Treatment of patients with therapy-resistant auditory verbal hallucinations

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Treatment of patients with therapy-resistant auditory verbal hallucinations

Behandeling van patiënten met therapie-resistente auditieve verbale hallucinaties

(met een samenvatting in het Nederlands)

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Introduction

1. INTRODUCTION

Ms. K suffered from severe mood swings, aggressive behaviour, automutilation and suicidal behaviour and had been diagnosed with a borderline personality disorder. She kept hearing the voice of her ex-boyfriend who had raped her in the past. The voice told her that she was ugly and useless. Furthermore, the voice commanded her to kill herself. The voice was present daily and even more so during stressful situations. In addition, she saw her ex-boyfriend in her bedroom and smelled blood. The voice made her feel frightened and depressed. As a consequence, she withdrew from her social life. Her family did not perceive the voice and therefore did not believe her.

Why did she hear this voice without an external cause (i.e. auditory verbal hallucination)? Did she have schizophrenia or another psychotic disorder as well? From this moment, my interest for auditory verbal hallucinations in borderline personality disorder started. The primary aim of this thesis was therefore to explore the phenomenology and ensuing distress of auditory verbal hallucinations in patients with borderline personality disorder.

Mr. B with schizophrenia came to the outpatient clinic for psychotic disorders because he suffered from hearing the voices of the children that had bullied him at primary school. The voices told him that he was an ugly redhead, stupid and useless. Despite the use of several antipsychotics, the voices persisted and were present every day, sometimes even every hour. Due to these voices, he did not trust people, had very few social contacts, and preferred to stay at home.

It would be very welcome to find a better treatment for this patient, such as repetitive transcranial magnetic stimulation (rTMS), a device that can influence brain activity by a rapidly changing magnetic field. This resulted in the second aim of this thesis, to explore the effect of rTMS as a treatment method for auditory verbal hallucinations.

This chapter starts with an overview of the knowledge of auditory verbal hallucinations and an introduction into borderline personality disorder, as conflicting opinions exist on psychotic features in this disorder. Furthermore, rTMS is introduced as a treatment tool for psychiatric disorders and symptoms and especially auditory verbal hallucinations.

1.1 AUDITORY VERBAL HALLUCINATIONS

Auditory verbal hallucinations are verbal auditory percepts (such as a word or phrase) experienced in the absence of an auditory stimulus from the extracorporeal world. The phenomenology can vary substantially according to frequency, duration, loudness, location, complexity (ranging from just one word to full phrases) and identity of the voice that is perceived; a voice can sound like the neighbour or the person's mother but

can be unfamiliar to the person as well. Furthermore, auditory verbal hallucinations can occur under stringent circumstances (such as during substance abuse, a fever, the phase between sleeping and awakening or being in a quiet surrounding). Auditory verbal hallucinations can show themselves as comments on the behaviour or self-concept of the person, but may also have an imperative character. The content of auditory verbal hallucinations can vary from harmless to extremely frightening and can even be dangerous (for example if one experiences a voice telling him to kill himself).

Non-auditory hallucinations such as visual, gustatory, olfactory and tactile hallucinations may accompany auditory verbal hallucinations. Delusions and formal thought disorder may also occur in combination with auditory verbal hallucinations.

The medical conditions associated with auditory verbal hallucinations are numerous. Auditory verbal hallucinations have been reported in (older) persons with partial or complete hearing loss [1-3]; 33% of elderly in an audiologic clinic reported auditory hallucinations [4]. Auditory verbal hallucinations may originate from neurological conditions, such as temporal lobe epilepsy (16%) [5] and brain tumours in the temporal lobe, diencephalon and midbrain [1].

A structural lesion or deficit in the auditory system is not necessary to experience auditory verbal hallucinations as they are prominent in schizophrenia (in 60 to 80%) [6]. An example of a patient with schizophrenia is a man who hears his neighbours' voices. He thinks that his neighbours want to get rid of him because he has dark skin and is unemployed. As a consequence, he avoids going out and keeps the curtains closed during the day. He has lost contact with his friends. The diagnosis schizophrenia can be made when symptoms last for at least six months and include at least one month of active-phase symptoms (i.e. two, or more, of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour or negative symptoms) [7]. The majority of the knowledge on auditory verbal hallucinations is obtained from patients with schizophrenia and will be described in the next paragraphs.

Auditory verbal hallucinations can also be present in other psychiatric disorders such as mood disorders, posttraumatic stress disorder, substance abuse and borderline personality disorder [1]. Furthermore, auditory verbal hallucinations are not necessarily due to pathological conditions. In the general population, 10 to 15% reported auditory verbal hallucinations to occur on a regular basis [8, 9].

In the majority of psychiatric patients and notably patients with schizophrenia, the content of auditory verbal hallucinations is percepted as negative, which may well influence attention, self-esteem, mood and social functioning in a negative manner. As a consequence of auditory verbal hallucinations, patients may reveal self-injurious and suicidal behaviour. Auditory verbal hallucinations in schizophrenia can even entail acts of violence and suicide [10, 11]. Individuals without a psychiatric diagnosis experience more control over their voices, perceive the content of voices as positive, and ensuing distress

is low [12, 13]. A recently published paper demonstrated that emotional valence of the content of auditory verbal hallucinations could accurately predict absence or presence of a psychotic disorder [13]; individuals who experienced a negative content in more than half of the auditory verbal hallucinations, had a chance of 88% of having a psychotic disorder. However, auditory verbal hallucinations can not be used to differentiate between various psychiatric disorders, as studies have consistently demonstrated that auditory verbal hallucinations and other hallucinations are found across different psychiatric disorders, without a diagnostically predictive value [14-17].

A strong association exists between auditory and other hallucinations and childhood abuse and neglect [18]; patients with adult bipolar affective disorder subjected to childhood sexual abuse were twice as likely to have auditory verbal hallucinations [19]. Among individuals without a psychiatric diagnosis, predisposition to auditory hallucinations was significantly higher in those cases which reported multiple traumas [20].

1.2 WHICH BRAIN AREAS ARE ACTIVE DURING THE EXPERIENCE OF AUDITORY VERBAL HALLUCINATIONS?

In the previous paragraph auditory verbal hallucations were described to be present in varying phenomenological ways and different psychiatric and neurological conditions. But which brain areas are involved in the perception of auditory verbal hallucinations?

Various neuroimaging studies have been conducted to determine which brain areas are active during the experience of auditory verbal hallucinations. The majority of these studies has been performed with the help of schizophrenia patients, including small patient numbers (up to ten patients) and have found many differences in activation of brain areas [21]. A summary has been provided of two functional magnetic resonance imaging (fMRI) studies which were performed during the experience of auditory verbal hallucinations in population numbers larger than ten participants per condition.

In an fMRI study with 24 patients suffering from psychotic disorder, especially the right inferior frontal area, including Broca's homologue and the right insula, were activated [22]. Furthermore, the left insula, bilateral supramarginal gyri and right superior temporal gyrus showed more activation. Patients with psychotic disorders were included for this study, indicating that they might have other psychotic symptoms or cognitive disturbances, which may influence brain activity during the experience of auditory verbal hallucinations as well. The study of Diederen et al. is of interest, as subjects with auditory verbal hallucinations in the absence of a psychiatric or neurologic disorder were included [23]. No significant differences in auditory verbal hallucination-related brain activation were found between 21 psychotic patients and 21 non-psychotic individuals; common areas of activation included the bilateral inferior frontal gyri, insula, superior

temporal gyri, supramarginal gyri, postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole, and right cerebellum.

Cortical activation during auditory verbal hallucinations has been identified in a meta-analysis, including sixty-eight patients with schizophrenia spectrum disorders [24]. During auditory verbal hallucinations, increased activation was demonstrated in a bilateral neural network including Broca's area, anterior insula, frontal operculum, precentral gyrus, middle and superior temporal gyri, inferior parietal lobule and hippocampus/parahippocampal region. It was concluded that experiencing auditory verbal hallucinations is associated with increased activation in frontotemporal areas involved in speech generation and speech perception, but also within the medial temporal lobe (notably involved in verbal memory).

In a number of studies the temporal course of brain activation associated with auditory verbal hallucinations was investigated. An fMRI study revealed that auditory verbal hallucinations are preceded by deactivation of the parahippocampal gyrus in 24 patients with a psychotic disorder [25]. In 11 patients with schizophrenia/schizoaffective disorder, fMRI revealed a higher correlation between left inferior frontal gyrus and right temporal activation for the hallucination group compared with non-hallucinating patients [26]. Furthermore, pre-hallucination deactivation was found in the right parahippocampal gyrus.

In summary, all studies showed activation in the temporal lobe during the experience of auditory verbal hallucinations; but even studies with larger patient numbers revealed increased activation in different brain regions. Some found activation in language production areas, others found increased activation in the primary auditory cortex (especially the middle and superior temporal gyrus) [1, 27].

1.3 A SUMMARY OF EXPLANATORY MODELS OF THE ORIGIN OF AUDITORY VERBAL HALLUCINATIONS

1.3.1 Cognitive models

Neuroimaging studies have revealed valuable information about the brain areas that are involved in the mediation of auditory verbal hallucinations, but do not provide insight into the underlying mechanism. Therefore, hypothetic models are needed. First, a cognitive model and its variants are introduced.

A number of cognitive models has been developed to explain the aetiology of auditory verbal hallucinations. The most prominent models will be described in this section. The first model proposes auditory verbal hallucinations to result from the misinterpretation of inner speech [28, 29, 30]. Inner speech is used to denote speech spoken by oneself without

vocalization (also referred to as verbal thought or "thinking in words") [31]. A variant of this view proposes that the misinterpretation of inner speech results from deficits in self-monitoring and therefore individuals with auditory verbal hallucinations may have difficulties to recognize inner speech as self-produced [29, 32, 33]. Another variant of this view is the model provided by Bentall that hallucinators are impaired in their ability to tell the difference between real and imagined events and show a specific bias towards attributing their thoughts to an external source [28]. Furthermore, Morrison linked the misattribution of hallucinations to an external source to intrusive thoughts and proposed that these intrusive thoughts become externalized due to motivational factors [34].

Evidence for this model is found in Green and Kinsbourne, who reported that the muscles involved in speech are activated during the experience of auditory verbal hallucinations [35]. Additional evidence is found in neuroimaging studies which revealed activation of frontal areas (Broca's area) during auditory verbal hallucinations [36, 37] and in a meta-analysis, concluding that self-recognition is impaired in patients with schizophrenia and especially auditory verbal hallucinations [38]. However, the specificity of such a deficit for auditory verbal hallucinations is questionable as impaired self-monitoring is also found in patients with delusions [39] and a number of studies has failed to show an association between hallucinations and self-monitoring [1]. Furthermore, subvocalization is only present in part of the patients with auditory verbal hallucinations and the majority of neuroimaging studies did not find activation of Broca's area. In addition, nonhallucinating patients also experience inner speech, yet do not misattribute these experiences as hallucinations, and the inner speech model cannot explain why auditory hallucinations are mostly experienced in the second or third person [1]. Therefore, it can be concluded that the evidence for impaired monitoring of inner speech relating to auditory verbal hallucinations is limited.

A second model hypothesizes that auditory verbal hallucinations are a result of 'unintentional activation of memories' or 'a failure to inhibit memories of prior events' [40, 41]. In a meta-analysis it is confirmed that brain areas involved in memory reveal increased activation during the experience of auditory verbal hallucinations [24]. Furthermore, there is evidence that auditory verbal hallucinations [20, 42] and especially auditory verbal hallucinations which take the form of commands to hurt oneself or others [19], are associated with earlier experiences of physical and sexual abuse. Indeed, previous research has shown that traumatic life events are associated with a diagnosis of psychosis with a dose-effect [18]. However, the phenomenology from which this argument originates, is based on a limited number of auditory verbal hallucinations [43]; only 7% of individuals with auditory verbal hallucinations were rated as demonstrating clear concordance between the theme and content of the trauma and the themes and content of the voices, while 42% of persons having current problems with past trauma had no association between the content of their hallucinations and their trauma [44].

1.3.2 Neurobiological models

In addition to cognitive models, neurobiological models have been proposed to explain the origin of auditory verbal hallucinations. Firstly, abnormalities in the balance between intrinsic activation of the thalamocortical circuit and hippocampus and the sensory input to the thalamus may predispose to hallucinations [45]. The thalamocortical circuits are involved in the processing of sensory auditory information. Only a minor part of this circuit is devoted to the transfer of sensory information; the biggest part is geared to the generation of internal functional modes [46]. Sensory stimulation can reset and enhance gamma oscillatory activation recorded from the neocortex during awakeness [47]. Via the primary cortices sensory information is processed in the temporal and parietal association cortices. The hippocampus can rapidly integrate stimulus-related and contextual information processed in the association cortices [48]. It receives information from the amygdala and orbitofrontal cortex. Glutamatergic projections from the amygdala stimulate the integration of neocortical inputs in emotionally arousing situations and the spread of neocortical activity to the hippocampus [49]. Auditory verbal hallucinations may arise from a change in activation between the different areas involved in the integration of sensory information.

A variant of this hypothesis suggests that auditory verbal hallucinations may arise from aberrant activation in the non-dominant (i.e. right, in most cases) hemisphere [50]. This activation could be misinterpreted by a left hemisphere conscious verbal system, giving rise to auditory verbal hallucinations [51]. Indeed, it has been hypothesized that there is more bilateral language activation in patients with schizophrenia, resulting from increased language activity in the right hemisphere [52, 53]. Further evidence for this hypothesis comes from the results of a neuroimaging study with 24 patients with a psychotic disorder, in which the right inferior frontal area was predominantly activated during the experience of auditory verbal hallucinations [22]. However, exclusive bilateral language representation is not enough to cause auditory verbal hallucinations as bilateral language representation is also found in healthy (left-handed) subjects [54]. Furthermore, not all neuroimaging studies revealed activation of the right inferior frontal gyrus.

1.3.3 Conclusions from the neurobiological and cognitive models

The origin of auditory verbal hallucinations without a structural lesion has not been completely unravelled yet. The majority of the cognitive and neurobiological hypotheses appears to explain a subgroup of auditory verbal hallucinations; voices that comment on the persons' behaviour, are in line with the inner speech model. Furthermore, auditory verbal hallucinations which are comparable to traumatic experiences, fit in with the model which hypothesizes that auditory verbal hallucinations may originate from unintentional activation of memories. In addition, some neuroimaging studies revealed activation in language production areas during the experience of auditory verbal hal-

lucinations (which is in line with the inner speech model), others showed activation in the brain areas involved in memory.

The model of Behrendt provides an explanation for a broad range of auditory verbal hallucinations, but a dysbalance in activation does not inform us about the underlying mechanism of auditory verbal hallucinations. Neither do the other models. However, it is important to further develop these and/or new models in order to achieve more knowledge of the aetiology of auditory verbal hallucinations.

Perhaps different models fit specific kinds of auditory verbal hallucinations. Or it is the other way around; auditory verbal hallucinations originate from one underlying cause that is unknown at this point in time [43].

At this moment one can say that a change of activation in the region from the cochlea to the brain areas that are associated with the perception of speech and the limbic system, may give rise to auditory verbal hallucinations.

Beyond an introduction into borderline personality disorder in the next paragraph, the subject of auditory verbal hallucinations will be further discussed in paragraph 1.4.2.

1.4 BORDERLINE PERSONALITY DISORDER

1.4.1 Introduction

Before a review of the literature considering auditory verbal hallucinations in borderline personality disorder is presented, it is important to understand what is meant by this diagnosis as conflicting opinions exist on psychotic features in this patient group.

Therefore, we present Ms. A, 21 years old, who has tried to kill herself by taking twelve sleeping tablets in combination with alcohol. The reason for this behaviour was that her boyfriend had ended their relationship. However, two days later her boyfriend reversed his decision and everything was fine. She was known to have a mood that could rapidly change from very happy to such anger that she would hit her boyfriend. When having feelings of extreme sadness, she sometimes cut herself in order to end this awful feeling. Patients are diagnosed with borderline personality disorder if they fulfill at least five out of nine criteria presented in Table 1.1 (Diagnostic and statistical manual of mental disorders fourth edition, text revision [7]).

Nowadays, borderline personality disorder is conceptualized as a combination of affective dysregulation, impulsive-behavioural dyscontrol, cognitive-perceptual symptoms (such as suspiciousness, ideas of reference, paranoid ideation, illusions, derealization, depersonalization and hallucination-like symptoms), and disturbed interpersonal relatedness [55, 56]. Severe behavioural problems such as substance abuse, aggressive behaviour, suicidal actions and self-injurious behaviour, may be in the foreground.

Table 1.1 Criteria for the diagnosis borderline personality disorder

1.	Frantic efforts to avoid real or imagined abandonment
2.	A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3.	Identity disturbance: markedly and persistently unstable self-image or sense of self
4.	Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)
5.	Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
6.	Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7.	Chronic feelings of emptiness
8.	Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9.	Transient, stress-related paranoid ideation or severe dissociative symptoms

Criteria according to DSM-IV-TR [7]

Borderline personality disorder affects 1 to 2% of the general population, including up to 10% of psychiatric outpatients and 20% of inpatients. In treated patients, borderline personality disorder is more common in women than in men (approximately 70 to 75% and 30% respectively) [57, 58]. Physical and sexual abuse in childhood is frequent among this population [59].

Treatment consists of psychotherapy, such as schema-focussed therapy [60] , mentalization-based therapy [61] and dialectical behavioural therapy [62] in an individual or group setting. Psychotherapy can be combined with psychopharmacological agents aimed to reduce symptoms of borderline personality disorder or comorbid disorders [63, 64].

Clinical experience suggests that a high percentage of patients with borderline personality disorder meet criteria for Axis I disorders during the course of outpatient and inpatient treatments. Comorbid disorders that were found among patients with borderline personality disorder who were hospitalized for psychiatric reasons, included mood disorder (97%), anxiety disorder (89%), substance abuse 62% and eating disorder (54%) [65].

Auditory verbal hallucinations are not included in the criteria to diagnose borderline personality disorder, although these patients can hear voices without an external cause. What is the connection between borderline personality disorder and auditory verbal hallucinations?

1.4.2 Borderline personality disorder and auditory verbal hallucinations

Psychiatrists and other caregivers working in the field of personality disorders, see patients with borderline personality disorder who experience auditory verbal hallucinations and demonstrate automutilation and suicidal behaviour in reaction to their voices. Few studies investigated the presence of auditory verbal hallucinations, which varied

between 21 to 54% of patients with borderline personality disorder [66-68]. But one needs to be careful with the interpretation of these results as the patient samples were small with 13 to 48 patients per study. Only one study investigated the phenomenological characteristics of auditory verbal hallucinations in this population in a structural manner; Kingdon and colleagues investigated differences and similarities between auditory verbal hallucinations in patients with borderline personality disorder (n = 15), BPD *and* schizophrenia (n = 17) and schizophrenia alone (n = 35) [67]. The only differences that could be revealed were higher scores for distress and negative content of voices in the group with solely borderline personality disorder.

Auditory verbal hallucinations in borderline personality disorder tend to be explained in four different ways. Firstly, they are conceptualized as 'pseudohallucinations'. The term as well as the concept were originally introduced by Hagen [69], and elaborated further by Kandinsky [70] and many others, which eventually resulted in an impressive number of terms and connotations (for an overview see Blom [31]) that all differ somewhat from Hagen's original version. As a result true consensus is lacking, although there is a level of agreement that pseudohallucinations might be perceptions that are experienced inside the head, with preserved insight into their nature [71]. From that point of view, psychotic features in borderline personality disorder are described as transient, limited to one or two life areas (such as work or family), atypical (possibly reality-based or totally fantastic in content) or not really psychotic [56, 72, 73]. Some of the terms used to designate such auditory verbal hallucinations are 'quasipsychotic experiences' [73] , 'traumatic-intrusive hallucinations' [74] , 'transient, stress-related ideation' [75] , and 'hallucination-like symptoms' [56]. These terms would seem to suggest a milder form or a different type of auditory verbal hallucinations than those occurring in the context of psychotic disorders, but whether this is true, remains to be seen. Secondly, auditory verbal hallucinations experienced by patients diagnosed with borderline personality disorder are considered quite similar to those occurring in individuals without a psychiatric or neurological diagnosis. Daalman and colleagues [13] compared the phenomenological characteristics and ensuing distress of auditory verbal hallucinations experienced by individuals without a diagnosis with those in patients with a psychotic disorder, and only found differences in the frequency of auditory verbal hallucinations and the emotional valence of their content, with higher scores for the patients diagnosed with a psychotic disorder. In addition, individuals without a diagnosis were found to have more control over the voices. Auditory verbal hallucinations in borderline personality disorder may be viewed in a similar vein as those in healthy individuals. In the third place, auditory verbal hallucinations occurring in the context of borderline personality disorder are conceptualized as lying on a continuum with those experienced by individuals without a diagnosis or diagnosed with schizophrenia, with the borderline personality disorder group holding some sort of middle ground. And fourth, auditory verbal hallucinations are considered to be occur-

ring across different psychiatric disorders, including borderline personality disorder. So far, it is unknown whether the voices experienced by patients diagnosed with borderline personality disorder comply with the given explanations, as most studies have failed to systematically assess the phenomenology and severity of auditory verbal hallucinations and other psychotic features in this patient group. Perhaps this is due to the diagnostic process and exploration of psychotic features, which is complicated by the fact that a substantial part of patients with borderline personality disorder have a comorbid Axis I disorder [65]. Finally, the interpretation of the results of earlier studies has been hampered by the tendency to use the terms "psychotic" or "psychotic-like", to designate auditory verbal hallucinations as well as other psychotic symptoms [73].

In conclusion, auditory verbal hallucinations in borderline personality disorder are frequently described as less severe and qualitatively different from those in psychotic disorders. The few (small) studies that systematically investigated the prevalence and phenomenological characteristics of auditory verbal hallucinations in patients with borderline personality disorder imply that those auditory verbal hallucinations may occur in a regular manner, and that the ensuing burden is high among this group. But to gain more insight into this issue, studies with larger patient samples would be necessary.

1.5 TREATMENT OF AUDITORY VERBAL HALLUCINATIONS

In the preceding part of this thesis, the phenomenological characteristics and explanatory models of the origin of auditory verbal hallucinations were discussed. Furthermore, a tension exists regarding the clinical practice with patients with borderline personality disorder experiencing auditory verbal hallucinations and the theoretical impossibility of this combination, as auditory verbal hallucinations are not included in the criteria for the diagnosis borderline personality disorder and auditory verbal hallucinations in borderline personality disorder are considered being less severe and qualitatively different from those in psychotic disorders. Auditory verbal hallucinations do not always need to be treated. In case of ensuing burden of the patient or his/her surroundings, treatment is desirable or even necessary. Antipsychotic agents are the first option in the treatment of auditory verbal hallucinations. Antipsychotics induce a blockade of the dopamine type 2 receptor [76] , thereby compensating for the increased signal transmission of dopamine, but the exact mechanism is unknown. However, in 25 to 30% of the patients with schizophrenia, auditory verbal hallucinations are medication-resistant [77]. Treatment options are sparse for this subgroup. Cognitive-behavioural therapy (CGT) may be an option, although it tends to offer only a modest short-term improvement with regard to auditory verbal hallucinations and illness-insight [78]. CGT may help to cope with auditory verbal hallucinations, but the voices do not disappear [79]. This was confirmed by two

randomized controlled trials; group CBT versus treatment-as-usual revealed no general effect of group CBT on severity of hallucinations [80] and patients receiving group CBT could better resist voices and perceived them as less malevolent than patients receiving enhanced supportive therapy [81]. A reason for the disappointing results may be that CBT deals with reactions to distress, not with hallucinations themselves [1].

In addition to CGT, psycho-education of the patient and his/her family [82, 83] , and application of peer-support groups [84] might be useful. Furthermore, electroconvulsive therapy (ECT) can be an option in the treatment of medication-resistant psychosis as a meta-analysis of ECT versus placebo resulted in a relative risk of 0.78 for clinical improvement in the treatment of schizophrenia patients in favour of ECT [85] , but a subanalysis exploring the effect of ECT on (auditory verbal) hallucinations was not performed.

In conclusion, for the patients who fail to benefit from antipsychotic medication, alternative treatments such as CBT do not influence the frequency and duration of auditory verbal hallucinations, but may help to better cope with auditory verbal hallucinations. Therefore, additional treatments are very welcome.

