MSc in Clinical Psychology

Effects of repetitive transcranial magnetic stimulation as a treatment for persistent auditory verbal hallucinations

May, 2019

Student name: Viktor Díar Jónasson

Social security number: 160591 – 2349

Supervisor: Dr. Brynja Björk Magnúsdóttir

Effects of repetitive transcranial magnetic stimulation as a treatment for persistent auditory verbal hallucinations

Viktor Díar Jónasson
Reykjavík University

Preface

Auditory verbal hallucinations are common in schizophrenia and can severely affect patients' quality of life and cause a great deal of suffering, functional debility and risk to themselves and/or others. Current treatments are not always effective at relieving patients' symptoms and suffering. Further explorations of effective treatments are needed. Studies have shown that transcranial magnetic stimulations might be an effective treatment option for persistent auditory verbal hallucinations.

This study is part of a cooperation between the M.Sc. programme in clinical psychology at the University of Reykjavík, the Institute of Biomedical and Neural Engineering at the University of Reykjavík, the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA (NINDS/NIH) and the Neurology Department / Clinical Neurophysiology Unit at Landspítali - The National University Hospital of Iceland. The study took one and a half year to execute under the supervision of Dr. Brynja. B Magnúsdóttir, Assistant Professor at the University of Reykjavík. The thesis was formulated at the end of the first semester of the master programme. In the second semester the literature was reviewed and the scientific ethics committee at Landspítali - The National University Hospital of Iceland gave permission for the study. The study was initiated in the third semester and every psychiatrist at the hospital was approached and asked to refer patients with treatment refractory auditory verbal hallucinations to the study. In the third semester the method section was written. During the last semester treatment and data collection continued and the final draft of this thesis was written.

I am grateful to the staff at the Department of Clinical Neurophysiology for conducting the transcranial magnetic stimulation treatment and to the Institute of Biomedical and Neural Engineering for their help in conducting measures and data analysis. I am also grateful to Baldur

Heiðar Sigurðsson and Óttar Guðbjörn Birgisson for their mentorship in the use of the psychotic symptom rating scale. A special thanks goes to Magnús Haraldsson who gave me part of his valuable time to assist in the difficult phase of patient recruitment for this study. My sincerest thanks goes to my supervisor Brynja Björk Magnúsdóttir who made this whole project into a reality. I wish to thank her for her valuable collaboration, guidance and support.

The idea for the project was born on a mountain hike to the top of Esjan with my brother, Aron Dalin Jónasson and his co-worker and our friend Ovidiu Constantin Banea, both of whom worked tirelessly on this project from start to finish. I will forever owe them my deepest gratitude.

I am also grateful to have had the opportunity to work with many dedicated researchers. I am especially thankful for the opportunity to work with Eysteinn Íngvarsson, Alec Shaw, Sara Marcu, Elena Pegolo, Fabio Barollo, Paolo Gargiulo and Eric Wassermann. My love and everlasting gratitude goes to my family for their endless support. Finally, I wish to thank the patients at the hospital for their time and efforts to participate in this study. Hopefully their participation will lead to a new treatment option for patients with persistent auditory verbal hallucinations in Iceland.

Abstract

Auditory verbal hallucinations (AVHs) are perception-like experiences that occur without an external stimulus. Phenomenological studies suggest that AVHs can vary along eight dimensions: loudness, clarity, complexity, frequency, control, location, content and personification. AVHs are experienced by 70% of patients with schizophrenia and can cause high levels of stress and functional debility. Atypical antipsychotic drugs are the recommended treatment for AVHs but are non-effective in 25-30% of cases. Cognitive behavioral therapy (CBT) has proven reasonably effective but improvements can still be made to the treatment for some patients that experience AVHs. Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation that can inhibit cortical activity in brain regions shown to be hyperactive during AVHs. We studied the effectiveness of repetitive TMS (rTMS) as a treatment for persistent AVHs. The hypotheses were that TMS could reduce 1) AVH, 2) depression, anxiety and stress, and 3) increase quality of life. A total of 6 patients diagnosed with primary psychotic disorder that were seeking services at the University Hospital of Iceland were randomized to either active (n=2) or sham (n=4) rTMS treatment. AVHs, depression, anxiety, stress and quality of life were assessed before and after treatment and at a one and three month's follow-up. Active rTMS significantly reduced frequency and duration of AVH compared to the sham group. RTMS treatment did not show statistically significant effects on depression, anxiety, stress or quality of life. These results indicate that rTMS can be an effective treatment for AVH.

Keywords: Transcranial magnetic stimulation, auditory verbal hallucinations, depression, anxiety, stress, quality of life, medication and cognitive behavioral therapy

Effects of repetitive transcranial magnetic stimulation as a treatment for persistent auditory verbal hallucinations

Hallucinations are defined as: "perception-like experiences that occur without an external stimulus" (American Psychiatric Association, 2013, p. 87). AVHs are vivid experiences, without voluntary control and are generally experienced as voices. AVHs are common in many forms of mental illness and can cause patients great distress, functional disability and risk to themselves and/or others (Braham et al., 2004).

AVHs can be experienced in many different forms. Sometimes the AVHs say what the person is thinking and sometimes the AVHs constantly comment on everything a person does. AVHs can be two or more voices communicating between each other, usually about the individual (American Psychiatric Association, 2013). The voices tend to be negative and commanding, criticizing the individual and instructing him to hurt himself or others (Chadwick & Birchwood, 1994).

Phenomenological studies of AVHs have suggested that AVHs vary along eight dimensions. (1) *Loudness*: AVHs can vary from being experienced as load yelling to whispers or even nonverbal sounds that still carry meaning. (2) *Clarity*: ranging from clear, fully understandable speech to unintelligent muttering. (3) *Complexity*: some report hearing full sentences and conversations while others only report hearing single words or utterances. (4) *Frequency*: some hear AVHs constantly, others only a couple of times each day while still others only hear AVHs a few times a week or just during psychotic episodes. (5) *Control:* Some can turn their AVHs on or off and/or completely ignore the AVHs while others cannot. This factor may be the most important with regard to health, since it seems to distinguish between pathophysiology and non-pathophysiology. (6) *Location*: some people report experiencing AVHs

as being inside their head while others report them coming from outside the head. (7) *Content*: AVHs can be negative, neutral or positive. (8) *Personification*: voices can be male or female, young or old, known or unknown, good or bad, or even some creatures or beings other than humans (Larøi et al., 2012).

Treatment

Medication

Clinical guidelines recommend antipsychotic medication for treatment of AVHs since they have been shown to be effective in the majority of cases (Gaebel, Weinmann, Sartorius, Rutz, & McIntyre, 2005). However, symptoms are refractory to atypical antipsychotic medication in 25-30% of cases (Hasan et al., 2012; Mortimer, Singh, Shepherd, & Puthiryackal, 2010; Shergill et al., 1998).

Common antipsychotic treatments are olanzapine, ziprasidone and quetiapine but side effects tend to severely affect patients. Common side effects include weight gain and sedation for the -pine class of drugs and dystonia, parkinsonism and akathisia for the -done class of drugs (Sommer et al., 2012). Some of these side effects can drastically increase patient mortality rates, while others only cause mild discomfort. However, it is important to note that sometimes there are no side effects at all (Uçok & Gaebel, 2008).

