The Hallucinating Brain

Kelly M.J. Diederen

Research in this thesis was supported by a VENI and a VIDI grant from the Netherlands Organization for Scientific Research to Prof. dr. I.E.C. Sommer.

Publication of this thesis was financially supported by the Rudolf Magnus Institute of Neuroscience.

ISBN: 978-90-5335-483-4
Printed by: Ridderprint BV, Ridderkerk, the Netherlands
Lay-out by: Nikki Vermeulen, Ridderprint BV, Ridderkerk, the Netherlands

The Hallucinating Brain

Het hallucinerende brein

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht op gezag van
de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
maandag 14 november 2011 des ochtends te 10.30 uur

door

Kelly Maria Johanna Diederen

geboren op 27 oktober 1983
te Heerlen

Promotoren: Prof. dr. I.E.C. Sommer
Prof. dr. R.S. Kahn

Co-promotor: Dr. S.F.W. Neggers

Voor Bram

Voor mijn ouders

Any intelligent fool can make things bigger and more complex...
It takes a touch of genius - and a lot of courage to move in the opposite direction.

- Albert Einstein

Table of contents

Chapter 1

General introduction

In 1971, in a village in the Philippines, a woman was found unconscious and fevered in a field were she had been plucking fruit. The woman later reported, *'As I busied myself plucking fresh fruit I felt as though a gush of strong wind passed by. Then all of a sudden I heard human voices crying, pleading, and asking not to be shot. Some were cursing. Then there was silence. A few minutes later the voices came again, agonizing groans of men about to die, writhing in pain. I started to run but I could not move my legs. I tried to shout but I couldn't. Then the world started to turn round; I did not know what happened next.'* According to the villagers, her experiences were caused by spirits called *bahoy*, which haunt places where violent deaths have happened in the past [1].

While auditory verbal hallucinations (AVH) or 'voices' are frequently attributed to possession by a spirit in non-Western societies, in modern Western societies they are generally considered an aspect of disease [2]. This contrasts with earlier Western accounts, in which powerful men were supposedly being guided by gods speaking to them. The Greek philosopher Socrates, for instance, was reportedly aided by a voice to make important decisions, and in the 19th century Joan of Arc, the "iron maiden", was declared a Saint by the Catholic Church because she had heard the voice of God telling her how to liberate France from English domination.

AVH can occur in a wide variety of individuals, including patients with a neurological or neurodegenerative disease, patients with a psychiatric disorder, and healthy individuals in the general population [3, 4]. Moreover, they can be induced by illicit substances such as cannabis, amphetamines and cocaine, as well as by prescribed drugs and alcohol [4], although it should be noted that substance-induced hallucinations tend to occur most frequently in the visual modality. They have also been reported in association with progressive deafness [5]. But irrespective of the context in which they occur, AVH often co-occur with hallucinations in any of the other sensory modalities, as well as with delusions and formal thought disorder [4, 6].

1. Outline

Over time, various approaches evolved to study AVH. First, a number of studies investigated the prevalence rates of AVH in different clinical subgroups and in the general population. These studies will be described in part 2 of this chapter. The next part focuses on investigations into the phenomenology of AVH and the comparison of specific voice characteristics between psychiatric and healthy individuals.
In addition to these studies, numerous studies investigated the neurobiological basis of AVH by applying various research methods such as neuropsychological testing and brain imaging. As the studies described in the following chapters used functional MRI as the main method of investigation, functional neuroimaging studies into AVH will be described in part 4 of this chapter. In part 5 current treatment options for these hallucinations will be described. Finally part 6 provides a short introduction into the principles of functional MRI and part 7 provides an outline of the current thesis.

2. Hallucinations among different groups of the population

2.1. Patients with a neurological or neurodegenerative disorder

AVH tend to occur in the context of a number of neurological disorders, including epilepsy, brainstem pathology, brain tumors, cerebrovascular infarctions, migraine, and delirium [4, 7, 8]. They can also occur in the context of neurodegenerative diseases such as Lewy Body dementia, Parkinson's disease, and Alzheimer's disease [9-11].

Although several studies investigated the prevalence rates of hallucinations in patients with a neurodegenerative disorder, only a handful of them focused exclusively on AVH. For instance, Inzelberg et al. [10] reported that 37% of a group of patients with Parkinson's disease experienced hallucinations, that 29% of their sample experienced only visual hallucinations, and that 8% experienced visual as well as auditory verbal hallucinations. In agreement with this, Fénelon et al. [12] showed that hallucinations were present in 39.8% of patients diagnosed with Parkinson's disease, while hallucinations in the auditory modality were experienced by 9.7%. Interestingly, cognitive impairment was more common among the hallucinating patients.
In an early study, Wolff and Curran [13] found auditory hallucinations to occur in 41.5% of patients diagnosed with Alzheimer's disease. Almost seventy years later, Bassiony and Lyketsos [9] reviewed all prior studies on Alzheimer's disease, and showed that prevalence rates ranged from 4 to 76% for all types of hallucination, and from 1 to 29% for auditory hallucinations. In addition, the authors reported that hallucinations tended to persist over time, to recur over the course of the disease process, and to be associated with negative consequences such as functional impairment and aggression.

From those studies it can be concluded that although auditory hallucinations are relatively common in Parkinson's disease and Alzheimer's, visual hallucinations tend to occur more frequently in those patient groups. This is in sharp contrast with patients diagnosed with a psychiatric disorder, in whom hallucinations of the auditory modality are the most prevalent ones [14].

2.2. Patients with a psychiatric disorder

AVH frequently occur in the context of bipolar disorder, major depressive disorder, borderline or schizotypal personality disorder, post-traumatic stress disorder, and dissociative identity disorder [15-17]. However, they are the most prevalent in patients diagnosed with schizophrenia, as defined by the DSM-IV-TR [18].

A number of studies have investigated the prevalence rates of auditory hallucinations in psychiatric patients. For instance, the International Pilot Study of Schizophrenia [19] recorded AVH in 74% of patients diagnosed with schizophrenia. In agreement with this, Sartorius et al. [20] reported them to occur in 70% of their cases. However, Slade and Bentall [5] reported a somewhat lower prevalence rate (60%).

In patients diagnosed with bipolar disorder, the frequency of hallucinations was established in 22.9% in patients with a mixed episode, 11.2% in those with a manic episode, and 10.5% in those with a depressive episode. Of the bipolar patients who presented with hallucinations 56.9% heard voices [14]. Of patients with a unipolar disorder 5.9% reported experiencing hallucinations, of which group 40.6% experienced AVH [14]. Reviewing studies published between 1922 and 2007, Goodwin and Geddes [21] showed that auditory hallucinations were present in 18% of all patients diagnosed with bipolar disorder. Finally, Kingdon et al. [22] found that 50% of the patients diagnosed with borderline personality disorder, 66% of those diagnosed with schizophrenia, and 90% of those with both diagnoses experienced auditory hallucinations. Among those, auditory hallucinations were reported most frequently.

Some studies found sex differences associated with the prevalence rates for hallucinations in psychiatric patients. For instance, Marneros [23] reported a significantly higher prevalence of auditory hallucinations among women (25%) than among men (15%) diagnosed with schizophrenia. Interestingly, the prevalence rates of hallucinations in that sample are much lower than generally reported [5, 19, 20]. This might be due to the fact that the authors only included patients who were hospitalised for the first time. Rector and Seeman [24] showed that while 54% of the male participants in their study experienced auditory hallucinations, 78% of the female patients

experienced them. Cetingok et al. [25] reported that hallucinations were more frequent among married Turkish women diagnosed with schizophrenia than among unmarried Turkish women, Turkish men, and Americans of either sex. However, another study of the prevalence rates of AVH in individuals diagnosed with schizophrenia did not report any sex differences [26]. As regards mood disorders, various studies showed a higher prevalence of hallucinations in women than men [14, 27].

2.3. The general population

Although AVH are often associated with some pathological condition, they also occur in healthy individuals in the general population [28, 29].

More than a century ago, Sidgwick et al. [28] were the first to study hallucinations in the general population. In their sample of 17,000 individuals who were primarily of British descent, 9.9% claimed having experienced visual, tactile or auditory hallucinations. AVH were reported by 3.6% of all respondents. Over a century later, Tien [29] reported that visual, tactile or auditory hallucinations occurred in 13% of all healthy individuals in the US. The frequency of AVH varied with age, ranging from 1.5% to 3.2%. Roughly similar rates for AVH were found in New Zealand (3.4%) [30] and in the Netherlands (2-4%) [31]. A much higher prevalence rate (16%) was reported in a French study by Verdoux et al. [32].

The reported differences in prevalence rates are probably at least partially due to differences in study design and demographic characteristics of the cohorts under study [33, 34].

While the prevalence rates of hallucinations are rather similar across population groups in Western countries, there are striking differences to be found among specific subgroups of those populations. For instance, 14 to 71% of US college students report having experienced AVH at least once in their lives [35-37]. This is substantially more frequent than in the general population [28-32].

In concordance with the prevalence rates recorded in individuals with a psychiatric disorder, it was found that female students had a significantly greater propensity to hallucinate than men [38]. Likewise, in Tien's sample [29], women reported more auditory and olfactory hallucinations, whereas visual hallucinations were reported slightly more frequently by men.

Prevalence rates for hallucinations would also seem to depend on ethnic and cultural differences. Jocano [1], for instance, reported that 13.3% of the individuals in a village in the Philippines experienced supernatural experiences which to us would qualify as auditory hallucinations. In addition, Johns et al. [39] found a higher prevalence rate for

hallucinatory experiences in subjects of the general Western population as compared to (originally) non-Western individuals living in the UK. Interestingly, subjects belonging to ethnic minorities reported fewer hallucinations when they were born abroad and had migrated later in life, as compared to those who were born in the UK. The exception was a Caribbean subgroup, where hallucinations were reported 2.5-fold more often than by Caucasian respondents.

2.4. A continuum of AVH

As AVH present in psychiatric patients as well as in the general population a number of authors argued that clinical and non-clinical hallucinations lie as points on a continuum and do not differ qualitatively from one another [3, 33, 40-42]. Therefore, it is usually assumed that AVH in clinical and non-clinical groups result from the same underlying mechanism. This view furthermore implies that need for treatment depends on the individuals' reaction to, and the severity and associated dysfunction of the AVH, not solely on the presence of AVH itself. At present, it is, however, still unclear if AVH in clinical and non-clinical individuals can indeed be considered the same phenomenon [33, 43, 44]. Comparing phenomenology of AVH in different groups could shed light on this matter [43].

3. Phenomenology

A striking aspect of AVH is the diversity of this phenomenon. While one person may hear a single voice giving friendly advice approximately once per hour, someone else may continuously hear multiple voices gossiping about him. The variegated nature of AVH has been recognized for a long time, and has led to the conception of numerous subclassifications and investigations into the differences in AVH-characteristics among different subgroups.

3.1. Classifications

Although early classification studies generally defined subgroups of hallucinations based on observation and clinical experience, contemporary studies predominantly use data-driven approaches to identify independent clusters of AVH characteristics. For instance, Haddock et al. [45] identified three hallucination factors, comprising emotional characteristics (i.e., distress and negative content), physical characteristics (i.e., frequency, loudness, etc.), and a cognitive interpretation factor (i.e., beliefs about the voices, control, etc.). Stephane et al. [46] reported two clusters of which the first included components such as control strategies, self attribution and repetitive content and the second included systematized content, high linguistic complexity and a number of

other components. Singh et al. [47] also identified two factors, which they called 'reality of hallucinatory perception' and 'immersion in the hallucination'. Finally, Hayashi et al. [48] identified four independent factors, consisting of 'the intractable nature of the experience' (comprising negative voice content, negative patient responses, and uncontrollability of the voices), 'delusional reality distortion', 'influence', and 'externality' (which was composed of perception of external or internal voices and their origins).

The variability in identified factors derived from these studies is quite apparent. Differences between these studies might result from a number of factors including ethnicity of the participants and the use of dissimilar interview scales [45, 49, 50].

3.2. Comparison psychiatric patients and healthy individuals

The first study comparing AVH in psychotic and non-psychotic voice-hearers focused on pragmatic properties of AVH [51], such as the familiarity of voices, the type of action demanded by those voices, and the degree of dialogical engagement of voices and voice-hearers. Honig [52] reported that the form of hallucinatory experiences was not significantly different among patients diagnosed with schizophrenia or dissociative identity disorder, and healthy voice- hearers. However, in contrast to the patient groups, healthy voice-hearers perceived their voices as predominantly positive: they were not alarmed or upset by their voices, and felt in control of the experience. Daalman et al. [53] studied the phenomenological characteristics of AVH in a substantial sample of psychotic and healthy voice-hearers. Differences between the groups included the emotional valence of their content, the frequency of AVH, and the control subjects experienced over their AVH. An additional difference was that the onset of AVH tended to be at a younger age in the healthy subjects, which might well be due to an - as yet unknown - difference in the underlying mechanisms of origin. Other characteristics of AVH, such as experienced location and loudness, perceived reality, the number of voices, and personification, i.e., attribution to a person, of the AVH were similar in both groups.

4. Aetiology

Although the origin of AVH is still largely unknown, previous studies point to the influence of genetic factors, dopamine dysfunction, psychological trauma, stress and cognitive deficits in the genesis of these hallucinations [3]. The precise role of these factors is, however, still unclear and currently a main focus of investigation. Various studies applied functional brain imaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) to further

investigate the role of neurocognitive dysfunction in AVH. As the studies described in this thesis applied fMRI as the main research method the next section describes functional neuroimaging studies in subjects with AVH.

PET and fMRI studies on AVH can be divided into two categories. The first group comprises investigations into what happens in the brain when someone experiences AVH. These studies are generally referred to as symptom-capture or *state* studies. By contrast, the second group focuses on comparing brain activation, during a cognitive task, between individuals with and without AVH. The rationale of these *trait* studies is that differences in brain activation between hallucinating and non-hallucinating subjects may reveal specific mechanisms predisposing a person to experience AVH.

4.1. State studies

The first studies into brain activation during AVH were conducted using PET, or the related technique SPECT. In these studies two scans were acquired per patient. The first when a subject presented with AVH and the second when these hallucinations were no longer present. More direct comparisons between hallucination and non-hallucination episodes were made in later fMRI studies. In most fMRI studies, patients were instructed to indicate the presence of AVH by button-presses while in the scanner. As a result, AVH and non-AVH episodes were obtained within one scan [54].

In the first PET study, McGuire et al. [55] observed that AVH were related to increased activation of Broca's area, the left temporal area and the anterior cingulate cortex, regions which are involved in language perception, production and self-monitoring. Involvement of the temporal and anterior cingulate cortex was also reported by Suzuki et al. [56]. Silbersweig et al. [57] also found activation of the anterior cingulate cortex. However, in this study most extended signal change was observed in subcortical areas.

These results were partly replicated by later fMRI studies which also reported increased activation in the middle and superior temporal gyri [58-62]. Besides, some of these studies observed activation in the auditory cortex [60, 63], as well as in frontal [58, 60, 61] and subcortical regions [58, 61].

In addition, several studies investigated brain activation preceding AVH, as this might reveal an internal trigger for these hallucinations. These investigations reported involvement of the right middle temporal gyrus, left inferior frontal gryus, anterior cingulate cortex, parahippocampal gyri and insula prior to AVH [58, 64, 65].

In summary, most studies reported activation of temporal areas which are involved in auditory and language perception. In addition, several studies found activation of frontal language production areas, areas involved in self-monitoring and subcortical areas. Therefore it is likely that these cognitive functions are related to the experience of AVH. It should, however, be noted that the reliability of these studies is questionable as most studies included only a small number of subjects.

4.2. Trait studies

The majority of trait studies were designed with a certain theory in mind. Although numerous theories have been proposed to underlie AVH [3], most imaging studies focussed on either of three models. Imaging studies into these models will be described in the next section.

4.2.1. Inner speech theory

The most influential model proposes that AVH occur due to a failure to recognize self-generated inner speech [66, 67]. This misattribution was hypothesized to result from malfunction of the corollary discharge mechanism: a neuronal circuit that suppresses the sensory consequences of self-generated actions [68]. This corollary discharge is thought to be sent from frontal language production areas to temporoparietal language perception areas, either directly through the arcuate fasciculus tract or via the anterior cingulate cortex.

