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Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory–verbal hallucinations in schizophrenia: A randomized controlled trial ☆

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ABSTRACT

Background: Neuroimaging findings implicate bilateral superior temporal regions in the genesis of auditory–verbal hallucinations (AVH). This study aimed to investigate whether 1 Hz repetitive transcranial magnetic stimulation (rTMS) of the bilateral temporo-parietal region would lead to increased effectiveness in the management of AVH, compared to left rTMS or placebo.
Methods: 38 patients with schizophrenia (DSM-IV) and medication-resistant AVH were randomly assigned to 1 Hz rTMS treatment of the left temporo-parietal region, bilateral temporo-parietal regions, or placebo. Stimulation was conducted over 6 days, twice daily for 20 min, at 90% of the motor threshold. Effect measures included the Auditory Hallucination Rating Scale (AHRS), Positive and Negative Affect Scale (PANAS), and a score for hallucination severity obtained from the Positive and Negative Syndrome Scale (PANSS).
Results: All groups showed some improvement on the total AHRS. Hallucination frequency was significantly reduced in the left rTMS group only. The bilateral rTMS group demonstrated the most remarkable reduction in self-reported affective responsiveness to AVH. A modest, but significant decrease on the PANSS hallucination item was observed in the combined rTMS treatment group, whereas no change occurred in the placebo group. The left rTMS group showed a significant reduction on the general psychopathology subscale.
Conclusion: Compared to bilateral or sham stimulation, rTMS of the left temporo-parietal region appears most effective in reducing auditory hallucinations, and additionally may have an effect on general psychopathology. Placebo effects should however not be ruled out, since sham stimulation also led to improvement on a number of AVH parameters.

1. Introduction

Auditory–verbal hallucinations (AVH) constitute one of the core symptoms of schizophrenia. Approximately 50 to 70% of all patients with schizophrenia report hearing 'voices' at some point during the course of the illness (Andreasen and Flaum, 1991). Furthermore, AVH persist in about 25% of cases, despite

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adequate treatment with antipsychotic agents (Shergill et al., 1998). Since the advent of neuroimaging techniques, there has been considerable interest in relating AVH to underlying brain structures and functions. Converging evidence from neuroimaging studies points to the involvement of speech production and perception areas in the genesis of AVH. Several structural neuroimaging studies have linked increased severity of AVH to volume reductions of temporal structures, particularly of the superior temporal gyrus (STG), mostly in the left hemisphere, but sometimes bilaterally (Onitsuka et al., 2004; Gaser et al., 2004; Neckelmann et al., 2006). Functional neuroimaging studies furthermore suggest that in addition to secondary, and occasionally primary sensory cortices, abnormal activation in a distributed network of prefrontal, cingulate, limbic, subcortical and cerebellar regions appears to contribute to the experience of AVH (Shergill et al., 2000; Lennox et al., 2000, and for a review, see Allen et al., 2008).

Transcranial magnetic stimulation (TMS) is a non-invasive technique that enables safe, relatively painless focal brain stimulation in humans. In repetitive TMS (rTMS) a train of pulses of the same intensity is delivered to a single brain area at a given frequency. Low frequencies (≤1 Hz) can suppress excitability of cortical neurons (Pascual-Leone et al., 2002). This observation suggests a therapeutic value against pathological neuronal hyperactivity observed in AVH (Hoffman and Cavus, 2002). Several studies have reported that application of low frequency rTMS over the left temporo-parietal cortex in patients suffering from AVH leads to an amelioration of symptoms, lasting for several weeks following treatment cessation (Poulet et al., 2005; Chibbaro et al., 2005; Hoffman et al., 2003; Hoffman et al., 2005; Lee et al., 2005; d'Alfonso et al., 2002). In contrast, some experimental trials have yielded null effects or mixed results (Schonfeldt-Lecuona et al., 2004;McIntosh et al., 2004). On closer inspection, methodological variables, such as the use of intermittent rather than continuous stimulation, may explain the absence of effect in these studies. Taken together results have generally been positive. This has been supported by two recently published meta-analyses that confirmed the superiority of rTMS over placebo treatment in reducing medication-resistant AVH (Aleman et al., 2007; Freitas et al., 2009).