1.5.1 Transcranial magnetic stimulation

The search for additional treatment strategies for auditory verbal hallucinations has led to the exploration of the effect of rTMS for this symptom. TMS is a device in which a strong but brief electric current is sent through a coil (see figure 1.1 for an example of a TMS device). This results in a fluctuating magnetic field that can depolarize neurons up to a depth of 2 cm in a non-invasive manner. The properties of the electric current are as follows: the duration is 1/4000 second, typical peak voltages and currents are respectively 2,000 Volt and 10,000 Ampere and the magnetic field it produces has a strength of 1.5 to 2.5 Tesla [86]. The electric current can be given as a single pulse, as a paired pulse, and in a repetitive manner, in which the interval between the stimuli is stable (repetitive TMS, rTMS). The effects of TMS depend on the following variables: the focus, frequency, percentage of the motor threshold (i.e. the intensity in which movements of the fingers can barely be seen when the motor cortex is stimulated), the number of stimuli per session, the number of sessions, and the type of coil that is used. TMS can be used as a brain mapping tool, as a device to measure cortical excitability, to measure neural networks and to influence brain function. An advantage of rTMS is that side effects are mild; transient headache, scalp discomfort and itching of the facial musculature are mentioned on a regular basis. In the early days of rTMS epileptic seizures occurred in some individuals having received high-frequency rTMS. Since safety guidelines have been developed [87] epileptic seizures have become extremely rare.

Repetitive TMS can result in a decrease of cortical excitability when applied in a frequency of one hertz; the findings for high-frequency rTMS, i.e. a frequency of ≥ 5 hertz, are controversial [88]. Repetitive TMS is able to change and modulate activity beyond the

stimulation period, which makes it suitable for therapeutic purposes. It is suggested that this is achieved by long-term potentiation and/or depression of brain activation [89]. The after-effects induced by rTMS may well be due to synaptic plasticity, but this has not been proved [88]. Furthermore, NMDA receptors (N-methyl-D-aspartate, a glutamate receptor), dopaminergic receptors and brain-derived neurotrophic factors may play a role in the induction of rTMS effects, but the exact mechanism is unknown [88, 90-93].

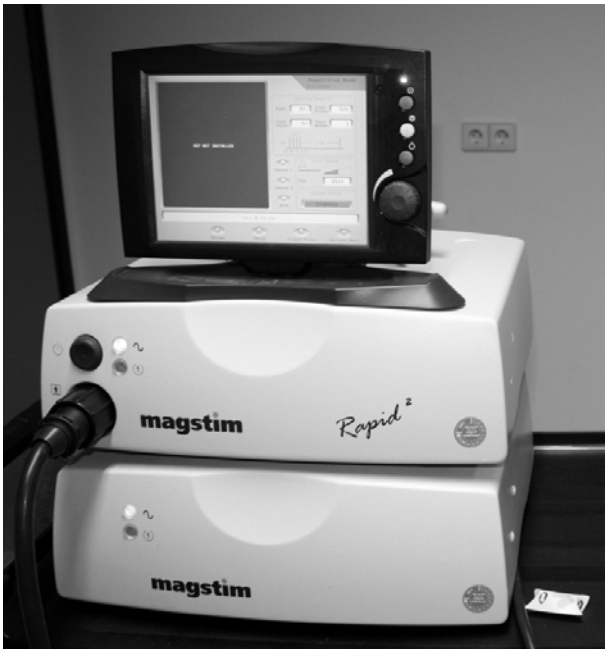

Figure 1.1 Example of a TMS device

1.5.2 Transcranial magnetic stimulation in the treatment of auditory verbal hallucinations

Repetitive TMS as a treatment tool for depression has extensively been investigated. The possibility of using rTMS was driven by functional imaging evidence that patients with depression have reduced activation in the left prefrontal cortex [94, 95]. Meta-analyses considering rTMS for depression revealed a moderate effect size [96-99]. The effects of rTMS on other psychiatric disorders or symptoms, such as negative symptoms of schizophrenia, obsessive-compulsive disorder, posttraumatic stress disorder, substance abuse, mania and auditory verbal hallucinations in patients with schizophrenia, are still under investigation.

Hoffman and colleagues were the first to explore rTMS in the treatment of auditory verbal hallucinations, finding a decrease in the severity of auditory verbal hallucinations

when rTMS was applied to the left temporoparietal cortex (Brodmann area 40, involved in the perception of speech [100]) in a frequency of one hertz [101]. In the meantime several studies have been published with controversial results. In the majority of studies rTMS was directed at the left temporoparietal cortex and applied in a frequency of one hertz. See figure 1.2 for an example of an rTMS-treatment for auditory verbal hallucinations. Three meta-analyses of rTMS versus sham treatment revealed moderate to good effect sizes varying from 0.51 to 1.0 in favour of real rTMS [102-104]. They included studies with a cross-over design, which is a disadvantage as patients cannot remain blinded for the treatment received because the real TMS treatment is associated with tactile stimulation, while the sham condition that was used in the majority of those studies, is not.

In conclusion, rTMS is investigated in a number of psychiatric disorders and symptoms and especially depression. The introduction of rTMS gave hope to patients with severe, treatment-resistant auditory verbal hallucinations and their caregivers, even more because it is a safe treatment tool with mild side effects. More studies are needed to increase the efficacy of rTMS for depression and auditory verbal hallucinations and to further explore the effect of rTMS in other psychiatric disorders.

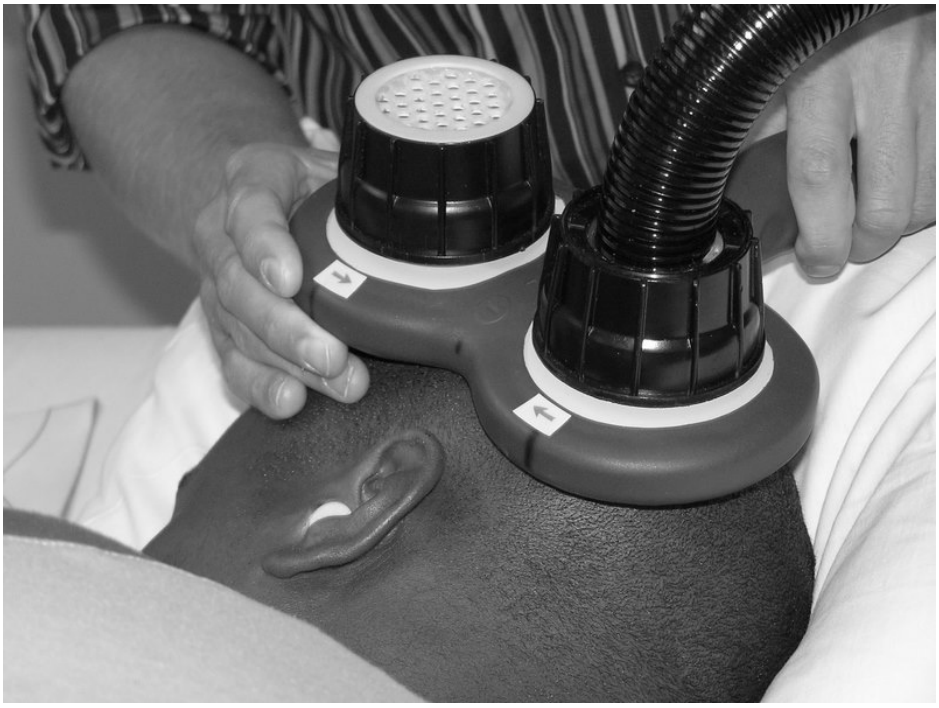

Figure 1.2 Repetitive TMS in the treatment of auditory verbal hallucinations

1.6 OUTLINE OF THE PRESENT THESIS

The aim of the present thesis is to answer the following questions:

1. What are the phenomenological features and ensuing distress of auditory verbal hallucinations experienced by patients diagnosed with borderline personality disorder? (Chapter 2)
2. What are the differences and/or similarities in auditory verbal hallucinations between patients with borderline personality disorder, schizophrenia and healthy subjects? (Chapter 2)
3. Is repetitive transcranial magnetic stimulation effective in the treatment of psychiatric disorders and symptoms, such as auditory verbal hallucinations? (Chapter 3)
4. Could the effect of repetitive transcranial magnetic stimulation on auditory verbal hallucinations be increased, by
    a. directing repetitive transcranial magnetic stimulation at the brain area with maximal hallucinatory activation? (Chapter 4 and 5)
    b. using low-frequency repetitive transcranial magnetic stimulation preceded by brief high-frequency (i.e. priming) repetitive transcranial magnetic stimulation? (Chapter 6)

In Chapter 7 the meaning of the findings and implications for future research will be discussed.

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2

Auditory verbal hallucinations in patients with borderline personality disorder are similar to those in schizophrenia

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Submitted

ABSTRACT

Objective

Auditory verbal hallucinations (AVH) in patients with borderline personality disorder (BPD) are frequently claimed to be brief, less severe and qualitatively different from those in schizophrenia, hence the term 'pseudohallucinations'. AVH in BPD may be more similar to those experienced by healthy individuals, who experience AVH in a lower frequency and with a more positive content than AVH in schizophrenia. The aim of this study was to compare the phenomenology of AVH in BPD patients to those in schizophrenia and to AVH experienced by healthy individuals.

Methods

In a cross-sectional setting, the phenomenological characteristics of AVH in 33 BPD patients were compared to those in 51 patients with schizophrenia/schizoaffective disorder and to AVH of 66 healthy subjects, using the Psychotic Symptom Rating Scales (PSYRATS). All participants were female.

Results

BPD patients experienced AVH for a mean duration of 17 years, with a mean frequency of at least daily during several minutes or more. The ensuing distress was high. No differences in the phenomenological characteristics of AVH were revealed among patients diagnosed with BPD and those with schizophrenia/schizoaffective disorder, except for 'disruption of life', which was higher in the latter group. Compared to healthy subjects experiencing AVH, BPD patients had higher scores on almost all items.

Conclusions

AVH in BPD patients are phenomenologically similar to those in schizophrenia, and different from those in healthy individuals. As AVH in patients with BPD fulfil the criteria of hallucinations proper, we prefer the term AVH over 'pseudohallucination', so as to prevent trivialization and to promote adequate diagnosis and treatment.

2.1 INTRODUCTION

Since the 1940s transient psychotic episodes have been recognized as possible symptoms of the borderline personality disorder (BPD) [1], but it took until 1987 before they were included in the Diagnostic and statistical manual of mental disorders third edition revised (DSM-III-R) which stated that "during extreme stress, transient psychotic symptoms may occur" [2]. With the introduction of the DSM-IV in 1994, all that remained of this

criterion was "transient, stress-related paranoid ideation" [3]. As BPD is conceptualized as a combination of affective dysregulation, impulsive-behavioural dyscontrol, cognitive-perceptual symptoms (such as suspiciousness, ideas of reference, paranoid ideation, illusions, derealization, depersonalization, and hallucination-like symptoms), and disturbed interpersonal relatedness [4, 5], psychotic symptoms occurring in the context of BPD are by definition considered to be transient, and misperceptions to be at best 'hallucination-like' in nature.

And yet there is currently no consensus on the phenomenology and severity of hallucinations and other psychotic phenomena associated with BPD. As the diagnostic criteria of BPD fail to account for the occurrence of longer-lasting hallucinations, clinicians and researchers often find themselves struggling for words when confronted with AVH experienced by patients thus diagnosed. This is reflected in the BPD-related nomenclature, which features such varying terms as 'micropsychotic episodes' [6], 'hysterical psychosis' [7], 'factitious psychosis' [8], 'quasi-psychotic thought' [9], 'traumatic-intrusive hallucinosis' [10], 'stress-related psychosis' [11], 'pseudohallucinations' [12], and 'hallucination-like symptoms' [5]. Like the DSM criteria, these terms would seem to suggest that psychotic symptoms in BPD are short-lasting, less severe, and qualitatively different from those in psychotic disorders such as schizophrenia. However, empirical evidence for this suggestion is virtually lacking. In fact, the few studies that explored BPD-related psychotic symptoms in a structural manner focussed on auditory hallucinations that were present in 21% and 54% of the cases [13, 14]. The prevalence of auditory vérbal hallucinations (AVH) was 50% in a sample of 33 patients [15]. This is the only study that charted the phenomenological characteristics of AVH, in 15 BPD patients; the results suggest that they would seem to be equally severe as those in schizophrenia [15]. What all those studies indicate is that the occurrence and severity of AVH in BPD are underexposed and in need of further study. More specifically, it would seem necessary to assess the phenomenological characteristics of AVH in BPD patients, and to determine whether they are perhaps more similar to the non-pathological types often encountered in the healthy population [16 17]. We therefore performed a prospective, cross-sectional study to answer the following questions:

1. What are the phenomenological characteristics and the ensuing distress of AVH in BPD?
2. What are the differences and similarities between AVH in BPD, schizophrenia/schizoaffective disorder, and healthy voice hearers?

2.2 METHODS

Participants

In the present study we included only women, as the majority of the patients treated for BPD are female [18]. Patients diagnosed with either BPD or schizophrenia/schizoaffective disorder were recruited from the Parnassia Bavo Psychiatric Institute and the University Medical Centre Utrecht from May 2007 till April 2011.

Inclusion criteria for the patients diagnosed with BPD were: 1. age of 18 years or older, 2. AVH more than once per month, and for a duration of over one year, 3. the diagnosis BPD was confirmed with the aid of the Structured Clinical Interview for DSM-IV, axis II personality disorders (SCID II) [19], and 4. the patient did not meet the criteria for schizophrenia, schizoaffective disorder, bipolar disorder, major depression with psychotic symptoms or schizotypal personality disorder according to the Comprehensive Assessment of Symptoms and History (CASH) [20] and the SCID II. As a consequence, all BPD patients presenting with delusions were excluded.

Patients diagnosed with schizophrenia/schizoaffective disorder were allowed to participate if the following criteria were met: 1. age of 18 years or older, 2. AVH for at least once a month, and for a duration of over one year, and 3. a diagnosis of schizophrenia/schizoaffective disorder was established with the aid of the CASH by a psychiatrist experienced in the field of psychotic disorders.

Reasons for exclusion in both groups were alcohol abuse of three or more units per day, the use of hard drugs during the month prior to inclusion, and daily use of cannabis.

Healthy females experiencing AVH were recruited with the help of a Dutch website called 'Explore Your Mind' (www.verkenuwgeest.nl). They were selected if they had a high score on the items 8 and 12 ('In the past, I have had the experience of hearing a person's voice and then found that no-one was there' and 'I have been troubled by voices in my head', respectively) of the Launay-Slade Hallucination Scale (LSHS) [21]. In addition, the following inclusion criteria were used: 1. age of 18 years or older, 2. AVH at least once a month, and for a duration of over one year, 3. no diagnosed psychiatric disorder, other than depressive or anxiety disorder in complete remission, and 4. no alcohol or drug abuse for at least 3 months. The healthy individuals and some of the patients with schizophrenia/schizoaffective disorder of this study show some overlap with the study of Daalman and colleagues [16].

The study was approved by the Institutional Review Board of the University Medical Centre Utrecht (UMCU) and the Parnassia Bavo Psychiatric Institute, the Netherlands. Prior to the onset of the study, the participants received oral and written information considering the content and goals of the study. Written informed consent was obtained from all the participants.

Interviews and questionnaires

The SCID II was used to confirm the diagnosis of BPD and to exclude a schizotypal personality disorder. With the aid of the CASH, the diagnoses schizophrenia, schizoaffective disorder, bipolar disorder, and major depression with psychotic symptoms were either confirmed or ruled out.

The Psychotic Symptom Rating Scales PSYRATS – AVH – related items [22] were used to describe the phenomenological characteristics and ensuing distress of AVH (see Appendix I). The following dimensions of AVH were explored on a five-point scale (0 – 4): frequency, duration, perceived location, loudness, beliefs about origin, amount of negative content, degree of negative content, degree of distress, intensity of distress, disruption of life, and controllability.

Statistics

A One-Way Analysis of Variance (ANOVA) was performed to compare continuous demographic data among the three groups. In case of significant differences this variable was used as a covariate in the analysis of the AVH-related items of the PSYRATS.

The differences and similarities between AVH experienced by the members of the three groups were analyzed by means of a Multivariate General Linear Model analysis with grouping variables 'BPD', 'schizophrenia/schizoaffective disorder', and 'no diagnosis'. The Benjamini-Hochberg correction was used for multiple comparisons.

2.3 RESULTS

Thirty-three patients diagnosed with BPD, 51 patients with schizophrenia/schizoaffective disorder (schizophrenia n = 36 and schizoaffective disorder n =15), and 66 healthy subjects were included. The demographic data are presented in Table 2.1. All the participants were females. The mean ages of the three groups did not differ significantly ($F = 1.678$, df 2,147, $p = 0.19$). Except for two patients in the schizophrenia/schizoaffective disorder group, all of the patients were treated in an outpatient setting.

Table 2.1 Demographic data

	Controls with AVH (n = 66)	BPD (n = 33)	Schizophrenia/schizoaffective disorder (n = 51)	p
Age, mean (sd)	37 (11.4)	33 (10.4)	37 (9.8)	0.19
Outpatient, n (%)	66 (100)	33 (100)	49 (96)	0.14

Abbreviations: AVH = auditory verbal hallucinations, BPD = borderline personality disorder, sd = standard deviation

Phenomenology of auditory verbal hallucinations and ensuing distress in borderline personality disorder

The mean scores of the AVH-related items of the PSYRATS are presented in Figure 2.1 and Table 2.2. Patients diagnosed with BPD experienced AVH for a long duration (mean 17 years). The majority of them experienced AVH more than once per day, with a duration of at least several minutes. The hallucinations were mostly experienced inside the head, and attributed to intracorporeal causes. Scores on the items 'negative content', 'distress', 'disruption of life', and 'controllability' were high among this group.

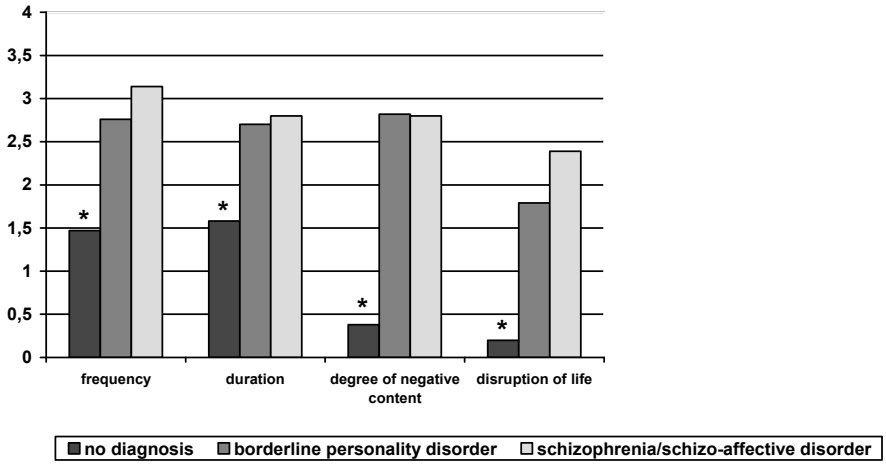

Fig. 2.1 Mean score on Auditory Verbal Hallucinations-related items of the Psychotic Symptom Rating Scales

Differences and similarities between auditory verbal hallucinations and other hallucinations in borderline personality disorder, schizophrenia/schizoaffective disorder, and healthy subjects

The results of the analyses are presented in Figure 2.1 and Table 2.2. The number of years during which AVH were experienced by patients with BPD was not significantly different from the duration among patients with schizophrenia/schizoaffective disorder or healthy individuals with AVH. The mean age of onset of AVH was 13, 16, and 20 years for healthy subjects, BPD, and schizophrenia/schizoaffective disorder respectively. Significant differences were found for all AVH-related items between the three diagnostic groups, except for 'length of time experiencing AVH', 'perceived location', and 'loudness'. Post hoc analyses revealed significant differences between the group without a diagnosis and the BPD group for all other items ($F \geq 15.771$, df 1,96, $p < 0.001$). No significant differences were found between patients with BPD and those with schizophrenia/schizoaffective disorder, except for 'disruption of life' ($F = 10.772$, df 2,82, $p = 0.002$) which was higher in patients with schizophrenia/schizoaffective disorder.

Table 2.2 Results of the Psychotic Symptom Rating Scales – auditory verbal hallucination-related items

	Controls with AVH (n = 66)	BPD (n = 33)	Schizophrenia/schizo-affective disorder (n = 66)	F	p
Frequency, mean (sd)	1.5 (1.2)	2.8 (1.0)	3.1 (0.95)	36.011	**<0.001***
Duration, mean, (sd)	1.6 (0.8)	2.7 (1.2)	2.8 (1.1)	25.302	**<0.001***
Perceived location, mean (sd)	2.1 (1.2)	1.7 (1.0)	2.2 (1.2)	1.870	0.16
Loudness, mean (sd)	1.9 (0.6)	2.0 (1.0)	1.9 (0.9)	0.005	1.0
Beliefs about origin, mean (sd)	3.3 (1.1)	2.0 (1.2)	2.4 (1.3)	13.869	**<0.001***
Amount of negative content, mean (sd)	0.4 (1.0)	2.8 (1.4)	2.8 (1.2)	72.827	**<0.001***
Degree of negative content, mean (sd)	0.5 (1.1)	2.7 (1.1)	3.0 (1.1)	83.302	**<0.001***
Amount of distress, mean (sd)	0.6 (1.2)	3.0 (1.4)	3.1 (1.1)	77.628	**<0.001***
Intensity of distress, mean (sd)	0.4 (0.9)	2.6 (1.1)	2.6 (0.8)	112.020	**<0.001***
Disruption of life, mean (sd)	0.2 (0.6)	1.8 (0.9)	2.4 (0.8)	131.017	**<0.001***
Controllability, mean (sd)	1.7 (1.4)	2.7 (1.4)	3.0 (1.1)	19.514	**<0.001***
Length of time AVH, yr, mean (sd)	24.0 (15.7)	17.0 (10.4)	17.0 (11.7)	3.891	0.023

* significant after Benjamini-Hochberg correction
Abbreviations: AVH = auditory verbal hallucinations, BPD = borderline personality disorder, F = F test, degrees of freedom 2, sd = standard deviation

2.4 DISCUSSION

Auditory verbal hallucinations (AVH) in patients diagnosed with borderline personality disorder (BPD) are frequently claimed to be less severe and qualitatively different from those in psychotic disorders, hence the somewhat trivializing terms 'pseudohallucination' and 'transient psychotic symptom'. The usage of those terms was not justified by our data. In contrast, we found that AVH experienced by BPD patients were severe, and that they lasted for long periods of time, i.e. for a mean duration of 17 years. In the majority of these patients, the AVH were experienced at least daily and for at least several minutes. Moreover, 61% of the BPD patients experienced those AVH only inside the head, and the majority had the conviction that their voices were internally generated. The scores on the items 'negative content', 'distress', and 'disruption of life' were high among this group. For most of the time, the subjects experienced no control over their voices.

When we compared the AVH experienced by patients with BPD and schizophrenia/schizoaffective disorder, no significant differences were revealed as regards their phenomenological characteristics. Neither did we find any differences on the items relating to their ensuing distress, except for 'disruption of life', which was scored higher by the patients with schizophrenia/schizoaffective disorder. In contrast, many significant differences were found between patients with BPD and the group of healthy individuals ex-

periencing AVH. In BPD, AVH occurred in a higher frequency and with a longer duration. BPD patients presented with higher scores on ensuing distress (i.e. the items 'negative content', 'distress', and 'disruption to life'). Furthermore, the controllability of the voices was lower in BPD.

These results confirm - and extend - the study by Kingdon et al., who also identified many similarities between AVH in BPD and in schizophrenia [15]. However, in contrast to our results, the BPD patients in Kingdon's sample presented with higher scores on the items 'distress' and 'negative content of voices'. This difference might be explained by a doubling in sample size of the patients with BPD in our study compared with the study by Kingdon et al.

Limitations

Although this is the largest study to date assessing the phenomenological characteristics of AVH in the context of BPD, the population sample of patients diagnosed with BPD can still be considered modest. And yet the majority of the differences between AVH in BPD and in healthy subjects were highly significant, with p values < 0.001, while the similarities between AVH in BPD and in schizophrenia were striking.

Another matter of concern is the possibility that the BPD patients might go on to develop a psychotic disorder such as schizophrenia in the future. However, we do not expect the patients in our sample to do so, given their relatively old age, and the fact that they have been experiencing AVH for a mean duration of 17 years already.