To investigate this theory, a number of authors employed verbal imagery or inner speech tasks. For instance, McGuire et al. [69] found reduced activation in the left middle temporal gyrus and the rostral supplementary motor area during verbal imagery in patients with AVH. Dysfunctional inner speech-related activation was also found by Shergill et al. [70, 71]; areas of aberrant activation included the right temporal, parietal and subcortical areas.

A second group of studies investigated functional connectivity during language tasks. Although task-related dysfunctional connectivity was indeed observed in schizophrenia patients, the location of aberrant connectivity varied between studies [72-77]. Some authors observed aberrant frontotemporal connectivity [75] while others found faulty integration of frontal areas and the anterior cingulate cortex [77] or aberrant connectivity between the anterior cingulate cortex and temporal regions [76]. Interestingly, another study found that frontotemporal connectivity was modulated by the anterior cingulate cortex [73].

In summary, these studies reveal aberrant regional activation as well as connectivity in schizophrenia patients with AVH during inner speech. While aberrant regional activation and connectivity were often observed in frontotemporal langage production and perception regions as well as in the anterior cingulate cortex, the exact locations of dysfunction vary substantially between studies.

4.2.2. Central auditory processing theory

A second model suggests that AVH result from dysfunctional central auditory processing [59, 78]. This has been investigated by measuring the response of auditory and language perception regions in the temporal cortex to external auditory stimuli.

For instance, David et al. [79] observed a decrease in response of the temporal cortex to auditory stimuli when the patient under study was actively hallucinating. A reduced response of the temporal cortex was also observed by Woodruff et al. [62]. However, no difference could be found between hallucinating and non-hallucinating patients. Although Copolov et al. [80] failed to find aberrant activity of the temporal cortex, the majority of studies in schizophrenia did observe a dysfunctional temporal response to external speech [81-83].

In summary, although dysfunctional auditory processing is found by the majority of studies in schizophrenia, this deficit does not seem to be specifically related to AVH.

4.2.3. Language lateralization theory

Finally, AVH have been hypothesized to result from decreased left cerebral dominance for language. In this model AVH result from the release of language activity in the right hemisphere, which is not recognized as self-produced [84]. Studies into this theory focussed on investigating lateralization of brain activity when participants performed a language task.

These studies used a number of tasks including language perception [85, 86] and free speech [87]. Most studies, however, used a verbal fluency task which involves the generation of words from verbal cues [88-93].

Irrespective of task, decreased language lateralization was consistently reported in schizophrenia patients [85-94], individuals with psychotic depression and mania [95] and monozygotic twins discordant for schizophrenia [96]. Results from the latter study suggest that decreased language lateralization represents a predisposition for psychosis.

In summary, decreased left cerebral dominance for language is a well-replicated finding in schizophrenia patients. However, schizophrenia is a complex syndrome

comprising positive, negative and cognitive symptoms. It is, therefore, unclear if this hallmark of schizophrenia is related to schizophrenia in general or to specific symptoms of schizophrenia such as auditory hallucinations.

5. Treatment

At present, the primary treatment for AVH consists of antipsychotic medication which is often combined with cognitive behavioural therapy. The first antipsychotic medication, chlorpromazine, was discovered 'by accident' by French surgeon Henri Laborit who observed that a new antihistamine called chlorpromazine had unusual tranquilizing effects which, he proposed, could treat psychosis without major sedation [97].

Nowadays, most patients are prescribed with either *typical* (i.e. classic) or the newer *atypical* antipsychotics which seem to cause less side-effects [98]. Both classes of antipsychotics block dopamine receptors, however, *atypical* antipsychotics also target serotonergic and/ or GABA-ergic neurotransmission.

Although antipsychotic medication is largely effective in treating hallucinations, AVH do not respond to antipsychotic medication in 25-30% of schizophrenia patients [99]. As a result, development of new treatment options for this symptom is of major importance.

An alternative treatment option for AVH might consist of repetitive Transcranial Magnetic Stimulation (rTMS), a noninvasive method for altering activation of cortical neurons by rapidly changing magnetic fields [100, 101]. By inhibiting aberrant activation in language perception regions, these hallucinations might be inhibited as well. Supposedly, neurophysiological mechanisms such as long term potentiation (LTP) in the latter areas, resulting from repeated exposure to rTMS on subsequent days, might lead to prolonged inhibition of hallucinatory hyperactivation.

Studies applying rTMS in the treatment of AVH most frequently targeted a fixed position on the skull, corresponding to speech perception areas. However, other studies used a tailor-made treatment in which the rTMS coil is directed to the location where hallucinatory activation is maximal, as identified by fMRI scans of individual patients.

As recent meta-analyses provide evidence for the efficacy of rTMS in the treatment of AVH [100-102], it appears an adequate treatment-option for these hallucinations.

6. Functional MRI

Functional MRI is an extension of MRI which enables the mapping of brain function in addition to brain structure. The first study on fMRI was published in 1992 [103] and triggered a revolution in neuroscience as fMRI has a number of advantages over its predecessor PET. First, fMRI is non-invasive as participants do not have to be injected with a radioactive tracer. Secondly, a better spatial resolution (in the order of millimetres) and temporal resolution (in the order of seconds) can be obtained with fMRI. Moreover, a high resolution anatomical MRI scan can be obtained in the same scan session. Finally, fMRI is much cheaper than PET. However, fMRI also has some disadvantages over PET such as a greater sensitivity to subject motion, noise generated by the scanner and a larger instability in general.

6.1. Basic principles of fMRI

To understand the basic principle of fMRI, it is important to provide some information on MRI. An MRI scanner consists of a large magnet with a magnetic field strength of 1 to 7 Tesla in most human studies. When a person is placed in a magnetic field a minority of protons align themselves with the direction of the magnetic field and rotate around their axis with a very high frequency depending on the local magnetic field strength. A radio frequency (RF) pulse is then applied at exactly this rotation frequency which is subsequently absorbed by the aligned protons ('RF excitation'), causing them to assume a non-aligned direction. The protons, however, gradually realign themselves with the main magnetic field while emitting radio waves which are captured by a receiver coil. Switching magnetic field gradients can then create an image of this signal, as the frequency of the absorbed RF excitation is a function of local magnetic field strength.

FMRI is a variation on MRI, in which the varying magnetic properties of the oxygen transporter molecule haemoglobin are used to examine brain function. In short, neuronal activation requires energy as supplied by adenosine triphosphate (ATP) which is formed via glucose consumption in the presence of oxygen. When neuronal activation takes place, local glucose consumption rises sharply. As neurons have no internal reserves for glucose and oxygen, more neuronal activity requires more glucose and oxygen which is delivered rapidly through the blood stream. The increased need for oxygen is, however, overcompensated by a large increase in blood flow due to a dilation of the microvasculature which results in increasing blood volume near the site of neuronal activation. As a result, the concentration of oxyhaemoglobin (i.e. haemoglobin with oxygen attached to it) increases and the concentration of

deoxyhaemoglobin decreases. As deoxyhaemoglobin is paramagnetic (i.e. it disturbs the regional magnetic field) and oxyhaemoglobin is diamagnetic (i.e. it does not disturb the regional magnetic field) an increase in oxygenated haemoglobin reduces local distortion of the magnetic field which results in a signal increase in areas were neural activation increases. This contrast is referred to as the blood-oxygenation-level-dependent (BOLD) [103] and forms the basis for the fMRI signal.
It is, however, important to note that the relationship between neural activity and the BOLD signal involves multiple vascular, metabolic, and neural processes and is at present incompletely understood.

6.2. FMRI experiments

In fMRI studies, a large series of scans is rapidly acquired to record BOLD signal changes over time. Each scan consists of several thousand volume elements (i.e. voxels) which represent the smallest unit of spatial resolution (usually in the order of e.g. 4x4x4mm for scanners with a field strength of 1.5 or 3T). During an experiment, the task of interest is generally alternated with a reference condition, as fMRI cannot be used to measure absolute signal intensity. To detect changes that correlate significantly with the condition of interest and to deal with the relatively large noise in the fMRI signal, task conditions have to be repeated over the course of the experiment. An efficient approach for comparing responses in different states consists of a block design in which different conditions are alternated in relatively long blocks (e.g. 30 seconds).

7. Outline of this thesis

The research presented in this thesis aims at providing more insight into the pathophysiology of auditory verbal hallucinations (AVH). The first part of this thesis consists of *state* studies which aim at investigating brain activation during the experience of AVH. The second part describes *trait* studies which focus at comparing brain activation between individuals with and without AVH. The rationale of these trait studies is that differences in brain activation between hallucinating and non-hallucinating subjects may reveal specific mechanisms predisposing a person to experience AVH.

7.1. State studies

The study described in chapter 2 focuses on investigating brain activation during AVH in a substantial number of psychotic patients. The rationale for this investigation is that previous studies only included a small number of subjects, rendering the reliability of the obtained results questionable. A second aim of this study is to compare AVH-related brain activation to brain activation during inner speech.

Chapter 3 further discusses the results presented in chapter 2. In this chapter a new model is proposed to account for the occurrence of AVH.

Although functional imaging of activity during hallucinations is helpful in understanding which regions are involved in the experience of AVH, it cannot explain how and where these experiences originate in the brain. Therefore, the study described in chapter 4 investigates brain activation shortly before AVH, as this might reveal how these hallucinations are triggered.

State studies may also be of aid in developing tailor-made treatments for AVH. Examples of this strategy are the focal treatment of these hallucinations with repetitive Transcranial Magnetic Stimulation (rTMS) or invasive electrocortical stimulation, in which the focus of maximum activation during AVH in individual patients is used as the target position for treatment. In order to apply such a treatment it is, however, important to determine whether brain activation during AVH can be reliably detected with fMRI. With this aim, the study described in chapter 5 investigates spatial reproducibility of AVH-related brain activation.

Although the studies described in the previous chapters may reveal which regions are involved in the experience of AVH in psychotic patients, it is unclear if a similar pattern of activation can be observed in other subgroups with AVH. If these hallucinations are caused by comparable mechanisms in different groups, one should observe a similar pattern of brain activation during AVH. Therefore, the study described in chapter 6 aims at comparing AVH-related brain activation between psychotic patients and non-psychotic (healthy) individuals with AVH.

7.2. Trait studies

Previous studies implicated that AVH result from decreased left cerebral dominance for language, i.e. language lateralization, which is a well-replicated finding in schizophrenia. It is, however, unclear if this abnormality is indeed related to AVH or to another symptom of schizophrenia, or schizophrenia in general. To elucidate this, the study described in chapter 7 investigates language lateralization in non-psychotic individuals with AVH as these subjects experience AVH in relative isolation.

Another influential theory proposes that AVH result from deviant integration of frontal and temporoparietal brain areas. While this is confirmed by a number of studies in schizophrenia patients, a direct link between dysfunctional connectivity and AVH has thus far not been established. To elucidate if these hallucinations are indeed related

to aberrant integration, the study presented in chapter 8 investigates resting state connectivity in non-psychotic subjects with AVH, as these subjects experience AVH in relative isolation.

7.3. Summary and general discussion

Finally, chapter 9 provides a summary and general discussion of the findings described in this thesis.

References

1. Jocano FL. Varieties of supernatural experiences among Filipino peasants: hallucination or idiom of cultural cognition? by F. LANDA JOCANO. Paper pre sented at the reconvened Annual Meeting of the American Psy chiatric Association, Honolulu, Hawaii, May 1970. Type. 31 pp. *Transcultural Psychiatry* April 1, 1971 1971;8(1):43-45.
2. al-Issa I. The illusion of reality or the reality of illusion. Hallucinations and culture. *Br J Psychiatry* Mar 1995;166(3):368-373.
3. Aleman A, Laroi F. *Hallucinations : The Science of Idiosyncratic Perception*.: American Psychological Association: Washington, DC; 2008.
4. Asaad G, Shapiro B. Hallucinations: theoretical and clinical overview. *Am J Psychiatry* Sep 1986;143(9):1088-1097.
5. Slade PD, Bentall RP. *Sensory Deception: A Scientific Analysis of Hallucination*: John Hopkins Press, Baltimore; 1988.
6. Sommer IE, Derwort AM, Daalman K, de Weijer AD, Liddle PF, Boks MP. Formal thought disorder in non-clinical individuals with auditory verbal hallucinations. *Schizophr Res* May 2010;118(1-3):140-145.
7. Brasic JR. Hallucinations. *Percept Mot Skills* Jun 1998;86(3 Pt 1):851-877.
8. Brasic JR, Perry R. Unilateral auditory hallucinations in a boy with ipsilateral conductive hearing loss. *J Neurol Neurosurg Psychiatry* Mar 1997;62(3):302.
9. Bassiony MM, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: review of the brain decade. *Psychosomatics* Sep-Oct 2003;44(5):388-401.
10. Inzelberg R, Kipervasser S, Korczyn AD. Auditory hallucinations in Parkinson's disease. *J Neurol Neurosurg Psychiatry* Apr 1998;64(4):533-535.
11. McKeith IG, Perry RH, Fairbairn AF, Jabeen S, Perry EK. Operational criteria for senile dementia of Lewy body type (SDLT). *Psychol Med* Nov 1992;22(4):911-922.
12. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain* Apr 2000;123 (Pt 4):733-745.
13. Wolff HG, Curran D. Nature of delirium and allied states: the dysergastic reaction. *Arch Neurol Psychiatry* June 1, 1935 1935;33(6):1175-1215.
14. Baethge C, Baldessarini RJ, Freudenthal K, Streeruwitz A, Bauer M, Bschor T. Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. *Bipolar Disord* Apr 2005;7(2):136-145.
15. Ross CA, Miller SD, Reagor P, Bjornson L, Fraser GA, Anderson G. Schneiderian symptoms in multiple personality disorder and schizophrenia. *Compr Psychiatry* Mar-Apr 1990;31(2):111-118.
16. Siegel RK. Hostage hallucinations. Visual imagery induced by isolation and life-threatening stress. *J Nerv Ment Dis* May 1984;172(5):264-272.
17. Skaf CR, Yamada A, Garrido GE, Buchpiguel CA, Akamine S, Castro CC, Busatto GF. Psychotic symptoms in major depressive disorder are associated with reduced regional cerebral blood flow in the subgenual anterior cingulate cortex: a voxel-based single photon emission computed tomography (SPECT) study. *J Affect Disord* Apr 2002;68(2-3):295-305.
18. AmericanPsychiatricAssociation. *Diagnostic and statistical manual of mental disorders (4th ed., text rev.)*. : Washington, DC: Author. ; 2000.
19. Wing JK. Psychiatry in the Soviet Union. *Br Med J* Mar 9 1974;1(5905):433-436.
20. Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, Day R. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med* Nov 1986;16(4):909-928.

