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USE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT OF AUDITORY HALLUCINATIONS: A CASE REPORT AND BRIEF REVIEW

İŞİTSEL VARSANILARIN TEDAVİSİNDE TRANSKARANİAL MANYETİK UYARIM KULLANIMI: BİR OLGU SUNUMU VE KISA GÖZDEN GEÇİRME

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Abstract

In this case we report the efficacy of repetitive transcranial magnetic stimulation for treatment resistant auditory verbal hallucinations. The majority of protocols have utilized low-frequency suppressive repetitive transcranial magnetic stimulation over the left temporoparietal cortex with some therapeutic benefits in ameliorating auditory hallucinations. Normalizing the functional connectivity between the temporoparietal and frontal brain regions may underlie the therapeutic effect of repetitive transcranial magnetic stimulation on auditory hallucinations in schizophrenia. Regarding side effects, the rTMS intervention was well tolerated in this case. Future research must focus on the optimum stimulation site and parameters.

Keywords: transcranial magnetic stimulation, rTMS, schizophrenia, auditory hallucinations

Özet

Bu olgu sunumunda tekrarlayan transkranial manyetik uyarımın tedaviye dirençli işitsel varsanılarda etkinliği bildirilmektedir. Literatürde işitme varsanılarında tedavisel etkinliği oldığu bildirilen protokollerin çoğunda sol temporoparietal bölgeye baskılayıcı düşük frekanslı transkraniyal manyetik uyarım kullanılmıştır. Temporoparietal ve frontal beyin bölgeleri arasındaki işlevsel bağlantının düzeltilmesi, şizofrenide işitsel varsanılarda transkranial manyetik uyarımın etkinliğinin altında yatan mekanizma olabilir. transkranial manyetik uyarım bu olguda bildirilen hasta tarafından iyi tolere edilmiştir. Gelecekteki çalışmalar optimum uyarım bölgesi ve parametreleri üzerine yoğunlaşmalıdır.

Anahtar Kelimeler: *transkranial manyetik uyarım, rTMS, şizofreni, işitsel varsanılar*

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1.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 (Kole et al., 1999).

2.Case:

Mr. M is a 43-year-old, right handed male who was diagnosed with schizophrenia 20 years ago. He was on haloperidol 10 mg/day and clozapine 300 mg/day oral antipsychotic treatment. He had a history of treatment resistance to several typical and atypical antipsychotics and also to their combinations. For the last 2 years he was on a stable regimen which leaded to a significant decline in his persecution delusions, however, commenting hallucinations and non-verbal auditory hallucinations persisted. He reported that the auditory hallucinations produce severe distress and respond poorly to antipsychotic medication and electroconvulsive treatment. A detailed assessment did not reveal any other disease or TMS contraindications. Auditory hallucinations were assessed by using the Auditory Hallucination Rating Scale (AHRS) and the patient had a score of 33 at baseline (range of the scale: 2-40). The patient gave informed consent and was included in a rTMS protocol. His current dose of antipsychotic medication was maintained during treatment. 1 Hz TMS applied over the left TPC by figure-of-eight air-cooled coil using the Magstim Superrapid Stimulator (Magstim Company, Whitland, England) for 5 daily sessions per week (1000 pulses per session) for 4weeks. The location of stimulation was given halfway between the left temporal (T3) and left parietal (P3) electroencephalogram electrode sites on the basis of the international 10-20 placement system.

After a week of treatment, AH were improved with a 30% reduction in AHRS score and the improvement was 60% compared to baseline at the end of 4 weeks. This effect continued during the 2 months that followed the acute response. This protocol was well tolerated by the patient

3.Discussion:

About 60–80% of schizophrenic patients experience auditory hallucinations [AH]. 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. AH often produce severe distress and disability. In about 25% of patients, auditory hallucinations respond poorly to antipsychotic medication (Gromann et al., 2012). 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 (Alpert, 1985). 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 (Dierks et al., 1999). 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 (Benson et al., 2001). It is hypothesized that 1-Hz rTMS delivered to areas of the brain dedicated to speech perception might reduce auditory hallucinations (Hoffman et al., 2000). Various studies have been conducted recently investigating the effects of rTMS on AH. As AH 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 AH (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 AH. 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 (Slotema et al., 2010).

Aleman et al. observed a significant mean weighted effect size for rTMS versus sham across the 10 studies, involving 212 patients. When only

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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 (Aleman et al., 2007).

Tranulis et al. applied a meta-analysis to explore the efficacy of rTMS in treating medication-resistant AH. 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 AH. 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 AH (Tranulis et al., 2008). Similarly, Freitas et al. 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 (Freitas et al., 2009).

Although low-frequency stimulation over left TPC seems to be effective in relieving AH 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 AH, 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 (Geller et al., 1997). 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. (Feinsod et al., 1998) 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 (Klein et al., 1999).

Bagati et al. (Bagati et al., 2009) 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. AH was significantly reduced in the rTMS group of patients. Similarly, Vercammen et al. (Vercammen et al., 2009) 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 AH. A case report presented the successful treatment of AH with 20 sessions of 1 Hz targeting areas of elevated metabolic activity in the TPC (Schulz et al., 2015).

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 AH 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 (Cole et al., 2015). 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. (Hoffman et al., 2003). 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 (d'Alfonso et al., 2002; Poulet et al., 2005). Lee and colleagues (Lee et al., 2005) designated 39 patients with treatment-resistant AH 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 (Chibbaro et al.,2005) 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. (Fitzgerald et al., 2008) 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 AH with TMS for 10 days (Saba et al., 2006). 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. (Rosa et al., 2007) 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 (Slotema et al., 2011) 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. (de Jesus et al., 2011) 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 (Cole et all., 2015). 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 (Slotema et al., 2014) 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 (McIntosh et al., 2004), 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. (Fitzgerald et al., 2005), 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.

4.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. Normalizing the functional connectivity between the temporoparietal and frontal brain regions may underlie the therapeutic effect of rTMS on auditory hallucinations in schizophrenia Given the often disabling nature of these symptoms, clinical use of this technique could be justified in certain cases. Regarding side effects, the active rTMS intervention was well tolerated.

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