A third limitation is that only females were included in this study. This yielded optimal uniformity among the groups, but reduced the possibility of extrapolating our findings to male patients. However, the current results apply to 75% of the BPD population, as BPD is diagnosed most frequently in women [18].

In sum, the patients diagnosed with BPD experienced AVH for long periods of time, with a high frequency, and high levels of ensuing distress. No differences were found in the phenomenological characteristics of AVH, and in six out of seven of the PSYRATS items pertaining to the associated distress between patients diagnosed with BPD and those diagnosed with schizophrenia/schizoaffective disorder. In comparison with healthy subjects experiencing AVH, the BPD patients scored much higher on almost all of those items.

These results imply that AVH experienced by patients with BPD are hardly different from those experienced by patients diagnosed with schizophrenia/schizoaffective disorder. Therefore, it is neither justifiable nor helpful to designate those AVH as 'hallucination-like symptoms', 'pseudohallucinations' or 'micropsychotic episodes'. As a corollary, we argue that more attention should be paid to the occurrence, the associated distress, and the need for treatment of the AVH experienced by BPD patients.

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APPENDIX I

Psychotic Symptom Rating Scales, scoring criteria auditory verbal hallucinations-related items

Gillian Haddock, University of Manchester, 1994

1. FREQUENCY

How often do you experience voices? e.g. every day, all day long etc.

0 Voices not present or present less than once a week (specify frequency if present).
1 Voices occur for at least once a week.
2 Voices occur at least once a day.
3 Voices occur at least once an hour.
4 Voices occur continuously or almost continually i.e. stop only for a few seconds or minutes.

2. DURATION

When you hear your voices, how long do they last e.g. a few seconds, minutes, hours, all day long?

0. Voices not present.
1. Voices last for a few seconds, fleeting voices.
2. Voices last for several minutes.
3. Voices last for at least one hour.
4. Voices last for hours at a time.

3. LOCATION

When you hear your voices where do they sound like they're coming from?

- *Inside your head and/or outside your head?*
- *If voices sound like they are outside your head, whereabouts do they sound like they're coming from?*

0 No voices present.
1 Voices originate inside head only.
2 Voices outside the head, but close to ears or head.
Voices inside head may also be present.
3 Voices originate inside or close to ears and outside head away from ears.
4 Voices originate from outside space, away from head only.

4. LOUDNESS

How loud are your voices?
Are they louder than your voice, about the same loudness, quieter or just a whisper?

0 Voices not present.
1 Quieter than own voice, whisper.
2 About the same loudness as own voice.
3 Louder than own voice.
4 Extremely loud, shouting.

5. BELIEFS RE-ORIGIN OF VOICES

What do you think has caused your voices?

- *Are the voices caused by factors related to yourself or solely due to other people or factors?*
  If patient expresses an external origin:
- *How much do you believe that your voices are caused by ----------*
  (add patient's attribution) on a scale from 0-100 with 100 being that you are totally convinced, have no doubts and 0 being that it is completely untrue?

0 Voices not present.
1 Believes voices to be solely internally generated and related to self.
2 Holds a less than 50% conviction that voices originate from external causes.
3 Holds 50% or more conviction (but less than 100%) that voices originate from external cause.
4 Believes voices are solely due to external causes (100% conviction).

6. AMOUNT OF NEGATIVE CONTENT OF VOICES

Do your voices say unpleasant or negative things?

- *Can you give me some examples of what the voices say? (record these e.g.s)*
- *How much of the time do the voices say these types of unpleasant or negative items?*

0 No unpleasant content.
1 Occasional unpleasant content.
2 Minority of voice content is unpleasant or negative (less than 50%).
3 Majority of voice content is unpleasant or negative (more than 50%).
4 All of voice content is unpleasant or negative.

7. DEGREE OF NEGATIVE CONTENT

[Rate using criteria on scale, asking patient for more detail if necessary]

0 Not unpleasant or negative.
1 Some degree of negative content, but not personal comments relating to self or family e.g. swear words or comments not directed to self, e.g. "The milk man is ugly".
2 Personal verbal abuse, comments on behaviour e.g. "Shouldn't do that, or say that".
3 Personal verbal abuse relating to self-concept e.g. "You're lazy, ugly, mad, perverted".
4 Personal threats to self e.g. threats to harm to self or family, extreme instructions or commands to harm self or others and personal verbal abuse as in (3).

8. AMOUNT OF DISTRESS

Are your voices distressing?
How much of the time?

0 Voices not distressing at all.
1 Voices occasionally distressing, majority not distressing.
2 Equal amounts of distressing and non-distressing voices.
3 Majority of voices distressing, minority not distressing.
4 Voices always distressing.

9. INTENSITY OF DISTRESS

When voices are distressing, how distressing are they?

- *Do they cause you minimal, moderate, severe distress?*
- *Are they the most distressing they have ever been?*

0 Voices not distressing at al.
1 Voices slightly distressing.
2 Voices are distressing to a moderate degree.
3 Voices are very distressing, although subject could feel worse.
4 Voices are extremely distressing, feel the worst he/she could possibly feel.

10. DISRUPTION TO LIFE CAUSED BY VOICES.

How much disruption do the voices cause to your life?

- *Do the voices stop you from working or other daytime activity?*
- *Do they interfere with your relationships with friends and/or family?*
- *Do they prevent you from looking after yourself, e.g. bathing changing clothes etc.*

0 No disruption to life, able to maintain independent living with no problems in daily living skills. Able to maintain social and family relationships (if present).
1 Voices cause minimal amount of disruption to life e.g. interferes with concentration although able to maintain daytime activity and social and family relationships and be able to maintain independent living without support.
2 Voices cause moderate amount of disruption to life causing some disturbance to daytime activity and/or family or social activities. The patient is not in hospital although may live in supported accommodation or receive additional help with daily living skills.
3 Voices cause severe disruption to life so that hospitalisation is usually necessary. The patient is able to maintain some daily activities, self-care and relationships whilst in hospital. The patient may also be in supported accommodation but experiencing severe disruption of life in terms of activities daily living skills and/or relationships.
4 Voices cause complete disruption of daily life requiring hospitalisation. The patient in unable to maintain any daily activities and social relationships. Self-care is also severely disrupted.

11. CONTROLLABILITY OF VOICES

Do you think you have any control over when your voices happen?
Can you dismiss or bring on your voices?

0 Subject believes they can have control over their voices and can always bring on or dismiss them at will.
1 Subject believes they can have some control over the voices on the majority of occasions.
2 Subject believes they can have some control over their voices approximately half of the time.
3 Subject believes they can have some control over their voices but only occasionally. The majority of time the subject experiences voices which are uncontrollable.
4 Subject has no control over when the voices occur and cannot dismiss or bring them on at all.

3

Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation? A meta-analysis of the efficacy of repetitive transcranial magnetic stimulation for psychiatric disorders

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ABSTRACT

Objective

Repetitive transcranial magnetic stimulation (rTMS) is a safe treatment method with few side effects. However, efficacy for various psychiatric disorders is currently not clean.

Data sources

A literature search was performed from 1966 through October 2008 using PubMed, Ovid Medline, Embase Psychiatry, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PsycINFO. The following search terms were used: *transcranial magnetic stimulation, TMS, repetitive TMS, psychiatry, mental disorder, psychiatric disorder, anxiety disorder, attention-deficit hyperactivity disorder, bipolar disorder, catatonia, mania, depression, obsessive-compulsive disorder, psychosis, posttraumatic stress disorder, schizophrenia, Tourette's syndrome, bulimia nervosa,* and *addiction*.

Study selection

Data were obtained from randomized, sham-controlled studies of rTMS treatment for depression (34 studies), auditory verbal hallucinations (AVH, 7 studies), negative symptoms in schizophrenia (7 studies), and obsessive-compulsive disorder (OCD, 3 studies). Furthermore, studies of rTMS versus electroconvulsive treatment for depression (ECT, 6 studies) were meta-analyzed.

Data extraction

Standardized mean effect sizes of rTMS versus sham were computed based on pretreatment-posttreatment comparisons.

Data synthesis

The mean weighted effect size of rTMS versus sham for depression was 0.55 ($p < 0.001$). Monotherapy with rTMS was more effective than rTMS as adjunctive to antidepressant medication. ECT was superior to rTMS in the treatment of depression (mean weighted effect size -0.47, $p = 0.004$). In the treatment of AVH, rTMS was superior to sham treatment, with a mean weighted effect size of 0.54 *(*$p < 0.001$). The mean weighted effect size for rTMS versus sham in the treatment of negative symptoms in schizophrenia was 0.39 *(*$p = 0.12$) and for OCD, 0.16 *(*$p = 0.52$). Side effects were mild, yet more prevalent with high-frequency rTMS at frontal locations.

Conclusions

It is time to provide rTMS as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms. We do not recommend rTMS for the treatment of OCD.

3.1 INTRODUCTION

The first modern transcranial magnetic stimulation (TMS) device was developed during the early 1980s by Barker et al. [1, 2]. The device creates a strong pulse of electrical current which is sent through a coil and induces a magnetic field pulse in a small area underlying the coil. When applied over the skull, this pulse has the capacity to depolarize local neurons up to a depth of 2 cm. TMS can be used as a brain-mapping tool, as a tool to measure cortical excitability, as a probe of neuronal networks, and as a modulator of brain function. When repetitive TMS (rTMS) pulses are applied, a longer lasting effect can be induced which is thought to result from a long-term potentiation or depression at the neuronal level [3]. High-frequency rTMS can induce an epileptic seizure, which is a dangerous side effect. However, since the introduction of specific safety guidelines, rTMS is considered a safe treatment method [4]. Its side effects are generally mild. They include headache, local discomfort as a consequence of direct stimulation of the facial musculature, and transient changes in the auditory threshold. To prevent this latter side effect, the use of earplugs is recommended [5]. Initially, rTMS was investigated chiefly as a tool for the treatment of depression [6]. A few years later, it was explored by Hoffman and colleagues [7] for the treatment of auditory verbal hallucinations (AVH). Further research with rTMS has involved the experimental treatment of mood disorders, negative symptoms of schizophrenia, obsessive-compulsive disorder (OCD), Tourette's syndrome, posttraumatic stress disorder, panic disorder, Alzheimer's disease, bulimia nervosa, conversion, catatonia, and various forms of substance addiction.

Twenty-three years after its introduction, the number of publications reporting on the effects of rTMS treatment in psychiatric disorders has increased dramatically (263 published studies between 2000 and June 2008, as compared to 26 between 1990 and 2000). This 10-fold increase in the number of publications was accompanied by an even larger increase in sample size, which developed from single cases to samples of over 100 patients in recent publications [8,9]. Furthermore, the US Food and Drug Administration approved rTMS for the treatment of depression in October 2008.

Due to its mild side effects and its relatively low costs, rTMS tends to be considered an attractive therapeutic tool. The TMS equipment can be obtained at the price of approximately €25,000, and the stimulation technique is relatively easy to acquire. However, mental health professionals may hesitate to embrace rTMS as a routine treatment

method because its efficacy is as yet uncertain. A number of meta-analyses quantified the effects of rTMS for depressive disorder, but even these results are ambiguous [10-15]. As the effect sizes of these studies differed substantially, no general conclusions can be drawn. More details are presented in the Discussion. The effects of rTMS treatment in AVH have been meta-analyzed once before, indicating a moderate mean effect size [16]. No meta-analyses have been published on the effects of rTMS for other psychiatric disorders or symptom clusters. According to Loughlin et al. [17] and Kozel et al. [18] , the mean costs of an rTMS treatment for depression, consisting of 15 treatment sessions, are £1,444 and $1,422, respectively. The duration of the effect of rTMS is as yet unknown, but for an effect of 4 months [19] , the mean costs of antidepressant agents for the same period lie around $110. The question remains whether patients benefiting from medication are comparable with patients having rTMS treatment. In our opinion, the data currently available do not allow for any firm conclusions about the costs of rTMS versus medication.

This review aims to assess the value of rTMS as a therapeutic tool for psychiatric disorders and for individual psychiatric symptoms.

3.2 METHOD

Study selection

A literature search was performed using PubMed 1990 through October 2008, Ovid Medline 1990 through October 2008, Embase Psychiatry 1997 through October 2008, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and PsycINFO 1990 through October 2008.

The following search terms were used: *transcranial magnetic stimulation, TMS, repetitive TMS, psychiatry, mental disorder, psychiatric disorder, anxiety disorder, attention-deficit hyperactivity disorder, bipolar disorder, catatonia, mania, depression, obsessive-compulsive disorder, psychosis, posttraumatic stress disorder, schizophrenia, Tourette's syndrome, bulimia nervosa,* and *addiction.*

The following criteria for inclusion were used:

1. Treatment with repetitive TMS.
2. Symptom severity of a psychiatric disorder is used as an outcome measure, and the psychiatric disorder being diagnosed in accordance with *DSM* and/or *ICD* criteria.
3. No specific 'narrow' diagnosis or subgroup, such as depression after stroke or vascular depression.
4. The study was performed in a double-blind, randomized controlled parallel design using a sham condition; an exception was made to the criterion 'double-blind' for studies comparing rTMS with ECT, which cannot be blinded. We chose for parallel

designs only, because patients cannot remain blinded in crossover studies, which may influence the results.
5. The data were sufficient to compute Hedges' g (sample size, means, and standard deviations or exact t or p values for rTMS main effect for change scores).
6. At least 3 studies per psychiatric disorder/symptom cluster.
7. More than 3 patients per study.
8. Articles written in English. When various articles described overlapping samples, the article with the largest sample size was included.

Data extraction

The following data were acquired: number of treated patients, mean and standard deviation of the outcome measure at baseline and at the end of treatment (or exact F or p value), study design, and treatment parameters (type of coil used, localization of treatment, frequency, intensity, number of stimuli per session, and number of treatment sessions). Whenever publications contained insufficient or incomplete data, the authors in question were contacted and invited to send additional data so that their study could be included in the meta-analysis. All meta-analyses were checked for cross-references.

Effect size calculation

Effect sizes were calculated for the mean differences (sham treatment versus rTMS) of the pretreatment-posttreatment change in rating scales. The mean gain for each study was computed using Comprehensive Meta-Analysis Version 2.0 (Biostat, Englewood, New Jersey) in a random effects model. After the computation of individual effect sizes for each study, meta-analytic methods were applied to obtain a combined, weighted effect size, Hedges' g, for each psychiatric disorder or symptom. The means of separate studies were weighted according to sample size. A homogeneity statistic, I^2, was calculated to test whether the studies could be taken to share a common population effect size [20]. A high I^2 statistic (i.e., 30% or higher) indicates heterogeneity of the individual study effect sizes, which poses a limitation to a reliable interpretation of the results. Whenever significant heterogeneity was found, a moderator analysis was performed to investigate the potential moderating factors. We expected the effects of rTMS to vary substantially according to localization, frequency, number of stimuli, and treatment sessions; as a consequence, subanalyses were performed to investigate different treatment conditions. The parameters were correlated with Hedges' g using Pearson's correlations in SPSS version 12 (SPSS Inc, Chicago, Illinois).

In studies comparing 3 treatment conditions, the 2 actual treatments were compared separately with the sham condition. In a number of studies on depression, rTMS was started simultaneously with antidepressant drug therapy or compared with electro-

Table 3.1 Number of included studies and reasons for exclusion

Psychiatric disorder	No. of RCTs included in meta-analysis	Reasons for exclusion of other studies	No. of excluded studies
Depression	40	No (randomized) sham condition	58
		Overlap	15
		Insufficient data	14
		Outcome no severity of psychiatric symptoms	9
		Not in English	8
		Crossover design	6
		Patient no. lower than 3	3
		Maintenance or second rTMS treatment	3
		Single-pulse TMS	2
		rTMS as add-on with ECT	1
		Vascular depression	1
Auditory verbal hallucinations	7	Overlap	4
		Crossover design	4
		Insufficient data	3
		rTMS maintenance therapy	4
		No sham condition	2
		Outcome not severity of psychiatric symptoms	2
Negative symptoms of schizophrenia	7	Insufficient data	4
		No sham condition	3
		Crossover design	1
		Outcome not severity of psychiatric symptoms	1
		Not in English	1
		Overlap	1
Obsessive-compulsive disorder	3	No sham condition	2
		Insufficient data	1
		Outcome not severity of psychiatric symptoms	1
		Not in English	1
Tourette's syndrome	2	Insufficient data	1
Panic disorder		Not in English	1
Bulimia nervosa		Less than 3 studies for this disorder	
Mania		No sham condition	2
Posttraumatic stress disorder		No sham condition	2
Cigarette addiction		Insufficient data	1
		Not in English	1
Alzheimer's disease		Insufficient data	1
		Crossover design	1
Cocaine addiction		No sham condition	1
Motor conversion		Patient no. < 3	1
Catatonia		Case reports	2

Abbreviations: ECT= electroconvulsive therapy, RCT = randomized controlled trial

convulsive therapy (ECT). The results of these studies, including studies with rTMS as monotherapy, are analyzed separately.

Because the effect size can be overestimated due to the omission of studies in which rTMS was not effective, the fail-safe number of studies was computed [21]. This fail-safe number is an estimation of the number of missing studies that is needed to change the results of the meta-analysis to nonsignificant.

Side effects and dropouts are presented according to rTMS frequency and localization.

3.3 RESULTS

The following disorders and individual symptoms were included in the meta-analysis: depression (40 studies), AVH (7 studies), negative symptoms of schizophrenia (7 studies), and OCD (3 studies).

One hundred sixty-nine studies were excluded from the meta-analysis (for reasons for exclusion, see Table 3.1). No meta-analysis could be performed on rTMS for the treatment of Tourette's syndrome, panic disorder, posttraumatic stress disorder, mania, and bulimia nervosa, due to the small number of studies, i.e. < 3. None of the studies concerning attention-deficit hyperactivity disorder, somatoform disorder, Alzheimer's disease, addiction, and catatonia fulfilled the stated criteria for inclusion.

Repetitive transcranial magnetic stimulation in the treatment of depression

Forty studies were included in the meta-analysis. The studies were divided into 2 groups: rTMS versus sham (34 studies) and rTMS versus ECT (6 studies).

REPETITIVE TMS VERSUS SHAM IN THE TREATMENT OF DEPRESSION – Thirty-four studies fulfilled the criteria for inclusion in the meta-analysis [22-53]. The studies and treatment parameters are listed in Table 3.2. Seven hundred fifty-one patients were randomly assigned to rTMS treatment and 632 patients for the sham condition. Patients were free of antidepressant agents in 7 studies, antidepressant agents were continued during rTMS in 17 studies, and rTMS was started simultaneously with an antidepressant agent in 5 studies. Results of the meta-analysis are shown in Figure 3.1.

Effect sizes were computed for each study and weighted according to sample size. The mean weighted effect size for all studies comparing rTMS with sham treatment was 0.55 ($p < 0.001$). I^2 was 54% ($p < 0.001$). The fail-safe number was 18,462 studies. Since heterogeneity was high, moderator analyses were performed for the different stimulation parameters. When correlating the individual effect sizes of the studies to stimulation parameters, such as localization, frequency, intensity (percentage of motor threshold), number of stimuli per session, total number of stimuli, and number of sessions, no significant correlations emerged *(*p value between 0.38 and 0.95). The mean

Table 3.2 rTMS parameters in the treatment of depression

Study	Location	Frequency, Hz	Motor treshold, %	No. of stimuli	No. of sessions
O'Reardon et al. 2007 [8]	L DLPF	10	120	3,000	25
Herwig et al. 2007 [9]	L DLPF	10	110	2,000	15
Mogg et al. 2008 [22]	L DLPF	10	110	1,000	10
Anderson et al. 2007 [23]	L DLPF	10	110	1,000	12
Bortolomasi et al. 2007 [24]	L DLPF	20	90	800	5
Koerselman et al. 2004 [25]	L DLPF	20	80	800	10
Fitzgerald et al. 2008 [26]	R DLPF	6 and 1	110	1,500	10
Loo et al. 2007 [27]	L DLPF	10	110	1,500	10
Stern et al. 2007 [28]	L DLPF	10	110	1,600	10
	L DLPF	1	110	1,600	10
	R DLPF	1	110	1,600	10
Fitzgerald et al. 2006 [29]	L and R DLPF	10 and 1	100 and 110	750 and 420	10
Garcia-Toro et al. 2006 [30]	LR DLPF	20 and 1	110	1,800 and 1,200	10
	L and R DLPF, PET	20 and 1	110	1,800 and 1,200	10
Janual et al. 2006 [31]	R DLPF	1	90	120	16
Su et al. 2005 [32]	L DLPF	20	100	1,600	10
	L DLPF	5	100	1,600	10
Buchholtz Hansen et al. 2004 [33]	L DLPF	10	90	2,000	15
Holtzheimer et al. 2004 [34]	L DLPF	10	110	1,600	10
Kauffmann et al. 2004 [35]	R DLPF	1	110	120	10
Mosimann et al. 2004 [36]	L DLPF	20	100	1,600	10
Fitzgerald et al. 2003 [37]	L DLPF	10	100	100	10
	R DLPF	1	100	300	10
Herwig et al. 2003 [38]	L or R DLPF, PET	15	110	3,000	10
Hoppner et al. 2003 [39]	L DLPF	20	90	400	10
	R DLPF	1	110	120	10
Loo et al. 2003 [40]	LR DLPF	15	90	1,800	15
Boutros et al. 2002 [41]	L DLPF	20	80	800	10
Garcia-Toro et al. 2001 [42]	L DLPF	20	90	1,200	10
Manes et al. 2001 [43]	L DLPF	20	80	800	5
Berman et al. 2000 [44]	L DLPF	20	80	800	10
George et al. 2000 [45]	L DLPF	20	100	1,600	10
	L DLPF	5	100	1,600	10
Avery et al. 1999 [46]	L DLPF	10	80	1,000	10
Klein et al. 1999 [47]	R DLPF	1	110	120	10
Loo et al. 1999 [48]	L DLPF	10	110	1,500	10
Padberg et al. 1999 [49]	L DLPF	0.3	90	250	5
	L DLPF	10	90	250	5
Rossini et al. 2005 [50]	L DLPF	15	100	900	10
Haussmann et al. 2004 [51]	L DLPF and half R	20	100	2,000	10
Poulet et al. 2004 [52]	L DLPF	10	80	400	10
Garcia-Toro et al. 2001 [53]	L DLPF	20	90	1,200	10

Abbreviations: DLPF = dorsolateral prefrontal cortex, L = left, LR = bilateral, PET = positron emission tomography, R = right

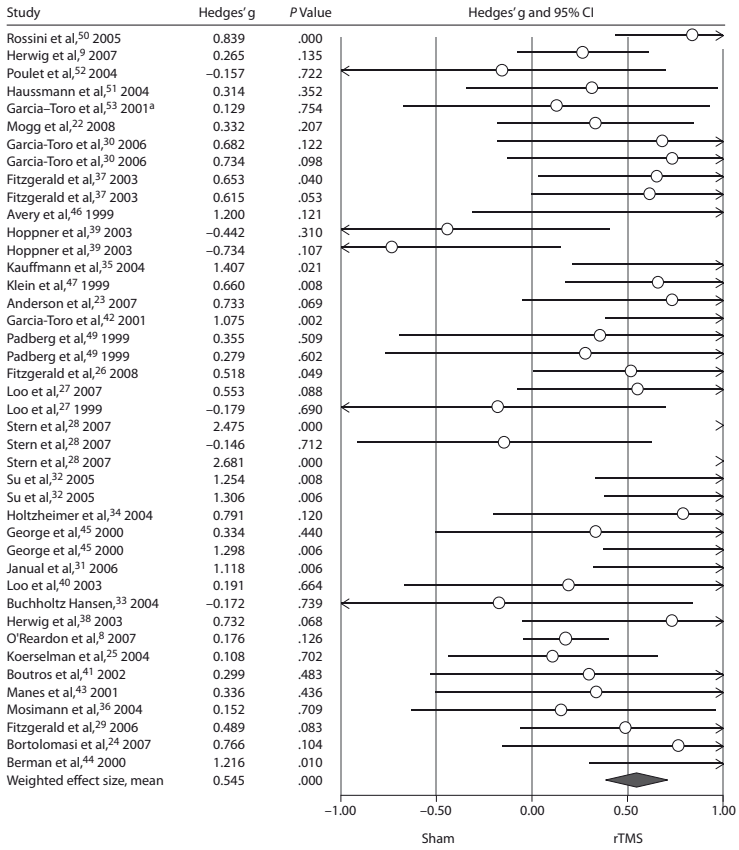

Figure 3.1 Repetitive TMS for depression, results of the meta-analysis

effect size for rTMS applied at the left dorsolateral prefrontal cortex (DLPF) was 0.53 ($p < 0.001$); for rTMS directed to the right DLPF, it was 0.82 *(*$p < 0.001$); and for rTMS applied to both left and right DLPF (not simultaneously), it was 0.47 *(*$p = 0.03$). Mean Hedges' g for rTMS focused on the left DLPF was not statistically different from rTMS to the right DLPF *(*$t = -9.66$, $p= 0.34$). Another reason for heterogeneity was the variation in inclusion criteria. We calculated whether rTMS as a monotherapy was more effective than rTMS started simultaneously with antidepressant medication or during continuation of pre-existing antidepressant treatment. The mean weighted effect sizes for rTMS as a monotherapy was 0.96 *(*$p < 0.001$) ($I^2 = 81\%$, $p < 0.001$); for rTMS with continuation of an antidepressant agent, it was 0.51 ($p < 0.001$) ($I^2 = 32\%$, $p = 0.08$); and for rTMS started simultaneously with an antidepressant agent, it was 0.37 ($p = .03$) ($I^2 = 44\%$, $p = 0.13$). The difference in efficacy between rTMS as a monotherapy and rTMS with continuation of an antidepressant agent was marginally significant in favour of rTMS as a monotherapy ($t = 2.12$, $p = 0.06$). There was a trend for rTMS being more effective as a

monotherapy than as an adjunctive to priory started antidepressant agents (t = 1.747, p = 0.09). There was homogeneity if studies with rTMS as a monotherapy were excluded (I^2 = 23.9, p = 0.11); Hedges' g became 0.46 (p < 0.001). No difference between baseline mean severity scores for these 3 groups could be found (t = 9.34, p = 0.36), thus ruling out severity as a confounding factor. In a minority of studies (6 studies), patients with

