Auditory verbal hallucinations and the brain

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Colofon

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Auditieve verbale hallucinaties en het brein
(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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Remko van Lutterveld

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Prof.dr. R.S. Kahn

Voor mijn ouders

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Chapter 1

General introduction

"Tomorrow you have to burn down the library. This is very important to change the world order. If you don't do this your children will fall ill and you won't be able to go on holiday.

You just have to burn down the library.
You just have to burn down the library."

Mr. A. hears voices like this almost continuously. These voices are very loud and appear very real – yet no-one else is able to hear them. Mr. A. suffers from auditory verbal hallucinations (AVH) and is diagnosed with schizo-affective disorder. One can imagine that these voices severely impact his daily life and functioning.

AVH are generally thought to be related to mental illness. As such, it may come as a surprise that many well-known influential people heard voices. In ancient times, Pythagoras and Socrates both experienced AVH. Socrates called his voice the daimonion ("the divine"), as it issued warnings if he was about to act in a way that was not in his best interest. In the Middle Ages, Joan of Arc's voices helped her win battles for France against the English. In modern history Winston Churchill and Mahatma Ghandi heard voices. In fact, AVH are a fairly ordinary phenomenon. A rather large minority of the general population regularly experiences AVH. The commonness of this symptom is illustrated by the fact that its prevalence is similar to the percentage of people with red hair in the Netherlands.

1. Auditory verbal hallucinations

Auditory verbal hallucinations (AVH) are defined as perceptions of speech without actual auditory stimulation. These hallucinations can be very diverse across individuals. They can differ in many aspects, such as frequency, duration, loudness, and emotional valence of the voices (Daalman et al., 2011). Even within an individual the characteristics of AVH can be highly different since duration and frequency often fluctuate during the day.

AVH are encountered in several populations. They may be a symptom in neurological or neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, hearing loss, and epilepsy (Bassiony et al., 2000; Gloor et al., 1982; Matsui et al., 2007; Sommer et al., 2012). AVH also frequently occur in psychiatric disorders such as bipolar disorder, major depressive disorder, borderline and schizotypal personality disorder (Baethge et al., 2005; Kingdon et al., 2010).

However, AVH are most well-known in the context of schizophrenia. AVH are a core symptom of this disorder, with the majority of patients (± 70%) experiencing AVH (Nayani and David, 1996; Slade and Bentall, 2002). These voices can be highly distressing and often severely affect quality of life. They also increase risk for suicide (Cheung et al., 1997; Falloon and Talbot, 1981).

Although AVH are prevalent in several neurologic and psychiatric disorders, they are not inevitably associated with disease. Studies employing strict definitions of hearing a voice report that between 2-4% of the general population experiences AVH without a need for care (Beavan et al., 2011). This observation has led several authors to hypothesize that clinical and non-clinical hallucinations are located on a continuum of psychotic symptoms, ranging from normal perceptual experiences to AVH experienced by psychiatric patients (Strauss, 1969; van Os et al., 2009). Auditory hallucinations in the general population can then be considered to take a halfway position on this scale.

2. Comparison of schizophrenia patients and non-psychotic individuals

The majority of research has focused on investigating AVH in schizophrenia. However, interpretation of the findings is hampered by various confounding factors. Schizophrenia patients often suffer from other symptoms related to their disease such as delusions, disorganization, and cognitive and negative symptoms (Tandon et al., 2009). Moreover, patients have generally used antipsychotic medication for many years. These confounds can be circumvented by investigating non-psychotic individuals with AVH, if we assume that AVH in this group are indeed a similar phenomenon on the spectrum of psychosis. These non-psychotic individuals experience AVH in relative isolation and thus do not have many of the additional symptoms observed in schizophrenia patients, nor do they use medication.

A first question then is whether AVH in patients and in the general population can be considered the same phenomenon. A recent study compared the phenomenology of non-psychotic individuals with AVH and schizophrenia patients. Both groups were similar in several characteristics of AVH. There were for instance no differences in the loudness and perceived

location of the voices. Moreover, the number of voices and the personification (attribution to a real and familiar person) of the voices was similar. However, several characteristics of AVH were different across groups. Frequency, emotional valence of the content, and the control over AVH were dissimilar. In addition, onset of AVH was at a significantly younger age in the non-psychotic individuals (Daalman et al., 2011). What these findings illustrate is that the phenomenology of AVH in both groups can at least partially be considered dissimilar. However, it remains unclear whether (partially) different pathophysiological mechanisms are at the basis of AVH in both groups. For instance, one may argue that certain differences in AVH characteristics, such as the negative emotional content and the lack of control, might be explained by other symptoms of schizophrenia, such as depression and anxiety, or cognitive dysfunction. Studies of brain activity related to AVH in both groups may shed more light on this issue. One neuroimaging study investigated this by assessing brain activity during AVH in patients and non-psychotic individuals. In this study, a similar pattern of activation was observed (Diederen et al., 2011), which implicates the involvement of the same cortical network in the experience of AVH in both groups, and is suggestive of similar underlying neurobiology of the symptom.

3. Neuroimaging and auditory verbal hallucinations

How does the brain generate AVH? At present, the exact pathophysiological mechanism remains unknown. However, neuroimaging studies have provided valuable information regarding brain activity related to AVH. These studies commonly use one of two main approaches to study this symptom. In the first strategy, hallucination episodes are contrasted with hallucination-free episodes to investigate the "state" of AVH. Using this symptom-capture approach, brain activity related to the experience of AVH can be investigated. The second strategy investigates the tendency or "trait" to hallucinate. This can be achieved by correlating overall severity of AVH with brain activity during a neuroimaging task. Alternatively, the trait to hallucinate can be investigated by comparing brain activity during a cognitive task or during the resting state between hallucinating and non-hallucinating individuals. However, this strategy is vulnerable to several confounds, such as the impact of antipsychotic medication.
The state and trait approaches have been investigated using neurophysiological methodologies such as electroencephalography (EEG) and magnetoencephalography (MEG), as well as with functional magnetic resonance imaging (fMRI).

3.1 Neurophysiology (EEG and MEG)

EEG and MEG are neuroimaging techniques that distinguish themselves from other methods by their excellent temporal resolution. Both are neurophysiological techniques that allow investigators to track brain activity on a millisecond time-scale. Moreover, they are silent techniques, ensuring that no external sounds interact with brain processes related to AVH.
EEG measures the electrical signals related to neuronal activity. When a group of neurons of sufficient size fires together, the resulting electrical discharges can be measured with EEG

sensors on the scalp. These electrical discharges also induce magnetic fields, which can be picked up by MEG sensors outside the head (Luck, 2005).
Although EEG and MEG originate from the same neurophysiological processes, there are several major differences. For instance, EEG is sensitive to both tangentially (parallel to the skull) and radially oriented sources, while MEG is only sensitive to tangentially oriented sources (Cohen and Cuffin, 1983). As the current sources in the brain are usually perpendicular to the cortical surface, EEG is sensitive to activity in both the sulci and the top of cortical gyri, while MEG is primarily sensitive to activity in the sulci of the brain. Another main difference is that the electrical signals picked up by EEG are smeared out by the skull and skin, theoretically interfering with accurate source localization. The magnetic signals picked up by MEG in contrast are hardly affected by these structures (Ramantani et al., 2006).
To date, four small studies have used EEG and MEG to localize brain activity related to the state of AVH. All showed changes in activity in the left superior temporal gyrus (Ishii et al., 2000; Reulbach et al., 2007; Ropohl et al., 2004; Sritharan et al., 2005). This is not a surprising finding, as this area is involved in auditory processing and AVH are in the auditory domain (Friederici et al., 2000). Neurophysiological studies investigating the trait to hallucinate produced heterogeneous results. For example, some studies observed correlations between event-related potentials (ERPs) and AVH, while others did not (Fisher et al., 2008b; Kasai et al., 2002; Schall et al., 1999; Youn et al., 2003)

3.2.1 Functional magnetic resonance imaging

3.2.1.1 Activation studies

In the last two decades fMRI has become a highly popular technique to map brain activity. Unlike EEG and MEG, it does not provide a direct measurement of neuronal activity. Instead, it measures the demand for oxygen related to activity in the brain. Its spatial resolution is excellent while its temporal resolution is in the seconds-range.
A recent meta-analysis investigating the state of AVH analyzed eight fMRI and two older positron emission tomography (PET) studies. This study implicated activation of speech-production areas, such as the bilateral inferior frontal gyri, as well as auditory and speech perception areas in the left hemisphere, such as the superior temporal gyrus and supramarginal gyrus. Furthermore, memory-related structures as the parahippocampal gyrus and the hippocampus became more active during the experience of AVH (Jardri et al., 2010). The trait to hallucinate, as measured by tasks in which the participant listened to verbal stimuli or generated inner speech, is related to decreased activation in areas involved in auditory processing and monitoring (Kuhn and Gallinat, 2011).

3.2.1.2 Functional connectivity studies

The activation studies described above emphasize the specialization of functions in brain regions. However, function generally emerges from the flow of information between brain

areas (Ramnani et al., 2004). This process can be investigated by assessing the relationship between neuronal activation patterns of anatomically separate regions, as this is suggested to reflect the level of functional communication between these areas (van den Heuvel et al., 2010). Lately, there is increasing interest in functional connectivity during resting-state scans. A major advantage of this approach is that the results are unlikely to be influenced by differences in performance between participant groups.
Several trait studies investigated functional connectivity related to AVH during resting state, with heterogeneous results. Some studies observed increases in connectivity, while others reported reduced connectivity. Also, the loci of aberrant connectivity varied among studies (Gavrilescu et al., 2010; Hoffman et al., 2011; Rotarska-Jagiela et al., 2010; Vercammen et al., 2010). Several factors could explain this diversity in results. The selection of different seed regions across studies is an obvious factor, while the presence of AVH during image acquisition may also have influenced results. Moreover, the use and dose of antipsychotic medication and the presence and severity of additional symptoms of schizophrenia are also likely sources of differences across studies.

4. Theories

A number of theoretical frameworks have been proposed to explain the origin of AVH. Three influential models explaining the genesis of AVH are presented below. These hypotheses offer the background for the studies in later chapters of this thesis.

4.1 Inner speech

An influential theory explaining the experience of AVH is that they arise from misattributing inner speech to external sources. Support for this model comes from neuroimaging state studies that consistently implicated speech-production and auditory and language perception areas during AVH (Jardri et al., 2010; Sommer et al., 2008). Additional support comes from EEG studies investigating the corollary discharge mechanism. With this mechanism, sensory areas get a "heads-up" from motor areas when a motor act is initiated. In this way, the sensory consequences of self-generated actions are suppressed (Sperry, 1950; Von Holst, 1950). For example, one cannot tickle oneself, as the forthcoming sensations were already forecast. Another example is the lacking response to changes in the visual field when these are initiated by head movements. The corollary discharge mechanism is also thought to be involved in thinking. In a similar vein, auditory and language perception areas are warned by the speech-production areas that a thought is self-generated. Malfunctioning of this system may then result in the erroneous labelling of inner speech as not coming from the self, resulting in the experience of AVH (Feinberg, 1978). Dysfunctional connectivity between frontal speech production areas and temporal language perception areas has indeed been observed in hallucinating patients (e.g. Ford and Mathalon, 2005).

4.2 Top-down/Bottom-up processing

A second theory focuses onto top-down and bottom-up processes. Bottom-up processes are driven by information coming from the sensory organs, while top-down processing describes the concurrent manipulation of this information by higher cognitive processes. These higher processes are based on expectations and internal hypotheses. For example, prior attained knowledge about the frequency of a target stimulus makes it easier to detect it.
Perhaps AVH originate from imbalances in top-down and/or bottom-up processing (Aleman et al., 2003; Behrendt, 1998; Fisher et al., 2008b; Frith and Done, 1988; Frith et al., 1992; Northoff and Qin, 2011). Indeed, several lines of research suggest that aberrations in top-down processing are related to the experience of AVH. For example, non-psychotic subjects with the tendency to experience hallucinations were more likely to report hearing a word that fit the sentence context when it was not presented (Vercammen and Aleman, 2008), and hallucinating patients with schizophrenia show increased sensitivity to speech stimuli in a signal detection task (Vercammen et al., 2008). Deviances in bottom-up processes related to AVH have also been found. For example, associations between an electrophysiological measure of automatic auditory processing and AVH have been reported (Fisher et al., 2008a; Fisher et al., 2008b; Youn et al., 2003).
A recently developed model includes both top-down and bottom-up influences in the genesis of AVH. This framework states that AVH arise at the intersection of bottom-up and top-down processing. Heightened resting-state activity in the auditory cortex (increased bottom-up processing) is influenced by a weakening of top-down control by prefrontal and other areas. This then leads to a breakdown in correct monitoring of auditory activity and to the experience of an auditory percept while no actual auditory stimulation took place (Allen et al., 2008).

4.3 Memory

A third framework stipulates that AVH result from spontaneous memory recollection. Support for this hypothesis comes from the fact that AVH are often highly repetitive, which suggests a memory component. Several cognitive studies have also highlighted the role of memory processes in the genesis of AVH. For example, Badcock et al (2005) observed that hallucinating patients made significantly more false alarms to distracters seen on previous runs of a recognition task, which suggests that AVH are related to a failure to suppress memories that are not relevant to the present moment.
Additional support comes from neuroimaging studies. A recent meta-analysis implicated the parahippocampal gyrus and the hippocampus in the experience of AVH (Jardri et al., 2010). These two brain structures are involved in memory processes. Interestingly, fMRI studies investigating brain activity *before* the onset of AVH also implicated the parahippocampal gyrus (Diederen et al., 2010; Hoffman et al., 2008). This may suggest that activity in this memory-related structure triggers or increases vulnerability to AVH. The memory theory could potentially explain the strong association between traumatisation and AVH, which has been observed both in patient and in non-psychotic individuals with AVH (Daalman et al., 2012).

5. Treatment

The first treatment option for clinicians to treat AVH in psychotic disorders is usually pharmacotherapy. A psychological treatment option that is often combined with pharmacological intervention is cognitive behavioral therapy (CBT). Unlike pharmacotherapy, the primary purpose of CBT is not to stop the voices, but rather to help the patient cope with this symptom.

Antipsychotic medication can be very effective in the treatment of hallucinations, as the AVH in most schizophrenia patients subside after prescription of antipsychotics. Still, approximately 25 percent of patients with AVH are medication resistant. There is therefore a clear need to develop new treatments, and this has spurred researchers to look for new biological therapeutic options. In the 1990s, such a treatment emerged. With repetitive transcranial magnetic stimulation (rTMS), magnetic pulses are applied to the brain in order to alter brain activity. By stimulating the brain with low-frequency rTMS, cortical activity in the targeted brain area is reduced (Chen et al., 1997). When stimulation with rTMS is applied repeatedly, for example for several consecutive days, the targeted area is thought to become less active for a longer period of time. This effect may be comparable to Long-Term Depression (LTD) as observed in single-cell recordings after prolonged stimulation (Christie et al., 1994; Hoffman and Cavus, 2002).

Hoffman et al (1999) were the first to use rTMS to treat medication-resistant AVH. They applied rTMS to the left temporoparietal cortex, which is an important center for speech perception. Three patients were stimulated for several consecutive days and reported strong improvements in AVH severity. After publication of this report, a number of research groups has successfully used this paradigm to treat AVH. Morevoer, the usefulness of rTMS in treating hallucinations was supported by several meta-analyses (Aleman et al., 2007; Freitas et al., 2009; Slotema et al., 2010b; Tranulis et al., 2008). However, two large studies have recently failed to find an effect compared to sham stimulation (Loo et al., 2010; Slotema et al., 2010a). These mixed results suggest the value of rTMS to treat AVH is still uncertain and highlight the need for further research.

6. Outline

The aim of the research presented in this thesis is to gain more insight into the pathophysiological mechanisms underlying AVH. The first part consists of a review of neurophysiological studies (EEG and MEG) investigating AVH. Part II focuses on state studies investigating brain activity during the experience of AVH. Part III describes trait studies investigating the predisposition to hallucinate. Finally, chapter IV describes an rTMS treatment study.

6.1 Part I: Reviews

Over the years, an abundance of research has investigated AVH using neurophysiological methods. In chapter 2 and 3 this literature is reviewed and discussed.

6.2 Part II: State studies

Previous studies have implicated several brain regions in the experience of AVH. These brain areas can be used as targets for neuromodulation to treat AVH, e.g. with electrocortical stimulation or neurofeedback. However, some of these areas are probably not involved in the genesis of AVH, but rather in other cognitive processes such as auditory stimulus detection and motor responses related to indicating the presence of AVH. To gain insight in which brain areas may be more specifically involved in the genesis of AVH, we performed meta-analyses of neuroimaging studies investigating AVH and auditory stimulus detection in chapter 4.
In chapter 5, we investigated the state of AVH using MEG. To date, most source-localization studies investigating brain activity during AVH used fMRI. This technique provides an indirect measure of neuronal activity and scanner noise may interact with brain activity related to AVH. In contrast, MEG is a silent technique, directly reflects neuronal activity, and provides information about the frequency bands involved in the experience of AVH. As previous MEG studies only included a small number of subjects, we conducted a study in a larger sample which enabled us as the first group to use group-wise statistics. Moreover, the high temporal resolution of the technique allowed us to focus on the time-frame surrounding AVH onset.

6.3 Part III: Trait studies

Studies investigating the trait to hallucinate in schizophrenia patients may be susceptible to confounding factors such as medication use and other aspects of the disease. To circumvent these limitations, we focus on non-psychotic individuals with AVH in chapters 6 and 7. In the first study the neuronal correlates of attention were investigated using EEG. The rationale behind this study is to investigate top-down processing as aberrations herein may underlie the genesis of AVH. In chapter 7, the predisposition to hallucinate was investigated using a recently developed method to locate areas that are more functionally connected with the rest of the brain in this group compared to controls (so-called "hubs").

6.4 Part IV: Treatment

In studies assessing the effect of rTMS as a new therapeutic option to treat AVH, daily rTMS sessions are usually repeated for a number of days to summate effects. However, these studies have yielded inconsistent results, with two large studies failing to find an effect. In chapter 8, we look into the acute effects of a single session of rTMS to assess whether there is an initial effect of this treatment.

6.4 Summary and general discussion

Finally, chapter 9 gives a summary of the chapters followed by a general discussion of the findings.

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Part I

Reviews

Chapter 2

The neurophysiology of auditory hallucinations – a historical and contemporary review

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Abstract

Electroencephalography (EEG) and magnetoencephalography (MEG) are two techniques that distinguish themselves from other neuroimaging methodologies through their ability to directly measure brain-related activity and their high temporal resolution. A large body of research has applied these techniques to study auditory hallucinations. Across a variety of approaches, the left superior temporal cortex is consistently reported to be involved in this symptom. Moreover, there is increasing evidence that a failure in corollary discharge, i.e. a neural signal originating in frontal speech areas that indicates to sensory areas that forthcoming thought is self-generated, may underlie the experience of auditory hallucinations.

1. Introduction

Electroencephalography (EEG) and magnetoencephalography (MEG) are neuroimaging techniques that distinguish themselves from other methods by their excellent temporal resolution. Both are neurophysiological techniques that allow investigators to track brain activity on a millisecond time-scale. EEG measures the electrical signals produced by groups of neurons in the brain, and MEG measures the concurrent magnetic signals elicited by these electrical signals. For source-localization, however, MEG may be a more suitable technique than EEG, as the electrical signals related to neuronal activity are smeared out by the skull, hampering accurate EEG source-localization. The magnetic signals measured by MEG are not substantially affected by the skull and can therefore be located more reliably. EEG, on the other hand, has two clear advantages over MEG: its accessibility to a large number of investigators, as EEG equipment is available at most hospitals, and its relatively low cost.

Many studies have used neurophysiological methods to study auditory hallucinations. Already in 1955, Sem-Jacobsen et al reported on brain activity related to hallucinations. Over time, several approaches have evolved. These approaches can be divided into five main paradigms, which we describe below.

The most intuitive strategy is to use symptom-capture, in which patients indicate the presence of hallucinations, for example by button-press. Brain activity during hallucinations is then compared to hallucination-free periods. A second approach is to combine symptom-capture with event-related potentials (ERPs, these are measured with EEG. Its MEG counterparts are called event-related fields (ERFs)) to assess the processing of auditory information during the active "state" of an auditory hallucination. A third approach associates ERPs with the tendency or the "trait" to hallucinate. In this approach the severity of hallucinations is correlated with an index of auditory processing. In a fourth approach, repetitive transcranial magnetic stimulation (rTMS, a method that applies magnetic pulses to the brain in order to activate or deactivate brain activity) has been used to study EEG correlates of auditory hallucinations. A fifth approach is to study basic neurophysiological mechanisms that may underlie the tendency to hallucinate. Each of these paradigms will be described in detail together with a summary of the findings.

2. Symptom capture studies

2.1 Early symptom capture studies

Before the era of anti-psychotic medications, depth electrocorticography (ECoG) studies were sometimes conducted in conjunction with neurosurgery for relief of severe psychotic symptoms. In one such ECoG study, Sem-Jacobsen et al (1955) reported: "A close relationship between the patient's acute episodes of psychotic behavior and the electric activity was found. The findings in this study draw attention to the presence of focal spike discharges in some chronically psychotic patients during episodes of disturbance or hallucinations or both and to the presence of changes in the activity of the temporal lobe and probably the frontal lobe

during hallucinations."

Thirteen years later, Marjerrison et al (1968) used scalp recorded EEG for the first time to capture the electrophysiological signal associated with auditory hallucinations. They reported that newly admitted or readmitted acute schizophrenia patients who experienced hallucinations during the experiment had lower variation in mean integrated amplitude of the EEG than similar patients who were not hallucinating during the experiment. In the next two decades, EEG studies investigating hallucinations were scarce. In the 1970's, Whitton et al (1978) recorded the spectral power preceding an auditory hallucination in 6 unmedicated patients. This was compared to EEG power preceding a response in healthy controls performing tests of creativity. They reported that EEG power was predominant in the delta and theta bands in the 4-sec interval prior to reports of hallucinations and creative responses, and suggested that the intrusiveness of the hallucinatory experience may be similar to the sudden internal experience of solving a creative task.

In a telemetry study, Stevens et al (1979) equipped schizophrenia patients with EEG electrodes, and the EEG signal was sent through radio-waves to a base-station. With this system, the patients were able to walk freely about the ward or dayroom. Hallucinatory behavior (e.g. muttering) was coded by a trained observer, enabling the comparison of hallucination episodes with non-hallucination episodes ('symptom-capture'). In this study, Stevens and her team published EEG recordings of a hallucinating patient, reporting power increases during hallucinations in all frequency bands and scalp derivations with the exception of alpha in the left temporal region. In a follow-up study using the same paradigm, Stevens and Livermore (1982) reported that hallucinations correlated with the presence of ramp spectra in the EEG, i.e. spectra characterized by a smooth decline in power from lowest to highest frequencies. According to the authors, such spectra have previously been found in conjunction with subcortical spike activity of epilepsy, suggesting hallucinations were present subsequent to some abnormal subcortical discharge. However, ramp spectra can also emerge from eye and body movement, and the authors acknowledge that this may have influenced results. In general, EEG data from patients in an uncontrolled environment should be interpreted with caution, because of muscle artefacts potentially confounding results.

A few years later, Serafetinides et al (1986) investigated the influence of verbal versus button-press methods to indicate auditory hallucinations on oscillations in the EEG. The method used to determine the presence of hallucinations had a marked effect on EEG results. Verbal reporting was associated with a bilateral increase of high frequency activity, while nonverbal reporting was associated with an asymmetry in power between the left and right hemisphere. After this publication, no study made use of verbal reporting of hallucinations anymore.

2.2. Contemporary symptom capture studies

With the advent of better analysis algorithms and greater computing power, EEG and MEG data can be decomposed into precise information in the time-frequency domain, while also providing better spatial resolution than the older clinical EEG methods. However, modern EEG and magnetoencephalography (MEG) symptom capture studies investigating hallucinations

are scarce. To date, only one EEG study and three MEG studies have been published. In the EEG study, Sritharan et al (2005) reported an increase in alpha band power in the left superior temporal cortex during auditory hallucinations in seven schizophrenia patients. Moreover, an increase in synchronization between the left and right superior temporal cortices was found during auditory hallucinations, suggesting an increase in functional coupling between these brain regions during hallucinations.

Ishii et al (2000) were the first to investigate auditory hallucinations using MEG in a symptom-capture design. In a case-study they reported an increase in theta-band activity in the left superior temporal cortex during hallucinations. In another case-study, the same structure was implicated, albeit in the beta-band (Ropohl et al., 2004). Reulbach et al (2007) studied five patients with nonverbal auditory hallucinations (e.g. noise, music) and three patients with command hallucinations. Hallucinations in the former group were associated with an increase in beta-band activity in the left superior temporal cortex, while hallucinations in the latter group were associated with the same activation pattern extending into the left dorsolateral prefrontal cortex. According to the authors, these findings suggest that the lack of frontal lobe involvement in nonverbal hallucinations could be interpreted as a sign of diminished cortical involvement compared to the complex mechanisms involved in the generation of voices. In sum, heterogeneous results regarding involved frequency bands were observed. The theta, alpha, and beta bands were all reported to be implicated in the experience of auditory hallucinations. A possible explanation for these heterogeneous results could be the small sample sizes of the studies (see Table 1), as studies with small sample sizes lead to more variable and less reliable results. Results regarding location were more consistent, as all studies showed increases in power in the left superior temporal gyrus (STG).

Table 1. Summary of contemporary symptom capture studies. STG = Superior temporal gyrus; DLPFC = Dorsolateral prefrontal cortex

Study	Technique	N	Findings
Sritharan et al (2005)	EEG	7	Increase in power in the left STG **(alpha band)** and increase in bitemporal coherence **(alpha band)**
Ishii et al (2000)	MEG	1	Increase in power in the left STG **(theta band)**
Ropohl et al (2004)	MEG	1	Increase in power in the left STG **(beta band)**
Reulbach et al (2007)	MEG	5	Increase in power in the left STG during auditory non-verbal hallucinations **(beta band)** and
		3	Increase in power in the left STG extending into the left DLPFC during auditory verbal hallucinations **(beta band)**

3. Combined ERP/ERF-symptom capture studies

Another approach to study auditory hallucinations is to combine symptom capture with EEG-based event-related potentials (ERPs). ERPs are evoked by a stimulus, and the components

of interest usually occur within one second after stimulus-presentation. With the combined symptom-capture-ERP method, ERPs are studied during hallucinatory periods and compared to ERPs during non-hallucinatory periods. A frequently used ERP in this approach is the N100 component. The N100 is generated in the auditory cortex (Hari et al., 1984), and is considered to be a standard metric of auditory cortex activation. As such, the N100 provides the opportunity to compare auditory cortex activity during the hallucinatory state with the non-hallucinatory state. Tiihonen et al (1992) measured N100 amplitude and latency to tones presented to two patients suffering from intense auditory hallucinations. In both patients, the N100 was delayed during the experience of auditory hallucinations compared to when the patients were not hallucinating. Moreover, in one patient N100 amplitude was also lower during hallucinations. In a larger study, Hubl et al (2007) investigated N100 amplitude in seven patients with a psychotic disorder with acute auditory hallucinations, and found smaller amplitudes during hallucinations. Moreover, the largest differences in N100 source strength between periods with and without hallucinations were located in the left superior temporal cortex. The authors concluded that these findings indicate competition between auditory stimuli and auditory hallucinations for physiological resources in the primary auditory cortex, and that abnormal activation of this brain region could be a component of auditory hallucinations.

Line et al (1998) took advantage of the rapid time-scale of EEG to study the time-frame surrounding auditory hallucinations. They presented eight schizophrenia patients with flickering visual stimuli, leading to the generation of electrical activity in the brain at the same frequency of the flashing stimulus (so-called steady state visual evoked potentials). In the second before the onset of an auditory hallucination, patients showed a large and significant decrease in latency of brain responses in the right temporoparietal area, suggesting involvement of this area in the genesis of hallucinations.

In a very recent EEG study, transiently stable neuronal states were investigated (Kindler et al., 2010). Kindler et al. found that a so-called microstate associated with error monitoring was shorter during hallucinatory periods compared to non-hallucinatory periods. The authors speculated that the early termination of this microstate facilitated the misattribution of self-generated inner speech to external sources during hallucinations. Like the contemporary symptom-capture studies, combined ERP/ERF-symptom capture studies have small sample sizes (Table 2). Symptom capture studies are challenging since patients are required to hallucinate intermittently and for a considerable time of the experiment, and patients have to be able to reliably indicate onset and offset of their hallucinations (Ford et al., 2009).

Table 2. Summary of combined ERP/ERF-symptom capture studies

Study	Technique	N	Findings
Tiihonen et al (1992)	EEG and MEG	2	Delay in N100 amplitude during hallucinations **(both patients)** Smaller N100 amplitude during hallucinations **(one patient)**
Hubl et al (2007)	EEG	7	Smaller N100 amplitude during hallucinations
Line et al (1998)	EEG	8	Decrease in latency in brain responses to flickering stimuli in the right temporoparietal area in the second before hallucination onset
Kindler et al (2010)	EEG	9	Shorter microstate in the EEG related to error monitoring during hallucinations

4. Associations between hallucinatory trait and EEG/MEG measures

Another strategy to study hallucinations is to investigate the association between EEG and MEG measures and the tendency to hallucinate. Lee et al (2006) used quantitative EEG and source imaging to investigate 25 schizophrenia patients with treatment-refractory auditory hallucinations and 23 schizophrenia patients who were hallucination-free for at least two years. Resting-state EEG in the hallucinating patients showed significantly increased beta-band activity in the left inferior parietal lobule and the left medial frontal gyrus compared to non-hallucinating patients. Moreover, gamma and beta frequencies were significantly correlated in hallucinating patients, but not in non-hallucinating patients. The authors suggested that the strong correlation between gamma and beta frequency oscillations may indicate that the brains of hallucinating patients act as if they were experiencing "real" auditory stimulation, as previous studies have shown strong correlations between gamma and beta frequency oscillations in normal populations in response to auditory stimuli (e.g. Haenschel et al., 2000).
Several authors have used ERPs to study associations with auditory hallucinations. Still, the relationship between ERPs and clinical symptoms of schizophrenia remains controversial. Havermans et al (1999) studied the P3b evoked potential, which is regarded as a standard measure of effortful attention. The authors reported reductions in P3b amplitude in chronic hallucinating patients compared to non-hallucinating patients. Turetsky et al (1998) found a strong association between a frontal P3b subcomponent and severity of auditory hallucinations. However, other studies failed to find any association between P3b amplitude and positive symptoms (Eikmeier et al., 1992; Liu et al., 2004). As most schizophrenia patients with auditory hallucinations also experience other symptomatology like delusions, some degree of disorganisation, and negative symptoms, the diverse P3b findings may be related to this diversity in symptoms. In addition, antipsychotic medication may have affected the results.
To circumvent these problems, Van Lutterveld et al (2010) investigated P3b amplitude in non-schizophrenic individuals with auditory verbal hallucinations as an isolated symptom. These individuals functioned at normal professional and social levels and were free of medication. If

the P3b amplitude reduction typically seen in schizophrenia patients (Jeon and Polich, 2003) is due to the tendency to hallucinate, then non-schizophrenic subjects who hallucinate should also have reduced P3b amplitudes. Contrary to expectations, they found an increase in P3b amplitude, which was interpreted as refuting a pivotal role of decreased effortful attention in the pathophysiology of auditory verbal hallucinations.