21. Goodwin GM, Geddes JR. What is the heartland of psychiatry? *Br J Psychiatry* Sep 2007;191:189-191.
22. Kingdon DG, Ashcroft K, Bhandari B, et al. Schizophrenia and borderline personality disorder: similarities and differences in the experience of auditory hallucinations, paranoia, and childhood trauma. *J Nerv Ment Dis* Jun 2010;198(6):399-403.
23. Marneros A. Frequency of occurrence of Schneider's first rank symptoms in Schizophrenia. *Eur Arch Psychiatry Neurol Sci* 1984;234(1):78-82.
24. Rector NA, Seeman MV. Auditory hallucinations in women and men. *Schizophr Res* Sep 1992;7(3):233-236.
25. Cetingok M, Chu CC, Park DB. The effect of culture on the sex differences in schizophrenia. *Int J Soc Psychiatry* Winter 1990;36(4):272-279.
26. Mueser KT, Bellack AS, Brady EU. Hallucinations in schizophrenia. *Acta Psychiatr Scand* Jul 1990;82(1):26-29.
27. Smith MH. A Statistical Study of Hallucinations in the Manic-depressive Psychosis. (Amer. Journ. Psychiat., September, 1931.) Bowman, K. M, and Raymond, A. F. *Journal of Mental Science* April 1, 1932 1932;78(321):428-b-429.
28. Sigdwick H, Johnson A, Myers FWH, Podmore F, Sigdwick E. *Report on the Census of Hallucinations. In: Proceedings of the Society for Psychical Research. London: Kegan Paul, Trench, Trübner & Co* Vol XXVI; 1894.
29. Tien AY. Distributions of Hallucinations in the Population. *Soc Psychiatry Psychiatr Epidemiol* 1991;26:287-292.
30. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry* May 15 2005;57(10):1117-1127.
31. Escher S, Hayward M, Kingdon D, Pembroke L, Thomas P. Learning to live with voices. *Ment Health Today* Dec-2006 Jan 2005:18-20.
32. Verdoux H, Maurice-Tison S, Gay B, Van Os J, Salamon R, Bourgeois ML. A survey of delusional ideation in primary-care patients. *Psychol Med* Jan 1998;28(1):127-134.
33. Linscott RJ, van Os J. Systematic reviews of categorical versus continuum models in psychosis: evidence for discontinuous subpopulations underlying a psychometric continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annu Rev Clin Psychol* Apr 27 2010;6:391-419.
34. Beavan V, Read J, Cartwright C. The prevalence of voice-hearers in the general population: A literature review. *Journal of Mental Health* 2011;20(3):281-292.
35. Barrett TR, Etheridge JB. Verbal hallucinations in normals, I: People who hear 'voices'. *Applied Cognitive Psychology* 1992;6(5):379-387.
36. Bentall RP, Slade PD. Reality testing and auditory hallucinations: a signal detection analysis. *Br J Clin Psychol* Sep 1985;24 (Pt 3):159-169.
37. Posey TB, Losch ME. Auditory hallucinations of hearing voices in 375 normal subjects. *Imagination, Cognition and Personality* 1983;2(5):99-113.
38. Young HF, Bentall RP, Slade PD, Dewey ME. The role of brief instructions and suggestibility in the elicitation of auditory and visual hallucinations in normal and psychiatric subjects. *J Nerv Ment Dis* Jan 1987;175(1):41-48.
39. Johns LC, Nazroo JY, Bebbington P, Kuipers E. Occurrence of hallucinatory experiences in a community sample and ethnic variations. *Br J Psychiatry* Feb 2002;180:174-178.
40. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophr Res* Sep 29 2000;45(1-2):11-20.

41. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* Feb 2009;39(2):179-195.
42. Strauss JS. Hallucinations and delusions as points on continua function. Rating scale evidence. *Arch Gen Psychiatry* Nov 1969;21(5):581-586.
43. David AS. Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychol Med* Dec 2010;40(12):1935-1942.
44. Lawrie SM, Hall J, McIntosh AM, Owens DG, Johnstone EC. The 'continuum of psychosis': scientifically unproven and clinically impractical. *Br J Psychiatry* Dec 2010;197:423-425.
45. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* Jul 1999;29(4):879-889.
46. Stephane M, Thuras P, Nasrallah H, Georgopoulos AP. The internal structure of the phenomenology of auditory verbal hallucinations. *Schizophr Res* Jun 1 2003;61(2-3):185-193.
47. Singh G, Sharan P, Kulhara P. Phenomenology of hallucinations: a factor analytic approach. *Psychiatry Clin Neurosci* Jun 2003;57(3):333-336.
48. Hayashi N, Igarashi Y, Suda K, Nakagawa S. Phenomenological features of auditory hallucinations and their symptomatological relevance. *Psychiatry Clin Neurosci* Dec 2004;58(6):651-659.
49. Carter DM, Mackinnon A, Howard S, Zeegers T, Copolov DL. The development and reliability of the Mental Health Research Institute Unusual Perceptions Schedule (MUPS): an instrument to record auditory hallucinatory experience. *Schizophr Res* Aug 1 1995;16(2):157-165.
50. Chadwick P, Birchwood M. The omnipotence of voices. A cognitive approach to auditory hallucinations. *Br J Psychiatry* Feb 1994;164(2):190-201.
51. Leudar I, Thomas P, McNally D, Glinski A. What voices can do with words: pragmatics of verbal hallucinations. *Psychol Med* Jul 1997;27(4):885-898.
52. Honig A, Romme MA, Ensink BJ, Escher SD, Pennings MH, deVries MW. Auditory hallucinations: a comparison between patients and nonpatients. *J Nerv Ment Dis* Oct 1998;186(10):646-651.
53. Daalman K, Boks MP, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IE. Auditory Verbal Hallucinations in Healthy and Psychotic Individuals. *J Clin Psychiatry* in press.
54. Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev* 2008;32(1):175-191.
55. McGuire PK, Murray RM, Shah GMS. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *The Lancet* 1993;342(8873):703-706.
56. Suzuki M, Yuasa S, Minabe Y, Murata M, Kurachi M. Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucination: A longitudinal case study using¹²³I-IMP SPECT. *European Archives of Psychiatry and Clinical Neuroscience* 1993;242(5):257-261.
57. Silbersweig DA, Stern E, Frith C, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature* Nov 9 1995;378(6553):176-179.
58. Lennox BR, Park SBG, Medley I, Morris PG, Jones PB. The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Research: Neuroimaging* 2000;100(1):13-20.
59. Lennox BR, Park SB, Jones PB, Morris PG. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* Feb 20 1999;353(9153):644.
60. Dierks T, Linden DEJ, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W. Activation of Heschl's Gyrus during Auditory Hallucinations. *Neuron* 1999;22(3):615-621.
61. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* Nov 2000;57(11):1033-1038.

62. Woodruff P, Brammer M, Mellers J, et al. Auditory hallucinations and perception of external speech. *The Lancet* 1995;346(8981):1035-1036.

63. van de Ven VG, Formisano E, Röder CH, et al. The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *NeuroImage* 2005;27(3):644-655.

64. Hoffman RE, Anderson AW, Varanko M, Gore JC, Hampson M. Time course of regional brain activation associated with onset of auditory/verbal hallucinations. *Br J Psychiatry* Nov 2008;193(5):424-425.

65. Shergill SS, Brammer MJ, Amaro E, Williams SCR, Murray RM, McGuire PK. Temporal course of auditory hallucinations. *The British Journal of Psychiatry* December 1, 2004 2004;185(6):516-517.

66. Frith C. Positron emission tomography studies of frontal lobe function: relevance to psychiatric disease. *Ciba Found Symp* 1991;163:181-191; discussion 191-187.

67. Frith C, Done J. Positive symptoms of schizophrenia. *Br J Psychiatry* Apr 1989;154:569-570.

68. Ford JM, Roach BJ, Faustman WO, Mathalon DH. Synch Before You Speak: Auditory Hallucinations in Schizophrenia. *Am J Psychiatry* March 1, 2007 2007;164(3):458-466.

69. McGuire PK, David AS, Murray RM, Frackowiak RSJ, Frith CD, Wright I, Silbersweig DA. Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *The Lancet* 1995;346(8975):596-600.

70. Shergill SS, Brammer MJ, Fukuda R, Williams SCR, Murray RM, McGuire PK. Engagement of brain areas implicated in processing inner speech in people with auditory hallucinations. *The British Journal of Psychiatry* June 1, 2003 2003;182(6):525-531.

71. Shergill SS, Bullmore E, Simmons A, Murray R, McGuire P. Functional Anatomy of Auditory Verbal Imagery in Schizophrenic Patients With Auditory Hallucinations. *Am J Psychiatry* October 1, 2000 2000;157(10):1691-1693.

72. Boksman K, Théberge J, Williamson P, et al. A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophrenia Research* 2005;75(2-3):247-263.

73. Fletcher P, McKenna PJ, Friston KJ, Frith CD, Dolan RJ. Abnormal Cingulate Modulation of Fronto-Temporal Connectivity in Schizophrenia. *NeuroImage* 1999;9(3):337-342.

74. Jennings JM, McIntosh AR, Kapur S, Zipursky RB, Houle S. Functional network differences in schizophrenia: a rCBF study of semantic processing. *NeuroReport* 1998;9(8):1697-1700.

75. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological Psychiatry* 2002;51(12):1008-1011.

76. Mechelli A, Allen P, Amaro E, Fu CHY, Williams SCR, Brammer MJ, Johns LC, McGuire PK. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Human Brain Mapping* 2007;28(11):1213-1222.

77. Spence SA, Liddle PF, Stefan MD, et al. Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *Br J Psychiatry* Jan 2000;176:52-60.

78. McKay CM, Headlam DM, Copolov DL. Central Auditory Processing in Patients With Auditory Hallucinations. *Am J Psychiatry* May 1, 2000 2000;157(5):759-766.

79. David AS, Woodruff PW, Howard R, et al. Auditory hallucinations inhibit exogenous activation of auditory association cortex. *Neuroreport* Mar 22 1996;7(4):932-936.

80. Copolov DL, Seal ML, Maruff P, Ulusoy R, Wong MT, Tochon-Danguy HJ, Egan GF. Cortical activation associated with the experience of auditory hallucinations and perception of human speech in schizophrenia: a PET correlation study. *Psychiatry Res* Apr 1 2003;122(3):139-152.

81. Ford JM, Roach BJ, Jorgensen KW, et al. Tuning in to the Voices: A Multisite fMRI Study of Auditory Hallucinations. *Schizophrenia Bulletin* January 1, 2009 2009;35(1):58-66.

82. Plaze M, Bartrés-Faz D, Martinot J-L, et al. Left superior temporal gyrus activation during sentence

perception negatively correlates with auditory hallucination severity in schizophrenia patients. *Schizophrenia Research* 2006;87(1-3):109-115.

83. Zhang ZJ, Hao GF, Shi JB, Mou XD, Yao ZJ, Chen N. Investigation of the neural substrates of voice recognition in Chinese schizophrenic patients with auditory verbal hallucinations: an event-related functional MRI study. *Acta Psychiatrica Scandinavica* 2008;118(4):272-280.
84. Sommer IE, Diederen KM. Language production in the non-dominant hemisphere as a potential source of auditory verbal hallucinations. *Brain* 2009.
85. Dollfus S, Razafimandimby A, Delamillieure P, Brazo P, Joliot M, Mazoyer B, Tzourio-Mazoyer N. Atypical hemispheric specialization for language in right-handed schizophrenia patients. *Biological Psychiatry* 2005;57(9):1020-1028.
86. Razafimandimby A, Maiza O, Herve PY, et al. Stability of functional language lateralization over time in schizophrenia patients. *Schizophr Res* Aug 2007;94(1-3):197-206.
87. Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK. Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. *Psychol Med* Apr 2002;32(3):439-449.
88. Artiges E, Martinot JL, Verdys M, Attar-Levy D, Mazoyer B, Tzourio N, Giraud MJ, Paillere-Martinot ML. Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophr Bull* 2000;26(3):709-721.
89. Sommer IE, Ramsey NF, Kahn RS. Language lateralization in schizophrenia, an fMRI study. *Schizophr Res* Oct 1 2001;52(1-2):57-67.
90. Sommer IE, Ramsey NF, Mandl RC, Kahn RS. Language lateralization in female patients with schizophrenia: an fMRI study. *Schizophr Res* Apr 1 2003;60(2-3):183-190.
91. Crow TJ. Invited commentary on: Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. *The British Journal of Psychiatry* January 1, 2000 2000;176(1):61-63.
92. Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Brinkhoff C, Kremser C, Felber S, Fleischhacker WW. Brain activation patterns during a verbal fluency test-a functional MRI study in healthy volunteers and patients with schizophrenia. *Schizophr Res* Oct 1 2004;70(2-3):287-291.
93. Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Felber S, Fleischhacker WW. Language lateralization in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. *Psychiatry Res* Mar 31 2006;146(2):185-190.
94. van Veelen NM, Vink M, Ramsey NF, Sommer IE, van Buuren M, Hoogendam JM, Kahn RS. Reduced language lateralization in first-episode medication-naive schizophrenia. *Schizophr Res* Apr 2011;127(1-3):195-201.
95. Sommer IE, Vd Veer AJ, Wijkstra J, Boks MP, Kahn RS. Comparing language lateralization in psychotic mania and psychotic depression to schizophrenia; a functional MRI study. *Schizophr Res* Jan 2007;89(1-3):364-365.
96. Sommer IEC, Ramsey NF, Mandl RCW, Van Oel CJ, Kahn ReS. Language activation in monozygotic twins discordant for schizophrenia. *The British Journal of Psychiatry* February 1, 2004 2004;184(2):128-135.
97. Weinberger DR. Schizophrenia drug says goodbye to dopamine. *Nat Med* 2007;13(9):1018-1019.
98. Barnes TR, McPhillips MA. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. *Int Clin Psychopharmacol* Mar 1998;13 Suppl 3:S49-57.
99. Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophr Res* Aug 17 1998;32(3):137-150.
100. Aleman A, Sommer IE, Kahn RS. Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *J Clin Psychiatry* Mar 2007;68(3):416-421.

101. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010;71(7):873-884.

102. Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. *Schizophrenia Research* 2009;108(1-3):11-24.

103. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences* July 1, 1992 1992;89(13):5951-5955.

Part I

State studies

Chapter 2

Auditory verbal hallucinations predominantly activate the right inferior frontal area

Iris EC Sommer[1]
Kelly MJ Diederen[1]
Jan Dirk Blom[2,3]
Anne Willems[1]
Leila Kushan[1]
Karin Slotema[2]
Marco PM Boks[1]
Kirstin Daalman[1]
Hans W Hoek[2,3]
Sebastiaan FW Neggers[1]
René S Kahn[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands
[2]Parnassia Bavo Group, The Hague, the Netherlands
[3]Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

Brain (2008) 131 (12): 3169-3177

Abstract

Introduction

The pathophysiology of auditory verbal hallucinations (AVH) is largely unknown. Several functional imaging studies have measured cerebral activation during these hallucinations, but sample sizes were relatively small (one to eight subjects) and findings inconsistent.

Methods

In this study cerebral activation was measured using fMRI in 24 psychotic patients while they experienced AVH in the scanner and, in another session, while they silently generated words. All patients were right handed and diagnosed with schizophrenia, schizo-affective disorder or psychotic disorder not otherwise specified.

Results

Group analysis for AVH revealed activation in the right homologue of Broca's area, bilateral insula, bilateral supramarginal gyri and right superior temporal gyrus. Broca's area and the left superior temporal gyrus were not activated. Group analysis for word generation in these patients yielded activation in Broca's and Wernicke's areas and to a lesser degree in their right-sided homologues, bilateral insula and anterior cingulate gyri. Lateralization of activity during AVH was not correlated with language lateralization, but rather with the degree to which the content of the hallucinations had a negative emotional valence.

Conclusions

The main difference between cerebral activity during AVH and activity during normal inner speech appears to be the lateralization. The predominant engagement of the right inferior frontal area during AVH may be related to the typical low semantic complexity and negative emotional content.

1. Introduction

Auditory verbal hallucinations (AVH) are a cardinal feature of psychosis [1]. Indeed, in schizophrenia the one month prevalence of these hallucinations exceeds 70% [2] and in 25–30% of patients these perceptions are resistant to medication, leading to functional disability and a low quality of life [3, 4]. Therapeutic options for these patients are currently sparse and the development of new therapeutic strategies would benefit from better knowledge of the pathophysiology of AVH.

Despite several functional imaging studies, the neuropathological mechanism of the disorder has remained unclear, possibly as a result of the complexity of scanning cerebral activation during hallucinations. Specifically, patients are required to experience AVH for a substantial part of the scan time in order to generate enough power for a meaningful comparison between activity during hallucinations and the baseline. On the other hand, patients should not hallucinate continuously, since sufficiently long epochs without hallucinations are needed for a useful comparison with hallucinating periods. This may explain why sample sizes of previous functional imaging studies that have assessed cerebral activation *during* AVH have been small, ranging from one to eight patients [5-12]. Apart from the small sample sizes, previous studies applied rather liberal thresholds for significance. This combination can easily result in both type I and type II errors, which may have created inconsistent results regarding which areas are activated during hallucinations [13]. For example, Silbersweig et al. [5] observed activation predominantly in subcortical structures, while Shergill et al. [10] found activation of Broca's area and bilateral temporal cortices. Dierks et al. [7] reported hallucinatory activity in the primary auditory cortex, which could not be replicated by Copolov et al. [11] who instead observed prominent activity in the parahippocampal gyrus. The largest sample of patients hallucinating during fMRI recordings to date was reported recently by Hoffman et al. [12] who found activity during AVH in temporal and frontal areas of both hemispheres in eight patients. Since it has been shown that over 20 subjects are needed in a typical fMRI experiment to obtain appropriate reproducibility [14, 15], we acquired fMRI scans of 24 psychotic patients while they were experiencing AVH. Since these perceptions obviously consist of words or sentences, we hypothesized that this analysis would reveal activity in language-related structures, such as Broca's and Wernicke's areas. Apart from these classical language areas, AVH may activate other brain regions that could be specific to the presence of hallucinations. In a previous study [16], we found that the majority of schizophrenia patients showed prominent activity in the right-sided homologues of the classical language areas during AVH (i.e. in the right inferior frontal gyrus, right superior temporal and supramarginal gyrus), while normal language is generally produced in the left hemisphere in right-handed

subjects. To explore a difference in lateralization between hallucinatory activation and normal language production, the same patients also performed a silent word generation task while fMRI scans were acquired.