Table 3.3 Side effects of rTMS treatment

Side effect	High-frequency DLPF, n (%)	Low-frequency DLPF, n (%)	Low-frequency temporoparietal, n (%)	Sham, n (%)
Depression				
Headache	46 (9.7)	4 (3.7)		12 (2.5)
Scalp discomfort	45 (9.3)	2 (1.8)		9 (1.9)
Facial twitching	9 (1.9)	5 (4.6)		0
Tearfulness	7 (1.5)	0		0
Local erythema	6 (1.3)	0		0
Drowsiness	12 (2.5)	0		0
Other	22 (4.7)	1 (0.9)		11 (2.4)
Total	145/472 (30.7)	12/109 (11)		32/461 (6.9)
Auditory verbal hallucinations				
Headache			6 (5.7)	2 (1.9)
Dizziness			2 (1.9)	1 (0.9)
Amnesia			1 (1.9)	0
Other			0	1 (0.9)
Total			9/105 (8.6)	4/84 (4.8)
Negative symptoms of schizophrenia				
Headache	6 (10.3)	2 (12.5)		1 (1.4)
Scalp discomfort	5 (8.6)	0		1 (1.4)
Facial twitching	0	3 (25)		0
Increase of akathisia	0	1 (6.3)		0
Increase of OCD symptoms	0	1 (6.3)		0
Total	11/58 (19)	7/16 (43.8)		2/74 (2.7)
Obsessive-compulsive disorder				
Headache	7 (70)	1 (3.6)		1 (3.6)
Scalp discomfort	12	0		0
Dizziness/fainting	3 (30)	0		1 (3.6)
Tearfulness	2 (20)	0		0
Total	24/10	1/28 (3.6)		2/28 (7.1)
Total for all groups	180/540 (33.3)	20/153 (13.1)	9/105 (8.6)	40/647 (6.2)

Abbreviations: DLPF = dorsolateral prefrontal cortex, OCD = obsessive-compulsive disorder

psychotic features were explicitly excluded. These studies yielded a better effect of rTMS than studies that did not use this exclusion criterion (t = 0.128, p = 0.04).

Reported side effects and dropouts for rTMS delivered at high frequency, at low frequency, and for sham treatment are presented in Tables 3.3 and 3.4. Reports of frequent headache, scalp discomfort, facial twitching, tearfulness, local erythema, and drowsiness were mentioned. Side effects occurred more often in high-frequency than in low-frequency rTMS.

REPETITIVE TMS VERSUS ECT IN THE TREATMENT OF DEPRESSION – ECT is a potent intervention in the treatment of depression, but complications associated with anaesthesia [54], cardiac risks, and memory disturbances are disadvantages [55] that are absent in rTMS treatment. For this reason, 6 additional studies were analyzed in which rTMS was compared with ECT in a randomized fashion [56-61]. A total of 215 patients were included in the meta-analysis,

Table 3.4 Reasons for dropout

Reason	High-Frequency DLPF, n (%)	Low-Frequency DLPF, n (%)	Low-Frequency Temporoparietal, n (%)	Sham, n (%)
Depression				
Side effects	22 (4.7)	0		11 (2.3)
Worsening of symptoms	17 (3.6)	1 (0.9)		12 (2.5)
Other/unknown	11 (2.3)	8 (7.3)		26 (5.3)
Total	50/472 (10.6)	9/109 (8.3)		49/486 (10.1)
Auditory verbal hallucinations				
Side effects			2 (1.9)	1 (0.9)
Worsening of symptoms			0	3 (2.8)
Other/unknown			0	0
Total			2/105 (1.9)	4/84 (3.7)
Negative symptoms of schizophrenia				
Side effects	3 (5.2)	0		1 (1.4)
Worsening of symptoms	1 (1.7)	2 (12.5)		0
Other/unknown	1 (1.7)	0		3 (4.1)
Total	5/58 (8.6)	2/16 (12.5)		4/74 (5.4)
Obsessive-compulsive disorder				
Side effects	0	0		0
Worsening of symptoms	0	0		0
Other/unknown	0	0		0
Total	0/10	0/28		0/28
Total for all groups	55/540 (10.2)	11/153 (7.2)	2/105 (1.9)	57/672 (8.5)

Abbreviation: DLPF = dorsolateral prefrontal cortex

Table 3.5 rTMS parameters for depression versus electroconvulsive therapy

Study	Location	Frequency, Hz	Motor threshold, %	No. of stimuli	No. of sessions
Eranti et al. 2007 [56]	L DLPF	10	110	1,000	15
Rosa et al. 2006 [57]	L DLPF	10	110	2,500	20
Grunhaus et al. 2003 [58]	L DLPF	10	90	1,200	20
Janicak et al. 2002 [59]	L DLPF	10	110	1,500	15
Grunhaus et al. 2000 [60]	L DLPF	10	90	800	20
Pridmore 2000 [61]	L DLPF	20	100	1,300	12

Abbreviations: DLPF = dorsolateral prefrontal cortex, L = left

among which 113 were treated with rTMS, and 102 with ECT. The parameters of the rTMS treatment conditions are presented in Table 3.5. ECT consisted of unilateral and/or bilateral treatment at a frequency of 2 or 3 times a week.

The results of the meta-analysis are presented in Figure 3.2. Analysis showed that ECT yields more favourable results than rTMS, with a weighted effect size of -0.47 (p = 0.004).

Heterogeneity was moderately low: I^2 = 28%, p = 0.23. The fail-safe number for these studies was 106 studies. See Tables 3.3 and 3.4 for side effects and dropouts.

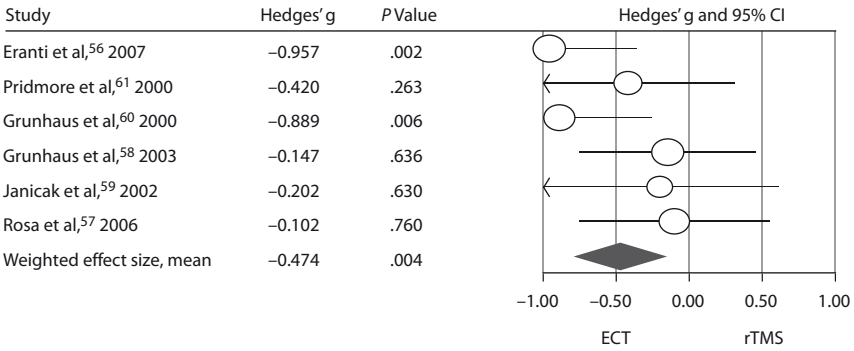

Figure 3.2 Meta-analysis of rTMS versus ECT in the treatment of depression

Repetitive transcranial magnetic stimulation in the treatment of auditory verbal hallucinations

Seven randomized controlled trials were included in the meta-analysis, with a total number of 189 patients, of which 105 received rTMS treatment and 84 sham treatment [19, 62-67]. The parameters of the rTMS treatments are presented in Table 3.6.

In 7 studies, rTMS treatment was applied to the left temporoparietal cortex (i.e. T3P3, according to Electroencephalogram Electrodes, Wernicke's area), and in 1 study to its right-sided homologue. The results of the meta-analysis are presented in Figure 3.3.

Table 3.6 rTMS parameters for auditory verbal hallucinations

Study	Location	Frequency, Hz	Motor threshold, %	No. of stimuli	No. of sessions
Hoffman et al. 2005 [19]	T3P3	1	90	900	10
Rosa et al. 2007 [62]	T3P3	1	90	960	10
Brunelin et al. 2006 [63]	T3P3	1	90	1,000	10
Fitzgerald et al. 2005 [64]	T3P3	1	90	900	10
Lee et al. 2005 [65]	T3P3	1	100	1,600	10
	T4P4	1	100	1,600	10
Saba et al. 2004 [66]	T3P3	1	80	300	10
Chibbaro et al. 2005 [67]	T3P3	1	90	900	4

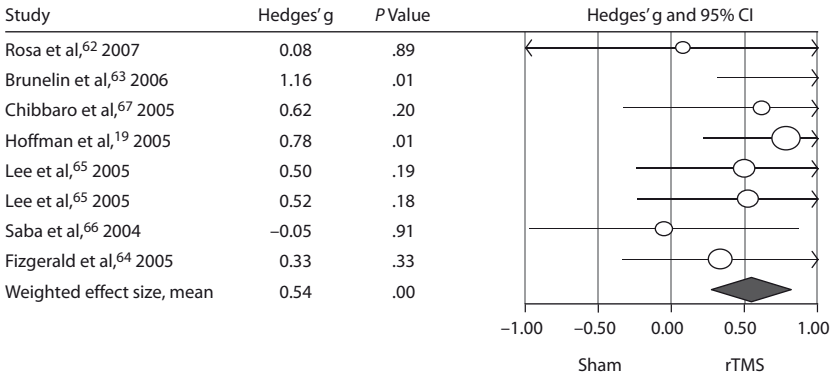

Figure 3.3 Results of the meta-analysis of rTMS in the treatment of auditory verbal hallucinations

The effect size of rTMS was 0.54 ($p < 0.001$), indicating a moderate effect. The percentage for heterogeneity was 0 ($p = 0.61$). Therefore, no additional moderator analysis was performed. The fail-safe number was 269 studies.

Side effects are described in Table 3.3. They occurred in 8.6% of the participants during rTMS treatment and in 3.9% during sham treatment. Reasons for dropout are listed in Table 3.4.

Repetitive transcranial magnetic stimulation in the treatment of negative symptoms of schizophrenia

A meta-analysis of 7 studies was performed, with a total number of 148 participating patients, of which 74 received rTMS treatment, and an equal number sham treatment [68-74]. Table 3.7 lists the parameters of rTMS in the treatment of negative symptoms of schizophrenia. Except for 1 study, the left DLPF served as the focus of treatment. Figure 3.4 shows details of the results of the meta-analysis. Hedges' g was 0.39 ($p = 0.12$). I^2 was 56% ($p = 0.03$). The fail-safe number was 13 studies. Because of the high heterogeneity a moderator analysis was performed; no significant correlation was found between indi-

Table 3.7 rTMS parameters in the treatment of negative symptoms of schizophrenia

Study	Location	Frequency, Hz	Motor threshold, %	No. of stimuli	No. of sessions
Fitzgerald et al. 2008 [68]	L and R DLPF	10	110	1,000	15
Mogg et al. 2007 [69]	L DLPF	10	110	2,000	10
Prikyl et al. 2007 [70]	L DLPF	10	110	1,500	15
Novak et al. 2006 [71]	L DLPF	20	90	2,000	10
Hajak et al. 2004 [72]	L DLPF	10	110	1,000	10
Holi et al. 2004 [73]	L DLPF	10	100	1,000	10
Klein et al. 1999 [74]	R DLPF	1	110	120	10

Abbreviations: DLPF = dorsolateral prefrontal cortex, L = left, R = right

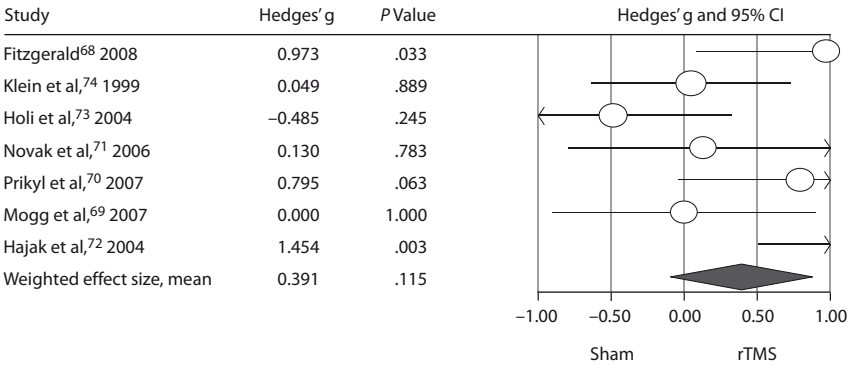

Figure 3.4 Meta-analysis of rTMS for negative symptoms of schizophrenia

vidual effect sizes and rTMS parameters such as frequency, number of sessions, duration, percentage of the motor threshold, and total number of stimulations.

In Tables 3.3 and 3.4, side effects and dropouts are presented. Side effects occurred in 24% of the patients during rTMS treatment, compared to none during placebo treatment. They consisted of headache, scalp discomfort, facial twitching, increase in akathisia, and increase in comorbid OCD symptoms.

Transcranial magnetic stimulation for obsessive-compulsive disorder

Three articles were included in the meta-analysis of rTMS for the treatment of OCD, yielding a total number of 38 patients receiving rTMS and 28 receiving sham treatment [75-77]. Details of the rTMS parameters are listed in Table 3.8.

Figure 3.5 displays the results of the meta-analysis. Hedges' g was 0.16 ($p = 0.52$), which is not significantly more favourable than sham treatment. The score for heterogeneity was 0 ($p = 0.89$), indicating no bias as a consequence of moderators. See Table 3.3 for an overview of the side effects, which consisted of headache, scalp discomfort, dizziness, and tearfulness. Dropouts did not occur.

Table 3.8 Parameters of rTMS for obsessive-compulsive disorder

Study	Location	Frequency, Hz	Motor threshold, %	No. of stimuli	No. of sessions
Sachdev et al. 2007 [75]	L DLPF	10	110	1,500	10
Prasko et al. 2006 [76]	L DLPF	1	110	1,800	10
Alonso et al. 2001 [77]	R DLPF	1	110	1,200	18

Abbreviations: DLPF = dorsolateral prefrontal cortex, L = left, R = right

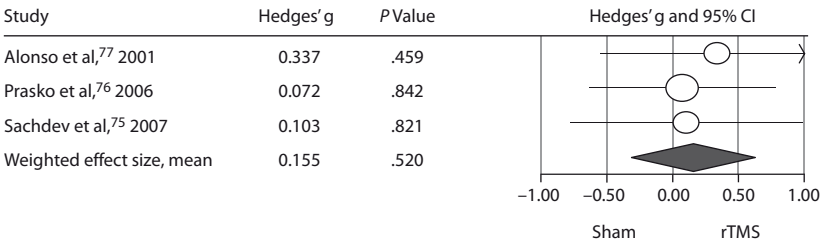

Figure 3.5 Repetitive TMS for obsessive-compulsive disorder, results of the meta-analysis

3.4 DISCUSSION

This study provides a critical and quantitative summary of clinical studies using rTMS as a treatment method for psychiatric indications. It aims to formulate a carefully considered recommendation for psychiatric professionals whether or not to adopt this treatment method as a standard therapy. The literature includes ample high-quality studies to allow for meta-analyses of the efficacy of rTMS for depression, AVH, negative symptoms in schizophrenia, and OCD. We also meta-analyzed the efficacy of rTMS versus ECT in the treatment of depression.

The new information presented in this article is based primarily on the inclusion of the highest number of studies to date considering rTMS for depression, and the performance of subanalyses of rTMS as monotherapy, of rTMS as an adjunctive to antidepressant medication, and of rTMS started simultaneously with an antidepressant agent. This study provides more evidence that ECT is superior to rTMS in contrast to the previous meta-analysis by Burtin et al. [11], who found no significant difference between ECT and rTMS. Moreover, this is the first meta-analysis of rTMS as a treatment method for negative symptoms of schizophrenia and OCD.

Our results indicate that rTMS is more effective than sham treatment in the treatment of depression, but less effective than ECT. Repetitive TMS is also effective for AVH in schizophrenia, even for AVH resistant to antipsychotic medication. We found a trend toward an effect of rTMS for negative symptoms in schizophrenia, but more studies are needed to confirm this finding. Repetitive TMS is not superior to sham treatment for the treatment of OCD. Thus it appears to be a useful method in the treatment of common conditions such as depression and AVH. In addition, it is one of the very few treatment

methods that may have some effect on negative symptoms of schizophrenia, although the evidence for this indication is currently insufficient. Findings for the different disorders are discussed in detail below.

Repetitive transcranial magnetic stimulation for depression

Repetitive TMS directed to the DLPF (either left or right) has a moderate mean effect size in the treatment of depression according to the results of 34 studies. In comparison with sham treatment, the highest effect size was found for studies using rTMS as monotherapy, followed by studies with rTMS as an adjunctive to continuation of pharmacotherapy. The analysis of 5 randomized controlled studies shows evidence for a small, but significant additional effect of rTMS when it is started simultaneously with pharmacotherapy. This lower effect of cotherapy as compared to monotherapy was not explained by a difference in baseline depression severity or by differences in stimulation parameters. Rather, the different effect sizes may be due to variability in treatment resistance among the 3 treatment groups or to an additional effect following the withdrawal of medication. Furthermore, lower expectations and hope to benefit from this treatment could form an alternative explanation. Low-frequency right-sided rTMS showed a trend toward better response than high-frequency left-sided rTMS, but full statistical significance was not achieved. Repetitive TMS had a better effect in studies that explicitly excluded patients with psychotic depression, as compared to samples that did not exclude this patient group.

The mean effect size found for rTMS treatment in depression (i.e. 0.55) is high when compared to effect sizes commonly reported for pharmacotherapy in depression (i.e. between 0.17 and 0.46) [78-81]. Our results are in concordance with the meta-analysis of Schutter et al. [15] who found an effect size of 0.39 in 30 studies. The established difference may be explained by the inclusion of only high-frequency rTMS treatments directed to the left DLPF in their meta-analysis. The effect sizes of 2 meta-analyses of 33 studies by Herrmann et al. [14], [82] were 0.65 and 0.59 respectively, which were comparable to our results, although those meta-analyses also included crossover studies. In a crossover design, patients cannot remain completely blind in the treatment condition, as actual rTMS produces loud clicks and twitching sensations in the skin that are difficult to mimic in a sham condition and may influence the results in favour of rTMS.

Burt et al. [11] included studies with other conditions (such as high- versus low-frequency rTMS, and rTMS with antidepressant agents, versus antidepressant agents alone) and found equal results for 16 studies with an effect size of 0.67. Holtzheimer et al. [10] meta-analyzed 12 studies, some of which used a crossover design, and found a large mean effect size of 0.81. Conversely, no effect was found in comparison with sham treatment in the meta-analysis by Couturier et al. [13] in which only 6 trials were included due to stringent criteria for sham treatment, side of treatment, and statistical methods. Thir-

teen studies were analyzed by Martin et al. [12] showing a significantly more favourable effect of rTMS focused on the left DLPF (standardized posttreatment difference of 0.35) as compared to sham treatment.

Our meta-analysis including 6 studies comparing rTMS for depression to ECT showed that rTMS cannot replace ECT, as patients improved significantly better with ECT. As only patients indicated for ECT participated in these studies, the majority had severe depression. Burt et al. [11] also performed a meta-analysis of 3 studies comparing rTMS to ECT and found a nonsignificant difference in favour of ECT. The difference with our mean effect size (-0.47) is explained by the inclusion of 3 more studies with negative effects in our analysis. Thus, when considering rTMS for depression, it appears to be more effective when given as a monotherapy. Depressive patients with psychotic symptoms may profit less from rTMS treatment, and the results of rTMS are less favourable than those of ECT.

Repetitive transcranial magnetic stimulation for auditory verbal hallucinations

Meta-analysis shows a moderate effect of rTMS on the severity of AVH in 7 studies. Most studies include patients with medication-resistant AVH, indicating a group with intractable symptomatology. A mean effect size of 0.76 was found in a previous meta-analysis investigating rTMS for AVH by Aleman et al.[16]. This mean effect was higher than that of the current study (0.54), which may be due to the exclusion of crossover studies in our analysis. As patients with medication-resistant AVH have few other possibilities for treatment, we definitely recommend offering rTMS treatment for this group.

Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia

Following the results of 7 studies, rTMS directed at the DLPF may improve negative symptoms of schizophrenia compared to sham, but the number of included studies was too low to reach statistical significance. Given the mild side effect profile of rTMS and the current poverty of therapeutic options for negative symptoms, we recommend that rTMS may be attempted as a possibility to improve negative symptoms.

Repetitive transcranial magnetic stimulation for obsessive-compulsive disorder

For the treatment of OCD no significant effect of rTMS was found in the 3 included studies. In spite of the small number of studies, the results were homogeneous. This indicates that OCD is not a psychiatric indication for rTMS.

Tolerability

Side effects reported for different indications were headache, scalp discomfort, drowsiness, facial muscle twitching, tearfulness, dizziness, and nausea. All of these side effects

were transient and mild and occurred more often with high-frequency than with low-frequency rTMS, and more often in rTMS directed to the DLPF than in rTMS to the temporoparietal areas. The percentage of dropouts was equal for rTMS and sham treatment, and lower for AVH and OCD than for depression and negative symptoms.

Limitations

Study numbers and patient samples were rather small in the meta-analyses for AVH, negative symptoms of schizophrenia and OCD. Another matter of concern is that half of the studies including patients with major depression and AVH selected patients who were 'therapy-resistant' using varying definitions. This may have led to the selection of patients with refractory symptoms, which may in turn have lowered the success rate of rTMS. Thirdly, several studies mentioned the number of dropouts but not the reasons for it. It is important to know the reasons for dropout and the way the data on dropout were analyzed, since this may have affected the final results.

Although the efficacy of rTMS in the treatment of depression and AVH may be considered proven, the duration of the effect is as yet unknown. Effect sizes were measured immediately after the cessation of rTMS treatment. There are indications that the effect of rTMS may last for several weeks to months [19, 22-25, 67]. Future studies should assess symptom relief with longer follow-up periods to assess the cost effectiveness of rTMS treatment, and to indicate its economic advantages and disadvantages. A few case reports have described rTMS as maintenance therapy for AVH; long-term treatment with rTMS resulted in a marked improvement of AVH [83-87] , but more studies are needed to decide which maintenance treatment strategy may yield the best results.

3.5 CONCLUSION

Repetitive TMS deserves a place in the standard toolbox of psychiatric treatment methods, as it is effective for depression and AVH and has a mild side effect profile. Although the working mechanism of rTMS has not been fully elucidated, it would seem to affect the central nervous system in a way that is fundamentally different from pharmacotherapy. This may well be the reason why it may be effective in patients who are resistant to medication, both in depression and in individuals suffering from AVH. A trend was observed toward efficacy of rTMS treatment of negative symptoms of schizophrenia. On the other hand, OCD patients appeared not to benefit from it. It is noteworthy that rTMS was more effective for depression when applied in the form of a monotherapy, which indicates that rTMS should not be regarded as an adjuvant treatment for this disorder. Although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication.

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4

Can fMRI-guidance improve the efficacy of repetitive transcranial magnetic stimulation treatment for auditory verbal hallucinations?

