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MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory hallucinations

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) has shown promise as a treatment for refractory auditory hallucinations (AH) in Schizophrenia. Most previous studies have examined the effect of low frequency, left-sided stimulation (LFL) (1 Hz) to the temporoparietal cortex (TPC). Priming stimulation (6 Hz) prior to LFL stimulation (hereby simply referred to as priming) has been shown to enhance the neurophysiological effects of LFL rTMS alone and, as such, may lead to greater attenuation of AH.
Objective: Therefore, this study evaluated the efficacy of priming rTMS and LFL rTMS compared to sham rTMS using MRI targeting of Heschl's gyrus (HG) within the TPC of subjects with SCZ experiencing refractory auditory hallucinations (AH).
Methods: Subjects between the ages of 18 and 65 were recruited from a tertiary care university hospital. Fifty-four subjects with medication resistant AH were randomized to receive LFL, priming, or sham rTMS for 20 treatments. The primary outcome was reduction of hallucinatory symptoms as indexed by response rates on the Psychotic Symptoms Rating Scale (PSYRATS).
Results: The response rates did not differ among the three treatment groups using an intention to treat analysis. The response rates did not differ in any of the secondary outcome measures. The treatment was well tolerated with minimal adverse effects including no changes in cognition during the study.
Conclusion: These findings suggest that neither priming nor LFL rTMS of Heschl's gyrus are effective at ameliorating refractory AH in schizophrenia.
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Introduction

Despite advances in pharmacotherapy over the last 20 years, a significant percentage of patients with schizophrenia experience disabling refractory symptoms [1,2]. Nearly 40 percent of patients achieve only a partial response and 10 percent experience no response at all [3]. Furthermore, current pharmacotherapy for schizophrenia has a high rate of intolerability, metabolic side effects, and early discontinuation [4]. To date, only a few alternatives have been available for patients with refractory schizophrenia: these generally include ECT and clozapine. Both, however, are associated with significant side effects. Clozapine is associated with hyperlipidemia, blood dyscrasias, diabetes, seizures and cardiomyopathy [5,6]. Similarly, ECT is associated with cognitive impairment [7] and the stigma associated with ECT limits its broader use in treatment refractory patients. Thus, researchers and clinicians have sought novel treatments to target refractory symptoms in schizophrenia. One of the most prevalent refractory symptoms of schizophrenia is auditory hallucinations (AH). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation modality with an excellent tolerability and safety profile [8,9] that has shown some promise in ameliorating refractory AH [10,11].

The majority of previous rTMS studies have broadly targeted the temporoparietal-cortex (TPC) as the primary site of stimulation. Although there are some contradictory findings, a number of

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studies have suggested that the pathophysiology of AH is related to hyperactivity in the left TPC [12,13]. Based on this understanding, Hoffman and colleagues developed a low frequency rTMS protocol applied to the left TPC to modulate the overactive state that drives AH [14,15]. Improvement in the frequency and intensity of AH were observed with a sustained response over 15 weeks [16]. In a larger controlled study, the efficacy of this rTMS protocol was confirmed and the treatment demonstrated an excellent safety and tolerability profile [17].

Numerous investigators have attempted to replicate and extend these findings using open, crossover and parallel randomized controlled designs with mixed results [18–30]. An initial meta-analysis of all acute rTMS treatment studies of AH found an effect size of 0.76 (95% CI = 0.36–1.17) for LFL rTMS applied to the left TPC, despite variation in the duration and methods of stimulation [31]. Two recent meta-analyses confirmed the finding of a medium to large effect size [10,11]. The authors point out that there is a large degree of heterogeneity in these studies. Potential sources of heterogeneity issues included: protocol duration and intensity, differing placebo controls, lack of adequate control of medications and variable assessment of treatment resistance. Overall, the authors suggested that future studies should expand the number of treatment sessions to at least 10 sessions, control for concomitant medications and seek to target cortical hallucinatory activity using fMRI or PET [10,11].