Finally, one study investigated the P3a event-related potential to speech sounds in hallucinating and non-hallucinating patients with schizophrenia. Unlike the P3b, the P3a is not associated with effortful attention, but with involuntary shifts to auditory changes and processing of novelty. Fisher et al (2010) found that hallucinating patients had smaller P3a amplitudes than non-hallucinating patients, and that for the hallucinating patients P3a amplitude was negatively correlated with auditory-hallucination symptomatology. The authors suggested that auditory verbal hallucinations are associated with impaired processing of external speech sounds, perhaps due to competition between external and internal auditory verbal stimuli (i.e. hallucinations).

Other studies have investigated mismatch negativity (MMN) and hallucinations. Mismatch negativity is an event-related potential related to automatic auditory change detection. However, like P3b findings, results are inconsistent. Some studies reported an association between MMN amplitude and auditory hallucinations (Fisher et al., 2008a; Fisher et al., 2008b; Youn et al., 2003), while others did not (Kasai et al., 2002; Schall et al., 1999). These diverse findings may be at least partly explained by the different methodologies used. For instance, Schall et al presented visual and auditory stimuli simultaneously, while others did not.

Recently, interest has been growing in auditory steady-state evoked potentials elicited by click-trains. With this paradigm, a steady stream of clicks is presented (hence steady-state), and the brain's responses are measured over the presentation epoch (Uhlhaas and Singer, 2010). Spencer et al (2009) presented click trains pulsing at 40 Hz to patients and healthy controls. They found that patients with higher gamma-band activity (~40Hz) in the left primary auditory cortex had a greater liability for experiencing auditory hallucinations. Moreover, this activity was influenced by delta-wave activity. The authors raise the possibility that aberrant oscillatory synchronization in the temporal cortex could interact with dysfunctional corollary discharge mechanisms (i.e. a malfunctioning in neural signals originating in frontal speech areas that indicate to sensory areas that forthcoming thought is self-generated), leading to the experience of auditory hallucinations. The reported correlations in this study were based on lifetime hallucination ratings, and the medicated patients were not actively hallucinating at the time of the study. Still, these findings extended earlier results of this laboratory, in which a correlation between gamma-band activity and hallucination severity of first-episode psychosis patients was found (Spencer et al., 2008).

5. Neurophysiology and repetitive transcranial magnetic stimulation

In the last decade, repetitive transcranial magnetic stimulation (rTMS) has emerged as a new potential treatment option for auditory hallucinations. With rTMS, electromagnetic induction is used to non-invasively increase or decrease brain activity. Two studies have investigated the

effect of rTMS on the EEG in the context of auditory hallucinations. Jandl et al (2006) reported that a subgroup of patients benefited from rTMS over the left superior temporal cortex as revealed by a decrease in auditory hallucination severity, while no changes in whole-head EEG were reported. Horacek et al (2007) applied rTMS to the left temporoparietal cortex for ten days and reported a significant improvement in hallucination severity. TMS treatment caused a decrease in activity in the beta-1 and beta-3 bands in the left temporal lobe, whereas an increase was found for the beta-2 band in the right temporal cortex and the inferior parietal lobule, indicating transcallosal signal transmission involvement. A possible explanation for the divergent findings of the two studies is that data-analysis procedures were different. In the former study the EEG was assessed on sensor-level and in the latter study a source-localization procedure was used.

6. Studies of a basic neural mechanism that might underlie auditory hallucinations

Feinberg (1978) suggested that malfunctioning of the corollary discharge mechanism might underlie the experience of auditory hallucinations. Corollary discharge is a basic feed-forward system involved in suppressing the sensory consequences of self-generated actions (Sperry, 1950; Von Holst, 1950). It has been documented across the animal kingdom (Crapse and Sommer, 2008), and its action allows all species to suppress sensations that result from their own actions and to tag them as coming from the self. Such feed-forward systems have been well described in the visual and somatosensory systems, but also serve the auditory system across species from crickets (Poulet and Hedwig, 2002) to song-birds (McCasland and Konishi, 1981) to non-human (Eliades and Wang, 2003) and human primates (e.g. Ford et al., 2007b; Paus et al., 1996). Because the corollary discharge mechanism operates on a rapid time-scale, this theory has most extensively been investigated using neurophysiological recordings. In humans, EEG (Ford et al., 2010) and MEG (Curio et al., 2000; Houde et al., 2002) have been used for studies of the auditory system; only EEG-based methods have been used in studies of schizophrenia.

While this mechanism explains suppression and tagging of sensations resulting from overt motor acts, Feinberg et al (1978) suggested that thinking may conserve and utilize the computational and integrative mechanisms that evolved for physical movement. In a well-functioning corollary discharge system a signal is sent from frontal areas involved in inner speech generation to temporal speech reception areas, tagging the perception as self-generated. When this mechanism is malfunctioning, a person may experience an auditory hallucination through misperceiving his or her own thoughts as being externally generated.

Several lines of research support the hypothesis of corollary discharge dysfunction in schizophrenia. The first line explored whether this system is deviant in schizophrenia patients versus healthy controls. In these studies, control subjects and patients first uttered syllables and then listened passively to a recording of that speech played back. EEG was recorded during both talking and listening conditions, and the amplitude of the N100 component of the ERP to speech onset was used as a measure of auditory cortical responsiveness. Consistent with the action of the corollary discharge system, N100 amplitude was smaller during talking

than listening in healthy controls. Interestingly, there was significantly less N100 suppression in patients, suggesting aberrations in the corollary discharge system (Ford et al., 2007a; Ford et al., 2001a; Ford et al., 2007b). In another N100 study, the effects of thinking on auditory cortical responsiveness were investigated. It was shown that thinking affected N100 amplitude in healthy controls, but not in schizophrenia patients (Ford et al., 2001b).

In a second line of research, functional connectivity, as measured by EEG coherence between frontal and temporal lobes in the gamma band, was found to be higher during talking than during listening in healthy controls. This pattern was disrupted when the uttered syllables were pitch-shifted while the subjects were talking, resulting in a non-self experience of the spoken sounds. In schizophrenia patients, distortion of the auditory feedback did not result in alteration of gamma-band frontotemporal coherence, again suggesting a malfunctioning corollary discharge system (Ford and Mathalon, 2005). In another coherence study, it was found that theta-band frontotemporal coherence was higher for talking than for listening for controls, but not for schizophrenia patients. This effect was carried by the hallucinating patients, as the non-hallucinators tended to show the pattern seen in the healthy controls. The authors suggested that a failure in the frontal-temporal network during overt speech may also occur during covert speech, leading to misattribution of self-generated thoughts to external sources (Ford et al., 2002). Given that N100 recorded from auditory cortex is suppressed during talking, the net result of coherent communication between frontal and temporal lobes was to suppress auditory sensation.

The corollary discharge theory can also be investigated by examining the small time-frame before speech starts. In such a study, pre-speech neural synchrony was reported to be related to subsequent suppression of N100 amplitude in healthy controls, but not in patients. Moreover, time-frequency analyses showed greater pre-speech synchrony in healthy controls than in patients, especially in those with severe auditory hallucinations. The authors interpreted these findings as suggesting that EEG synchrony preceding speech reflects the action of the corollary discharge system, which dampens auditory responsiveness to self-generated speech and is deficient in patients who hallucinate (Ford et al., 2007b).

Another line of research explored the influence of pitch-shifting auditory stimuli on auditory cortex activation. In this paradigm, hallucinating schizophrenia patients, non-hallucinating schizophrenia patients and controls were asked to utter meaningless sounds. Simultaneously, they were presented with auditory feedback of the uttered sounds, or pitch-shifted feedback of the uttered sounds, or feedback of sounds uttered by someone else, or pitch-shifted feedback uttered by someone else. It was found that N100 amplitude to the unaltered self-voice was dampened relative to the altered self-voice or the alien auditory feedback. This pattern was not seen in hallucinating patients, and this imprecision correlated with the severity of hallucinations (Heinks-Maldonado et al., 2007).

Finally, in a recent study, subjects were asked to initiate auditory stimuli by button-press. It was found that N100 suppression was normalized in patients after adding a delay of 50 ms in the presentation of the stimulus, suggesting a temporal delay in corollary discharge. (Whitford et al., 2010). Moreover, this normalization correlated with white-matter integrity of the arcuate fasciculus, a fiber bundle connecting speech/motor initiation areas in the frontal lobe with the

auditory cortex in the temporoparietal lobe. These data suggest that structural deficits of the arcuate fasciculus may lead to temporally delayed corollary discharges, and that abnormalities in this fiber tract may be involved in the pathophysiology of auditory hallucinations.

7. Neurophysiology and hallucinations--what does it tell us?

Neurophysiological methods have been used in many different ways to understand auditory verbal hallucinations. The symptom capture approach has intuitive appeal and face validity, but it is operationally difficult and does not provide insight into the mechanisms by which voices might be heard. However, symptom capture studies do provide a wealth of information regarding the neural activity associated with the experience of hallucinations. Unfortunately, there is little consistency regarding the frequency of neural activity invoked by the hallucinatory experience, with evidence for increases in theta, alpha, and beta band activity associated with hallucinations. There is more consistency regarding the location of the activity invoked, with evidence that structures in the left temporal lobe are more active during a hallucination period than a non-hallucination period. Similarly, although ERPs elicited by probes during a hallucination provide little information about mechanisms, they do provide excellent support for the involvement of auditory cortex in the generation of the hallucination. This is in line with structural and functional magnetic resonance imaging (sMRI and fMRI) studies, in which left superior temporal cortex is implicated in the experience of auditory hallucinations (Allen et al., 2008; Barta et al., 1990; Diederen et al., 2010a; Dierks et al., 1999).
ERP studies of the trait to hallucinate suggest that the tendency to hallucinate is associated with reduced resources available for processing the probe. This is consistent with fMRI studies comparing hemodynamic activation to external probes in hallucinators and non-hallucinators (Ford et al., 2009), in which left temporal activation to auditory probes was reduced in patients who hallucinate compared to patients who do not. One EEG study reported greater beta band activity in the left inferior parietal lobe in patients who tended to hallucinate. Given the poor spatial resolution of EEG, it is possible that the increase in beta power was due to activity in the left auditory cortex. Finally, rTMS has provided indirect evidence of the involvement of left auditory cortex in hallucinations: In one study, treatment with rTMS over the left superior temporal cortex caused a decrease in activity in the beta band in the left temporal lobe with clinical improvement in hallucinations.

Future Directions. While mechanistic studies lack the intuitive face-validity of the symptom capture work, they converge on the involvement of the temporal cortex in the generation and experience of auditory hallucinations, consistent with the report that voices sound loud and real. Mechanistic studies also offer translation to bench neuroscience and translation to other species, and hence open the door to invasive manipulations that are not possible with in vivo human studies. For one example, studies like the ones reviewed above can be applied in the future to animals who make social calls, such as song-birds (Brainard and Doupe, 2000) and non-human primates (Eliades and Wang, 2003). In such an experiment, perturbations of the neurotransmitters implicated in schizophrenia might produce a pattern in the neural

signature of the mechanism that resembles the pattern seen in schizophrenia patients who hallucinate. Because symptom capture studies are infeasible in animal models, and because the relationship between the experience of auditory hallucinations and related frequency bands is unclear, we suggest that future research exploits a mechanistic approach in animal models of schizophrenia.

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Chapter 3

Neurophysiological studies of auditory verbal hallucinations

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Abstract

We discuss 3 neurophysiological approaches to study auditory verbal hallucinations (AVH). First, we describe "state" (or symptom capture) studies where periods with and without hallucinations are compared "within" a patient. These studies take 2 forms: passive studies, where brain activity during these states is compared, and probe studies, where brain responses to sounds during these states are compared. EEG (electroencephalography) and MEG (magnetoencephalography) data point to frontal and temporal lobe activity, the latter resulting in competition with external sounds for auditory resources. Second, we discuss "trait" studies where EEG and MEG responses to sounds are recorded from patients who hallucinate and those who do not. They suggest a tendency to hallucinate is associated with competition for auditory processing resources. Third, we discuss studies addressing possible mechanisms of AVH, including spontaneous neural activity, abnormal selfmonitoring, and dysfunctional interregional communication. While most studies show differences in EEG and MEG responses between patients and controls, far fewer show symptom relationships. We conclude that efforts to understand the pathophysiology of AVH using EEG and MEG have been hindered by poor anatomical resolution of the EEG and MEG measures, poor assessment of symptoms, poor understanding of the phenomenon, poor models of the phenomenon, decoupling of the symptoms from the neurophysiology due to medications and comorbidites, and the possibility that the schizophrenia diagnosis breeds truer than the symptoms it comprises. These problems are common to studies of other psychiatric symptoms and should be considered when attempting to understand the basic neural mechanisms responsible for them.

Neurophysiology of Auditory Verbal Hallucinations: Current State of Knowledge

In this section, we describe the current state of knowledge about the neurophysiology of auditory verbal hallucinations (AVH). First, we describe "state" studies in which periods of hallucinations and nonhallucinations are compared within a patient; these are also known as "symptom capture" studies. These studies take 2 forms: passive studies and probe studies. Second, we describe "trait" studies in which patients who hallucinate are compared with those who do not, with some studies using hallucination severity as a continuous variable. Third, we describe studies attempting to understand a basic neural mechanism using neurophysiological methods that may underlie AVH.

Assessments of State (Symptom Capture)

"Symptom capture" is a naturalistic approach where neurobiological data are collected as patients experience a hallucination. While this approach is conceptually simple, it is extremely difficult in practice because it relies not only on the timely occurrence of an illusive subjective experience but also on the ability of the patient to reliably report its initiation and completion. Symptom capture studies require patience from the research team and cooperation and insight from the patient. To control for the effects of attention and button pressing, ideally patients need to be able to indicate both when they hear voices and when they do not. Because it is difficult to satisfy all these criteria, only a small percentage of patients interviewed are enrolled in symptom capture studies.

Two main approaches have been used in symptom capture studies. The most obvious involves comparing "spontaneous" neural activity during periods with and without hallucinations. A slightly less direct approach involves comparing responses to external auditory "probes" during periods with and without hallucinations. Auditory cortex should be relatively active during periods of hallucinations, and thus, less responsive to external auditory probes. That is, if the brain is busy listening to an internal auditory stream, it should be less responsive to external sounds. The literature largely supports that prediction.

Symptom Capture. As reviewed by Van Lutterveld et al (2011), before the era of antipsychotic medications, depth electrocorticography studies were sometimes conducted in conjunction with neurosurgery for relief of severe psychotic symptoms. Other than providing a fascinating historical note, old electroencephalography (EEG) findings are not easy to incorporate into the contemporary literature with more sophisticated data collection and analysis. Using newer methods, one group reported an increase in alpha band (8–12 Hz) power in the left superior temporal cortex during AVH in 7 schizophrenia patients and an increase in synchronization between the left and right superior temporal cortices, suggesting an increase in functional coupling between these brain regions (Sritharan et al, 2005). Others using magnetoencephalography (MEG) showed increased theta (4–8 Hz) and beta band (12.5–30 Hz) activity in the left superior temporal cortex during AVH in a single subject (Ishii et al, 2000; Ropohl et al, 2004). A third study included 5 patients with nonverbal auditory hallucinations

(eg, noise, music) and 3 patients with verbal command hallucinations (Reulbach et al, 2007). In both groups, hallucinations were associated with an increase in beta-band activity in the left superior temporal cortex. In patients hearing voices, the activation pattern extended into left dorsolateral prefrontal cortex suggesting more complex mechanisms are involved in the generation of voices than music. Most recently, increased phase coupling in the alpha band, both inter and intrahemispherically between temporal and frontal lobes, was reported during AVH (Angelopoulos et al, 2011). Although it is difficult to understand the functional significance of the different neural frequency bands during AVH in these different reports, they are generally consistent with functional magnetic resonance imaging (fMRI) data, pointing to activity in both right and left temporal and frontal regions of the brain during AVH (Allen et al, 2007).

Recently, microstates (described below) have been used to study state changes in neural activity associated with periods of AVH. A microstate that correlates with a dorsal attention-reorientation resting-state network was observed to be shortened by several milliseconds during periods with AVH (Britz et al, 2010; Kindler et al, 2010). Shortening of this microstate might indicate a premature termination of the delicate balance between goal-directed and salience-driven processes, compatible with the observed psychopathology. It should be noted that microstates are spatial maps of activity that are indifferent to EEG frequency bands; as such, microstate data are difficult to reconcile with the EEG data described above.

Symptom Capture With External Probes. Activity elicited by external probes can be studied by assessing the various components of the event-related potential (ERP) or its MEG counterpart, the event-related field. The auditory ERP is illustrated in figure 1 where we show the earliest to the latest occurring components. We indicate the brain regions believed to be responsible for the generation of each component, what function the component might reflect, and how it is affected by the state or trait of hallucinations. While AVH involve a number of cortical and subcortical areas (Allen et al, 2007), ERPs are best able to assess activity in the cortical mantle, particularly auditory cortex. Thus, most probe studies focus on auditory cortex because that's where the "light is best."

The N1 component of the auditory ERP is the only component shown in figure 1 that has been reported during symptom capture studies. Although N1 is affected by activity in the frontal lobes and other areas of the brain, it primarily emanates from primary and secondary auditory cortex (Näätänen et al, 1987), and as such, it is an excellent probe of auditory cortical activity, albeit, as affected by activity in other areas of the brain.

Hubl and colleagues (2007) recorded ERPs to 1000 Hz tones while 7 schizophrenia subjects indicated by button press the beginning and ending of an AVH. Patients were instructed to listen to their voices and ignore the tones. In every patient, N1 amplitude was reduced during AVH; further, N1 reduction localized to left primary auditory cortex, consistent with an earlier study using both EEG and MEG methods (Tiihonen et al, 1992). Finding diminished responses in the primary auditory cortex rather than in secondary auditory cortex or Wernicke's area may have been due to the use of a pure-tone probe rather than a speech probe. Together, these findings indicate competition between auditory probes and hallucinations for auditory

resources, with activation of the primary auditory cortex reflecting the physical acoustic image of verbal thoughts that are misperceived as voices.

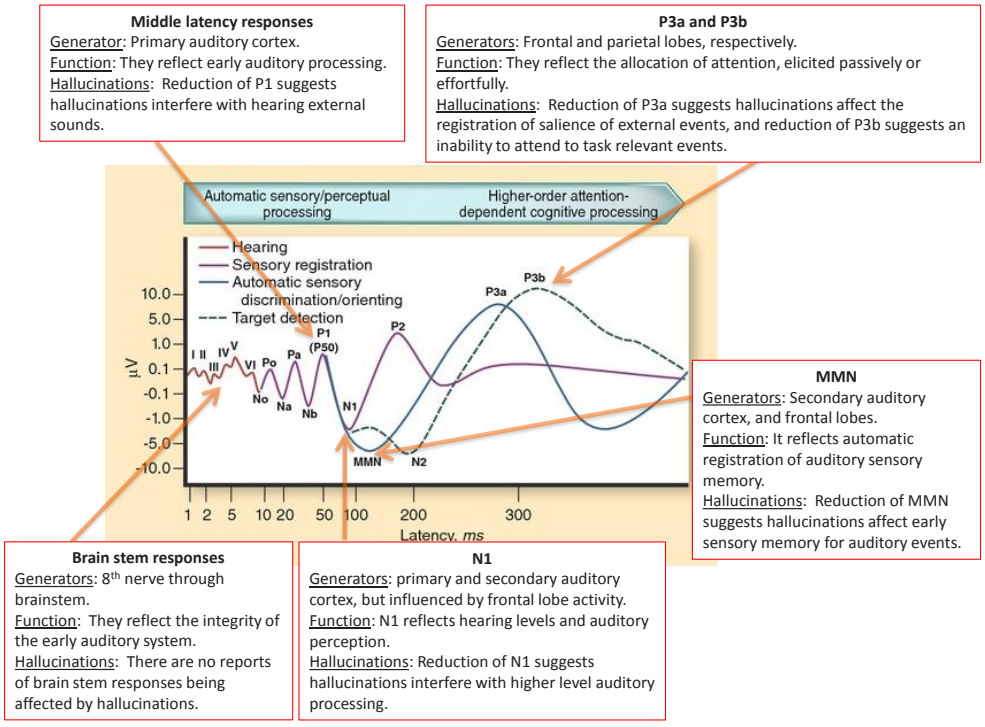

Fig. 1. A schematic representing the idealized components of the auditory ERP plotted on logarithmic scales to allow the visualization of the smallest and fastest early components emanating from the brain stem. Time in milliseconds is on the x-axis, and voltage in microvolts is on the y-axis. The components are labelled according to convention with N referring to a negative going potential and P referring to a positive potential. MMN refers to the mismatch negativity. The idealized event-related potential resembles waveforms recorded from the vertex and referred to the mastoids. The center image is taken from Rissling et al (2010) and adapted from Picton et al (1974). It is reproduced here with permission from SpringerImages.com.

Assessments of Trait

As illustrated in figure 1, other components of the auditory ERP reflect responsiveness of auditory cortex or other areas of the brain involved in auditory processing. Each is described briefly below.

P1. P1 (also referred to as P50) is an early positive ERP component peaking at about 50 ms. Like N1, P1 also depends on auditory cortex for its generation and as such should be a valid probe of auditory cortical responses to external stimuli. Smith D.M., Grant B., Fisher D.J., Borracci G., Labelle A., and Knott V.J. (unpublished data) asked patients to listen to click pairs, followed by questions regarding the duration, loudness, and clarity of any hallucinations they had just experienced during the recording session. They found that P1 to the first click was

significantly reduced in patients with AVH, with more severe hallucinations being associated with smaller P1. Additional significant correlations between P1 amplitude to the first click and individual items on the Psychotic Symptom Rating Scales, such as amount of negative content of voices, degree of negative control, amount of distress, and disruption to life caused by voices were also reported.

N1. To our knowledge, there are no reports of relationships between N1 and the trait to hallucinate. This could be due to a failure to find a positive relationship or a failure to test for such a relationship. The history of ERPs in psychiatry started with an effort to find relationships between neurobiology and diagnosis, rather than symptoms, perhaps explaining the lack of data on this relationship.

Mismatch Negativity. As can be seen in figure 1, mismatch negativity (MMN) occurs after N1 and is a measure of automatic auditory sensory memory. It is considered automatic because it does not require any behavioral response and can be elicited in the absence of explicit instructions to attend to the auditory stream (Näätänen, 1992). However, it is affected by concurrent auditory (but not visual) discrimination tasks, suggesting that sounds compete with ongoing processing of auditory information (Dittmann-Balcar et al, 1999). MMN can be elicited by any auditory event (tones, clicks, phonemes, etc.) that is deviant from the preceding events in a sequence, such as a change of sound duration, intensity, frequency, pattern, rhythm, and so on. Its elicitation indicates that a sequence was learned and that an auditory change was detected.
Perhaps for the reasons given above for N1, few articles have reported relationships between MMN and AVH (Umbricht et al, 2005). Schizophrenia patients with clear persistent AVH have smaller MMNs elicited by duration and phoneme deviants than nonhallucinating patients and controls (Fisher et al, 2008a; Fisher et al, 2008b). Additionally, hallucinating patients show altered processing of across-phoneme change, as indexed by the MMN (Fisher et al, 2008b). Using hallucination severity as a continuous variable, others have reported decreased MMN amplitude with increase in hallucination severity (Fisher et al, 2011; Hirayasu et al, 1998; Youn et al, 2003). These findings support the suggestion that either the storage of auditory information in short-term (echoic) memory or the registration that a deviant occurred, or both, is altered in patients who have a predisposition to hallucinate. While MMN reduction is associated with a tendency to hallucinate, it is closely linked to schizophrenia-related changes in global function and gray matter volume, with reductions of left temporal gray matter being associated with increased frequency and duration of AVH (Light et al, 2005; Neckelmann, 2006; Rasser et al, 2011).

P300. Task-relevant target stimuli elicit a P300 (see figure 1). While the target status of a stimulus is essential for eliciting the parietally maximal P300 (also called "P3b"), a large robust fronto-centrally maximal P300 (also called "P3a") is generated by infrequent distractor, novel or otherwise salient stimuli, with no necessary target value. It has been suggested that P3a is, in fact, a reflection of the orienting response, perhaps reflecting a shift in attention (Roth

and Kopell, 1973).

Given that over 100 articles have reported P300 reductions in schizophrenia, it is surprising that so few report a relationship between P300 and AVH (Fisher et al, 2010; Jeon and Polich, 2003; Havermans et al, 1999; Turetsky et al, 1998). As mentioned above for N1, this could reflect a failure to find a relationship or a failure to try. One study found P3a reductions in hallucinating compared with nonhallucinating patients consistent with a deficit in attributing significance to incoming stimuli (Fisher et al, 2010). Alternatively, though not necessarily contradictorily, the deficits in P300 amplitude observed may be symptomatic of the tonic "tuning" to internal stimuli, over external stimuli, observed in hallucinating patients (Ford et al, 2009). If schizophrenia patients with auditory hallucinations preferentially attend to voices through internal auditory channels, perhaps there are insufficient cortical resources to switch attention, either automatically or effortfully, to an external stimulus, which would result in diminished P300 amplitude.

Studies of chronic patients are often complicated by comorbidities and medication confounds. A study by van Lutterveld and colleagues (2010) avoided these problems by using healthy people who hallucinate. Surprisingly, they found that these people had larger P300s than healthy nonhallucinating subjects, suggesting the P300 reduction typically seen in schizophrenia is not due to the tendency to hallucinate.

Auditory Steady State Response. Not illustrated in figure 1 is the auditory steady-state response (ASSR). When an auditory stimulus is repeated at a fixed rate, it drives the cortical response at that rate. Although both higher and lower frequencies have been tested, the ASSR reaches a maximum at a 40 Hz repetition rate. This likely reflects a resonant response in the auditory system, possibly in the primary auditory cortex where the ASSR is generated (Brenner et al, 1999).

Using dipole source localization, Spencer et al (2009) found that chronic patients with "greater" intertrial phase coherence of the 40 Hz ASSR in the left primary auditory cortex had more "severe" AVH over their lifetimes. These findings extended their earlier findings of positive correlations between hallucination ratings and oscillation measures in the auditory and visual modalities in first episode and chronic patients, respectively. These findings are also consistent with a case report of abnormally large beta activity in a hallucinating patient (Ropohl et al, 2004).

Using EEG and MEG to Test Models of AVH

Most studies described above point to auditory cortical involvement in AVH but do not indicate why auditory cortex is busier in hallucinators and during hallucinations and why the resulting percepts are misperceived as coming from external sources. Below we discuss possible mechanisms and the few studies that have used EEG and MEG to assess them.

Spontaneous Neural Activity Model of AVH. What is the auditory raw material of AVH? Do auditory percepts result from random activity of neural assemblies, from unbidden thoughts

during mind wandering, or from thoughts colliding with random noise? Indeed, random noise increases sensitivity to weak signals through stochastic resonance (Jaramillo et al, 1998), and patients with schizophrenia are known to have "noisier" systems as indexed with EEG methods. This concept is further described below, under "A Neural Network model of AVH."
Northoff and Qin (2010) suggested voices may be "traced back to abnormally elevated resting-state activity in auditory cortex itself, abnormal modulation of the auditory cortex by anterior cortical midline regions as part of the default mode network, and neural confusion between auditory cortical resting-state changes and stimulus induced activity." The symptom capture studies described above showing greater neural activity in the temporal lobe and synchrony between frontal and temporal lobes are consistent with these ideas (Angelopoulos et al, 2011; Ishii et al, 2000; Reulbach et al, 2007; Ropohl et al, 2004; Sritharan et al, 2005).

The Self-Monitoring Model of AVH. How is this activity in auditory cortex misperceived as voices? It has been suggested that a deficit in self-monitoring of inner speech is responsible. Before describing the neurophysiological studies of this model, we ask, "what is self-monitoring?" and "what is inner speech?"
In its simplest form, the self-monitoring model of AVH suggests that patients misattribute, or misperceive, their thoughts and inner experiences as coming from alien sources. However, it could be argued that "self-monitoring" connotes a higher degree of intention and cognition than is appropriate. Similarly, "inner speech" is a broad term and refers to internal verbal experiences, ranging from the intentional silent rehearsal of an argument to unbidden fleeting thoughts experienced during daydreaming. AVHs are unbidden, but differ from normal daydreaming as the content is often disturbing and disarming, and experienced as coming from external sources.
In spite of these limitations, the self-monitoring of inner speech model has been the one most studied using functional imaging (Allen et al, 2007). One early version of this model was proposed by Feinberg (1978) who suggested that self-monitoring failures could result from specific dysfunctions of the efference copy and corollary discharge mechanisms. These mechanisms act across the animal kingdom to suppress sensations resulting from self-initiated motor actions and tag them as coming from self. Feinberg linked these concepts to AVH and suggested thinking is our most complex motor act and, as such, it might conserve and utilize the computational and integrative mechanisms evolved for physical movement. Feinberg reasoned that in the motor systems of thought, these mechanisms would act to distinguish self-produced thoughts from externally generated events.
Frith (1987) expanded this concept and prompted a series of behavioral experiments confirming the possibility of corollary discharge dysfunction in schizophrenia. Ford et al (2007) tested efference copy and corollary discharge dysfunction in schizophrenia by inspecting auditory cortical responsiveness to speech sounds "ah" during the act of talking. Consistent with the action of the corollary discharge system documented in human and nonhuman primates, N1 amplitude was smaller during talking than listening in healthy controls but less so in patients. The amount of suppression of N1 to speech sounds during talking was not related to AVH; however, neural synchrony in the beta band, 100 ms before speech onset, was. Because

prespeech neural synchrony was related to subsequent suppression of N1 during talking in controls, EEG synchrony preceding speech may reflect the action of the efference copy of the motor command to speak.

Interregional Communication in the Brain. Functional connectivity analyses of brain activity are motivated by findings that coordination between brain regions affects whether neural activity is experienced consciously as percepts (Melloni et al, 2007). Indeed, hyperconnectivity between different regions might contribute to false perceptions, and hypoconnectivity might result in failures of mechanisms, such as efference copy, that tag those percepts as coming from self (Feinberg, 1978). The lack of EEG theta band coherence (hypoconnectivity) between frontal and temporal lobes during talking has been associated with a tendency to hallucinate in patients with schizophrenia, and fMRI hyperconnectivity within the corticostriatal loop has been implicated in the hallucination itself (Ford et al, 2002; Hoffman et al, 2011). Functional connectivity analyses of EEG and fMRI data will provide further tests of these ideas.

Methodological Issues

Assessments of State. One clear advantage of symptom capture work is the ability to observe neural activity preceding, and during, a hallucinatory experience. Although mechanisms cannot be directly inferred from observation of the neural activity associated with the phenomenon, EEG can provide temporal information. In spite of this potential advantage, few studies have used EEG in symptom capture perhaps because symptom capture studies require patience from the research team and cooperation and insight from the patient. Another disadvantage is the unknown contributions of shifting attention away from the voices and toward signalling, and of the motor responses themselves, at the onset of a hallucination. Although symptom capture studies are infeasible in animal models, the neural signature of auditory hallucinations (eg, increased power in temporal lobe and synchrony between frontal and temporal lobes) may provide a target for testing pharmacologic challenges and genetic models.

