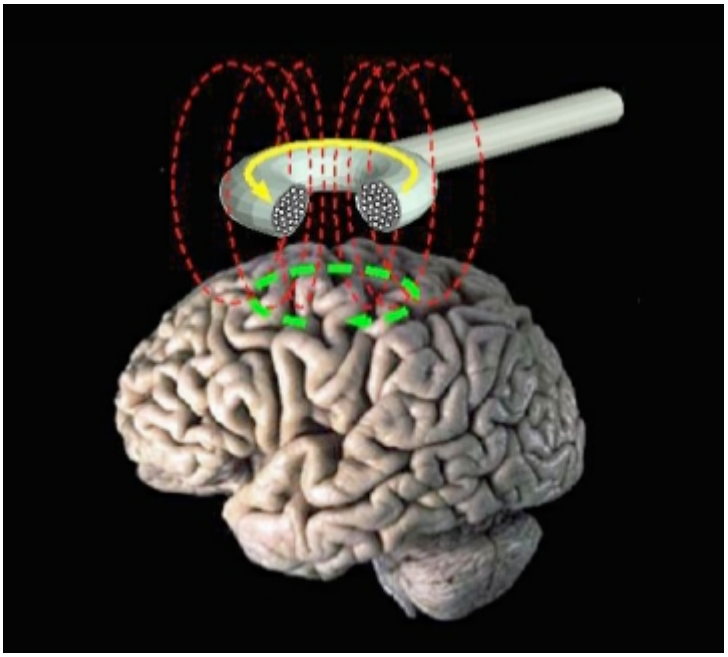
Utrecht University

Master Neuropsychology

Thesis

The efficacy of fMRI guided 1 Hz versus 20 Hz repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of Auditory Verbal Hallucinations (AVH)



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Abstract

Despite treatment with pharmacotherapy, some patients continue to suffer from auditory verbal hallucinations (AVH). Several studies concluded that low and high frequency repetitive Transcranial Magnetic Stimulation (rTMS) could offer an alternative treatment for these patients. The aim of this study is to verify whether 1 Hz (low) or 20 Hz (high) fMRI guided rTMS is more effective in the treatment for AVH. 16 psychotic patients with treatment-resistant auditory verbal hallucinations were included and randomly allocated to one of the two treatment conditions, 1 Hz or 20 Hz fMRI guided rTMS. Three measures were used for determining the severity of AVH; the Auditory Hallucination Rating Scale (AHRS) total score, the Hallucinations Change Scale (HCS) and Positive and Negative Syndrome Scale (PANSS) item three. The AHRS total score and the HCS showed improvement in both groups after rTMS treatment. The HCS showed a trend towards significance indicating greater improvement after 20 Hz rTMS treatment compared to 1 Hz rTMS treatment. At last, the patients in the 20 Hz treatment condition had lower scores in general on the AHRS total score, and there was a trend towards significance for the same effect for the scores on the HCS. More placebo-controlled research with larger sample sizes is needed to investigate the potential of high frequency rTMS in the treatment of AVH.

Introduction

Auditory verbal hallucinations (AVH) are a common symptom in several psychiatric disorders. AVH are often experienced as highly distressing and disrupt social functioning, especially when verbal content is negative or intrusive (Hoffman et al., 2003). Approximately 50 to 70% of all patients with schizophrenia report hearing 'voices' at some point during the course of the illness (Andreasen & Flaum, 1991). In a quarter of these cases the hallucinations persist despite adequate treatment with pharmacotherapy (Shergill, Murray, & McGuire, 1998).