2. Methods

2.1. Subjects

Subjects were included who experienced frequent AVH as well as frequent moments without these hallucinations. Twenty-four right-handed patients with a diagnosis of schizophrenia-spectrum disorder participated in this study. All subjects used antipsychotic medication during the study, but continued frequently to experience AVH. The clinical characteristics of the patients are summarized in Table 1.

Table 1. Clinical description of the 24 participants

Age	37 years (SD 10)
Age at onset AVH	22 years (SD 12)
Diagnosis	18 schizophrenia
	3 schizo-affective disorder
	3 psychosis not otherwise specified
Medication	13 clozapine, mean dose 316 mg
	4 flupentixol depot, mean dose 16 mg/week
	1 haloperidol depot 50 mg/week
	1 chlorprotixen 200 mg
	1 olanzapine 30 mg
	2 risperidone, mean dose 4 mg
	2 quetiapine, mean dose 600 mg
Sex	17 male
	7 female

Abbreviations: AVH, auditory verbal hallucinations; SD, standard deviation; mg, milligram

Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) [17] according to DSM-IV criteria by an independent psychiatrist. All subjects were strongly right-handed as assessed by the Edinburgh Handedness Inventory [18]. The Positive and Negative Syndromes Scale (PANSS) [19] was used for assessment of symptoms over the last week. Detailed characteristics of the hallucinations were assessed using the Psychotic Symptom Rating Scales-Auditory Hallucinations Rating Scale (PSYRATS-AHRS) [20]. Clinical ratings were performed on the day of the fMRI scan by trained interviewers.

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

2.2. Experimental design and data acquisition

Activation during hallucinations was measured over 8 min, during which fMRI scans were made continuously. Patients were instructed to squeeze a balloon when they experienced AVH, and to release it when the hallucinations subsided (adapted from Hoffman et al. [12]). Language activation was also measured, again over 8 min during which a paced letter fluency task was presented. Patients were asked to silently generate a word starting with the letter displayed on a screen placed in front of them. Letters were presented in eight activation blocks, each block lasting 30 s. In each activation block 10 different letters were displayed at a rate of one letter every 3 s. As a reference, a crosshair was projected on the screen. After finishing the language activation task, two additional letter fluency trials were presented, in which subjects had to generate words aloud, without the scanner noise. These two blocks were used to measure behavioural performance of the subjects while they were in the scanner.

Activation maps were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner.

In order to improve the power to detect significant activation, we applied a very fast scan sequence; the 3D PRESTO SENSE sequence, developed in-house [21], which achieves full brain coverage within 0.609 s. This was important because we intended to be as sensitive as possible for BOLD signal changes during the periods of hallucination. The patients investigated here are difficult to study in an MR environment because the sometimes brief hallucination periods are unpredictable, and not all patients tolerate long scanning sessions well. This scan sequence combines a 3D-PRESTO pulse sequence with parallel imaging (SENSE) in two directions using a commercial 8-channel SENSE. First, the shifted echo of PRESTO (readout of excited signal after the next excitation pulse) ensured very efficient readout, using the normally unused time between excitation and the optimal echo train for BOLD contrast. Next, multiple receiver coils in modern parallel imaging techniques allow that every second line (or more) in K-space to be skipped, is compensated for by opposing receiver coil sensitivity profiles (SENSE, see Pruesmann et al. [22]) which greatly accelerates acquisition. SENSE is a new parallel imaging technique optimally using multiple receiver head coils that can be used to either increase imaging speed or resolution [23]. Recently SENSE has become commercially available on Philips Achieva MR scanners. We successfully implemented this technique for fMRI [21]. Finally, when using 3D acquisition as in PRESTO, K-space is 3D and this accelerated readout technique can be applied in two dimensions (here LR and AP). Mainly because the almost 4-fold number of volumes acquired in the same

amount of scanning time, BOLD signal changes are detected with a higher sensitivity as compared to conventional 2D-EPI of about 2 s./volume. Eight hundred 3D PRESTO sensitivity encoding (SENSE) images depicting BOLD contrast were acquired with the following parameter settings: 40 (coronal) slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224 × 256 × 160, matrix 64 × 64 × 40, voxelsize 4 mm isotropic. Since these PRESTO SENSE images have little anatomical contrast, an identical scan, but with a flip angle of 27° (fa27) was made to improve realignment and co-registration during the preprocessing. After completion of the functional scans, a high resolution anatomical scan, with the following parameters: TR/TE: 9.86/4.6 ms, 0.875 x 0.875 x 1 voxels, flip angle 8°, was acquired to improve localization of the functional data.

2.3. Data analysis

2.3.1. Preprocessing

FMRI data were analysed using Statistical Parametric Mapping (SPM2; Welcome Department of Cognitive Neurology, London, UK). Preprocessing included reorientation and within-subject image realignment with rigid-body transformations using the fa27 as the reference to correct for the effects of head motion. After co-registration of the fa27 and the anatomical image and spatial normalization to a standard MNI template, images were smoothed using an 8-mm full width at half maximum (FWHM) Gaussian kernel.

2.3.2. Statistical analysis of fMRI responses

In order to compare hallucination periods to non-hallucinating (resting) periods during the hallucination paradigm, an activation model was created using balloon squeezes as signalling the hallucination onset and the time between squeezes and releases as the duration of the AVH. This model was co-evolved with the standardized haemodynamic response function from SPM2 to introduce typical delays of fMRI responses, and fitted to the data using a GLM estimation [24]. These hallucination periods were then compared to non-hallucinating (resting) scans.

Similarly, for the letter fluency paradigm an activation model was created to contrast activity during presentation of the letters versus rest blocks. Functional images were analysed on a voxel by voxel basis using multiple regression analysis [24] with one factor coding for activation (task versus rest). Following the first level analyses, second level random-effects analyses were conducted for both the hallucination and the letter fluency paradigm to determine activation on a group-level (one sample *t*-tests). All thresholds corresponded to a $P < 0.05$ corrected for all voxels in the brain by the False Discovery Rate (FDR).

In addition to the group analyses for the hallucinations and the letter fluency task, a multiple regression analysis without a constant, and hallucinations and letter fluency as the two covariates, was used to conduct a random effects group-wise conjunction analysis [25]. A conjunction analysis identifies a 'common processing component' for two or more tasks by finding areas activated in independent subtractions (hallucinations versus rest and letter fluency versus rest).

Finally, lateralization indices were calculated on individual t-tests for both the letter fluency and the hallucination paradigm. For this purpose, a mask was created using the Anatomical Automatic Labeling (AAL) atlas [26] comprising the main areas where language processing is thought to be mediated and their contralateral homologues [27]. Language areas consisted of the inferior frontal triangle, the insula, the middle temporal gyrus, the superior temporal gyrus, the supramarginal gyrus and the angular gyrus. Lateralization indices were defined as the difference in 'thresholded' signal intensity changes in the left versus the right hemisphere (within the selected language regions) divided by the total sum of 'thresholded' signal intensity changes. Using this method, activity measures are based on signal intensity changes in those voxels that exceed a predefined activation level, as recommended by Jansen et al. [28]. Differences in lateralization indices between the hallucination and the letter fluency activation were compared by means of a paired sample *t*-test.

Pearson's correlations were used to assess associations between subjective loudness of the AVH and activation of Heschl's gyrus, number of voices associated with activation of the superior temporal gyrus, and correlation between the lateralization index of AVH activity and the degree to which the emotional content of the AVH was scored as negative. A difference in activation during AVH between individuals with voices inside or outside the head was tested by direct comparison of patient groups.

3. Results

3.1. Clinical evaluation

Subjects were chronically psychotic with a mean total PANSS score of 73 (SD 13). The mean score on the positive subscale was 19 (SD 4), as was the mean score on the negative subscale (19 SD 4). The phenomenology of voices interview showed that patients on average experienced AVH several times per hour with a mean duration of a few minutes. Most patients heard the voices both within their head as well as coming from outside their head, but located close to the ears. On average, the loudness of the experienced voices was described as comparable to normal speaking. Most patients described the voices as coming from the outside world, rather than attributing them to an internal source. Though all 24 patients had a strict personal content of their

voices, they did have several aspects in common. There appeared to be two main themes in the content of AVH: the vast majority (18 patients) heard voices with a derogatory content, for example voices calling them names or telling them to hurt/kill themselves. A smaller group, consisting of six patients, experienced more neutral voices commenting on their thoughts and actions. Details about the AVH, as rated with the PSYRATS-AHRS interview are listed in Table 2.

3.2. Performance during the functional scans

The mean number of hallucinations during the 8 min hallucination scans was 18 (SD 13). The mean duration of a hallucination was 20 s (SD 36), adding up to a mean total duration of the hallucinations of 362 s (SD 144).

For the letter fluency task, the 24 patients showed a mean accuracy of 19.2 words (SD 1.4), which is a 96% (SD 7) correct performance. Eight of the participants reported AVH during the language task. All eight patients indicated that the hallucinations were present during the language blocks as well as in the rest condition, which indicates that it will be lost in the subtraction. A between-group test comparing these eight patients to the others showed no significant differences, although this may partly be attributed to limited power.

Table 2. Specific aspects of the AVH, as quantified with the PSYRATS-AHRS interview

Item PSYRATS	*Range*	*Mean (SD)*
Frequency	0–4	3.5 (0.9)
Duration	0–4	2 (1)
Location	0–4	1.9 (1)
Loudness	0–4	1.8 (0.9)
Beliefs about source	0–3	2.8 (1.1)
Negative content	0–4	3 (1)
Severity of negativity	0–4	2.6 (0.8)
Distress	0–4	3 (1.2)
Intensity of distress	0–4	2.7 (0.9)
Control over AVH	0–4	3.3 (1.1)
Number of voices	0–…	13.1 (11.5)

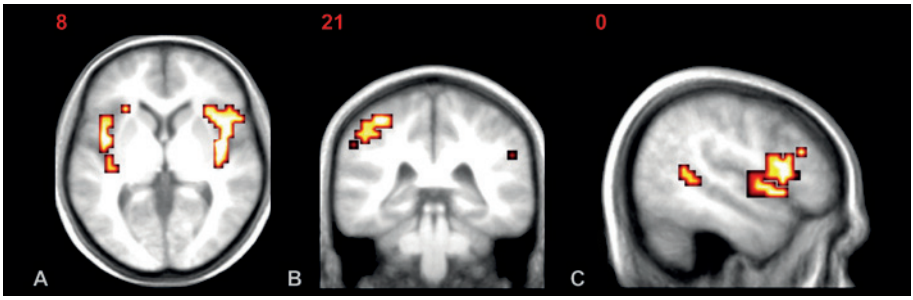
Abbreviations: PSYRATS, Psychotic Symptoms Rating Scales; AVH, auditory verbal hallucinations; SD, standard deviation; mg, milligram

3.3. FMRI results

3.3.1. Group analysis AVH

The group analysis for AVH revealed activation in multiple brain regions. Most extended activation was found in the right inferior frontal area, including the right insula and Broca's homologue (Fig. 1A and C). Other regions with significant activation during AVH included the left insula, the bilateral supramarginal gyri (Fig. 1B) and the right superior temporal gyrus (Fig. 1C). Broca's area and the left superior temporal gyrus were not significantly activated. There was also highly significant activation in the left motor cortex and the right cerebellum, most likely as a result of the balloon squeezes. Table 3 shows the coordinates of all local maxima significantly activated in the group analysis.

Figure 1. SPM(T)'s for the group hallucination analysis, $n = 24$.

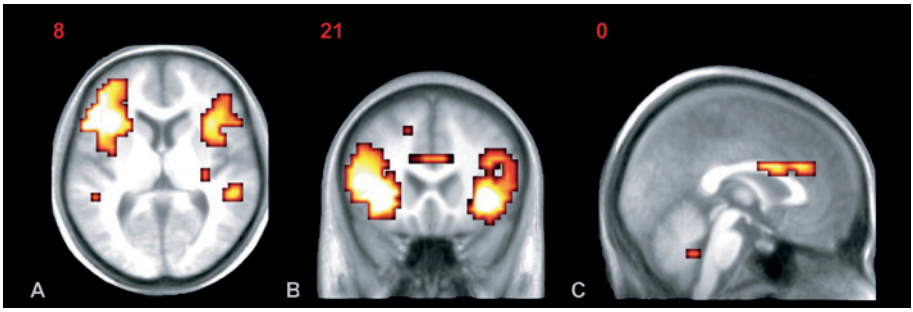


Abbreviations: SPM, Statistical Parametric Mapping; n, number

3.3.2. Group analysis language task

The group analysis for the language task revealed extensive activation of multiple confluent brain regions. These regions included Broca's area and to a lesser degree its contralateral homologue, both extending into the insula (Fig. 2A), the bilateral temporal area (superior and middle gyri), left more than right (Fig. 2B), and the anterior cingulate gyri (Fig. 2C). For more clarity with respect to the different functional regions implicated in the group letter fluency analysis, several masks, created with the AAL atlas [26] were overlaid on the group results. Anatomic regions were chosen based on the locations of significantly activated local maxima in the group letter fluency analysis. Masks consisted of the bilateral inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, precentral gyrus, insula, thalamus, anterior cingulum, fusiform gyrus, middle temporal gyrus, superior temporal gyrus, superior parietal lobule, inferior parietal lobule, middle occipital gyrus and cerebellum. For every masked region, the amount of voxels significantly activated, the coordinates of the local maximum and its z-score are reported in Table 4. The table also shows the coordinates of all local maxima significantly activated in the group analysis; note that activation is confluent between many of these local maxima.

Figure 2. SPM(T)'s for the group language analysis, n = 24.



