Effects of Sequential Frontotemporal Repetitive Transcranial Magnetic Stimulation (rTMS) on Schizophrenia

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Abstract

The study was designed to investigate the influence of sequential fronto-temporal high frequency rTMS on schizophrenic symptoms in a single blind randomized design. The cortical silent period (CSP), which reflects a deficit of the cortical inhibition as an objective marker of reactivity, was also measured.

The rTMS treatment was divided into two parts. The patient was treated with sham rTMS during the first three weeks and then with actual rTMS during the next three weeks. Both rTMS treatments were applied 5 times per week, up to a total of 15 treatments per three week. The actual rTMS procedure included two subsequent stimulations: a high-frequency rTMS above the left dorsolateral prefrontal cortex followed by a low-frequency rTMS above the left TPC with a 5 minutes delay between treatments. Severity of the psychopathology was rated on the Positive and Negative Syndrome Scale (PANSS) before and after sham treatment and after actual rTMS treatment. The CSP was measured at the same times

The stimulation paradigm caused a 50% reduction in positive subscale PANSS. In addition to the complete disappearance of the auditory hallucinations there was also a significant reduction in delusions. A reduction in the severity of schizophrenic symptoms which occurred during rTMS therapy was associated with a prolongation of the CSP interval.

The unipolar left sequential fronto-temporal rTMS caused alleviation of the symptoms of schizophrenia and was well tolerated. Therefore it may represent a new alternative for treatment of schizophrenic patients.

INTRODUCTION

Because the treatment of schizophrenia has not been satisfactory, despite the fact that new antipsychotics have been developed, researches have focus on new treatment methods which improve the prognosis of patients with schizophrenia. Repetitive transcranial magnetic stimulation (rTMS) is one of the new treatments which can affect the symptoms of schizophrenia (Zaman *et al* 2008). This method, which has been classified as an up-to-date brain neurostimulation techniques, is a non-invasive technique but also influences, via trans-synaptic transmission, indirect modulation of neuronal activity, especially in the cortical regions of the brain as well as relevant neuronal circuits (Dell'osso & Altamura 2009; Klirova *et al* 2008). rTMS has been therapeutically used in the treatment of schizophrenia since the late nineteen nineties and covers the basic symptomatic dimensions of schizophrenia. While the benefit of rTMS with regard to the negative symptoms of schizophrenia remains questionable (Freitas *et al* 2009) there is a consensus regarding the potent therapeutic effect of rTMS in the treatment of isolated auditory hallucinations (Aleman *et al* 2007; Freitas *et al* 2009).

However, few studies refer to the benefit of rTMS in the treatment of delusions. The positive effects on delusions have only been occasionally reported (Pascual-Leone *et al* 1996a). According to a meta-analyses, low-frequency (1Hz) rTMS applied above the left temporoparietal cortex (TPC) is not suitable for treatment of delusions (Aleman *et al* 2007; Freitas *et al* 2009). Delusions, not like the auditory hallucinations, are associated with dysfunction of the orbitofrontal rather than temporoparietal cortex (Premkumar *et al* 2008; Baas *et al* 2008). Impaired gyrification of the orbitofrontal cortex, especially the lower volume of the medial orbital gyrus, is frequently found. They are associated with formal cognition disorders (Nakamura *et al* 2007, 2008). Other findings originated from Diffusion Tensor Imaging (DTI) show a reduction of the white matter of the frontal cortex that correlates with impaired working memory (Schlösser *et al* 2007). On the other hand, the parietal and cerebellar alterations of white matter cause delusions in the early stages of psychosis (Picard *et al* 2008; Kyriakopoulos *et al* 2008). All these findings show that other stimulation paradigms including the stimulation of sites other than the ones used in the previous studies need to be found for treatment of positive symptoms (e.g. delusions) of schizophrenia that go beyond isolated auditory hallucinations.