Repetitive Transcranial Magnetic Stimulation (rTMS) could offer an alternative treatment for these medication-resistant patients (Fitzgerald & Daskalakis, 2008). TMS is a non-invasive technique that enables safe, relatively painless focal brain stimulation. In rTMS a train of pulses of the same intensity is delivered to a single brain area at a given frequency. Low frequencies (e.g. 1 Hz) can suppress excitability of cortical neurons, while high

frequencies (e.g. 20 Hz) can stimulate excitability of cortical neurons (George, Wassermann, & Post, 1996; Haraldsson, Ferrarelli, Kalin, & Tononi, 2004). The precise cortical mechanism by which rTMS exerts its effects remains unknown (Lopez-Ibor, Lopez-Ibor, & Pastrana, 2008). Recent studies show that TMS induces not only local effects in the underlying region of application, but can also influence remote brain areas interconnected with the stimulation site (Tracy et al., *in press*; Ruff, Driver, & Bestmann, 2009).

Functional Magnetic Resonance Imaging (fMRI) guidance could improve the efficacy of rTMS treatment (Sommer et al., 2007; Boksa, 2009). Functional activation studies have generally reported increased activity in language areas and in the primary auditory cortex during AVH, although various other areas have also been implicated (Boksa, 2009; Anthony, 2004). The need of using individual assessment of the functional anatomy of hallucinations has been reported by several authors (e.g. Freitas et al., 2009). During functional scans, patients indicate the presence of AVH by squeezing an air-mediated button and holding it until the AVH stop (Sommer et al., 2007). These hallucination periods are then compared to scans during periods without hallucinations. The cerebral area with the largest number of continuous activated voxels during hallucinations is used as rTMS focus.

Most of the studies that investigated rTMS as treatment for AVH have focused primarily on 1 Hz rTMS, based on the assumption that low frequency rTMS suppresses cortical excitability of the neurocircuits involved with AVH, which would lead to less AVH (Hoffman et al., 2000). Three meta-analyses concluded that low frequency rTMS is an effective treatment for AVH, with effect sizes of .51 (Tranulis, Sepehry, Galinowski, & Stip, 2008), 0.76 (Aleman, Sommer, & Kahn, 2007) and 1.04 (Freitas, Fregni, & Pascual-Leone, 2009). Because not all patients respond to low frequency rTMS other strategies are being applied, including fMRI guided high frequency rTMS. This recently studied treatment seems to have a better effect as treatment for AVH (Dollfus, et al., 2008; Montagne-Larmurier, Etard, Razafimandimby, Morello, & Dollfus, 2009). In the study of Montagne-Larmurier et al. (2009) an effect size of 1.26 was found. All patients except one had a decrease in total score of an auditory hallucination scale (AHRS; Hoffman et al., 2003).

To my knowledge, no comparative research has been conducted to assess whether a certain rTMS frequency has an advantage over another in treating AVH. The need of this kind of research has been reported by a recent article in which the results so far, with regard to rTMS treatment for auditory verbal hallucinations, are being reviewed (Blumberger, Fitzgerald, Mulsant, & Daskalakis, 2010). Therefore, the aim of this study is to verify whether 1 or 20 Hz rTMS is more effective in the treatment of AVH. Psychotic patients who suffer from AVH were included and randomly allocated to one of the two treatment conditions. The rTMS treatment was fMRI guided.

Methods

Subjects

18 patients were referred to the study by psychiatrists of the psychiatry department of the UMC Utrecht or by colleagues from the research department of Parnassia in The Hague. 10 patients had a DSM-IV diagnose of schizophrenia, 5 psychotic disorder not otherwise specified (NOS) and 3 schizoaffective disorder. All patients reported medication resistant AVH at least a few times per hour. They were treated with stable doses of antipsychotic medication for at least 2 weeks prior to study inclusion, and this dose was unchanged for the duration of the study. Exclusion criteria included TMS and MRI contraindications: pregnancy, alcohol abuse, drug use (with the exception of cannabis), panic attacks in small spaces, anti-epileptic medication and benzodiazepines. If the patient was using benzodiazepines an alternative sedative was offered like promethazine, zolpidem and zoplicon. Two patients (both with psychotic disorder NOS) were excluded, because no proper functional scans could be obtained.