MRI and fMRI techniques to more specifically target the neuroanatomical structures involved in AH have been investigated as a method to optimize efficacy. The first study to attempt fMRI localization gave patients one week blocks of stimulation applied to either the superior temporal gyrus, inferior frontal gyrus (Broca's area) or a control position in the occipital cortex [32]. In half of these, positioning was based on fMRI activation and in the other half, on a structural MRI scan. Overall a significant benefit of rTMS was not evident, and no effect was found for either of the two active stimulation sites. In contrast, another group treated 15 patients openly, with low frequency rTMS targeted to the area of greatest activation observed in fMRI scanning during the experience of AH [33]. There was an overall group reduction in AH severity, but no significant benefit of the fMRI guiding over the TPC localized treatment. In another study, low frequency left-sided (LFL) rTMS was applied to a series of sites activated on fMRI scan for 8 subjects with intermittent AH or to a series of sites proximal to Wernicke's area in 8 patients with continual AH [34]. Stimulation at the left TPC site resulted in a greater rate of reduction in AH severity compared to stimulation at other sites. Interestingly, one of the anatomical sites associated with AH in schizophrenia that has not been studied to date is Heschl's gyrus. This anatomical region is primarily involved in auditory perception and could theoretically be involved in the pathogenesis of AH [35]. In fact, this region of the cortex has been found to be associated with functional imaging [36–38] and structural imaging changes [39,40] in patients with AH and schizophrenia. Anatomically, Heschl's gyrus is typically located 0.7–1.3 cm below the surface. Therefore, this anatomical site holds some potential as a more optimal stimulation target, as the magnetic field of rTMS can penetrate the cortex to a depth and diameter of 3 cm when using intensity at 115% of the resting motor threshold (RMT) [41].

A recent, large study that extended treatment duration to 15 sessions, did not demonstrate a difference between fMRI-guided LFL rTMS to the area of maximal activation during AH, LFL rTMS approximated to the TPC and sham [42]. Others have suggested that novel protocols such as theta burst stimulation and priming stimulation be applied in clinical rTMS trials in schizophrenia in order to optimize efficacy [43]. Priming stimulation, which involves high frequency (6 Hz) rTMS stimulation followed by low frequency rTMS, has been shown to have greater inhibitory effects than low-frequency rTMS alone when applied to the motor cortex [44] and to have greater antidepressant effects than LFL rTMS when applied to right DLPFC [45]. As schizophrenia is associated with cortical hyperexcitability and deficits in cortical inhibition, it was hypothesized that enhanced inhibition with priming stimulation would be more effective for refractory AH and better tolerated than higher frequency stimulation paradigms [44,46].

Therefore, the present randomized, sham-controlled study sought to examine the efficacy of rTMS in treating refractory AH by optimizing the following factors: (1) using MRI-guided localization of Heschl's gyrus (a TPC region not specifically targeted in previous studies); (2) increasing the treatment duration to 4 weeks; and (3) enhancing LFL with priming stimulation. We hypothesized that priming rTMS would show greater efficacy than LFL alone and sham rTMS and that LFL would show greater efficacy than sham rTMS. Secondarily, differences in tolerability and adverse effects profile among the three groups were evaluated.

Methods

Subjects

Subjects were recruited from the Schizophrenia Program and from posted flyers within the Centre for Addiction and Mental Health, a university teaching hospital that provides psychiatric care to a large urban catchment area. Subjects were recruited through posted flyers and clinician referrals. Subjects were recruited between January 1, 2004 and January 1, 2009. Subjects were included if they: (1) were voluntary and capable to consent based on the subjects' ability to provide a spontaneous narrative description of the key elements of the study; (2) had a diagnosis of Schizophrenia or Schizoaffective Disorder as confirmed by the Structure Clinical Interview for the DSM-IV (SCID-IV [47]); (3) were between the ages of 18 and 65; (4) met criteria for at least moderate severity on item 3 of the positive sub-scale of the Positive and Negative Symptom Scale (PANSS) [48]; (5) were willing to keep the dose of antipsychotic stable for the duration of the study; and (6) met criteria for medication resistance, defined as daily AH despite 2 adequate 6-week trials of at least 2 antipsychotic medications and including 1 atypical antipsychotic medication [16]. Subjects were excluded if they met any of the following criteria: (1) DSM-IV history of substance abuse or dependence in the last 6 months; (2) presence of concomitant major and unstable medical or neurologic illness or a history of seizures; (3) pregnant; (4) received rTMS for any reason in the past; (5) psychotropic dosage change in the four weeks preceding study entry. Medication therapy was continued during the trial although changes in antipsychotic medication were not allowed from 4-weeks prior to commencement of the trial and throughout. Concomitant medications including (1) benzodiazepines, (2) mood stabilizers (3) antidepressants and anticholinergics were permitted. Written informed consent was obtained on a form approved by the research ethics board of the Centre for Addiction and Mental Health.

Treatment protocol

After enrollment and collection of baseline demographic and clinical data, individuals were randomized to one of three rTMS treatment arms (sham, LFL, priming). By necessity, operators administering the treatment learned the condition immediately prior to treatment initiation (and were aware of the treatment allocation). However, these operators were not involved in any other aspect of the study (i.e., recruitment or clinical evaluation). Subjects and clinical raters were blind to randomization group.