Abbreviations: SPM, Statistical Parametric Mapping; n, number

Table 3. *Z*-scores, cluster size and locations of local maxima active in the group hallucination analysis, *n* = 24

Lobe	*Area*	*MNI Coordinates*			*z-score*	*Cluster size*
		X	*Y*	*Z*		
R sub-lobar	Insula	40	–4	4	5.13	466
R frontal lobe	Middle frontal gyrus, DLPFC	48	21	28	3.55	
R frontal lobe	Inferior frontal gyrus	28	27	–5	2.78	
R frontal lobe	Inferior frontal gyrus, Broca's homologue	44	16	10	3.24	
R temporal lobe	Superior temporal gyrus, Wernicke's homologue	51	11	–4	3.02	
L frontal lobe	Postcentral gyrus	–44	–17	45	4.64	227
L frontal lobe	Superior frontal gyrus	–20	–8	67	3.10	
L parietal lobe	Inferior parietal lobule, Supramarginal gyrus	–55	–37	39	3.07	
L sub-lobar	Insula	–44	0	4	3.47	79
L sub-lobar	Lentiform nucleus	–32	–4	0	3.70	
L frontal lobe	Precentral gyrus	–55	4	11	3.04	
L limbic lobe	Cingulate gyrus	–12	2	44	3.89	165
R frontal lobe	Medial frontal gyrus	8	3	62	3.69	
L frontal lobe	Medial frontal gyrus	–4	–9	48	3.49	
R cerebellum	Anterior lobe, Culmen	24	–52	–21	3.87	126
R cerebellum	Posterior lobe, Pyramis	20	–64	–30	3.14	
L parietal lobe	Postcentral gyrus	–55	–19	16	3.19	10
L cerebellum	Anterior lobe, Dentate gyrus	–20	–59	–24	3.31	60
R temporal lobe	Superior temporal gyrus	48	–46	13	3.06	11
R parietal lobe	Supramarginal gyrus	51	–37	30	3.02	12
L frontal lobe	Inferior frontal gyrus, DLPFC	–51	6	33	3.33	9

Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute; DLPFC, dorsolateral prefrontal cortex

Table 4. Z-scores, locations of local maxima active in the group letter fluency analysis, n = 24

Lobe	*Area*	*MNI Coordinates*			*z-score*	*N voxels*
		X	*Y*	*Z*		
L frontal lobe	Inferior frontal gyrus	–56	12	16	6.31	366
R frontal lobe	Inferior frontal gyrus	36	24	–8	6.04	289
L frontal lobe	Middle frontal gyrus	–28	–4	52	5.17	125
R frontal lobe	Superior frontal gyrus	36	–4	60	5.08	116
L frontal lobe	Superior frontal gyrus	–24	–4	56	5.21	38
R frontal lobe	Superior frontal gyrus	32	–4	60	5.06	40
L frontal lobe	Precentral gyrus	–48	4	32	5.69	132
R frontal lobe	Precentral gyrus	48	4	32	6.03	65
L sub-lobar	Insula	–36	20	0	6.33	140
R sub-lobar	Insula	36	24	–4	6.63	115
L sub-lobar	Thalamus	–12	–8	12	3.85	50
R sub-lobar	Thalamus	12	–8	8	3.77	44
Limbic lobe	Anterior cingulum	4	8	28	4.72	58
L temporal lobe	Fusiform gyrus	–44	–56	–16	4.82	26
R temporal lobe	Fusiform gyrus	44	–56	–20	4.77	55
L temporal lobe	Middle temporal gyrus	–44	–64	–4	4.56	41
R temporal lobe	Middle temporal gyrus	52	–36	4	4.33	42
L temporal lobe	Superior temporal gyrus	–44	4	–12	3.41	5
R temporal lobe	Superior temporal gyrus	52	–36	8	4.13	20
L parietal lobe	Superior parietal lobule	–28	–60	48	5.32	73
R parietal lobe	Superior parietal lobule	32	–64	52	4.56	48
L parietal lobe	Inferior parietal lobule	–28	–56	44	5.36	181
R parietal lobe	Inferior parietal lobule	48	–44	52	4.71	65
L occipital lobe	Middle occipital gyrus	–28	–68	36	4.26	44
R occipital lobe	Middle occipital gyrus	28	–92	0	6.23	44
L cerebellum	Posterior lobe	–32	–60	–28	3.80	15
R cerebellum	Posterior lobe	23	–76	–24	5.36	235

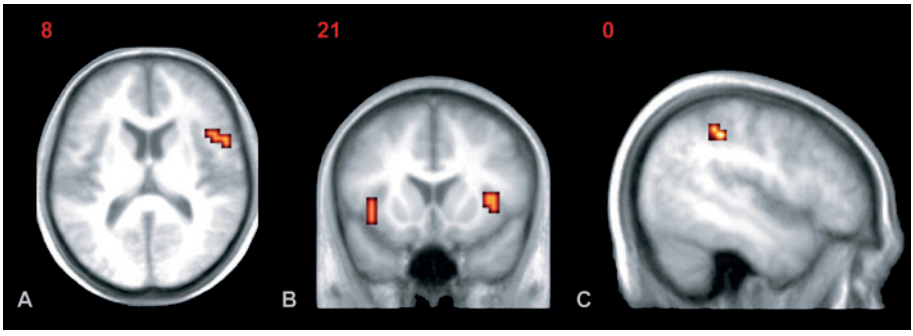
Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute

Table 5. *Z*-scores, cluster size and locations of local maxima active in the conjunction analysis, $n = 24$

Lobe	*Area*	*MNI Coordinates*			*z-score*	*Cluster size*
		X	*Y*	*Z*		
R frontal lobe	Inferior frontal gyrus, ba 9 DLPFC	51	9	29	4.40	114
R frontal lobe	Inferior frontal gyrus, ba 47	40	23	–8	4.21	
R frontal lobe	Inferior frontal gyrus, ba 44 Broca's homologue	55	12	14	3.64	
R frontal lobe	Precentral gyrus, ba 6	44	1	29	4.12	
R frontal lobe	Middle frontal gyrus, ba 6	44	2	44	3.87	
R sub-lobar	Insula, ba 13 (anterior)	44	12	12	3.58	
R sub-lobar	Insula, ba 13 (anterior)	36	16	7	3.40	
L frontal lobe	Medial frontal gyrus, ba 6	0	3	59	4.78	96
L frontal lobe	Superior frontal gyrus, ba 8	0	26	50	4.05	
L sub-lobar	Claustrum, ba 14	–28	23	–1	4.01	10
L sub-lobar	Insula, ba 13	–36	4	0	3.83	11
L frontal lobe	Middle frontal gyrus, ba 6	–36	–1	55	3.76	13
R frontal lobe	Middle frontal gyrus, ba 46 DLPFC	44	32	21	3.76	11
L parietal lobe	Inferior parietal lobule, ba 40, supramargical gyrus	–48	–33	42	3.66	9
R cerebellum	Posterior lobe, declive	28	–63	–20	3.56	9

Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute; ba; Brodmann area; DLPFC, dorsolateral prefrontal cortex

Figure 3. SPM(T)'s for the conjunction analysis language-hallucinations, $n = 24$.



Abbreviations: SPM, Statistical Parametric Mapping; n, number

3.3.3. Conjunction analysis

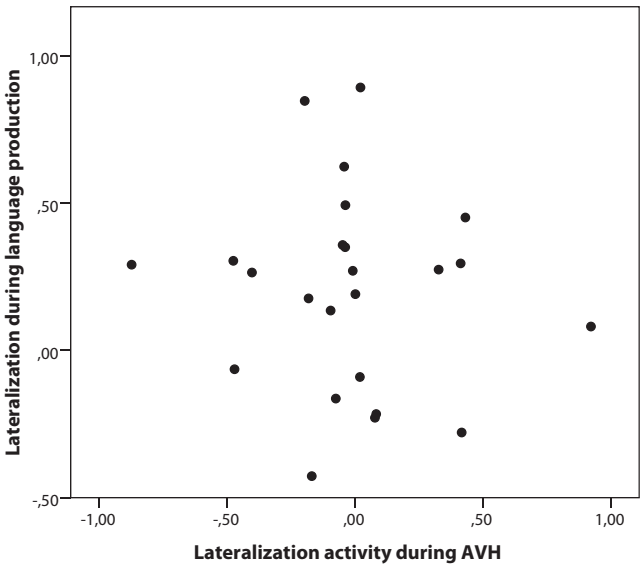
The group conjunction analysis showed several areas that were significantly activated in both paradigms which consisted of the right inferior frontal gyrus including Broca's homologue, the right dorsolateral prefrontal cortex (DLPFC), the left insula and the right anterior insula. The SPM(T)s from this analysis are shown in Fig. 3. Table 5 provides the location of the voxels with maximum activation in these regions.

3.3.4. Lateralization

The mean lateralization index was –0.11 (SD 0.41) for the hallucination paradigm and 0.14 (SD 0.34) for the word generation task. The paired sample *t*-test revealed significantly lower lateralization during AVH as compared to covert word generation [$t(23) = -2.4$, $P < 0.02$].

The individual lateralization indices of hallucinatory activation were not correlated to the lateralization indices of word generation (Pearson's $\rho = 0.11$, $P = 0.63$, shown in Fig. 4).

Figure 4. No correlation between language lateralization (*y* axis) and lateralization of activity during AVH

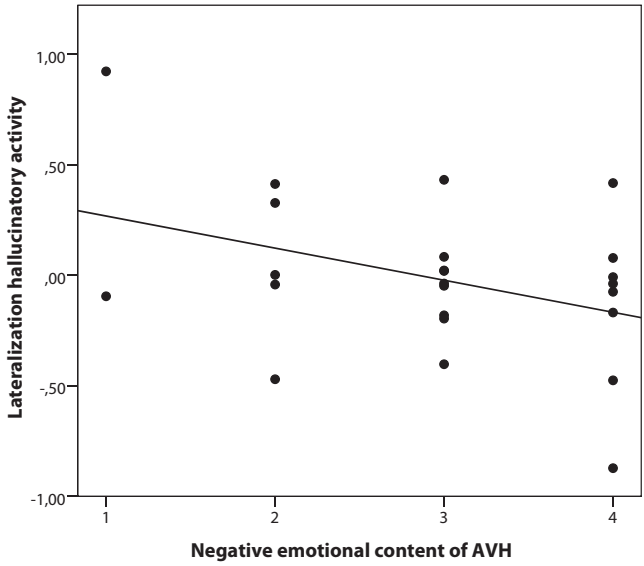


Abbreviations: AVH, auditory verbal hallucinations

There was no significant association between subjective loudness of the AVH and activation of Heschl's gyrus (Pearson's $\rho = -0.06$, $P = 0.77$), nor was the number of voices associated with activation of the superior temporal gyrus ($\rho = -0.05$, $P = 0.82$). We

could not find a difference in activation during AVH between individuals with voices inside or outside the head. The negative emotional content of the AVH, as rated on item 6 of the PSYRATS, correlated with the lateralization index of the AVH (Pearson's $\rho = -0.5$, $P = 0.01$), with a more negative emotional content of voices associated with stronger lateralization of hallucinatory activation to the right hemisphere (Fig. 5). Since four correlations are tested, Bonferoni correction identifies a *P*-value of maximal 0.0125 for significance, which is achieved for the association with negative emotional content ($P = 0.01$).

Figure 5. Correlation between the lateralization index of hallucinatory activation and the degree to which the emotional content of AVH is negative, as scored on item 6 of the Psychotic Symptoms Rating Scales.



Abbreviations: AVH, auditory verbal hallucinations

4. Discussion

This study investigated cerebral activity using fMRI in a sample of 24 psychotic patients while they were experiencing AVH in the scanner. Results were contrasted to cerebral activity during normal language production (silent word generation) in the same patients. Group-wise analysis of activity during AVH yielded most extensive activation in the right inferior frontal area (including the right insula and the right homologue of Broca's area). Other areas that showed significantly increased activation during AVH were the superior temporal and supramarginal gyri (predominantly in

the right hemisphere), and the left insula. Interestingly, Broca's area did not show significant activation during AVH, nor did the left superior temporal gyrus. In contrast to activation during AVH, the group-wise analysis of the word production task yielded most pronounced activity in the left inferior frontal area (including Broca's area and the left dorsolateral prefrontal cortex) extending into the left insula, the left superior and middle temporal gyri and the anterior cingulate gyrus. The right-sided homologues of these areas were also activated, but to a smaller degree. Activation during inner speech was more extended as compared to hallucinatory activity, which primarily results from the difference in the applied paradigm. Inner speech was activated in a block design, which yields robust activation. The number and duration of AVH during the functional scans differed between patients, which lead to more variable and less extended activation. In order to correct for this difference in power, a conjunction analysis was applied rather than a direct subtraction to compare the activation patterns of both paradigms [25]. This analysis showed that several cortical language areas were activated during both conditions, including right and left frontal areas, the anterior part of the right insula and the left inferior parietal lobule.

The difference between activity during AVH and that during normal language production indicates that hallucinations mainly activate the *right* homologues of the language areas, especially the insula and the homologue of Broca's area, while normal language production predominantly activates frontal and temporal language areas in the *left* hemisphere. Lateralization of hallucinatory activity showed large inter-individual differences, ranging from strongly left lateralized, through bilateral to strongly right lateralized. Since there was a large inter-individual variability in the lateralization of activity during AVH, we explored possible correlations between lateralization of hallucinatory activity and individual characteristics, such as language lateralization and emotional content of the AVH.

It appeared not to be correlated with language lateralization, but rather with the degree to which the content of the AVH had a negative emotional valence.

This is not the first study to describe reversed lateralization of cerebral activity during AVH as compared to normal language activity. In an early case report, Woodruff et al. [6] noted that AVH mainly activates the right language areas, while speech activates the left. Copolov et al. [11] also reported hallucinatory activation in the right hemisphere homologue of Broca's region, but not in Broca's region. Most other studies, however, emphasized the role of Broca's area during hallucinations [10, 29, 30]. Our study does not confirm activity in Broca's area during AVH, although it may have been present in some individuals. In addition to hallucination-related activity in language areas, both Shergill et al. [10] and Copolov et al. [11] reported activation in the left (para) hippocampal area. Even when we lowered the statistical threshold for detection to a more liberal

value (i.e. $P < 0.001$ uncorrected for multiple comparisons), no (para) hippocampal activity in either hemisphere could be observed. The absence of hallucinatory activity in the (para) hippocampal gyri is consistent with the results of Hoffman et al. [12] who found hallucinatory activation in several frontal, temporal and temporo-parietal areas of both hemispheres, but detected no (para) hippocampal activation. Previous reports on activation in Broca's area during hallucinations have led to the conclusion that AVH arise from language produced in the usual speech production area, which is not recognized as such, but 'mis-attributed' to an external source as a result of inadequate self-monitoring [13, 29, 30]. It remains unclear, however, why some language fragments become misattributed, giving rise to AVH, while other internally generated speech (i.e. verbal thoughts) is processed normally. Our analyses offer an alternative explanation, as they show that cerebral activity arising from the right inferior frontal area is associated with AVH, while covert speech as produced in a word generation task originates from the usual speech production area (i.e. Broca's area). Activation of predominantly the right inferior frontal area during hallucinations may be related to the typical content of AVH.

In most right-handed subjects, the right hemisphere is inferior to the left in language production [31, 32]. When the left hemisphere is dysfunctional, as in aphasia patients, the right hemisphere is usually capable of producing a few short phrases of low linguistic complexity [31, 33] such as swearwords or terms of abuse, typically with a negative emotional content [34]. In general, AVH in psychotic patients also consists of single words or truncated sentences [35] and have a predominantly negative emotional content [4], suggesting that they may indeed be the product of right hemisphere language areas. Neuroimaging investigations revealed that emotional valence effects are strongly right lateralized in studies using compact blocked presentation of emotional stimuli [36].

4.1. Limitations

Although this study clearly points to activity of the right inferior frontal area during AVH, there are some difficulties in interpreting the provided data. A first problem is that non-specific acoustic activation due to scanner sounds may have dampened activity in the primary auditory cortex during AVH. Another limitation is that the cerebral activation pattern observed during the hallucination paradigm consists of activity related to AVH *and* motor activity, because participants indicated the presence of voices by squeezing a balloon. However, motor activity from squeezing with the right hand is mainly to be expected in the motor cortex and SMA of the contralateral hemisphere and in the right cerebellum [37], while our main finding was that AVH activate the right inferior frontal area, which would be a very unusual area to result from ipsilateral motor activity.

In summary, the group-wise analyses showed that AVH predominantly engage the right inferior frontal area, including the right insula and the right homologue of Broca's area, while normal language production does activate Broca's area. The association between AVH and activity in right hemisphere language areas could explain the low linguistic complexity and derogatory content, characteristic for AVH in psychotic patients.

References

1. Nayani TH, David AS. The auditory hallucination: a phenomenological survey. *Psychol Med* Jan 1996;26(1):177-189.
2. Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, Day R. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med* Nov 1986;16(4):909-928.
3. Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophrenia Research* 1998;32(3):137-150.
4. Copolov D, Trauer T, Mackinnon A. On the non-significance of internal versus external auditory hallucinations. *Schizophr Res* Jul 1 2004;69(1):1-6.
5. Silbersweig DA, Stern E, Frith C, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature* Nov 9 1995;378(6553):176-179.
6. Woodruff P, Brammer M, Mellers J, et al. Auditory hallucinations and perception of external speech. *The Lancet* 1995;346(8981):1035-1036.
7. Dierks T, Linden DEJ, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W. Activation of Heschl's Gyrus during Auditory Hallucinations. *Neuron* 1999;22(3):615-621.
8. Lennox BR, Park SB, Jones PB, Morris PG. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* Feb 20 1999;353(9153):644.
9. Lennox BR, Park SBG, Medley I, Morris PG, Jones PB. The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Research: Neuroimaging* 2000;100(1):13-20.
10. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* Nov 2000;57(11):1033-1038.
11. Copolov DL, Seal ML, Maruff P, Ulusoy R, Wong MT, Tochon-Danguy HJ, Egan GF. Cortical activation associated with the experience of auditory hallucinations and perception of human speech in schizophrenia: a PET correlation study. *Psychiatry Res* Apr 1 2003;122(3):139-152.
12. Hoffman RE, Hampson M, Wu K, et al. Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. *Cerebral Cortex* November 1, 2007 2007;17(11):2733-2743.
13. Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev* 2008;32(1):175-191.
14. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods* Aug 30 2002;118(2):115-128.
15. Thirion B, Pinel P, Meriaux S, Roche A, Dehaene S, Poline JB. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *Neuroimage* Mar 2007;35(1):105-120.
16. Sommer IEC, Slotema CW, de Weijer AD, et al. Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? *Schizophrenia Research* 2007;93(1-3):406-408.
17. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.
18. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 1971;9(1):97-113.
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.

20. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* Jul 1999;29(4):879-889.

21. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.

22. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: Sensitivity encoding for fast MRI. *Magnetic Resonance in Medicine* 1999;42(5):952-962.

23. de Zwart JA, van Gelderen P, Golay X, Ikonomidou VN, Duyn JH. Accelerated parallel imaging for functional imaging of the human brain. *NMR in Biomedicine* 2006;19(3):342-351.

24. Worsley KJ, Friston KJ. Analysis of fMRI Time-Series Revisited--Again. *NeuroImage* 1995;2(3):173-181.

25. Price CJ, Friston KJ. Cognitive Conjunction: A New Approach to Brain Activation Experiments. *NeuroImage* 1997;5(4):261-270.

26. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* Jan 2002;15(1):273-289.

27. Springer JA, Binder JR, Hammeke TA, et al. Language dominance in neurologically normal and epilepsy subjects. *Brain* November 1, 1999 1999;122(11):2033-2046.

28. Jansen A, Menke R, Sommer J, Förster AF, Bruchmann S, Hempleman J, Weber B, Knecht S. The assessment of hemispheric lateralization in functional MRI--Robustness and reproducibility. *NeuroImage* 2006;33(1):204-217.

29. McGuire PK, Murray RM, Shah GMS. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *The Lancet* 1993;342(8873):703-706.

30. Shergill SS, Brammer MJ, Amaro E, Williams SCR, Murray RM, McGuire PK. Temporal course of auditory hallucinations. *The British Journal of Psychiatry* December 1, 2004 2004;185(6):516-517.

31. Strauss E, Wada J. Lateral preferences and cerebral speech dominance. *Cortex* Jun 1983;19(2):165-177.

32. Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Flöel A, Ringelstein EB, Henningsen H. Handedness and hemispheric language dominance in healthy humans. *Brain* December 1, 2000 2000;123(12):2512-2518.

33. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* Aug 2005;36(8):1759-1763.

34. Van Lancker D, Cummings JL. Expletives: neurolinguistic and neurobehavioral perspectives on swearing. *Brain Res Brain Res Rev* Dec 1999;31(1):83-104.

35. Stephane M, Thuras P, Nasrallah H, Georgopoulos AP. The internal structure of the phenomenology of auditory verbal hallucinations. *Schizophr Res* Jun 1 2003;61(2-3):185-193.

36. Schirmer A, Kotz SA. Beyond the right hemisphere: brain mechanisms mediating vocal emotional processing. *Trends in Cognitive Sciences* 2006;10(1):24-30.

37. Cramer SC, Weisskoff RM, Schaechter JD, Nelles G, Foley M, Finklestein SP, Rosen BR. Motor cortex activation is related to force of squeezing. *Human Brain Mapping* 2002;16(4):197-205.

Chapter 3

Language production in the non-dominant hemisphere as a potential source of auditory verbal hallucinations

Iris EC Sommer[1]
Kelly MJ Diederen[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands

Brain (2009) 132 (10): e124

Sir, in his comment, Dr Craig [1] raises an interesting hypothesis. He poses that an important aspect of auditory verbal hallucinations (AVH), namely the experience of the alien or non-self origin, results from an imbalance between the anterior cingulated gyrus and the anterior insula in the right hemisphere. This non-self aspect of AVH is an important and characteristic factor inducing patients to attribute the voices they experience to an external source, be it humans, spirits or demons. This attribution to a non-self source increases fear and delusional belief and greatly contributes to psychopathology [2, 3]. Understanding the neurobiology of the non-self aspect would therefore be helpful in elucidating the pathophysiology of AVH and perhaps, as Craig stated, have consequences for future therapy.

The lack of activity in the right anterior cingulated cortex during the experience of AVH was correctly observed by Craig. In fact, post hoc region of interest (ROI) analysis of this area demonstrated no significant activation, neither in the left nor in the right anterior cingulated gyrus, although there was bilateral activity in the middle cingulated region and the superior frontal gyri during AVH. In contrast, the verbal fluency task induced robust activity in the bilateral anterior cingulated area (left more than right) in the same subjects. We agree with Craig that the striking absence of anterior cingulated activity during AVH may reflect the lack of conscious control the patients had over these experiences.

Craig makes another suggestion, namely that the prominent activity in the right insula during AVH may represent the 'feeling' or 'awareness' of the sensation. In the absence of anterior cingulated gyrus activity, this awareness may lead to the perception of a disembodied voice. Indeed, there is considerable evidence suggesting that the sense of awareness is one of the functions of the anterior insula [4-6]. However, the insula is a large cortical region, serving many different functions, including language, emotion, attention and movement [7-9]. In our data, activity during AVH was not confined to the right anterior insula, but extended into the posterior insula and Broca's homologue [10]. We hypothesized that activity of this large cortical region reflects the (unconscious) generation of language. Although the right inferior frontal and insular region is not a classical language area, there is evidence that this area has limited capacity for language production [11, 12]. We hypothesize that the right inferior frontal-insular area is insufficiently inhibited in patients with auditory verbal hallucinations, leading to unintended 'ectopic' language production.

A similar mechanism of a right hemispheric area generating 'ectopic speech' has been described in aphasia patients [13]. Patients with severe aphasia are frequently observed to emit repetitive simple, but fully intact utterances classified as 'automatic speech' [14]. These utterances show little variation, generally repetitions of the same word or short sentence, and frequently consist of terms of abuse or swear words [15]. As Jackson

noted in 1915: 'The speechless patient may occasionally swear' (cited in Van Lancker and Cummings [14]). This observation is striking in global aphasia where speech is almost non-existent, yet the terms of abuse flow fluently and effortless with normal articulation and prosody [16]. Aphasic patients are, however, not able to produce these utterances on command. For example, Van Lancker and Cummings [14] describe a patient with severe aphasia who recurrently said the word 'mother fucker' fluently and with adequate prosody. Yet, he could not produce a single word when asked. Other examples of automatic speech are found in patients with left hemispherectomy at adult age [17, 18]. The content and repetitive nature of the automatic utterances in aphasia patients, as well as the lack of voluntary control over these utterances, bear resemblance to AVH in schizophrenia patients [19]. An obvious difference is that automatic utterances are spoken, while AVH are heard. However, before being heard, AVH are probably generated in speech production areas that may coincide with the source of automatic speech in aphasia.

Several groups have studied cerebral activation patterns of automatic speech. Functional imaging studies by Noppeney et al. [20], Thivard et al. [21], Blank et al. [22], Thiel et al. [23] and Winhuisen et al. [13] identified the right inferior frontal area as a compensatory language resource following stroke of left hemisphere language areas. Interestingly, patients with prominent language activity in the right inferior frontal areas had worse residual language function than patients, whose residual language activity was restricted to remaining left areas, indicating that the compensatory language capacity of the right hemisphere is rather low [13]. This implies that destruction of left eloquent language areas may reduce transcallosal inhibition, leading to 'release' language activity in the right frontal areas, rather than active recruitment of a valid compensatory language system [13]. Thiel and co-workers [11] confirmed this principle of release activity in language areas of the right hemisphere by simulating a brain lesion applying repetitive Transcranial Magnetic Stimulation (rTMS) over Broca's area in healthy subjects, while simultaneously measuring language activity with PET. Interference with rTMS decreased activity in Broca's area and simultaneously increased it in the right homologue in all subjects. Voets et al. [12] further showed that 'release' language activation in subjects with left hemisphere damage is not restricted to the homologue of Broca's area, but extends further posterior to encompass the right anterior and even the posterior insula. The regions (Broca's homologue and the right insula) coincide with the areas that showed greatest activation during AVH in our analysis of 24 patients [10]. It could therefore be hypothesized that AVH result from 'release' language activity in the right inferior frontal area that is inhibited in the healthy brain.

During normal language functions, such as speaking, listening to speech and reading, the dominant frontal language area inhibits its contralateral homologue through

reciprocal callosal connections [11, 24]. Activity of the right inferior frontal-insular area during AVH may result from insufficient inhibition of these non-dominant language areas. Indeed, in schizophrenia patients, who frequently experience AVH, lateralization of productive language functions is decreased [25-28]. The lower degree of language lateralization is caused by increased language activity in frontal and temporal areas of the right hemisphere [25-27]. Increased language activity of the right hemisphere is also present in unaffected monozygotic co-twins of schizophrenia patients [28], indicating that decreased language lateralization is a genetic predisposition for schizophrenia. Decreased cerebral dominance may lead to insufficient inhibition of right hemisphere areas with some language capacity, which facilitates inappropriate activity of these areas. Inappropriate language activity of Broca's homologue and the right insula may engender AVH.

At this point it is difficult to confirm either Craig's or our explanation about the function of right insula activity during AVH. A possibility to differentiate between these two hypotheses is to investigate cerebral activity during non-verbal hallucinations, such as musical or visual hallucinations. Craig's hypothesis would predict similar activity of the right anterior insula in these types of hallucinations, as the 'awareness' aspect is similar in these experiences. In contrast, we hypothesize that right insular activity during AVH is specific for the verbal aspect of hallucinations and will thus be absent in visual or musical hallucinations. Unfortunately, very few studies have investigated cerebral activity during non-verbal hallucinations. Izumi et al. [29] reported on cerebral activity during musical and verbal hallucinations in the same patient. However, the SPECT technique they applied provided insufficient spatial resolution to identify activity in the insular cortices. Another case report assessed activity during visual hallucinations with functional MRI [30] and found no insular activity. However, one patient is definitely too little evidence to refute Craig's interesting hypothesis in favour of ours…

References

1. Craig AD. Disembodied hallucinatory voices: Comment on Sommer et al., 2008 Brain 131, 3169-77. *Brain* October 1, 2009 2009;132(10):e123.
2. Garcãa-Montes J, Pãcrez-ãlvarez M, Fidalgo ãn. Influence of metacognitive variables and thought suppression on number of thoughts, discomfort they produce and number and quality of auditory illusions. *Cognitive Behaviour Therapy* 2011/08/09 2004;33(4):181-186.
3. Engh JA, Friis S, Birkenaes AB, et al. Delusions Are Associated With Poor Cognitive Insight in Schizophrenia. *Schizophrenia Bulletin* July 1, 2010 2010;36(4):830-835.
4. Gutschalk A, Micheyl C, Oxenham AJ. Neural Correlates of Auditory Perceptual Awareness under Informational Masking. *PLoS Biol* 2008;6(6):e138.
5. Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U. Levels of emotional awareness and autism: an fMRI study. *Soc Neurosci* 2008;3(2):97-112.
6. Craig AD. How do you feel [mdash] now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009;10(1):59-70.
7. Shibasaki H. Central mechanisms of pain perception. *Suppl Clin Neurophysiol* 2004;57:39-49.
8. Volz KG, Schubotz RI, von Cramon DY. Decision-making and the frontal lobes. *Curr Opin Neurol* Aug 2006;19(4):401-406.
9. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. *Dialogues Clin Neurosci* 2007;9(2):141-151.
10. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.
11. Thiel A, Schumacher B, Wienhard K, Gairing S, Kracht LW, Wagner R, Haupt WF, Heiss W-D. Direct demonstration of transcallosal disinhibition in language networks. *J Cereb Blood Flow Metab* 2006;26(9):1122-1127.
12. Voets NL, Adcock JE, Flitney DE, Behrens TEJ, Hart Y, Stacey R, Carpenter K, Matthews PM. Distinct right frontal lobe activation in language processing following left hemisphere injury. *Brain* March 2006 2006;129(3):754-766.
13. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* Aug 2005;36(8):1759-1763.
14. Van Lancker D, Cummings JL. Expletives: neurolinguistic and neurobehavioral perspectives on swearing. *Brain Res Brain Res Rev* Dec 1999;31(1):83-104.
15. Code C. On the origins of recurrent utterances in aphasia. *Cortex* Apr 1982;18(1):161-164.
16. Van Lancker D. Rags to Riches: Our Increasing Appreciation of Cognitive and Communicative Abilities of the Human Right Cerebral Hemisphere. *Brain and Language* 1997;57(1):1-11.
17. Smith A, Burklund CW. Dominant Hemispherectomy: Preliminary Report on Neuropsychological Sequelae. *Science* September 9, 1966 1966;153(3741):1280-1282.
18. Zangwill OL. Speech and the minor hemisphere. *Acta Neurol Psychiatr Belg* Nov 1967;67(11):1013-1020.
19. Gould LN. VERBAL HALLUCINATIONS AS AUTOMATIC SPEECH: The Reactivation of Dormant Speech Habit. *Am J Psychiatry* August 1, 1950 1950;107(2):110-119.
20. Noppeney U, Price CJ, Duncan JS, Koepp MJ. Reading skills after left anterior temporal lobe resection: an fMRI study. *Brain* June 2005 2005;128(6):1377-1385.
21. Thivard L, Hombrouck J, Tézenas du Montcel S, et al. Productive and perceptive language reorganization in temporal lobe epilepsy. *NeuroImage* 2005;24(3):841-851.

22. Blank SC, Bird H, Turkheimer F, Wise RJS. Speech production after stroke: The role of the right pars opercularis. *Annals of Neurology* 2003;54(3):310-320.

23. Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, Heiss W-D. Plasticity of language networks in patients with brain tumors: A positron emission tomography activation study. *Annals of Neurology* 2001;50(5):620-629.

24. Bloom J, Hynd G. The Role of the Corpus Callosum in Interhemispheric Transfer of Information: Excitation or Inhibition? *Neuropsychology Review* 2005;15(2):59-71.

25. Sommer IE, Ramsey NF, Kahn RS. Language lateralization in schizophrenia, an fMRI study. *Schizophr Res* Oct 1 2001;52(1-2):57-67.

26. Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A. Handedness, language lateralisation and anatomical asymmetry in schizophrenia. *The British Journal of Psychiatry* April 1, 2001 2001;178(4):344-351.

27. Sommer IE, Ramsey NF, Mandl RC, Kahn RS. Language lateralization in female patients with schizophrenia: an fMRI study. *Schizophr Res* Apr 1 2003;60(2-3):183-190.

28. Sommer IEC, Ramsey NF, Mandl RCW, Van Oel CJ, Kahn ReS. Language activation in monozygotic twins discordant for schizophrenia. *The British Journal of Psychiatry* February 1, 2004 2004;184(2):128-135.

29. Izumi Y, Terao T, Ishino Y, Nakamura J. Differences in regional cerebral blood flow during musical and verbal hallucinations. *Psychiatry Research: Neuroimaging* 2002;116(1-2):119-123.

30. Oertel V, Rotarska-Jagiela A, van de Ven VG, Haenschel C, Maurer K, Linden DEJ. Visual hallucinations in schizophrenia investigated with functional magnetic resonance imaging. *Psychiatry Research: Neuroimaging* 2007;156(3):269-273.

Chapter 4

Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia

Kelly MJ Diederen[1]
Sebastiaan FW Neggers[1]
Kirstin Daalman[1]
Jan Dirk Blom[2,3]
Rutger Goekoop[2]
René S Kahn[1]
Iris EC Sommer[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands
[2]Parnassia Bavo Group, The Hague, the Netherlands
[3]Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

American Journal of Psychiatry (2010) 167: 427-435

Abstract

Introduction

Activation in a network of language-related regions has been reported during auditory verbal hallucinations (AVH). It remains unclear, however, how this activation is triggered. Identifying brain regions that show significant signal changes preceding AVH might reveal the origin of these hallucinations.

Methods

Twenty-four patients with a psychotic disorder indicated the presence of AVH during 3-Tesla functional magnetic resonance imaging by squeezing a handheld balloon. A one-sample t test was performed to reveal group-wise activation during hallucinations. To enable analysis of brain activation 6 to 0 seconds preceding hallucinations, a tailored 'selective averaging' method, without any a priori assumptions concerning the hemodynamic response profile, was performed. To control for motor-related activation, 15 healthy comparison subjects squeezed a balloon at matched time intervals.

