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Use of Repetitive Transcranial Magnetic Stimulation in Schizophrenia

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ABSTRACT

In this chapter, we explore the evidence concerning the efficacy of repetitive transcranial magnetic stimulation (rTMS) to treat schizophrenia. The majority of protocols have utilized low-frequency suppressive rTMS over the left TPC with some therapeutic benefits in ameliorating auditory hallucinations. Add on priming, however, leads to particularly better responses in means of faster reduction in loudness of AVH. 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. Also, studies should examine the factors that may affect the response to rTMS, such as age, genetics, symptom dimensions and concomitant medications. Future studies will also need to identify predictive markers to target accurately patient subgroups with a high likelihood to respond to rTMS.

Keywords: Transcranial Magnetic Stimulation; rTMS; Schizophrenia

INTRODUCTION

Schizophrenia is a debilitating psychiatric disorder with unknown etiology. Genetics and early environment appear to be relevant contributory factors. The symptomology of schizophrenia is typically divided into two categories: positive symptoms (hallucinations, delusions, etc.) and negative symptoms such as avolition, alogia, blunted affect, anhedonia. Although positive symptoms respond well to medication, the response of negative symptoms to medication is often limited.

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. 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]. Following high-frequency stimulation, up-regulation of 5-HT1A and 5-HT2 serotonin receptors occurs [2]. Animal and human studies have shown that high-frequency rTMS applied over the left PFC modulates the dopamine release in the mesolimbic and mesostriatal dopaminergic pathways [3].

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 [4]. Patients with prominent negative symptoms often exhibit reduced activation in frontal brain regions, a state known as hypoactivation [5]. 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 prepulse 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 [6].

The most straight forward TMS-based method for assessing cortical excitability is to determine the threshold for eliciting motor activity through electromyographic recordings of peripheral

muscles MEPs while administering single-pulse TMS to the motor cortex. Lower motor threshold (MT) can be interpreted as higher cortical excitability. A study by Puri et al. found that the latency of MEPs in response to TMS was significantly shorter in the patients with schizophrenia, implying dysfunction of inhibitory mechanisms [7]. Pascual- Leone et al. [8] also reported abnormalities in laterality of MT in patients with schizophrenia. They found that there was nearly a 10% higher MT for the left hemisphere compared with the right hemisphere in healthy subjects.

Study results suggest a possible role of reduced inhibitory processes in the pathogenesis of schizophrenia. In paired-pulse TMS paradigm, an initial, conditioning subthreshold 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 interpulse interval. Shorter interpulse intervals (i.e., 1–6 msec) produce reductions in the MEP response to the test pulse, whereas longer interpulse 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 [9]. 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. Boroojerdi 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 [10,11]. 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 reduced 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 [12]. Antipsychotic drugs may extend the duration of transcallosal inhibition induced by TMS. Daskalakis et al.'s study results suggest that schizophrenia is associated with reduced cortical inhibition that is reversed in part by antipsychotic drugs [13]. Abnormally short-interval intracortical inhibition has also been reported in patients with schizophrenia [14]. 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 unmedicated cases [13]. Abnormal cortical-inhibition has been hypothesized to contribute to social cognition deficits in schizophrenia [14,15].

Arbabshirani et al. [16] researched resting-state functional network connectivity in schizophrenia. 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 [17]. These high-frequency neural oscillations also have been suggested as biomarkers for schizophrenia.

EFFECTS OF RTMS ON AUDITORY VERBAL HALLUCINATIONS [AVH]

About 60–80% of schizophrenic patients experience auditory verbal hallucinations [AVH]. There are four commonly recognized types of auditory hallucinations: commanding or commenting hallucinations, voices of one's thought, thought broadcasting auditory hallucinations and non-verbal auditory hallucinations. AVH often produce severe distress and disability. In about 25% of patients, auditory hallucinations respond poorly to antipsychotic medication [18]. The fMRI studies suggest a direct involvement of speech perception neurocircuitry. Support for this view derived from the observation that patients with auditory hallucinations, compared with healthy control subjects, are more likely to experience perceptual illusions of words or word phrases when listening to acoustic noise [19]. These early findings suggest excessive sensitivity or reactivity of speech perception systems.