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Schizophrenia Research 2007, 93, 406-408 Letter to the Editors, 12 March 2007

CAN FMRI-GUIDANCE IMPROVE THE EFFICACY OF RTMS TREATMENT FOR AUDITORY VERBAL HALLUCINATIONS?

Dear Editors,

The majority of auditory verbal hallucinations (AVH) are responsive to antipsychotic medication, but in 25–30% hallucinations persist despite adequate pharmacotherapy [1]. Low-frequency repetitive transcranial magnetic stimulation (rTMS) offers an alternative treatment for this medication-resistant group [2]. A recent meta-analysis concluded that rTMS is an effective treatment for AVH, with an effect size of 0.76 [3]. So far, rTMS was mostly applied to the left temporoparietal area. However, functional magnetic resonance imaging (fMRI) studies show that in approximately 50% of patients hallucinatory activation mainly involves the right hemisphere [4]. The effect of rTMS may therefore be increased when the treatment is applied exactly over the cortical area that is active in hallucinations. In this study we used individual fMRI scans of hallucinatory activation to stereotactically guide TMS treatment to the cerebral area with maximal hallucinatory activation.

Fifteen male schizophrenia patients with medication-resistant AVH were included in an open-label study. Comorbidity, such as current depression or substance abuse, was an exclusion criterion. Patients were maintained on medication at steady dosages from 4 weeks before treatment until the last follow-up ten weeks after treatment. Symptoms were assessed three days before treatment started (baseline), at the end of each treatment week and at two follow-up measurements at 6 and 13 weeks after baseline. Primary outcome measure was the frequency of hallucinations measured with the Auditory Hallucination Rating Scale (AHRS) [5]. Secondary outcome measure was the total score on the positive items of the Positive and Negative Symptom Scale (PANSS).

Functional scans were obtained in three sessions of 15 min. Patients indicated the presence of AVH by squeezing an air-mediated button and holding it until the AVH subsided. We used a BOLD sensitive, 20-slice gradient EPI sequence (TR/TE 1200/35 ms, flip angle: 35° , FOV: 256 × 10 × 204.80 mm, voxel size 4 × 4 × 4 mm, scan-time per fMRI volume 1.2 s, 750 scans per session) on a Philips Achieva 3 T scanner. An anatomical scan was obtained for detailed localisation (TR/TE: 25/1.68 ms, voxel size 1 × 1 × 1 mm, flip angle: 30°, FOV: 256 × 180 × 208, 200 slices). Functional MRI data were analysed using SPM2. After realignment and co-registration, a model of expected hallucination-related BOLD signal change, was created using a box-car signal, with button squeezes as hallucination onsets and the time between squeezes and releases as the duration of the hallucinations, which was convolved with the standard hemodynamic response function from SPM2 to mimic the delayed BOLD response. These hallucination periods were compared to scans during non-hallucinatory episodes. Beta values were tested

against zero in a 2nd level T-test (threshold $p < 0.01$, cluster size >10 voxels). The cerebral area with the largest number of continuous activated voxels was used as rTMS focus. Image-guided stereotaxy was performed with a Neural Navigator [6], in which the activation map was projected upon the brain's anatomy. The anatomical scan was transformed to a skin rendering, which was co-registered to the patients' head using 3D craniotopic coordinates marked in the software on the skin rendering, mapped onto the same craniotopic landmarks measured directly on the patients' head with a 3D digitizer pen (MiniBIRD position tracker system, Acension Technologies). The point on the scalp exactly overlying the largest activated area was marked by a surgical skin marker.

When no adequate activation maps could be acquired (no activation of >10 continuous voxels below $p = 0.01$) or when hallucinatory activation was inaccessible to rTMS, patients were assigned to the unguided treatment group. In the unguided condition stimulation was focussed on the left temporo-parietal cortex, midway between positions T3 and P3 on a 10–20 EEG electrode cap [2]. Repetitive TMS was administered for 20 min at 1 hertz at 90% of the patients' motor threshold using a Magstim Rapid2 with an air-cooled 70 mm figure-of-eight coil. Patients received daily treatments, except for the weekends, for three weeks.

The effect of treatment in the two groups was analyzed with a GLM using the factors time (baseline, three ratings during treatment and two follow-ups) and treatment type (fMRI-guided versus non-guided).

From 15 participating patients, valid hallucination-related activation maps were obtained in 12 cases. The three patients with unsuccessful scans did not experience enough hallucinations while inside the scanner. From the 12 patients with successful scans, four had hallucinatory activation predominately within the left temporoparietal areas, five mainly in the right-sided temporoparietal areas (see Figure 4.1) and three patients showed hallucination-related activation located deep within the contralateral homologue of Broca's area. As this latter location is out of reach for rTMS, these three

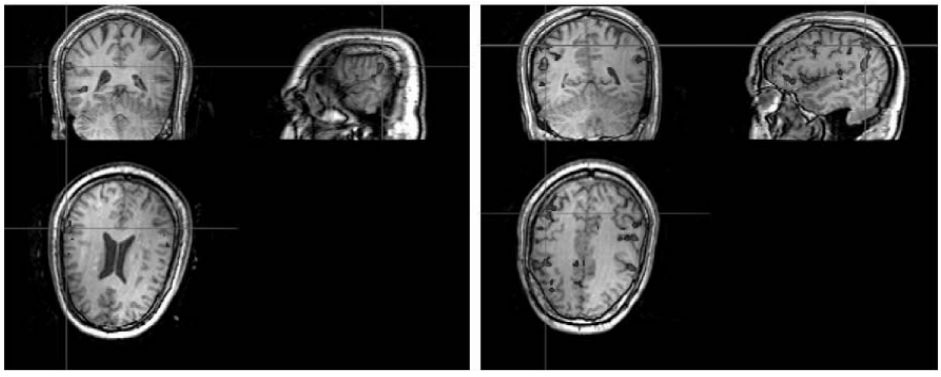

Fig. 4.1 Examples of hallucinatory activation in two patients (right = left in the figure)

patients received non-guided rTMS treatment. The other nine patients were treated with fMRI-guided rTMS.

Two patients wished to abort the study at the second and eighth day of treatment, respectively, because they experienced anxiety and suspicion. Both patients received fMRI-guided rTMS treatment to left temporoparietal areas. Thirteen patients completed the study, from whom seven received fMRI-guided rTMS treatment.

At baseline, there were no differences in severity of AVH, severity of psychotic symptoms or any other clinical characteristic between the two groups (see Table 4.1).

The frequency of AVH showed a significant main effect for time ($F = 4.2$, $p = 0.02$), indicating decreasing severity of AVH in both groups. The time by type of treatment interaction was not significant ($F = 0.8$, $p = 0.5$). Ten weeks after the last treatment severity of AVH was still lower than at baseline ($t = 2.6$, $p = 0.03$).

The severity of psychosis increased during the first week of treatment, possibly as a result of moving to a new ward. In the second and third week of treatment severity of psychosis decreased. Overall the severity of psychosis did not improve significantly (main effect for time: $F = 0.8$, n.s.), while the time by type of treatment interaction showed a trend towards more improvement in the fMRI-guided group ($F = 2.3$, $p = 0.10$).

The results of this study suggest that fMRI-guidance for rTMS treatment of AVH is feasible in the majority of patients with frequent AVH. Interestingly, most patients (eight out of 12) had predominantly right-sided hallucinatory activity. Repetitive TMS treatment guided by individual hallucination-activation maps was compared to rTMS treatment at a fixed position (left temporoparietal), rendering no significant difference upon the frequency of AVH. This may well be a result of the limited power of our study. In contrast to the findings for frequency of AVH, fMRI-guided rTMS appeared superior to non-guided rTMS (at trend level) in decreasing severity of general psychosis. This may indicate that fMRIguidance can improve efficacy of rTMS treatment, though replication in a larger sample is needed.

Table 4.1 Clinical characteristics of the patients that completed the study

Characteristics	fMRI-guided (n=7)	Non-guided (n=6)
Age, mean (sd)	36 (9)	38 (5)
Handedness	6 right, 1 left	6 right, 0 left
AVH for .. years, mean (sd)	14 (11)	14 (8)
Years after diagnosis of schizophrenia, mean (sd)	12 (7)	12 (5)
Baseline severity of AVH, mean (sd)	29 (5)	29 (5)
Baseline severity of psychosis, mean (sd)	18 (6)	19 (3)

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5

Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial

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ABSTRACT

Background

Several studies have applied low-frequency repetitive transcranial magnetic stimulation (rTMS) directed at the left temporoparietal area (TP) for the treatment of auditory verbal hallucinations (AVH), but findings on efficacy are inconsistent. Furthermore, recent functional magnetic resonance imaging (fMRI) studies indicate that the left TP is not a general focus of activation during the experience of AVH. The aims of this study are twofold: to investigate the effects of rTMS on AVH in a double blind, randomized, sham-controlled study; and to investigate whether the efficacy can be improved when rTMS is guided by individual fMRI scans of hallucinatory activation.

Methods

Sixty-two patients with medication-resistant AVH were randomized over three conditions: rTMS targeted at the area of maximal hallucinatory activation calculated from individual fMRI scans during AVH, rTMS directed at the left TP, and sham treatment. Repetitive TMS was applied during 15 sessions of 20 min each, at 1 hertz and 90% of the individual motor threshold. The severity of AVH and other psychotic symptoms were monitored during treatment and 3-month follow-up, with the Auditory Hallucination Rating Scale, the Positive and Negative Syndrome Scale, and the Psychotic Symptom Rating Scales.

Results

The effects of fMRI-guided rTMS and left TP rTMS on the severity of AVH were comparable to those of sham treatment. No differences in severity of general psychotic symptoms were found among the three treatment conditions.

Conclusions

Low-frequency rTMS administered to the left TP or to the site of maximal hallucinatory activation is not more effective for medication-resistant AVH than sham treatment.

5.1 INTRODUCTION

Auditory verbal hallucinations (AVH) are a prominent symptom of various psychiatric disorders, notably schizophrenia. Auditory verbal hallucinations can disrupt social functioning and are associated with acts of violence and suicide [1, 2]. They tend to be medication-resistant in 25 to 30% of the patients with a clinical diagnosis of schizophrenia [3]. Unfortunately, the therapeutic options for this group are limited. Cognitive-

behavioural psychotherapy [4] might offer some improvement, and the effectiveness of biological treatments such as repetitive transcranial magnetic stimulation (rTMS) is still under investigation. Hoffman was the first to report that low-frequency rTMS can decrease the severity of medication-resistant AVH when the coil is directed at the left temporoparietal (TP) [5] area, which is believed to overlay Brodmann area 40 [6]. Since that initial report, 16 studies have been performed with a similar treatment paradigm and focus [7-22]. Approximately one-half of these studies found that rTMS was superior to sham treatment (see Table 5.1 for an overview of the randomized controlled trials).

Table 5.1 Randomized controlled trials considering the effect of rTMS on AVH

Studies	N	Focus of treatment	Questionnaire	Significantly better than sham	Design
Hoffman et al. 1999 [5]	3	left TP	HCS	+	parallel
Hoffman et al. 2000 [7]	12	left TP	HCS	+	parallel
McIntosh et al. 2004 [18]	16	left TP	PANSS	–	crossover
Schönfeldt-Lecuona et al. 2004 [20]	12	superior temporal gyrus or Broca´s area	Haddock self-rating scale	–	crossover
Chibbaro et al. 2005 [12]	16	left TP	SAPS	+	parallel
Fitzgerald et al. 2005 [21]	33	left TP	HCS	–	parallel
Hoffman et al. 2005 [15]	50	left TP	HCS	+	parallel
Lee et al. 2005 [14]	39	left or right TP	PANSS	+ left and right TP	parallel, 3 arms
Poulet et al. 2005 [17]	10	left TP	AHRS	+	crossover
Brunelin et al. 2006 [13]	24	left TP	AHRS	+	parallel
Jandl et al. 2006 [19]	16	left or right TP	PSYRATS	–	crossover
Saba et al. 2006 [8]	18	left TP	PANSS	–	parallel
Hoffman et al. 2007 [16]	24	fMRI-guided	HCS	+ left TP	crossover
Rosa et al. 2007 [11]	11	left TP	AHRS	–	parallel
Loo et al. 2009 [10]	39	left or right TP	AHRS	–	parallel, 3 arms
Vercammen et al. 2009 [9]	38	left and right or left TP	AHRS	–	parallel, 3 arms

+ = significant; – = not significant

Abbreviations: AHRS = Auditory Hallucination Rating Scale, AVH = auditory verbal hallucinations, HCS = Hallucination Change Scale, n = number of patients, PANSS = Positive and Negative Syndrome Scale, SAPS = Scale for the Assessment of Positive Symptoms, PSYRATS = Psychotic Symptom Rating Scales, TP = temporoparietal cortex

Only a few studies examined the effect of low-frequency rTMS targeted at brain regions other than the left TP. One study reported reductions in severity of AVH after rTMS directed at the right TP [14], but this was not replicated by others [10, 19]. Repetitive TMS treatment of the bilateral TP regions revealed no significant differences in comparison with sham treatment [9]. Likewise, stimulation of Broca's area or the left superior temporal gyrus [20] was no more effective than sham treatment. Hoffman et al. [16] stimulated the

left superior temporal gyrus and the adjacent supramarginal gyrus, Broca's area, the left primary auditory cortex, and their contralateral homologues with rTMS. Only rTMS delivered to the left posterior superior temporal gyrus and the adjacent supramarginal gyrus yielded a greater improvement of AVH than sham stimulation. The lack of efficacy of rTMS directed at more frontally located areas, such as Broca's area and its right-sided homologue, might be due to the facial musculature overlying the skull in this area. Because rTMS can only reach a depth of 1–2 cm, additional muscle layers might prevent the rTMS pulse from affecting the Broca's area [16]. Furthermore, Broca's area and associated cortical regions are less closely related to auditory hallucinations compared with Wernicke's area [23].

Although the left TP seems to be the best focus for treatment with rTMS, recent fMRI studies showed that activation patterns during AVH tend to vary significantly among individual patients. The left TP is not generally involved in the mediation of AVH, and in approximately one-half of the patients activation during AVH was predominantly present in right-hemispheric areas [22, 23]. Therefore, it is debatable whether the left TP is indeed the optimal focus for the rTMS treatment of AVH. Perhaps the best focus might vary among individual patients. In theory, the effect of rTMS can be improved by directing the rTMS coil to the location where hallucinatory activation is maximal, as demonstrated with the aid of fMRI scans of individual patients. This tailor-made approach has proved to be feasible in a pilot study where individual fMRI scans of hallucination-related activation were employed to guide the TMS coil for the treatment of AVH [22]. Following that pilot study, we now present the results of a large, double blind, parallel, randomized controlled study, in which rTMS targeted at the focus of maximal hallucinatory activation is compared with rTMS directed at the left TP. To investigate the efficacy of rTMS in comparison with placebo, a sham condition was also included.

5.2 METHODS AND MATERIALS

Subjects

Between January 2007 and January 2009 patients were recruited at the Parnassia Bavo Psychiatric Institute, The Hague, and the University Medical Centre Utrecht. They were included if the following criteria were fulfilled: 1. AVH more frequently than once/hour; 2. medication-resistant AVH (defined as insufficient response to at least two antipsychotic agents, administered at adequate dosages for at least 6 weeks) [24]; 3. a stable dosage of antipsychotic medication since a month before inclusion; and 4. an fMRI scan showing significant hallucinatory activation in at least one superficially located brain area (i.e. in the left or right temporal or parietal lobe).

Reasons for exclusion were a history of epilepsy, unremovable metal objects inside or around the body, the use of cannabis or other drugs during the study or up to 1 month before participation, alcohol consumption of more than 3 U/day, and the use of benzodiazepines or antiepileptic agents. Demographic and clinical data of the participants are provided in Table 5.2.

Table 5.2 Demographic data according to treatment condition

TP left	fMRI (*n* = 20)		T3P3 (*n* = 22)		Sham (*n* = 20)		Significant
Sex, male/female	10	10	16	6	10	10	ns
Age, mean (sd)	36	(10.0)	38	(9.6)	41	(10.3)	ns
Diagnosis, n (%)							ns
Schizophrenia	12	(60)	16	(7.3)	15	(75)	
Schizoaffective disorder	0	(9.1)	1	(4.5)	3	(15)	
Bipolar disorder	0	(0)	0	(0)	1	(5)	
Psychotic disorder NOS	7	(35)	4	(18.2)	1	(5)	
Duration of AVH, mean yrs (sd)	15.2	(11.4)	14.4	(10.5)	16.3	(12.9)	ns
Medication, n (%)							ns
Classic antipsychotics	7	(35)	5	(23)	4	(20)	
Atypical antipsychotics	10	(50)	18	(82)	16	(80)	
Lithium	3	(15)	1	(4.5)	4	(20)	
Antidepressant agents	6	(30)	7	(32)	4	(20)	
In-/outpatients, n (%)	0	(0)	2	(9.1)	1	(5)	ns
AHRS baseline, mean (sd)	26.6	(6.3)	26	(6.6)	28	(7.1)	ns
PANSS positive items baseline, mean (sd)	15.5	(3.8)	16.4	(4.2)	18.6	(4.7)	ns
PANSS negative items baseline, mean (sd)	11.2	(3.8)	13.7	(5)	13.3	(5.9)	ns
PANSS general items baseline, mean (sd)	28.2	(6.7)	33.7	(7.8)	31.5	(8.9)	ns
PANSS total score, mean (sd)	56.4	(12.3)	63.8	(14.3)	63.8	(16)	ns

fMRI = functional magnetic resonance imaging, NOS = not otherwise specified, P3 = left parietal , T3 = left temporal; other abbreviations as in Table 5.1

The study was approved by the Human Ethics Committee of the University Medical Centre Utrecht. After complete description of the study to the subjects, written informed consent was obtained according to the Declaration of Helsinki.

Participants were randomized for three treatment arms (i.e. fMRI-guided rTMS, rTMS directed at the left TP, and sham treatment). It was decided that 20 patients were needed per arm of the study (a 5%, power 80%, estimated effect size 0.50, and the maximum correlation was estimated between 0.7 and 0.8) [25]. The randomization was performed with the aid of www.randomizer.org/form.htm; the three treatment conditions were assigned in a random order by a psychologist who was not involved in the study. Patients were enrolled by a research psychologist coordinating the trial, and the psychiatrist who

performed the rTMS treatments assigned the participants to the interventions according to the randomization list. Participants were notified of the treatment condition after the last follow-up assessment.

fMRI

All participants underwent an fMRI scan of the brain before randomization. The blood oxygenation level dependent response was measured in two sessions of 8 min 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 [23]. Activation maps were obtained with a Philips Achieva 3 Tesla Clinical MRI scanner (Philips, Best, the Netherlands).

Eight hundred three-dimensional (3D) principle of echo-shifting with a train of observations (PRESTO) sensitivity encoding images depicting blood oxygenation level dependent contrast were acquired with the following parameter settings: 40 (coronal) slices, repetition time/echo time 21.75/32.4 msec, flip angle 10°, field-of view 224 x 256 x 160, matrix 64 x 64 x 40, voxel size 4 mm isotropic. Because these PRESTO sensitivity encoding images have little anatomical contrast, an identical scan with a flip angle of 27° was made to improve realignment and co-registration during the preprocessing. After completion of the functional scans, a highresolution anatomical scan (repetition time/echo time: 9.86/4.6 msec, 1 x 1 x 1 voxels, flip angle 8°) was acquired to improve the localization of functional data. The fMRI session with the best performance (i.e. optimal number and duration of hallucinations) was analyzed. An fMRI session was not used for the guidance of rTMS if it comprised a very small number of hallucination episodes and resting states, combined with a brief duration (i.e. less than three hallucination episodes or < 15 sec of total duration of hallucination periods or resting periods). When neither fMRI session yielded sufficient hallucinatory activation and resting state, the patient was excluded from the study.

Data analysis

PREPROCESSING – Functional MRI data were analyzed with statistical parametric mapping (SPM2 and SPM5; Wellcome Department of Cognitive Neurology, London, United Kingdom). Preprocessing of the scans consisted of reorientation, realignment, co-registration of the anatomical and functional scans, and smoothing with a kernel of 8-mm full-width at half-maximum.

STATISTICAL ANALYSIS OF FMRI RESPONSES – To compare hallucinatory periods and nonhallucinatory (resting) periods, an activation model was created with balloon squeezes as hallucination onsets and the intervals between squeezes and releases as the duration of individual hallucinatory periods. This model was convolved with the standardized hemodynamic response function from SPM to introduce typical delays of fMRI responses

and fitted to the data with generalized linear model estimation [26]. These T-maps were used to determine the focus for fMRI-guided treatment or sham, with the following criteria: the area within the temporal or parietal cortex, with the highest intensity, and the largest number of suprathreshold voxels located within reach of rTMS (i.e. at a cortical depth of < 2 cm). The areas around the central sulcus (pre- and postcentral gyrus) were excluded, because activation around this sulcus is most likely motor-related (i.e. related to the hand movements for the balloon squeezes). The bilateral inferior frontal areas were likewise excluded, because the facial musculature might prevent effective stimulation of these areas [16, 20]. The selected focus for treatment was marked as a region of interest on the fMRI scan with MRIcro (http://www.mricro.com).

NEURONAVIGATION – In the fMRI-guided group and the sham group, image-guided stereotaxy was performed with the aid of a Neural Navigator (NordicNeuroLab, Bergen, Norway) [27], which projected the region of interest upon the anatomical brain scan. The anatomical scan was then transformed to a 3D-rendered image of skin surface. These 3D representations and the head of the patient were co-registered with 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 heads of patients with a 3D digitizer pen (the MiniBIRD position tracker system, Acension Technologies, Merrillville, Indiana). The bridge and tip of the nose and the ear ridges were used as craniotopic landmarks. The choice of these craniotopic landmarks was based on the results of Neggers et al. [27], in which the validity and exactitude of the Neural Navigator (NordicNeuroLab) technique were outlined. After this mapping procedure, accurate stereotactic navigation allowed us to mark the location on the scalp directly overlying the area of maximal hallucinatory activation. This spot was marked with the ink of a surgical skin marker. The latter procedure has been validated extensively and allows for the pinpointing of focal brain structures with an accuracy of approximately 4 mm [27].

In the nonguided rTMS group, the 10–20 electrode placement system was used to localize Brodmann area 40, halfway between the left temporal (T3) and left parietal (P3) electroencephalogram electrode sites. Patients in this condition were told that the focus of their treatment was based on the results of their fMRI scan.

Repetitive transcranial magnetic stimulation

A Magstim Rapid 2 (Magstim Company, Whitland, Wales) with an air-cooled 70-mm figure-of-eight coil was used for rTMS treatment. Before the first treatment session, the motor threshold was determined to conform to Schutter and van Honk [28], by stimulating the motor cortex on the ipsilateral side. The motor threshold was ascertained only once, because two studies have investigated the changes in motor threshold during rTMS treatment, and neither of them found any significant differences [29, 30]. 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. Repetitive TMS was administered for 20 min at 1 Hz and 90% of the personal motor threshold of the patient. Patients received daily treatments, except during weekends, for 3 weeks in a row, totalling 15 treatments/person. In individuals receiving sham treatment, the coil was tilted away from the scalp at an angle of 90°. Part of the perimeter of the coil was marked on the scalp of the patient to prevent it from shifting. The coil was hand-held by a trained physician during the whole session to allow for optimal fixation and correction whenever slippage threatened to occur. Furthermore, a stand was used to support the coil.

Outcome parameters

The primary outcome measure was the severity of AVH as quantified by the Auditory Hallucination Rating Scale (AHRS) [31]. Secondary outcome measures were the severity of other psychotic features on the basis of the positive items of the Positive And Negative Syndrome Scale (PANSS) [32] and the Psychotic Symptom Rating Scales (PSYRATS) [33].

Between March 2007 and June 2009 assessments were made at baseline; at the end of the first, second, and last week of rTMS treatment, and at 1 month and 2 and 3 months after the treatment was terminated. On the first, second, and third week of rTMS treatment, patients were asked whether they had side effects. Treatment conditions were unknown to both participants and raters. During the final assessment, patients were asked which study treatment they thought they had undergone (active or sham rTMS).

Statistical methods

Differences between demographic and baseline clinical data among the three treatment conditions were tested with the X^2 test and one-way analysis of variance. The effect of treatment was analyzed with the aid of a general linear model, repeated measures, with the factors time (baseline, three ratings during treatment, and three follow-ups) and type of treatment (fMRI-guided rTMS, nonguided rTMS, and sham treatment). In case of a significant difference between groups, a post hoc analysis was performed with the aid of the independent samples t test. Comprehensive Meta-Analysis Version 2.0 (Biostat, Englewood, New Jersey) was used in a random effects model to compute the effect size between baseline and the end of treatment for each treatment arm and each outcome parameter.