For cases resistant to treatment with atypical antipsychotic medication, clozapine is the only approved medication and is able to significantly reduce symptoms in 30-60% of cases. However, clozapine can have very serious side effects, including death due to leukopenia, which is why close monitoring of leukocytes is a requirement (Lieberman et al., 1994; Locatelli, 1998). Other side effects include myocarditis, seizure, weight gain and type 2 diabetes.

Furthermore, antipsychotic medication treatment adherence is low as 53% of patients discontinue treatment early (Leucht, Arbter, Engel, Kissling, & Davis, 2009; Liu-Seifert, Adams, & Kinon, 2005; Nosé, Barbui, & Tansella, 2003).

Cognitive Behavioral Therapy

Over the last two decades, a number of randomized control trial (RCT) studies have indicated that cognitive behavioral therapy (CBT) is effective in the treatment of positive symptoms (i.e. hallucinations and delusions) in psychosis, including AVHs. The CBT model for psychosis was developed to help manage treatment resistant symptoms, grounded in the stress-vulnerability model, to reduce the distress caused by hallucinations and other symptoms (Tarrier & Johnson, 2015). The aim is not to reduce frequency or severity of symptoms but to help patients cope with their symptoms.

Chadwick and Birchwood (1994) developed a specialized CBT model for treatment resistant AVHs that targets the beliefs patients have about their voices, helping them see that the AVHs are not as powerful as they first appear to be. Other CBT treatments for AVHs have since been developed. Berny et al (2007) used social rank theory to develop the social rank CBT for AVHs where the main objective is to reduce the power difference between the voice hearer and the AVHs. This kind of treatment is especially effective against command hallucinations where the safety of the patient and others around him is at risk.

Valmaggie, Gaag, Tarrier, Pijnenborg and Slooff (2005) conducted a large RCT in the Netherlands with 72 in-patients to test the effect that CBT intervention had on medication resistant AVHs (including clozapine). They provided 16 hours of therapy sessions over a 22 week period. The focus in therapy was cooperation, goal setting and to challenge current beliefs about AVHs. The study showed a reduction in frequency, duration, loudness as well as a change

in location. Total positive symptom reduction was 20%, but treatment effects were lost at six month follow-up.

Meta-analysis of the effectiveness of CBT for AVHs has shown effect sizes (Hedges'g) ranging from low to medium. Zimmermann, Favrod, Trieu and Pmini (2005) found that the effect of CBT for positive symptoms (i.e. they did not differentiate between hallucinations and delusion) was 0.57 for psychotic episodes but dropped to 0.27 for persistent symptoms. Another meta-analysis conducted by Jauhar, McKenna, Radua, Fung, Slvador and Laws (2014) found 33 studies that looked at the effect of CBT for positive symptoms and found a low effect size of 0.25; participants were a mixed group of patients with both persistent and non-persistent symptoms. Only one meta-analysis was found that specifically targeted individually tailored formulation-based CBT for hallucinations. Their results indicated that the effect size of CBT for hallucinations was 0.44 when treatment continued as usual. However, when CBT was compared to active treatment the difference was not significant (van der Gaag, Valmaggia, & Smit, 2014). No meta-analysis was found that looked specifically at the effect CBT has on persistent AVHs.

CBT for AVHs has shown some promising results in reducing severity, distress, improvements in feelings of control and general beliefs about the voices but does not seem to effectively reduce frequency or duration of AVHs (Chadwick & Birchwood, 1994; Jenner et al., 1998; Nagui Rizk et al., 2016; Pontillo et al., 2016).

Problems also arise with regard to treatment adherence where 75% of patients do not follow through with CBT treatment after discharge (Gaudiano & Herbert, 2006). Another problem is that patients' symptoms tend to fluctuate, and patients often lack insight, both of which can cause problems for the therapeutic alliance, which is a prerequisite for CBT (Shergill et al., 1998). Furthermore, schizophrenia patients tend to show some neurocognitive deficits in

seven domains: working memory, attention, verbal memory, visual learning, problem solving, cognitive speed and interpretation of social events (Green, et al, 2004). All of these domains are important for the effectiveness of CBT. These neurocognitive deficits might therefore be negatively affecting the CBT process, effectively reducing treatment impact (Zimmermann, et al, 2005).

Transcanial magnetic stimulation

Transcranial magnetic stimulation (TMS) was developed in 1985 by Anthony T. Barker and colleagues as a tool that allowed researchers to investigate the central nervous system by stimulating the cortex through the scalp non-invasively, using a pulsed magnetic field (Barker, Jalinous, & Freeston, 1985). Since then this tool has been extensively studied. In 2008 TMS received the Food and Drug Administration (FDA) approval as a treatment for medication-resistant depression (Rotenberg, Horvath, & Pascual-Leone, 2014). TMS has been used as a clinical diagnosis application (Chen et al., 2008) and researchers have been studying its use as a possible treatment for a variety of neurological and pathophysiological diseases (Lefaucheur et al., 2014). TMS is a painless treatment method and is very safe when the appropriate safety guidelines are followed (Wassermann, 1998).

TMS works by using Faraday's electromagnetic law of induction which states that a changing electric field produces a change in the magnetic field by causing current in nearby conducting material through the electromotive force. This magnetic force is strong enough to depolarize conducting neurons two centimeters beneath the skull by producing current in the intracellular and extracellular space. If the depolarization is strong enough it will produce an action potential (Fitzgerald & Jeff Daskalakis, 2013). Uniform repetitive transcranial magnetic stimulation (rTMS) of the same brain region is thought to be capable of producing lasting effect

on neuronal plasticity by producing long-term-depression (LTD) and long-term-potentiation (LTP) with low frequency (1 Hz) rTMS producing an inhibitory effect and high frequency (20 Hz) rTMS yielding excitatory effect, respectively (Wassermann, 1998).

Brain regions that are known to be involved in auditory and linguistic processing have been shown to be hyperactive during AVHs (Silbersweig et al., 1995), specifically the superior temporal gyrus (Dierks et al., 1999). Since TMS had been shown to be capable of reducing cortical activity (Chen et al., 1997) it was theorized that rTMS could possibly reduce AVHs by stimulating and modifying the left temporal parietal cortex (TPC), an important brain region for the process of speech perception (Hoffman et al., 1999).

Transcranial magnetic stimulation as a treatment for auditory verbal hallucinations

Hoffman et al. (1999) were the first group to try using TMS as a treatment for AVHs. They conducted a double-blind cross over study with three patients who had treatment refractory AVHs. They stimulated the left temporoparietal junction (T3-P3), as measured with the 10-20 international electroencephalograph (EEG) system, using 80% motor threshold over four sessions. They used loudness, frequency, content and level of distress as measures for AVHs. Results showed a complete relief of AVHs symptoms for two patients and some relief for the third, and effects remained at two weeks post treatment follow-up (Hoffman et al., 1999). Hoffman and colleagues (2000) replicated the study with 12 patients a year later and showed a positive response rate for 8 out of 12.

