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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

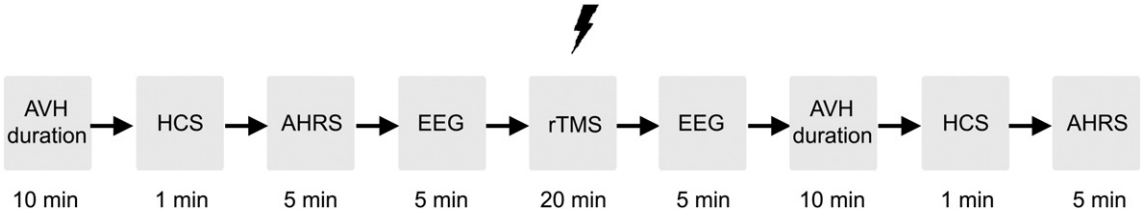

Fig. 1. Outline of the experimental procedure. AVH = auditory verbal hallucination, HCS = hallucination change scale, AHRS = auditory hallucinations rating scale, EEG = electroencephalography.

was performed with BioSemi hardware (Amsterdam, The Netherlands) using a cap with 64 Active Two electrodes, arranged according to the 10–20 system. Signals were digitized on-line by a computer at a rate of 2048 Hz.

2.6. Data analysis

Detailed information regarding EEG power and graph analysis is provided in Supplementary data S1.

2.7. Statistical analyses

All statistical analyses were performed with SPSS (version 15.0). The Greenhouse–Geisser correction was used to adjust the degrees of freedom when the assumption of sphericity was violated in repeated-measures Analysis Of Variance (ANOVA). Pair-wise tests of non-normally distributed data were conducted by Wilcoxon-rank tests instead of paired t-tests. Correlation analyses were conducted using Pearson's correlation coefficient for normally distributed data; otherwise Kendall's tau was used.

2.7.1. Scalp sensations

Scalp sensations across rTMS target sites were analyzed using Friedman's ANOVA.

2.7.2. Patient assessments

The effects of 1-Hz rTMS on AVH duration, HCS score, and AHRS score were analyzed through repeated-measures ANOVA with within-subject factors 'target site' (left temporoparietal cortex, right temporoparietal cortex and occipital cortex) and 'treatment' (pre-rTMS and post-rTMS). Post-hoc paired t-tests were used to examine significant interaction effects, with correction for multiple comparisons using false discovery rate (FDR) correction (Benjamini and Hochberg, 1995).

2.7.3. Electrophysiology

Detailed information regarding statistical testing of EEG power and graph analysis is provided in Supplementary data S2.

3. Results

3.1. rTMS

The treatment was tolerated well by all patients, and no patients experienced phosphenes during rTMS.

3.2. Scalp sensations

Friedman's ANOVA did not reveal any significant differences in scalp sensations across rTMS target-sites [Chi-square = 2.95; df = 2; P = 0.23].

3.3. Patient assessments

Repeated-measures ANOVAs revealed significant main effects of treatment on AVH duration [$F(1,23) = 7.187$; $P = 0.013$], HCS score [$F(1,23) = 13.718$; $P = 0.001$], and AHRS score [$F(1,23) = 10.218$; $P = 0.004$], indicating lower AVH-severity after rTMS. A treatment × location interaction effect was found for HCS score [$F(1,23) = 3.622$; $P = 0.035$]. Post-hoc testing revealed a significant difference after left temporoparietal rTMS and occipital rTMS [$t(23) = -2.300$; $P = 0.0465$], indicating lower HCS score decrease after left temporoparietal rTMS compared to occipital rTMS. Fig. 2 shows average pre-rTMS and post-rTMS AVH duration, HCS scores, and AHRS scores.

3.4. Electrophysiology

3.4.1. Absolute power

Repeated-measures ANOVA revealed significant main effects of treatment on whole-head theta-band power [$F(1,23) = 10.998$; $P = 0.003$] and alpha-band power [$F(1,23) = 6.795$; $P = 0.016$], indicating significant increases in whole-head theta band and alpha-band power after rTMS treatment. No significant main effect was found for the beta band. A treatment × location interaction effect was found for whole-head alpha-band absolute power [$F(1,23) = 3.816$; $P = 0.044$]. Post-hoc testing with false discovery rate (FDR) correction did however not reveal any significant differences. Repeated-measures ANOVAs investigating the local effect of rTMS revealed no significant three-way interactions for all three frequency bands, indicating that rTMS treatment did not lead to different changes in power at the brain area underlying the target site compared to the two non-used target sites across the three stimulation sessions.

3.4.2. Network characteristics

Repeated-measures ANOVA revealed significant main effects of treatment for the clustering coefficient (C) in the alpha-band [$F(1,23) = 4.400$; $P = 0.047$], indicating a decrease in clustering after rTMS. For small-worldness (C/L), significant main effects of treatment were found in the theta band [$F(1,23) = 9.212$; $P = 0.006$] and beta band [$F(1,23) = 4.727$; $P = 0.040$], indicating decreases after rTMS in these frequency bands. No treatment × location interaction effects were observed.