5.3 RESULTS

Efficacy

Sixty-two patients were included and randomized over the three treatment arms (fMRI-guided n = 20, standard rTMS n = 22, sham condition n = 20). The demographic data

and mean baseline values of the outcome measures did not differ significantly among groups (Table 5.2). In the group with fMRI-guidance two patients aborted the study because of facial muscle twitching (n = 1) and increase of psychosis (n = 1). In the standard treatment group three patients dropped out for the following reasons: inability to continue visiting the hospital (n = 1), headache and lack of therapeutic effect (n = 1), and an increase of psychotic symptoms (n = 1). Six patients in the sham condition discontinued the study due to an increase of psychotic symptoms (n = 3), dizziness and tremor (n = 1), and unknown reasons (n = 2).

The location of the rTMS treatment was fixed in the standard treatment group and variable in the fMRI-guided group and in the sham condition. Table 5.3 lists the exact locations of the treatment foci for the latter two groups, on the basis of fMRI scans obtained during AVH. Because the numbers of patients/treatment site were low, a subanalysis investigating any differences in effect for these sites could not be performed.

Table 5.3 Focus of treatment

	fMRI		**TP left**	**Sham**	
	left	right		left	right
Superior temporal gyrus	3	2		7	4
Medial temporal gyrus	4	2		1	2
Inferior temporal gyrus	1	3			
Transversal temporal gyrus	3	0		1	0
Supramarginal gyrus	0	1			
Angular gyrus	1	0			
TP			22	5	0
Total	12	8	22	14	6

fMRI = functional magnetic resonance imaging, TP = temporoparietal cortex;
other abbreviations as in Table 5.1 and 5.2

The results are presented in Figure 5.1 and Table 5.4. For the mean summed AHRS score and the items 'frequency', 'number of voices' and 'distress', a significant main effect was found for the factors time: mean summed AHRS ($F = 7.794$, df 1,36, $p = 0.008$), frequency ($F = 6.566$, df 1,40, $p < 0.001$), number of voices ($F = 2.047$, df 1,40, $p = 0.015$), and distress ($F = 2.460$, df 1,41, $p = 0.025$). However, no significant differences were observed in the mean summed AHRS score (or any subscores) among the three treatment conditions over time ($F = 0.619$, df 2,36 $p = 0.54$). Nor did the PANSS positive items and the sum of the AVH-related scores from the Psychotic Symptom Rating Scales reveal any significant differences among the three treatment conditions ($F = 1.467$, df 2,40, $p = 0.24$ and $F = 0.989$, df 2,33, $p = 0.38$, respectively), although a significant time effect was found for the positive items of the PANSS ($F = 3.658$, df 1,41, $p = 0.002$).

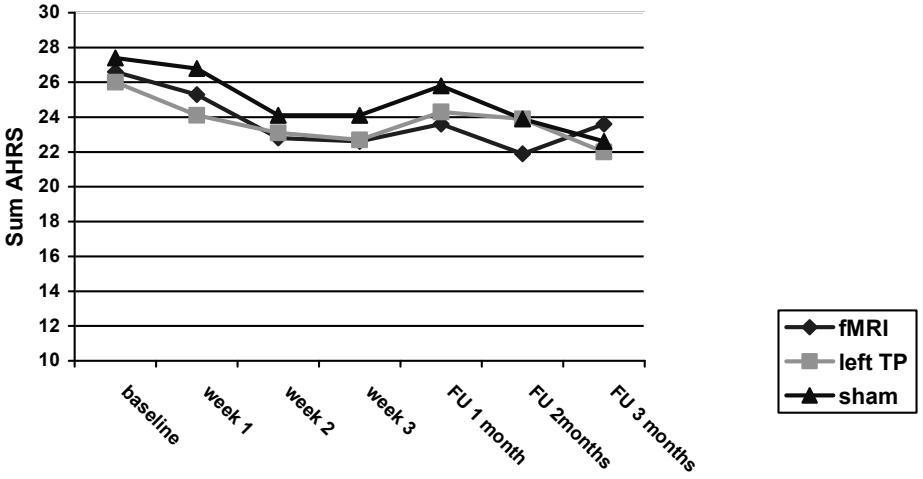

Figure 5.1 Effects of rTMS treatment on the sum of the Auditory Hallucination Rating Scale (AHRS)

When guided and nonguided rTMS (n = 42) were combined and compared with sham treatment (n = 20), no significant differences in efficacy were observed between groups (mean summed AHRS score, F = 1.172, df 1,37, p = 0.29). This lack of difference remained unaffected when the analysis was limited to patients with a diagnosis of schizophrenia (F = 0.130, df 1,24, p = 0.72). Nor was there any difference in outcome between male and female patients (F = 1.122, df 1,37, p = 0.30).

Table 5.4 Effects of rTMS treatment on specific features of AVH

	fMRI				**T3P3**				**Sham**			
	Baseline		End rTMS		Baseline		End rTMS		Baseline		End rTMS	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
Frequency	5.8	3.2	4.5	3.0	5.5	3.0	4.5	3.2	5.4	2.8	4.6	3.4
Reality	3.8	2.0	3.3	2.0	3.9	1.4	3.5	1.9	4.0	1.3	3.7	1.9
Loudness	2.6	1.1	2.3	1.1	2.9	1.2	2.4	1.3	3.2	1.4	2.8	1.3
Number of voices	3.5	1.9	3.2	2.1	3.8	2.0	3.7	2.0	3.9	2.0	3.2	2.1
Length	3.4	1.0	3.0	1.2	3.3	1.1	2.9	1.1	3.2	1.0	3.0	1.1
Attentional salience	4.3	1.5	3.5	1.6	3.8	1.6	2.9	1.3	4.3	1.3	3.7	1.6
Distress	3.3	1.5	2.8	1.4	3.2	1.1	2.7	0.9	3.4	1.3	2.8	1.3
Sum AHRS	26.6	6.3	22.6	7.4	26.0	6.6	22.7	6.4	27.4	6.9	24.1	8.1
Positive items PANSS	15.5	3.8	14.0	5.7	16.4	4.2	15.5	3.9	18.7	4.7	15.9	3.5
AVH-related items PSYRATS	26.2	7.5	21.8	10.0	27.0	5.5	25.1	8.6	28.0	7.0	25.4	8.9

Abbreviations as in Table 5.1 and 5.2

A categorical analysis was performed, but no significant difference in the number of patients achieving > 20% reduction on the total score of the AHRS was found among the three treatment conditions (Pearson $X^2 = 0.618$, $p = 0.734$). Furthermore, dichotomization into high- and low-frequency of hallucinations (cut-off score > 4 versus ≤ 4 on the sub-item 'frequency' of the AHRS) did not reveal any differences in outcome ($F = .317$, df 1,34, $p = 0.52$).

It is debatable whether patients using 3 U of alcohol/day should have been included in this randomized controlled trial. There were two patients who consumed 1 or 2 U of alcohol/day, and only 1 patient who used 3 U of alcohol/day; none of the other participants used any alcohol daily. When these patients were excluded from analyses, the results did not change.

Because the analysis of the drop-outs showed a trend toward a significantly higher number of drop-outs in the sham condition (Fisher exact test $p = 0.085$), we also performed a Last Observation Carried Forward analysis without changing the results ($F = 0.863$, df 2,45, $p = 0.43$).

Effect sizes of the individual treatment conditions are presented in Table 5.5.

Table 5.5 Effect sizes between baseline and end of rTMS treatment of the specific outcome parameters

	fMRI st diff in means (p)		T3P3 st diff in means (p)		Sham st diff in means (p)	
Sum AHRS	0.524	(0.10)	0.508	(0.10)	0.439	(0.17)
Positive items of the PANSS	0.310	(0.33)	0.222	(0.46)	0.676	(0.04)
AVH-related items of the PSYRATS	0.583	(0.07)	0.263	(0.39)	0.325	(0.31)

st diff in means = standardized difference in means;
other abbreviations as in Table 5.1 and 5.2

Blinding

Thirteen of 17 patients (76%) in the fMRI-guided group, 14 of 16 patients (88%) in the T3P3 rTMS group, and 2 of 15 patients (13%) in the sham treatment group guessed their treatment condition correctly. There was a significant difference in the number of patients guessing the right treatment condition among the three treatment arms ($X^2 = 20.699$, $p < 0.001$). This outcome confirms that patients were actually blind for their treatment conditions, because the vast majority of patients in all three groups expected to have had active rTMS treatment.

Tolerability

Side-effects in the fMRI-guided treatment group were facial muscle twitching (n = 7), headache (n = 3), scalp discomfort (n = 1), cervical pain (n = 1), and nausea (n = 1). In the standard treatment condition, headache (n = 5), dizziness (n = 1), abdominal pain (n =

1), and fatigue (n = 1) were mentioned. In the sham condition the following side-effects occurred: subjective facial muscle twitching (n = 1), and dizziness (n = 1).

5.4 DISCUSSION

Our study constitutes the largest double-blind randomized controlled trial applying rTMS for medication-resistant AVH to date. Sixty-two patients were randomized over three conditions: rTMS targeted at the area of maximal hallucinatory activation as indicated by individual fMRI scans, rTMS directed at the left TP, and sham treatment. Although the mean severity of AVH significantly decreased over time, no significant difference in reduction of AVH or any other psychotic symptom was revealed among the three treatment conditions. Even when the two groups receiving guided and nonguided rTMS were combined (n = 42), rTMS was not superior to sham treatment in reducing AVH or other psychotic symptoms.

There have been 15 previous studies that applied rTMS for AVH in a randomized controlled trial, summarized in Table 5.1. Only two of these studies involved more than 15 participants/arm [15, 21]. Our findings are consistent with the first but not with the second study, although the baseline severity of psychotic features in our sample was comparable to that of the previous studies. Furthermore, the methods used in our study are not the same as in the study by Hoffman et al. [16]. In their study, the first five patients were treated with rTMS directed at the three most prominent cortical sites, on the basis of fMRI maps (either activation maps of hallucination events or Wernicke's-referenced correlation maps). For the remaining patients, up to six active sites could be targeted with rTMS. This method is in contrast to our randomized controlled trial, in which rTMS was directed either at the area with maximal hallucinatory activation of the individual patient or at T3P3 or sham treatment.

Four meta-analyses [34-37], including two from our group, have summarized the results of previous rTMS studies for AVH, and all concluded that rTMS is more effective than sham treatment. However, a publication bias might have affected this outcome, because most previous studies included relatively small patient samples, and small studies with positive results have a much higher chance to be published than small studies with negative results [38].

Study limitations

An alternative conclusion of the negative findings would be that rTMS does work but that this study was underpowered to detect an effect. Because the mean difference of the summed AHRS score (baseline versus end of treatment) between rTMS directed at the left TP cortex and sham treatment is zero, one would need an infinite number of

patients to find a significant difference between the two conditions. Therefore, we do not think that the study was underpowered and uphold our conclusion that rTMS applied with these paradigms simply does not work.

The aim of our study was to increase the efficacy of rTMS by comparing a new paradigm to standard and sham treatment. The design of this study was based on four independent meta-analyses, all showing moderate to good mean effect sizes of rTMS compared with sham. However, in this study, which is the largest so far, standard rTMS turned out not to be superior to sham. Given this outcome, we had better divided the 62 participants over two groups (sham and standard rTMS) to obtain maximal power for this comparison.

The result of our randomized controlled trial implies that rTMS directed at T3P3 and the area with maximal hallucinatory activation is not an effective treatment for medication-resistant AVH or at least not more effective than a well-matched sham treatment. However, this can only be stated for low-frequency rTMS. High-frequency rTMS has been studied for the treatment of AVH in one single study, which reported a strong positive effect after no more than two treatment sessions [39] but did not include a sham condition. There are no published studies comparing high-frequency rTMS with sham treatment. Furthermore, a study using an individual motor threshold above 100% or a treatment duration of 4 weeks or more has not been performed so far. It would be of interest to investigate these paradigms in addition to high-frequency rTMS.

In summary, low-frequency rTMS directed at the area of maximal hallucinatory activation and rTMS directed at the left TP are no more effective in the treatment of medication-resistant AVH than fMRI-guided sham treatment. It might be time for a change of paradigm and for a search for more effective treatment regimens, such as high-frequency rTMS – or perhaps invasive cortical stimulation – to expand the number of treatment options for medication-resistant AVH.

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6

Priming does not enhance the efficacy of one-hertz repetitive transcranial magnetic stimulation for the treatment of auditory verbal hallucinations: results of a randomized controlled study

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Brain stimulation, accepted

ABSTRACT

Background

Low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the left temporoparietal area (TP) has been investigated as a treatment method for auditory verbal hallucinations (AVH) yielding inconsistent results. In vitro studies have indicated that the effects of low-frequency rTMS can be enhanced by a brief pre-treatment phase consisting of high-frequency rTMS (i.e. priming rTMS).

Objective

The aim of this single-blind, randomized controlled study was to investigate whether the effects of rTMS on AVH can be enhanced with priming rTMS.

Methods

Twenty-three patients with medication-resistant AVH were randomized over two groups: one receiving low-frequency rTMS preceded by five minutes of six-hertz rTMS; and another receiving low-frequency rTMS without priming. Both treatments were directed at the left TP. The total duration of stimulation was equal in the two groups, namely 15 sessions of 20 minutes each. The severity of AVH and other psychotic features were measured with the aid of the Auditory Hallucination Rating Scale (AHRS), the Positive And Negative Syndrome Scale (PANSS) and the Psychotic Symptom Rating Scales (PSYRATS).

Results

The severity of AVH and other psychotic symptoms in the group with priming was not significantly lower after three weeks of treatment in comparison to baseline. The group treated with standard rTMS showed a trend towards improvement after three weeks of treatment. No significant differences were observed on any of the rating scales between the group with and without priming.

Conclusion

This study does not provide evidence that priming rTMS is an effective treatment for AVH.

6.1 INTRODUCTION

Auditory verbal hallucinations (AVH) are common in various psychiatric disorders. Despite treatment with antipsychotic medication, 25 to 30% of the patients with a clinical diagnosis of schizophrenia suffer from persistent AVH [1]. Intractable AVH are associated with acts of violence and suicide [2, 3] and significantly reduce the quality of life. In these

medication-resistant patients, repetitive transcranial magnetic stimulation (rTMS) may aid to decrease the severity of AVH. Initial studies showed moderate to high efficacy of low-frequency rTMS (one hertz, Hz) by directing the coil at the left temporoparietal area (TP) [4, 5]. Several studies have been published that tried to replicate these findings, with mixed results [6-20]. Four meta-analyses compared the effect of low-frequency rTMS directed at the left TP to sham rTMS, finding a moderate to large efficacy (effect sizes vary between 0.52 and 1.04) [21-24]. However, more recent studies that were not included in these meta-analyses, found little or no superiority of low-frequency rTMS as compared to sham treatment [19, 20]. In an attempt to improve the efficacy of rTMS for the treatment of AVH, varying strategies have been tested, such as bilateral stimulation [19] and fMRI guidance [20] - without any success, however. One open-label study showed a great improvement in reduction of AVH after only two sessions of high-frequency rTMS [25], but this study did not include a sham condition, and the findings have not been replicated yet.

Low-frequency rTMS has been demonstrated to depress excitatory activation at the site of application [26]. This effect is thought to be comparable with long term depression (LTD) [27] as observed in single-cell recordings after prolonged stimulation. In a single mono-synaptic pathway LTD can be increased by a brief period of lateral-path synaptic activation at five Hz lasting at least two hours [28]. As a corollary, it has been suggested that the potential of low-frequency rTMS to depress local neuronal activation can be enhanced by brief pre-treatment with rTMS in a frequency of five to six Hz [28-30]. This was confirmed in vivo in a study investigating the effects of priming rTMS on the motor cortex in healthy volunteers. In this latter study, priming rTMS was applied during 10 minutes with a frequency of six Hz or with a frequency which modulated between four and eight Hz each second, yielding an increased efficacy of one-Hz-rTMS in depressing the motor cortex in both priming conditions in comparison with simple one-Hz stimulation [31]. For the treatment of psychiatric disorders, priming rTMS has been tested only in a single study [32]. In this double-blind, randomized controlled trial among patients with major depressive disorder, the priming procedure involved 600 stimuli, applied in a frequency of six Hz, at 90% of the individual motor threshold, which was followed by low-frequency rTMS. As compared to low-frequency rTMS with sham priming, an additional positive effect was found in the priming group. No major side effects occurred.

Hypothesis

Based on these findings, we assumed that the effects of low-frequency rTMS on AVH could also be increased by pre-treatment with priming rTMS. The first aim of this study was to explore the effect of priming rTMS for AVH and the second aim was to compare this effect to standard rTMS treatment. To investigate this possibility, a randomized controlled study was carried out in which the clinical raters were blind to the treatment condition of the patients.

6.2 MATERIALS AND METHODS

Subjects

Patients were recruited from Parnassia Bavo Psychiatric Institute, The Hague, and the University Medical Centre in Utrecht. They were allowed to participate when they were aged 18 years or older and experienced AVH in a frequency of at least once per hour. Criteria for exclusion were 1. history of epilepsy, 2. daily use of cannabis, 3. use of hard drugs during the month prior to the study or during the study, 4. alcohol consumption of more than three units per day, 5. daily use of benzodiazepines, and 6. use of anti-epileptic agents. Patients only participated after written informed consent was obtained. Approval for this study was granted by the Medical Ethical Board of the University Medical Centre Utrecht and was carried out in accordance with the Declaration of Helsinki.

After inclusion, the participants were randomized over two treatment conditions: low-frequency rTMS, and low-frequency rTMS preceded by priming rTMS. Randomization took place with the aid of www.randomizer.org/form.htm.

Repetitive transcranial magnetic stimulation

Repetitive TMS was performed with a Magstim Rapid2 (Magstim Company Ltd, Whitland, Wales) with an air-cooled 70 mm figure-of-eight coil. Prior to the first treatment session, the motor threshold was determined conform Schutter and van Honk [33] by stimulating the motor cortex on the ipsilateral side. The international 10-20 electrode placement system was used to localize Brodmann's area 40, halfway the left temporal (T3) and left parietal (P3) electrode sites. A cardboard template was employed to position the centre of the coil, where the magnetic fields of both rings are summated, exactly over the left TP, which served as the focus of treatment in both conditions.

Priming was performed with the aid of an E-prime paradigm (www.pstnet.com). It consisted of five minutes of rTMS treatment at a frequency of six Hz, applied at 80% of the individual motor threshold. This treatment phase was followed immediately by 15 minutes of low-frequency rTMS (one Hz), applied at 90% of the individual motor threshold. The control condition involved 20 minutes of rTMS at a frequency of one Hz at 90% of the individual motor threshold. Both treatments were repeated on consecutive working days for a total duration of 15 days (i.e. three weeks).

Outcome parameters

As the primary outcome measure we chose the sum of the scores on the Auditory Hallucination Rating Scale (AHRS) [34], which is deemed to reflect the global severity of auditory hallucinations. The secondary outcome measure was the severity of general psychotic features as measured by the positive items of the Positive And Negative Syndrome Scale (PANSS) [35] and the AVH-related items of the Psychotic Symptom Rating Scales

(PSYRATS) [36]. Assessments were made at baseline, and at the end of the first, second and third week of rTMS treatment.

The patients were asked daily whether they had experienced any side effects during or immediately after the rTMS treatment.

Follow-up measurements were performed at one, two and three months after completion of the treatment phase. The clinical raters were blind for the treatment conditions. Participants were relatively blind: before onset of the study, participants were explained that they would receive one of the two kinds of TMS treatments and that it was unknown which treatment paradigm was superior.

Statistical methods

The Mann-Whitney Test and Fisher´s Exact Test were used to test baseline clinical and demographic differences among the two treatment groups.

The analyses of the effect of the separate treatment conditions were carried out with Wilcoxon Signed Rank Tests. A difference in effects between the two treatment conditions was analyzed with a General Linear Model, repeated measures, using the factors time (at baseline, three ratings during treatment, and three during follow-up) and type of treatment (priming rTMS versus non-priming). Post hoc analyses were performed in case of significant main effects. Statistical Package for the Social Sciences (SPSS) version 18 was used for the analyses. All tests were performed in a two-sided manner.

6.3 RESULTS

Twenty-three patients were included in this study. The demographic and clinical data are presented in Table 6.1. No significant differences could be found between the two treatment groups except for the total score of the PANSS; this was compensated by the fact that we analyzed the difference in scores between baseline and end of treatment. Although patients in the priming group appeared to be younger and had a shorter duration of AVH, these differences were not statistically significant.

One patient in the priming group and one in the non-priming group ceased their participation. The first one after a technical malfunction; when the problem was solved, she did not want to participate any longer. The reason for withdrawal in the first week of rTMS treatment of the second patient is unknown.

No difference could be shown between baseline and end of treatment summed AHRS scores in the priming rTMS group (Wilcoxon Signed Rank Test $Z = -0.365$, $p = 0.72$). Although the mean summed AHRS score of the non-priming group decreased over time, statistical significance could not be reached (Wilcoxon Signed Rank Test baseline versus end-of-treatment $Z = -1.843$, $p = 0.065$).

Table 6.1 Demographic data according to treatment condition

	Priming (n = 11)		Non-priming (n = 12)		p
Sex, n males, (%)	6 (54.5)		7 (58.3)		1.00
Age, mean years (sd), median	34.9 (12.4)	32.0	42.3 (10.5)	42.5	0.17
Diagnosis, n (%)					0.60
Schizophrenia	9 (81.8)		8 (66.6)		
Schizoaffective disorder	1 (9.1)		2 (16.7)		
Psychotic disorder NOS	1 (9.1)		2 (16.7)		
Duration of AVH, mean years (sd), median	14.6 (9.9)	12.0	21.3 (16.4)	22.5	0.32
Medication, n (%)					
Classic antipsychotics	3 (27.3)		2 (16.7)		0.40
Atypical antipsychotics	7 (63.6)		10 (83.3)		0.36
Mood stabilizers	2 (18.2)		1 (8.3)		0.57
Antidepressant agents	4 (36.4)		2 (16.6)		0.40
Inpatients, n (%)	2 (18.2)		2 (16.2)		0.82
AHRS baseline, mean (sd), median	27.7 (7.0)	27.0	27.9 (7.0)	29.0	0.77
PANSS positive items baseline, mean (sd), median	13.5 (4.3)	13.0	16.6 (5.3)	16.0	0.19
PANSS total score, mean (sd), median	41.7 (6.9)	40.5	61.0 (15.0)	63.0	0.02
AVH-related items PSYRATS, mean (sd), median	28.7 (5.8)	29.5	27.9 (6.8)	28.5	1.00

Abbreviations: AHRS = Auditory Hallucination Rating Scale, AVH = auditory verbal hallucinations, n = number of patients per group, NOS = not otherwise specified, PANSS = Positive And Negative Syndrome Scale, PSYRATS = Psychotic Symptom Rating Scales, sd = standard deviation

The mean summed AHRS scores did not reveal any significant differences for the factor time ($F = 1.417$, df 1, 9, $p = 0.26$), nor any main effects for group ($F = 1.220$, df 1, 9, $p = 0.30$). Detailed data are provided in Table 6.2 and Figure 6.1.

An analysis with Last Observation Carried Forward method showed a significant effect for time ($F = 7.221$, df = 1, 18, $p = 0.02$), but did not change the results for the summed AHRS scores between the two groups ($F = 0.444$, df = 1, 18, $p = 0.51$). Inclusion of the covariates 'age' and 'years of duration of AVH' did not reveal a difference between the two treatment conditions ($F = 0.205$, df 1, 7, $p = 0.40$). Neither did the total score of the PANSS when it was added as a covariate ($F = 0.201$, df = 1, 7, $p = 0.67$). Furthermore, no significant differences were found for any of the subscores of the AHRS within and between groups on any rating moment.

Nor did we observe any effects on the scores of the positive items of the PANSS (time: $F = 0.731$, df 1, 13, $p = 0.41$, group: $F = 0.113$, df 1, 13, $p = 0.74$) or the AVH-related items of the PSYRATS (time factor $F = 0.652$, df 1, 7, $p = 0.45$ and group factor $F = 1.140$, df 1, 7, $p = 0.32$).