Assessments of Trait. Comparing patients who do and do not hallucinate is far simpler than comparing periods with and without hallucinations. Successful studies using this method are consistent with findings from the symptom capture literature: Auditory cortex is "busy" in people who tend to hallucinate. However, it is not always easy to find relationships between our biological measures and symptoms for reasons listed under "Impediments to Progress," below.

Mechanistic Studies. Mechanistic studies offer translation to bench neuroscience and translation to other species, and hence open the door to invasive manipulations that are not possible with in vivo human studies while not requiring the animal to hallucinate. For example, studies of the corollary discharge mechanism can be studied in animals that make social calls, such as songbirds and nonhuman primates. In such experiments, perturbations of the neurotransmitters implicated in schizophrenia might produce a neural signature of

the mechanism that resembles the pattern seen in schizophrenia patients who hallucinate. Excessive spontaneous neural noise and both hypo- and hyperconnectivity among brain regions could also be studied in animals using similar approaches. In spite of their ability to elucidate mechanisms underlying AVH, these studies would lack the intuitive appeal of symptom capture studies.

EEG/MEG Methodologies. EEG and MEG provide noninvasive measures of brain activity by recording electrical and magnetic activity at the scalp. Furthermore, due to their superior temporal resolution (milliseconds), they have the appropriate temporal resolution for the investigation of rapidly occurring processes that are likely to underlie transitory hallucinations. Another advantage of EEG and MEG methodologies is the relative silence in which the auditory cortex can be investigated compared with the noisy environment of the MR scanner. Compared with fMRI, EEG, and MEG perform poorly when separating activity from brain regions that are not separated by a sufficient spatial distance.

Time-Voltage Analyses. EEG and MEG derived event-related components are elicited in response to a discrete event (ie, tones, light flashes); their amplitudes and latencies allow for an objective assessment of the strength and timing of perceptual and cognitive processes tightly locked in time to the event. The primary advantage is that information processing can be probed without requiring any active overt response from the subject. This feature provides 2 advantages: First, they are ideal for studies of psychiatric populations, who may be unable to perform behavioral tasks due to cognitive and/or motor deficits; second, they allow assessment of sensation and perception of events people have not been asked to attend to.

Frequency and Time Frequency Analysis of EEG. The spontaneous or "background" EEG is typically assessed in the frequency domain and yields unique information about the functional state (namely arousal) of brain regions (Ishii et al, 2000; Reulbach et al, 2007; Ropohl et al, 2004; Sritharan et al, 2005). Ongoing EEG reflects a mixture of oscillations synchronized within neuronal assemblies that are involved in activities of the mind, including sensing, perceiving, thinking, and responding. Furthermore, a stimulus not only elicits an ERP but also elicits changes in the EEG frequency spectrum that reflect adaptive changes of brain state. Changes in EEG related to a stimulus or response are typically quantified in time-frequency analyses.
EEG data are also analyzed in the spatial domain to test the hypothesis that problems experienced by schizophrenia patients might result from dysfunctional communication between regions. Interest in this hypothesis coupled with novel analytic tools and computation power has triggered a wealth of studies on connectivity and synchronization. Besides confusion with terminology (eg, "coherence" can refer to spatial coherence of signals between areas or to temporal coherence with an area across trials), there is an ever-widening gap between the findings themselves and the ability of the larger schizophrenia research community to understand them.

Microstates. Some groups have begun to take advantage of algorithms enabling calculation of

microstates. Microstates are scalp potential maps that remain quasi-stable for 70–125 ms and indicate transient states of highly coordinated brain activity (Lehmann et al, 1998). Different microstates represent different modes of information processing; indeed, the content of spontaneous mentation is influenced by microstate class (Lehmann et al, 1998). Resting-state data show 4 different classes of microstates that are reliable within and between subjects (Koenig et al, 2002). They are closely related to specific resting-state networks, as measured by the blood oxygen level–dependent response in fMRI Britz et al, 2010). They may offer a view into the resting-state activity of the brain preceding AVH and interrupted by them.

Impediments to Progress

Here, we list some impediments to relating neurobiology to AVH. First, our success is limited by our ability to understand and quantify the patients' symptoms; patients can be guarded, and clinicians may not give them time to "leak psychoticism." Furthermore, many interview instruments fail to assess important details about the AVH experience. Second, the preponderance of schizophrenia patients are medicated, and medication may decouple the symptoms from the neurobiology by attenuating symptoms but not affecting the sensitivity of the neurobiological measures to the "propensity" to experience those symptoms. Third, other symptoms may combine with hallucinations to affect the neurobiology but not the severity of the hallucinations themselves. Fourth, some drugs of abuse might affect the neurobiology but not the current severity of the symptoms. Fifth, ERP component amplitudes can be both a personal trait of the patient and a reflection of AVH, making cross-sectional comparisons problematic.

Knowledge Gaps

The research described above has primarily addressed AVH in general. With few exceptions, (Smith D.M., Grant B., Fisher D.J., Borracci G., Labelle A., and Knott V.J., unpublished data) the field has not addressed some of the specific features and content of the voices such as the typically negative content, the predominance of male voices even in female patients, the number of voices, and the familiarity of the voices. While these features are intriguing in their own right, it may not be necessary to study them in order to understand the mechanism by which unbidden thoughts are heard as voices. Similarly, music hallucinations should work by the same mechanism as AVH; most people experience unwilled, unbidden musical jingles (music "worms"), but normal people understand the origin of those sounds and do not develop odd beliefs to explain them.

The "nonverbal" auditory hallucinatory experiences reported in clinical ultra high-risk patients have also not been studied. While healthy normal people have unbidden verbal experiences constantly during the day, we do not typically experience "inner" footsteps or bonks.

Future Research

Symptoms vs Syndrome. Most AVH research using EEG and MEG methods has focused on patients with schizophrenia. Although it is unlikely that biology cleaves at current diagnostic joints, with the exception of the study by van Lutterveld et al (2010) of healthy voice-hearers, we know of no other EEG or MEG study of other groups who hear voices. Indeed, to get traction on the differential contribution of symptoms and syndromes to our neurobiological assays, it may be important to include other groups who hear voices but do not have a diagnosis of schizophrenia, such as psychotic depression, bipolar depression with psychotic features, temporal lobe epilepsy, and hypothyroidism. In addition, our efforts to understand perceptions in the absence of external stimulation might be promoted by studying tinnitus and dreaming.

The symptom-dimensional approach has many obvious advantages over the diagnosis approach. However, we have been more successful at relating biology to enduring features of the disease (the diagnosis itself, or its subtypes) than to symptoms. Perhaps the diagnosis of schizophrenia breeds truer than the symptoms it comprises (Berenbaum et al, 1985).

New Approaches

As a field, we welcome new approaches to understanding the pathophysiology of AVH using neurophysiological methods. Here, we describe 2 such approaches.

Contributions of Baseline States to AVH. We know various regions of the brain are active during an AVH; however, we do not know what happens seconds before the voices are heard and whether voices can be predicted from fluctuations in the baseline state. Nor do we know how specific baseline states affect the processing of internal and external information that might serve as a trigger for, or interruptions of, AVH. These type questions can be addressed using a combination of methods. For example, global measures of poststimulus N1 amplitude could be used as a regressor for prestimulus EEG spectral power. Also, change point analysis of EEG data might reveal whether state changes precede the onset of voices and how soon they occur before voices are signalled (Lindquist et al, 2007).

EEG and fMRI data acquired simultaneously in a symptom capture study could provide information about the fleeting spontaneous EEG activity immediately preceding AVH and the involvement of auditory cortex in the default mode network during the hallucination. In addition, it would allow the identification of the EEG spectral signature of arousal, attention, and impaired function heralding the onset of voices.

A Neural Network Model of AVH. If a neural network is constantly stimulated with a certain set of stimuli, synapses that lead to the neurons that respond to these stimuli will be strengthened as has been shown in a simulation study using spiking neurons (Fründ et al, 2009). In the absence of external stimuli, the neurons with strong synaptic connections will be the most likely to respond to noise. They are the neurons that represent objects that have

been repeatedly perceived—such as one's own name. The human brain cannot differentiate between the neurons that fire due to noise (hallucination) and those that fire due to external stimulation. Thus, AVH might be the neural response of strongly connected neurons in the absence of external input (Hermann et al, 2005). One example of evidence for such processes are the so-called Ganzfeld-induced hallucinatory experiences (Wackermann et al, 2008).

Data Sharing. Given the difficulty of gathering sufficient amounts of data, we should consider sharing analysis tools and/or data. The application of different methods to the same data would allow us to compare and contrast findings resulting from different analytic methods. In addition, we should attempt to establish simple but comprehensive standards for clinical and neurobiological data, which can be gathered for meta-analyses.

Conclusions

In the 1960s, improving the accuracy of the diagnosis was a primary goal of neurophysiological studies of schizophrenia. As the field matured and evidence accumulated that P1, N1, MMN, and P300 were all were disrupted in schizophrenia, efforts were made to understand which symptoms were responsible for the group effects. As discussed above, these efforts have been modestly successful: In the "trait" studies discussed above, P1, MMN, and P300 were all reduced in patients who hallucinate compared with those who do not. In the "state" studies, N1 was smaller during periods of hallucinations than during periods free of hallucinations. Also, EEG power across many frequencies was greater over left temporal lobe during the experience of hallucinations, as was phase coupling between frontal and temporal lobes. Together, these data suggest that both the hallucination state and trait tend to render auditory cortex "busy" or otherwise unavailable to process external auditory events. Attempts to use EEG and MEG data to study basic neural mechanisms, which may be responsible for AVH, have also met with some success. Our efforts to use human EEG and MEG data to understand the pathophysiology of AVH has been hindered by a number of factors, including poor anatomical resolution of the measures, poor assessment of symptoms, poor understanding of the phenomenon, poor models of the phenomenon, and decoupling of the symptoms from the neurophysiology with medications, and various medical and psychiatric comorbidities. Nevertheless, we are optimistic that thoughtful application and combination of new methods will provide critical information about antecedents of AVH, the circuitry supporting them, and the basic neural mechanisms responsible for them.

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Part II

State studies

Chapter 4

About the baby and the bathwater; the influence of stimulus detection on activation patterns during auditory hallucinations.

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Abstract

Introduction: Neuroimaging studies investigating auditory verbal hallucinations (AVH) have revealed involvement of several cortical structures. These findings may however be biased by brain activity related to stimulus detection and motor processes associated with the task to indicate the presence of AVH. Disentangling brain activation specifically related to AVH and to additional cognitive processes may help focus on the true neuronal substrates of AVH and strengthen the development of new focal treatment strategies.
Methods: Brain activation during AVH as indicated by button press was compared to brain activation during auditory stimulus detection indicated by button press. We performed two neuroimaging meta-analyses, assessing 10 AVH and 11 auditory stimulus detection studies. A random-effects activation likelihood estimation was performed using GingerALE to assess commonalities and differences across AVH and stimulus detection studies.
Results: Activity in the claustrum, pulvinar area, medial geniculum body, pyramis, culmen, putamen, insula, and parahippocampal, medial frontal, precentral, postcentral, superior temporal and right inferior frontal gyri was found to be specifically related to AVH. The pars opercularis of the left inferior frontal gyrus and the left transverse temporal gyrus were activated to a similar extent during AVH and auditory stimulus detection.
Discussion: Development of new focal treatment strategies for AVH may focus on the areas uniquely activated in the AVH analysis. The pars opercularis and the transverse temporal gyrus may not be directly involved in the experience of AVH itself, but rather in auditory stimulus detection.

1. Introduction

Auditory verbal hallucinations (AVH) are one of the prominent symptoms of psychosis. Indeed, approximately 70% of schizophrenia patients present with this symptom (Nayani and David, 1996; Slade and Bentall, 2002). AVH can be highly distressing, often disrupt social functioning and increase the risk for suicide (Cheung et al., 1997; Falloon and Talbot, 1981). Although the precise pathophysiological mechanism of AVH remains unknown, previous studies put a step forward in elucidating the brain processes related to this symptom by assessing brain activation during the state of AVH. In these 'symptom-capture' studies, hallucination episodes were contrasted with hallucination-free episodes, and results revealed significant activation of the bilateral inferior frontal gyri, bilateral (parieto)temporal areas and medial temporal lobe structures during AVH (Diederen et al., 2010; Jardri et al., 2010). One problem with this approach is that activation of some of the areas implicated in the experience of AVH may not be specific for the actual experience, but related to additional cognitive processes needed to indicate the presence of voices during the scans such as stimulus detection and motor activity. The non-specific parts of these paradigms resemble auditory target detection studies, in which a subject is typically asked to respond to a target sound that is contrasted to a baseline sound. Indeed, auditory target detection studies elicit activation patterns that resemble those observed during AVH, including activation in the inferior frontal and (parieto) temporal areas (Arja et al., 2010; Kiehl et al., 2001; Kiehl et al., 2005b). Elucidating the involvement of brain regions that are not specifically involved in AVH may help focus on the true neurobiological underpinnings of hallucinations. To this end, we conducted two meta-analyses, with one analysis assessing the AVH symptom-capture literature and the other one assessing auditory target detection studies.

2. Methods

2.1 Selection of studies

A systematic search of peer-reviewed articles in the English language was conducted to identify studies on AVH and auditory target detection published between January 1990 and October 2011, using the databases Pubmed and Embase. The following key words were used for studies on AVH: "Hallucinations" <AND> ("fMRI" <OR> "PET"). The following key words were used for studies on target detection: "Target detection" <OR> "stimulus detection" <OR> "novel stimuli" <OR> "novelty" <OR> "search task" <OR> "oddball" <AND> ("fMRI" <OR> "PET"). Furthermore, reference lists of the included studies were used to identify additional studies. A total of 484 target detection studies and 302 AVH studies were retrieved. These articles were assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/statement.htm; Supplementary Data S1 and S2). Articles on AVH and stimulus detection were excluded if they did not meet the following criteria:

1) A whole-brain analysis was conducted. Region of interest (ROI) analyses were excluded as this might bias the results towards predefined regions.
2) Independent component analyses (ICA) were excluded since they are not easily comparable with other fMRI or PET analyses (Tie et al., 2008).
3) Studies investigating fMRI signals during event-related potentials (ERPs) were excluded as possible mismatches between electroencephalography (EEG) and fMRI may influence the comparability of these studies with fMRI/PET-only studies (Ritter and Villringer, 2006).
4) Participants indicated the presence of auditory target stimuli or AVH by button press.

An additional criterion for the AVH analysis was:

5) A within-subjects contrast of periods of hallucinations versus non-hallucinations was studied.

Additional criteria for the stimulus detection analysis included:

6) The paradigm is an *auditory* target detection task with non-speech sounds. Auditory target detection tasks with speech targets were excluded to prevent identifying brain regions associated with the perception of speech instead of with the detection of an auditory stimulus. Stimulus detection studies have been conducted in several sensory modalities, including tactile, visual and auditory. We focused our analysis on auditory studies as the experience of AVH is in this domain.
7) A within-subjects contrast of brain activity during target sounds with non-target sounds was studied.

For studies with missing or incomplete data, an attempt was made to complete the data by email contact with the corresponding author. This attempt was successful only for the non-psychotic individuals with AVH in Diederen et al. (2011). Additional details regarding inclusion and exclusion of specific studies is provided in Supplementary Data S3. In total, 10 whole-brain AVH imaging studies were included with a total of 80 participants and 158 foci. In addition, 11 whole-brain target detection imaging studies were included with a total of 284 participants and 334 foci. All of the included AVH studies are provided in table 1 and the included stimulus detection studies are provided in table 2. From each of these studies, the significant ($P < .05$) coordinates (x,y,z) that were observed were extracted. Coordinates that were reported in Talairach space were converted to MNI coordinates using the Lancaster transform tal2icbm (Lancaster et al., 2007).

Table 1. Included studies measuring brain activity associated with auditory verbal hallucinations

Study	Imaging method	N	Nr of foci	Coordinates
Blom et al. (2011)	fMRI	1	31	Talairach
Diederen et al. (2011)	fMRI	21	19	MNI
Sommer et al. (2008)	fMRI	24	21	MNI
Hoffman et al. (2008)	fMRI	6	6	Talairach
Shergill et al. (2004)	fMRI	2	5	Talairach
Copolov et al. (2003)	PET	8	6	Talairach
Shergill et al. (2000)	fMRI	6	27	Talairach
Lennox et al. (2000)	fMRI	1 (x4)	19	Talairach
Dierks et al. (1999)	fMRI	1 (x3)	15	Talairach
Silbersweig et al. (1995)	PET	5	9	Talairach

Table 2. Included studies measuring brain activity associated with auditory target detection

Study	Imaging method	N	Nr of foci	Coordinates	Contrast
Witt et al. (2010)	fMRI	33	28	MNI	Target tone vs baseline tone
Arja et al. (2010)	fMRI	34	40	MNI	Target tone vs baseline tone
Petit et al. (2007)	fMRI	8	24	MNI	Target tone vs baseline tone
Laurens et al. (2005)	fMRI	10	48	Talairach	Go vs NoGo tone
Kiehl et al. (2001)	fMRI	10	35	Talairach	Target tone vs baseline tone
Stevens et al. (200)	fMRI	10	23	Talairach	Target tone vs baseline tone
Friedman et al. (2009)	fMRI	15	35	MNI	Target tone vs baseline tone
Vouloumanos et al. (2001)	fMRI	15	5	Talairach	Complex nonspeech vs baseline tone
Kiehl et al. (2005b)	fMRI	100	38	MNI	Target tone vs baseline tone
Liddle et al. (2006)	fMRI	28	31	Talairach	Target tone vs baseline tone
Wolf et al. (2008)	fMRI	21	27	MNI	Target tone vs baseline tone

2.2 Meta-analysis procedure: Activation likelihood estimation (ALE)

The two meta-analyses were performed using a widely used technique for coordinate-based meta-analysis of neuroimaging studies. Data were analyzed using the activation likelihood estimation (ALE) method implemented in the GingerALE 2.1 software (http://brainmap.org/ale; Eickhoff et al, 2009). This method treats reported foci as spatial probability distributions centered at the given coordinates. In this method, all the reported activation foci for each study are first modelled as three-dimensional Gaussian probability functions, which are summed across the experiments to generate a map of interstudy consistencies that estimate the likelihood of activation on a voxel-to-voxel basis. To find statistically significant areas of convergence between studies, a reference distribution was made to represent a random distribution between studies. The false discovery rate (FDR) method was used to correct for multiple comparisons at a significance threshold of $P < 0.05$ and a cluster size threshold of 100 mm^3. The analysis was constrained to the grey matter mask implemented in GingerALE. To test for overlap between the convergence found in the AVH and the auditory target detection analysis we computed a conjunction analysis between the ALE maps of the two meta-analyses. ALE results were exported as NifTI files into the Mricron software (http://www.sph.sc.edu/comd/rorden/mricron/) and overlaid on an anatomical template for visualization purposes.

3. Results

3.1 Auditory verbal hallucinations

Significant convergence across AVH-studies was found in several brain regions. The largest clusters of activation were found in the left putamen, the right insula and the left postcentral gyrus. Furthermore, activation was observed in the right medial frontal gyrus, the right inferior frontal gyrus and left insula. Other significantly activated brain regions across studies included the right postcentral gyrus, the bilateral claustrum, the left superior temporal gyrus, left precentral gyrus and the left parahippocampal gyrus. Cerebellar and thalamic regions were also activated. Detailed information about the coordinates of local maxima is shown in table 3 and a visual representation of the results is provided in figure 1.

3.2 Auditory target detection

Significant convergence across auditory target detection studies was found in the bilateral superior temporal gyrus, the anterior cingulate gyrus, the bilateral insula, the right claustrum, left postcentral gyrus, left posterior cingulate gyrus and left precentral gyrus. Furthermore, activation was observed in the bilateral inferior parietal lobule, left amygdala, bilateral putamen, bilateral culmen, inferior occipital gyrus, bilateral middle frontal gyrus, right inferior frontal gyrus and left superior frontal gyrus. Cerebellar and thalamic regions were also activated. Detailed information about the coordinates of local maxima is shown in table 4 and a visual representation of the results is provided in figure 1.

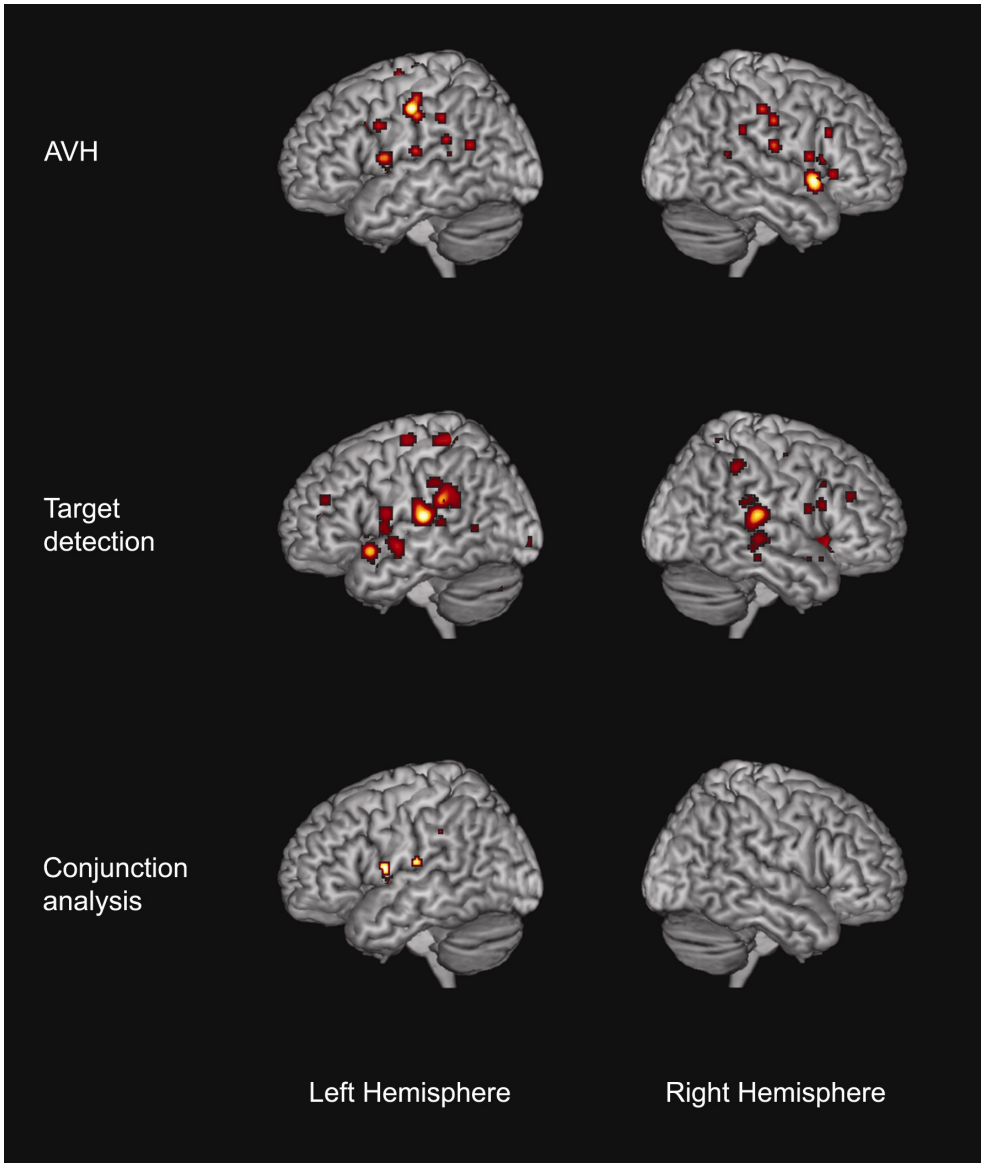

Figure 1. ALE-maps of converging activation across AVH-studies (first row), auditory target detection studies (second row) and an AVH target detection conjunction (third row). Abbreviations: L = left, R = right. All clusters were >100 mm^3 corrected with false discovery rate (FDR), $P < 0.05$.

3.3 Areas solely activated during AVH

The left thalamic pulvinar area, left claustrum, right medial frontal gyrus, left medial geniculum body, right postcentral gyrus, left parahippocampal gyrus and right pyramis of the cerebellum were found to be activated during AVH and not during auditory stimulus detection.

Table 3. Results of the AVH meta-analysis.

Cluster	Brain region	Laterality	MNI coordinates[a]			Cluster size (mm^3)
			x	y	z	
1	Putamen extending into the insula and precentral gyrus	Left	-44	0	6	1640
2	Insula	Right	53	11	-4	1304
3	Postcentral gyrus	Left	-47	-17	46	928
4	Pulvinar (Thalamus) extending into the claustrum	Left	-30	-29	6	568
5	Medial frontal gyrus	Right	6	6	61	504
6	Culmen	Right	20	-54	-21	440
7	Inferior frontal gyrus (pars opercularis)	Right	60	8	12	224
8	Inferior frontal gyrus (pars orbitalis)	Right	48	24	0	208
9	Medial geniculum body	Left	-16	-24	-4	192
10	Insula	Left	-55	-19	16	176
11	Postcentral gyrus	Right	56	-16	20	168
12	Insula	Left	-48	-40	24	168
13	Postcentral gyrus	Right	64	-16	36	160
14	Postcentral gyrus	Right	60	-24	44	160
15	Claustrum	Right	40	-4	4	152
16	Insula	Right	44	16	10	152
17	Superior temporal gyrus	Left	-60	-56	20	152
18	Postcentral gyrus	Left	-60	-20	40	152
19	Precentral gyrus	Left	-50	6	33	136
20	Parahippocampal gyrus	Left	-24	-33	-6	128
21	Claustrum	Right	28	27	-5	128
22	Pyramis	Right	20	-64	-30	112

[a]Coordinates are in the stereotaxic space of the weighted center for each cluster showing converging activation across AVH-studies.

3.4 Areas activated during AVH and auditory stimulus detection at spatially distinct regions

The left putamen, bilateral insula, left precentral and postcentral gyrus, right culmen, right inferior frontal gyrus, right claustrum and left superior temporal gyrus were activated in both meta-analyses, but at spatially distinct regions.

3.5 Conjunction analysis

A conjunction analysis on AVH and auditory target detection showed overlap between activated brain regions in the pars opercularis of the left inferior frontal gyrus and the left transverse temporal gyrus (figure 1). Detailed information about the coordinates of local maxima is shown in table 5 and a visual representation of the results is provided in figure 1.

4. Discussion

We compared brain activity during auditory stimulus detection to activity during auditory verbal hallucinations (AVH) using two meta-analyses. The aim of this comparison was to disentangle brain activity specifically related to AVH (the baby) from potentially non-specific aspects related to the detection and signalling of AVH (the bathwater). We found that the left thalamic pulvinar area, left claustrum, right medial frontal gyrus, left medial geniculum body, right postcentral gyrus, left parahippocampal gyrus and right pyramis of the cerebellum were uniquely activated during AVH. The left putamen, bilateral insula, left precentral and postcentral gyrus, right culmen, right inferior frontal gyrus, right claustrum and left superior temporal gyrus were activated in both meta-analyses, but at spatially distinct regions, suggesting different involvement in AVH compared to stimulus detection. Convergent activity at the same locations during AVH and stimulus detection was observed in the pars opercularis of the left inferior frontal gyrus (IFG) and the left transverse temporal gyrus (Heschl's gyrus). This implies that activity observed in these areas during AVH symptom capture studies may not be specific for AVH, but could be related to the signalling of AVH, and hence may prove to be merely bathwater. Future research could therefore better focus on areas that activated only during AVH, as these areas may turn out to be the baby.

Among the areas that uniquely activated during AVH were three peaks located in the right postcentral gyrus. Activity in this area may be related to the generation of inner speech (Shergill et al., 2002) and incorrect interpretation of inner speech has been hypothesized to underlie the genesis of AVH (Feinberg, 1978). Furthermore, activation of the left parahippocampal gyrus was found in the AVH meta-analysis only, suggesting that this region is specifically associated with AVH. Activity in this area during the experience of AVH has previously been linked to memory processes involved in the genesis of AVH (Jardri et al., 2010). Both meta-analyses showed activation in similar brain areas at spatially distinct regions, including the right IFG. AVH were related to activity in the pars opercularis and the pars orbitalis, while stimulus detection was related to activity in the pars triangularis and a distinct part of the pars opercularis. This implies that activation of right IFG regions during the experience of AVH is not related to stimulus detection or manual signalling. Perhaps activation of the right IFG in AVH reflects language production as has been suggested in previous studies (Sommer et al., 2008; Sommer and Diederen, 2009). The results of our two meta-analyses suggest that the areas in the AVH analysis having spatially distinct locations compared to the stimulus detection analysis may provide targets for neuromodulation to alter AVH proneness. Fore

example, individuals may be trained to decrease activity of these regions with a neurofeedback paradigm (McCarthy-Jones, 2012).

Findings from the conjunction analysis suggest that activation of the left transverse temporal gyrus and the pars opercularis of the left inferior frontal gyrus may not be specific for AVH but could also be related to the process of auditory target detection and the manual response to signal the hallucinatory episode. This suggestion contrasts with the widely accepted view that activity of the left inferior frontal area during AVH is related to speech generation as it includes Broca's area (Jardri et al., 2010). However, it may be hard to distinguish between specific and non-specific activity in these areas in studies that apply button-press paradigms to signal AVH. These findings show that button-press designs for symptom capture studies are problematic as they introduce additional neurocognitive processes related to stimulus detection, motor preparation and execution. Shergill et al. (2000) proposed an alternative design to circumvent this problem, the random-sampling paradigm, in which no manual response is required. This sparse imaging design capitalizes on the lag of several seconds between neuronal activity and the maximum blood-oxygen-level dependent (BOLD) signal. The patient verbally indicates when the random starts whether he or she hallucinated in the few seconds preceding the scan. In this way, the acquired scans can contain AVH episodes that are not contaminated with motor-related activity. While this design elegantly circumvents several problems of the button-press design, many hallucinatory episodes will be missed by means of random sampling, which severely decreases power. Moreover, similar to the button-press paradigm, attention effects are likely to be induced by this design, aspatients are required to continuously monitor whether they experienced hallucinations in the preceding seconds.

Independent component analysis (ICA) may provide a method to circumvent this problem (van de Ven et al., 2005), however which of the many obtained components are specifically related to AVH still warrants validation.

4.1 Limitations

The results of the present study should be interpreted with some caution. A difference in power may exist between the two meta-analyses. First, meta-analysis of neuroimaging AVH studies is limited by the small sample sizes of most studies (Kompus et al., 2011). Although both meta-analyses included a similar number of studies, the meta-analysis concerning auditory stimulus detection consisted of a significantly greater overall sample, leading to greater power in the stimulus detection meta-analysis than the AVH meta-analysis. Increasing power in the AVH analysis may lead to an increased number of uniquely activated areas in the AVH analysis, and subsequently to additional conjoint activity with the stimulus detection analysis. Second, AVH are heterogeneous across subjects, while the tones presented in the auditory detection tasks are kept constant within a study. This may also have affected power in the AVH studies compared to the auditory detection studies. Third, the tones that were presented in the auditory target detection studies were presented for a short time (typically

Table 4. Results of the auditory stimulus detection meta-analysis.