A few studies have tried to replicate these findings but with differing results. Although some studies with a small number of participants (n = 10-14) have been able to replicate Hoffman's et al (1999) positive results with 10 rTMS sessions (Brunelin et al., 2006; Poulet et

al., 2005), other studies with larger sample sizes (n = 51-61) using even longer treatments (15-20 session), could not achieve replicable results (Blumberger et al., 2012; Slotema et al., 2011).

This variance in the results of these studies is not surprising sincethe number of participants in most studies tends to be small and inclusion criteria differ. Furthermore, studies tend to vary in their primary outcome measurement of AVHs using different instruments, including positive and negative symptom scale (PANSS), auditory hallucination rating scale (AHRS), hallucination change scale (HCS) and psychotic symptom rating scale (PSYRATS). These studies differed in other ways, e.g. in the treatment protocol (1 Hz vs Theta burst), sham method (45% coil tilt, 90% coil tilt and sham coil), motor threshold (ranging from 80-120%), number of session (ranging from 3-20), session duration (ranging from 4-40 min), number of pulses (ranging from 200-1200), and navigation method (10-20 EEG system, MRI scan or PET scan). Nevertheless, meta-analyses measuring effect sizes for low frequency rTMS applied over TPC as a treatment for AVHs have repeatedly shown a medium to large effect sizes ranging from 0.4 to 1 (Lefaucheur et al., 2014; Slotema et al., 2014).

Therefore, research on the effect of TMS indicates promising results in reducing treatment refractory AVHs above and beyond what CBT has managed to do, as is clearly shown by the effect sizes, although further research is needed to tailor the most effective treatment. TMS over the left T3-P3 area has an effect size of 0.63 for treatment resistant AVHs compared to an effect size for CBT of 0.44 for AVHs that are not necessarily treatment resistant. CBT generally does not aim to reduce AVHs but instead tries to make them more bearable to the patient. TMS on the other hand has been shown to be able to reduce frequency, loudness and duration of persistent AVHs (Sommer et al., 2012).

Hypothesis

AVHs can be debilitating and dangerous. Common treatments include medication and CBT but in many cases these treatments do not relieve symptoms and patients' suffering. Research suggest that TMS might be effective in relieving patients' treatment refractory symptoms. TMS has shown larger effect sizes than CBT but the optimal rTMS protocol for AVHs treatment has not been established and studies on non-treatment resistant AVHs are needed. To the authors' knowledge, only one clinical trial is underway exploring TMS as treatment on non-medicated resistant AVHs, at the National Institute of Health in the United States

The aim of the current study is to assess the effectiveness of low frequency (1 Hz) rTMS over the left T3-P3 area with a randomized-sham control-trial. We expect to find greater reduction in AVHs, depression, anxiety and stress, as well as improvements to quality of life in patients that receive the active rTSM stimulation compared to the sham stimulation.

Method

Participants

Participants in the study were recruited by approaching psychiatrists at Landspítali - The National University Hospital of Iceland, and asking them to indicate patients with treatment resistant AVHs and introduce the TMS treatment to them. Inclusion criteria were: 1) Patients between 18-60 years of age 2) with treatment resistant AVHs due to schizophrenia, schizotypal or schizoaffective disorder 3) for at least one month and 4) experiencing AVHs at least once every day. Treatment resistant AVHs refers to two pharmacotherapy attempts that used recommended dosage for at least 6-8 weeks (Suzuki et al., 2012). Exclusion criteria were: 1) epilepsy 2) multiple sclerosis 3) daily cannabis use 4) use of hard drugs 5) daily drinking 6) daily

use of benzodiazepine 7) does not speak English or Icelandic or 8) meet any of the exclusion criteria on the rTMS safety screening list.

A total of 24 patients were referred to treatment by their psychiatrists. From those, 18 patients were excluded due to not meeting inclusion criteria: not having daily AVHs (n = 1), over 60 years of age (n = 2), multiple sclerosis (n = 1), not speaking Icelandic or English (n = 1), not passing rTMS safety screening list (n = 3), heavy alcohol or drug use (n = 10).

From the initial eight participants that fit the inclusion criteria two dropped out mid treatment, one from the treatment group and one from the sham group. The reason for dropout was a change of mind due to the fact that this is a new and unfamiliar treatment (1) and emergency hospitalization because of sudden increase in symptoms prior to rTMS treatment (1).

Six patients were randomly allocated to either the active treatment group (n = 2) or the sham control group (n = 4). Table 1 shows the characteristics of the two groups. Other treatments continued as usual. Participants received 10.000 ISK for participation.

Table 1

Characteristics of participants

Characteristics	Sham (n=4)	Active (n=2)
Age (M(SD))	28 (3)	39 (13)
Gender F/M	1 / 3	0 / 2
Diagnosis	Paranoid schizophrenia (3*) Hebephrenic schizophrenia (1)	Paranoid schizophrenia (2)

Medicine	Clozapine(3) Olanzapine(3) Solian(2) Paratsin(2) Abilify(1) Xeplion(1)	Clozapine(1) Rivotril(1) Solian(1) None(1)
Years of education (M(SD))	11(2)	15(6)
Age of onset of AVHs (M(SD))	24(5)	24(14)
Months since last remission (M(SD))	26(7)	180(16)
Number of inpatients/ outpatients	1 / 3	0 / 2
Number of hospitalisations (M(SD))	8(6)	28(35)

Note. M(SD) is mean and standard deviation.

* indicates the number of patients

The rTMS protocol was clearly explained to participants both orally and in a written form. Written informed consent was obtained before proceeding with treatment. All patients were able to discontinue the treatment at any point during the study without any influence on

their current treatment. Permission from the Health Research Ethics Committee at Landspítali - The National University Hospital of Iceland was obtained (approval no. 21.2018).

Measures

AVHs were assessed with the Psychometric Symptom Rating Scales (PSYRATS), which is a structured interview that measures auditory hallucinations (11 items) and delusions (6 items) rated on a five-point ordinal scale (0-4) (Haddock, McCarron, Tarrier, & Faragher, 1999). PSYRATS has been reported to have excellent inter-rater reliability and good discriminant and convergent validity for both chronic and first episode psychosis (Drake, Haddock, Tarrier, Bentall, & Lewis, 2007; Haddock, McCarron, Tarrier, & Faragher, 1999). The scale was translated into Icelandic by Baldur Heiðar Sigurðsson and Óttar Guðbjörn Birgisson in 2016. It has not been standardized here in Iceland as of yet.

Depression, anxiety and stress were assessed with the Depression, Anxiety and Stress Scale (DASS). DASS is a 42 item, self-report 4 point Likert-type measure. The scale has shown good internal consistency and convergent and discriminant validity in non-clinical samples (Lovibond & Lovibond, 1995). In clinical samples the scale has shown excellent internal consistency and temporal stability as well as excellent discriminant validity and good convergent validity (Brown, Chorpita, Korotitsch, & Barlow, 1997). An Icelandic study supports those findings (Ingimarsson, 2010). The scale was translated by Pétur Tyrfingsson. Cronbach's alpha was calculated and was 0.984.