Demographical and clinical characteristics of the subjects are provided in table 1. There were no significant differences between the groups in age or in age at onset of AVH.

Design

This study had a between-subjects design with two conditions. Condition 1 was fMRI guided low frequency (1 Hz) rTMS treatment and condition 2 was fMRI guided high frequency (20 Hz) rTMS treatment. The subjects were randomly assigned to one of these two conditions.

A double blind design was used, in which only the rTMS administrator was aware of the intervention type. The subjects, clinical raters and all personnel responsible for the clinical care of the patients were blind to the allocated condition.

Table 1. *Demographical and clinical characteristics of the subjects*

Characteristic	1 Hz	20 Hz	*p-value*
Age, mean (SD)	32.4 (11.6)	44.4 (12.2)	0.06
Age at onset AVH, mean (SD)	18.3 (8.3)	30.1 (18.3)	0.12
Male / Female	5/3	3/5	
DSM Diagnose			
Schizophrenia	6	4	
Psychosis NOS	1	2	
Schizoaffective	1	2	

Procedure

Prior to participation, patients received written and oral information of the procedures and goals of the study, and informed consent was obtained.

After this, the functional scans were obtained. Three days prior to the rTMS treatment, the subject was invited to the UMC Utrecht for neuronavigation and clinical assessment (baseline; T0). Then the rTMS treatment was given five times in one week (Monday-Friday). After the last treatment, the subject was rated again (T1) with the same questionnaires as at T0. The procedures are further specified below.

fMRI procedure

The Blood Oxygenation Level Dependent (BOLD) response was measured in 2 sessions of 8 minutes each, in which fMRI scans were acquired continuously. Patients were instructed to squeeze a balloon when they experienced AVH, and to release it when the hallucinations subsided (Sommer et al., 2007). Activation maps were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner.

In order to compare hallucinatory periods to non-hallucinatory (resting) periods, an activation model was created using the intervals between squeezes and releases as the duration of individual hallucinatory episodes. The area with the highest intensity and the largest number of supra-threshold voxels located within reach of rTMS (i.e. at a cortical depth of less than 2 cm) was used as the focus of the rTMS treatment. In table 2 an overview is given of the stimulated sides of the brain in both groups.

Table 2. *Number of left/right focuses of rTMS treatment based on the fMRI scans.*

Stimulated side	1 Hz	20 Hz
Right	5	5
Left	3	3

Neuronavigation

Image-guided stereotaxy was performed with the aid of a Neural Navigator (NeNa) (Neggers et al., 2004), which projected the Region Of Interest (ROI) upon the brain's anatomy. The anatomical scan was then transformed to a skin rendering, providing a 3D representation of the patients' skin surface. These 3D representations and the patients' head were co-registered using sets of 3D craniotopic coordinates as marked in the software on the skin surface and mapped onto the corresponding craniotopic landmarks as measured directly on the patients' head with a 3D digitizer pen (the MiniBIRD position tracker system Acension Technologies). The bridge and tip of the nose and the ear ridges were used as craniotopic landmarks. After this mapping procedure, accurate stereotactic navigation allowed us to mark the location on the scalp directly overlying the area of maximal hallucinatory activity. This spot was marked with the aid of a surgical skin marker. The latter procedure has been validated extensively and is capable of pinpointing focal brain structures with an accuracy of about 4 mm (Neggers et al., 2004).

Clinical ratings

The outcome measure was the change in *severity of AVH*. This was quantified using the total score on the Auditory Hallucination Rating Scale (AHRS), the Hallucination Change Scale (HCS), both from Hoffman and colleagues (2003), and item three 'hallucinatory

behavior' of the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987).

The clinical ratings were obtained three days before the first rTMS treatment (baseline; T0) and directly after the last rTMS treatment (T1).

rTMS

A Magstim Rapid2 (Magstim Company Ltd, Whitland, Wales) with an air-cooled 70 mm figure-of-eight coil was used for rTMS treatment. Prior to the first treatment session, the motor threshold was determined conform Schutter and Van Honk (2006) by stimulating the motor cortex on the ipsilateral side to the intended treatment. A cardboard template was used to position the centre of the coil, where the magnetic fields of both rings are summated, exactly over the marked target area.

