaluation of the studies with any high-frequency stimulation of the left PFC, the effect of the treatment was low (d=0.43); when only the studies with 10 Hz frequency were included in the analysis, the effect of the treatment was moderate (d=0.63). In the event the studies without the presence of a stable antipsychotic medication during the course of stimulation had been excluded from the analysis, the effect of the treatment dropped to 0.34. The reason of such a decrease in the treatment effect consisted in the exclusion of the Goyal's study, since patients without medication had been included in the therapy and only during the course of the stimulation therapy antipsychotic drugs were started (Goyal *et al.* 2007). Another important conclusion of the meta-analysis is the finding that a longer stimulation therapy (three and more weeks) turned out to be more efficient than a shorter stimulation time (d=0.58 versus d=0.32).

SUMMARY

Adequately significant influence of negative schizophrenia symptoms represents one of the basic prerequisites for successful schizophrenia treatment. Since the present pharmacotherapy has probably reached its limit in this area, there is a logical effort to use also other, non-pharmacological approaches. One of the most promising and in the clinical practice relatively long verified complement of the pharmacotherapy is rTMS. Most of the open studies have shown reduction in the negative symptoms upon the application of this method. However, there is a justified reproach regarding the additional placebo effect which is included in this method as such. Therefore, from the methodological point of view, double-blind, placebo stimulation controlled studies are more contributing. Although the conditions of the double-blinding are not optimal, the additional placebo effect is minimized if compared with the open studies. Most of those studies led to the conclusion that rTMS is an efficient method in the treatment of negative schizophrenia symptoms. However, there remains the problem of a low number of included patients, miscellaneous profile of negative symptoms, various stimulation parameters or absence of longer monitoring of the stimulation effect in most of the studies. Therefore, the valuable contribution for the assessment of rTMS application in the treatment of negative symptoms is brough about by meta-analyses. They have shown that the rate of effect is mild to moderate (d=0.43 to 0.68) based on the character of studies included into the statistic analysis. It can be summarized that a higher probability of rTMS efficacy on negative symptoms will be shown in case of 10 Hz stimulation frequency for a longer stimulation time to the extent of at least three, ideally four to six weeks.

CONCLUSION

Although rTMS represents a promising potential, especially for the augmenting treatment of negative symptoms resistant to antipsychotic drugs treatment, further studies are necessary for the verification of really clinically significant efficacy of rTMS in this clinical indication.

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