Neuroimaging studies show activation of brain areas during auditory hallucinations that are active during speech perception [20]. fMRI studies have detected activation in TPC during auditory hallucinations which is nearby the Wernicke's area and is also active during perception of speech [21]. It is hypothesized that 1-Hz rTMS delivered to areas of the brain dedicated to speech perception might reduce auditory hallucinations [22]. Various studies have been conducted recently investigating the effects of rTMS on AVH. As AVH is linked to cortical hyperexcitability, the majority of protocols have utilized low-frequency suppressive TMS over the left temporoparietal cortex [TPC]. Typical parameters are 1 Hz frequency (inhibitory), to left TPC, with subthreshold intensity.

Several studies have been reported the efficacy of 1 Hz rTMS treatment, but results were inconsistent. Slotema et al. performed a literature search from 1966 through October 2008 for trials of rTMS mental disorders. They obtained data from randomized, sham-controlled studies of rTMS treatment for AVH (7 studies) and negative symptoms in schizophrenia (7 studies) The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms of schizophrenia was found to be 0.39 and 0.54 in the treatment of AVH. With these results, rTMS was superior to sham treatment. Side effects were reported to be mild. They concluded that rTMS

is a promising treatment option for depression, for auditory verbal hallucinations, and possibly for negative symptoms [23].

Aleman et al. [24] observed a significant mean weighted effect size for rTMS versus sham across the 10 studies, involving 212 patients. When only studies that used continuous stimulation (9 studies) were included, the mean effect size increased even more. In this meta-analysis, authors did not report any significant effect of rTMS on a composite index of general psychotic symptoms. They concluded that rTMS does not appear to be an efficacious treatment for positive symptoms beyond auditory hallucinations.

Tranulis et al. [25] applied a meta-analysis to explore the efficacy of rTMS in treating medication-resistant AVH. They searched the electronic databases for studies comparing the effect of low-frequency rTMS over the left TPC to sham stimulation in patients suffering from AVH. From 265 available abstracts, 6 parallel-arm, double-blind placebo-controlled and 4 crossover controlled trials, they found that low-frequency rTMS over the left TPC has a medium effect size action on medication-resistant AVH. Similarly, Freitas et al. [26] conducted meta-analyses in 2009 which includes the all prospective studies of the rTMS in schizophrenia evaluating the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) to treat negative symptoms, and 1 Hz rTMS to the left TPC to treat auditory hallucinations and overall positive symptoms. When analyzing controlled and uncontrolled studies together, the effect sizes showed significant and moderate effects of rTMS on negative and positive symptoms. However, the analysis of the sham-controlled studies revealed a small non-significant effect size for negative (0.27, p=0.42) and positive symptoms (0.17, p=0.13). When specifically analyzing auditory hallucinations, the effect size for the sham-controlled studies was large and significant (1.04; p=0.002). The authors decided that there was a need for additional controlled, extended trials to evaluate the efficacy of rTMS on positive and negative symptoms of schizophrenia. They also suggested the need for exploration for alternative stimulation protocols.

Although low-frequency stimulation over left TPC seems to be effective in relieving AVH symptoms, it does not appear to have any impact on other positive symptoms of schizophrenia. Although Freitas and colleagues were able to find a significant impact in their meta-analysis for AVH, when all non-sham studies were eliminated from the analysis, all therapeutic effects of TMS on other positive symptoms disappeared. Further research examining the stimulation of different cortical areas using different stimulatory paradigms is recommended.