Quality of life was assessed with the Quality of Life Scale (QoL) (Flanagen ,1978; Flanagen, 1982). QoL is a 16 item self-report scale consisting of five conceptual domains of quality of life: material and physical well-being, relationships with other people, social community and civic activities, personal development and fulfilment, and recreation. The scale

has been shown to have good test-retest reliability and good convergent and discriminant validity (Burckhardt & Anderson, 2003). The scale was translated by Pétur Tyrfingsson but psychometric properties have not been tested in the Icelandic version. Cronbach's alpha was calculated and found to be 0.936.

In order to ensure safety in treatment, the safety screening standard questionnaire for rTMS was used. The rTMS safety screening questionnaire is a 15 item, self-report questionnaire intended to gather basic information for risk assessment before treatment (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). The questionnaire was used to uphold international rTMS safety guidelines (Wassermann, 1998) and was translated to Icelandic for this study by the present author.

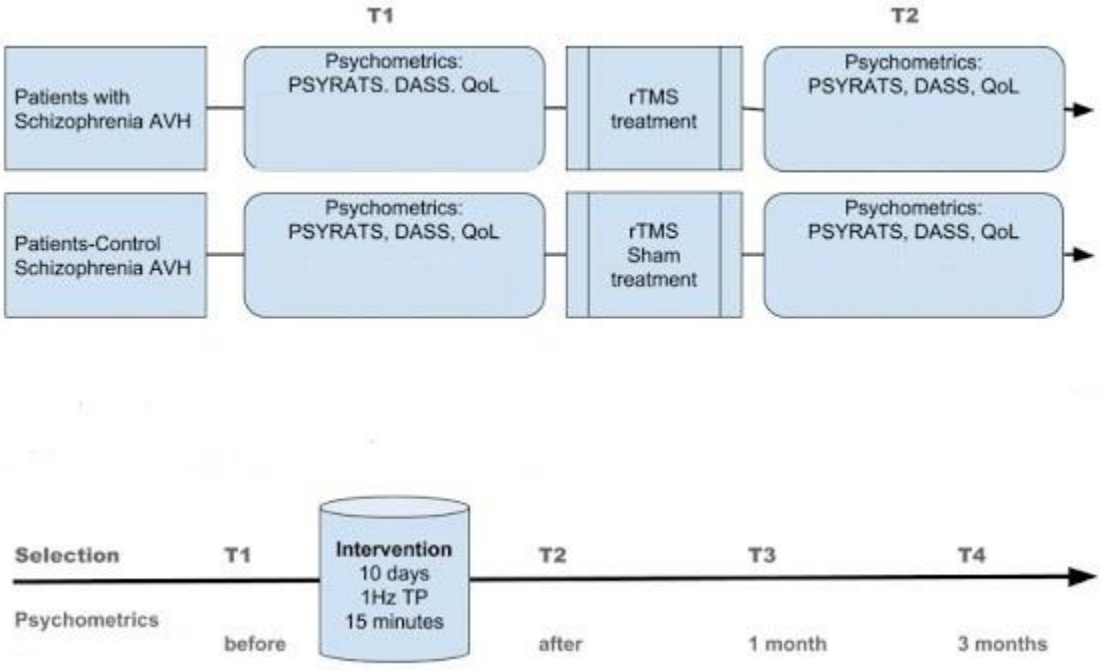
Design

The study used a randomized double-blind placebo-control trial design. It included two groups, one group which received active rTMS treatment and the other group receiving sham treatment at a control location. A Medtronic MagPro stimulator TMS machine from Denmark was used. In the active treatment the figure of eight coil (MC-B70) was placed on the scalp between T3-P3 on the TPC as measured with the 10-20 international system, while for control treatment, the coil was placed at the vertex. Stimulation was delivered at 100% of the resting motor evoked potential (MEP) threshold (RMT) for the right abductor pollicis brevis muscle, determined before each rTMS. RMT was defined as the minimum intensity required to evoke five MEPs in 10 consecutive trials. Treatment consisted of ten sessions over the course of two weeks. Each session lasted 15 minutes and included 900 pulses delivered at 1 Hz.

Procedure

Patients were randomized to receive either active or sham rTMS by using a randomization generator and the list was kept by a researcher who had no role in assessing the AVHs. AVHs were evaluated by a researcher who was blind to the experimental conditions, three to five days before and after treatment, as well as at one and three months follow-up measures. Each time AVHs were assessed with PSYRATS the patients were asked to fill out the DASS and QoL scales as well (Figure 1).

Figure 1. Flow chart describing the procedure and protocol of the study.



Data analysis

A power analysis was carried out before the study was conducted requiring 80% power with 5% alpha level assuming a 30% reduction of symptoms and a standard deviation of 9 and a mean of 28 on the PSYRATS interview. Results indicated that 16 participants would be needed

(Haddock, McCarron, Tarrier, & Faragher, 1999) and the aim is therefore to continue the research until 16 participants have taken part. Preliminary results based on data from six participants will be described here.

Six participants are thought to be the minimum number required to conduct a mixed analysis of variance (ANOVA) with two groups while still staying within an acceptable error rate range with Bayes liberal interpretation. However, this is assuming the group sizes are equal. It is important to note that in this preliminary analysis the active and sham groups are not equal in size; this may produce some inflation in type I error rates (Keselman, Kowalchuk & Boik, 2000).

The SPSS 25.0 statistical analysis software was used to compare treatment and sham conditions using mixed ANOVA. PSYRATS, DASS, and QoL scores over time were used as within subject factors and treatment condition (active and sham) was used as between subject factor. Alpha level was set at 5%.

Results

The main hypothesis of the study was that rTMS would reduce AVHs as measured with PSYRATS. A second hypothesis was that the active rTMS group would show greater reduction in depression, anxiety and stress compared to the sham group. Finally, the third hypothesis was that the active rTMS group would show greater improvements in quality of life compared to the sham group.

Baseline measures showed a significant difference on PSYRATS between the active (M = 25, SD = 2.8) and sham groups (M = 30.25, SD = 1.7) (t(4), = 2.9, p = .04, 95% CI = -10.17 to -.33). There was no difference between the groups at baseline on DASS (depression: (t(4), = 0.11, p = .92, 95% CI = -30.7 to 28.8); anxiety: (t(4), = .86, p = 0.43, 95% CI = -20.65 to 39.65);

stress: (t(4), = 0.25, p = .81, 95% CI = -29.49 to 35.47)); and QoL: (t(4), = .02, p = 0.98, 95% CI = -56.97 to 57.97).

Effect of rTMS on AVHs. Repeated measure mixed ANOVA was used to test the effects of rTMS on the reduction of AVHs immediately post treatment and at one month follow-up, comparing the active treatment and sham groups. In those cases where the assumption for sphericity was not met, a Greenhouse-Geisser correction was used.

The first hypothesis, that active rTMS would show greater reduction on PSYRATS compared to sham group was supported. A significant main effect was found when comparing the active and sham groups ($F(1, 4) = 7.82$, $p < .05$, partial $\eta_p^2 = .66$) but no significant main effect for time ($F(1, 4) = 1.8$, $p = .23$, partial $\eta_p^2 = .31$) or a significant interaction between group and time ($F(1, 4) = 1.00$, $p = .37$, $\eta_p^2 = .2$) (table 2).