In condition 1 the rTMS was administered for 20 minutes at 1Hz at 90% of the patients' personal motor threshold, and in condition 2 the rTMS was administered for 18 minutes at 20Hz at 80% of the patients' personal motor threshold. Patients received daily treatments for 1 week, Monday-Friday, adding up to 5 treatments per person in total.

Analyses

The data were analyzed using the Statistical Package for Social Sciences (SPSS 15.0).

First, the distributions of scores were examined using a normal probability plot and skewness analyses. Since all data were normally distributed, parametric statistics were used. Demographical data were analyzed using independent-samples T-tests.

The scores on the outcome measure were analyzed with a mixed between-within ANOVA to examine whether there was a main effect for treatment, main effect for time and to see if there was an interaction effect. The between variable in these analyses was the type of treatment (1 Hz versus 20 Hz) and the within variable was time (baseline; T0 versus after rTMS treatment; T1).

A p-value of < 0.05 was judged as statistically significant.

Results

Table 3. *Mean (SD) scores at baseline (T0) and after rTMS treatment (T1)*

	1 Hz		20 Hz	
	T0	T1	T0	T1
AHRS total score	39.0 (3.7)	35.1 (6.0)	33.1 (5.7)	23.8 (12.9)
Hallucination change scale	10.0 (0.0)	8.9 (2.2)	10.0 (0.0)	6.4 (3.3)
PANSS item three	5.1 (0.64)	4.8 (0.7)	4.8 (0.7)	4.4 (1.1)

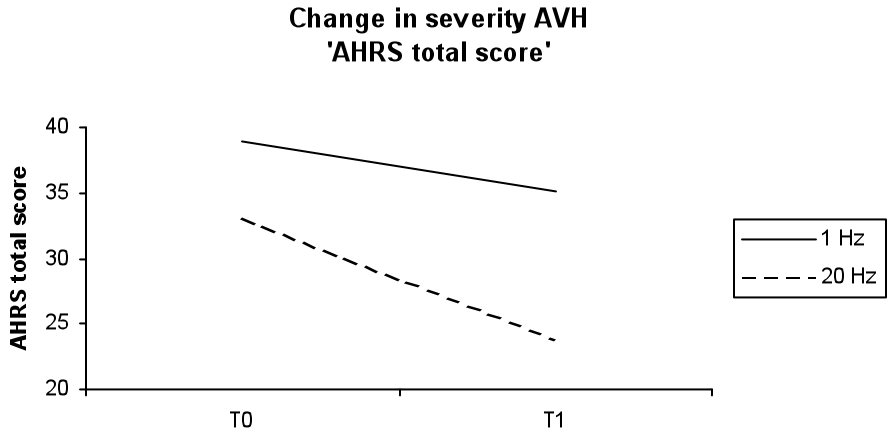

Figure 1. Total score on the AHRS before (T0) and after (T1) rTMS treatment.

