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Review Article

Use of Repetitive Transcranial Magnetic Stimulation in Treatment of Negative Symptoms of Schizophrenia

Abstract

In this review, we explore the evidence concerning the efficacy of repetitive transcranial magnetic stimulation (rTMS) to treat negative symptoms of schizophrenia. The majority of protocols have utilized high-frequency excitatory rTMS over the left dorsolateral prefrontal cortex (DLPFC) with limited therapeutic benefits in ameliorating negative symptoms. Although there are many promising results, current evidence does not fully support the clinical use of rTMS in the treatment of negative symptoms or cognitive dysfunction in patients with schizophrenia. Due to the disabling nature of these symptoms, clinical use of this technique could be justified in certain cases although overall response rates are not likely to be high. Treatment of cognitive dysfunction with rTMS is a promising but new area of research. Regarding side effects, the active rTMS intervention was well tolerated. Future research must focus on the clinical efficacy of patterned rTMS (e.g., theta burst stimulation), and optimum stimulation site and parameters.

Introduction

Neuromodulation techniques like repetitive transcranial magnetic stimulation (rTMS) have been a promising option in schizophrenia. rTMS is a neurostimulation method permitting brain neuronal metabolism modulation in a non-invasive way. Possible mechanism of action of TMS depends on the creation of a transmembrane potential. By the magnetic stimulation, a charge is moved across an excitable cellular membrane, creating a transmembrane potential, or nerve depolarization voltage. If sufficient, this voltage can cause membrane depolarization and initiate an action potential, which then propagates along a nerve like any other action potential. It has repeatedly been demonstrated that high-frequency rTMS (10-25 Hz) enhances brain excitability, and low-frequency rTMS (1 Hz and low) reduces it. It has also been found that high-frequency rTMS applied over the left prefrontal cortex (PFC) increases brain perfusion, while low-frequency rTMS has the opposite effect [1]. Extensive series of studies have suggested the efficacy of high-frequency stimulation applied to the left dorsolateral prefrontal cortex in depression. There is also good evidence for the efficacy of low-frequency stimulation applied to the right dorsolateral PFC.

Cortical excitability and inhibition abnormalities in schizophrenia

Typical pathophysiological models of schizophrenia demonstrate the cortical excitability and inhibition abnormalities. TMS motor evoked potential (MEP), and pre-pulse inhibition studies with schizophrenic subjects exhibit a dysfunction to suppress responses to inputs, which is known as hyperexcitability [2]. Patients with prominent negative symptoms often exhibit reduced activation in frontal brain regions, a state known as hypoactivation [3]. As

rTMS has been linked to cortical modulation, many researchers have explored its therapeutic potential across several schizophrenic symptoms. rTMS uses alternating magnetic fields to increase local cortical excitability via high frequency and decrease excitability via low frequency.

Studies of pathophysiological mechanisms of schizophrenia have often considered cortical excitability and inhibition. Studies of sensory processing using repulse inhibition and evoked potentials suggest that the cerebral cortex is less able to suppress responses to inputs in patients with schizophrenia. Functional magnetic resonance imaging (fMRI) studies confirm that auditory hallucinations are accompanied by activation of speech processing areas of the brain, involving Broca's area and temporal cortex, suggesting an increased excitability [4].

Study results suggest a possible role of reduced inhibitory processes in the pathogenesis of schizophrenia. In paired-pulse TMS paradigm, an initial, conditioning sub threshold TMS pulse is followed shortly after that by a second suprathreshold test TMS pulse. The amplitude of MEP changes produced by the conditioning pulse can be mapped to the inter pulse interval. Shorter inter pulse intervals (i.e., 1–6 msec) produce reductions in the MEP response to the test pulse, whereas longer inter pulse intervals (i.e., 10–20 msec) amplify MEP answers to the test pulse. A decrease in paired-pulse inhibition was detected in patients with schizophrenia when compared with normal control subjects [5]. Inhibitory effects negotiated by cross-callosal projections can also be examined via TMS. TMS of the motor cortex has been shown to inhibit tonic electromyographic activity in ipsilateral muscle groups. Borojerdi et al reported that the delay between transcallosal stimulation and inhibition of electromyographic response was significantly prolonged in schizophrenic patients compared with

normal control subjects [6]. It also reported longer transcallosal suppression of motor contractions in schizophrenia group compared with healthy subjects, although no change in the latency of effect was observed. Certainly medication effects need to be considered in interpreting these group differences.