To understand what specific aspects of AVHs the rTMS treatment was affecting, a mixed ANOVA was conducted for each question on PSYRATS. *Frequencies*: there was a significant main effect for both time ($F(1, 4) = 8.08$, $p < .05$, $\eta_p^2 = .67$) and group ($F(1, 4) = 64.12$, $p < .05$, $\eta_p^2 = .94$) as well as a significant interaction between time and group ($F(1, 4) = 5.26$, $p < .05$, $\eta_p^2 = .45$). *Duration*: there were significant main effects for time ($F(1, 4) = 3.29$, $p < .05$, $\eta_p^2 = .45$) and group ($F(1, 4) = 13.33$, $p < .05$, $\eta^2 = .77$) but not a significant interaction between time and group ($F(1, 4) = 1.10$, $p = .38$, $\eta_p^2 = .22$). *Loudness*: There was not a significant main effects for time ($F(1, 4) = 4.41$, $p = .78$, $\eta_p^2 = .54$) or group ($F(1, 4) = 0.19$, $p = .685$, $\eta_p^2 = .05$) but there was a significant interaction between time and group ($F(1, 4) = 6.87$, $p > .05$, $\eta_p^2 = .63$). RTMS treatment did not have a significant effect on location, belief, amount of negativity, degree of negativity, amount of distress, intensity of distress or control of AVHs ($p > .05$) (see table 2).

To follow-up on these interactions a Bonferroni post hoc test was used. Results for both frequencies and loudness of AVHs showed that there was no significant difference between the two groups on any of the three time points ($p > .05$).

Table 2

Descriptive statistics, main effects, interactions, statistical significance and effect sizes for each dependent variable across four different time points on PSYRATS.

Variables		Active group (M(SD))	Sham group (M(SD)	Effect	F	*p*	η_p^2
PSYRATS							
Frequency	Pre	3.0(1.4)	4.0(0.0)	Time	8.08	*p*<.05	.67
	Post	2.5(0.7)	4.0(0.0)	Group	64.12	*p*<.05	.94
	1 month	0.5(0.7)	3.8(0.5)	Time*Group	5.26	*p*<.05	.57
Duration	Pre	2.5(0.7)	3.5(1.0)	Time	3.29	*p*<.05	.45
	Post	1.5(0.7)	4.0(0.0)	Group	13.33	*p*<.05	.77
	1 month	1.0(1.4)	2.5(1.0)	Time*Group	1.10	.38	.22
Location	Pre	2.5(2.1)	1.8(1.5)	Time	0.16	.71	.04
	Post	2.5(2.1)	1.8(1.5)	Group	0.00	.00	.00
	1 month	1.0(1.4)	2.5(1.7)	Time*Group	1.40	.30	.26
Loudness	Pre	2.0(0.0)	2.3(0.5)	Time	4.41	.05	.52

	Post	3.0(0.0)	1.5(0.6)	Group	0.19	.69	.05
	1 month	1.0(1.4)	1.8(0.5)	Time*Group	6.87	$p<.05$	.63
Belief	Pre	3.0(1.4)	2.5(2.1)	Time	0.85	.46	.18
	Post	2.5(2.1)	3.0(1.4)	Group	0.00	1.00	.00
	1 month	2.0(2.8)	2.3(1.5)	Time*Group	0.85	.42	.18
Amount of negativity	Pre	2.0(1.4)	3.3(0.5)	Time	0.29	.66	.07
	Post	3.5(0.7)	2.0(1.2)	Group	0.01	.92	.00
	1 month	2.0(2.8)	2.5(1.3)	Time*Group	2.19	.20	.35
Degree of negativity	Pre	3.0(0.0)	3.0(0.8)	Time	1.14	.37	.22
	Post	1.0(0.0)	3.3(0.5)	Group	3.43	.14	.46
	1 month	2.0(2.8)	3.3(1.0)	Time*Group	1.89	.24	.32
Amount of distress	Pre	1.5(2.1)	3.0(0.0)	Time	0.14	.80	.04
	Post	2.5(0.7)	2.3(1.0)	Group	1.40	.30	.26
	1 month	1.5(2.1)	2.5(1.3)	Time*Group	0.80	.45	.17
Intensity of distress	Pre	1.5(2.1)	2.3(1.0)	Time	0.01	.85	.02
	Post	2.0(1.4)	2.3(1.0)	Group	2.33	.20	.37
	1 month	1.0(1.4)	2.8(0.5)	Time*Group	0.69	.49	.15

Disruption	Pre	2.0(0.0)	2.3(0.5)	Time	6.46	$p<.05$	.62
	Post	1.0(1.4)	2.5(0.6)	Group	7.00	.06	.64
	1 month	0.0(0.0)	2.0(0.8)	Time*Group	4.00	.06	.50
Control	Pre	2.0(1.4)	2.8(1.3)	Time	1.01	.41	.20
	Post	2.0(1.4)	2.5(1.3)	Group	0.71	.45	.15
	1 month	1.0(1.4)	2.3(1.5)	Time*Group	0.23	.68	.05
Total	Pre	25.0(2.8)	30.3(1.7)	Time	1.80	.23	.31
	Post	24.0(5.7)	29.0(1.8)	Group	7.82	$p<.05$	.66
	1 month	13.0(18.4)	28.0(5.65)	Time*Group	1.00	.37	.2

Note: M(SD) is mean and standard deviation

Effect of rTMS on depression, anxiety and stress

The second hypothesis was that the active rTMS group would show a greater reduction in depression, anxiety and stress compared to the sham rTMS group. The hypothesis was not supported since there was not a significant difference between active and sham rTMS for depression, anxiety or stress, although there was some reduction on all measures over time. There was no interaction effect between group and time on any measure on DASS (see table 3).

Table 3

Descriptive statistics, main effects, interactions, statistical significance and effect sizes for depression, anxiety and stress across four different time points on DASS.

Variables		Active group (M(SD))	Sham group (M(SD)	Effect	F	*p*	η_p^2
DASS							
Depression	Pre	19.5(9.2)	20.5(11.7)	Time	1.40	.31	.26
	Post	17.5(4.9)	15.5(11.2)	Group	0.02	.90	.01
	1 month	11.5(13.4)	16.3(13.2)	Time*Group	0.42	.60	.09
Anxiety	Pre	23.0(11.3)	13.5(12.9)	Time	1.16	.36	.23
	Post	18.0(4.2)	12.8(8.2)	Group	1.16	.34	.22
	1 month	20.5(4.9)	10.3(8.0)	Time*Group	0.76	.46	.16
Stress	Pre	22.5(13.4)	19.5(13.5)	Time	1.30	.32	.25
	Post	22.0(0.0)	13.5(11.0)	Group	0.54	.50	.12
	1 month	19.5(7.8)	12.0(9.3)	Time*Group	0.40	.56	.09

Note. M(SD) is mean and standard deviation

Effect of rTMS on quality of life

The third hypothesis was that the active rTMS group would report greater improvements in quality of life then the sham group. The hypothesis was not supported since there was not a

significant main effect for time or group on quality of life and there was not a significant interaction between time and group (see table 4).