The stimulation parameters of the studies with rTMS differ mostly with regard to stimulation frequency, frequency of rTMS applications, stimulation intensity, or the overall number of stimulation impulses. There are relatively few studies involving stimulation of two brain regions. Simultaneous stimulation means that two brain regions are stimulated by rTMS at the same time using two stimulation doses. During sequential stimulation, we stimulate with one stimulation coil the first region followed by stimulation of the second region. This method of stimulation has been used in several rTMS studies focused on the treatment of depression and has yielded various results (Daskalakis *et al* 2008). Only one study has been published regarding the treatment of schizophrenia using rTMS. However this work did not find any benefit of bilateral stimulation compared to unilateral stimulation of the left TPC in patients with resistant auditory hallucinations (Vercammen *et al* 2009).

The human prefrontal cortex (PFC) is thought to be the brain structure responsible for control and integration of emotions, cognition, and the autoimmune nervous system. Common bilateral neuronal connections link the PFC with other cortical association areas such as the insula, limbic system, thalamus, and basal ganglia (Fuster 1997; Langguth *et al* 2007). The PFC also modulates the activity of dopaminergic neurons in the mesolimbic brain system by means of activation and inhibition pathways (Bertolino *et al* 2000; Laruelle *et al* 2003; Meyer-Lindenberg *et al* 2002). Animal and human studies have shown that high-frequency rTMS applied over the PFC modulates the release of dopamine in the mesolimbic and mesostriatal system of the brain (Keck *et al* 2002; Taber & Fibiger 1995). The receptor, in vivo SPECT (single photon emission computed tomography) studies, has demonstrated a negative correlation between the density of benzodiazepine receptors and the positive symptoms of schizophrenia (Busatto *et al* 1997). Due to the fact that the density of benzodiazepine receptors corresponds to the functional status of the type A subunit of the gamma butyric acid ($GABA_A$) inhibitory receptor, we can assume that the inhibitory system of the brain in schizophrenia is impaired. Because GABA neurons play a significant role in inhibition of brain interneurons, it is clear that schizophrenia is characterized by impairment of cortical inhibition. An imbalance of the fronto-temporal dopaminergic neurotransmitter system in the brain is considered to be a possible etiopathogenetic basis of schizophrenic symptoms (Prikryl *et al* 2009). Therefore, we can theoretically assume that modulation of these pathways, using rTMS from two different stimulation sites, can produce more significant affects on these pathways and hence increase the therapeutic effects of rTMS on the basic symptoms of schizophrenia.

The present case report was designed to investigate the influence of sequential fronto-temporal high frequency rTMS on schizophrenic symptoms in a single blind randomized design. To assess the impact of innovative stimulation paradigm on brain, the cortical silent period (CSP), which reflects a deficit of the cortical inhibition as an objective marker of reactivity, was also measured.

METHODS

The study was carried out on a 35-year-old schizophrenic patient (paranoid subtype). He had been suffering from schizophrenia for 6 years and taking paliperidone 9 mg per day as monotherapy for the previous six months. The patient signed the informed consent before inclusion in the trial. The study was carried out in accordance with the Declaration of Helsinki; the study design was reviewed by the local ethics committee.

The rTMS treatment was divided into two parts. The patient was treated with sham rTMS during the first three weeks and then with actual rTMS during the next three weeks. Both rTMS treatments were applied 5 times per week (Monday through Friday), up to a total of 15 treatments per three weeks. The severity of the psychopathology was rated on the Positive and Negative Syndrome Scale (PANSS) before and after sham treatment and after actual rTMS treatment (Kay *et al* 1987).

The actual rTMS procedure included two subsequent stimulations: a high-frequency rTMS above the left dorsolateral prefrontal cortex followed by a low-frequency rTMS above the left TPC with a 5 minutes delay between treatments. Both stimulation intensities were determined to be 110% of the individual motor threshold (MT). The stimulation parameters of high frequency rTMS were as follows: frequency: 10 Hz, duration of the pulse series: 10 s, interval between individual sequences: 30 s, total number of stimuli applied 1,500; the place of the stimulation: left dorsolateral prefrontal cortex (5 cm dorsally from the site of the motor cortex where the MT was registered). The stimulation parameters of low frequency rTMS were as follows: frequency: 0.9 Hz, duration of the pulse series: 20 minutes, total number of stimuli applied 1,080. Stimulation coil was placed over the left TPC defined as midway between the T3 and P3 EEG electrode sites in the international 10–20 system (Hoffmann *et al* 2003).