Detailed information for all dependent variables including means and standard deviations are provided in Supplementary data S3.

3.5. Correlation analysis

3.5.1. Power

No significant correlations were found between changes in whole-head theta-band power for each stimulation session and changes in AVH duration, HCS, or AHRS measures. Also no significant correlations were found between changes in whole-head alpha-band power and changes in AVH duration, HCS, or AHRS scores.

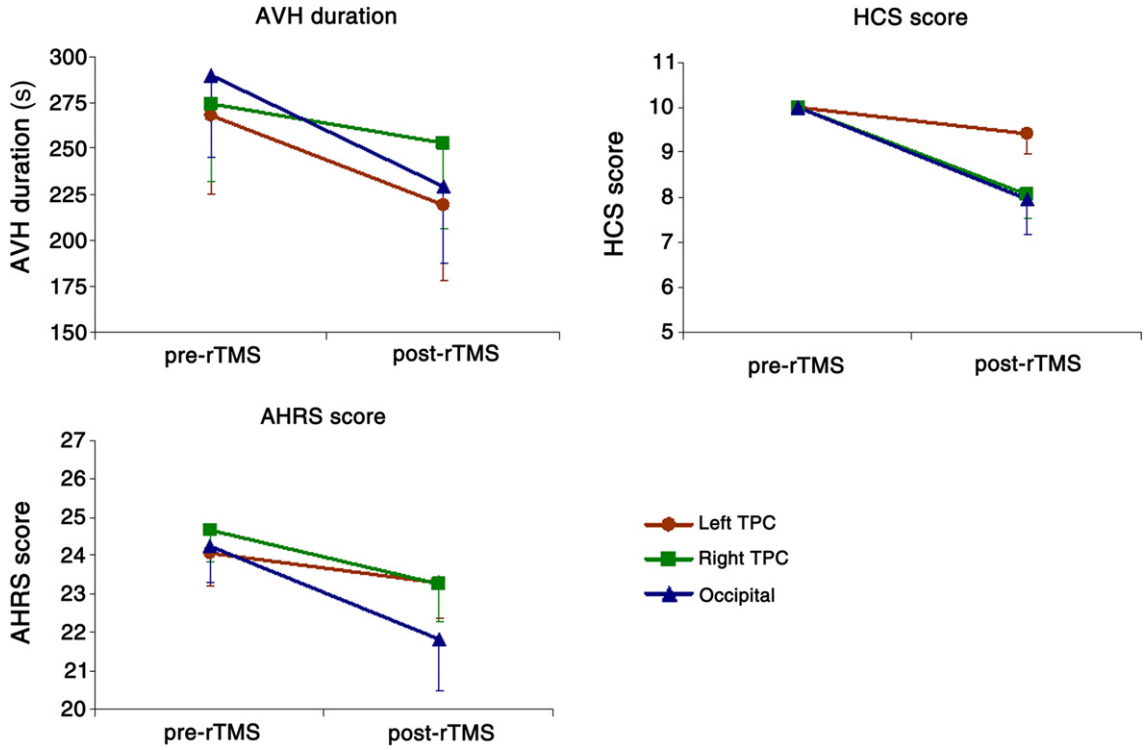

Fig. 2. Average effect of rTMS on Auditory Hallucination Rating Scale (AHRS), Hallucination Change Scale (HCS), and AVH duration. TPC: temporoparietal cortex. Error bars indicate standard error of the mean (SEM).

3.5.2. Network characteristics

A significant correlation between a change in clustering coefficient in the alpha band after left temporoparietal rTMS was found with AVH duration [$r = 0.671$; $P = 0.005$]. This effect was carried by an outlier (on both clustering coefficient and AVH duration). Removal of the outlier led to an insignificant outcome.

4. Discussion

This is the first study to investigate the acute effect of repetitive transcranial magnetic stimulation (rTMS) on auditory verbal hallucinations (AVH). Application of rTMS to the left temporoparietal cortex, right temporoparietal cortex, and the occipital control site all significantly decreased AVH-severity as measured by hallucination duration, the Hallucination Change Scale (HCS), and the Auditory Hallucinations Rating Scale (AHRS). For the HCS, stimulation of the left temporoparietal cortex was less effective in reducing AVH-severity than stimulation of the control site. This effect could not be observed on the duration of hallucinations and on the AHRS. The general observation was that stimulation at therapeutic locations and at the control site all led to symptom decrease, without much difference between the three locations.