Table 4

Descriptive statistics, main effects, interactions, statistical significance and effect sizes for quality of life across four different time points for QoL.

Variables		Active group (M(SD))	Sham group (M(SD)	Effect	F	*p*	η_p^2
QoL	Pre	77.0(22.6)	76.0(24.3)	Time	0.37	.70	.09
	Post	85.0(15.6)	80.8(2.6)	Group	0.02	.89	.01
	1 month	79.0(18.4)	79.3(2.1)	Time*Group	0.06	.83	.01

Note. M(SD) is mean and standard deviation

Three months follow-up: Effect of rTMS on AVH, depression, anxiety, stress and quality of life

Only four participants had completed all measures at three months follow-up, and of those only one received active treatment. Since participants were too few to allow statistical analysis, descriptive statistics for each participant will be provided instead. Some minor details in the patients' histories have been changed in order make them unrecognisable.

The first participant was randomly assigned into active rTMS treatment. He reported hearing AVHs almost constantly. The AVH was a woman constantly harassing him and telling him lies. Post treatment he reported reduction in AVH and at one month follow up his AVH had

been absent for a few weeks. At three months follow-up he reported that the AVHs had returned but their frequencies were only a portion of what they were at baseline. He also reported some reduction in anxiety but reported an increase in depressive symptoms as well as stress. Finally, an 18% increase in quality of life was reported. (see table 5).

The second participant received sham treatment. He reported constant AVHs for the last 2 years. AVHs were usually incomprehensible nonsense but sometimes he could make out what they said. Unfortunately his medication treatment changed during the study–Olanzapine Lyrica and Sobril became optional for him to take which might explain some AVHs reduction at three month follow-up. He reported reduction in depression, anxiety and stress during the study. He also reported some reduction in quality of life after sham treatment and at one and three month follow-up (see table 5).

The third participant received sham treatment. She reported almost constant AVHs for the past 18 months. After treatment she reported an increase in duration of AVH but a decrease in the amount of negativity and distress caused by AVHs. At the three month follow-up, she reported a decrease in frequency and loudness of AVHs but an increase in duration. The patient was hospitalized at the beginning of treatment but had moved out into her own apartment at 1 month follow-up. At the same time she reported reductions in depression, anxiety and stress and an increase in quality of life (see table 5).

The fourth participant received sham treatment. At baseline he reported almost constant AVH for the last three years. At three month follow up he reported reduction in frequency and duration of AVHs as well as some decrease in anxiety. Measures also showed a 7% reduction in quality of life at three month follow-up (see table 5).

Table 5

Exact values and % Change on PSYRATS for each of the participants pre treatment and at three month follow-up.

Variables	Patient	Pre	3 months follow-up	T4-T1
PSYRATS				
Frequency	Active	4	2	-50%
	Sham1	4	3	-25%
	Sham2	4	3	-25%
	Sham3	4	2	-50%
Duration	Active	2	2	0%
	Sham1	4	4	0%
	Sham2	2	3	50%
	Sham3	4	2	-50%
Location	Active	4	4	0%
	Sham1	1	1	0%
	Sham2	4	4	0%
	Sham3	1	1	0%
Loudness	Active	2	3	50%
	Sham1	3	3	0%
	Sham2	2	1	-50%
	Sham3	2	2	0%
Belief	Active	2	3	50%
	Sham1	1	3	200%
	Sham2	2	1	-50%

	Sham3	3	2	-33%
Amount of negativity	Active	1	0	-100%
	Sham1	4	0	-100%
	Sham2	3	2	-33%
	Sham3	3	3	0%
Degree of negativity	Active	3	0	-100%
	Sham1	2	0	-100%
	Sham2	4	4	0%
	Sham3	3	3	0%
Amount of distress	Active	0	4	100%
	Sham1	3	4	33%
	Sham2	3	2	-33%
	Sham3	3	3	0%
Degree of distress	Active	0	3	100%
	Sham1	3	3	0%
	Sham2	1	3	200%
	Sham3	3	3	0%
Disruption	Active	2	1	-50%
	Sham1	2	3	50%
	Sham2	3	3	0%
	Sham3	2	2	0%
Control	Active	3	4	33%

	Sham1	3	1	-67%
	Sham2	4	3	-25%
	Sham3	3	2	-33%
Total	Active	23	24	4%
	Sham1	30	23	-23%
	Sham2	32	30	-6%
	Sham3	31	25	-19%
DASS				
Depression	Active	11	16	45%
	Sham1	6	4	-33%
	Sham2	26	26	0%
	Sham3	33	33	0%
Anxiety	Active	15	13	-13%
	Sham1	1	2	100%
	Sham2	26	23	-12%
	Sham3	22	12	-45%
Stress	Active	13	18	38%
	Sham1	3	6	100%
	Sham2	27	19	-30%
	Sham3	34	29	-15%
QoL				
Quality of life	Active	93	110	18%
	Sham1	96	81	-16%
	Sham2	41	71	73%

Sham3	86	80	-7%

Note. T1 = pre and T4 = 3 month follow-up.

% change is calculated as 1-T4/T1.

Adverse effects of rTMS

After rTMS treatment participants were asked if they had experienced any adverse events during the treatment. None of the six participants reported any adverse experiences during treatment.

Discussion

This study examined the effectiveness of low frequency (1 Hz) rTMS over the T3-P3 brain areas as a treatment for persistent AVHs. Patients in the active rTMS treatment group showed medium to large effect sizes in reduction of frequency and duration of AVHs as compared to sham rTMS treatment. Previous studies using comparable treatment protocols have shown similar results for reduction of frequency and duration of AVHs (Sommer et al., 2012). The largest effect seemed to be on the frequency of AVHs which went from being chronic to being experienced only a few times each day or even not at all. The second largest effect was observed on the duration of AVHs where they went from lasting more than an hour to lasting only a few seconds or minutes. The third noticeable change, although not statistically significant, was the disturbing effect AVHs had on patients' daily life. They went from being severely disturbing to patients' life to causing almost no noticeable disturbance at all.

Evidence over the past few decades has shown that AVHs cause patients great anxiety and distress (Chadwich & Birchwood, 1994; Ratcliffe & Wilkinson, 2016) and severely reduce quality of life while increasing the risk of suicide (Sommer, et al., 2012). Furthermore, it is well known that stress over a long period of time can cause depression (Yang et al., 2015) and some data suggest that AVHs can also cause depression (de Leede-Smith & Barkus, 2013). The second

hypothesis, that rTMS could reduce depression, anxiety and stress by alleviating patients AVHs symptoms, was not supported. The third hypothesis, that rTMS could increase quality of life by reducing AVHs, was also not supported since there were no significant differences between the active and the sham group. However, the three month follow-up showed an 18% increase in quality of life for the participant that received active rTMS treatment. One participant in the sham group experienced a 73% increase in quality of life but changes in living arrangements may also explain that.