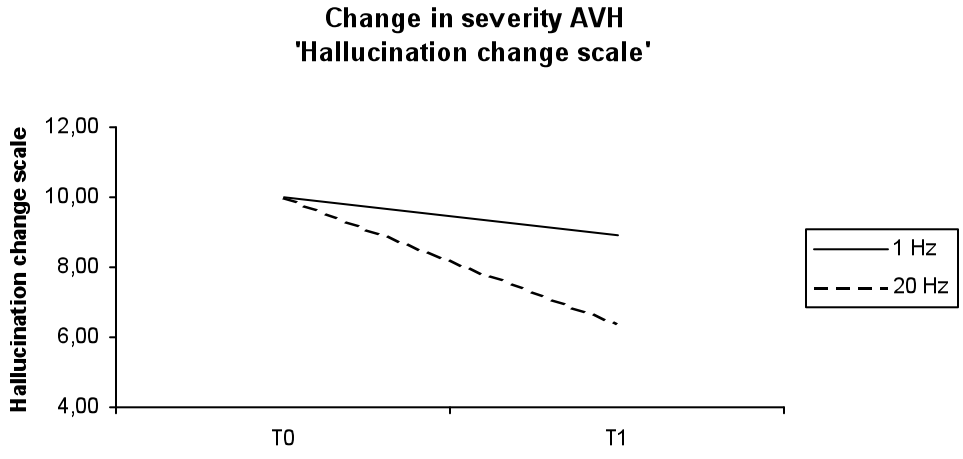

Figure 2. Score on the HCS before (T0) and after (T1) rTMS treatment.

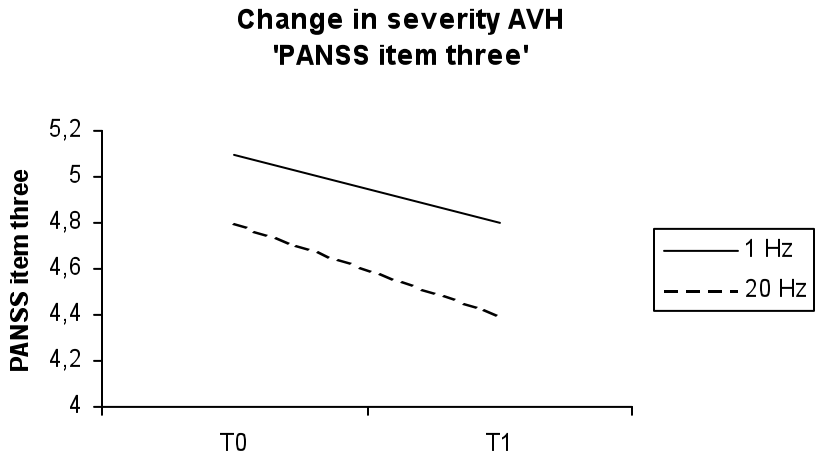

Figure 3. Score on PANSS item three before (T0) and after (T1) rTMS treatment.

The outcome measure in this study was the change in *severity of AVH* after low or high frequency rTMS treatment. The Auditory Hallucination Rating Scale (AHRS) total score, the Hallucination Change Scale (HCS), and the Positive And Negative Syndrome Scale (PANSS) item three were analyzed to see if there was a time, treatment and/or interaction effect. In table 3 the mean scores of these outcome measures are described and in the figures below this table the timelines are presented.

With regard to the AHRS total score, there was a main effect of time, $F(1,14) = 8.88$, $p < .05$. The scores in both groups were lower after rTMS treatment compared to baseline level. There was also a main effect of treatment, $F(1,14) = 7.05$, $p < 0.05$. The patients in the group which received 20 Hz rTMS had lower scores in general on this measure. There was no Time x Group effect, $F(1,14) = 1.53$, $p = 0.24$.

The analyses of the HCS also showed a main effect of time, $F(1,14) = 11.21$, $p < .01$. The scores in both groups were lower after rTMS treatment compared to baseline level. There was a trend towards significance with regard to main effect of treatment, $F(1,14) = 3.10$, $p = 0.10$, and also with regard to Time x Group effect, $F(1,14) = 3.10$, $p = 0.10$. These results indicate that the group which received 20 Hz rTMS had lower scores in general on this measure and showed a greater improvement after rTMS treatment compared to the group which received 1 Hz rTMS.

The analyses of PANSS item three showed no main effect of time, $F(1,14) = 2.69$, $p = 0.12$, no main effect of treatment, $F(1,14) = 1.33$, $p = .27$, and no Time x Group effect, $F(1,14) = 0.00$, $p = 1$.