Electroencephalography (EEG) recording before and after rTMS treatment revealed that rTMS therapy increased whole-head theta-band power, alpha-band power, and decreased 'small-worldness' in the theta and beta bands. In addition, a decrease in alpha-band clustering coefficient was observed. These overall changes did not correlate with changes in AVH-severity. Also, no differential effect of rTMS target-site was found on whole-head, local, and network-based EEG measures. Similar to the clinical effects, we found neuronal responses to all three locations, without a difference between therapeutic and control sites.

It is currently unclear if 1-Hz rTMS can be used effectively to treat AVH. Since 25% of schizophrenia patients with AVH are medication-resistant, an alternative treatment is most welcome. However, if we wish to apply rTMS for AVH, we need to obtain more information about the neuronal mechanisms by which rTMS may affect this symptom. We showed that a single rTMS-session to therapeutic locations was not superior to control-site stimulation. These findings may suggest a placebo effect of 1-Hz rTMS on AVH-severity, possibly through scalp sensations, or relaxation during treatment associated with rTMS stimulation. The absence of any correlations between improvements in AVH-severity and changes in neuronal activity could be seen as in line with this interpretation.

The fact that several randomized controlled trials *did* observe an effect on AVH-severity through repeatedly stimulating the left temporoparietal cortex with 1-Hz rTMS may be explained by their inactive sham condition (Hoffman et al., 1999, 2000; Chibbaro et al., 2005; Hoffman et al., 2005; Poulet et al., 2005; Brunelin et al., 2006). In these studies sham rTMS was applied using a placebo coil or by tilting the rTMS coil by 45°. While these sham conditions produce some acoustic stimulation, scalp sensations are absent or greatly diminished (Aleman et al., 2007). As such, patients who experience stronger scalp sensations during real rTMS may feel they are receiving more powerful treatment. Indeed, placebo effects have been shown to be greatly enhanced in case of suggestion of stronger treatment, as for example ingestion of two placebo pills elicits stronger effects than ingestion of only one, and injection of placebo is more powerful than oral administration (Blackwell et al., 1972; de Craen et al., 2000). In this study, stimulation of the control site produced similar scalp sensations as stimulation of the temporoparietal sites, thereby controlling for these effects.

However, an important alternative explanation regarding the interpretation of the present results as a placebo effect concerns the possible remote effects of rTMS. RTMS is able to influence brain activity in regions distant from the stimulated brain region through neuronal connections (Horacek et al., 2007). The power, clustering, path length, and small-worldness measures in the various frequency bands may not have been sensitive enough to pick up these signals.

As such, we cannot for example rule out the possibility that control-site stimulation affected brain activity in regions associated with auditory verbal hallucinations through intra-hemispheric connections. The same line of reasoning goes for the absence of significant correlations with measures of AVH severity. Perhaps spatial and temporal analyses in source space may provide more sensitivity to establish significant differences across conditions as well as correlations with AVH severity. Neuroimaging methods with a high spatial resolution, such as functional magnetic resonance imaging (fMRI) may be especially suitable to investigate this issue and give a more definite answer on the matter.

4.1. Limitations

In this study no differential effect of rTMS target site was observed on EEG measures. It can however not be excluded that rTMS applied to the temporoparietal and occipital cortex leads to a generalized effect on EEG-based power and network characteristics instead of to local effects. However, two studies investigated the effect of 1-Hz rTMS on EEG spectral power during rest, and did observe differential effects of rTMS on brain regions instead of a generalized effect (Schutter et al., 2001; Brignani et al., 2008). Lastly, the present study investigated the acute effects of rTMS, and was as such unable to detect any delayed effects. However, most larger RCTs failed to find a difference between real and sham rTMS, suggesting that there are no delayed effects of rTMS on AVH symptomatology (Fitzgerald et al., 2005; Vercammen et al., 2009; Loo et al., 2010; Slotema et al., 2010a).

In sum, this is the first placebo-site controlled study assessing both clinical and neuronal effects of rTMS on AVH. Stimulation of the temporoparietal cortices was not more effective in reducing AVH symptoms than control-site stimulation. Moreover, electrophysiological measures were not affected differently by rTMS at therapeutic sites as compared to control-site stimulation. These results imply that a single session of 1-Hz rTMS applied to the temporoparietal region does not improve AVH better than occipital cortex stimulation and may suggest a placebo effect of 1-Hz rTMS on AVH-severity.

Supplementary materials related to this article can be found online at doi:10.1016/j.schres.2012.01.010.

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Contributors

Remko van Lutterveld designed the study, processed and analyzed the data, and wrote the manuscript. Sanne Koops collected the data, was involved in data analysis, and wrote the first draft of the paper. Dennis J.L.G. Schutter was involved with study design and edited the paper. Ellen Geertsema collected the data and was involved in data analysis. Cornelis J. Stam was involved in data analysis and edited the paper. René S. Kahn supervised the study. Iris E.C. Sommer supervised the study, edited the manuscript, and was involved with study design. All authors contributed to and have approved the final manuscript.

Conflict of interest statement

The authors have no conflicts of interest to report.

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