A surprising result from this study was that treatment did seem to need a few days to take effect. Post rTMS treatment measures did show some immediate improvements, but improvement became increasingly noticeable as the effect was greater at one month follow-up. However, at the three month follow-up, symptoms had returned but were not as severe as measured at baseline. These results are in line with previous studies (Kubera, Barth, Jirjak, Thomann, & Wolf, 2015). However, the results of the current study indicated that rTMS treatment may take a few weeks to reach maximum effect while in previous studies the immediate post treatment effect was stronger than the effect observed in subsequent follow-ups. In order to capture this change more precisely, future studies should take measures more frequently in the weeks following treatment and follow-up measures need to reach beyond three months in order to find out how frequent booster sessions might need to be. In addition, future studies should assess the effectiveness of rTMS on AVHs that are not necessarily medication refractory.

Strengths and limitations: A clear limitation of the study is its lack of statistical power, unequal sample sizes and possibly inflated type I error rates. There were very few participants in each group, only two in the active rTMS group and four in the sham group. This severely limits

generalizability from this study. Any major or minor change in each participant's life might have affected the results. Medication changes were made for two participants in the sham group and a major change in living arrangements occurred for another participant in the sham group. Both of these changes might explain some of the results on PSYRATS, DASS and QoL. One participant in the active rTMS group also underwent major surgery one month after treatment and was on strong pain medication for a few weeks, which might be affecting his results.

Consensus remains to be found for the most effective rTMS treatment protocol for AVHs. However, most studies seem to indicate that the protocol used in this study, i.e. 1 Hz over the T3-P3 area with 100% MT power for 3-10 sessions, is the most effective treatment paradigm known today (Slotema et al., 2014).

An important strength of the current study is the vertex control condition which was designed to produce a similar local sensation and sonic artefact to active treatment, but without the physiological effects. Older studies used a 45° or 90° angle of the figure of eight coil as a placebo but newer studies tend to use a placebo coil which makes sounds but does not cause any sensations (Rotenberg, Horvath, & Pascual-Leone, 2014).

Conclusion: Studies indicate that medication does not work in 8-18% of cases of AVHs, and though CBT has shown promising results in helping patients deal with their AVHs it does not reduce their frequency or duration. The preliminary results of this study indicate that TMS might be an effective treatment option for patients with persistent AVHs. The current study will be continued until the number of participants has reached 16 at which point the full data will be analysed.

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Pub.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-Invasive Magnetic Stimulation of Human Motor Cortex. *The Lancet*, *325*(8437), 1106–1107. doi: 10.1016/s0140-6736(85)92413-4

Blumberger, D. M., Mulsant, B. H., Fitzgerald, P. B., Rajji, T. K., Ravindran, A. V., Young, L. T., … Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *13*(6), 423–435. doi: 10.3109/15622975.2011.579163

Brown, T. A., Chorpita, B. F., Korotitsch, W., & Barlow, D. H. (1997). Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behaviour Research and Therapy, 35(1), 79–89. doi: 10.1016/S0005-7967(96)00068-X

Braham, L. G., Trower, P., & Birchwood, M. (2004). Acting on command hallucinations and dangerous behavior: a critique of the major findings in the last decade. *Clinical Psychology Review*, *24*(5), 513–528. doi: 10.1016/j.cpr.2004.04.002

Brunelin, J., Poulet, E., Bediou, B., Kallel, L., Dalery, J., D'amato, T., & Saoud, M. (2006). Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. *Schizophrenia Research*, *81*(1), 41–45. doi: 10.1016/j.schres.2005.10.009

Chadwick, P., & Birchwood, M. (1994). The Omnipotence of Voices. *British Journal of Psychiatry*, *164*(02), 190–201. doi: 10.1192/bjp.164.2.190

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, *48*(5), 1398–1403. doi: 10.1212/wnl.48.5.1398

Chen, R., Cros, D., Curra, A., Di Lazzaro, V., Lefaucheur, J.-P., Magistris, M. R., … Ziemann, U. (2008). The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *119*(3), 504–532. doi: 10.1016/j.clinph.2007.10.014

de Leede-Smith, S., & Barkus, E. (2013). A comprehensive review of auditory verbal hallucinations: lifetime prevalence, correlates and mechanisms in healthy and clinical individuals. Frontiers in Human Neuroscience, 7, 367.

Dierks, T., Linden, D. E. J., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., & Singer, W. (1999). Activation of Heschl's Gyrus during Auditory Hallucinations. *Neuron*, *22*(3), 615–621. doi: 10.1016/s0896-6273(00)80715-1

Drake, R., Haddock, G., Tarrier, N., Bentall, R., & Lewis, S. (2007). The Psychotic Symptom Rating Scales (PSYRATS): Their usefulness and properties in first episode psychosis. *Schizophrenia Research*, *89*(1-3), 119–122. doi: 10.1016/j.schres.2006.04.024

Fitzgerald, P. B., & Jeff Daskalakis, Z. (2013). *Repetitive Transcranial Magnetic Stimulation Treatment for Depressive Disorders: A Practical Guide*. Springer Science & Business Media.

Flanagan, J. C. (1978). A research approach to improving our quality of life. American Psychologist. https://doi.org/10.1037//0003-066x.33.2.138

Flanagan, J. C. (1982). Measurement of quality of life: current state of the art. Archives of Physical Medicine and Rehabilitation, 63(2), 56–59.

Gaebel, W., Weinmann, S., Sartorius, N., Rutz, W., & McIntyre, J. S. (2005). Schizophrenia practice guidelines: international survey and comparison. *The British Journal of Psychiatry: The Journal of Mental Science, 187*, 248–255. doi: 10.1192/bjp.187.3.248

Gaudiano, B. A., & Herbert, J. D. (2006). Acute treatment of inpatients with psychotic symptoms using Acceptance and Commitment Therapy: pilot results. *Behaviour Research and Therapy*, *44*(3), 415–437. doi: 10.1016/j.brat.2005.02.007

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., … Marder, S. R. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. Biological Psychiatry, 56(5), 301–307.

Haddock, G., McCarron, J., Tarrier, N., & Faragher, E. B. (1999). Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychological Medicine*, *29*(4), 879–889. Doi:

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F., … World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia. (2012). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *13*(5), 318–378. doi: 10.3109/15622975.2012.696143

Hoffman, R. E., Boutros, N. N., Berman, R. M., Roessler, E., Belger, A., Krystal, J. H., & Charney, D. S. (1999). Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated “voices.” *Biological Psychiatry*, *46*(1), 130–132. doi: 10.1016/s0006-3223(98)00358-8

Hoffman, R. E., Boutros, N. N., Berman, R. M., Roessler, E., Belger, A., Krystal, J. H., & Charney, D. S. (1999). Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated "voices." *Biological Psychiatry*, *46*(1), 130–132.

Jenner, J. A., van de Willige, G., & Wiersma, D. (1998). The effectiveness of cognitive therapy with coping training for persistent auditory hallucinations in an out-patient population. *Schizophrenia Research*, *29*(1-2), 163–164. doi: 10.1016/s0920-9964(97)88722-1

Keselman, H. J., Kowalchuk, R. K., & Boik, R. J. (2000). An examination of the robustness of the empirical Bayes and other approaches for testing main and interaction effects in repeated measures designs. The British Journal of Mathematical and Statistical Psychology, 53 (Pt 1), 51–67.