Table 6.2 Effects of rTMS treatment on the Auditory Hallucination Rating Scale (AHRS)

	Priming (n = 11)		Non-priming (n = 12)		F	df	p
	baseline	end rTMS	baseline	end rTMS			
Frequency, mean (sd)	4.8 (3.3)	5.3 (3.3)	6.9 (3.3)	5.8 (3.5)	0.139	1, 15	0.71
Reality, mean (sd)	4.6 (1.0)	4.3 (1.4)	4.7 (0.5)	3.4 (1.9)	0.102	1, 14	0.75
Loudness, mean (sd)	2.8 (0.6)	2.8 (1.0)	2.5 (0.8)	2.3 (0.8)	0.114	1, 13	0.74
Number of voices, mean (sd)	3.9 (1.8)	3.9 (2.0)	3.5 (2.1)	3.6 (2.1)	0.023	1, 15	0.88
Length, mean (sd)	3.1 (1.0)	3.3 (1.1)	3.2 (0.9)	3.4 (0.7)	0.419	1, 12	0.26
Attentional salience, mean (sd)	4.7 (1.3)	4.6 (1.3)	4.3 (1.3)	4.1 (1.2)	0.731	1, 15	0.41
Distress, mean (sd)	3.7 (1.6)	3.5 (1.5)	3.1 (1.2)	3.1 (1.1)	0.007	1, 15	0.93
Sum AHRS, mean (sd)	27.7 (7.0)	28.6 (8.4)	27.9 (7.0)	23.7 (7.4)	1.220	1, 9	0.30

Abbreviations: df = degrees of freedom, F = F test between group comparison, n = number of patients, p = p value, sd = standard deviation

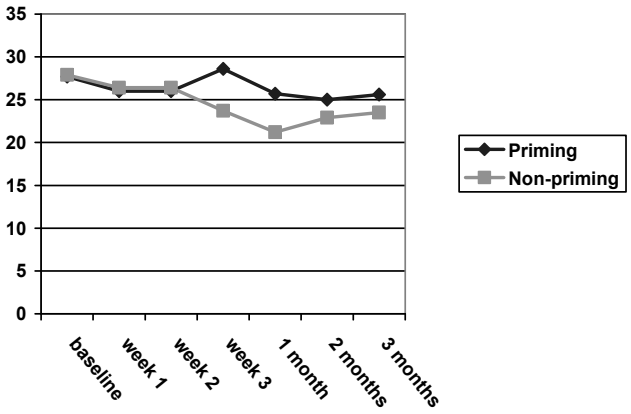

Figure 6.1 Effects of rTMS treatment on the sum of the scores on the Auditory Hallucination Rating Scale (AHRS)

Side effects

Scalp discomfort (n = 2), dizziness (n = 2), headache (n = 1), facial muscle twitching (n = 1) and stiff neck (n = 1) were mentioned in the priming group and headache (n = 1), facial muscle twitching (n = 1) and increase of headache and neck pain (n = 1) in the non-priming group. Side effects were more frequent in the priming group, but this difference was not significant (Pearson Chi-Square 3.486, p = 0.062). Side effects were mild, and constituted no reason for withdrawal in either treatment group.

6.4 DISCUSSION

We here present the first randomized controlled trial in which the effects of priming repetitive transcranial magnetic stimulation (rTMS) are assessed for the treatment of patients with medication-resistant auditory verbal hallucinations (AVH). Priming rTMS treatment did not significantly change the severity of AVH or any other psychotic feature. A modest decrease of the mean summed AHRS score and of the subscore 'frequency of AVH' and 'reality of AVH' was observed for the non-priming rTMS group, but this reached only trend-level statistical significance. Furthermore, no significant difference in effect could be revealed between the two groups on any measurement.

An effective and safe augmentation treatment for patients with medication-resistant AVH is most welcome, as the degree of suffering in this group is high. Repetitive TMS appeared to have the potential to provide such an augmentation strategy. It is a safe and painless method with very mild side effects. However, little or no superiority as compared to sham rTMS was found in recent studies with increasing sample sizes [19, 20]. Given the positive enhancing effect of the priming pretreatment in depression, we selected this method in order to design a more effective stimulation protocol. The results of our study imply that priming rTMS over the temporoparietal area has no positive effect on AVH, but other studies with larger patient samples are needed to replicate this finding. That being said, it would seem precocious to conclude that the effect of rTMS can not be improved for AVH because the parameters frequency, intensity and duration of rTMS treatment have not been fully investigated in this field. It would be interesting to perform a randomized controlled study with either high-frequency rTMS (using theta-burst for example), an individual motor threshold above 100% or a treatment duration of four weeks or more.

Limitations and strengths

The modest size of our patient sample may well have influenced the results. However, as the priming group performed even less favourably than the group with one-hertz (Hz) rTMS treatment, it was decided to stop inclusions for this study after initial analysis, as the chance of finding a more potent stimulation protocol was minimal.

A second limitation is that the duration of stimulation with one Hz was five minutes shorter (15 instead of 20 minutes) in the priming condition. However, no significant differences in effect could be revealed between the two treatment conditions *and* between baseline versus end of treatment of the priming condition at all.

A third limitation is that the randomisation lead to a somewhat younger group with a shorter duration of AVH for the priming rTMS condition and a significant difference in the total score of the PANSS; if these variables were included as covariates, the results remained the same.

Finally, the participants could not be completely blinded for the treatment condition, as they could hear the rhythm of the rTMS treatment they were obtaining. On the other hand, they were not aware of the rhythm of the other treatment group and no expectations or motivated explanations were given to the participants about either treatment condition until after completion of all the follow-up visits.

Conclusion

On the basis of these results we cannot recommend priming rTMS for the treatment of AVH in psychotic patients.

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7

General discussion

7. GENERAL DISCUSSION

The main aims of this thesis were twofold. Firstly, the phenomenology and the ensuing distress of auditory verbal hallucinations in borderline personality disorder were explored and compared to those in patients with schizophrenia and individuals without a diagnosis. Secondly, repetitive transcranial magnetic stimulation (rTMS) was investigated as a treatment tool for psychiatric disorders and notably auditory verbal hallucinations.

This chapter provides an overview of the results of the previous chapters and the conclusions that can be drawn. Furthermore, implications for future research and clinical practice are discussed.

7.1 AUDITORY VERBAL HALLUCINATIONS IN BORDERLINE PERSONALITY DISORDER

As we saw in Chapter 2, only a few studies have systematically assessed the phenomenology and severity of auditory verbal hallucinations and other psychotic features in borderline personality disorder [1]. We also saw that various investigators have proposed to designate hallucinations in borderline personality disorder as 'pseudohallucinations', thus giving expression to the conviction that they are less severe or qualitatively different from those in psychotic disorders [2-9].

In addition, the results of a cross-sectional study were presented, in which 33 patients with borderline personality disorder, 51 patients with schizophrenia/schizoaffective disorder, and 66 individuals without a diagnosis were assessed [10]. All participants experienced auditory verbal hallucinations and were female. Patients with borderline personality disorder heard voices for a mean duration of 17 years, in a mean frequency of at least once per day, and for a duration of several minutes or more. The scores for the ensuing distress were high. No differences could be revealed in the phenomenological characteristics between patients diagnosed with borderline personality disorder and schizophrenia/schizoaffective disorder, except for the scores on the item 'disruption of life', which were higher in the latter group. Compared to healthy subjects with auditory verbal hallucinations, patients with borderline personality disorder had higher scores on almost all items.

Although the number of patients with borderline personality disorder was modest, the similarities with schizophrenia/schizoaffective disorder and the differences with auditory verbal hallucinations in individuals without a diagnosis were striking. The finding that patients with borderline personality disorder tend to experience auditory verbal hallucinations on a regular basis might suggest that they are prone to the

development of a full-blown psychotic disorder in the future. However, there are two reasons why we do not expect this to happen; firstly, because the diagnosis schizophrenia/schizoaffective disorder was ruled out with the aid of a structured interview by a psychiatrist experienced in the field of psychotic disorders. Secondly, because patients with borderline personality disorder experienced their auditory verbal hallucinations for a mean duration of 17 years, which is extremely long, and certainly much longer than the average prodromal phase in psychosis. A limitation of this study is that the results can only be extrapolated to other women, because men were not included. But that does not compromise the purpose of the present study, considering the fact that 70 to 75% of all patients with borderline personality disorder are women [11].

Our results also imply that auditory verbal hallucinations experienced in the context of borderline personality disorder fulfil the criteria of hallucinations proper, and that they should therefore be designated as such. After all, making use of an inappropriate nomenclature may well entail trivialization, and, in the worst case, the withholding of adequate treatment. In addition, auditory verbal hallucinations occurring in the context of borderline personality disorder are different from those experienced by individuals without a psychiatric diagnosis. Further research among voice hearers with other psychiatric diagnoses is needed to explore the issue whether auditory verbal hallucinations in borderline personality disorder can be said to lie on a continuum with those in individuals without a diagnosis and with those in patients diagnosed with schizophrenia, or whether auditory verbal hallucinations can be said to simply occur in multiple psychiatric disorders, including borderline personality disorder.

Little is known about the prevalence, phenomenology and severity of other psychotic features in borderline personality disorder. Perhaps psychotic features in borderline personality disorder share the same neurobiological mechanism as those in schizophrenia but this is not investigated until now. Furthermore, treatment options such as cognitive behavioural therapy have not been explored in a controlled setting. Antipsychotics have been investigated in patients with borderline personality disorder, but measurements assessing the severity of psychotic features have rarely been used, several studies excluded patients with a psychotic disorder not otherwise specified (thus excluding patients with persistent auditory verbal hallucinations) or did not specify if these patients experienced psychotic features or not.

In conclusion, it would seem advisable to pay more attention to the occurrence of genuine auditory verbal hallucinations in borderline patients, as well as to the burden these symptoms may cause. Therefore, health professionals are strongly advised to explore the occurrence of auditory verbal hallucinations in any patient with borderline personality disorder under their care.

Moreover, future studies should aim at charting the prevalence, phenomenology, and severity of other psychotic symptoms in borderline personality disorder, and at assessing

their neurobiological underpinnings. Last but not least, I recommend the development of treatment strategies for this disabling symptom.

7.2 REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Repetitive TMS is a promising treatment tool that deserves further investigation. A benefit of rTMS is that it is considered a safe treatment method with only mild side effects. In the next paragraph the results of a meta-analysis considering rTMS in the treatment of psychiatric disorders and symptoms, and three clinical trials of rTMS for auditory verbal hallucinations are presented. Details of these studies are described in Chapter 3, 4, 5 and 6 of the present thesis [12].

7.2.1 Repetitive transcranial magnetic stimulation in the treatment of psychiatric disorders and symptoms: results

Results of a meta-analysis of repetitive transcranial magnetic stimulation in the treatment of psychiatric disorders and symptoms

Since the introduction of rTMS as a treatment method for depression [13], the number of publications has increased dramatically. In 2008 the US Food and Drug Administration (FDA) approved rTMS for the treatment of depression.

Thirty-four studies with a total number of 1383 patients were included in the meta-analysis of treatments for depression; rTMS turned out to be superior to sham treatment in all studies, regardless whether they applied high-frequency rTMS directed at the left dorsolateral prefrontal cortex (DLPF), low-frequency rTMS directed at the right DLPF, or a combination of the two. No significant differences were revealed between the effects of stimulation of the left and the right DLPF. Repetitive TMS as monotherapy appeared to be more effective than rTMS in combination with antidepressive agents, but these differences did not reach statistical significance. The six studies that excluded patients with psychotic symptoms yielded better effects of rTMS than those that did not use this criterion for exclusion.

Six studies with a total number of 213 patients were included in a meta-analysis comparing high-frequency rTMS directed at the left DLPF to electro-convulsive therapy (ECT) for depression. A significant effect was found in favour of ECT.

A meta-analysis of seven sham-controlled studies with a total of 189 patients with auditory verbal hallucinations yielded a significant, yet moderate effect size in favour of real rTMS; rTMS was applied to the left temporoparietal cortex in the majority of those studies.

High-frequency rTMS directed at the DLPF was not superior to sham treatment in seven studies with a total number of 148 patients experiencing negative symptoms in the context of schizophrenia.

In three studies among patients with obsessive-compulsive disorder, which made use of varying TMS paradigms, the effects of rTMS were equal to sham treatment. The population samples were small, with a total number of 38 patients.

Side effects reported for different indications were headache, scalp discomfort, drowsiness, facial muscle twitching, tearfulness, dizziness and nausea. All side effects were transient and mild. The results suggest that high-frequency rTMS is associated with a higher percentage of drop-outs and side effects than low-frequency rTMS. Repetitive TMS directed at the DLPF appears to be accompanied with more dropouts and side effects than rTMS directed at the temporoparietal cortex. Reasons for dropout were side effects and worsening of symptoms.

Results of three clinical trials using repetitive transcranial magnetic stimulation for the treatment of auditory verbal hallucinations

A meta-analysis of the effect of rTMS for auditory verbal hallucinations revealed a moderate, significant effect size in favour of real TMS. We performed three studies in order to increase the efficacy of rTMS for auditory verbal hallucinations.

Repetitive TMS was applied to the left temporoparietal cortex in the majority of publications in the literature. This is in contrast with fMRI findings implying that in approximately 50% of the patients hallucinatory activity is found in the right hemisphere [14]. Could the efficacy of rTMS for auditory verbal hallucinations be increased if rTMS were to be directed at the area with maximal hallucinatory activation? The feasibility and efficacy of fMRI-guided rTMS were investigated in an open-label study. Details of this study are described in Chapter 4 of this thesis [15]. Valid hallucination-related activation maps were obtained in 12 out of 15 patients (80%). There was a significant effect over time, indicating a decrease in the severity of auditory verbal hallucinations in both groups, even ten weeks after cessation of the therapy; however, no differences in effect could be revealed between the two groups (fMRI-guided rTMS versus rTMS directed at the left temporoparietal cortex), but the sample was too small to provide a good reflection of possible group differences.

Based on these promising findings, a randomized controlled trial was performed with 62 patients divided over three conditions: fMRI-guided rTMS, rTMS directed at the left temporoparietal cortex, and sham treatment; rTMS was applied in a frequency of one hertz, with 12,000 stimuli per session during three weeks (i.e. 15 sessions in total). This study was described in Chapter 5 [16]. The effects of fMRI-guided rTMS on the severity of auditory verbal hallucinations and other psychotic symptoms were comparable to those of rTMS directed at the left temporoparietal area, and of sham treatment.

In addition, the effects of priming rTMS (i.e. low-frequency rTMS preceded by a brief period of high-frequency rTMS) was investigated in a randomized controlled trial with low-frequency rTMS directed at the left temporoparietal area as a control condition. The details of that study were presented in Chapter 6 [17]. Twenty-three patients were included; no significant benefits of priming rTMS were found.

7.2.2 Methodological considerations

This paragraph provides a summary of the limitations and strengths of the meta-analyses of psychiatric disorders and symptoms and clinical trials considering rTMS for auditory verbal hallucinations.

Meta-analyses considering repetitive transcranial magnetic stimulation in the treatment of psychiatric disorders and symptoms

For the indications auditory verbal hallucinations, negative symptoms of schizophrenia and obsessive-compulsive disorder the number of patients and studies that were included in the meta-analyses were low. Another matter of concern is that patients experienced medication-resistant auditory verbal hallucinations in 80% of the studies in our meta-analysis. The literature proposed medication-resistance to be associated with smaller effect sizes, but this could not be confirmed in three meta-analyses considering rTMS for depression [17, 18, 24].

Strengths of these meta-analyses were the exploration of new indications for rTMS treatment (negative symptoms of schizophrenia and obsessive-compulsive disorder) and the exclusion of cross-over studies. Second, subanalyses were performed of rTMS as monotherapy, rTMS as an adjunctive to antidepressant medication, and rTMS started simultaneously with an antidepressive agent. Furthermore, this study provides more evidence that ECT is superior to rTMS in contrast to the previous meta-analysis by Burt and colleagues [19], who found no significant differences between ECT and rTMS.

Limitations and strengths of three clinical trials using repetitive transcranial magnetic stimulation for the treatment of auditory verbal hallucinations

Limitations of the pilot study exploring the effect of fMRI-guided rTMS for auditory verbal hallucinations were the small patient sample, the lack of randomization and the open-label design.

Based on the results of four meta-analyses, we chose for a randomized, sham-controlled design with three arms to investigate the additional effect of fMRI-guided rTMS. Had we known that the effect of the standard paradigm, i.e. low-frequency rTMS directed at the left temporoparietal area, was lower, we would have investigated standard TMS versus sham treatment only with the same patient number. A strength of this study was the long follow-up period. Furthermore, we checked if the patients indeed were blind for

their treatment condition. The outcome confirms that the study was well blinded as the vast majority of patients in all three groups expected to have had active rTMS treatment.

Small patient samples were included to participate into the priming study. But as not even the slightest change could be shown in the severity of auditory verbal hallucinations in the priming group, we should have included an infinite number of patients to change the results of this study. A disadvantage is that the patients could not be blinded for their treatment condition as they were able to hear the rhythm of the rTMS treatment. But no expectations or motivated explanations were given about either treatment conditions until after completion of all the follow-up visits.

7.2.3 Meaning of findings

Repetitive transcranial magnetic stimulation for psychiatric disorders and symptoms

The mean effect size found for rTMS treatment in depression (i.e. 0.55) is relatively high when compared to effect sizes commonly reported for pharmacotherapy in depression (i.e. between 0.17 and 0.46) [19-23], which is in line with other meta-analyses on this subject (0.59 to 0.67) [19, 25, 26]. A recent meta-analysis of randomized controlled trials with only high-frequency rTMS directed at the left dorsolateral prefrontal cortex revealed a lower mean effect size of 0.39 [18]. A separate analysis of low-frequency rTMS applied to the right DLPF resulted in a mean effect size of 0.63 [27].

The results imply that high-frequency rTMS directed at the left DLPF, low-frequency rTMS directed at the right DLPF, and a combination of the two, are valuable treatment options for therapy-resistant depression, especially for depression without psychotic features. In these studies rTMS was used as monotherapy, and in combination with an antidepressive agent.

However, ECT is superior to rTMS in the treatment of depression.

The majority of studies included medication-resistant patients, who are thought to have a relatively small chance of improvement [28]. However, no differences in effect were found between medication-resistance and nonmedication-resistance in a meta-analysis exploring TMS for depression [17] and our own meta-analysis.

We now continue on the subject negative symptoms of schizophrenia. A trend was observed toward efficacy of rTMS directed at the left DLPF. But the number of included studies was low; therefore one needs to be careful with the interpretation of the results. However, the inclusion of two more recent randomized controlled trials resulted in a significant mean effect size of 0.43 in favour of real rTMS [29]. This result is very welcome as treatment options for negative symptoms of schizophrenia are poor.

No significant effect of rTMS could be revealed for obsessive-compulsive disorder, but different paradigms were used and only three studies could be included with small patient samples. No firm conclusions can be drawn, but a recent randomized controlled

trial with thirty patients regarding high-frequency rTMS directed at the left DLPF during 6 weeks, was not superior to sham treatment [30]. Therefore, rTMS appears not to be effective in the treatment of obsessive-compulsive disorder.

Repetitive transcranial magnetic stimulation for auditory verbal hallucinations

The results of our meta-analysis are in line with two other meta-analyses, which found a moderate effect size (i.e. 0.51 and 0.76) for the effectiveness of rTMS for auditory verbal hallucinations [31, 32]. The mean effect size of 1.0 reported by Freitas and colleagues can be explained by the inclusion of open-label studies in their meta-analysis [33].

The results of our own meta-analysis are not quite in accordance with the negative results of our randomized controlled study [16]. With the inclusion of this study, as well as two other recent studies [34, 35], the mean effect size will decrease to 0.37 ($p = 0.002$) for all ten studies, and to 0.42 ($p = 0.006$) for studies in which the left temporoparietal cortex was the focus of treatment, in favour of real TMS. It appears that the effects of rTMS decline with an increase of the number of randomized controlled trials. This may be due to a positive-outcome or publication bias, i.e. the increased likelihood that studies with a favourable or statistically significant outcome will be published rather than studies of a similar quality that show unfavourable or 'no-difference' results [36]. In addition, there is a trend of effect sizes to decrease with the year of publication [37]. As can be seen in the scatter plot in Figure 7.1, two small studies with negative results were included and it

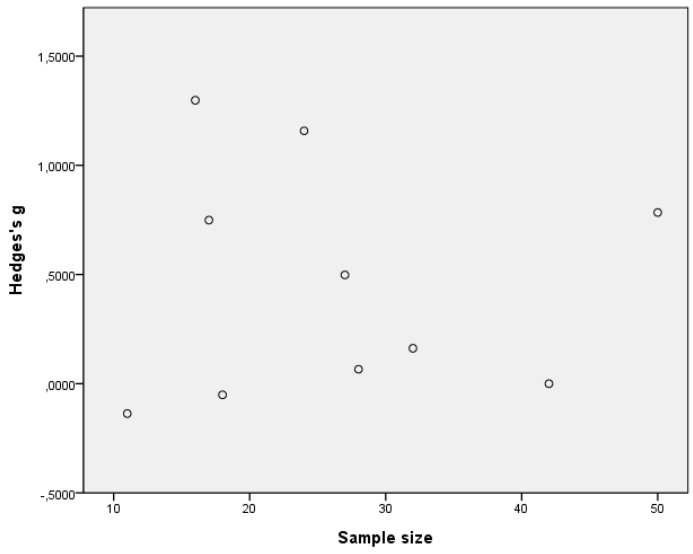

Figure 7.1 Scatter plot of sample size versus the effect size of studies using low-frequency rTMS directed at the left temporoparietal cortex for auditory verbal hallucinations

appears that the effect sizes decline with an increase of the patient number. Therefore, we expect that the mean effect size will decrease further with the inclusion of more randomized controlled trials with larger patient samples, and that many more studies will be needed to change the negative results into 'nonsignificant'.

Priming rTMS and rTMS directed at the area with maximal hallucinatory activation appear not to be effective in the treatment of auditory verbal hallucinations, but larger studies are needed to confirm these results.

7.2.4 Implications for future research considering repetitive transcranial magnetic stimulation for psychiatric disorders

Implications for future research and treatment in depression, negative symptoms of schizophrenia and obsessive-compulsive disorder

Now that rTMS has been acknowledged by the Food and Drug Administration as a treatment method for depression - albeit with a moderate mean effect size - it is of the utmost importance to improve its efficacy. With an increase of studies using low-frequency rTMS directed at the right DLPF in the future, a more benevolent effect may be found for treatments according to this paradigm, especially when compared to high-frequency rTMS applied to the left DLPF. This may be good news for patients receiving rTMS, because the latter paradigm is associated with more side effects.

Which measures can be made to increase the efficacy of rTMS? Higher precision can be achieved with the aid of individual fMRI-guided stimulation, especially as compared to less sophisticated approaches, including the placement of the coil using the international 10/20 EEG electrode system [38]. Therefore, it is to be expected that effect sizes may benefit from neuroimaging guidance [39].

Studies considering other brain regions as a focus for rTMS are sparse; Schutter et al. explored the effect of rTMS on the parietal cortex in a randomized, sham-controlled study; no differences in severity of depression were revealed between the two conditions, but the number of partial clinical responders was higher in the real TMS group [40].

Fitzgerald et al. found a positive effect in favour of priming rTMS for depression in a randomized, sham-controlled trial [41], but these findings need to be replicated.

As an alternative for the figure-of-eight coil (used in most randomized controlled trials), an H1 coil is designed to maximize the electrical field in deep brain tissues by the summation of separate fields projected into the skull from several points around its periphery [42]. This deep brain TMS appears to be effective in the treatment of depression [43, 44], but no randomized, sham-controlled trials have been performed so far.

Few studies explored the duration of effect of rTMS for depression, which is estimated at several weeks [45]. Maintenance rTMS treatment is only investigated in case studies and open label studies.

Finally, the effect of rTMS on negative symptoms of schizophrenia and obsessive-compulsive disorder needs to be further explored as the number of studies was low.