The motor threshold was registered using an electromyograph attached to the abductor pollicis brevis lat. dx. The motor threshold was defined as the lowest stimulation activity to produce at least 5 motor potentials of amplitude 50 mV or greater per 10 individual impulses. Stimulation was performed using a Magstim Super Rapid TMS machine equipped with a focal figure 8-shaped coil, which allowed continuous air cooling to prevent overheating during stimulation. Inefficacy of the sham rTMS was achieved by maintaining an angle between the coil and the head surface of 90 degrees. In addition, stimulation was blinded by preserving the sound during both sham and active stimulation.

For the TMS measurements two magnetic stimulators (Magstim 200) were used and they were interconnected using a Bistim module (Magstim, Dyfed, UK) and a figure-eight stimulation coil with a diameter of 70 mm. The stimulation coil was placed on the surface of the patient's head in such a position relative to the motor cortex of the left brain hemisphere, so as it produced motor evoked potentials (MEP) with maximum peak to peak amplitude on the contralateral target muscle (musculus abductor digiti minimi). The optimal position of the stimulation coil was defined and fixed using recommended standards (Rossini & Rossi 1998). The stimulation coil attached to the scalp was directed occipitally with its holder and formed an angle of approximately 45 grades to the sagittal axis (i.e. approximately at a right angle to the central sulcus) (Brasil-Neto *et al* 1992). With the stimulation coil in this position the induced electrical current expands in a anteromedial to posteriolateral direction approximately perpendicular to the direction of the central sulcus and preferentially activates the trans-synaptic corticospinal neurons (Werhahn *et al* 1994). The induced cortical silent period was acquired using the application of single TMS pulses over the area of the motor cortex with an intensity of 1994 of the rest MT on the target muscle (musculus abductor digiti minimi) during willful weak tonic contraction. Duration of the CSP was defined as the time between the initiation of the MEP and return of willful EMG activity. This is called the absolute CSP and is concluded by any deviation of the EMG wave. (Wu *et al* 2000). In total ten measurements were performed and then the CSP was acquired using automatic analysis performed by the EMG Medelec-Synergy software.

RESULTS

The single PANSS scores, including the subscores basally after sham rTMS and actual rTMS are described in Tab. 1. The mean values of CSP basally after sham rTMS and actual rTMS are described in Tab. 2. No adverse events were observed.

DISCUSSION

Our case study demonstrates the effects of unipolar, left-sided, sequential fronto-temporal repetitive transcranial magnetic stimulation (rTMS) particularly on the positive but also on negative symptoms as well as the general symptoms of schizophrenia. A possible placebo effect was minimized by inclusion of a sham stimulation period, during which the patient was not informed about which type of rTMS therapy they were receiving. It is the first rTMS study which combines the two most widely used stimulation paradigms in the treatment of schizophrenia: (i) a high-frequency stimulation in the area of the left prefrontal cortex used especially in the treatment of negative symptoms of schizophrenia and (ii) a low-frequency stimulation of the left temporoparietal cortex which has proved to be effective in the treatment of isolated auditory hallucinations. A combination of both approaches may be provided promising clinical outcomes; probably based on enhanced modulation effects of rTMS on dopaminergic mesocortical and mesolimbic brain pathways.