Koops, S., van Dellen, E., Schutte, M. J. L., Nieuwdorp, W., Neggers, S. F. W., & Sommer, I. E. C. (2016). Theta Burst Transcranial Magnetic Stimulation for Auditory Verbal Hallucinations: Negative Findings From a Double-Blind-Randomized Trial. *Schizophrenia Bulletin*, *42*(1), 250–257. doi: 10.1093/schbul/sbv100

Kubera, K. M., Barth, A., Hirjak, D., Thomann, P. A., & Wolf, R. C. (2015). Noninvasive brain stimulation for the treatment of auditory verbal hallucinations in schizophrenia: methods, effects and challenges. Frontiers in Systems Neuroscience, 9, 131.

Larøi, F., Sommer, I. E., Blom, J. D., Fernyhough, C., Ffytche, D. H., Hugdahl, K., … Waters, F. (2012). The characteristic features of auditory verbal hallucinations in clinical and nonclinical groups: state-of-the-art overview and future directions. *Schizophrenia Bulletin*, *38*(4), 724–733. doi: 10.1093/schbul/sbs061

Lataster, T., Valmaggia, L., Lardinois, M., van Os, J., & Myin-Germeys, I. (2013). Increased stress reactivity: a mechanism specifically associated with the positive symptoms of

psychotic disorder. Psychological Medicine, 43(7), 1389–1400.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., … Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *125*(11), 2150–2206. doi: 10.1016/j.clinph.2014.05.021

Leucht, S., Arbter, D., Engel, R. R., Kissling, W., & Davis, J. M. (2009). How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry*, *14*(4), 429–447. doi: 10.1038/sj.mp.4002136

Lieberman, J. A., Safferman, A. Z., Pollack, S., Szymanski, S., Johns, C., Howard, A., … Kane, J. M. (1994). Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *The American Journal of Psychiatry*, *151*(12), 1744–1752. doi: 10.1176/ajp.151.12.1744

Liu-Seifert, H., Adams, D. H., & Kinon, B. J. (2005). Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. *BMC Medicine*, *3*, 21. doi: 10.1186/1741-7015-3-21

Locatelli, F. (1998). The impact of haematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity - the experience of the Lombardy Dialysis Registry. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *13*(7), 1642–1644. doi: 10.1093/ndt/13.7.1642

Mortimer, A. M., Singh, P., Shepherd, C. J., & Puthiryackal, J. (2010). Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clinical Schizophrenia & Related Psychoses*, *4*(1), 49–55. doi:

10.3371/CSRP.4.1.4

Nagui Rizk, D., Salama, H., Molokhiya, T., & Kassem, L. (2016). Effectiveness of Brief Individual Cognitive Behavioral Therapy for auditory hallucinations in a sample of Egyptian patients with schizophrenia. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *33*, S259–S260. doi: 10.1016/j.eurpsy.2016.01.662

Nosé, M., Barbui, C., & Tansella, M. (2003). How often do patients with psychosis fail to adhere to treatment programmes? A systematic review. *Psychological Medicine*, *33*(7), 1149–1160.

Pontillo, M., De Crescenzo, F., Vicari, S., Pucciarini, M. L., Averna, R., Santonastaso, O., & Armando, M. (2016). Cognitive behavioural therapy for auditory hallucinations in schizophrenia: A review. *World Journal of Psychiatry*, *6*(3), 372–380. doi: 10.5498/wjp.v6.i3.372

Poulet, E., Brunelin, J., Bediou, B., Bation, R., Forgeard, L., Dalery, J., … Saoud, M. (2005). Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. *Biological Psychiatry*, *57*(2), 188–191. doi: 10.1016/j.biopsych.2004.10.007

Ratcliffe, M., & Wilkinson, S. (2016). How anxiety induces verbal hallucinations. *Consciousness and Cognition*, *39*, 48–58. Doi: 10.1016/j.concog.2015.11.009

Rotenberg, A., Horvath, J. C., & Pascual-Leone, A. (2014). The Transcranial Magnetic Stimulation (TMS) Device and Foundational Techniques. In *Neuromethods* (pp. 3–13). doi: 10.1007/978-1-4939-0879-0_1

Shergill, S. S., Murray, R. M., & McGuire, P. K. (1998). Auditory hallucinations: a review of psychological treatments. *Schizophrenia Research*, *32*(3), 137–150. doi: 10.1016/s0920-9964(98)00052-8

Silbersweig, D. A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., … Schnorr, L.

(1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature*, *378*(6553), 176–179. Doi: 10.1038/378176a0

Slotema, C. W., Blom, J. D., de Weijer, A. D., Diederen, K. M., Goekoop, R., Looijestijn, J., … Sommer, I. E. C. (2011). Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biological Psychiatry*, *69*(5), 450–456. doi: 10.1016/j.biopsych.2010.09.051

Slotema, C. W., Blom, J. D., van Lutterveld, R., Hoek, H. W., & Sommer, I. E. C. (2014). Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biological Psychiatry*, *76*(2), 101–110. Doi: 10.1016/j.biopsych.2013.09.038

Sommer, I. E. C., Slotema, C. W., Daskalakis, Z. J., Derks, E. M., Blom, J. D., & van der Gaag, M. (2012). The Treatment of Hallucinations in Schizophrenia Spectrum Disorders. *Schizophrenia Bulletin*, *38*(4), 704–714. doi: 10.1093/schbul/sbs034

Tarrier, N., & Johnson, J. (2015). *Case Formulation in Cognitive Behaviour Therapy: The Treatment of Challenging and Complex Cases*. Routledge.

Uçok, A., & Gaebel, W. (2008). Side effects of atypical antipsychotics: a brief overview. *World Psychiatry: Official Journal of the World Psychiatric Association* , *7*(1), 58–62.

Valmaggia, L. R., van der Gaag, M., Tarrier, N., Pijnenborg, M., & Slooff, C. J. (2005). Cognitive–behavioural therapy for refractory psychotic symptoms of schizophrenia resistant to atypical antipsychotic medication. *British Journal of Psychiatry*, *186*(04), 324–330. doi: 10.1192/bjp.186.4.324

van der Gaag, M., Valmaggia, L. R., & Smit, F. (2014). The effects of individually tailored formulation-based cognitive behavioural therapy in auditory hallucinations and delusions: a meta-analysis. *Schizophrenia Research*, *156*(1), 30–37. doi: 10.1016/j.schres.2014.03.016

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology*, *108*(1), 1–16.

Yang, L., Zhao, Y., Wang, Y., Liu, L., Zhang, X., Li, B., & Cui, R. (2015). The Effects of Psychological Stress on Depression. Current Neuropharmacology, 13(4), 494–504.

Zimmermann, G., Favrod, J., Trieu, V. H., & Pomini, V. (2005). The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: A meta-analysis. Schizophrenia Research. https://doi.org/10.1016/j.schres.2005.02.018

Zonnenberg, C., Niemantsverdriet, M. B. A., Blom, J. D., & Slotema, C. W. (2016). [Auditory verbal hallucinations in patients with borderline personality disorder]. *Tijdschrift voor psychiatrie*, *58*(2), 122–129.