Most treatment studies of rTMS effects on hallucination symptoms have restricted stimulation to the left superior temporal area. However, evidence from neuroimaging studies point to potential bilateral temporal cortex involvement in the genesis of auditory hallucinations (Shergill et al., 2000; Lennox et al., 2000; Lennox et al., 1999). The current study sought to investigate whether bilateral stimulation could improve the efficacy of the rTMS protocol, compared to left STG stimulation alone, and sham stimulation. Whereas left superior temporal areas are hypothesized to be involved in 'speech' perception during hallucinations, i.e. the comprehension of the phonological and semantic characteristics of the hallucinated content, right temporal cortex may be more associated with the processing of prosody and the emotional salience, as AVH are often derogatory and hostile in content. Accordingly, left STG stimulation seems most effective in treating relatively simple characteristics of AVH, such as frequency, loudness and attentional salience. We hypothesized that a bilateral treatment would contribute towards a more complete management of the symptoms, not only diminishing frequency of AVH, but also affecting emotional salience.

2. Materials and methods

2.1. Subjects

Thirty-eight patients were recruited from in- and outpatient facilities of four local psychiatric hospitals (Mental Health Care Centers of the provinces Drenthe, Groningen, and Friesland, and the Department of Psychiatry at the University Medical Center Groningen, The Netherlands). Prior to participation, patients received written and oral information on the procedures and goals of the study, and informed consent was obtained. One subject withdrew from the study, during the first week of treatment, due to exacerbation of psychotic symptoms, which her clinician ascribed to personal circumstances and not to any specific rTMS-related effect. A second subject was excluded, because she failed to comply with the medication requirement (i.e. she started using additional medication during the course of the rTMS treatment). All patients fulfilled the DSM-IV criteria for schizophrenia. Diagnoses were based on clinical assessment by the patient's physician and subsequently confirmed by a trained interviewer (A.V.), using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Giel and Nienhuis, 1996) prior to inclusion in the study. Patients were admitted to the study if they reported frequent medication resistant AVH (at least daily). Medication resistance was defined as the daily AVH occurring in face of at least two adequate trials of antipsychotic medications. All subjects were treated with stable doses of antipsychotic medication for at least 4 weeks prior to study inclusion, and this dose was unchanged for the duration of the study. Exclusion criteria included TMS and MRI contraindications: a personal or family history of epileptic seizures, a history of significant head trauma or neurological disorder, the presence of intracerebral or pacemaker implants, inner ear prosthesis or other metal prosthetics/implants, severe behavioral disorders, current substance abuse, and pregnancy. Competence to give informed consent was assessed by the patient's physician. Enrolment in the study spanned the period of September 2006 to January 2009. Patients were either admitted to an inpatient care unit for the duration of the trial (e.g. when daily travel to the research center was too demanding), or participated as outpatients, admitted to the day-hospital. Demographical and clinical characteristics are provided in Table 1.

2.2. Procedure

2.2.1. rTMS protocol

Institutional review board approval (University Medical Center Groningen, The Netherlands) was obtained for the procedure as described below. Patients were randomly allocated to one of three treatment conditions. A power analysis based on a study with a similar design (Brunelin et al., 2006) revealed that a power of .80 would be attained with the inclusion of 12 subjects per group. One group of 12 patients received left sided rTMS, and another group of 12 patients received bilateral rTMS, each over the course of 6 consecutive work days, with two sessions each day, similar to the procedure of Brunelin et al. (2006). A third group of 12 patients constituted the placebo control group and received sham stimulation for the same amount of time. A double blind parallel design was used, in which only the TMS administrator (A.V.) was aware of the intervention type. Thus participants, clinical raters, and all