Discussion

This is the first study examining the question whether 1 Hz or 20 Hz rTMS is more effective as treatment for auditory verbal hallucinations in a group of patients with medication resistant symptoms.

Two out of the three measures which assessed the severity of auditory verbal hallucinations, the AHRS total score and the HCS, showed that both groups improved after receiving rTMS treatment. The HCS showed a trend towards significance indicating a greater improvement after 20 Hz rTMS treatment compared to 1 Hz rTMS treatment. The patients who received 20 Hz rTMS had lower scores in general on the AHRS total score, and there was a trend towards significance for the same effect for the scores on the HCS. With regard to item three of the PANSS, no effects were found.

The results of this study are consistent with the meta-analyses and other studies described above in which both low and high frequency rTMS seem to be effective as treatment for AVH (Tranulis, Sepehry, Galinowski, & Stip, 2008; Aleman, Sommer, & Kahn, 2007; Freitas, Fregni, & Pascual-Leone, 2009; Dollfus, et al., 2008; Montagne-Larmurier, Etard, Razafimandimby, Morello, & Dollfus, 2009). In line with the studies by Dollfus and colleagues (2008) and Montagne and colleagues (2009), this study found that high frequency rTMS may have an advantage over low frequency rTMS. However, the results are not significant.

An improvement of this study in comparison with previous research is the use of fMRI guidance in applying rTMS. In the past it has been speculated that the pathological anatomy of AVH differ between patients (e.g. McIntosh, et al., 2004). Therefore, individual assessment of the functional anatomy of hallucinations should be obtained before giving rTMS treatment. This study also found differences in patients with regard to the functional anatomy of AVH. On the basis of the functional scans, individual rTMS focuses were calculated for all patients. In both groups more than the half of the patients were stimulated on the right side of the brain and a minority on the left side of the brain. Although fMRI

guidance may have an enhancing effect, it should be taken into account that this is a time-consuming method and not all patients are suitable. In this study two patients were excluded because no proper functional scans could be obtained. The advantages and disadvantages of fMRI guidance should be investigated in future research in order to optimize the rTMS procedure.

There were several limitations of this study which also should be addressed in future research so that the utility of rTMS in treatment of AVH can be further validated. First, this study was not placebo-controlled. The results that were found could be the product of placebo induced effects. Second, a small sample size is a common problem in this type of research (Mogg et al., 2007). In this study, both groups had only eight patients each, where the ideal number is around thirty per group. Perhaps with a larger sample size, more evidence will be found for the appliance of high frequency rTMS.

Another methodological issue is the choice of self-report scales and clinical interviews. A new method for registering auditory verbal hallucinations, called 'clickeren', is currently being investigated in the research group at the UMC Utrecht. With this method, patients indicate when they are experiencing AVH by pressing a key, for example the spacebar, on a keyboard. Although it is still dependent of the patients, no faulty interpretations of answers can be made by the assessors. Also, the patients do not have to categorize their experiences into the one that fits best, which is often necessary in questionnaires. With this new method different components such as frequency and duration of AVH can be investigated, for example before and after rTMS treatment.

Finally, of particular clinical relevance is the durability of the treatment effect. It is still unclear whether repeated rTMS treatments results in additional benefit (Vercammen, et al., 2009). This issue is also being investigated at the moment in the research group at the UMC Utrecht. Patients who currently receive rTMS treatment are being assessed for up to six months after this rTMS treatment to investigate the long term effects. Also, responders have the opportunity to continue the rTMS treatment in a so called 'maintenance treatment'. In this type of treatment, the patients receive rTMS treatment once a week for six months, after the first effective rTMS phase of one week. This method will give a greater insight into the long term effects of rTMS and the benefits of maintenance treatment.

In conclusion, the results of this study may indicate an advantage of 20 Hz over 1 Hz rTMS in treatment of AVH. However, the results were not significant. Further research is needed to investigate the potential of high frequency rTMS in the treatment of AVH, and to investigate the long term effects of rTMS treatment in general.

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