When we take all the results in the account, schizophrenia is related to reduce cortical inhibition and enhanced cortical excitability. However, drug effects may be complicated, since one study found that antipsychotic medication produced less early inhibition of MEPs [7]. Antipsychotic drugs may extend the duration of transcallosal inhibition induced by TMS. Study results suggest that schizophrenia is associated with reduced cortical inhibition that is reversed in part by antipsychotic drugs [8]. Abnormally short-interval intracortical inhibition has also been reported in patients with schizophrenia [9]. Short-interval intracortical inhibition abnormalities may link to core symptoms of schizophrenia with several studies reporting correlations between positive symptoms and short-interval intracortical inhibition strength. Short-interval intracortical inhibition deficits are also thought to be related to deficient cortical inhibition in different stages of schizophrenia, including chronic and medicated or recently diagnosed and unmediated cases [8]. Abnormal cortical-inhibition has been hypothesized to contribute to social cognition deficits in schizophrenia [10].

Resting-state functional network connectivity in schizophrenia is another research area. Functional connectivity is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions. Examining the brain as a network of functionally interacting regions can provide new insights about neuronal communication. Functional connectivity studies using electroencephalography measure synchronization. Especially, such synchronous activity has been measured using gamma band oscillations. Neural oscillation is rhythmic or repetitive neural activity observed in the brain. When neurons fire in a synchronous manner, their rhythmic input is reflected in the extracellular field potential as brain oscillations. Examining dysfunction in rhythmic activity in mental disorders has recently emerged as a convincing passageway to define the underlying neural dysfunction. Recently, schizophrenia is at the focus of brain oscillations studies. Resting state gamma oscillations, although less studied, have been found to be deviant in patients with schizophrenia [11]. These high-frequency neural oscillations also have been suggested as biomarkers for schizophrenia.

Effect of rtms on negative symptoms

Negative symptoms are deficits of normal thought processes and emotional responses and are less responsive to antipsychotic medications. They lead to a reduced quality of life, decreased functional ability, and the burden on others than do positive symptoms. Due to the poor response to medications, the development of novel treatments for negative symptoms of schizophrenia is critical. rTMS has been offered as a promising treatment for the negative symptoms of schizophrenia. During the past decade, several trials have reported on the efficacy of rTMS treatment; however, the results were inconsistent.

The first study examining effects of higher-frequency rTMS

delivered to PFC in patients with schizophrenia with predominantly negative symptoms was reported by Cohen et al [12]. rTMS at 20 Hz was given daily to patients in an open-label fashion to left PFC for 10 days. The results after rTMS indicated no change in hypofrontality; however, negative symptoms presented an overall decrease. An improvement in neuropsychological test performance was also noted, although only performance in a delayed visual memory task achieved statistical significance.

Rollnik et al. examined, in a double-blind, crossover design, the effects of higher frequency rTMS delivered to left prefrontal cortex in 12 schizophrenia patients with negative symptoms [13]. In this study, rTMS was delivered to left DLPFC each day for 2 weeks. Each stimulation session consisted of twenty 2-second pulse trains at 20 Hz and 80% of MT. The Brief Psychiatric Rating Scale score significantly decreased following active rTMS compared with sham stimulation, whereas depressive and anxiety symptoms did not change significantly.

Wobrock et al. evaluated the efficacy of 10-Hz rTMS applied to the left DLPFC for the treatment of predominant negative symptoms in schizophrenia. They conducted a randomized, sham-controlled, double-blind trial in which 76 patients were treated with 10-Hz rTMS applied 15 sessions over the left DLPFC as added to the ongoing treatment, and 81 patients were given sham rTMS. There was not any statistically significant difference noted in improvement in negative symptoms, cognitive function or depression between the two groups at day 21 or subsequently through day 105. However, there was a small, but statistically significant, improvement in positive symptoms in the active rTMS group, limited to day 21. They concluded that application of 10-Hz rTMS to the left DLPFC was well tolerated but was not found to be superior compared with sham rTMS in correcting negative symptoms [14].