In a study reported by Geller et al. 10 patients with schizophrenia and 10 patients with depression were examined to determine if mood changes could be induced and whether different effects could be obtained in various patient groups [27]. Very-low-frequency (once per 30 seconds) rTMS was administered on each side of the brain, 15 pulses each. Two of 10 patients with schizophrenia appeared to improve, at least transiently. Feinsod et al. [28] reported a non-blind study in which 7 of 10 patients with schizophrenia experienced decreased anxiety and

restlessness in response to low-frequency frontal rTMS. On the other hand, a later double-blind study examining the effects of low frequency rTMS delivered to right DLPFC did not report any improvement following active stimulation relative to sham stimulation [29].

Bagati et al. [30] conducted a study in 2009 that included 40 patients with schizophrenia who were randomized to either an rTMS group or a control group. Both groups were treated with standard antipsychotics following a 10-day preliminary phase in which the experimental group received low-frequency TMS over the left TPC. AVH was significantly reduced in the rTMS group of patients. Similarly, Vercammen et al. [31] reported a significant reduction in hallucination frequency in patients with schizophrenia who received TMS to the left TPC, as well as a decrease in self-reported affective responsiveness in patients who received TMS to bilateral TPC.

Self-mutilation is one of the most perilous complications confronted in psychiatric patients and is often related to AVH. A case report presented the successful treatment of AVH with 20 sessions of 1 Hz targeting areas of elevated metabolic activity in the TPC [32].

Results vary across controlled and uncontrolled studies in the treatment of auditory hallucinations using low-frequency TMS to the left TPC. This could be attributed to the heterogeneity of study methodology. One out of three studies that used a dose of 80 % MT showed positive results (33%) in reducing AVH while the positive result ratio is seven out of 12 studies that used 90 percent of MT dose (58%) and two out of two studies (100%) that used a dose of 100 % MT [33]. However, further data are required to explain the relationship between the parameters of stimulation and efficacy in treating auditory hallucinations. Also, the other factors that are likely to impact the effectiveness of TMS include treatment-resistant symptoms, use of associated medication, such as anticonvulsants.

A sample of 50 patients who diagnosed with schizophrenia or schizoaffective disorder was studied by Hoffman et al. [34]. Forty-two of the patients met criteria for medication resistance. Patients were randomly allocated to either active rTMS or sham stimulation. The length of time of unremitting auditory hallucinations was extended, with a mean of approximately 10 years in each group. Patients were classified as responders if hallucination severity was reduced by at least 50%. Using this criterion, they found that 14 of 27 patients [51.9%] achieved responder status in the active group, compared with 4 of 23 (17.4%) in the sham group. Those patients with more frequent auditory hallucinations demonstrated a greater differential effect when compared with patients receiving sham stimulation, whereas patients with lower hallucination frequency showed less robust differences between active and sham rTMS.

Clinical trials using rTMS successfully for treatment of auditory hallucinations have been reported by other groups [35,36]. Lee and colleagues [37] designated 39 patients with treatment-resistant AVH to three groups: active rTMS to the left TPC, active rTMS to the right TPC and sham stimulation. Active rTMS delivered both to left and to right temporoparietal sites produced greater overall symptomatic improvements relative to sham stimulation. Chibbaro and colleagues [38]

studied 16 patients with schizophrenia and auditory hallucinations. rTMS at 1 Hz was administered at 90% of MT during four sessions on successive days. The duration of each stimulation session was 15 minutes. Half the patients received active rTMS, and half received sham stimulation. Both patient groups demonstrated a significant reduction in auditory hallucinations as well as in other positive symptoms after 7 sessions of rTMS. However, at later time points up to and including 8 weeks following the trial, improvements in the sham group disappeared, whereas improvement was retained for patients receiving active rTMS.

