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# The effect of rTMS on auditory hallucinations: Clues from an EEG-rTMS study

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ABSTRACT

*Objective:* Repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal region has been proposed as a therapeutic option for auditory verbal hallucinations (AVH). However, most large randomized controlled trials failed to demonstrate a superior effect of rTMS treatment as compared to sham. Previous studies applied daily rTMS sessions for one or more weeks to summate its effects. However, the effect of a single rTMS treatment on AVH-severity has never been studied, making it unclear if there is an initial effect that could be increased by repeated treatment.
*Methods:* In three separate sessions, twenty-four patients with a psychotic disorder received 1-Hz rTMS to the left temporoparietal cortex, its right-sided homologue or a centro-occipital control site. Severity of AVH was assessed before and after each rTMS session and resting-state EEGs were recorded to investigate the neuronal effects of rTMS.
*Results:* Stimulation of the temporoparietal cortices was not more effective in reducing AVH-severity than control-site stimulation. In addition, EEG-related power and connectivity measures were not affected differently across stimulation sites and changes in neuronal activity did not correlate with changes in AVH-severity.
*Conclusions:* These results may suggest a placebo effect of a single session of 1-Hz rTMS treatment on AVH-severity.



## 1. Introduction

Auditory verbal hallucinations (AVH) are one of the core symptoms of schizophrenia (Nayani and David, 1996). About one-fourth of patients have AVH that are refractory to antipsychotic medication (Shergill et al., 1998). Medication-resistant AVH can lead to severely disrupted social functioning and increased risk for suicide (Falloon and Talbot, 1981; Cheung et al., 1997). For this group, low-frequency repetitive transcranial magnetic stimulation (rTMS), a non-invasive method that uses magnetic pulses to alter brain activity, appears to be a promising treatment option (Hoffman et al., 1999; reviewed by Slotema et al., 2010b). However, the exact mechanism by which low-frequency rTMS may improve AVH remains elusive. When low-frequency rTMS (±1-Hz) is applied over the scalp for at least 15 min, cortical activity at the targeted region is reduced for a short duration of time (Chen et al., 1997). When stimulation with rTMS is applied repeatedly, the targeted area is thought to become less active for a longer period. This effect may be comparable to Long-Term Depression (LTD) as observed in single-cell recordings after prolonged stimulation (Christie et al., 1994; Hoffman and Cavus, 2002). For the treatment of AVH, low-frequency rTMS is usually repeated for several consecutive days, typically daily for 1–3 weeks (Hoffman et al., 1999; Fitzgerald et al., 2005; Slotema et al., 2010a).

Initial randomized-controlled trials (RCTs) have shown a remarkable efficacy of rTMS in reducing AVH as compared to an inactive placebo condition (Hoffman et al., 2000, 2003; Chibbaro et al., 2005; Hoffman et al., 2005; Poulet et al., 2005; Brunelin et al., 2006), which was summarized in several meta-analyses (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010b). However, several large RCTs published after these meta-analyses failed to find a significant difference between real and sham-rTMS (Vercammen et al., 2009; Loo et al., 2010; Slotema et al., 2010a). These recent studies suggest that 1-Hz stimulation may not be effective. It remains unclear whether this lack in effect is caused by a fundamental inability of 1-Hz TMS to affect cerebral areas that are crucially involved in AVH, or, alternatively, if there is an initial

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effect, appropriate summation of this effect is not achieved with once or twice daily repetition. This study aims to further explore the neuronal mechanisms underlying the rTMS effect on AVH by investigating the acute effects of 1-Hz rTMS on AVH-severity and on resting-state electroencephalography (EEG). If a single low-frequency rTMS session can be demonstrated to affect AVH, we expect to find larger decreases in AVH-severity when rTMS is applied to the temporoparietal cortex compared to rTMS at a control area. In addition, decreases in AVH-severity due to rTMS are expected to be associated with changes in brain activity as recorded with EEG before and after each rTMS session.

## 2. Methods

### 2.1. Subjects

Thirty-two schizophrenia-spectrum patients experiencing frequent auditory verbal hallucinations (AVH) were recruited at the University Medical Center in Utrecht in The Netherlands. Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992) according to DSM-IV criteria by an independent psychiatrist. The main inclusion criteria were: AVH more frequently than once per hour and treatment-resistance for at least two antipsychotic agents, administered at adequate dosages and for at least six weeks (Hoffman et al., 2003). Antipsychotic and other psychotropic medication were stable for at least three weeks before entering the study and were kept stable during the three weeks of participation. Exclusion criteria were: history of epilepsy, a first-degree relative with epilepsy, head trauma or other cerebral pathology, metal objects inside or around the body that could not be removed, pregnancy, use of benzodiazepines or anti-epileptics, and alcohol use of more than three units per day.