Dlabac et al. performed a meta-analysis with 9 randomized controlled trials including 213 patients, to assess the efficacy of prefrontal rTMS for managing negative symptoms of schizophrenia. The mean weighted effect size for rTMS versus sham was in the small-to-medium range and statistically significant. When only the studies with a stimulation frequency of 10 Hz included, the mean effect size increased to 0.63. Studies with at least 3 weeks duration had a larger mean effect size when compared to studies with shorter treatment duration. They concluded that the results of this meta-analysis warrant further study of rTMS as a potential treatment of negative symptoms of schizophrenia [15].

Another study by Hajak et al. included 20 patients with schizophrenia who received high-frequency TMS over 10 days to the left DLPFC [16]. At the end of the study, functional neuroimaging was performed. There was a significant decrease in negative symptoms and depressive symptoms while positive symptoms seemed to worsen. However, no changes were noted on the neuroimaging. Goyal et al. [17], showed improvement in negative symptoms in their double-blind, sham-controlled study of 10 right-handed patients diagnosed with schizophrenia. Prikryl et al. [18], also found improvement in negative symptoms in their randomized, sham-controlled study of 22 patients with schizophrenia who had prominent negative symptoms and were stabilized on antipsychotic medication. Schneider et al. [19],

used 10Hz TMS at 110 percent of the motor threshold over the left DLPFC in 51 patients with schizophrenia, which showed significant benefit in reducing negative symptoms as well as neurocognitive deficits. Cordes et al. [20], found mild to moderate effect using 10 Hz stimulation at 110 % MT in a sham-controlled trial of 35 individuals with chronic schizophrenia. In a group of 22 chronic, hospitalized patients with schizophrenia, high-frequency TMS was not found to have a therapeutic effect [21]. Novak et al. [22], were unable to show that high-frequency rTMS over the left DLPFC would decrease negative symptoms in 16 patients with schizophrenia. This study only used 90- percent motor threshold with a total of 2000 stimuli per session. Although Mogg et al. [23], in negative symptoms, they did see some improvement in cognitive function in their study of 17 patients with schizophrenia who were treated with TMS. Possibly, rTMS may provoke neural plasticity in the prefrontal circuits of the brain by facilitating dopaminergic, GABAergic and glutaminergic neurotransmission [24] and this may be reflected by a change in cognition after rTMS treatment.

In another double-blind, randomized controlled study, authors assessed the therapeutic effects of high-frequency left DLPFC rTMS on negative symptoms of schizophrenia. In the study, 117 patients with negative symptoms were randomized to a 20-day course of either active rTMS applied to the left DLPFC or sham rTMS. They reported that treatment with high-frequency rTMS for 6 weeks significantly improved negative symptoms in the high-frequency group as compared to the sham group. The decline of negative symptoms persisted to the 6-months follow-up assessment [25].

Two previous studies have investigated the effect of rTMS treatment in patients with schizophrenia on neuronal activation [26,27]. Both of the studies applied rTMS treatment to the left DLPFC. However, both studies did not reveal any statistically significant differences in neuronal activation between the sham and the active rTMS groups. It has been proposed that using a relatively high number of rTMS stimuli may be more efficient and effects of different rTMS parameters and fMRI tasks targeting relevant brain circuitry deserve further investigation [28].