There have also been a number of negative studies on the use of TMS in patients with schizophrenia. Fitzgerald et al. [39] did not find a difference in therapeutic effect in domains such as frequency, duration, location, intensity, and disruption of voices between the active and sham groups of 20 patients with the diagnosis of either schizophrenia or schizoaffective disorder. However, authors reported a significant reduction in the loudness of hallucinations. In 2006, Saba et al. treated 18 patients with schizophrenia and refractory AVH with TMS for 10 days [40]. The patients received active or sham rTMS for 10 days over the left TPC. Psychopathological dimensions were measured with the positive and negative syndrome scale and clinical global impression at baseline and after 10 sessions of rTMS. Both groups were improved at the end of the trial, but there was not any statistically significant differences were found between groups. In that study authors concluded that active rTMS failed to show superiority over sham stimulation in the treatment of schizophrenic symptoms. Rosa et al. [41] reported safe administration of TMS concurrently with clozapine in 11 patients with schizophrenia but did not reveal a significant reduction in auditory hallucinations. A large randomized trial [42] in 2011 using fMRI to guide TMS treatment site failed to produce positive results in reducing the severity of auditory hallucinations. This study involved 63 patients who specifically suffered from treatment- resistant auditory/visual hallucinations. In 2011, a study by DeJesus et al. [43] was done using rTMS on 17 patients with refractory schizophrenia who suffered from auditory hallucinations and was being treated with clozapine. The authors reported no significant reduction in auditory hallucinations using r TMS. In a recent meta-analysis Cole et al., we found sixteen controlled studies and two open-label studies using low-frequency TMS [33]. Of the randomized, controlled studies, 10 studies involving a total of 257 subjects with psychosis revealed positive results in treating auditory hallucinations with TMS, while eight studies involving a total of 284 subjects with psychosis did not show any efficacy using TMS.

A systematic review done by Slotema [44] compared 25 randomized, control trials using the severity of the hallucinations or psychosis as the primary outcome measure. No differences were seen with the severity of psychosis. The severity of hallucinations was significantly reduced with the paradigm of left TPC rTMS at 1 Hz. Other models were measured and were unable to make a difference in hallucination severity.

McIntosh and colleagues [45], used the lower-dosed 4-day protocol and found no significant improvement in auditory hallucinations for active rTMS versus sham stimulation. Of note is that

the stimulation was halted every minute for 15 seconds, which may have disrupted physiological effects of rTMS. Another study, reported by Fitzgerald et al. [46], studied 33 patients with treatment-resistant auditory hallucinations. rTMS was applied for 10 sessions for 15 minutes at 1 Hz and 90% of MT. Although active rTMS was found to be related to a significant reduction in the loudness of hallucination, the other measures related to general psychopathology did not result in a greater therapeutic effect.

BILATERAL STIMULATION

rTMS of the left TPC area has been studied as a treatment option for AVH. Although the right temporoparietal junction area has also shown involvement in the genesis of AVH, no studies have used bilateral stimulation. Moreover, little is known about persistence of therapeutic effects. With the aim of investigating short and long term effects of left and bilateral rTMS in schizophrenia patients with AVH, a randomized controlled trial conducted. Bais et al. studied the short and long term effects of 1 Hz treatment of the left temporoparietal junction area compared to sham stimulation, and added an extra treatment arm of bilateral TPJ area stimulation. In this randomized controlled trial, 51 patients with persistent AVH were randomly designated to the left or bilateral temporoparietal junction area stimulation or sham treatment. Patients were treated for six days, twice daily for 20 minutes. Short-term efficacy follow-up measures at four weeks and three months were done. Although self-reported hallucination scores decreased significantly during the trial period, there were no differences between the three treatment groups. Bais et al. did not report reasonable proof for the efficacy of active rTMS, compared to sham rTMS. Furthermore, bilateral rTMS was not found to be superior to left rTMS or sham stimulation in improving AVH [47]. Researchers suggest that the existence of different types of auditory hallucinations may reflect the dysfunction of various neural circuits that may differ in response to rTMS [48].