Cluster	Brain region	Laterality	MNI coordinates[a]			Cluster size (mm^3)
			x	y	z	
1	Superior temporal gyrus extending into the insula	Left	-60	-29	19	4232
2	Anterior cingulate gyrus	Right	0	12	42	3232
3	Superior temporal gyrus	Right	60	-27	13	1952
4	Insula extending into the precentral gyrus	Left	-47	1	8	1512
5	Claustrum extending into the putamen	Right	35	19	-4	1424
6	Lateral posterior nucleus (thalamus) extending into the mammilary body	Left	-14	-18	6	1096
7	Medial dorsal nucleus (thalamus)	Right	10	-15	4	1008
8	Superior temporal gyrus	Left	-49	12	-11	888
9	Postcentral gyrus	Left	-36	-38	65	736
10	Superior temporal gyrus	Left	-56	-6	-7	696
11	Anterior lobe extending into the culmen	Right	18	-56	-28	688
12	Superior temporal gyrus extending into the insula	Right	53	-24	-3	536
13	Posterior cingulate gyrus	Left	2	-30	26	496
14	Precentral gyrus	Left	-36	-14	65	376
15	Inferior parietal lobule	Right	54	-41	46	304
16	Amygdala extending into the putamen	Left	-30	-3	-13	296
17	Putamen	Right	24	3	-12	248
18	Inferior parietal lobule	Left	-51	-32	36	240
19	Inferior occipital gyrus	Left	-17	-94	-3	224
20	Culmen	Left	-6	-69	-3	176
21	Middle frontal gyrus	Left	-28	44	12	168
22	Inferior parietal lobule	Right	69	-33	24	168
23	Inferior frontal gyrus (pars triangularis)	Right	62	16	21	160
24	Superior frontal gyrus	Left	-38	42	24	144
25	Middle frontal gyrus	Right	39	36	26	136
26	Superior temporal gyrus	Left	-68	-36	9	128
27	Superior temporal gyrus	Right	45	-28	16	128
28	Inferior frontal gyrus (pars opercularis)	Right	52	7	18	120

[a]Coordinates are in the stereotaxic space of the weighted center for each cluster showing converging activation across target detection studies.

shorter than 1 second), while hallucinations are often longer in duration (Daalman et al., 2011). A further limitation is that most of the AVH studies included in the present meta-analysis were conducted in schizophrenia patients while the auditory detection studies were performed in healthy control subjects. Previous work indicated that although schizophrenia patients show a similar pattern of brain activity as healthy controls during auditory stimulus detection, this activity was lower as compared to the control subjects in several regions (Kiehl et al., 2005a).

In sum, we assessed commonalities in brain activation during AVH and auditory stimulus detection. Overlap in activation was found in the left inferior frontal gyrus and left transverse temporal gyrus, which indicates that activation in these areas might be merely bathwater rather than activity specifically related to AVH. Other areas, including the right postcentral gyrus and the left parahippocampal gyrus, were uniquely activated in the AVH paradigm and may prove to be the baby, on which future focal treatment strategies should focus.

Table 5. Results of the conjunction analysis.

Cluster	Brain region	Laterality	MNI coordinates[a]			Cluster size (mm^3)
			x	y	z	
1	Pars opercularis of the inferior frontal gyrus / precentral gyrus / amygdala	Left	-48	2	8	872
2	Transverse temporal gyrus	Left	-56	-20	15	160

[a]Coordinates are in the stereotaxic space of the weighted center for each cluster showing converging activation across target detection studies.

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Supplementary Data S1

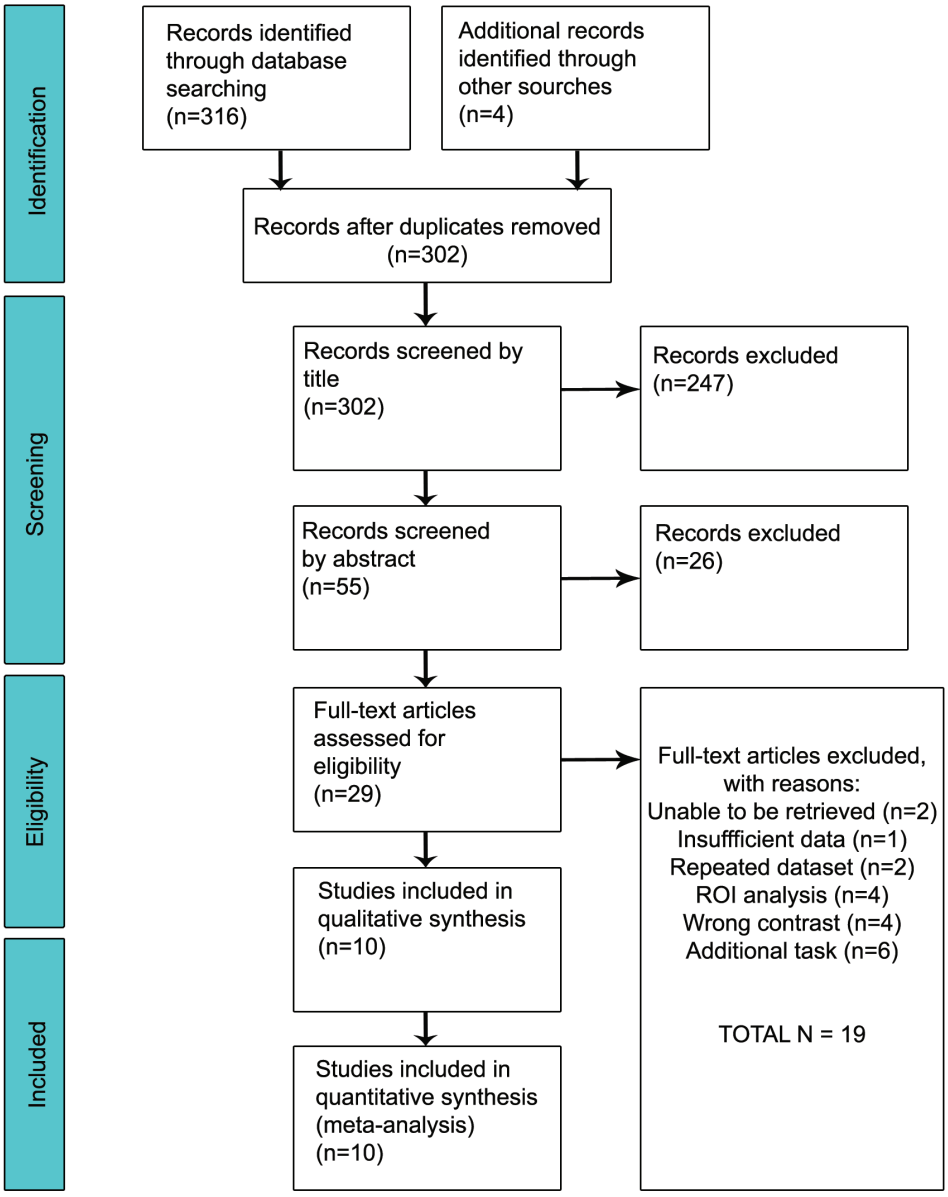

Fig 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the literature search for AVH studies.

Supplementary Data S2

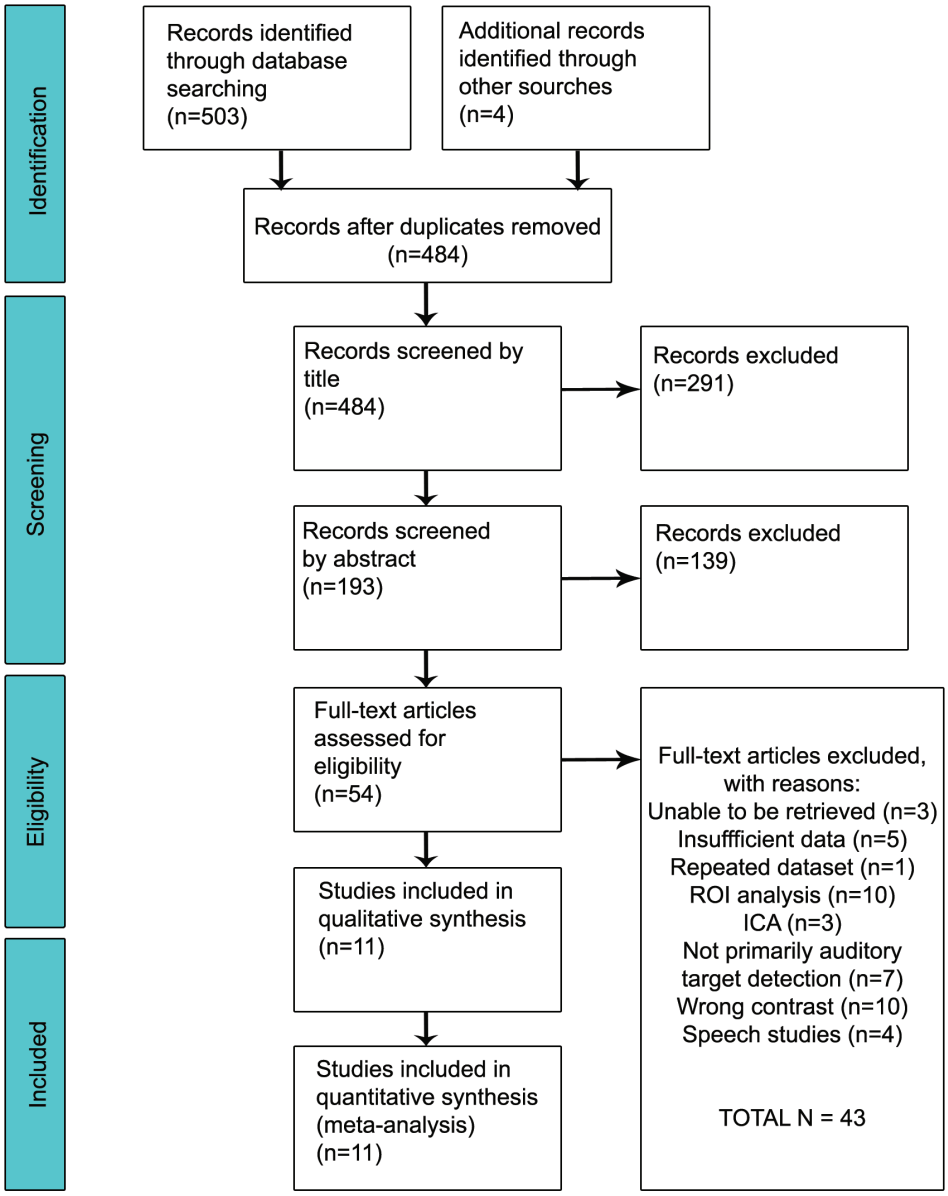

Fig 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the literature search for auditory stimulus detection studies.

Supplementary Data S3

From studies using the same dataset only the largest study was chosen for inclusion to ensure independent observations. In the target detection studies Stevens et al. (2005) and Kiehl et al. (2005) used the same dataset. As there was no evident preference for either one, Kiehl et al. (2005) was chosen randomly. Studies reporting foci for each patient separately were treated as separate studies with N = 1 (Dierks et al., 1999; Lennox et al., 2000). Single-case studies were not a problem as the activation likelihood estimation algorithm implements a weighting factor for the sample sizes of the included studies. Dierks et al. (1999) reported coordinates for two sessions of the same patient. To match the data of the other patients who only had one scanning session and thus increase reliability of the results, data of the first scanning session of this patient was chosen. From a study using two methods for determining AVH in each subject (Shergill et al., 2000), random sampling and button-press, only the foci reported for the button-press method were included as this method resembled the AVH-determining method of the other included studies.

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Chapter 5

Oscillatory cortical network involved in auditory verbal hallucinations in schizophrenia

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Abstract

Background: Auditory verbal hallucinations (AVH), a prominent symptom of schizophrenia, are often highly distressing for patients. Better understanding of the pathogenesis of hallucinations could increase therapeutic options. Magnetoencephalography (MEG) provides direct measures of neuronal activity and has an excellent temporal resolution, offering a unique opportunity to study AVH pathophysiology.

Methods: Twelve patients (10 paranoid schizophrenia, 2 psychosis not otherwise specified) indicated the presence of AVH by button-press while lying in a MEG scanner. As a control condition, patients performed a self-paced button-press task. AVH-state and non-AVH state were contrasted in a region-of-interest (ROI) approach. In addition, the two seconds before AVH onset were contrasted with the two seconds after AVH onset to elucidate a possible triggering mechanism.

Results: AVH correlated with a decrease in beta-band power in the left temporal cortex. A decrease in alpha-band power was observed in the right inferior frontal gyrus. AVH onset was related to a decrease in theta-band power in the right hippocampus.

Conclusions: These results suggest that AVH are triggered by a short aberration in the theta band in a memory-related structure, followed by activity in language areas accompanying the experience of AVH itself.

Introduction

Auditory verbal hallucinations (AVH) are one of the core symptoms of schizophrenia with approximately 70 % of all schizophrenia patients presenting with these symptoms (Nayani and David, 1996; Slade and Bentall, 2002). AVH can be highly distressing and often lead to a disrupted social life (Cheung et al., 1997). Treatment for AVH would benefit from a detailed understanding of the pathophysiology of AVH. This, however, remains elusive.

An intuitive way to investigate AVH-related brain activity is to contrast the AVH state with the non-AVH state. Several studies have used this approach (Copolov et al., 2003; Diederen et al., 2010; Dierks et al., 1999; Ishii et al., 2000; McGuire et al., 1993; Reulbach et al., 2007; Ropohl et al., 2004; Shergill et al., 2000; Silbersweig et al., 1995; Sommer et al., 2008; van de Ven et al., 2005). A recent meta-analysis implicated the bilateral insula, left middle and superior temporal gyrus, left hippocampus, left parahippocampal gyrus, left supramarginal gyrus, bilateral inferior frontal gyrus, and right internal globus pallidus in the experience of AVH (Jardri et al., 2010).

Another strategy to study AVH is to identify brain regions that show changes in activity surrounding the start of hallucinations, as this may shed light on its triggering mechanism. Five functional magnetic resonance (fMRI) studies examined this topic (Diederen et al., 2010; Hoffman et al., 2008; Hoffman et al., 2011; Lennox et al., 1999; Shergill et al., 2004). The three largest studies reported a decrease in activity in the parahippocampal gyrus preceding the experience of AVH, suggesting the involvement of memory processes in the genesis of AVH (Diederen et al., 2010; Hoffman et al., 2008; Hoffman et al., 2011).

The vast majority of neuroimaging studies investigating AVH used fMRI. However, MRI scanner noise may interact with hallucination-related brain activity, and blood oxygen level-dependent (BOLD) activity is an indirect measure of neuronal activity. More importantly, the temporal resolution of fMRI is poor, confounding precise analysis of brain activity surrounding AVH onset. In contrast, magnetoencephalography (MEG) is a silent technique and directly measures postsynaptic neuronal activity. Moreover, it has a high temporal resolution, which makes it especially suitable to study short time-windows surrounding AVH onset. Thus far, MEG studies investigated AVH in one or a few (maximal 3) patients, reporting increases in power in the left superior temporal gyrus and left dorsolateral prefrontal gyrus (DLPFC) during AVH (Ishii et al., 2000; Reulbach et al., 2007; Ropohl et al., 2004).

The first aim of the present study was to contrast the AVH and non-AVH state using MEG in a larger sample, enabling the use of group-level statistics in a region-of-interest (ROI) based design. The second aim was to investigate the neuronal correlates of AVH onset using MEG in a ROI based design.

Methods

Ethics statement

All patients gave their written informed consent and the study was approved by the ethics committees of the University Medical Center in Utrecht and the VU University Medical Center in Amsterdam.

Subjects

Twenty schizophrenia-spectrum patients experiencing frequent auditory verbal hallucinations (AVH) were recruited at the University Medical Center in Utrecht, the Netherlands. Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992) according to DSM-IV criteria by an independent psychiatrist. Eight out of twenty patients were excluded from analysis (3 patients experienced continuous AVH during recording, 3 patients did not experience AVH during recording, 1 experimental session was aborted because of anxiety of the patient, and we encountered technical difficulties during data-acquisition with 1 patient). Age and clinical characteristics for the 12 included patients (8 male, 4 female) are presented in table 1.

Data acquisition

Brain activity was recorded at the VU University Medical Center using a 151-channel whole-head neuromagnetometer (CTF Systems Inc., Port Coquitlam, BC, Canada) in a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany). Sampling rate was 625 Hz and the recording bandpass was 0 to 200 Hz. A third-order software gradient was applied for online noise cancellation (Vrba et al., 1999). At the beginning and end of each recording, the head position relative to the coordinate system of the helmet was recorded by leading small alternating currents through three head position coils attached to the subject's nasion and left and right pre-auricular points. Head position changes during the recording up to 1.0 cm were accepted. The three fiducial points were photographed for each participant for the purpose of co-registration of the MEG data to structural MRI scans.

During the MEG recording, patients lay in supine position and were instructed to close their eyes and move as little as possible. Subjects indicated the onset and offset of AVH by button-press. That is, subjects briefly pressed a button in the left hand at the start of AVH and briefly pressed a button in the right hand at the end of AVH. Neuromagnetic brain activity was recorded as continuous datasets of 1800 s duration. Due to practical considerations, the experiment was stopped early for 5 patients, resulting in datasets of 600, 1040, 1260, 1270 and 1770 seconds. To infer brain activation related to the button-presses, patients also performed a self-paced button-press task for 10 minutes, in which subjects alternatingly pressed the left and right buttons approximately every 10 seconds. Patients were specifically instructed not to relate the button-presses to the presence of AVH. Proper execution of this instruction was verbally verified after the experiment. Arousal levels were monitored

Table 1. Patient characteristics.

Subject	Sex	Age (years)	Age of onset AVH	Handedness	Psychiatric diagnosis	Antipsychotic medication / day
A	M	41	21	right	paranoid schizophrenia	clozapine 300 mg risperidone 3 mg
B	M	36	34	right	paranoid schizophrenia	none
C	F	52	19	right	psychosis NOS; borderline personality disorder	clozapine 600 mg
D	M	39	19	right	paranoid schizophrenia	chlorprothixene 200 mg
E	M	26	25	left	paranoid schizophrenia	flupenthixol 6 mg
F	F	57	8	right	paranoid schizophrenia	none
G	M	36	23	right	paranoid schizophrenia	clozapine 400 mg
H	M	41	6	right	paranoid schizophrenia	clozapine 300 mg
I	M	62	30	right	psychosis NOS	none
J	F	57	9	right	paranoid schizophrenia	quetiapine 600 mg
K	M	35	30	right	paranoid schizophrenia	none
L	F	42	26	right	paranoid schizophrenia	olanzapine 10 mg

AVH = auditory verbal hallucinations, M = male, F = female, NOS = not otherwise specified.

online and subjects were prompted when arousal levels dropped; these data segments were excluded from the analysis.

To facilitate source localization of the MEG data, high-resolution magnetic resonance imaging (MRI) scans were obtained with a 3 Tesla MRI scanner (Philips Medical Systems, Best, the Netherlands) (TR/TE: 9.86/4.6 ms, 1 mm^3 voxels, flip angle 8°). Co-registration of the MEG and MRI data was achieved by selecting the location of the nasion and pre-auriculars on the anatomical MRI. The fiducials were subsequently displayed on a 3D display of the head surface, as obtained from the segmented MRI, and visually compared with the location of the fiducials in the digital photographs taken during the MEG experiment. The location of the fiducials in the MRI was adjusted if there was a mismatch between the location of the fiducials on the MRI surface and the photographs. Severity of AVH during scanning was assessed directly after data acquisition using the Auditory Hallucinations Rating Scale (AHRS). This questionnaire assesses multiple characteristics of AVH such as the frequency of occurrence, loudness of the voices, length of AVH, and influence and discomfort of AVH as experienced by the patient (Hoffman et al., 2003). In addition to the above, the Positive and Negative Syndrome Scale (PANSS) was used to assess clinical symptomatology (Kay et al., 1987).

Data selection

Artifact-free segments were selected by visual inspection by two experienced MEG investigators

(RvL and AH). In the present study, the neural correlates of AVH were investigated by contrasting the AVH state versus the non-AVH state. In addition, the neural correlates of AVH onset were investigated by contrasting the first 2 seconds of the AVH state versus the 2 seconds preceding AVH onset. Data selection procedures were different for both analyses:
i) For the AVH-state vs. non-AVH state analysis, duration and number of selected time segments were identical for the hallucinatory and non-hallucinatory states within each subject, but these parameters were dissimilar across subjects in order to maximize the total amount of useful data for each participant. As the selection of longer segments led to fewer usable segments (because of large intra-individual heterogeneity in AVH and non-AVH duration and a higher chance of artifacts being present), maximization of data was achieved by selecting the segment length for which the product of number of segments and segment length was largest. Segments started at the button-presses' offset. To verify the effect of the button-presses, 5 s segments were selected from the control experiment, with segments starting at the left and right button-presses' offset. The number of segments in the control and AVH analysis was individually matched. Individual data regarding selected segments are provided in Supplementary Table S1.
ii) For the onset of AVH analysis, 2 seconds prior and 2 seconds following AVH onset were selected. This timeframe was chosen because of practical considerations; selection of longer timeframes would result in a sharp drop in useful segments because of the large heterogeneity in AVH and non-AVH duration, presence of artifacts, and decreased matching possibilities with the control experiment. Individual data regarding selected segments are provided in Supplementary Table S1. As a control condition, the same analyses were performed for the control experiment, with artifact-free segments of 2 seconds surrounding the left button-press serving as a control condition for the AVH onset analysis. The number of selected segments in the control analysis was matched individually to the AVH onset analysis, and duration of the incorporated button-press was matched at the group-level.

Data analysis

Electromagnetic source analysis was conducted with the Synthetic Aperture Magnetometry (SAM) beamformer algorithm as implemented in the CTF software (Robinson et al., 1999). With this approach, an optimal spatial filter is constructed for each location in the brain individually using the entire array of MEG sensors. Estimates of neuronal activity in the target locations can then be obtained by projecting sensor power through the filter. These estimated timeseries have the same millisecond temporal resolution as the original MEG recording (Hillebrand et al., 2005) and are usually referred to as virtual electrode signals (Barnes and Hillebrand, 2003). Differential images of source power (pseudo-t maps) can then be constructed by contrasting the neuronal power in each location for two conditions (divided by a projection of the estimated sensor noise (Vrba and Robinson, 2001). In this experiment, beamformer images were constructed on a 5 mm^3 grid throughout the whole brain. Four separate frequency bands were selected for analysis (delta 0.5 – 4 Hz, theta 4 – 8 Hz, alpha 8 – 13 Hz, beta 13 – 30 Hz. The gamma frequency band (30 – 48 Hz) was not included as

high-frequency bands may be contaminated by muscle artefacts (Whitham et al., 2007).
The individual participants' beamformer images were spatially normalized to a template brain and then averaged across participants, following the procedure described in Singh et al (Singh et al., 2002). As a nonparametric approach was most appropriate given the small sample size, statistical analysis was performed using a nonparametric permutation test (SnPM) (Singh et al., 2003), using all possible permutations. The family-wise error (FWE) correction threshold was set at P = 0.05, combined with an extent threshold of 6 contiguous voxels (Binder and Urbanik, 2006; Prat et al., 2007; Schipul et al.). For the hypothesis-driven focus on specific areas, the analysis was conducted on anatomically defined ROIs, based on previous literature: i) For the AVH state versus non-AVH state analysis, ROIs were selected based on a recent neuroimaging meta-analysis that implicated the bilateral insula, left middle and left superior temporal gyri, left hippocampus and left parahippocampal gyrus, left supramarginal gyrus, bilateral inferior frontal gyrus, and right globus pallidus in the experience of AVH (Jardri et al., 2010). To increase sensitivity of the statistical tests, motor areas were not included in the mask, as any potential activation in these regions is likely to be related to the button-presses. ii) For the AVH onset analysis, ROIs included the bilateral hippocampus and parahippocampal gyrus (Diederen et al., 2010; Hoffman et al., 2008; Hoffman et al., 2011). Recent studies have demonstrated the efficacy of MEG in detecting and localizing hippocampal activity (Cornwell et al., 2010; Hanlon et al., 2011; Quraan et al., 2011; Riggs et al., 2009). In order to explore whether findings in this analysis are prolonged or primarily occurring in the small-time-frame surrounding AVH onset, this reduced mask was also applied to the AVH state versus non-AVH state data. Time-frequency plots were calculated at peak loci for each individual using a Morlet wavelet transform. These peak loci were located in close proximity to the peaks observed in the group analysis.
To elucidate potential associations between symptomatology and changes in neuronal activity, in a secondary analysis correlations between changes in delta, theta, alpha and beta-band activity in analysis i) and analysis ii) and scores on the AHRS and the positive symptom scale of the PANSS were investigated. Detailed information regarding this analysis is provided in Supplementary data S2.
ROIs were defined using the WFU Pickatlas software tool (version 2.4, Wake Forest University, Winston-Salem, NC, USA; http://fmri.wfubmc.edu/cms/software) and the AAL library (Tzourio-Mazoyer et al., 2002), and subsequently resliced to the coordinate system of the spatially normalized MEG datasets. To be able to assess cortical activity at the boundaries of the masks, both masks were inflated by 2 mm. Anatomical labelling of significant activation clusters was performed with the WFU Pickatlas using the AAL library, and MRIcron was used for visualization of group activation maps (http://www.sph.sc.edu/comd/rorden/mricron/).

Results

Behavioral

Patients had an average of 35 AVH per 30 minutes during the experiment (SD 25; range 12 – 88). Average duration of AVH was 27 s (SD 18; range 6 – 66) and average duration of the

non-AVH periods was 40 s (SD 30; range 2 – 108). Mean total AHRS score was 26 (SD 6; range 19 – 41). Mean total score on the positive subscale of the PANSS was 16 (SD 3; range 11 - 22), mean total score on the negative subscale was 15 (SD 5; range 10 -26), and mean total score on the general psychopathology subscale was 28 (SD 7; range 21 - 42).

AVH versus non-AVH state analysis

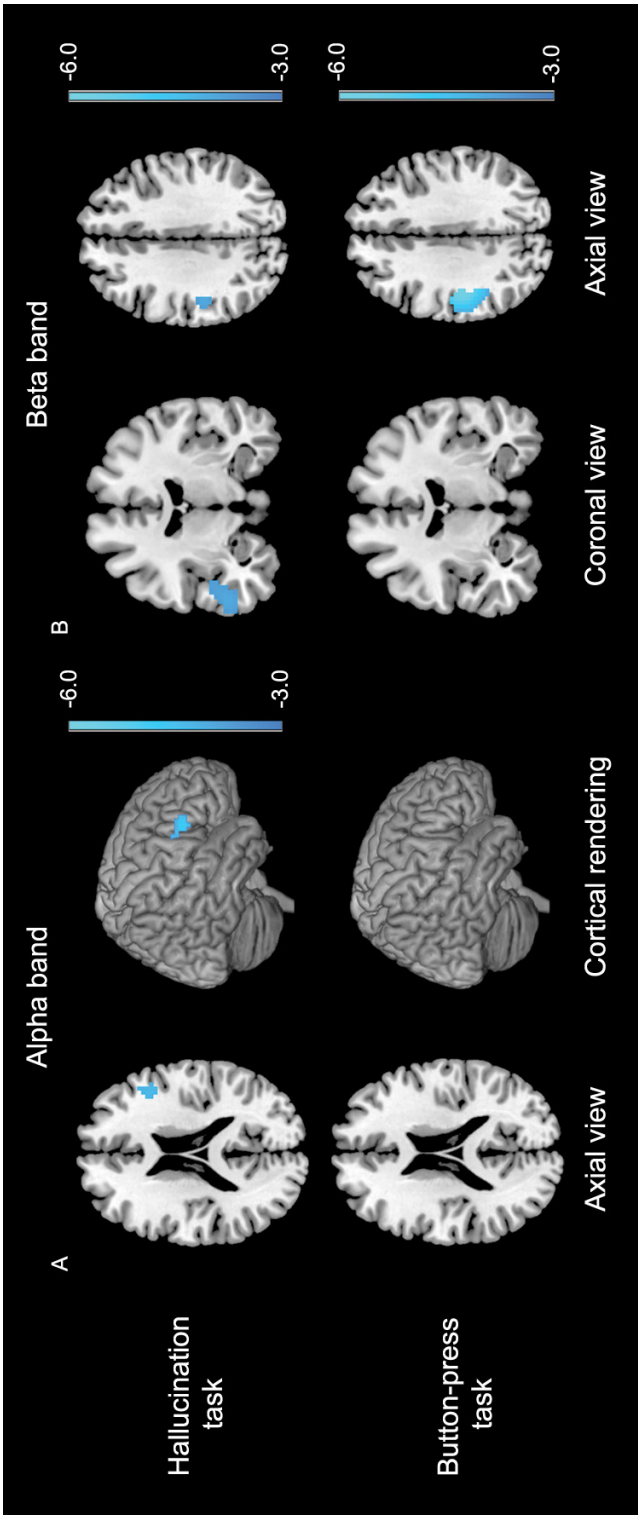
MEG imaging revealed a statistically significant relative decrease in alpha-band neuronal power in the right inferior frontal gyrus, while no changes in alpha-band power were found in the control experiment (fig 1a). For the beta band, significant relative decreases in power were observed in the left middle temporal gyrus extending into the left superior gyrus and in the left supramarginal gyrus. Changes in beta-band power in the latter region was also found in the control experiment (fig 1b). Detailed information about the coordinates of local maxima and corresponding cluster sizes is shown in table 2.

AVH onset analysis

A significant relative decrease in theta-band power was found in the right hippocampus extending into the amygdala in the 2 seconds following AVH onset versus the 2 seconds preceding AVH onset. For the self-paced button-press task, no change in theta-band power was found (fig 2), while for the other frequency-bands no changes in power were observed in both experiments. Detailed information about the coordinates of local maxima and corresponding cluster sizes are shown in table 3, and time-frequency representations of two representative subjects are shown in Supplementary Data S3. Application of the AVH-onset mask to the AVH state versus non-AVH state data yielded no significant results in any frequency band.

Associations between clinical symptoms and changes in neuronal activity

No significant correlations were found between total AHRS scores and changes in neuronal activity related to either the experience of AVH or the onset of AVH. Sum scores of the positive symptom scale of the PANSS correlated positively with AVH-related changes in beta band power in the left inferior frontal gyrus ($k = 27$; MNI coordinates -18 21 -18), indicating that increased levels of positive symptoms were related to increased changes in beta-band neuronal power during the occurrence of AVH in this structure. No significant correlations were found between sum scores on the positive symptom scale of the PANSS for the AVH onset analysis.



Figs 1a and 1b. Results for the AVH versus non-AVH analysis for the alpha and beta frequency bands. Data are superimposed on a template brain and are presented in neurological convention (right is right). P<0.05, FWE corrected. The color bar indicates t-values.

Table 2. Significantly activated voxels and locations of local maxima during auditory verbal hallucinations in the group hallucination task and button-press task.