Implications for future treatments with repetitive transcranial magnetic stimulation for auditory verbal hallucinations

The effects of rTMS depend on the following variables: focus of treatment, frequency, percentage of the motor threshold, number of stimuli and sessions, and the type of coil that is being used. Only few studies examined the effect of low-frequency rTMS targeted at other brain regions than the left temporoparietal cortex. One study reported reductions in severity of auditory verbal hallucinations after rTMS directed at the right temporoparietal cortex [46], but this was not replicated by others [47, 48]. Repetitive TMS treatment of the bilateral temporoparietal regions revealed no significant differences in comparison with sham treatment [35]. Likewise, stimulation of Broca's area or the left superior temporal gyrus [49] was no more effective than sham treatment. Hoffman and colleagues [50] stimulated the left temporoparietal cortex and the adjacent supramarginal gyrus, Broca's area, the left primary auditory cortex and their contralateral homologues with rTMS. Only rTMS delivered to the left temporoparietal cortex and the adjacent supramarginal gyrus yielded a greater improvement of auditory verbal hallucinations than sham stimulation.

Functional MRI-guidance may provide a higher precision to focus rTMS treatment [38].

All randomized controlled trials involved in the treatment of auditory verbal hallucinations applied rTMS in a frequency of one hertz. In one open label study high-frequency rTMS directed at the left superior temporal sulcus reported successful treatment of auditory verbal hallucinations [51]. There are currently no published studies comparing high-frequency rTMS to sham treatment. The effect of theta-burst stimulation, which involves three 50-hertz pulses repeated every 200ms, is a relatively new rTMS protocol that modulated activity in the underlying region in a shorter period of time, enabling more potent and longer-lasting post stimulation effects compared with standard rTMS [52, 53]. No clinical trials for auditory verbal hallucinations (or depression) have been performed on this subject until now. One open label study revealed a positive effect of theta-burst stimulation directed at the cerebellar vermis on the negative subscale of the Positive And Negative Syndrome Scale in eight treatment-refractory patients with schizophrenia [54].

It would be of interest to apply rTMS with a motor threshold of more than 100% as higher motor thresholds appear to be associated with a longer duration of effect [55] and

so far motor thresholds between 80 and 100% have only been investigated in the treatment of auditory verbal hallucinations.

A greater number of sessions has been associated with increased rTMS efficacy [45, 56-59], but this has not resulted in a better outcome in the treatment of auditory verbal hallucinations [16, 31, 35].

In contrast with the figure-of-eight coil used in the randomized controlled trials, Rosenberg and colleagues investigated the effect of deep transcranial magnetic stimulation with an H1 coil apparatus in an open label study, demonstrating a significant improvement in the severity of hallucinations [60]. The results are promising but need to be replicated in randomized, sham-controlled trials.

7.2.5 Repetitive transcranial magnetic stimulation in the treatment of psychiatric disorders and symptoms: conclusions

Repetitive TMS is effective in the treatment of depression in the form of monotherapy, as well as in combination with (simultaneous onset of) antidepressive agents. Significant mean effect sizes in favour of real TMS were found for the paradigms 'high-frequency rTMS directed at the left DLPF', 'low-frequency rTMS directed at the right DLPF', and a combination of the two. However, ECT is superior to rTMS, and the effects of rTMS are stronger in studies that explicitly excluded patients with psychotic symptoms.

Future studies should aim at improving the efficacy of TMS by exploring the effects of bilateral TMS and other treatment paradigms, by stimulating other brain areas (such as the parietal cortex and the cerebellum) and by exploring the effects of deep-brain TMS.

Repetitive TMS might be better than sham treatment for negative symptoms of schizophrenia but is not superior to sham treatment for obsessive-compulsive disorder. More studies are warranted to further explore these two indications.

With the increase of larger studies with negative results, the effect of rTMS for auditory verbal hallucinations is declining but still significant. This does not indicate that rTMS may not be beneficial for auditory verbal hallucinations. Future studies should explore other paradigms with higher motor thresholds, theta-burst stimulation, and deep-brain TMS.

7.3 CONCLUSIONS

1. Patients with borderline personality disorder experience auditory verbal hallucinations in a frequency, duration and distress that is comparative to patients with those in schizophrenia/schizoaffective disorder. As auditory verbal hallucinations in patients with borderline personality disorder fulfil the criteria for hallucinations proper, we propose to use the term auditory verbal hallucinations for this patient

group, as inappropriate naming may induce trivializing of hallucinations in borderline personality disorder and prevent adequate treatment.

2. Repetitive transcranial magnetic stimulation (rTMS) is effective in the treatment of depression, although electroconvulsive therapy was superior to rTMS. A trend was observed toward efficacy of rTMS treatment for negative symptoms of schizophrenia and the effect of rTMS on obsessive-compulsive disorder was not superior to sham treatment, but more studies are needed to confirm these results.
3. Our meta-analysis implies that low-frequency rTMS directed at the left temporoparietal area has a moderate effect on auditory verbal hallucinations. This is in contrast with the negative results of the randomized sham-controlled trial we have performed on this subject; rTMS directed at the left temporoparietal area, at the focus with maximal hallucination activation and sham rTMS revealed no significant differences on any of the measurements. We expect the mean effect size will further decrease with the inclusion of more randomized controlled trials with larger patient samples.
4. Priming rTMS (it is low-frequency rTMS preceded by a brief period of high-frequency rTMS) directed at the left temporoparietal area is not effective in the treatment of auditory verbal hallucinations.
5. The above mentioned in 3. and 4. does not indicate that rTMS should not be used in the treatment of auditory verbal hallucinations; a number of paradigms have not been (fully) investigated, such as high-frequency rTMS (theta-burst rTMS), rTMS with a higher percentage of the motor threshold and deep brain TMS.

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Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Een jonge vrouw was in behandeling vanwege een borderline persoonlijkheidsstoornis. Zij hoorde met enige regelmaat een stem van degene die haar seksueel had misbruikt in het verleden. De stem zei dat ze maar beter een einde kon maken aan haar leven; ze had al twee keer een suïcidepoging gedaan. Haar familie geloofde niet dat ze stemmen hoorde.

Wat was er met deze vrouw aan de hand? Had zij schizofrenie of een andere psychotische stoornis? Hier begon mijn interesse voor auditieve verbale hallucinaties, het horen van stemmen zonder externe oorzaak.

In dit proefschrift zullen allereerst de karakteristieken en de lijdensdruk van auditieve verbale hallucinaties bij patiënten met een borderline persoonlijkheidsstoornis worden gepresenteerd. In het overige deel van het proefschrift zal het effect van repetitieve transcraniële magnetische stimulatie (rTMS) op de ernst van auditieve verbale hallucinaties en andere psychiatrische stoornissen en symptomen worden besproken.

Auditieve verbale hallucinaties komen veelvuldig voor bij schizofrenie. De meeste kennis omtrent auditieve verbale hallucinaties is dan ook afkomstig van patiënten die bekend zijn met deze diagnose. Bij schizofrenie is sprake van psychotische verschijnselen (waaronder dingen waarnemen die er niet zijn, denkbeelden hebben die niet realistisch zijn en taalproblemen) en negatieve symptomen (zoals moeite hebben om activiteiten te plannen en te ondernemen en verlies van sociale contacten). Auditieve verbale hallucinaties komen niet alleen voor bij schizofrenie, maar ook bij andere psychiatrische aandoeningen zoals een depressie, manisch-depressieve stoornis en middelenmisbruik. Mensen kunnen veel last hebben van deze stemmen wanneer de stemmen een negatieve inhoud hebben en dat is vaak het geval bij patiënten met een psychiatrische diagnose. Onder invloed van auditieve verbale hallucinaties kunnen zij zichzelf of anderen zelfs ernstige schade berokkenen of zich van het leven beroven. Het spreekt voor zich dat deze patiënten behandeling nodig hebben hetgeen hoge kosten voor de maatschappij met zich mee brengt. Mensen kunnen ook stemmen horen zonder een psychiatrische diagnose; de stemmen hebben dan vaak een positieve inhoud en de lijdensdruk is meestal laag. In dat geval is geen behandeling nodig. Tot slot kunnen auditieve verbale hallucinaties voorkomen bij een afwijking in de hersenen zoals een tumor of wanneer iemand hardhorend of doof is.

Ook patiënten met een borderline persoonlijkheidsstoornis kunnen stemmen horen, maar daar is nog weinig over bekend. Er is sprake van een borderline persoonlijkheidsstoornis wanneer iemand last heeft van forse stemmingswisselingen gepaard gaand met heftig verlopende sociale contacten en in het bijzonder intieme relaties, een sterke

wisseling in het gevoel wie je bent en wat je wilt, forse impulsiviteit en woedeaanvallen. In een studie met 33 patiënten werd gevonden dat 50% van de patiënten met een borderline persoonlijkheidsstoornis stemmen hoort. In slechts één studie, met 15 patiënten met een borderline persoonlijkheidsstoornis, werden weinig verschillen qua fenomenologische karakteristieken en lijdendruk gevonden in vergelijking met auditieve verbale hallucinaties bij patiënten met schizofrenie. Deze resultaten impliceren dat het horen van stemmen bij de borderline persoonlijkheidsstoornis voldoet aan de criteria voor hallucinaties, maar vaak worden psychotische verschijnselen in deze populatie geduid als 'pseudohallucinaties' of 'quasipsychose', terwijl deze termen slecht zijn geoperationaliseerd.

In hoofdstuk 2 worden de resultaten vermeld van een studie naar de aard van auditieve verbale hallucinaties en de lijdensdruk die zij veroorzaken bij patiënten met een borderline persoonlijkheidsstoornis; deze resultaten worden vergeleken met de bevindingen bij patiënten met schizofrenie/schizoaffectieve stoornis en individuen die stemmen horen zonder een psychiatrische diagnose. Drieëndertig patiënten met een borderline persoonlijkheidsstoornis, 51 patiënten met schizofrenie of een schizoaffectieve stoornis en 66 individuen zonder psychiatrische diagnose werden geïncludeerd. Patiënten met een borderline persoonlijkheidsstoornis ervoeren auditieve verbale hallucinaties gedurende een gemiddeld aantal van 17 jaren, in een gemiddelde frequentie van eenmaal per dag of vaker en langer dan enkele minuten. Bij de meerderheid werden de stemmen door de patiënten toegeschreven aan een interne oorzaak. De lijdensdruk was hoog en er werd weinig controle over de stemmen ervaren.

Er werden geen verschillen gevonden ten aanzien van de aard van auditieve verbale hallucinaties en de daaruit voortkomende lijdensdruk tussen patiënten met een borderline persoonlijkheidsstoornis en patiënten met schizofrenie/schizoaffectieve stoornis, met uitzondering van het item 'verstoring van het leven', waarop de laatste patiëntengroep hoger scoorde. Daarentegen werden grote verschillen voor bijna alle items gevonden tussen auditieve verbale hallucinaties bij patiënten met een borderline persoonlijkheidsstoornis en stemmenhoorders zonder psychiatrische diagnose.

Het is daarom niet terecht om auditieve verbale hallucinaties bij patiënten met een borderline persoonlijkheidsstoornis als pseudohallucinaties aan te duiden.

Derhalve moeten behandelaren van patiënten met een borderline persoonlijkheidsstoornis vragen naar de aanwezigheid en de eventuele last van auditieve verbale hallucinaties. Bovendien is onderzoek nodig naar het voorkomen en de ernst van andere psychotische verschijnselen bij deze populatie. Ook is het van belang om te onderzoeken of de etiologie van auditieve verbale hallucinaties bij een borderline persoonlijkheidsstoornis overeenkomsten vertoont met die van auditieve verbale hallucinaties bij schizofrenie. Maar bovenal moet aandacht worden besteed aan onderzoek naar

de behandeling van auditieve verbale hallucinaties en eventuele andere psychotische verschijnselen bij patiënten met een borderline persoonlijkheidsstoornis.

Bij psychotische stoornissen is de behandeling van auditieve verbale hallucinaties en andere psychotische verschijnselen reeds uitgebreid onderzocht. Antipsychotica zijn daarbij de behandeling van eerste keus. Deze behandeling is effectief bij 70 tot 75% van de patiënten. Bij 25 tot 30% helpen antipsychotica echter niet afdoende, terwijl deze patiënten veel last kunnen ervaren van hun auditieve verbale hallucinaties. Bovendien kunnen patiënten last krijgen van bijwerkingen van antipsychotica, waaronder een toename in gewicht, gestoorde glucose- en/of vethuishouding, forse sedatie of bewegingsstoornissen.

Sinds 1996 wordt repetitieve transcraniële magnetische stimulatie (rTMS) onderzocht als behandeling voor psychiatrische aandoeningen, met name bij een depressie. Bij rTMS worden kortdurende, sterke elektrische stroompulsen door een spoel gestuurd, hetgeen een snel wisselend magnetisch veld oplevert, waarmee de hersenactiviteit kan worden beïnvloed. De methode is veilig en de bijwerkingen zijn mild en van korte duur; de meest genoemde bijwerkingen zijn hoofdpijn en het aanspannen van de aangezichtsmusculatuur ten tijde van de rTMS-behandeling. Omdat rTMS de werking van de gehoorszenuw kan beïnvloeden, wordt een oordop gedragen tijdens de behandeling. In het verleden trad een enkele keer een epileptische aanval op tijdens of kort na de TMS-behandeling; sinds een veiligheidsrichtlijn is ontwikkeld, komt deze bijwerking nog maar zeer zelden voor.

Inmiddels zijn meerdere gerandomiseerde, placebo-gecontroleerde studies verschenen naar het effect van rTMS op depressie, auditieve verbale hallucinaties en negatieve symptomen van schizofrenie, met wisselende resultaten. Repetitieve TMS wordt bijna altijd ingezet voor patienten die onvoldoend reageren op medicijnen. Het gaat dus om een groep met hardnekkige symptomen.

In hoofdstuk 3 worden de resultaten van een meta-analyse naar het effect van rTMS op psychiatrische aandoeningen en symptomen gepresenteerd. Een meta-analyse is een statistische methode waarmee het gemiddelde effect van een behandeling kan worden berekend. Daaruit kwam naar voren dat rTMS beter is dan placebo voor de behandeling van een depressie wanneer rTMS wordt toegepast als monotherapie, in combinatie met het continueren van een antidepressivum of in combinatie met een gelijktijdige start van een antidepressivum. Repetitieve TMS is werkzaam voor de volgende paradigma's: hoogfrequente TMS gericht op de linker frontale cortex, laagfrequente TMS gericht op de rechter frontale cortex en de combinatie van deze twee. Het effect van rTMS is groter bij depressieve patiënten zonder psychotische verschijnselen en elektroconvulsieve therapie werkt beter dan rTMS.

Bij auditieve verbale hallucinaties werd een matig, significant effect gevonden voor echte TMS-behandeling ten opzichte van placebo. Repetitieve TMS werd daarbij gegeven in een frequentie van 1 hertz en met name gericht op de linker temporopariëtale cortex.

Er werd een trend gevonden voor een beter effect van rTMS versus placebo voor de indicatie negatieve symptomen van schizofrenie. Dit is een belangrijke bevinding aangezien er weinig behandelopties bestaan voor deze indicatie.

Het effect van rTMS was gelijk aan dat van placebo bij de obsessieve-compulsieve stoornis. Hierbij moet vermeld worden dat het aantal studies voor de laatste drie indicaties laag was. Derhalve moet men voorzichtig zijn met het interpreteren van deze resultaten.

De resultaten van de meta-analyse naar het effect van rTMS op auditieve verbale hallucinaties zijn positief. Zou het effect van rTMS kunnen worden vergroot door de spoel te richten op het gebied met de meeste hersenactiviteit tijdens het ervaren van auditieve verbale hallucinaties? Deze vraagstelling berust op de bevinding dat bij meer dan 50% van de mensen de meeste hersenactiviteit gelegen is in de rechterhemisfeer tijdens het ervaren van auditieve verbale hallucinaties, terwijl de in het verleden onderzochte TMS-behandelingen op de linker hemisfeer waren gericht. Aangezien TMS de hersenactiviteit met name lokaal beïnvloedt, zou dat betekenen dat deze behandeling bij een aanzienlijk percentage op de verkeerde plaats werd gegeven. In hoofdstuk 4 en 5 worden twee studies beschreven die de toegevoegde waarde van functionele magnetische resonantie imaging (fMRI) voor de behandeling van auditieve verbale hallucinaties onderzochten.

In een open label studie werd rTMS gericht op het gebied met de meeste hersenactiviteit tijdens het ervaren van auditieve verbale hallucinaties vergeleken met rTMS gericht op de linker temporopariëtale cortex, het paradigma dat veelvuldig werd toegepast in de literatuur (standaard behandeling). Bij 12 van de 15 patiënten kon de fMRI-scan worden gebruikt als focus voor de behandeling. Bij een vergelijking van zes patiënten die een standaard behandeling kregen met zeven patiënten die een fMRI-geleide behandeling kregen werd een significante afname van de ernst van auditieve verbale hallucinaties aangetoond voor beide groepen. Er werd geen significant verschil in effect gevonden tussen de twee groepen, maar dat is bij zulke kleine aantallen ook niet te verwachten. Deze fMRI-gestuurde manier van TMS-behandeling bleek in elk geval technisch haalbaar.

Op grond van deze positieve resultaten werd een gerandomiseerde, placebo-gecontroleerde studie uitgevoerd, waarbij de fMRI-gerichte rTMS (n = 20) werd vergeleken met standaard rTMS-behandeling (n = 22) en placebobehandeling (n = 20). Geen enkel significant verschil kon worden aangetoond in effect tussen de drie behandelcondities

op de verschillende vragenlijsten voor ernst en hinder van auditieve verbale hallucinaties en andere psychotische verschijnselen.

Uit het bovenstaande blijkt dat fMRI-geleide rTMS-behandeling geen beter effect heeft op de behandeling van auditieve verbale hallucinaties dan een placebobehandeling. Echter, ook 'standaard' rTMS-behandeling bleek niet beter tegen hallucinaties te werken dan een placebo behandeling. Het lijkt er dus op dat rTMS gegeven in een frequentie van 1 hertz niet effectief is tegen hallucinaties, ondanks eerdere positieve bevindingen. Zou een verandering van de frequentie van de rTMS van toegevoegde waarde kunnen zijn voor de behandeling van auditieve verbale hallucinaties? Deze onderzoeksvraag komt voor uit de bevinding dat een behandeling met priming rTMS (laagfrequente TMS voorafgegaan door hoogfrequente rTMS) een beter effect heeft op depressies dan laagfrequente rTMS alleen. Dit onderzoek werd beschreven in hoofdstuk 6. Na randomisatie werden 12 patiënten behandeld met laagfrequente rTMS gericht op de linker temporopariëtale cortex en 11 met priming TMS met eenzelfde focus van behandeling. Priming rTMS gaf echter geen afname van de ernst van auditieve verbale hallucinaties of andere psychotische verschijnselen. Ook werd geen verschil in effect gevonden tussen de twee behandelcondities.

Samenvattend kon geen positief effect worden aangetoond van fMRI-geleide rTMS en ook niet van priming rTMS op de ernst van auditieve verbale hallucinaties. Bovendien was het effect van laagfrequente rTMS gericht op de linker temporopariëtale cortex vergelijkbaar met dat van placebo. Dit is in tegenspraak met de resultaten van de meta-analyse waarbij een matige, significante effectgrootte werd gevonden voor rTMS ten opzichte van placebo.

Hoe is dat mogelijk? Een verklaring zou kunnen zijn dat kleine studies met positieve resultaten eerder worden gepubliceerd dan kleine studies met negatieve resultaten. Ook wordt vaker gezien dat de gemiddelde effectgrootte afneemt naarmate grotere studies worden geïncludeerd. Dit laatste speelt in ieder geval een rol bij de studies naar het effect van rTMS op auditieve verbale hallucinaties; wanneer drie meer recent verschenen studies aan de meta-analyse worden toegevoegd (waaronder de hierboven genoemde gerandomiseerde, placebo-gecontroleerde studie), daalt de effectgrootte van 0,52 naar 0,37. De verwachting is dat de effectgrootte in de toekomst nog verder zal afnemen.

Is rTMS nu zinvol voor de behandeling van auditieve verbale hallucinaties of niet?

Vele studies met grote patiëntenaantallen zijn nodig om het verschil tussen rTMS en placebo niet meer significant te laten zijn. Maar het is vooral belangrijk om de toegevoegde waarde van andere rTMS-paradigma's te onderzoeken zoals zeer hoogfrequente rTMS (bijvoorbeeld thetaburst), deep brain TMS en rTMS gegeven met een hogere intensiteit.

CONCLUSIES

1. Patiënten met een borderline persoonlijkheidsstoornis kunnen langdurig en frequent auditieve verbale hallucinaties ervaren en daar veel hinder van ondervinden. Er zijn vrijwel geen verschillen te vinden tussen auditieve verbale hallucinaties bij patiënten met een borderline persoonlijkheidsstoornis en schizofrenie. Auditieve verbale hallucinaties bij patiënten met een borderline persoonlijkheidsstoornis voldoen daarom aan de criteria voor echte hallucinaties en het is dan ook een kunstfout om deze tot pseudohallucinaties te bestempelen. Derhalve is het van belang om meer aandacht te besteden aan het voorkomen, de lijdensdruk en de behandeling van auditieve verbale hallucinaties bij deze populatie.
2. Repetitieve TMS - als monotherapie of in combinatie met een antidepressivum - is effectief voor de behandeling van depressies, maar minder goed dan elektroconvulsieve therapie. Het effect van rTMS is groter dan placebo voor de behandeling van negatieve symptomen van schizofrenie, maar dit verschil is niet significant. Een positief effect van rTMS op de obsessieve-compulsieve stoornis kon niet worden aangetoond, maar het aantal studies was dan ook klein.
3. De meta-analyse naar het effect van rTMS op auditieve verbale hallucinaties heeft geresulteerd in een matige, significante effectgrootte van laagfrequente TMS gericht op de linker temporopariëtale cortex ten opzichte van placebo. Dit in tegenstelling tot de resultaten van de gerandomiseerde, placebo-gecontroleerde studie, waarbij het effect van rTMS gericht op de linker temporopariëtale cortex en rTMS gericht op het gebied met de meeste hersenactiviteit tijdens het ervaren van auditieve verbale hallucinaties vergelijkbaar was met de placeboconditie.
   Met de toevoeging van recent verschenen studies neemt de gemiddelde effectgrootte van rTMS tegen auditieve verbale hallucinaties af.
4. Priming rTMS (i.e. laagfrequente rTMS voorafgegaan door kortdurende hoogfrequente TMS) gericht op de linker temporopariëtale cortex lijkt niet effectief bij de behandeling van auditieve verbale hallucinaties.
5. Het onder 3. en 4. genoemde wil niet zeggen dat rTMS geen zinvolle behandeloptie zou kunnen zijn voor auditieve verbale hallucinaties, aangezien het effect van verscheidene paradigma's nog (vrijwel) niet is onderzocht, zoals hoogfrequente rTMS (thetaburst TMS), rTMS uitgevoerd met een relatief hoog percentage van de motorische drempelwaarde en deep brain TMS.

Dankwoord

DANKWOORD

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LIST OF PUBLICATIONS

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CURRICULUM VITAE

Karin Slotema werd op 11 maart 1972 geboren in Leiden. In 1990 behaalde zij haar vwo-diploma aan het Rijnlands Lyceum te Wassenaar en begon zij aan de studie Geneeskunde aan het Universitair Medisch Centrum Utrecht. In 1998 behaalde zij haar arts-examen en ging zij als arts-assistent werken op de afdeling Neurologie van het Academisch Medisch Centrum te Amsterdam. Aldaar deed zij onderzoek naar polyneuropathie, in samenwerking met het Universitair Medisch Centrum Utrecht. In 1999 ging zij als arts-assistent werken bij de afdeling Neurologie van het Haga Ziekenhuis te Den Haag en in 2001 begon zij aan haar opleiding tot neuroloog. Na een stage in de acute psychiatrie maakte zij in 2003 een overstap naar de psychiatrie en rondde zij in 2007 de opleiding tot psychiater af bij de Parnassia Bavo Groep te Den Haag, met als opleider prof. dr. H.W. Hoek. Tijdens de opleiding verrichtte zij onderzoek naar de behandeling van orofaciale tardieve dyskinesieën met behulp van botuline toxine onder leiding van prof.dr. P.N. van Harten en prof.dr. H.W. Hoek. Vanaf 2006 werkte zij aan haar promotieonderzoek. Zij verkreeg hiervoor in 2007 een OOG-subsidie van ZonMW (Opleiding Onderzoekers in de GGZ). Sinds mei 2007 is zij als psychiater werkzaam bij het Programma voor PersoonlijkheidsProblematiek van PsyQ Haaglanden, onderdeel van de Parnassia Bavo Groep te Den Haag.