Zhao et al., compare the effect of four different rTMS protocols in the treatment of the negative symptoms of schizophrenia. Ninety-six patients with predominantly negative symptoms were randomly allocated to four treatment groups: 10 Hz, 20 Hz, theta burst stimulation, and sham rTMS. In the first three groups, the left DLPFC was stimulated at 80% of the motor threshold five times per week for four weeks. Two subjects in the control group and one subject from the 20 Hz group dropped out during the trial. After 4 weeks of rTMS treatment, all the active rTMS groups had lower scores on the clinical scales of negative symptoms and general psychopathology scales, compared to the control group. The theta burst stimulation group had significantly more decline in these scores compared to the 10 Hz and the 20 Hz groups. There were not any significant differences noted between the 10 Hz and 20 Hz groups. There was no pre- versus post-treatment differences in the positive symptom scale scores between the four groups. There were not any serious adverse events reported. The authors concluded that rTMS, particularly the theta burst stimulation protocol for rTMS, is a safe and efficient treatment method for patients with prominent negative symptoms [29].

A recent study aimed to assess the effect of rTMS on their individual domains of negative symptoms, such as affective flattening, avolition, anhedonia, and impaired attention. Forty schizophrenic male patients on stable antipsychotic medication with prominent negative symptoms were included in the study. They were divided into 15 sessions of 10 Hz stimulation over the left DLPFC and sham groups. The active rTMS group demonstrated a statistically significantly higher reduction in all domains of negative symptoms of schizophrenia. They reported that high-frequency stimulation of the left DLPFC may represent an efficient augmentation of antipsychotics in relieving the negative symptoms of schizophrenia [30].

Cerebellum and cortico-thalamo-cerebellar circuit

The cerebellum and cortico-thalamic-cerebellar circuit have been implicated in the pathophysiology of schizophrenia. Patients with schizophrenia exhibit deficits supporting cerebellar dysfunction, such as neurological soft signs, impaired eyeblink conditioning, procedural learning deficits, dyscoordination, abnormal posture and poor cognitive performance. Stimulation of cerebellum might be a novel target for treating patients with schizophrenia. Resting state gamma activity is a biomarker related to functional brain connectivity. To investigate the effect of cerebellar-rTMS on resting state gamma activity, while studying its efficacy in 11 recent onset schizophrenia patients who received 10 sessions of high-frequency rTMS to midline cerebellum over 2 weeks. Over the treatment course, a significant decrease was seen on negative syndrome and depression scores. Gamma spectral power in left frontal and temporal segments reduced significantly after administration of rTMS. The authors concluded that cerebellar-rTMS might be a useful adjunct to treat negative and affective symptoms in schizophrenia [31].

Effect on social cognitive impairments

Schizophrenia patients often report poor functional abilities to be one of the most disturbing consequences of their disorder; improvement of functional outcomes has become an important treatment target. Neither typical nor atypical antipsychotic medication significantly improves deficits in facial affect recognition. However, adjuvant cognitive remediation focusing on social cognition in general or on facial affect recognition, in particular, has shown promising results. According to a recent meta-analysis, social cognitive training programs have moderate-to-large effects on both social cognitive performance (including facial affect recognition) and observer-rated community function [32]. Other add-on treatments, like brain stimulation methods, have not yet been investigated enough concerning their effects on social cognitive impairments in schizophrenia. A sham-controlled study evaluated the effects of adjunctive rTMS on facial affect recognition in patients with chronic schizophrenia. In this study 36 patients with a diagnosis of schizophrenia were randomly and double-blindly distributed to groups of 10 sessions 10 Hz rTMS or sham stimulation. Authors reported that the facial affect recognition improved significantly in the rTMS group. The authors also reported that there was no correlation between clinical improvement and facial affect recognition. The results indicate that prefrontal 10 Hz rTMS stimulation may help to correct impaired facial affect recognition in schizophrenia [33].

Conclusion

Several studies recently investigated the effects of rTMS on negative symptoms of schizophrenia. Although there are many promising results, current evidence does not fully support the clinical use of rTMS in the treatment of negative symptoms or cognitive dysfunction in patients with schizophrenia. Given the often disabling nature of these symptoms, clinical use of this technique could be justified in certain cases although overall response rates are not likely to be high. Treatment of cognitive dysfunction with rTMS is a promising but new area of research. Regarding side effects, the active rTMS intervention was well tolerated. Future studies will also need to identify predictive markers to target accurately patient subgroups with a high likelihood to respond to rTMS.

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