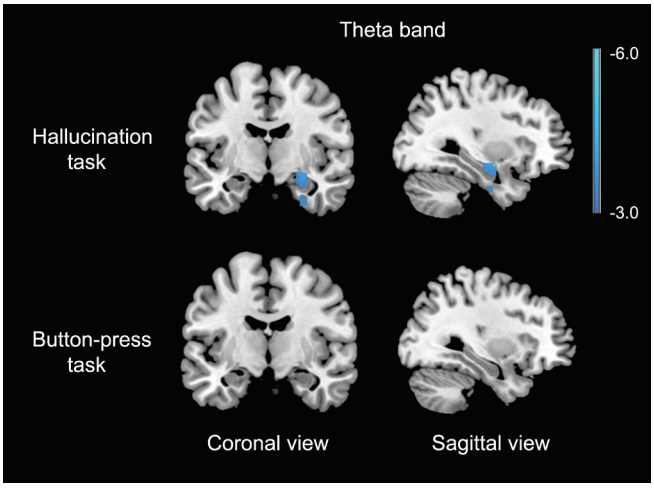
Task	Frequency band	Increase/ decrease power	Area	Montreal Neurological Institute Coordinates (x, y, z)	t	Cluster size
Hallucination task	Delta	-				
	Theta	-				
	Alpha	Decrease	Right inferior frontal gyrus	48 21 15	4.88	36
	Beta	Decrease	Left superior temporal gyrus / Middle temporal gyrus	-60 -12 -12	4.04	48
		Decrease	Left supramarginal gyrus	48 -33 33	4.00	12
Button-press task	Delta	-				
	Theta	-				
	Alpha	-				
	Beta	Decrease	Left supramarginal gyrus / Postcentral gyrus	-42 -24 33	5.76	229

Discussion

This is the first study to utilize the excellent temporal resolution of MEG to investigate brain activity related to AVH onset. It is also the first study investigating the neural correlates of AVH employing MEG in a substantial sample (n=12), enabling group-wise analysis.
AVH were associated with a decrease in alpha-band power in the right inferior frontal gyrus and with a decrease in beta-band power in the left middle and superior temporal gyrus. The motor control task did not result in any changes in neuronal power in these areas. AVH onset was accompanied by a decrease in theta-band power in the right hippocampus while in the control task no change in theta-band power was observed in this brain structure.

AVH state versus non-AVH state analysis

AVH-related changes in the left temporal cortex, where we observed a decrease in beta-band power, are usually interpreted as auditory processing related to the perception of voices (Dierks et al., 1999). It has been suggested that beta oscillations are involved in underscoring a stimulus as novel or salient (Kisley and Cornwell, 2006; Uhlhaas et al., 2008). The observed change in activity in this frequency band during the experience of AVH is as such in line with



Figs 2a and 2b. Results for the AVH onset analysis superimposed on a template brain. Data are presented in neurological convention (right is right). P<0.05, FWE corrected. The color bar indicates t-values.

Table 3. Significantly activated voxels and locations of local maxima in the group hallucination onset analysis for the hallucination task and the control task.

Task	Frequency band	Increase/ decrease power	Area	Montreal Neurological Institute Coordinates (x, y, z)	t	Cluster size
Hallucination task	Delta	-				
	Theta	Decrease	Right hippocampus / amygdala	30 -9 -12	3.93	28
	Alpha	-				
	Beta	-				
Button-press task	Delta	-				
	Theta	-				
	Alpha	-				
	Beta	-				

the fact that AVH are often of high emotional content (frightening) and therefore of high salience. An alternative explanation linking the decrease in beta-band power to AVH may be that the process of corollary discharge (i.e. a signal originating in frontal speech production areas that is sent to auditory perception areas to indicate that forthcoming thought is self-generated) is disturbed through the decrease in oscillatory power in this frequency band. For the observed decrease in alpha-band power in the right inferior frontal gyrus several explanations are possible, including processing of linguistic emotional information, detection

of salient events and dysfunctional inhibition processes (Hampshire et al., 2010; Lenartowicz et al., 2011; Rota et al., 2009).
The present findings are partially consistent with those of previous studies. Functional MRI studies have implicated changes in activity in the left middle and left superior temporal cortex and right inferior frontal gyrus during AVH (Allen et al., 2008; Diederen et al., 2010; Jardri et al., 2010; Sommer et al., 2008). Our findings are also partially in line with previous MEG studies, reporting increases in theta-band and beta-band power in the left superior temporal gyrus (STG) (Ishii et al., 2000; Ropohl et al., 2004), and an increase in beta-band activity in the left STG extending into the left dorsolateral prefrontal cortex (DLPFC) during AVH (Reulbach et al., 2007). In the current study, the left STG was associated with a decrease instead of an increase in beta-band power during AVH. The previously published MEG studies reported single cases (Ishii et al., 2000; Ropohl et al., 2004) or three cases analyzed individually (Reulbach et al., 2007). Single subject analyses yield more variable and less reliable results than group-wise analysis, providing a possible explanation for the divergent findings (van Lutterveld et al., 2011). An EEG study also implicated the left STG, albeit in the alpha band (Sritharan et al., 2005). The divergent findings in frequency bands between EEG and MEG may be explained by differences in methodologies. EEG sensors pick up electrical activity related to neuronal activity and these signals are smeared out by the skull. MEG measures magnetic activity, which is not substantially affected by the skull.

AVH onset analysis

We observed a decrease in theta-band power in the hippocampus during AVH onset. Animal research of the hippocampus has revealed some of the functions of theta-band oscillations in memory retrieval. Cell recordings in the hippocampus in rat models have provided support that theta and gamma oscillations together form a code for neural representations of memorized items (Behrendt, 2010; Jensen and Lisman, 1996). Each cycle of the fast gamma rhythm is generated by a different neural ensemble, and represents a single item in memory (Lisman and Idiart, 1995; O'Keefe and Recce, 1993). The gamma cycles are ordered by much slower theta-waves, i.e. theta waves form the 'punctuation' of the gamma oscillations and as such the items in memory they represent (Lisman and Idiart, 1995). Moreover, the theta waves on which the gamma oscillations are superimposed coordinate the pattern of neuronal firing over larger brain areas (Lisman and Buzsaki, 2008). The proposed function of theta oscillations would be to integrate different representations of perception, memory and association into one coherent concept, e.g. a congruent line of thoughts and experiences (Lisman and Buzsaki, 2008; Lisman and Idiart, 1995). The onset of a hallucination can be viewed as an interruption of this coherent line (Lisman and Buzsaki, 2008). Hence, the change in theta rhythm observed in the hippocampus and parahippocampal gyrus at the onset of hallucinations may reflect the cessation of a coherent line of thoughts and perception, and perhaps the transition from a state of consciousness that is focused around perception of information from the sense organs to a state that relies to a higher degree on internal representations collected from memory.
In the present study no changes in hippocampal theta-band activity were found in the AVH

state versus the non-AVH state, yet a transient change in theta-band activity surrounding AVH onset was found, suggesting that a temporary disturbance in theta-band activity may underlie the genesis of hallucinations through a short aberration in theta-band mediated integration of different representations. The present findings of changes in neuronal power in the theta band in the hippocampus surrounding AVH onset are partially in line with previous fMRI studies, which reported changes in activity in the parahippocampal gyrus to precede the onset of AVH (Diederen et al., 2010; Hoffman et al., 2008; Hoffman et al., 2011). This finding is also consistent with a recent cognitive model that postulates that AVH arise from dysfunctioning in memory processes and top-down inhibitory processing, in which the latter may be mediated by the right inferior frontal gyrus (Badcock, 2010; Badcock et al., 2005; Lenartowicz et al., 2011; Waters et al., 2006).

As AVH often consist of emotional content, future research could focus on elucidating the relationship between emotional valence of AVH and neuronal activity related to the symptom (Daalman et al., 2010).

Limitations

A limitation of this study is that AVH were assessed by self-report, rendering the precision of AVH onset and offset subject to the patients' accuracy. Furthermore, we used a self-paced button-press paradigm as a control task. Although this paradigm is often used to investigate the effect of button-presses in a hallucination task (Hoffman et al., 2011; Sommer et al., 2008), the process of attention may not be similar in both tasks, as patients are required to press the buttons to indicate the presence of hallucinations in the hallucination task ('externally triggered') and the control task is self-paced ('internally triggered'). As such, we recommend that future studies incorporate an additional non-self-paced control task, e.g. indicating the presence of externally presented auditory stimuli. Another limitation is that the presence of AVH during the control task may have influenced results. This is however not likely, as the self-paced button-presses were not related to the presence of AVH, leading to the presence of AVH in both parts of the contrast, and resulting in presumably no or minor impact on the analysis. Finally, most of the patients in the current study were on antipsychotic medication. This may have influenced results, as antipsychotic agents have been reported to affect theta-band activity (Centorrino et al., 2002).

To summarize, this is the first study focusing on the small time-frame surrounding AVH onset which could identify the triggering mechanism of hallucinations. The onset of AVH was accompanied by changes in theta-band power in the right hippocampus. Furthermore, AVH were associated with a decrease in alpha-band power in the right inferior frontal gyrus and with decreases in beta-band power in the left middle and superior temporal gyri, which are regions generally implicated in auditory and language processes. These results suggest that AVH are triggered by a short aberration in the theta band in the hippocampus, followed by activity in auditory areas accompanying the experience of hearing voices. We speculate that

these aberrations may disturb the coherency of thoughts and perception such that there is an increased focus on internal representations collected from memory. New treatment options, such as deep brain stimulation, may target hippocampal structures in order to restore their normal function and impede the onset of AVH.

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Supplementary Data S1

Table 1. Length and number of selected segments for the auditory verbal hallucination (AVH) analysis and the AVH onset analysis per subject.

	Subject	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**
AVH and non-AVH segments	Length (s)	8.1	15.1	25.2	14.1	4.0	16.0	10.8	6.2	7.0	5.0	5.0	5.8
	Number	13	8	5	9	29	6	4	22	13	5	6	12
	Total (s)	105	121	126	127	116	96	43	136	91	25	30	70
Before and after AVH onset segments	Length (s)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
	Number	20	12	3	14	26	4	5	25	17	9	7	16
	Total (s)	40	24	6	28	52	8	10	50	34	18	14	32

Supplementary Data S2

To elucidate potential associations between symptomatology and changes in neuronal activity, correlations between total AHRS scores and total PANSS positive subscale scores on one hand and changes in delta, theta, alpha and beta-band activity on the other hand were investigated.

i) Correlations between total AHRS scores and changes in neuronal activity in the AVH state versus non-AVH state analysis were investigated for each ROI separately (10 ROIs: the left insula, right insula, left middle and left superior temporal gyri, left hippocampus and left parahippocampal gyrus, left supramarginal gyrus, left inferior frontal gyrus, right inferior frontal gyrus, and right globus pallidus.

ii) Correlations between total AHRS scores and changes in neuronal activity during AVH onset were investigated for each ROI separately (4 ROIs: the left parahippocampal gyrus, right parahippocampal gyrus, left hippocampus and right hippocampus).

Non-parametric, multi-subject simple regression analyses were carried out to investigate whether total AHRS scores were correlated with changes in neuronal activity in any of the predefined ROIs using SnPM (5000 permutations). To correct for multiple comparisons, the family-wise error (FWE) correction threshold was set at $P = 0.0017$ (0.05 divided by the total number of tests), combined with an extent threshold of 6 contiguous voxels.

Supplementary Data S3

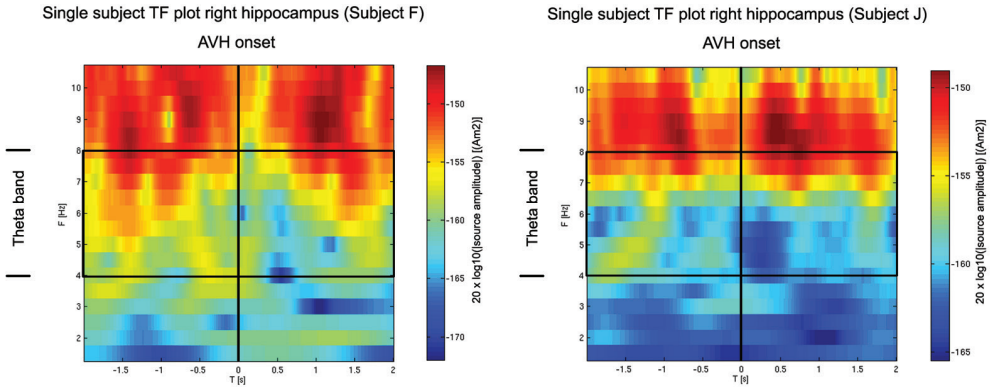

Fig. 1. Time-frequency representation (TRF) plots of source peak activity in the right hippocampus surrounding AVH onset in two representative subjects. The frequency band in which a significant difference was observed in this brain region (group analysis) is indicated by the black box. The vertical line indicates the onset of hallucinations. TF: time-frequency, AVH: Auditory verbal hallucinations.

Part III

Trait studies

Chapter 6

Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations

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Abstract

Objective: Schizophrenia is associated with aberrant event-related potentials (ERPs) such as reductions in P300, processing negativity and mismatch negativity amplitudes. These deficits may be related to the propensity of schizophrenia patients to experience auditory verbal hallucinations (AVH). However, AVH are part of extensive and variable symptomatology in schizophrenia. For this reason non-psychotic individuals with AVH as an isolated symptom provide an excellent opportunity to investigate this relationship.
Methods: P300 waveforms, processing negativity and mismatch negativity were examined with an auditory oddball paradigm in 18 non-psychotic individuals with AVH and 18 controls.
Results: P300 amplitude was increased in the AVH group as compared to controls, reflecting superior effortful attention. A trend in the same direction was found for processing negativity. No significant differences were found for mismatch negativity.
Conclusion: Contrary to our expectations, non-psychotic individuals with AVH showed increased rather than decreased psychophysiological measures of effortful attention compared to healthy controls, refuting a pivotal role of decreased effortful attention in the pathophysiology of AVH.

1. Introduction

Decreased electrophysiological measures of attention, such as reduced P300 amplitude, are among the most consistently reported neurobiological abnormalities in schizophrenia (for an overview see Jeon and Polich, 2003). The P300 event-related potential (ERP) is a positive deflection of the electroencephalogram (EEG), occurring approximately 300 ms after the presentation of infrequent (deviant) stimuli. Since the P300 amplitude is largest when subjects are requested to respond to the deviant stimulus, P300 waveforms are usually assessed in an oddball paradigm, in which the participant actively discriminates presented deviant stimuli from standard stimuli (Sutton et al., 1965). The P300 amplitude is thought to reflect aspects of further (conscious) processing of relevant stimuli (Näätänen, 1990), and is proportional to the amount of attentional resources that are allocated to the processing of a stimulus (Grillon et al., 1991; Kramer and Strayer, 1988; Sutton et al., 1965). The P300 amplitude has been proposed as a potential endophenotype for schizophrenia (Bramon et al., 2004), i.e. a biological marker that is meaningfully associated with the disease.

Another electrophysiological measure of attention associated with schizophrenia is processing negativity (PN). Processing negativity is elicited whenever a participant is requested to selectively attend to a certain stream of information, while having to ignore another (e.g. listen to a male voice, while ignoring a female voice or attend to stimuli to the left ear, while ignoring stimuli to the right ear). This negative deflection is thought to represent a mechanism by which the brain selectively attends to relevant stimuli (Näätänen, 1990). Reduced PN has been reported in medicated (Baribeau-Braun et al., 1983; Iwanami et al., 1998) as well as unmedicated schizophrenia patients (Michie et al., 1990; Ward et al., 1991).

In contrast to P300 and PN waveforms, mismatch negativity (MMN) is best elicited by an oddball paradigm in the absence of attention. This negative deflection to deviant stimuli is thought to reflect the automatic, pre-attentive detection of auditory changes (Näätänen et al., 1978; Näätänen, 1990). Reduced MMN amplitude in schizophrenia patients is a robust finding (Näätanen and Kahkonen, 2009; Umbricht and Krljes, 2005).

P300, PN and MMN waveform abnormalities may be related to the neuropathology of schizophrenia, or to specific parts of the disorder. Information about associations between attention and specific symptoms of schizophrenia could increase understanding of the role attention may play in the pathophysiology of schizophrenia. However, in schizophrenia patients it is difficult to disentangle specific associations with symptom clusters, as the presence and severity of many symptoms are usually correlated. A characteristic symptom of schizophrenia is auditory verbal hallucinations (AVH), occurring in at least 70% of the patients (Sartorius et al., 1986; Slade, 1988). Previous studies have found an association between P300 amplitude and AVH in schizophrenia patients. Havermans et al. (1999) reported a reduction in P300 amplitude in schizophrenia patients with chronic auditory hallucinations compared to patients without auditory hallucinations, and Turetsky et al. (1998) found an inverse correlation between the severity of auditory hallucinations and a frontal P300 subcomponent. It could therefore be hypothesized that the liability of schizophrenia patients to experience AVH may be associated to their decreased attentional capacity. However, most schizophrenia patients

with AVH also experience delusions, some degree of disorganisation, and negative symptoms. In addition, patients who do not experience AVH may still be predisposed to hallucinate and develop AVH in another stage of their illness. Interestingly, 10–15% of healthy individuals also experience AVH (Tien, 1991). In this population, AVH occur in the absence of delusions and negative or cognitive symptoms, although the tendency for schizotypal behavior and delusional beliefs is higher than in healthy individuals without AVH (Sommer et al., 2008). Moreover, these non-psychotic individuals with AVH are not using antipsychotic medication, nor do they have a history of hospitalization. Therefore, non-psychotic individuals with AVH provide an opportunity to study whether the deficits of attention associated with schizophrenia are specifically related to AVH, or rather to other aspects of the disease such as negative symptoms or cognitive dysfunction.

Because non-psychotic individuals with AVH and schizophrenia patients share a single isolated symptom, we hypothesize that abnormalities in P300, MMN, and PN amplitudes are similar to those found in schizophrenia patients and will be reduced compared to control subjects without AVH.

2. Methods

2.1. Subjects

Eighteen non-psychotic individuals with AVH and 18 controls were recruited via a website: www.verkenuwgeest.nl ("explore your mind"), see Sommer et al. (2008) for an extended description of the recruitment and selection procedure. All non-psychotic individuals with AVH participated in a previous study by our group, which had the following inclusion criteria (Sommer et al., 2008): (1) Voices were distinct from thoughts and had a "hearing" quality, (2) voices were experienced at least once a month, (3) absence of psychiatric disorders other than anxiety or depressive disorder in full remission as assessed in a psychiatric examination using the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) and the structured clinical interview for personality disorder (SCID-II) (First et al., 1995), (4) absence of alcohol or drug abuse for at least 3 months prior to the assessments, (5) no chronic somatic disorder.

Non-psychotic subjects with AVH and controls without AVH did not meet criteria for a DSM-IV diagnosis, as measured with the CASH and SCID-II interviews. Depressive disorder in complete remission was not an exclusionary criterion. Although the healthy subjects with hallucinations did not have clinical delusions, they did have an elevated schizotypal as shown on the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). The scores on the Peters et al. Delusions Inventory (PDI) (Peters and Garety, 1996) also showed an elevated paranoid tendency. The combination of hallucinations (perceptual aberrations) and magical ideation present in most non-psychotic individuals with AVH made them score on at least three items on the DSM-IVR criteria for schizotypal personality disorder. However, there was no lack in social capacity nor did the subjects have inadequate or constrained affect. Other important arguments why the subjects did not meet criteria for schizotypy were that their magical beliefs

were largely socially accepted (mainly spiritual ideas) and that they were functioning well. Individuals in the hallucinating group experienced AVH for a mean period of 31 years (s.d.: 15). Neither the non-psychotic individuals with AVH nor the healthy controls had ever participated in psychophysiological research before. To confirm the absence of drug abuse, urine samples were collected and tested for opiates, amphetamines/XTC, cocaine and cannabis. Subjects were tested at 500, 1000, and 6000 Hz (40 dB) to screen for hearing deficits. Smoking and intake of caffeine was not allowed from 1 h prior to testing. Mean age of the AVH group (3 males, 15 females) was 42.8 years (s.d. 11.7), while mean age of the healthy age and gender matched control group (3 males, 15 females) was 43.8 years (s.d. 13.1). The study was approved by the local ethics committees of the University Medical Center of Utrecht. All participants gave their written informed consent before participation in the study.

2.2. Stimulus presentation

All auditory stimuli were presented by a computer using Presentation® (Neurobehavioral systems Inc, Albany, CA, USA) software (soundcard: Creative soundblaster®, 5.1) and presented binaurally through stereo insert earphones (Eartone ABR, C and H Distributors Inc, Milwaukee, WI, USA). The soft- and hardware settings were calibrated by means of an artificial ear (Brüel and Kjær, type 2133; Brüel and Kjær, Naerum, Denmark) in order to make sure that the stimuli at the subjects' ears had the intended intensities.

2.3. Paradigm

The selective attention paradigm was described previously (see Oranje et al. (2008)), and consisted of 400 stimuli presented in a semi-random fashion (equally distributed) to the subjects' right and left ears. The currently used P300 paradigm has very recently been validated in a large group of antipsychotic naïve, first-episode patients with schizophrenia, who showed a highly significant reduction in P300 amplitude compared to their age and gender matched healthy controls (Oranje et al., submitted). Two types of stimuli were presented with a randomized interstimulus interval (ISI) between 700 and 900 ms: standard tones (1000 Hz, 75 dB, duration 50 ms), with a probability of 80% of the cases, and deviant tones (1200 Hz, 75 dB, duration 50 ms), with a probability of 20% (attended deviants were never presented immediately following each other). Subjects were required to push a button as quickly as possible if the deviant tone was perceived in the previously designated ear. Following this initial task, the subjects were presented an identical task in which they had to monitor the other ear for deviant stimuli. During the task, the subjects had to maintain their gaze at a fixation cross, situated at eye level on the opposite wall from which they were seated. Task performance was assessed by means of the numbers of correct responses and false alarms, as well as the mean reaction time to hits. Reaction time was measured as the latency of the subjects' response from the onset of the target. Responses to target stimuli were classified as a hit if they occurred within 200 to 900 ms following presentation of the target stimulus. A miss was designated as any target not followed by a response, and a false alarm was a

response to a non-target stimulus.

2.4. Electrophysiological recordings

Electroencephalography data were recorded with BioSemi hardware (BioSemi, Amsterdam, the Netherlands) using a cap with 32 Active Two electrodes, arranged according to the 10–20 system. Eight facial electrodes were attached for reference purposes and ocular corrections. Three reference electrodes were attached on the left and right mastoids and on the tip of the nose. Of the remaining five electrodes, two electrodes were placed under the right eye, one aligned with the pupil, the other electrode positioned just laterally. For horizontal electrooculography (EOG) assessment, two electrodes were placed at the outer canthus of each eye. For vertical EOG assessment one electrode was placed supraorbitally (aligned with the pupil) at the right eye. Signals were digitized on-line by a computer at a rate of 2048 Hz.

2.5. Signal analysis

EEG and EOG signals were processed using BESA software. Recordings were down-sampled to 250 Hz, filtered (40 Hz low-pass filter, 24 dB) and epoched between 100 ms prestimulus and 900 ms poststimulus. After this, epochs were baseline-corrected, and the EEG was corrected for eye artifacts (eye-blinks and movements) by using the adaptic method of BESA (Ille et al., 2002). Trials contaminated by artifacts were automatically removed from the database (criterion 100 μV).
Since in the current study the focus is on P300 amplitude, more specifically P3b amplitude, only data from electrode Pz were analyzed, because that is where the largest P3b amplitudes were to be expected (Comerchero and Polich, 1999). Data were collapsed over both ears, and averaged. Based on grand average scores, mean P300 amplitude was identified by an automatic peak detection procedure as the most positive peak within the time window 275–800 ms poststimulus, with average reference. Processing negativity (PN) difference waves were expressed as the average ERPs to the standard stimuli from the attended ear, subtracted with the average ERPs to the standard stimuli from the unattended ear. Based on grand average scores, PN was assessed at electrode Fz and scored between 200 and 400 ms poststimulus. Mismatch negativity difference waves were expressed as the average ERPs to the deviant stimuli in the unattended ear, subtracted with the average ERPs to the standard stimuli in the unattended ear. Based on grand average scores, mismatch negativity was assessed at electrode Cz and scored between 150 and 300 ms.

2.6. Statistical analysis

All statistical analyses were performed with SPSS (for Windows, version 11.0). All data were normally distributed; therefore only parametric statistics were applied. Outlying values were identified and subsequently removed from analysis based on 2 standard deviation (s.d.) limits around the group mean. The P300 amplitudes were analyzed through repeated measures

ANOVA with between factor 'group' (AVH or controls) and within factors 'stimulus type' (standard or deviant stimuli) and 'attention' (attended or non-attended stimuli). Independent samples Student's t-tests were used to further explore the significant data as revealed by the ANOVA. Independent samples Student's t-tests were also used to analyze performance data (hits, misses, false alarms) as well as PN and MMN difference waves.

3. Results

3.1. Behavioral data

No significant differences between groups were found in number of correct responses, number of false alarms, and reaction times. Group means are presented in Table 1.

Table 1. Mean behavioral data and standard deviations for controls and non-psychotic individuals with AVH.

Group	Hits (s.d.)	False alarms (s.d.)	Reaction time (ms)
Controls	37.4 (2.9)	1.9 (3.2)	465 (55)
AVH	36.3 (4.1)	1.5 (2.1)	490 (58)

3.2. ERP data

3.2.1. P300

Two outliers (one in the AVH group and one in the control group) were excluded from analysis. Further, one subject in the AVH group was excluded from analysis for not showing an identifiable P300 response to attention deviants ("non-responder"). Table 2 shows the electrophysiological data for the remaining 16 non-psychotic individuals with AVH and the 17 controls. The ANOVA revealed an attention main effect [$F(1,31)=61.993$; $P<0.0005$], a stimulus type main effect [$F(1,31)=176.538$; $P<0.0005$], and an attention×stimulus type interaction effect [$F(1,31)=72.396$; $P<0.0005$], indicating the for this task usual phenomena: a higher P300 amplitude to targets than to standards, higher P300 amplitudes in the attended channel (ear) than in the unattended channel and the highest P300 amplitude found to attended target stimuli (Figs. 1 and 2). In addition, a significant group main effect [$F(1,31)=6.718$; $P=0.014$] and a significant attention×stimulus×group interaction effect [$F(1,31)=5.057$; $P=0.032$] were found, indicating higher P300 amplitudes in the AVH group than in the control group and, more specifically, a higher P300 amplitude following deviant stimuli compared to standard stimuli in the AVH group than in the control group. Age and gender did not covariate significantly on the P300 amplitude data. The P300 amplitude to attention deviants was significantly higher in the AVH group than in the control group [$t(31)= -2.270$; $P=0.030$]. The groups did not differ significantly in P300 latency to attended deviants [$t(31)= -0.869$; $P=0.392$].

3.2.2. Processing negativity

Two outliers (one in the AVH group and one in the control group) were excluded from analysis. In both groups PN (mean controls: -1.37 μV, s.d.: 0.72, [t(16)= -7.838; P<0.0005], mean AVH: -1.78 μV, s.d.: 0.62, [t(16)= -11.868; P<0.0005]) was found, expressed as a difference from zero. These findings indicate enhanced processing activity to stimuli in the attended channel (Fig. 3). A trend was found for higher PN amplitude in the AVH group compared to the control group [t(32)=1.807; P=0.080]. No statistical difference in PN latency was found between the groups (mean controls: 314ms, s.d.: 54; mean AVH: 311 ms, s.d.: 54; [t(32)=0.164; P=0.870]).

3.2.3. Mismatch negativity

Two outliers (one in the AVH group and one in the control group) were excluded from analysis. In both groups MMN (mean controls: -1.53 μV, s.d.: 0.67, [t(16)=-9.424; P<0.0005], mean AVH: -1.59 μV, s.d.: 0.52, [t(16)= -12.508; P<0.0005]) was found, expressed as a difference from zero (Fig. 4). No statistical difference in MMN amplitude [t(32)=0.265; P=0.793] or MMN latency (mean controls: 224 ms, s.d.: 36; mean AVH: 244 ms, s.d.: 38; [t(32)= -1.661; P=0.106]) was found between the groups.

Table 2. Means and standard deviations for P300 amplitude and latency at Pz.

		Attended deviants	**Non-Attended deviants**	**Attended standards**	**Non-Attended standards**
Controls	Amplitude (uV)	4.45 (1.58)	2.22 (1.69)	0.92 (0.65)	0.51 (0.53)
	Latency (ms)	510 (109)	545 (96)	414 (144)	436 (156)
AVH	Amplitude (uV)	5.73* (1.65)	2.81 (1.16)	1.13 (0.84)	1.35** (0.79)
	Latency (ms)	543 (107)	527 (125)	461 (153)	472 (144)

* Significantly higher in the AVH group than in the control group (P<0.05).

** Significantly higher in the AVH group than in the control group (P=0.01).

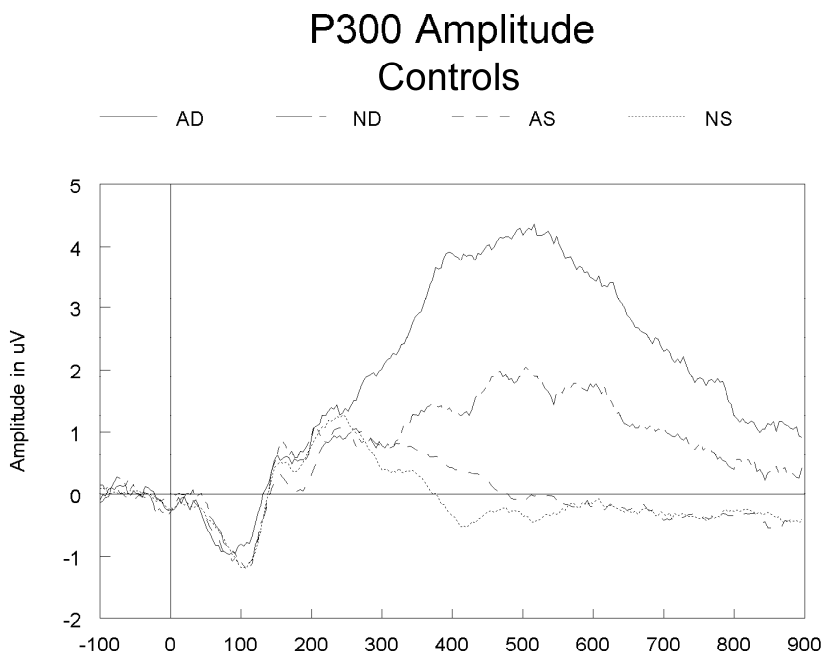

Fig. 1. Grand average ERPs for lead Pz for the control group. AD = attended deviant; AS = attended standard; ND = non-attended deviant; NS = non-attended standard.

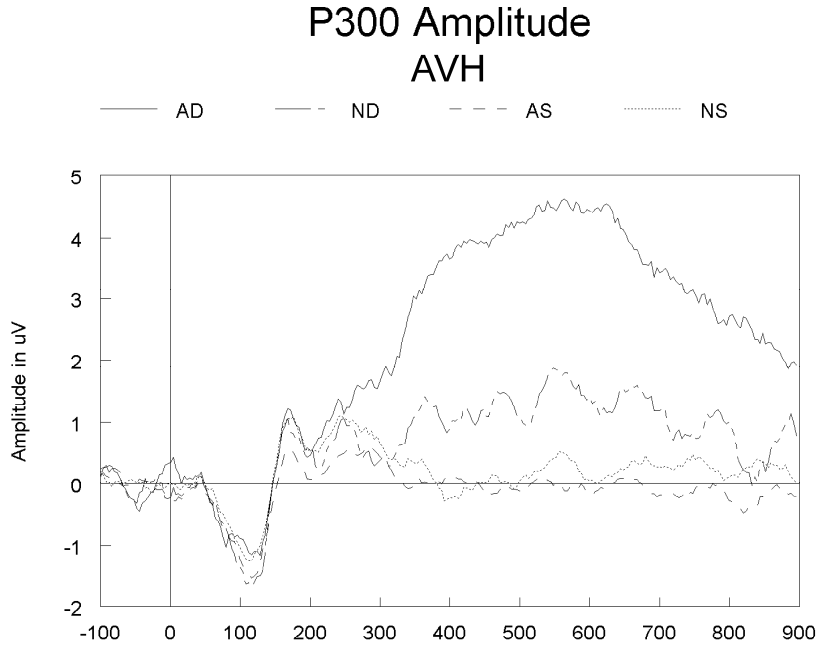

Fig. 2. Grand average ERPs for lead Pz for the AVH group. AD = attended deviant; AS = attended standard; ND = non-attended deviant; NS = non-attended standard.