Results

Group-wise analysis during AVH revealed brain activation in bilateral (right more than left) language-related regions and bilateral motor regions. Prominent deactivation preceding these hallucinations was observed in the left parahippocampal gyrus. In addition, significant deactivation preceding hallucinations was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum. No significant signal changes were revealed prior to the matched balloon squeezing among the comparison subjects.

Conclusions

AVH in patients with a psychotic disorder are consistently preceded by deactivation of the parahippocampal gyrus. The parahippocampus has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas. Dysfunction of this region could trigger inadequate activation of right language areas during auditory hallucinations.

1. Introduction

Auditory verbal hallucinations (AVH), or 'hearing voices,' constitute a cardinal feature of psychosis. At present, the pathophysiology of AVH remains largely unknown. However, previous research has shown that these hallucinations are responsive to antipsychotic medication in approximately 70% of patients with schizophrenia [1] and that the antipsychotic effect of these agents is most likely mediated by antagonism at the dopamine type 2 (D_2) receptors [2]. Therefore, a dopaminergic component is presumed to be involved in the origin of AVH.

A second line of evidence is derived from neuroimaging studies demonstrating consistent activation of bilateral language-related areas during AVH [3-8], with the most prominent activation in the right homologue of Broca's area [7]. However, since these language-related areas barely have any D_2 innervations [9, 10], this cannot easily be linked to the suspected dopaminergic component. Moreover, although functional imaging of activity during hallucinations is helpful in understanding which regions are involved in the experience of hearing voices, it cannot explain how and where these experiences originate in the brain. Because AVH arise without an external source (i.e., the experience of an actual voice), they must be triggered internally. Studying brain activation in the time period preceding the hallucinations might reveal this trigger. Therefore, we not only investigated brain activation during AVH but also identified brain activation prior to these hallucinations.

2. Methods

2.1. Subjects

Forty-two patients with a psychotic disorder were recruited from the Department of Psychiatry, University Medical Center, Utrecht, the Netherlands, and the Parnassia Bavo Group, The Hague, the Netherlands. Patients were selected for further participation if they met the following inclusion criteria: 1) AVH with a perceptual quality; 2) hallucination content that did not parallel thoughts (consisting of commands or derogatory critique); 3) right-handedness; 4) both hallucination and non-hallucination periods present during functional magnetic resonance imaging (fMRI); 5) a complete fMRI scan; and 6) hallucinations indicated correctly (i.e., onset of hallucinations followed by clear offset of hallucinations). To qualify for the analysis of brain activation preceding hallucinations, the following eighth inclusion criterion was added: a minimum of 6 seconds had to be present between successive hallucinations. A 6-second interval was chosen because fMRI blood-oxygen-level-dependent (BOLD) response lasts approximately 4 to 6 seconds (after neuronal activation) before reaching its peak. Also, since the time

frame in which hallucinations are prepared is unknown, an extended time window was preferred. Several patients were found unsuitable for inclusion because three did not fulfill criterion 2, two did not meet criterion 4, four did not meet criterion 5, seven did not fulfill criterion 6, and two did not fulfill criterion 7. An additional nine patients were excluded from the analysis of brain activation preceding hallucinations because they did not meet criterion 8. This resulted in the inclusion of 24 patients in the analysis of brain activation during hallucinations (analysis 1) and 15 patients in the analysis of brain activation prior to hallucinations (analysis 2). Eighteen of the 24 patients in the first analysis and 11 of the 15 patients in the second analysis also participated in a previous study conducted by our research group [7].

Patients were diagnosed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History interview [11] according to DSM-IV criteria. On the day of the fMRI scan, the Positive and Negative Syndrome Scale (PANSS) [12] was used for the assessment of symptoms. Detailed characteristics of hallucinations were assessed using the auditory hallucinations subscale of the Psychotic Symptom Rating Scales [13]. As a comparison group, 15 healthy subjects were recruited. A demographical description of the patients and comparison subjects is summarized in Table 1. The study was approved by the Human Ethics Committee of the University Medical Center, Utrecht, the Netherlands. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Experimental design and data acquisition

Patients signalled the presence of AVH by squeezing a handheld balloon while functional scans were obtained continuously [7]. To correct for brain activation related to balloon squeezes, the 15 healthy comparison subjects were instructed to squeeze the balloon approximately 10 times at random time intervals. This number was approximately matched to the mean number of hallucinations during the scanning periods in the first analysis.

Activation maps were obtained using a Philips Achieva 3 Tesla clinical MRI scanner (Philips Medical Systems, Best, the Netherlands). Eight-hundred BOLD fMRI scans were acquired with the following parameter settings: slices (coronal)=40, repetition time=21.75msec, echo time=32.4 msec, flip angle=10º, field of view=224x256x160, matrix=64x64x40, voxel size=4 mm isotropic. This scan sequence achieves full brain coverage within 609 msec by combining a three-dimensional PRESTO (principle of echo shifting with a train of observations) pulse sequence with parallel imaging (SENSE [sensitivity encoding]) in two directions, using a commercial eight-channel SENSE head coil [14]. After the functional scans were performed, a high-resolution anatomical scan was conducted with the following parameters: repetition time=9.86 msec,

echo time=4.6 msec, voxels=0.875x0.875x1, flip angle=8º. These parameters were acquired to improve localization of the functional data [14].

Table 1. Characteristics of patients with psychotic disorder and healthy comparison subjects

Group	*Patients analysis 1, n=24*	*Patients analysis 2, n=15*	*Control subjects, analysis 2, n=15*
Age	39 years (SD 10)	39 years (SD 10)	26 years (SD 4)
Sex	15 males 9 females	9 males 6 females	9 males 6 females
Mean age at onset AVH	23 years (SD 15)	22 years (SD 16)	No AVH
Diagnosis	16 Schizophrenia 2 Schizoaffective Disorder 1 Schizophreniform Disorder 5 Psychosis Not Otherwise Specified	10 Schizophrenia 2 Schizoaffective Disorder 1 Schizophreniform Disorder 2 Psychosis Not Otherwise Specified	No psychiatric Diagnosis
Antipsychotic Medication	7 clozapine, mean dose 375 mg 4 flupentixol, mean dose 52.5 mg/ 3 weeks 2 risperidon, 65 mg/ 2 weeks 1 olanzapine, 30 mg 1 pimozide, 2 mg 1 penfluridol, 30 mg/ week 1 risperidon, 3 mg and quetiapine, 100 mg 1 olanzapine, 20 mg and fluanxol, 4 mg 1 zuclopentixol, 10 mg 1 haloperidol, 40 mg 1 aripriprazol, dose unknown 1 fluanxol, 6 mg 1 chloorprotixeen, 45-150 mg 1 medication-free	3 clozapine, mean dose 375 mg 4 flupentixol, mean dose 52.5 mg/ 3 weeks 2 risperidon, 65 mg/ 2 weeks 1 olanzapine, 30 mg 1 pimozide, 2 mg 1 penfluridol, 30 mg/ week 1 risperidon, 3 mg and quetiapine, 100 mg 1 olanzapine, 20 mg and fluanxol, 4 mg 1 medication-free	15 medication-free

Abbreviations: AVH, auditory verbal hallucinations; N, number; SD, standard deviation; mg, milligram

2.3. Data analysis

2.3.1. Preprocessing

Functional MRI data were analyzed using Statistical Parametric Mapping (SPM2) (Wellcome Department of Cognitive Neurology, London). Preprocessing included realignment of fMRI time series to correct for head motion, coregistration of fMRI data with the T1-weighted anatomical image, and spatial normalization to a standard Montreal Neurological Institute template based on the T1-weighted scan with high anatomical contrast. Finally, images were smoothed using an 8-mm full-width at half maximum Gaussian kernel.

2.3.2. Statistical analysis of fMRI responses

2.3.2.1. Analysis 1: Brain activation during AVH

To compare activation during hallucination periods with activation during non-hallucination periods, a model was created using balloon squeezes as the onset of a hallucination and the time between squeezes and releases as the duration of the hallucination. This model was convolved with the standardized hemodynamic response function from SPM2 to introduce typical delays of fMRI responses and fitted to the data using general linear model estimation [15]. A one-sample t test was performed to enable group-wise analysis with a threshold of $p<0.05$, whole-brain corrected by the false discovery rate combined with an extent threshold of five voxels.

*2.3.2.2. Analysis 2: Brain activation preceding AVH and balloon squeeze*s

To detect brain activation preceding hallucinations and random balloon squeezes, the finite impulse response was chosen as the basis function. Most commonly, the canonical hemodynamic response function is used as a model to detect fMRI signal changes of interest. The hemodynamic response function reflects the average shape of the slow increase and subsequent decrease in BOLD signal after a very brief moment of neuronal activation [16]. However, a prerequisite of using the hemodynamic response function for the purpose of modelling fMRI data is a reasonably clear hypothesis about the onset time of the event of interest. Since it is unknown when regions implicated in the cascade of events that lead to the conscious experience of hallucinations will approximately activate, the hemodynamic response function does not represent a suitable basis function. Therefore, a set of finite impulse response functions was selected to detect brain activation preceding hallucinations. Finite impulse response function is the most general of the basis functions used to model fMRI responses and makes no assumptions about the shape and temporal resolution of the hemodynamic response. Using finite impulse response functions, a number of successive time bins ('miniboxcars') were created, typically following the onset of an event [17], with each independently modelling a single time point before the hallucination. To enable analysis of brain activation up to 6 seconds prior to the hallucination, 10 finite-impulse-response-function time bins were created, each coding for a period of 0.609 second, corresponding to the interscan interval. If the first hallucination occurred sooner than 6 seconds after the start of the paradigm, no finite-impulse-response-function time bins were modelled prior to the first hallucination. In the context of a general linear model consisting of finite-impulse-response basis functions fitted to fMRI time series on a voxel-by-voxel basis, we effectively corrected for possible overlap of subsequent BOLD responses [17]. Therefore, this method is sometimes referred to as 'selective averaging.' Seven additional postonset hallucination/balloon squeeze

finite-impulse-response-function time bins, designed to capture the prolonged BOLD responses of neuronal events preceding hallucinations, were entered as covariates in this analysis. In addition, since the hallucination/balloon squeeze itself was expected to explain a considerable amount of variance in the data [7], it was entered as a covariate, similar to the first analysis. To introduce typical delays of fMRI responses, this covariate was convolved with the hemodynamic response function from SPM2.
To enable group-wise analysis, data were examined through repeated-measures univariate analysis of variance (ANOVA), with the regression coefficients of the finite-impulse-response-function time bins as repeated measures. A nonsphericity correction was included in this ANOVA. Subsequently, F tests were used to calculate statistical maps, revealing voxels that showed significant signal changes at some point in the interval from 6 to 0 seconds prior to the hallucination. The threshold was set at $p<0.05$, whole-brain corrected by the false discovery rate combined with an extent threshold of five voxels.

Since F tests are two-tailed, revealing both activation and deactivation, inspection of time courses was necessary to determine the direction of the signal change. For this purpose, mean poststimulus time histograms displaying the average BOLD signal were constructed from the finite-impulse-response-function regression coefficients. Poststimulus time histograms were calculated from 6 to 0 seconds preceding hallucinations (averaged over all subjects).
Furthermore, since the finite impulse response function makes no assumptions about the shape and temporal resolution of the hemodynamic response, it is important to verify whether effects are indeed of a hemodynamic nature rather than being caused by movement artifacts, for instance, during the preparation of a balloon squeeze. For this reason, the realignment parameters describing head motion using three rotation and three translation parameters, derived from realignment during the preprocessing in SPM2, were acquired per subject for the 10 scans preceding the hallucination and tested using repeated-measures multivariate analyses of variance (MANOVAs). In addition, if movement led to any significant signal changes, effects would most likely be present throughout the scanned volume, including gray and white matter and out-of-brain voxels. To screen for such artifacts, average signal changes in gray and white matter and out-of-brain voxels were calculated and tested for the 10 scans preceding the hallucinations using repeated-measures ANOVAs. The analysis for the signal from out-of-brain voxels was identical to the other analyses except for the correction for temporal autocorrelation, which was not employed because voxels outside the head probably do not exhibit typical temporal dependencies known for BOLD signals acquired in the brain.

3. Results

3.1. Clinical evaluation

Patients were chronically psychotic, with a mean total PANSS score of 73 (SD=15) for the 24 patients in the analysis of brain activation during hallucinations (analysis 1). These patients had an average score of 19 (SD=5) on the positive subscale, an average score of 19 (SD=0.5) on the negative subscale, and an average score of 35 (SD=9) on the scale assessing general psychopathology. The 15 patients in the analysis of brain activation prior to hallucinations (analysis 2) had a mean total PANSS score of 73 (SD=18). Their average scores on the positive, negative, and general psychopathology subscales were 20 (SD=5), 19 (SD=6), and 35 (SD=10), respectively. Details about the hallucinations as rated using the Psychotic Symptom Rating Scales interview are listed in Table 2, in which a rating of '1' signifies absent hallucinations or a very mild form of hallucinations during the last 3 months.

3.2. Hallucinations during fMRI scans

The average number of hallucinations during the fMRI scans was 14 (SD=0.85) for patients in the first analysis. The average duration of a hallucination was 17 seconds (SD=0.28), adding up to a mean total duration of hallucinations of 151 seconds (SD=121). For the second analysis, the average number of hallucinations, average duration of a hallucination, and mean total duration of hallucinations were 11 (SD=5), 16 seconds (SD=15), and 129 seconds (SD=116), respectively. The average time between successive hallucinations was 38 seconds (SD=29).

In the comparison group, the average number of balloon squeezes was 12 (SD=4). The average duration of a balloon squeeze was 10 seconds (SD=6), adding up to a mean total duration of balloon squeezes of 122 seconds (SD=75). The average duration between successive balloon squeezes was 33 seconds (SD=20).

No statistical differences were found between the patient group in the second analysis and the comparison group for the mean number, mean duration, and total duration of the hallucinations/balloon squeezes and for the time between successive squeezes and releases.

3.3. FMRI

3.3.1. Analysis 1: Brain activation during AVH

As seen in Figure 1, the group analysis for hallucinations revealed activation of multiple confluent brain regions. These included language-related regions, such as the bilateral insula and inferior frontal gyrus (including Broca's homologue) as well as the middle temporal, superior temporal, and supramarginal gyri. Other significantly activated

regions consisted of the bilateral inferior parietal lobule, precentral gyrus, postcentral gyrus, cerebellum, and superior and middle frontal gyri.

Table 2. Characteristics of AVH in patients with psychotic disorder

Item of the PSYRATS	*Scale*	*Mean (n=24)*	*SD (n=24)*	*Mean (n=15)*	*SD (n=15)*
Frequency	1-6	5	1	5	1
Duration	1-4	2	1	2	1
Location	1-4	2	1	2	1
Loudness	1-4	2	1	2	1
Beliefs about source	1-4	3	1	2	1
Negative content	1-5	3	1	3	1
Severity of negativity	1-5	3	1	3	1
Distress	1-5	3	1	3	1
Intensity of Distress	1-5	2	1	2	1
Control over AVH	1-5	3	1	3	1
Number of voices	1-?	24	37	28	41

Abbreviations: PSYRATS, Psychotic Symptoms Rating Scales; AVH, auditory verbal hallucinations; N, number; SD, standard deviation

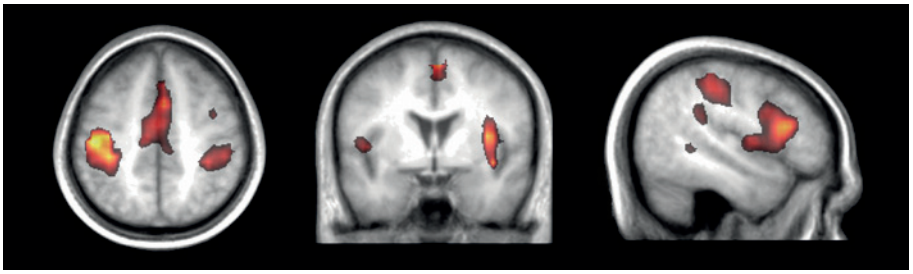
For more clarity with respect to the different functional regions implicated in the group hallucination analysis, masks, created using the Automatic Anatomical Labeling Atlas [18], were overlaid on the group results. Anatomic regions were chosen based on the locations of significantly activated local maxima in the group-wise hallucination analysis. Masks consisted of the bilateral inferior frontal, middle temporal, superior temporal, supramarginal, precentral, postcentral, middle frontal, and superior frontal gyri as well as the inferior parietal lobule, insula, and cerebellum. The amount of significantly activated voxels and the coordinates of the local maximum and its T values are reported for every masked region in Table 3.