The stimulation paradigm we chose caused a 50% reduction in positive subscale PANSS. In addition to the complete disappearance of the auditory hallucinations (P3) (improvement from to 6 to 1) there was also a reduction in delusions (P1) (improvement from 4 to 2) and suspicion (P6) (improvement from 4 to 2). Except for the full disappearance of the auditory hallucinations the sequential fronto-temporal stimulation also caused a reduction in the intensity of delusions and paranoia. While the effect of rTMS on auditory hallucinations is considered demonstrated, the positive effect on delusions has been reported only rarely (Pascual-Leone 1996a, 1996b). The problem of effectiveness of rTMS on delusions may be due to the effects of rTMS on the dopaminergic system. It appears that the high-frequency rTMS antagonizes dopamine blockade by first generation antipsychotics in schizophrenia, which is evidenced by the fact that schizophrenic patients treated with first generation antipsychotics and by rTMS had a 50% reduction in the prolactin levels (Yu *et al* 2002). Even if prolactin levels were not measured throughout stimulation therapy in our study, we may assume that the combination of high-frequency and low-frequency rTMS does not significantly interfere with dopamine blockade by antipsychotics. In addition, our patient was treated by paliperidone which is not a first-generation antipsychotic agent.

Except for positive symptoms, a considerable reduction in negative and general symptoms of schizophrenia occurred as well. This can be explained by activation of the PFC and mesolimbic dopaminergic pathways by high-frequency rTMS (Strafella *et al* 2003. Based on functional imaging studies, we know that hypofrontality in schizophrenia is associated with negative symptoms and cognitive deficits (Hill *et al* 2004; Weinberger *et al* 2001). Moreover, the PFC plays an important role in modulation of the dopaminergic system of the brain by means of activation and inhibitory neuronal pathways (Bertolino *et al* 2000; Laruelle *et al* 2003; Peleman *et al* 2009). Activation pathways from the PFC are mediated by direct and indirect glutamatergic projections into dopaminergic neurons. Inhibitory pathways are modulated by prefrontal glutamatergic efferent terminations on the GABA-ergic (gamma butyric acid) interneurons and striato-mesencephalic GABA neurons of the mid-brain. The dual modulation of the mesolimbic dopaminergic system by the PFC may be supported by studies which showed that the extracellular concentration of dopamine in the nucleus accumbens is increased or reduced by high-frequency or low-frequency stimulation of the PFC (Jackson *et al* 2001).

A reduction in the severity of schizophrenic symptoms which occurred during rTMS therapy was associated with a prolongation of the CSP interval, which can be evaluated as an adjustment of cortical inhibition that is impaired in schizophrenia (Daskalakis *et al* 2002). A reduced duration of the CSP is a marker of impaired cortical inhibition. The CSP duration is constantly found to be shortened in patients with schizophrenia, either without or with antipsychotics, compared to controls (Fitzgerald *et al* 2002). The antipsychotic therapy extends the CSP and therefore causes an adjustment of abnormal cortical inhibition processes. (Daskalakis *et al* 2002). A deficit of cortical inhibition in schizophrenia reflects the pathology of the cortical and subcortical brain areas. The abnormalities of the motor functions in schizophrenia are caused by the increased activity of the subcortical dopaminergic neurons which leads to disinhibition of cortical inhibitory neurotransmission (Walker 1994). It is assumed that a reduced number of GABA-ergic interneurons in the prefrontal cortex, anterior cingulum, and hippocampus accounts for the deficit of inhibitory functions in schizophrenia (Benes 1999). We speculate that the modulation of dopaminergic neurotransmission by rTMS affects the tone of not only dopaminergic but also associated GABA-ergic neurotransmission. This has been previously described in association with a reduction of auditory delusions together with a prolongation of the CSP (Langguth *et al* 2006). The dynamic change of CSP during rTMS could be an objective marker of reactivity.

Modulation of the symptoms of schizophrenia, with the exception of the auditory hallucinations, by rTMS requires a new stimulation paradigm. Unipolar, left-sided, sequential fronto-temporal rTMS produce a significant reduction in all schizophrenia symptoms, especially the positive ones. A reduction in schizophrenic psychopathology was associated with prolongation of the CSP period, which can be assessed as an objective marker of reactivity. Since dual stimulation was well tolerated, it represents an alternative stimulation paradigm for treatment of schizophrenia. Complete verification will require a larger patient population sample, and preferably a double-blind study protocol.

CONCLUSION

Unipolar, left side, sequential fronto-temporal rTMS caused alleviation of the symptoms of schizophrenia and was well tolerated. Therefore it may represent a new alternative therapy for schizophrenic patients.

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