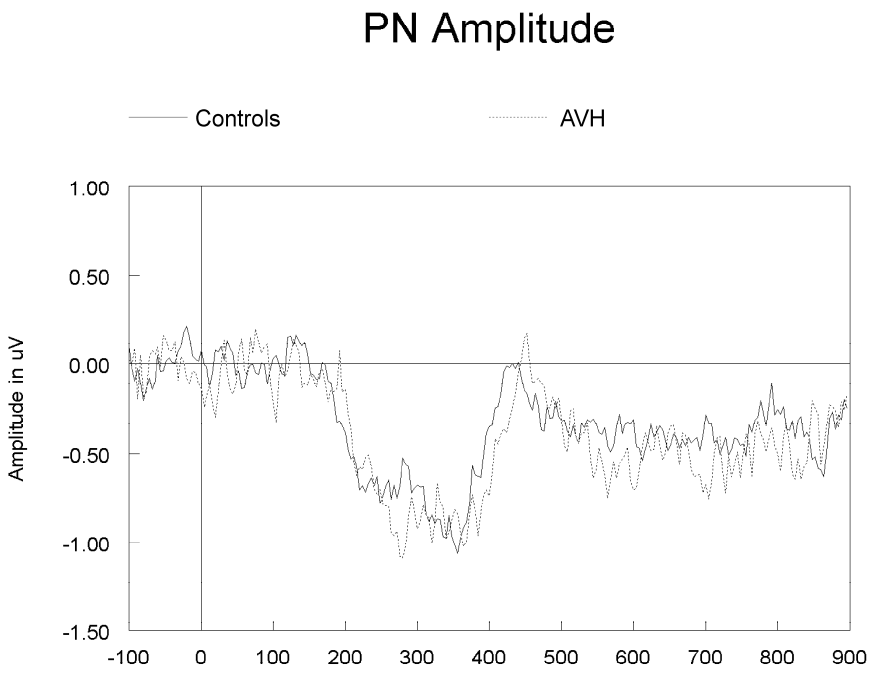

Fig. 3. Grand average difference waves (lead Fz) for processing negativity.

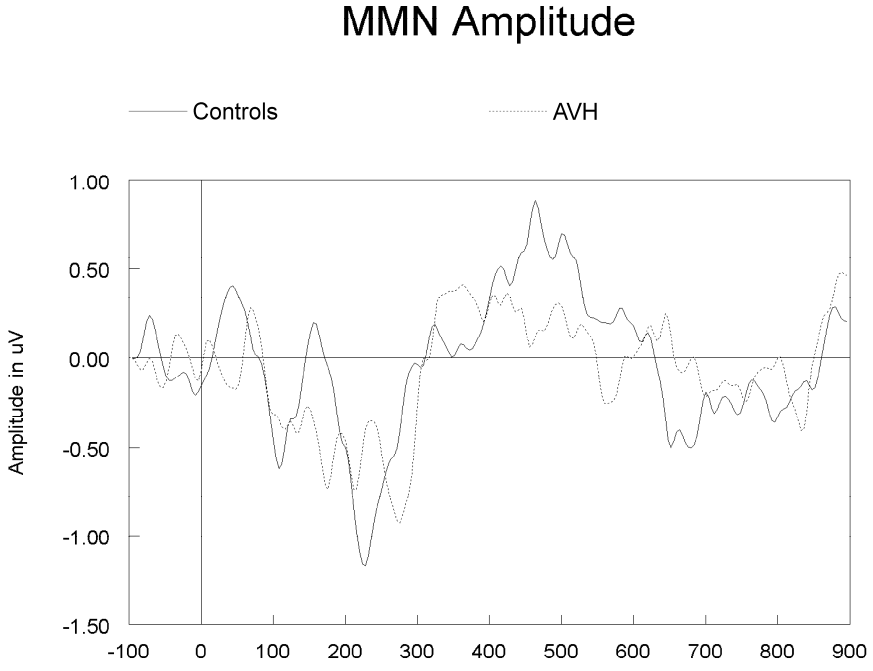

Fig. 4. Grand average difference waves (lead Cz) for mismatch negativity.

4. Discussion

This is the first study to investigate event-related potentials (ERPs) in non-psychotic individuals with auditory verbal hallucinations (AVH). The hypothesis that P300, PN, and MMN amplitudes were reduced in non-psychotic individuals with AVH as compared to controls could not be confirmed. Instead, P300 amplitude was found to be increased in the AVH group. Moreover, a trend in the same direction was found for processing negativity (PN). MMN was similar in both groups. These results suggest that effortful attention is increased in non-psychotic individuals with AVH, as compared to individuals without AVH, while automatic attention is similar.

The present findings are in sharp contrast to studies in schizophrenia patients, as reduced PN amplitude has been consistently shown in this population, and reduced P300 amplitude is one of the most robust neurobiological findings in schizophrenia (Baribeau-Braun et al., 1983; Iwanami et al., 1998; Jeon and Polich, 2003; Michie et al., 1990; Ward et al., 1991). There is strong evidence that P300 amplitude is also diminished in unaffected first-degree relatives of schizophrenia patients (Bramon et al., 2005; Frangou et al., 1997; Kidogami et al., 1991; Turetsky et al., 2000; Weisbrod et al., 1999). In addition, reduced P300 amplitude has been reported in individuals with schizotypal personality disorder (Mannan et al., 2001) and in non-clinical samples with high scores on schizotypy questionnaires (Kimble et al., 2000; Klein et al., 1999). However, in all these groups a mixture of (subclinical) positive, negative and cognitive symptoms is present, thereby obscuring the specific relation between these ERPs and isolated symptoms.

Several studies have reported inverse correlations between reduced P300 amplitude at midline electrodes and positive symptoms (Egan et al., 1994; Higashima et al., 2003), negative symptoms (Eikmeier et al., 1992; Liu et al., 2004; Pfefferbaumet al., 1989) or both (Mathalon et al., 2000), while other studies failed to find any association between decreased P300 amplitude and symptom severity (Blackwood et al., 1987; St Clair et al., 1989). However, severity of positive and negative symptoms in schizophrenia is state dependent and may fluctuate largely over time, while P300 amplitude is generally regarded as a trait characteristic (Bramon et al., 2005; Jeon and Polich, 2003; Mathalon et al., 2000). Since this study included a unique group that experienced AVH in the absence of delusions and negative symptoms, the absence of reductions in P300 amplitude and PN strongly suggests that AVH are not associated with decreased effortful attention. It remains unclear if increased effortful attention is a compensatory mechanism for other difficulties or if increased effortful attention may be a risk factor for AVH in its own. The P300 waveform has been shown to reflect alertness (Polich and Kok, 1995), and differences in alertness between the groups may be an alternative explanation for increased P300 amplitudes. However, in this study this seems unlikely, since no differences in accuracy or reaction times were present.

In contrast to the P300 findings, MMN amplitude was similar for both groups. Several studies have found significant correlations between MMN and measures of negative symptomatology in schizophrenia (Catts et al., 1995; Grzella et al., 2001; Hirayasu et al., 1998; Javitt et al., 2000; Kasai et al., 2002). The absence of negative symptoms in non-psychotic individuals with AVH may provide an explanation for the lack of anomalous MMN scores in non-psychotic

individuals with AVH in the present study.
A major limitation of the present study is that it is currently unclear whether auditory verbal hallucinations in non-psychotic individuals are indeed the same phenomenon as observed in schizophrenia. This implies that it is not known how representative people with AVH as a relatively isolated symptom are for schizophrenia patients.

In sum, in contrast to patients with schizophrenia, non-psychotic individuals with AVH show increased rather than reduced P300 amplitude compared to healthy controls. Processing negativity showed a trend towards increased amplitudes in the hallucinating group, while MMN was similar in both groups. These results suggest that decreased effortful attention does not play a pivotal role in the pathophysiology of AVH. In future studies we aim to investigate measures of sensory gating, as increased selective attention may be a compensation mechanism for dysfunctional filtering processing at a lower level.

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Chapter 7

Network analysis of auditory hallucinations in non-psychotic individuals

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Submitted

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Abstract

Background: Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia and can severely disrupt behavior and decrease quality of life. Identification of areas with high functional connectivity (so-called hub regions) that are associated with the predisposition to hallucinate may provide potential targets for neuromodulation in the treatment of AVH.
Methods: Resting-state fMRI scans during which no hallucinations had occurred were acquired from 29 non-psychotic individuals with AVH and 29 matched controls. These non-psychotic individuals with AVH provide the opportunity to study AVH without several confounds associated with schizophrenia, such as antipsychotic medication use and other symptoms related to the illness. Hub regions were identified by assessing weighted connectivity strength and betweenness centrality across groups using a permutation analysis.
Results: Non-psychotic individuals with AVH exhibited increased functioning as hub regions in the temporal cortices and the posterior cingulate/precuneus, which is an important area in the default mode network, compared to the non-hallucinating controls. In addition, the right inferior temporal gyrus, left paracentral lobule and right amygdala were less important as a hub region in the AVH group.
Conclusions: These results suggest that the predisposition to hallucinate may be related to aberrant functioning of the default mode network and the auditory cortices.

Introduction

Auditory verbal hallucinations (AVH) are one of the core symptoms of schizophrenia with approximately 70% of all schizophrenia patients presenting with this symptom (Nayani and David, 1996; Slade and Bentall, 2002). AVH can be highly distressing, often disrupt social functioning, and increase risk for suicide and acts of violence (Cheung et al., 1997; Falloon and Talbot, 1981).

It has been hypothesized that hallucinations arise from dysfunctional connectivity in the brain (Friston and Frith, 1995; Northoff and Qin, 2011). As task execution may induce alterations in brain connectivity and network properties, aberrations in functional connectivity are best observed in the absence of external tasks (Jin et al., 2011; Nicol et al., 2011). For this reason, several studies investigated functional connectivity related to AVH during the resting state. Hoffman et al (2011) reported increased functional connectivity along a loop comprising language areas and the putamen in hallucinating patients versus non-hallucinating patients. Gavrilescu et al (2010) observed reduced connectivity of the auditory system, while Rotarska-Jagiela et al (2010) found associations between hallucinations and connectivity in the hippocampus and a frontotemporal network. In addition, Vercammen et al (2010) observed a relationship between hallucination severity and connectivity between the left temporoparietal junction and the anterior cingulate and amygdala. As these studies were conducted in schizophrenia patients, this diversity in findings may be partly explained by other clinical symptoms related to the disease such as delusions, cognitive and negative symptoms. Moreover, the use of antipsychotic medication may have affected the results.

Although the previously published functional connectivity studies provide valuable information regarding auditory verbal hallucinations and schizophrenia, they do not inform us about the functioning of areas in a network context. More specifically, identification of areas with high functional connectivity (so-called hub regions) that are associated with the predisposition to hallucinate can be of particular importance, as these regions may provide potential targets for neuromodulation in the treatment of AVH (McCarthy-Jones, 2012). As the left hippocampus, inferior frontal gyrus, and superior temporal gyrus have consistently been implicated during the experience of AVH, we hypothesize that increased functioning of these areas as a hub region is related to the predisposition to hallucinate (Jardri et al., 2010).

These hub regions can be identified using graph theoretical measures, such as connectivity strength and betweenness centrality (Rubinov and Sporns, 2010). Connectivity strength represents the degree of coupling of a node with the rest of the network, while betweenness centrality is based on the number of shortest paths that pass through a given node in the network. With the former measure, regions can be identified that show a pattern of hypo- or hyperconnectivity with the rest of the brain, while the latter measure identifies regions that are important in bridging different subnetworks (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

To circumvent potential confounds associated with schizophrenia, we studied these two hub parameters in individuals with AVH as a relatively isolated symptom (Tien, 1991). In contrast to schizophrenia patients, AVH in this population occur in the absence of delusions

and negative or cognitive symptoms (Sommer et al., 2010a). Moreover, these non-psychotic individuals with AVH are not using antipsychotic medication.
In this study, we applied graph analysis to compare resting-state connectivity between 29 non-psychotic individuals with AVH who did not hallucinate during image acquisition with 29 matched controls, aiming to investigate whether increased functioning of the left hippocampus, inferior frontal gyrus and superior temporal gyrus as hub regions may underlie the predisposition to experience AVH.

Materials and methods

Subjects

Forty-eight non-psychotic individuals with AVH and 54 controls were recruited via a website: www.verkenuwgeest.nl ("explore your mind"). An extended description of the recruitment and selection procedure is provided in prior studies of our group (Daalman et al., 2011; Diederen et al., 2010a; Sommer et al., 2010a; van Lutterveld et al., 2010). Briefly, inclusion criteria were: (1) absence of psychiatric disorders other than anxiety or depressive disorder in full remission as assessed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) to exclude axis I pathology and the SCID-II interview to exclude axis II pathology (First et al., 1995), (2) no chronic somatic disorder, (3) absence of alcohol or drug abuse for at least 3 months prior to the assessments. To confirm the absence of drug abuse, urine samples were collected and tested for opiates, amphetamines/XTC, cocaine and cannabis. Additional inclusion criteria for the non-psychotic individuals with AVH consisted of (4) voices were distinct from thoughts and had a "hearing" quality, (5) voices were experienced at least once a month, (6) drug or alcohol abuse did not precede the first experience of AVH, (7) Because the presence of AVH is related to changes in cortical activity (Jardri et al., 2010), a further inclusion criterion was the absence of AVH during resting-state scan acquisition.
These non-psychotic individuals with auditory verbal hallucinations as a relatively isolated symptom can be considered to hold an intermediate position on a continuum of auditory verbal hallucinations, with healthy individuals at one end and individuals with a psychotic disorder at the other (Strauss, 1969; van Os et al., 2000). Being an intermediate on this scale, these individuals are affected to some extent as expressed by the presence of sub-clinical levels of suspicion, a tendency for magical ideation, a somewhat lower Global Assessment of Functioning scale score, and an elevated level of formal thought disorder (Sommer et al., 2010a; Sommer et al., 2010b). However, AVH occur in the absence of delusions and negative or cognitive symptoms in this population (Sommer et al., 2010a). Moreover, these non-psychotic individuals with AVH are not using antipsychotic medication. A recent study showed that cortical activation during AVH is similar in these non-psychotic individuals as in schizophrenia patients (Diederen et al., 2011), suggesting the same neurological substrate may underlie both types of AVH.
The study was approved by the local ethics committee of the University Medical Center of Utrecht. All participants gave their written informed consent before participation in the study.

Image acquisition

Imaging was performed on a Philips Achieva 3 Tesla Clinical MRI scanner. Six hundred blood-oxygenation-level-dependent (BOLD) resting-state fMRI images were acquired per subject with the following parameters settings: 40 (coronal) slices, TR = 21.75 ms, TE = 32.4 ms, flip angle 10º, field of view (FOV) 224 x 256 x 160, matrix 64 x 64 x 40, voxelsize 4 mm isotropic. This scan sequence achieves full brain coverage within 609 ms by combining a 3D-PRESTO pulse sequence with parallel imaging (SENSE) in 2 directions using a commercial 8-channel SENSE headcoil (Neggers et al., 2008). Since these PRESTO SENSE images have little anatomical contrast, 40 scans with a flip angle of 27º (fa27) were acquired to improve realignment and coregistration during preprocessing. After the functional scans, a high-resolution anatomical scan was acquired (TR/TE: 9.86/4.6 ms, 0.875 x 0.875 x 1 mm^3 voxels, flip angle 8º, FOV 224 x 160 x 168, 160 slices) to improve localization of the functional data. Resting-state scans were acquired for 6 minutes, and subjects were instructed to lie still with their eyes closed, not to think of anything in particular and not fall asleep. The absence of AVH during the scan was established by interviewing the participants directly after completion of the resting-state scan. Head motion was assessed by calculating the mean motion as suggested by Van Dijk et al (2012). Mean motion represented the mean absolute displacement of each brain volume as compared to the preceding volume and was calculated from the translation parameters in the x, y and z directions.

Data Analysis

Preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM8) (Wellcome Department of Cognitive Neurology, London, United Kingdom). First, the fMRI time-series were realigned to the first functional scan to correct for head motion. The realigned time-series were then coregistered to the first fa27 scan. The anatomical scan was hereafter coregistered to the first fa27 scan to provide alignment between the functional time-series and the anatomical image. The T1 image and the fMRI time-series were spatially normalized to MNI (Montreal Neurological Institute) space. It should be noted that the process of spatial normalization involved the interpolation of fMRI voxels, although common practice in most resting-state fMRI studies, can potentially introduce local artificial correlations between adjacent voxels (Fransson et al., 2011; Hayasaka and Laurienti, 2010; Tomasi and Volkow, 2011; van den Heuvel et al., 2008). In order to avoid introducing additional local spatial correlations, the images were not smoothed. To further remove artificial interdependencies, the mean time courses from the cerebral spinal fluid (CSF), deep white matter and 6 rigid-body parameters were regressed out from the time-series. After this, resting-state time series were band-pass filtered (0.01 – 0.1 Hz). Furthermore, a binary mask was used to isolate cerebral gray-matter voxels. This mask was created by first reslicing SPM8's gray-matter probability template to the resolution of the functional images (4 x 4 x 4 mm). After this, the cerebellar regions were removed using the cerebellar regions in the AAL library (Tzourio-Mazoyer et al., 2002). Finally, the template was binarized by applying a threshold of 0.55, yielding a total volume in

the mask of 10,108 voxels (Zalesky et al., 2011). In order to avoid the arbitrary nature of the dichotomizing procedure required to compute unweighted networks, our analysis was based on weighted networks. Recently, Hayasaka and Laurenti (2010) have shown the preferability of using a high spatial resolution in graph analysis. To this end, we focused on voxel-wise instead of region-based networks. Within the gray-matter mask, a weighted undirected network was constructed for all subjects, which was described by the graph $G = (N, W)$, where N is the set of all 10,108 voxels in the mask and $W = \{w_{ij}\}$ is the $N \times N$ symmetric weight matrix, where $w_{ii} = 0$ and w_{ij} the Fisher's z'-transformation normalized Pearson's correlation coefficient r between voxels i and j, with $z' = arctanh(r)$. Edges with negative z'-values were set to 0. Hereafter, global and local network characteristics were calculated using the C++ Boost Graph Library (Siek et al., 2002). Figure 1 provides a schematic outline of the analysis pipeline.

Graph analysis

Hub regions were identified using the graph theoretical measures connectivity strength and betweenness centrality. The connectivity strength represents the degree of coupling of a node with the rest of the network. With this measure, regions can be identified that show a pattern of hypo- or hyperconnectivity with the rest of the brain. The betweenness centrality relies on the identification of the number of shortest paths that pass through a node. The more passages, the higher the betweenness centrality. This measure identifies regions that are important in bridging different subnetworks (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

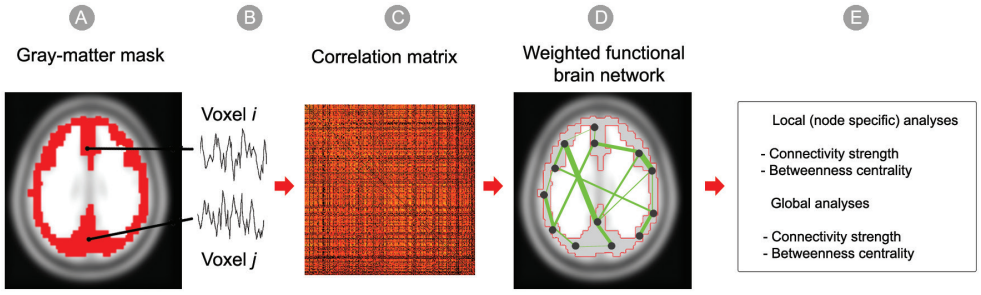

Fig 1. Analysis pipeline. In the first step, the pre-defined gray-matter mask was applied to the functional data (A). The second step consisted of calculating functional connectedness between all possible pairs of gray-matter voxels i and j in each subject (B). These correlations were represented as a correlation matrix with each cell holding the level of connectivity between voxel i and voxel j (C), after which a weighted functional brain network was constructed comprising of the positive correlations in the correlation matrix. This is shown in (D), where the thickness of the green lines indicates the strength of the connectivity between two voxels. After this, hub regions were identified by testing for local differences in connectivity strength and betweenness centrality among groups. Global (average) connectivity strength and betweenness centrality were also calculated for each individual network (E).

In these local graph analyses, the measures were analyzed in voxel-space to be able to locate differences among groups in the brain. In addition, an exploratory global graph analysis was conducted for connectivity strength and betweenness centrality to test for global differences in these measures across groups (Rubinov and Sporns, 2010). Calculation of these global metrics was performed by averaging the measures across all 10,108 voxels in the gray-matter mask per individual. An extensive description including mathematical forms of these network characteristics is given in Supplementary data S1.

Statistical analyses

Local graph analysis

Statistical testing for significant local differences across groups was performed by using a nonparametric permutation test (SnPM) using 10,000 permutations (Singh et al., 2003). To optimize statistical sensitivity for both spatially extended clusters and high intensity signals, we used a combined threshold based on voxel intensity and cluster volume, using a pseudo-t value of 3 (equally weighted meta-combined or combo test; Hayasaka and Nichols (2004)). The family-wise error (FWE) correction threshold to account for multiple comparisons was set at P = 0.05. Anatomical labelling of significant activation clusters was performed using the Talairach Client database (http://www.talairach.org/client.html) and MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/) was used for visualization purposes.

Global graph analysis

Independent-samples t-tests were employed to test for global differences in overall connectivity strength and betweenness centrality across groups for normally distributed data. For non-normally distributed data, Mann-Whitney's U test was used.

Results

Data selection

After scanning, 19 non-psychotic individuals with AVH were found unsuitable for inclusion, resulting in 29 non-psychotic subjects with AVH and 54 healthy control subjects included for data analysis. Sixteen of the 19 excluded non-psychotic subjects were excluded as they had experienced AVH during the resting state, while one subject was excluded because of not closing the eyes during resting-state acquisition, and another subject was excluded because of falling asleep during the scan. An additional subject was excluded because of major artefacts being present in the anatomical scan. Twenty-nine of the 54 control subjects were then selected to enable a good match (on age, sex, handedness and years of education) with the non-psychotic individuals with AVH. Data on these 29 non-psychotic individuals with AVH and 29 healthy control subjects were then used for further analyses.

Demographic variables

The groups did not differ significantly with respect to age, sex, and handedness and years of education. Table 1 provides a demographic description of the participants. A significant

difference was found regarding the number of participants diagnosed with depression in remission (control group: 4, AVH group: 13, $\chi^2 = 6.74$; P = 0.009). None of the participants used psychoactive medication.

Table 1. Subject characteristics

	Controls (N=29)	**Non-psychotic subjects with AVH (N = 29)**	
	Mean (SD)	Mean (SD)	Statistics
Age	41.3 (15.9)	43.1 (13.8)	t(56) = -0.45; P = 0.65
Sex (male/female)	9 / 20	9 /20	
Handedness (right/non-right)	22 / 7	22 / 7	
Years of education	13.9 (2.3)	13.5 (2.2)	U(56) = 372.5; P = 0.44
Anxiety disorder	0	0	
Depression in remission	4	13	

AVH: Auditory verbal hallucinations; N: Number; SD: Standard deviation.

Head motion

Groups did not differ significantly in mean head motion during image acquisition (mean controls: 0.09 mm, s.d. 0.02; mean AVH 0.10 mm, s.d. 0.04 [t(56) = -1.45; P = 0.15]).

Node specific analysis (local analysis)

Connectivity strength

A significant increase in connectivity strength in the AVH group compared to the control group was found in a cluster in the right posterior cingulate extending into the cingulate gyrus and the precuneus as well as in a cluster in the left superior temporal gyrus extending into the insula. In addition, an increase in connectivity strength was observed in the right middle temporal gyrus (fig 2A), indicating that these areas are more important hub regions in the AVH group as compared to the controls. Detailed information about the coordinates of local maxima is shown in table 2.

Betweenness centrality

A significant increase in betweenness centrality was found in a cluster in the left superior temporal gyrus, indicating that this region is a more important hub in the AVH group compared to the controls. In addition, significant decreases were observed in the right inferior temporal gyrus, left paracentral lobule and right amygdala (fig 2B), indicating that these areas are less important hubs in the AVH group compared to the controls. Detailed information about the coordinates of local maxima is shown in table 2.

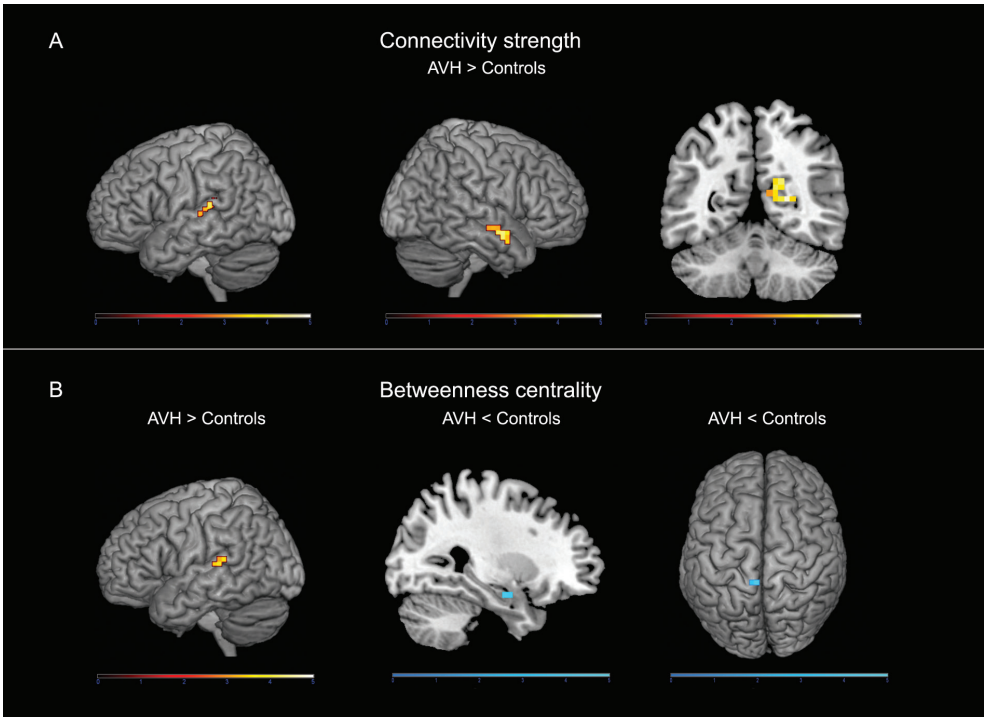

Fig 2. Local changes in activity in the AVH group compared to the control group in (A) connectivity strength and (B) betweenness centrality. Data are presented in neurological convention (right is right). P<0.05, FWE corrected.

Global analysis

A significant difference between the groups was found for average connectivity strength (mean controls: 1734, s.d. 638; mean AVH 1938, s.d. 550 [U = 287; P = 0.037]), indicating a pattern of hyperconnectivity in the AVH group compared to the controls. A plot of the connectivity distributions is provided in Supplementary Data S2. No differences were observed in average betweenness centrality across groups (mean controls: 0.000085, s.d. 0.000013; mean AVH: 0.000081, s.d. 0.000011 [t(56) = 1.474; P = 0.146]), indicating that groups were on whole-brain level not different in this measure for hubs.

Table 2. Significant local differences and locations of local maxima for connectivity strength and betweenness centrality. AVH = Auditory verbal hallucinations, k = cluster extent.

Measure	AVH subjects vs. Controls	Area	Montreal Neurological Institute Coordinates (x, y, z)			t	k
Connectivity strength	Increase	Right posterior cingulate /	22	-56	10	4.80	
		Right cingulate gyrus /	18	-56	22	4.27	25
		Right precuneus	6	-64	26	4.15	
	Increase	Left superior temporal gyrus	-46	-28	6	4.61	
		Left superior temporal gyrus	-54	-32	14	4.02	20
		Left insula	-46	-36	18	3.52	
	Increase	Right middle temporal gyrus	58	0	-14	4.20	11
		Right middle temporal gyrus	54	4	-22	3.38	
Betweenness centrality	Increase	Left superior temporal gyrus	-50	-32	10	3.86	7
	Decrease	Right inferior temporal gyrus	38	-60	-10	4.28	4
	Decrease	Left paracentral lobule	-6	-40	70	4.08	4
	Decrease	Right amygdala	30	-4	-22	3.78	3

Discussion

This is the first study to apply graph theory to investigate resting-state brain activity in relation to auditory verbal hallucinations (AVH). We investigated a group of non-psychotic individuals who experienced AVH in relative isolation in order to reveal brain characteristics of hallucination-proneness without the confounding variables associated with studying schizophrenia patients, such as delusions, cognitive dysfunction, negative symptoms, medication use and long-term hospitalization. The AVH group showed an increased pattern of overall connectivity as compared to the control group, and our hypothesis that the left hippocampus, inferior frontal gyrus and superior temporal gyrus (STG) would exhibit increased functioning as a hub region in the AVH group compared to controls could partially be confirmed. The left STG, right middle temporal gyrus (MTG) and the posterior cingulate/precuneus complex (PCC) were found to be more important hub regions in the AVH group. A second measure to investigate hub regions confirmed that the left STG was more important in the hallucinating group, while the right inferior temporal gyrus, the left paracentral lobule and the right amygdala were less important hub regions.

The present results indicate that temporal areas and the PPC take a more prominent place in the network in individuals with AVH than in non-hallucinating controls. Interestingly, these more important hubs are considered essential parts of the default mode network, which is a network implicated in wakeful resting (Raichle et al., 2001).

Posterior cingulate/precuneus complex (PPC)

In the default mode network, the PPC takes a central position. The default mode network consists of two subsystems, with one system involved in memory and associations and another system involved in self-referential processing (Buckner et al., 2008). Both systems converge in the PPC. As such, increased connectivity with this area may lead to a greater focus on memory processes and self-referential thoughts. Interestingly, a prominent feature of AVH is their repetitive nature, which implies a memory component (Stephane et al., 2003). This is in line with cognitive models that emphasize the role of memory processes in the genesis of AVH (Badcock et al., 2005; Jones and Fernyhough, 2009; Waters et al., 2006).
Moreover, hallucinations are self-generated and experienced as externally generated. This implies aberrant self-referential processing (Frith and Done, 1989). The memory and self-referential processes mediated by the PPC in the default mode network might therefore be linked to the genesis of AVH. AVH are sometimes compared to screen-savers; when a person is not in the midst of some cognitive task, and is just mind-wandering, AVH may come in. Schizophrenia patients are usually well aware of this feature and apply distraction and focusing as coping strategies to decrease AVH frequency (Haddock et al., 1998; Hayashi et al., 2007). This association between AVH and mind-wandering also implies a link with the default mode network, as these structures increase their activity during periods without explicit cognitive tasks. As such, the PPC may provide a target for neuromodulation to alter AVH proneness. For example, individuals may be trained to decrease activity of this region with a neurofeedback paradigm.