CEREBELLAR STIMULATION

Two distinct abnormal structural networks were recently identified in patients with persistent AVH, including a bilateral prefrontal system and a bilateral temporal/medial frontal network [49]. It is probable that unilateral temporoparietal stimulation might not be enough to induce a relevant neuronal change in both systems [50] Also, the relationship between structure and function remains unresolved, e.g., in individuals with persistent AVH the impact of neural loss to a neural network transmission, including effects in more remote neural networks, is unclear. Thus, single- site stimulation may not adequately cover all critical regions involved in AVH pathophysiology. In this regard, bilateral or bifocal stimulation could be a promising approach.

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 [51].

PRIMING

Priming rTMS is a novel paradigm, where low-frequency rTMS is preceded by a short period of high-frequency rTMS. Priming stimulation with high-frequency rTMS followed by 1Hz rTMS has been exhibited an enhanced neural response compared to low-frequency rTMS alone when applied to right DLPFC. It has been proposed that enhanced inhibition with priming stimulation would be more efficient in the treatment of refractory AVH. Moreover, it is better tolerated than higher frequency stimulation paradigms.

Two randomized sham-controlled studies, so far, have investigated the priming technique and found that it was not significantly better than 1-Hz rTMS [52,53]. Both these studies included patients with medication-resistant AVH. In another controlled study, 40 recent onset schizophrenia patients were randomized to groups of low-frequency rTMS preceded by priming and low-frequency rTMS without any priming. Both treatments were directed at the left TPC. The authors found that the severity of AVH and other psychotic symptoms significantly reduced over time without any difference between the two groups. However, a greater improvement on the loudness of AVH in the group with priming stimulation observed during the follow-ups. Add on priming; however, seems to be more effective in a faster reduction in loudness of AVH [54].

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 [55]. 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 [56].

EFFECT ON TOBACCO CONSUMPTION

Tobacco consumption is high and estimated to be 44-88% in schizophrenia patients. High-frequency rTMS over the left DLPFC appeared to decrease tobacco consumption and craving in nicotine-dependent people. Prikryl et al. [57] conducted a study with the aim of questioning the effect of stimulation of left DLPFC with 10 Hz rTMS to decrease cigarette smoking in 35 male subjects with a diagnosis of schizophrenia. The patients were randomized into active and sham stimulation groups. Seven days after the end of 21 sessions of stimulation, cigarette consumption was found to be statistically significantly lower in the active rTMS group. Moreover, the active rTMS group demonstrated significantly lower numbers of cigarettes even in the first week of stimulation.

EFFECT 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. [58]. 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. [59] 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. 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 decreased following active rTMS [$P<0.05$] compared with sham stimulation, whereas depressive and anxiety symptoms did not change significantly.

Wobrock et al. [60] 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 which76 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.

Dlabac et al. [61] 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.

Another study by Hajak et al. included 20 patients with schizophrenia who received high-frequency TMS over 10 days to the left DLPFC [62]. 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. [63] showed improvement in negative symptoms in their double-blind, sham-controlled study of 10 right-handed patients diagnosed with schizophrenia. Prikryl et al. [64] 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. [65] 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 [66] al 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 [67]. Novak et al. [68] 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. [69] 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 [70] 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 [71].

Two previous studies have investigated the effect of rTMS treatment in patients with schizophrenia on neuronal activation [72,73]. 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 [74].

Zhao et al. [75] 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.

A recent study aimed to assess the effect of rTMS on their individual domains of negative symptoms, such as affective flattening, alogia, apathy, 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 [76].

CONCLUSION

Several studies recently investigated the effects of rTMS on schizophrenia. The majority of protocols have utilized low-frequency suppressive rTMS over the left TPC with some therapeutic benefits in ameliorating auditory hallucinations. Add on priming, however, leads to particularly

better responses in means of faster reduction in loudness of AVH. 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 research must focus on the clinical efficacy of patterned rTMS [e.g., theta burst stimulation], optimum stimulation site and parameters. 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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