Eight out of thirty-two patients were excluded from analysis (1 patient did not experience AVH during the experimental sessions, 2 patients did not close their eyes during EEG acquisition, from 4 patients no full datasets were available, and 1 patient had trouble answering the questions in the AVH-related questionnaires). Mean age of the remaining 24 patients (17 male, 7 female) included in the analysis was 41 yrs (SD 14, range: 19–59). Demographic and clinical characteristics of participants are presented in Table 1. All patients gave their written informed consent and the study was approved by the ethics committee of the University Medical Center in Utrecht.

### 2.2. Study protocol

Patients received rTMS on three separate occasions on either the left temporoparietal cortex (i.e. midway between the T3 and P3 sites according to the international 10/20 system of EEG electrode placement (Jasper, 1958), the right temporoparietal cortex (i.e. midway between T4 and P4) or the centro-occipital cortex (i.e. the Oz position). As the V1 area of the visual cortex is neither involved in auditory language processing nor in the generation of AVH (Silbersweig et al., 1995; Kandel et al., 2000; Copolov et al., 2003; Jardri et al., 2010; Kuhn and Gallinat, 2011), and in a pilot experiment subjects reported similar scalp sensations during rTMS directed at this area as to left and right temporoparietal cortex stimulation, the centro-occipital cortex was chosen as an active control site. Stimulation of the three sites was interspersed with a week, and stimulation for each patient took place on the same time of day. To avoid bias in allocating patients to one of the six possible sequences of stimulation, patients were enrolled in each arm of the experiment by order of participation (i.e. patient 1 in arm 1, patient 2 in arm 2, etc., patient 7 in arm 1, patient 8 in arm 2 etc.). The design of the study was counterbalanced, i.e. each arm of the six sequences of stimulation was filled by four patients. To investigate whether patients saw phosphenes during occipital cortex stimulation, participants were asked whether they saw anything unusual during stimulation. This question was also asked after left and right temporoparietal cortex stimulation. After the last session, patients were asked to rank their physical sensations during rTMS treatment over the three rTMS sessions.

**Table 1**
Patient characteristics.

| | Patients |
|---|---|
| Age[a] | 41 (14) |
| Gender (F/M) | 7/17 |
| Diagnosis | Psychosis NOS (5); Katatonic schizophrenia (1); Paranoid schizophrenia (14); Disorganized schizophrenia (1); Schizo-affective (3) |
| Age of onset AVH[a] | 20 (12) |
| Antipsychotic medication | Atypical (21); Typical (2); Both (1) |

[a] Data reported as ± standard deviation. NOS = not otherwise specified. AVH = auditory verbal hallucinations.

### 2.3. rTMS

A 70-mm air-cooled figure-of-eight coil (Magstim Company Ltd., Whitland, UK) was used for rTMS treatment at 90% of the individual motor threshold (MT). Each individual's motor threshold was assessed by determining the lowest stimulation intensity at which an observable hand movement contralateral to the stimulated hemisphere could be elicited in five out of ten TMS administrations (Schutter and van Honk, 2006). The MT for occipital stimulation was 90% of the average of the MTs of the left and right hemisphere.

Patients received stimulation for 20 min at 1-Hz. During treatment patients sat in a comfortable chair while their head and the TMS coil were fixated. All participants wore sound attenuating earplugs during the study to prevent hearing damage.

### 2.4. Patient assessments

Before and after each treatment with rTMS, AVH-severity was assessed using three paradigms (Fig. 1). First, patients indicated the presence of AVH by button-press for 10 min. The length of all AVH episodes was added up to calculate total AVH duration in this timeframe. After this, a baseline score regarding AVH-severity during the button-press paradigm was set using the Hallucination Change Scale (HCS) (Hoffman et al., 2003). The HCS is an indication of the general severity of AVH as experienced by the patient. Pre-rTMS HCS scores were always assigned a score of 10. Subsequently, AVH-severity during the button-press paradigm was also assessed using the Auditory Hallucinations Rating Scale (AHRS). The AHRS is a questionnaire assessing multiple characteristics of AVH such as the frequency of occurrence, loudness of voices, length of AVH, influence and discomfort of AVH as experienced by the patient (Hoffman et al., 2003).

After rTMS treatment, patients again performed the button-press experiment for 10 min. After this they indicated the change in AVH-severity relative to the pre-rTMS HCS score of 10 on a scale from 0 to 20. A score of 0 indicated total absence of AVH, while a score of 20 indicated twice the severity of AVH compared to baseline. Subsequently AVH-severity was again assessed using the AHRS.

### 2.5. Electrophysiological recordings

After baseline patient assessments (AVH duration, HCS and AHRS), and preceding rTMS stimulation, resting-state eyes-closed electroencephalography (EEG) data were recorded for five minutes. The procedure was repeated after rTMS stimulation (Fig. 1). Data acquisition