Temporal structures

The observation that the left superior temporal gyrus was a more important hub region in the hallucinating group was further highlighted by a similar increase in the second measure for hubs. Activity in the left superior temporal gyrus is usually interpreted in light of auditory processing (Dierks et al., 1999). Recently, elevated interaction between the auditory cortices and the default mode network has been hypothesized to underlie the genesis of AVH (Northoff and Qin, 2011). Although from the present results it is not possible to infer increased interaction *between* temporal regions and the PCC, it is striking to see that increased interaction *from* these areas with the rest of the brain was observed.
However, the increased functioning as a hub region of the left superior temporal gyrus could alternatively be seen in light of its involvement in formal thought disorder. Non-psychotic individuals with AVH show similar increased levels of positive formal though disorder (i.e. disorganized speech) as schizophrenia patients compared to controls (Sommer et al., 2010b). This finding is in line with the proposition that AVH and formal thought disorder share a neurobiological substrate (Hoffman, 1986; Sommer et al., 2010b; Strik et al., 2008). Support for this notion comes from studies that consistently implicated the left superior temporal gyrus in AVH (Barta et al., 1990; Dierks et al., 1999; van Lutterveld et al., 2011) as well as in formal thought disorder (Horn et al., 2009; Kircher et al., 2001; Shenton et al., 1992), suggesting that

this area may be particularly involved in a possible common pathophysiological mechanism.

Other findings

Given the importance of medial temporal lobe (MTL) structures in the genesis of AVH (Diederen et al., 2010b; Jardri et al., 2010), it is interesting to see that the right amygdala is a less important hub in the hallucinating group. Functional connectivity of the amygdala has previously been linked to the experience of AVH (Vercammen et al., 2010). These authors found that reduced functional coupling between the amygdala and the left temporoparietal junction (TPJ) was associated with increased severity of AVH.
It should be noted that four control subjects and thirteen non-psychotic individuals with AVH were diagnosed with depression in remission. Non-psychotic individuals with AVH can be considered to take a halfway position on a continuum of auditory verbal hallucinations (Strauss, 1969; van Os et al., 2000). As such, these individuals are affected to some extent as expressed by the presence of sub-clinical levels of suspicion, formal thought disorder, and a tendency for magical ideation (Sommer et al., 2010a; Sommer et al., 2010b). As depression is a major comorbid symptom in schizophrenia, the higher prevalence of depression in remission in the AVH group may be expected in the framework of these individuals being on a continuum between healthy controls and clinical psychosis (Siris, 2000).

Comparison to previous functional connectivity studies

To date, several studies used graph analysis to investigate schizophrenia, although these studies did not focus on AVH. In these studies, lower clustering coefficients, alterations in path length and small-worldness, increased connection distance of various regions, and overall decreases in functional connectivity have all been reported (Bassett et al., 2008; Liang et al., 2006; Liu et al., 2008; Lynall et al., 2010; Ma et al., 2012; Micheloyannis et al., 2006; Rubinov et al., 2009; van den Heuvel et al., 2010; Zalesky et al., 2011).
Several studies with a seed-region design specifically addressed AVH by investigating resting-state functional connectivity in schizophrenia. Hoffman et al (2011) reported increased connectivity along a loop comprising language areas and the putamen in hallucinating patients versus non-hallucinating patients. Gavrilescu et al (2010) observed reduced connectivity of the auditory system, while Rotarska-Jagiela et al (2010) found associations between hallucinations and connectivity in the hippocampus and a frontotemporal network using an independent component analysis (ICA) approach. Using a similar approach, Liemburg et al (2012) observed decreased connectivity between auditory and language networks in schizophrenia patients. As the patients included in these studies also experienced other symptoms of schizophrenia and received antipsychotic treatment, the results may not be specific to AVH.

Limitations and methodological considerations

The present results should be interpreted with some caution. Recently, it has been shown

that various graph measures are dependent on average connectedness of the underlying network (van Wijk et al., 2011). As we observed an increase in overall connectedness in the AVH group, this could potentially confound subsequent analyses. However, van Wijk et al also found that for an average degree that is higher than 25, there was convergence to almost constant values for several graph measures, including number of hubs. In the present study this value was almost 2 orders of magnitude higher for both groups, suggesting that the observed differences in connectivity strength did not confound calculation of graph metrics. Still, the average connectivity strength was different across subjects, and we can not exclude the possibility that this influenced calculation of subsequent graph characteristics. It is furthermore important to note that the present results should be interpreted in context of the applied spatial scale, as the choice for voxel-wise or region-based approaches affects network measures (Hayasaka and Laurienti, 2010). In the present study, the data were spatially normalized to be able to investigate local differences in network metrics across groups. It should be noted that normalization involves the interpolation of fMRI voxels, possibly affecting local correlations. In order to avoid affecting local correlations as much as possible, the spatially normalized data were not smoothed. Hayasaka and Laurenti (2010) investigated the effect of local correlations by deleting connections between adjacent voxels in a spatially normalized dataset. They observed an effect on clustering coefficient and path length, however no significant effect on the distribution of correlation values was observed, suggesting that connectivity strength is not particularly affected by spatial normalization. Another limitation is that activation of temporal regions has consistently been reported to be associated with AVH (Jardri et al., 2010; van Lutterveld et al., 2011). Increased connectivity of the temporal cortices may be related to sustained activation of these areas after the occurrence of an AVH. However, the hallucinating group in this study experienced AVH with an average frequency of once every week, rendering this explanation quite unlikely. Another important limitation of this study is that it remains uncertain whether AVH in schizophrenia patients and in non-psychotic individuals can be considered exactly the same phenomenon. A recent study compared the phenomenology of non-psychotic individuals with AVH and schizophrenia patients. Both groups were similar in several characteristics of AVH. There were no differences in the perceived location of voices (inside/outside the head), the number of voices, loudness, and personification (attribution to a real and familiar person). However, both groups were different in emotional valence of the content, frequency of AVH and control over their AVH. Moreover, age of onset of AVH was at a younger age in the healthy individuals (Daalman et al., 2011), which may suggest a different aetiological origin. However, in contrast with this latter finding is a recent neuroimaging study that investigated brain activity during AVH in both groups. In this study a similar pattern of activation was observed, which is suggestive of similar underlying pathophysiology (Diederen et al., 2011). There are as such similarities and differences in AVH characteristics between groups. AVH in the non-psychotic individuals provide the advantage of studying the symptom in relative isolation and without the confounding factor of antipsychotic medication use, but whether the AVH in both groups should be considered precisely the same phenomenon remains unclear.

In sum, non-psychotic individuals with AVH showed increased functioning as a hub region in the temporal cortices and the posterior cingulate/precuneus as compared to non-hallucinating controls. These results suggest that the predisposition to hallucinate is related to aberrant functioning of the default mode network and the auditory cortices.

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Supplementary data S1

Weighted connectivity strength

The relative importance of a node within the graph was determined by two network characteristics of edge centrality (Opsahl et al., 2010). The first centrality measure was the weighted degree centrality, or strength. The strength for node i was defined as

$$d_i^w = \sum_{j \neq i}^{n} w_{ij}$$

The mean strength was defined as

$$D_{mean}^w = \frac{1}{n} \sum_{i=1}^{n} d_i^w$$

Weighted betweenness centrality

The weighted betweenness centrality was the second measure of centrality included and relies on the identification of the number of weighted shortest paths that pass through a node. The more passages, the higher the betweenness centrality. The weighted betweenness centrality is defined as

$$bc_i^w = \frac{1}{(n-1)(n-2)} \sum_{j \neq k, k \neq i, j \neq i}^{n} \frac{g_{jk}^w(i)}{g_{jk}^w}$$

where g_{jk}^w is the shortest path between two nodes and $g_{jk}^w(i)$ is the number of those nodes that pass through node i.

Weighted shortest path length

For a given node i in the graph, the shortest path algorithm finds the path with lowest cost (i.e. the shortest path length) between that node and every other node. For the weighted shortest path length, the path between two nodes i and j is found by minimizing the sum of weights assigned to the edges on their path. To be able to properly deal with disconnected edges, path length L was calculated as the mean geodesic length over all couples of nodes (Newman, 2003; Ponten et al., 2007). Shortest path length is considered a measure of overall network integration (Bullmore and Sporns, 2009; Ponten et al., 2007). L is defined as

$$L = \frac{n(n-1)}{\sum_{i,j \in n} \frac{1}{l_{ij}^w}} \quad \text{with} \quad l_{ij}^w = \min_{i \Leftrightarrow j}(sum(1/w_{ij}))$$

The mean weighted shortest path was defined as

$$L_{mean}^{w} = \frac{1}{n}\sum_{i=1}^{n} l_i^w$$

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Supplementary Data S2

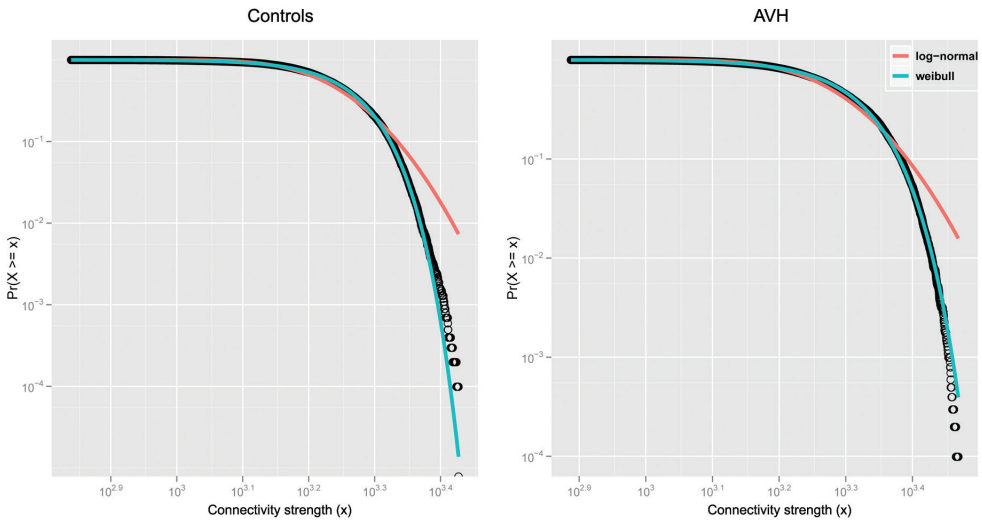

Fig 1. Average complimentary cumulative distribution Pr(X>x) for both groups. Black circles indicate connectivity strength per voxel. Both axes are log-transformed. Data of both groups were best fitted by a Weibull distribution (control group: shape parameter 6.64, scale parameter 1859; AVH group: shape parameter 6.01: scale parameter 2090). Groupwise testing revealed no differences between these parameters across groups.

Part IV

Treatment studies

Chapter 8

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

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Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal region has been proposed as a therapeutic option for auditory verbal hallucinations (AVH). However, most large randomized controlled trials failed to demonstrate a superior effect of rTMS treatment as compared to sham. Previous studies applied daily rTMS sessions for one or more weeks to summate its effects. However, the effect of a single rTMS treatment on AVH-severity has never been studied, making it unclear if there is an initial effect that could be increased by repeated treatment.

Methods: In three separate sessions, twenty-four patients with a psychotic disorder received 1-Hz rTMS to the left temporoparietal cortex, its right-sided homologue or a centro-occipital control site. Severity of AVH was assessed before and after each rTMS session and resting-state EEGs were recorded to investigate the neuronal effects of rTMS.

Results: Stimulation of the temporoparietal cortices was not more effective in reducing AVH-severity than control-site stimulation. In addition, EEG-related power and connectivity measures were not affected differently across stimulation sites and changes in neuronal activity did not correlate with changes in AVH-severity.

Conclusions: These results may suggest a placebo effect of a single session of 1-Hz rTMS treatment on AVH-severity.

1. Introduction

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

Initial randomized-controlled trials (RCTs) have shown a remarkable efficacy of rTMS in reducing AVH as compared to an inactive placebo condition (Brunelin et al., 2006; Chibbaro et al., 2005; Hoffman et al., 2000; Hoffman et al., 2005; Hoffman et al., 2003; Poulet et al., 2005), which was summarized in several meta-analyses (Aleman et al., 2007; Freitas et al., 2009; Slotema et al., 2010b; Tranulis et al., 2008). However, several large RCTs published after these meta-analyses failed to find a significant difference between real and sham-rTMS (Loo et al., 2010; Slotema et al., 2010a; Vercammen et al., 2009). These recent studies suggest that 1-Hz stimulation may not be effective. It remains unclear whether this lack in effect is caused by a fundamental inability of 1-Hz TMS to affect cerebral areas that are crucially involved in AVH, or, alternatively, if there is an initial effect, appropriate summation of this effect is not achieved with once or twice daily repetition. This study aims to further explore the neuronal mechanisms underlying the rTMS effect on AVH by investigating the acute effects of 1-Hz rTMS on AVH-severity and on resting-state electroencephalography (EEG). If a single low-frequency rTMS session can be demonstrated to affect AVH, we expect to find larger decreases in AVH-severity when rTMS is applied to the temporoparietal cortex compared to rTMS at a control area. In addition, decreases in AVH-severity due to rTMS are expected to be associated with changes in brain activity as recorded with EEG before and after each rTMS session.

2. Methods

2.1 Subjects

Thirty-two schizophrenia-spectrum patients experiencing frequent auditory verbal

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

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

Table 1. Patient characteristics

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

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

2.2 Study protocol

Patients received rTMS on three separate occasions on either the left temporoparietal cortex (i.e. midway between the T3 and P3 sites according to the international 10/20 system of EEG electrode placement (Jasper, 1958), the right temporoparietal cortex (i.e. midway between T4 and P4) or the centro-occipital cortex (i.e. the Oz position). As the V1 area of the visual cortex is neither involved in auditory language processing nor in the generation of AVH (Copolov et al., 2003; Jardri et al., 2010; Kandel, 2000; Kuhn and Gallinat, 2011; Silbersweig et al., 1995), and in a pilot experiment subjects reported similar scalp sensations during rTMS directed at

this area as to left and right temporoparietal cortex stimulation, the centro-occipital cortex was chosen as an active control site. Stimulation of the three sites was interspersed with a week, and stimulation for each patient took place on the same time of day. To avoid bias in allocating patients to one of the six possible sequences of stimulation, patients were enrolled in each arm of the experiment by order of participation (i.e. patient 1 in arm 1, patient 2 in arm 2, etc., patient 7 in arm 1, patient 8 in arm 2 etc.). The design of the study was counterbalanced, i.e. each arm of the six sequences of stimulation was filled by four patients. To investigate whether patients saw phosphenes during occipital cortex stimulation, participants were asked whether they saw anything unusual during stimulation. This question was also asked after left and right temporoparietal cortex stimulation. After the last session, patients were asked to rank their physical sensations during rTMS treatment over the three rTMS sessions.

2.3 rTMS

A 70-mm air-cooled figure-of-eight coil (Magstim Company Ltd, Whitland, UK) was used for rTMS treatment at 90% of the individual motor threshold (MT). Each individual's motor threshold was assessed by determining the lowest stimulation intensity at which an observable hand movement contralateral to the stimulated hemisphere could be elicited in five out of ten TMS administrations (Schutter and van Honk, 2006). The MT for occipital stimulation was 90% of the average of the MTs of the left and right hemisphere.
Patients received stimulation for 20 minutes at 1-Hz. During treatment patients sat in a comfortable chair while their head and the TMS coil were fixated. All participants wore sound attenuating earplugs during the study to prevent hearing damage.

2.4 Patient assessments

Before and after each treatment with rTMS, AVH-severity was assessed using three paradigms (fig 1). First, patients indicated the presence of AVH by button-press for ten minutes. The length of all AVH episodes was added up to calculate total AVH duration in this time-frame. After this, a baseline score regarding AVH-severity during the button-press paradigm was set using the Hallucination Change Scale (HCS)(Hoffman et al., 2003). The HCS is an indication of the general severity of AVH as experienced by the patient. Pre-rTMS HCS scores were always assigned a score of 10. Subsequently, AVH-severity during the button-press paradigm was also assessed using the Auditory Hallucinations Rating Scale (AHRS). The AHRS is a questionnaire assessing multiple characteristics of AVH such as the frequency of occurrence, loudness of voices, length of AVH, influence and discomfort of AVH as experienced by the patient (Hoffman et al., 2003).
After rTMS treatment, patients again performed the button-press experiment for 10 minutes. After this they indicated the change in AVH-severity relative to the pre-rTMS HCS score of 10 on a scale from 0-20. A score of 0 indicated total absence of AVH, while a score of 20 indicated twice the severity of AVH compared to baseline. Subsequently AVH-severity was again assessed using the AHRS.

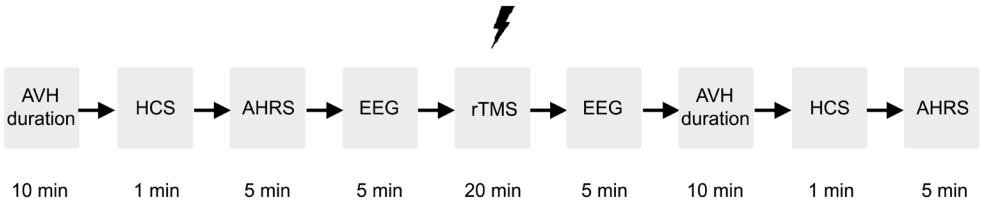

Fig 1. Outline of the experimental procedure. AVH = auditory verbal hallucination, HCS = hallucination change scale, AHRS = auditory hallucinations rating scale, EEG = electroencephalography.

2.5 Electrophysiological recordings

After baseline patient assessments (AVH duration, HCS and AHRS), and preceding rTMS stimulation, resting-state eyes-closed electroencephalography (EEG) data were recorded for five minutes. The procedure was repeated after rTMS stimulation (fig 1). Data acquisition was performed with BioSemi hardware (Amsterdam, the Netherlands) using a cap with 64 Active Two electrodes, arranged according to the 10–20 system. Signals were digitized on-line by a computer at a rate of 2048 Hz.

2.6 Data analysis

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

2.7 Statistical analyses

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

2.7.1 Scalp sensations

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

2.7.2 Patient assessments

The effects of 1-Hz rTMS on AVH duration, HCS score, and AHRS score were analyzed through repeated-measures ANOVA with within-subject factors 'target site' (left temporoparietal cortex,

right temporoparietal cortex and occipital cortex) and 'treatment' (pre-rTMS and post-rTMS). Post-hoc paired t-tests were used to examine significant interaction effects, with correction for multiple comparisons using false discovery rate (FDR) correction.

2.7.3 Electrophysiology

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

3. Results

3.1 rTMS

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

3.2 Scalp sensations

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

3.3 Patient assessments

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

3.4 Electrophysiology

3.4.1 Absolute power

Repeated-measures ANOVA revealed significant main effects of treatment on whole-head theta-band power [$F(1,23) = 10.998$; $P = 0.003$] and alpha-band power [$F(1,23) = 6.795$; $P = 0.016$], indicating significant increases in whole-head theta band and alpha-band power after rTMS treatment. No significant main effect was found for the beta band. A treatment × location interaction effect was found for whole-head alpha-band absolute power [$F(1,23) = 3.816$; $P = 0.044$]. Post-hoc testing with false discovery rate (FDR) correction did however not

reveal any significant differences. Repeated-measures ANOVAs investigating the local effect of rTMS revealed no significant three-way interactions for all three frequency bands, indicating that rTMS treatment did not lead to different changes in power at the brain area underlying the target site compared to the two non-used target sites across the three stimulation sessions.

3.4.2 Network characteristics

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

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

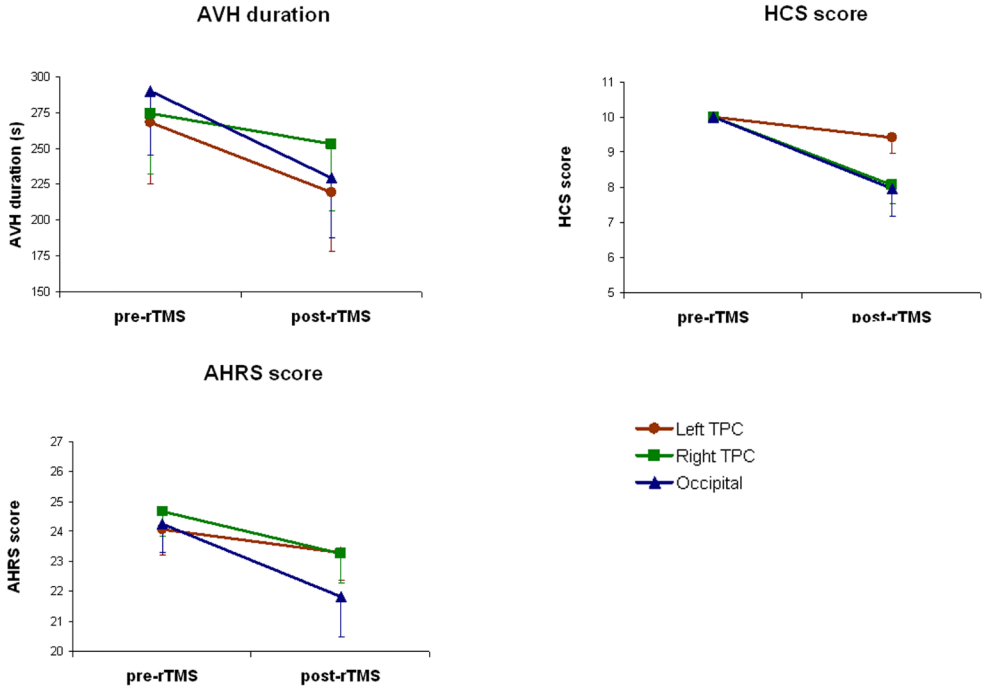

Fig 2. Average effect of rTMS on Auditory Hallucination Rating Scale (AHRS), Hallucination Change Scale (HCS), and AVH duration. TPC: temporoparietal cortex. Error bars indicate standard error of the mean (SEM).

3.5 Correlation analysis

3.5.1 Power

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

3.5.2 Network characteristics

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

4. Discussion

This is the first study to investigate the acute effect of repetitive transcranial magnetic stimulation (rTMS) on auditory verbal hallucinations (AVH). Application of rTMS to the left temporoparietal cortex, right temporoparietal cortex, and the occipital control site all significantly decreased AVH-severity as measured by hallucination duration, Hallucination Change Scale (HCS), and Auditory Hallucinations Rating Scale (AHRS). For the HCS, stimulation of the left temporoparietal cortex was less effective in reducing AVH-severity than stimulation of the control site. This effect could not be observed on the duration of hallucinations and on the AHRS. The general observation was that stimulation at therapeutic locations and at the control site all led to symptom decrease, without much difference between the three locations. Electroencephalography (EEG) recording before and after rTMS treatment revealed that rTMS therapy increased whole-head theta-band power, alpha-band power, and decreased 'small-worldness' in the theta and beta bands. In addition, a decrease in alpha-band clustering coefficient was observed. These overall changes did not correlate with changes in AVH-severity. Also, no differential effect of rTMS target-site was found on whole-head, local, and network-based EEG measures. Similar to the clinical effects, we found neuronal responses to all three locations, without a difference between therapeutic and control sites.

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

The fact that several randomized controlled trials *did* observe an effect on AVH-severity through repeatedly stimulating the left temporoparietal cortex with 1-Hz rTMS may be explained by their inactive sham condition (Brunelin et al., 2006; Chibbaro et al., 2005; Hoffman et al., 1999; Hoffman et al., 2000; Hoffman et al., 2005; Poulet et al., 2005). In these studies sham rTMS was applied using a placebo coil or by tilting the rTMS coil by 45 degrees. While these sham conditions produce some acoustic stimulation, scalp sensations are absent or greatly diminished (Aleman et al., 2007). As such, patients who experience stronger scalp sensations during real rTMS may feel they are receiving more powerful treatment. Indeed, placebo effects have been shown to be greatly enhanced in case of suggestion of stronger treatment, as for example ingestion of two placebo pills elicits stronger effects than ingestion of only one, and injection of placebo is more powerful than oral administration (Blackwell et al., 1972; de Craen et al., 2000). In this study, stimulation of the control site produced similar scalp sensations as stimulation of the temporoparietal sites, thereby controlling for these effects.
However, an important alternative explanation regarding the interpretation of the present results as a placebo effect concerns the possible remote effects of rTMS. RTMS is able to influence brain activity in regions distant from the stimulated brain region through neuronal connections (Horacek et al., 2007). The power, clustering, path length, and small-worldness measures in the various frequency bands may not have been sensitive enough to pick up these signals. As such, we cannot for example rule out the possibility that control-site stimulation affected brain activity in regions associated with auditory verbal hallucinations through intra-hemispheric connections. The same line of reasoning goes for the absence of significant correlations with measures of AVH severity. Perhaps spatial and temporal analyses in source space may provide more sensitivity to establish significant differences across conditions as well as correlations with AVH severity. Neuroimaging methods with a high spatial resolution, such as functional magnetic resonance imaging (fMRI) may be especially suitable to investigate this issue and give a more definite answer on the matter.

4.1 Limitations

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

In sum, this is the first placebo-site controlled study assessing both clinical and neuronal effects of rTMS on AVH. Stimulation of the temporoparietal cortices was not more effective in reducing

AVH symptoms than control-site stimulation. Moreover, electrophysiological measures were not affected differently by rTMS at therapeutic sites as compared to control-site stimulation. These results imply that a single session of 1-Hz rTMS applied to the temporoparietal region does not improve AVH better than occipital cortex stimulation and may suggest a placebo effect of 1-Hz rTMS on AVH-severity.

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Supplementary Data S1

1. Data analysis

1.1 EEG signal analysis

EEG signals were processed with Brain Vision Analyzer software (Brain Products GmbH, Munich, Germany). EEG recordings were downsampled to 400 Hz and band-pass filtered (0.5 – 48 Hz). An average reference montage was used. Ten artefact-free epochs of 10.238 seconds were manually selected from each resting-state EEG recording by visual inspection by two experienced EEG investigators (RvL and SK). EEG data was visually inspected to identify bad EEG channels.

1.1.1 EEG power analysis

To enable a proper comparison between EEG datasets before and after rTMS treatment for the three rTMS target locations, bad channels were excluded for all 6 datasets for that individual. Whole-head absolute power of each EEG epoch was assessed by filtering the data using the Fast Fourier Transform (FFT). Three separate frequency bands were selected for analysis (theta 4 – 8 Hz, alpha 8 – 13 Hz, beta 13 – 30 Hz). The delta frequency band (0 – 4 Hz) was not included in the study, as evidence on the functional role of these oscillations is limited at present (Uhlhaas et al., 2008), and the gamma frequency band (30 – 48 Hz) was not included as high-frequency bands may be heavily contaminated by muscle artefacts (Whitham et al., 2007). Absolute-power values of the ten selected epochs were averaged for each frequency band. The same analysis was also conducted for electrodes measuring the EEG on the sites of rTMS stimulation (left temporoparietal cortex (T3P3), right temporoparietal cortex (T4P4), and centro-occipital cortex (Oz)).

1.1.2 EEG graph analysis

To enable a proper comparison between graph analyses before and after rTMS treatment across subjects, bad channels were excluded for all datasets. Graph analysis was conducted for all ten EEG segments per dataset, and resulting network values for each epoch were subsequently averaged across the ten segments. In the present study graph analyses were executed based on synchronization likelihood (SL) for the same frequency bands as in the power analysis (theta 4 - 8 Hz, alpha 8 - 13 Hz and beta 13-30 Hz). An extensive description of the synchronization likelihood method and its mathematical theory is provided by Stam and van Dijk (2002) and Montez et al (2006). Briefly, SL is a measure for synchronization between time series and is sensitive to linear as well as to nonlinear interdependencies. Basically, SL is the conditional probability of pattern recurrence in time series Y, given a pattern recurrence in time series X. Its scale is between 0 and 1.
Average synchronization was computed over all ten EEG segments per dataset resulting in an

SL value for every combination of electrodes. SL computation for each epoch was performed with DIGEEGXP 2.0 (C.J. Stam, VU University Medical Center, Amsterdam). SL values were subsequently averaged and graph analysis was performed using the same software. Graph analysis yields two dimensions: the clustering coefficient C and the path length L (Watts and Strogatz, 1998). The clustering coefficient is a measure of local functional connectedness and path length is a measure of overall network integration (Bullmore and Sporns, 2009; Ponten et al., 2007). The functional connections between the electrodes can be categorized as weighted and unweighted. In an unweighted graph all connections are equal in strength, whereas in a weighted graph connections can be unequal in strength. This study was restricted to a weighted graph. To be able to properly deal with disconnected edges, L was calculated as the harmonic mean distance connecting any two electrodes in the graph (Newman, 2003; Ponten et al., 2007). The values of C and L were compared with the corresponding values of ensembles of fifty random graphs (C-s and L-s). C/C-s and L/L-s were the measures for normalized clustering and path length coefficients. Small-worldness, a measure of network efficiency, was then calculated by dividing the normalized clustering and path length values ((C/C-s)/(L/L-s)) (Humphries et al., 2006).

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Supplementary Data S2

1. EEG data

The effect of 1-Hz rTMS on EEG whole-head absolute power and network values was analyzed for each frequency band through repeated measures ANOVA with within subject factors 'target site' (left temporoparietal cortex, right temporoparietal cortex and occipital cortex stimulation) and 'treatment' (pre-rTMS and post-rTMS). Post-hoc paired t-tests were used to examine significant interaction effects, with correction for multiple comparisons using FDR correction. The local effect of rTMS on the target site was analyzed in relation to the other two (at that session) not stimulated target sites across sessions. This analysis was conducted through repeated measures ANOVA with within subject factors 'target site' (left temporoparietal cortex (T3P3), right temporoparietal cortex (T4P4) and occipital cortex (Oz) stimulation), 'treatment' (pre-rTMS and post-rTMS), and 'electrode' (T3P3, T4P4, and Oz) by testing for a three-way interaction for each frequency band. Furthermore, significant changes in whole-head EEG power, network parameters, and local EEG power as revealed by repeated measures ANOVA were correlated with AVH duration, HCS, and AHRS change scores with FDR correction for multiple comparisons. Outliers in the correlation analysis were identified based on 2 standard deviation limits around the group mean.

Supplementary Data S3

Table 1. Mean values and standard deviations (in parantheses) of dependent variables for each stimulation site and pre-rTMS and post-rTMS session.

Stimulation site	Pre / Post rTMS	Left temporoparietal (T3P3)	Right temporoparietal (T4P4)	Occipital (Oz)
AVH duration	Pre	268.0 (210.6)	274.6 (209.8)	290.0 (219.2)
AVH duration	Post	219.2 (202.7)	253.0 (227.6)	229.5 (204.4)
HCS	Pre	10.0 (0.0)	10.0 (0.0)	10.0 (0.0)
HCS	Post	9.4 (2.3)	8.1 (2.6)	8.0 (3.0)
AHRS	Pre	24.1 (4.3)	24.7 (4.1)	24.3 (4.7)
AHRS	Post	23.3 (4.5)	23.3 (4.8)	21.8 (6.7)
Theta power (whole-head)	Pre	0.19 (0.22)	0.19 (0.20)	0.19 (0.20)
Theta power (whole-head)	Post	0.21 (0.21)	0.21 (0.24)	0.20 (0.21)
Theta power T3P3	Pre	0.12 (0.18)	0.12 (0.18)	0.11 (0.18)
Theta power T3P3	Post	0.14 (0.20)	0.14 (0.24	0.13 (0.21)
Theta power T4P4	Pre	0.15 (0.19)	0.14 (0.18)	0.14 (0.17)
Theta power T4P4	Post	0.16 (0.18)	0.16 (0.24)	0.15 (0.18)
Theta power Oz	Pre	0.22 (0.22)	0.23 (0.22)	0.24 (0.22)
Theta power Oz	Post	0.26 (0.26)	0.26 (0.29)	0.23 (0.21)
Theta clustering coefficient	Pre	1.24 (0.07)	1.26 (0.06)	1.23 (0.07)
Theta clustering coefficient	Post	1.22 (0.07)	1.26 (0.07)	1.24 (0.11)
Theta path length	Pre	1.16 (0.07)	1.18 (0.09)	1.17 (0.08)
Theta path length	Post	1.16 (0.07)	1.20 (0.11)	1.19 (0.09)
Theta small-worldness	Pre	1.07 (0.06)	1.07 (0.07)	1.06 (0.07)
Theta small-worldness	Post	1.05 (0.07)	1.05 (0.07)	1.05 (0.07)
Alpha power (whole-head)	Pre	0.23 (0.21)	0.24 (0.25)	0.19 (0.16)
Alpha power (whole-head)	Post	0.24 (0.24)	0.24 (0.23)	0.23 (0.22)
Alpha power T3P3	Pre	0.12 (0.18)	0.15 (0.21)	0.12 (0.16)
Alpha power T3P3	Post	0.15 (0.25)	0.14 (0.18)	0.13 (0.18)
Alpha power T4P4	Pre	0.16 (0.16)	0.17 (0.16)	0.14 (0.12)
Alpha power T4P4	Post	0.18 (0.18)	0.18 (0.16)	0.16 (0.15)
Alpha power Oz	Pre	0.38 (0.35)	0.39 (0.40)	0.34 (0.27)
Alpha power Oz	Post	0.39 (0.38)	0.39 (0.40)	0.38 (0.34)
Alpha clustering coefficient	Pre	1.30 (0.11)	1.32 (0.11)	1.30 (0.11)
Alpha clustering coefficient	Post	1.28 (0.11)	1.31 (0.10)	1.29 (0.12)
Alpha path length	Pre	1.24 (0.11)	1.26 (0.11)	1.26 (0.11)
Alpha path length	Post	1.22 (0.11)	1.26 (0.11)	1.25 (0.12)
Alpha small-worldness	Pre	1.05 (0.05)	1.05 (0.05)	1.04 (0.05)
Alpha small-worldness	Post	1.05 (0.05)	1.04 (0.05)	1.03 (0.05)
Beta power (whole-head)	Pre	0.022 (0.016)	0.020 (0.014)	0.017 (0.012)
Beta power (whole-head)	Post	0.022 (0.017)	0.020 (0.014)	0.018 (0.011)
Beta power T3P3	Pre	0.015 (0.016)	0.016 (0.016)	0.016 (0.015)
Beta power T3P3	Post	0.015 (0.015)	0.015 (0.013)	0.015 (0.013)
Beta power T4P4	Pre	0.018 (0.021)	0.017 (0.015)	0.016 (0.015)
Beta power T4P4	Post	0.020 (0.022)	0.017 (0.014)	0.015 (0.011)
Beta power Oz	Pre	0.022 (0.017)	0.027 (0.023)	0.020 (0.014)
Beta power Oz	Post	0.024 (0.022)	0.023 (0.017)	0.019 (0.010)
Beta clustering coefficient	Pre	1.20 (0.08)	1.21 (0.06)	1.19 (0.07)
Beta clustering coefficient	Post	1.18 (0.07)	1.21 (0.09)	1.19 (0.11)
Beta path length	Pre	1.17 (0.07)	1.18 (0.09)	1.18 (0.09)
Beta path length	Post	1.16 (0.07)	1.19 (0.12)	1.19 (0.10)
Beta small-worldness	Pre	1.03 (0.06)	1.03 (0.06)	1.01 (0.07)
Beta small-worldness	Post	1.01 (0.06)	1.02 (0.06)	1.01 (0.07)

AVH: Auditory verbal hallucinations; HCS: Hallucination change scale; AHRS: Auditory hallucinations rating scale

Chapter 9

Summary and general discussion

In this chapter, the main findings of the research presented in this thesis are summarized. In the "state" studies, brain activity during AVH episodes was contrasted with brain activity during non-AVH episodes. This approach can inform us about the neural activity associated with AVH. In the "trait" studies, brain activity during a cognitive task or resting-state was compared between individuals with and without AVH. This approach provides information about neural mechanisms predisposing individuals to experience AVH. In addition, a treatment study is discussed and limitations of our studies are described.

1. Part I: Reviews

Over the years, a large body of research has investigated AVH with neurophysiological methods. To provide an overview of these EEG and MEG studies, **Chapters 2 and 3** review the historical and contemporary literature. It was found that the findings of the older studies are hard to translate into modern day science, as most early studies suffer from substantial weaknesses in study design. For instance, subjects were allowed to walk freely during data acquisition in some studies, which introduces large movement artefacts in the data.

Contemporary state studies

Recent studies investigating neural activity during AVH showed little consistency regarding the involved frequency bands. Increases in theta, alpha, and beta band activity were all reported. However, all studies implicated the left superior temporal gyrus, providing evidence for the involvement of the left auditory cortex in AVH (Ishii et al., 2000; Reulbach et al., 2007; Ropohl et al., 2004). Additional support for the involvement of this structure comes from studies in which auditory stimuli were presented. It was found that the auditory cortex showed reduced responsiveness during AVH compared to non-AVH episodes. This suggests that this area is "busy" during AVH and that external auditory stimuli compete with AVH for neural resources in this brain region (Hubl et al., 2007; Tiihonen et al., 1992).

Contemporary trait studies

The majority of recent trait studies investigating the relationship between EEG measures and AVH showed rather inconsistent findings. Although this can be partly explained by the diverse methodologies that were used, studies employing similar paradigms observed heterogeneous results as well. For instance, some studies found associations between event-related potentials and hallucinations, while others did not observe a relationship with hallucinations or positive symptoms (Eikmeier et al., 1992; Fisher et al., 2008a; Fisher et al., 2008b; Havermans et al., 1999; Kasai et al., 2002; Schall et al., 1999; Turetsky et al., 1998; Youn et al., 2003). As these studies were conducted in schizophrenia patients, this diversity in results may be related to additional symptoms related to the disease and medication confounds. More consistent findings have been obtained with trait studies examining the corollary discharge mechanism. Chapters 2 and 3 discussed a line of experiments that provide evidence that AVH arise from malfunctioning of this system. With the corollary discharge mechanism, sensory areas receive a warning signal from motor areas when a motor act is initiated. In this way, the sensory

consequences of self-generated actions are forecast (Sperry, 1950; Von Holst, 1950). This mechanism is also thought to be involved in speech and even in thinking (with verbal content). When this system is functioning correctly, speech production areas send a warning signal to speech perception areas that a forthcoming thought is self-generated. Dysfunction of this corollary discharge mechanism may then lead to not tagging the thought as coming from the self, resulting in the experience of an alien (i.e. non-self) voice.

2. Part II: State studies

Functional MRI and PET studies have shown that the state of AVH is related to increases in activity in several brain areas, including speech-production, speech-perception, and memory-related regions (Jardri et al., 2010). However, to be able to distinguish AVH from non-AVH periods, subjects were usually instructed to indicate the presence of AVH by button-press. It may thus be that activity in some of the areas implicated in AVH is not directly related to the genesis of AVH, but rather to additional cognitive processes such as the motor response to indicate the presence of AVH and the associated detection processes. In chapter 4 we investigated the influence of these processes by meta-analysis. We found that activity observed in the left inferior frontal gyrus and Heschl's gyrus during the state of AVH as measured with fMRI may be related to auditory stimulus detection and the motor response. However, several areas were found to be solely implicated in the AVH meta-analysis, including the thalamus and parahippocampal gyrus. These structures may provide important targets for neuromodulation to alleviate AVH symptoms.

The aim of the research described in chapter 5 was to investigate the neuronal correlates of AVH using a technique that directly reflects neuronal activity and does not produce scanner noise, as sounds may interact with brain activity related to AVH. The main finding of this MEG study was that the onset of AVH was accompanied by a decrease in theta-band power in the right hippocampus. Theta oscillations in the hippocampus have been hypothesized to integrate different representations of perception, memory and association into one coherent concept, such as a congruent line of thoughts and experiences (Lisman and Buzsaki, 2008; Lisman and Idiart, 1995). The change in theta rhythm at the onset of hallucinations may thus reflect aberrancies in this process and underlie the genesis of a hallucination.

In addition to the findings during AVH onset, decreases in power during AVH were observed in the beta band in the left superior temporal cortex and in the alpha band in the right inferior frontal gyrus. At present, it is difficult to understand the functional significance of the involvement of the alpha and beta frequency bands during AVH. In sum, these results show that AVH onset is accompanied by a short aberration in the theta band in a memory-related structure, and by activity in the alpha and beta band in language areas accompanying the experience of AVH itself.

Part III: Trait studies

The prime goal of trait studies is to test for specific hypotheses explaining the predisposition

to hallucinate. One influential hypothesis on the genesis of AVH is that aberrancies in top-down processing are related to its emergence (Aleman et al., 2003; Behrendt, 1998), and a way to investigate this is by investigating neuronal correlates of effortful attention, such as the P300 amplitude. As the previous P300 studies were conducted in schizophrenia patients, with the potential confounds of medication use and other symptoms related to the illness, we investigated this waveform in non-psychotic individuals with AVH as a relatively isolated symptom. The EEG study described in **chapter 6** showed that this group exhibited an increase in P300 amplitude compared to controls. This finding suggests that increased effortful attention to auditory channels may be related to the predisposition to hallucinate in non-psychotic individuals with AVH. It may also be a compensatory mechanism for other difficulties. This attention factor is absent in schizophrenia patients, as reduced P300 amplitude is a robust finding in this population (Bramon et al., 2004).
Another theory explains the genesis of AVH as resulting from dysfunctional connectivity. Therefore, the study described in **chapter 7** investigated the trait to hallucinate in non-psychotic individuals in a resting-state paradigm using network analysis. The main finding was that, compared to controls, non-psychotic individuals with AVH showed increases in functional connectivity with the rest of the brain in the bilateral temporal cortex and in the posterior cingulate/precuneus. The latter structure is a major constituent of the default mode network, which is a network involved in wakeful resting (Raichle et al., 2001). These results suggest that the trait to hallucinate may be related to aberrant functioning of the default mode network and the auditory cortices.

Part IV: Treatment studies

As a significant number of patients with schizophrenia experience medication-resistant hallucinations, there is a clear need for the development of new treatment options. Low-frequency rTMS to the left temporoparietal cortex has been proposed as a therapeutic tool to treat hallucinations (Hoffman et al., 1999; Hoffman et al., 2000). Despite several studies that show a beneficial effect of repeated treatments of rTMS on the severity of AVH, two recent large randomized controlled trials failed to find a significant effect compared to sham stimulation (Loo et al., 2010; Slotema et al., 2010). This may indicate that low-frequency stimulation does not affect the temporal cortex as effectively as previously thought. For this reason, the study described in **chapter 8** assessed the effect of a single session of rTMS to investigate whether there is an initial effect that can be increased by repeating stimulation sessions. The main clinical finding was that stimulation of experimental sites was not superior compared to occipital control site stimulation, as stimulation to all sites showed similar improvement in the severity of AVH. In line with a previous study by our group, this may imply that 1Hz stimulation is not that effective (Slotema et al., 2010). We also found that changes in AVH-severity did not correlate with changes in neuronal measures as observed with EEG. These results may point to a placebo effect of low-frequency rTMS on severity of AVH and as such question its efficacy as a treatment option.
The mixed effects of low-frequency rTMS on AVH-severity have led some researchers to

explore new stimulation paradigms. Priming with 6-Hz rTMS before low-frequency stimulation, deep rTMS using an H1 coil, as well as high-frequency stimulation, all did not significantly improve symptoms compared to sham or standard low-frequency stimulation (De Weijer et al, submitted; Rosenberg et al., 2012; Slotema et al., 2011). However, these treatments, like the randomized controlled trials investigating low-frequency rTMS, were directed at the left temporoparietal cortex. Perhaps this area is not critically involved in the genesis of AVH, although a recent meta-analysis did implicate this region in the state of AVH (Jardri et al., 2010). It is also possible that the duration of the sessions, the number of sessions, or the frequency or total number of pulses was not optimal. Alternatively, as it is likely that a complex interplay between brain regions is involved in the experience of AVH, it could be that it is not possible to disrupt this process adequately with rTMS directed at a single region.

5. Methodological considerations

The findings presented in this thesis should be interpreted in light of a number of potential limitations. A general consideration of studying AVH is that the presence of the symptom is indicated by self-report of the participants. As a result it is not possible to assess the accuracy and reliability of subject responses. Moreover, motor activity and attention effects related to signalling the presence of AVH in state studies are likely to contribute to the observed activity patterns. To be able to elucidate the effect of the button-presses, a self-paced motor control task is commonly used. However, one could argue that the design of such a control task may not be optimal. Pressing the button to indicate an AVH is preceded by a clear trigger (the start of the hallucination), while the self-paced task lacks such a cue. The design of a perfect control task remains elusive, as the use of externally presented triggers may also not be similar to the neurocognitive processes related to AVH onset.

Another general methodological consideration is that the findings in the present studies relate to highly selected populations. The majority of participating psychotic patients was medication resistant and suffered from AVH for many years. Moreover, patients had to be able to describe their AVH and, in the state MEG study, have both AVH and non-AVH episodes of sufficient length and frequency, rendering several patients unfit for participation. Selection of the non-psychotic individuals with AVH was performed by screening AVH-related questionnaires that were answered on a website. This also results in highly selected participants, and limits the ability to generalize the present results to the general population of non-psychotic individuals with AVH.

It should further be noted that the characteristics of AVH can vary considerably across individuals and often fluctuate within an individual over time. For example the content, number of different voices, controllability of the voices, and frequency and length of AVH often differ between participants. Moreover, anxiety and stress related to participation in the experiment (especially the noise and confined environment related to MRI experiments) may interact with these characteristics and influence results. For instance, many patients hallucinate more when feeling stressed. Elucidating the relationship between these various characteristics and brain activity may contribute to our further understanding of the symptom and constitutes a

recommendation for future research.

Although non-psychotic individuals with AVH present the opportunity to study hallucinations without several of the confounding factors observed in schizophrenia patients, it remains unclear if AVH in these populations represent exactly the same phenomenon. Diederen et al (2011) observed that AVH are related to similar patterns of activation in both groups, which suggests a similar neurobiological mechanism underlying the symptom. However, identical activation patterns may reflect a final common pathway triggered by different mechanisms. In line with this is the current debate whether AVH can be considered to lie on a scale of psychotic symptoms, with normal perceptual experiences on one end, non-psychotic individuals with AVH somewhere in the middle, and full-blown psychosis on the other end (Badcock and Hugdahl, 2012; David, 2010). In sum, it is unknown how representative people with AVH as a relatively isolated symptom are for schizophrenia patients, and this constitutes a major consideration of the present findings.

6. Conclusion

The aim of this thesis was to gain more insight into the pathophysiology of AVH. We found that the predisposition to hallucinate in non-psychotic individuals was associated with an increased neurophysiological correlate of top-down processing as well as increased connectivity from the temporal cortices and an area in the default mode network. In addition, we observed aberrant activation in the auditory and language network during AVH in schizophrenia patients. Moreover, the onset of AVH was accompanied by a change in activity in a memory-related structure. These findings highlight the importance of attention processes as well as the involvement of auditory, language and memory structures in the genesis of AVH, and suggest that AVH arise at the intersection of bottom-up and top-down processing. Future research should focus on investigating the pathophysiological mechanisms of hallucinations in other populations such as patients with hearing loss, Parkinson's disease, or epilepsy, as this may yield valuable knowledge regarding a possible common pathway in the genesis of AVH. This may expand our understanding of the basic mechanism behind hallucinations and open up avenues for new treatments in hallucinating patients who can currently not be helped.

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Addendum

Nederlandse samenvatting

Als iemand een stem hoort zonder dat er daadwerkelijk iemand spreekt, wordt dit een auditieve verbale hallucinatie (AVH) genoemd. Dit type hallucinaties komt veelvuldig voor bij schizofrenie, waarbij de stemmen vaak een negatieve, kwetsende inhoud hebben. Deze patiënten worden meestal behandeld met antipsychotische medicatie, waardoor bij de meeste patiënten de AVHs verdwijnen. Helaas zijn de AVHs bij een grote minderheid (~25%) ongevoelig voor medicatie, zodat deze patiënten vaak continu afgeleid worden door de stemmen die nare dingen zeggen. Dit heeft een grote invloed op de kwaliteit van het leven. Veel onderzoek richt zich op het ontrafelen van hersenprocessen die betrokken zijn bij AVHs omdat extra kennis kan helpen bij het ontwikkelen van nieuwe behandelmethoden. Het meeste onderzoek heeft zich gericht op AVHs in schizofrenie patiënten. Sinds kort is er echter ook aandacht voor AVHs bij mensen die geen psychiatrische of neurologische aandoening hebben. Deze populatie heeft als voordeel dat AVHs er bestudeerd kunnen worden zonder dat de resultaten beïnvloed worden door factoren als antipsychotische medicatie en andere symptomen die bij schizofrenie voorkomen.

Er zijn twee strategieën die vaak terugkomen bij studies naar hersenactiviteit gerelateerd aan AVHs. Bij zogenaamde 'state' studies wordt onderzocht welke hersengebieden actief worden terwijl proefpersonen of patiënten AVHs ervaren. Daarnaast zijn er zogenaamde 'trait' studies waarbij wordt onderzocht waardoor mensen de neiging hebben om te hallucineren. State en trait studies kunnen uitgevoerd worden met behulp van verscheidene beeldvormende technieken. Veelgebruikte technieken zijn o.a. electroencephalografie (EEG), magnetoencephalografie (MEG) en functionele magnetische resonantie imaging (fMRI). Een techniek die recentelijk in de belangstelling staat als mogelijke behandelwijze tegen stemmen is repetitieve transcraniële magnetische stimulatie (rTMS). Met deze methode worden magnetische pulsen op het hoofd gegeven met als doel om hersenactiviteit te veranderen.

Het doel van het onderzoek in dit proefschrift was om meer inzicht te verkrijgen in hersenprocessen die optreden tijdens AVHs en hersenprocessen die gerelateerd zijn aan de neiging om te hallucineren in het verbaal auditieve domein. Dit is met verschillende soorten beeldvormingstechnieken onderzocht. Een tweede doel van dit proefschrift was onderzoeken in hoeverre rTMS een adequate behandelmethode tegen AVH is.

Deel I. Literatuurstudies

In **hoofdstuk 2 en 3** wordt een uitgebreid literatuuronderzoek gepresenteerd van studies naar AVH die EEG en MEG hebben gebruikt. Moderne state studies laten zien dat er weinig overeenkomst zit in de frequentiebanden tijdens AVH. Wel vinden alle studies dat er activiteit is in de linker superieure temporaalschors, wat een gebied is dat betrokken is bij auditieve verwerking. De meeste trait studies laten een wisselend beeld zien. Deze studies werden alle uitgevoerd bij schizofreniepatiënten, en de verscheidenheid aan resultaten kan daarom mogelijk verklaard worden door andere symptomen van deze ziekte en het gebruik van antipsychotische medicatie.

Meer consistente resultaten werden gerapporteerd bij studies die het zogenaamde corollary

discharge systeem onderzochten. Er wordt vermoed dat dit systeem een rol speelt bij het toekennen van informatie aan een gedachte dat deze zelf is gegenereerd. Mogelijk wordt bij het slecht functioneren van dit systeem een gedachte ervaren als niet komende van jezelf, waardoor een AVH wordt waargenomen.

Deel II. State studies

Verscheidene state studies hebben aangetoond dat AVHs gepaard gaan met verhogingen in hersenactiviteit in specifieke hersengebieden. Bij deze studies hebben patiënten met knopdrukken aangegeven wanneer zij AVHs ervoeren, oftewel, stemmen hoorden. Het zou kunnen dat meerdere van deze gebieden niet zozeer betrokken zijn bij het ontstaan van AVHs, maar bij het detecteren van AVHs en het aangeven van AVHs met de knopdruk. Om dit te onderzoeken is in **hoofdstuk 4** hersenactiviteit bij detectieprocessen en knopdrukken vergeleken met hersenactiviteit tijdens AVHs. Er wordt gevonden dat beide processen gepaard gingen met activiteit in de linker inferieure frontale gyrus en de linker gyrus van Heschl, maar dat sommige gebieden alleen actief werden tijdens de AVHs. Voorbeelden zijn de rechter postcentrale en de linker parahippocampale gyrus. Deze hersenstructuren kunnen mogelijke aangrijppunten zijn voor nieuwe therapieën tegen AVHs.

Het grootste deel van de state studies naar AVHs gebruikte fMRI. Deze techniek maakt veel lawaai, wat van invloed is op het gehoorssysteem. Omdat AVHs ook 'gehoord' worden, zou het geluid van de MRI scanner de resultaten kunnen beïnvloeden. Ook leest fMRI vrij trage signalen, wat het lastig maakt om korte tijdsegmenten te onderzoeken. Om deze reden is het onderzoek in **hoofdstuk 5** uitgevoerd met een stille meetmethode die daarnaast de mogelijkheid biedt om korte tijdsegmenten te bestuderen (magnetoencefalografie). Er werd gevonden dat de start van AVHs samenhing met een verlaging in een theta band activiteit in de rechter hippocampus, wat een hersenstructuur is die betrokken is bij geheugenprocessen. Tijdens het stemmen horen werden er veranderingen in activiteit gevonden in de rechter inferieure frontale gyrus en in de linker superieure temporaalschors. Deze resultaten suggereren dat AVHs beginnen met geheugenprocessen en verder gepaard gaan met activiteit in taal- en gehoorgebieden.

Deel III. Trait studies

In **hoofdstuk 6** werd de invloed van aandacht onderzocht op het voorkomen van AVHs. Er werd gevonden dat niet-psychotische personen met AVHs een verhoogde hersenmaat hadden van bewuste aandacht. Dit resultaat toont aan dat bewuste aandacht betrokken kan zijn bij de neiging om AVHs te ervaren in deze populatie. In **hoofdstuk 7** werd het brein in rust onderzocht in niet-psychotische personen met AVHs. Er werd gevonden dat deze mensen meer functionele connectiviteit vanuit de temporaalschors en de posterieure cingulate cortex/precuneus hadden met de rest van het brein dan controlepersonen. Dit toont aan dat de neiging tot hallucineren gepaard gaat met verhoogde communicatie vanuit auditieve verwerkingsgebieden en een gebied dat betrokken is bij het zogenaamde default mode netwerk.

Deel IV: Behandelstudie

In **hoofdstuk 8** werd de effectiviteit van één enkele behandeling met repetitieve transcraniële magnetische stimulatie (rTMS) tegen AVHs onderzocht. Er werd gevonden dat rTMS op plekken die bij taal betrokken zijn niet beter werkt dan rTMS op een controleplek. Dit suggereert dat de effecten van rTMS op AVHs mogelijk door een placebowerking verklaard kunnen worden. Deze bevinding sluit aan bij de inconsistente resultaten van meerdaagse behandelingen.

Conclusie

Het doel van dit proefschrift was meer inzicht te verwerven in de pathofysiologie van AVHs. De resultaten wijzen naar een aantal fenomenen gerelateerd aan AVHs. Hersenactiviteit in taalgebieden tijdens AVH wordt waarschijnlijk getriggered door geheugenprocessen. Verder is de neiging om te hallucineren in niet-psychotische personen met AVHs gerelateerd aan zowel een verhoogde bewuste aandacht als een verhoogde functionele connectiviteit van auditieve gebieden. Ten slotte wordt gesteld dat er een herevaluatie nodig is van de therapeutische werking van rTMS ter behandeling van AVHs.

Dankwoord

Het volbrengen van dit promotietraject was niet mogelijk geweest zonder de bijdrage van een heleboel mensen. Hiervoor wil ik de volgende mensen hartelijk danken.

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mogen de talloze alcoholische versnaperingen (en een enkele peuk) die na het werk werden genuttigd natuurlijk niet onvermeld blijven. Veel succes in Cambridge!
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List of publications

1. Peer-reviewed journals

van Lutterveld R, Hillebrand A., Diederen KMJ, Daalman K., Kahn RS, Stam CJ, Sommer IEC: Oscillatory cortical network involved in auditory verbal hallucinations in schizophrenia. PLoS ONE 2012: doi:10.1371/journal.pone.0041149.t001

Ford JM, Dierks T, Fisher DJ, Hermann CS, Hubl D, Kindler J, Koenig T, Mathalon DH, Spencer KM, Strik W, **van Lutterveld R**: Neurophysiological studies of auditory verbal hallucinations. Schizophrenia Bulletin 2012; e-pub ahead of print; doi:10.1093/schbul/sbs009

Diederen KMJ, **van Lutterveld R**, Sommer IEC: Neuroimaging of voice hearing in non-psychotic individuals: A mini review of recent fMRI, PET, DTI and EEG studies. Frontiers in Human Neuroscience 2012 6:111: e-pub ahead of print; doi: 10.3389/fnhum.2012.00111

van Lutterveld R, Koops S, Schutter DJLG, Geertsema E, Stam CJ, Kahn RS, Sommer IEC: The effect of rTMS on auditory hallucinations: Clues from an EEG-rTMS study. Schizophrenia Research 2012:137: 174-179

Daalman K, Diederen KMJ, Derks EM, **van Lutterveld R**, Kahn RS, Sommer IEC: Childhood trauma and auditory verbal hallucinations. Psychological Medicine 2012: e-pub ahead of print; doi:10.1017/S0033291712000761

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van Lutterveld R, Oranje B, Kemner C, Abramovic L, Willems AE, Boks MPM, Glenthøj BY, Kahn RS, Sommer IEC: Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations. Schizophrenia Research 2010 121:153-159

2. Submitted manuscripts

van Lutterveld R, Diederen KMJ, Otte W, Sommer IEC: Network analysis of auditory hallucinations in non-psychotic individuals

van Lutterveld R, Diederen KMJ, Koops S, Begemann MJH, Sommer IEC: About the baby and the bathwater; the influence of stimulus detection on activation patterns during auditory hallucinations.

Diederen KMJ, Neggers SFW, De Weijer AD, **van Lutterveld R**, Daalman K, Eickhoff SB, Clos M, Kahn RS, Sommer IEC: Aberrant resting state connectivity in non-psychotic individuals with auditory hallucinations.

Aukes MF, Boks MPM, Willems AE, **van Lutterveld R**, Sommer IEC, Sitskoorn MM, Ophoff RA, Alizadeh BZ, and Kahn RS: A genome-wide linkage scan of theta band activity as a heritable endophenotype for schizophrenia.

Diederen KMJ, Charbonnier L, Neggers SFW, **van Lutterveld R**, Daalman K, Slotema CW, Kahn RS, Sommer IEC Reproducibility of brain activation during auditory verbal hallucinations: an fMRI study

3. Book chapters

Van Lutterveld R, Ford JM: Neurophysiological research: EEG and MEG. In: Hallucinations. Research and practice (edited by Blom JD and Sommer IEC). Springer, New York.

4. Conference abstracts

van Lutterveld R, Hillebrand A, Stam CJ, Kahn RS, Sommer IEC: Auditory verbal hallucinations are related to decreased beta-band power in the anterior superior frontal gyrus – An MEG study. Poster presentation at the Schizophrenia International Research Society conference, Florence, Italy 2010

van Lutterveld R, Hillebrand A, Stam CJ, Kahn RS, Sommer IEC: An MEG study on auditory verbal hallucinations in schizophrenia patients. Poster presentation at the Organization for Human Brain Mapping conference, Barcelona, Spain 2010

van Lutterveld R, Hillebrand A, Stam CJ, Kahn RS, Sommer IEC: An MEG study on auditory verbal hallucinations in schizophrenia patients. Poster presentation at the Federation of European Neurosciences conference, Amsterdam, the Netherlands 2010

van Lutterveld R, Diederen KMJ, Otte WM, Sommer IEC: Auditory verbal hallucinations in non-psychotic individuals – a graph theoretical study Poster presentation at the Schizophrenia International Research Society conference, Florence, Italy 2012

Curriculum Vitae

Remko van Lutterveld was born on November 30 1974 in Gouda in the Netherlands. He graduated from high school (Orduynen College in 's-Hertogenbosch) in 1993 after which he obtained a Bachelor's and Master's degree in Fundamental Biomedical Sciences at Utrecht University. After working several years for the government he went back to university and obtained a Bachelor's degree in Psychology after completing an electrophysiology internship in the lab of Ron Mangun in Davis, California. He was subsequently accepted in the prestigious Master's degree program in Cognitive Neuroscience at Utrecht University, during which he did an internship at the University Medical Center Utrecht under supervision of Prof.dr. Iris Sommer, in which he investigated electrophysiological measures of attention in non-psychotic individuals with auditory verbal hallucinations. He performed a second internship at the VU Medical Center in Amsterdam under supervision of Prof.dr. Cornelis Stam, in which he investigated auditory verbal hallucinations in schizophrenia patients using magnetoencephalography (MEG). After graduating cum laude in August 2008, he joined the Department of Psychiatry at the University Medical Center Utrecht as a PhD candidate under supervision of Prof.dr. Iris Sommer and Prof. dr. René Kahn. In November 2012 Remko will become a post-doctoral researcher at the group of Prof.dr. Iris Sommer, where he will continue his research into auditory verbal hallucinations.

Remko van Lutterveld werd geboren op 30 november 1974 in Gouda. Hij behaalde in 1993 zijn VWO diploma aan het Orduynen College in 's-Hertogenbosch, waarna hij zijn doctoraal haalde in Fundamentele Biomedische Wetenschappen aan de Universiteit Utrecht. Na enkele jaren voor de overheid gewerkt te hebben, begon hij aan de opleiding psychologie waarbij hij een electrofysiologie stage deed in het lab van Ron Mangun in Davis, Californië. Na het behalen van zijn Bachelor titel werd hij toegelaten tot de prestige onderzoeksmaster Cognitive Neuroscience aan de Universiteit Utrecht. Tijdens deze master liep hij stage bij de afdeling volwassenen psychiatrie van het UMC Utrecht onder leiding van Prof.dr. Iris Sommer. Tijdens deze stage onderzocht hij electrofysiologische maten van bewuste aandacht bij niet psychotische personen die stemmen horen. Hij volgde een tweede stage bij de afdeling Klinische Neurowetenschappen in het VUmc in Amsterdam onder leiding van Prof.dr. Cornelis Stam. Hierbij onderzocht hij het horen van stemmen bij schizofreniepatiënten met behulp van magnetoencephalografie (MEG). In augustus 2008 studeerde hij cum laude af, waarna hij begon met zijn promotie onderzoek bij de afdeling volwassenen psychiatrie in het UMC Utrecht, onder supervisie van Prof.dr. René Kahn en Prof.dr. Iris Sommer. Vanaf november 2012 zal Remko werkzaam blijven als post-doctorale onderzoeker in de groep van Prof.dr. Iris Sommer, waar hij het onderzoek naar auditieve verbale hallucinaties zal voortzetten.