3.3.2. Analysis 2: Brain activation preceding AVH and random balloon squeezes

The most prominent signal change preceding hallucinations was observed in the left parahippocampal gyrus. In addition, significant signal changes were found in the left superior temporal, right inferior frontal, and left middle frontal gyri as well as the right insula and left cerebellum. The largest significantly activated cluster consisted of the following two interconnected local maxima: one located in the left parahippocampal gyrus and one in the left cerebellum. Since these areas are anatomically unconnected, a functional connection of these maxima probably resulted from spatial smoothing.

Inspection of the cluster coordinates revealed that 11 voxels were located in the left parahippocampus, five were located in the left cerebellum, and one voxel was placed on the boundary between these regions. Table 4 shows the coordinates of all significant local maxima in the group analysis. SPM2 F statistics are shown in Figure 2.

Figure 1. Areas of significant activation during AVH in patients with psychotic disorder



SPM2 T statistics for the groupwise analysis depict significant activity in the precentral and postcentral gyri (left), insula (center), and right inferior frontal and right middle temporal gyri (right).

Table 3. Significantly activated voxels and locations of local maxima during AVH in patients with psychotic disorder

Lobe	*Area*	*MNI Coordinates*			*T-value*	*Cluster size*
		X	Y	Z		
L parietal lobe	Inferior parietal lobule	-52	-20	44	4.98	121
R parietal lobe	Inferior parietal lobule	36	-36	52	3.59	43
L frontal lobe	Precentral gyrus	-36	-16	64	4.77	99
R frontal lobe	Precentral gyrus	56	8	32	3.12	84
L fronta lobe	Postcentral gyrus	-36	-16	64	4.77	99
R frontal lobe	Postcentral gyrus	56	8	32	3.53	84
R sub-lobar	Insula	36	0	12	4.47	292
L sub-lobar	Insula	-48	0	4	3.28	218
R frontal lobe	Middle frontal gyrus	32	48	20	4.64	11
R frontal lobe	Superior frontal lobe	5	28	48	4.07	20
R frontal lobe	Inferior frontal gyrus	44	16	12	4.31	201
L frontal lobe	Inferior frontal gyrus	-48	4	8	3.72	44
R cerebellum	Anterior lobe	20	-48	-16	4.27	26
R cerebellum	Posterior lobe	24	-60	-44	3.85	9

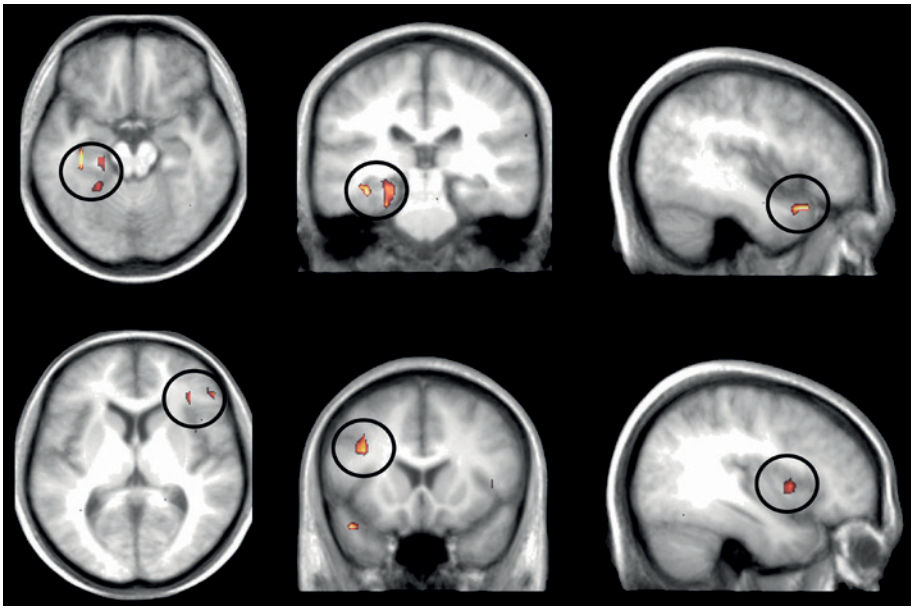
Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute

Figure 3 shows poststimulus time histogram plots from 6 to 0 seconds prior to hallucinations, averaged over all subjects, and a fitted sixth-order polynomial of all regions showing significant signal changes in the group analysis. From these poststimulus time histogram plots it can be concluded that the reported regions were significantly deactivated.

No significant effect of motion before the onset of hallucinations was revealed by the realignment parameters (for the three translation parameters as well as for the three rotation parameters), as identified by two separate repeated-measures MANOVAs, with the 10 scans preceding hallucinations as repeated measures.

Three independent repeated-measures ANOVAs, with gray and white matter and out-of-brain signal changes as dependent variables and the 10 scans preceding hallucinations as repeated measures, revealed no significant signal changes, indicating that motion artifacts cannot explain the effects detected with the finite-impulse-response analysis.

Figure 2. Areas of significant activation preceding AVH in patients with psychotic disorder



SPM2 F statistics for the interval 6 to 0 seconds preceding AVH depict significant signal changes in the left parahippocampal gyrus, left superior temporal gyrus, left cerebellum, left middle frontal gyrus, right insula, and right inferior frontal gyrus.

Figure 3. Time plots of global signal changes in regions of interest during the six seconds prior to AVH in patients with psychotic disorder

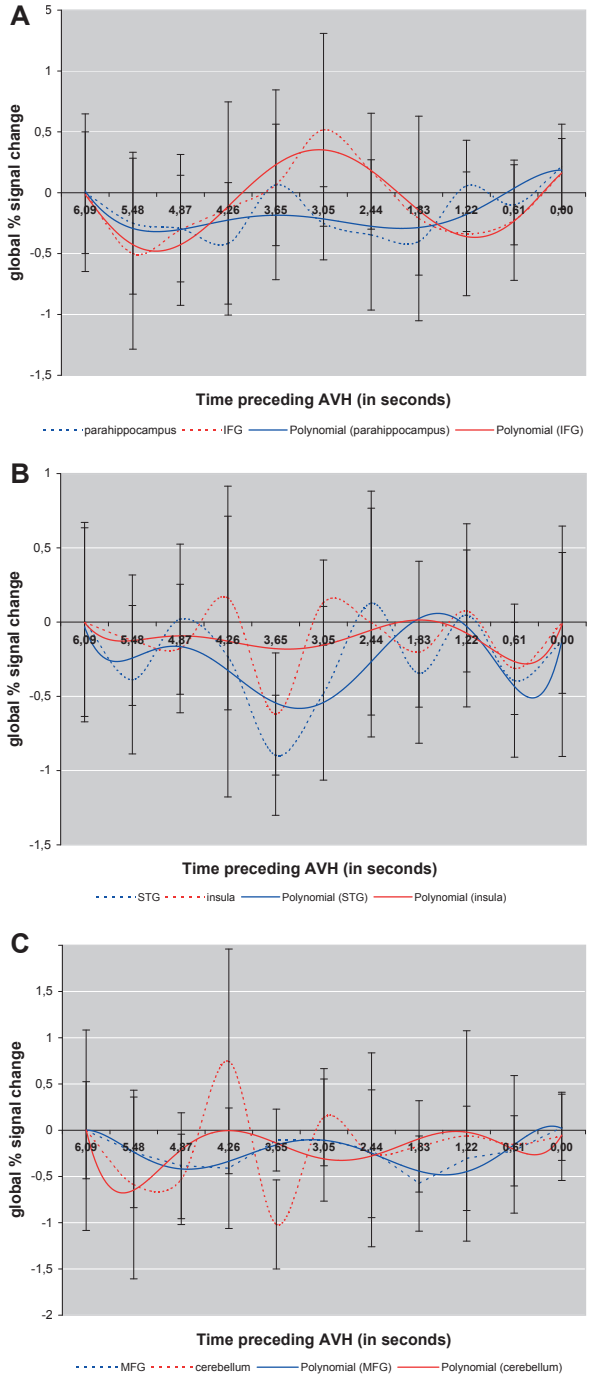


Table 4. Significantly activated voxels and locations of local maxima during 6 seconds preceding AVH in patients with psychotic disorder

Lobe	*Area*	*MNI Coordinates*			*F-value*	*Cluster size*
		X	Y	Z		
L Limbic	Parahippocampal gyrus	-36	-24	-16	7.52	9
L Temporal	Superior Temporal gyrus	-44	16	-24	6.38	6
L Frontal	Middle Frontal Gyrus	-36	16	28	5.47	11
L Limbic	Parahippocampal gyrus	-24	-28	-12	4.66	11
L cerebellum	Anterior lobe, Culmen	-28	-36	-28	5.17	5
R Frontal	Inferior Frontal Gyrus	52	36	8	5.07	5
R Frontal	Inferior Frontal gyrus	36	32	4	5.03	5
R Sub-lobar	Insula	40	8	4	4.89	5
L cerebellum	Anterior lobe, Culmen	-24	-44	-16	4.07	5

Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute

3.3.3. Brain activation preceding balloon squeezes

No significant signal changes were observed prior to the random balloon squeezes.

4. Discussion

This study investigated brain activation during auditory verbal hallucinations (AVH) in 24 patients with psychosis. Brain activation during these hallucinations was primarily present in bilateral language areas. Brain activation preceding hallucinations could be investigated in 15 subjects. Group-wise analysis of signal changes up to 6 seconds preceding hallucinations showed pronounced deactivation in the left parahippocampal gyrus. Additional deactivation was observed in the left superior temporal, left middle frontal, and right inferior frontal gyri as well as the right insula and left cerebellum. These findings could not be attributed to motor activation, since group-wise analysis of activity in the 6 seconds prior to random balloon squeezes revealed no significant signal changes. Bilateral activation of language regions during hallucinations is consistent with a previous study conducted by our research group [7].

Most prominent deactivation preceding hallucinations was observed in the parahippocampal gyrus. Because the parahippocampus is D_2innervated [19], this finding might represent an important link between dopaminergic overactivity and inadequate activation of bilateral language-related areas. The parahippocampus has been hypothesized to play a central role in memory recollection, since it receives

perceptual information from association cortices, such as the language areas, and forwards this information to the hippocampus in order to be 'recognized.' This perceptual information is then passed back to the parahippocampal gyrus from where it is redistributed to the association cortices involved in the original perception [20-23]. Indeed, activation of association cortices originally involved in the encoded fragment has consistently been shown during memory retrieval [24-26].In the case of AVH, increased dopaminergic stimulation may enhance the redistribution function of the parahippocampal gyrus, leading to erroneous activation of an association cortex and hence to incorrect recognition. Disinhibition of the parahippocampal gyrus, demonstrated as deactivation preceding hallucinations, then triggers the bilateral language-related areas originally involved in the perception of speech fragments, as shown in the first analysis of the preset study. According to this hypothesis, hallucinations result from the spontaneous re-experience of memories. Support for this hypothesis was provided in a study in which patients with hallucinations showed difficulties identifying the source of memories [27, 28]. Furthermore, increases in hallucinations have been associated with an increasing inability to inhibit irrelevant memories [28].

Deactivation instead of activation of the parahippocampus may seem at odds with its postulated role in memory recollection. However, deactivations have been reported to be realistic phenomena, probably caused by short decreases in neuronal activity [29, 30]. Previous studies on memory recollection have also reported deactivation of the parahippocampus [31-35].

Apart from parahippocampal deactivation, we observed significant deactivation preceding hallucinations in the left superior temporal and right inferior frontal gyri as well as right insula. These areas correspond with regions significantly activated during hallucinations and may result from the information redistributed to them by the parahippocampus, preparing them for activation in the course of hallucinations.

Our results are partially consistent with those of previous studies. Hoffman and colleagues [36] reported deactivation of the parahippocampal and anterior cingulate gyri preceding hallucinations in six patients as well as activation of the left anterior insula and right middle temporal gyrus. In addition, Lennox and colleagues [37] found activity in the right middle temporal gyrus in a single subject, while Shergill and colleagues [38] found activity in the left inferior frontal and right middle temporal gyri preceding hallucinations in two subjects. Deactivations were not discussed in these studies.

4.1. Limitations and suggestions for future research

A limitation of this study is that most patients were treated with antipsychotic medication. Since the effect of antipsychotic medication is probably mediated

by antagonism at the D_2 receptors [2] and the parahippocampus is D_2 innervated [19], parahippocampal function is expected to be influenced by D_2 blockade. The patients included in this study suffered from medication-resistant hallucinations. Therefore, deactivation of the parahippocampal gyrus is expected to be present in medication-free patients with psychosis prior to hallucinations, yet negative signal changes may be more pronounced in these patients. To further explore this effect, future studies should focus on brain activation preceding hallucinations in medication-free patients with psychosis.

Furthermore, a limitation of the finite impulse response can be that observed effects not necessarily reflect hemodynamic changes but instead any BOLD signal deviation from baseline. Nonetheless, in our study, analyses of signal changes in gray and white matter and out-of-brain voxels showed that movement artifacts could not have induced the observed deactivations because such artifacts should have been present in these regions also. Furthermore, the movement parameters describing head motion in the fMRI images did not differ significantly from zero before the hallucinations.

Since little a priori knowledge was available to indicate which neural and cognitive processes precede hallucinations, we selected a control condition that only controlled for motor preparation, enabling us to identify brain activation related to the actual hallucinations. A limitation of the control condition is that motor control was compared between subjects instead of within subjects. However, a within-subjects analysis was impractical as a result of the interference of hallucinations during random balloon squeezing among the patients.

In addition, a potential flaw is that significant deactivation preceding hallucinations may have resulted from subjects' delayed response to the hallucinations. In this case, peak deactivation would be expected to occur in the last seconds preceding hallucinations. However, in this study peak deactivation occurred between 4.87 and 2.44 seconds prior to hallucinations (Figure 3), which renders this explanation unlikely.

Finally, it can be argued that deactivation preceding hallucinations results from the 'poststimulus undershoot.' When applying BOLD fMRI, peak activation is followed by a short period of deactivation, which is the poststimulus undershoot. However, the poststimulus undershoot is typically present between 10 and 30 seconds after an event. Since the average time between successive hallucinations was 38 seconds in our study, this explanation also appears unlikely.

An important strength of this study is the large sample size and group-wise analyses. Furthermore, other explanations for the present findings were ruled out by including a comparison group and investigating the BOLD time course signals for motion artifacts. Finally, a particular strength is that an assumption-free finite-impulse-response model was used.

To test the model proposed in this study, future studies should focus on comparing hallucinations with word recall. An elegant design would be one in which patients recall their previous hallucinations

In summary, the present study showed that auditory verbal hallucinations are preceded by deactivation of the parahippocampus. Since the parahippocampus is implicated in memory recollection, dysfunction of this region could trigger inadequate activation of language-related regions, leading to auditory hallucinations. Indeed, activation of language regions was detected during these hallucinations.

References

1. Shergill SS, Murray RM, McGuire PK. Auditory hallucinations: a review of psychological treatments. *Schizophrenia Research* 1998;32(3):137-150.
2. Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 1976;261(5562):717-719.
3. Hoffman RE, Hampson M, Wu K, et al. Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. *Cerebral Cortex* November 1, 2007 2007;17(11):2733-2743.
4. McGuire PK, Murray RM, Shah GMS. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *The Lancet* 1993;342(8873):703-706.
5. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* Nov 2000;57(11):1033-1038.
6. Dierks T, Linden DEJ, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W. Activation of Heschl's Gyrus during Auditory Hallucinations. *Neuron* 1999;22(3):615-621.
7. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.
8. Sommer IEC, Slotema CW, de Weijer AD, et al. Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? *Schizophrenia Research* 2007;93(1-3):406-408.
9. Levey AI, Hersch SM, Rye DB, et al. Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. *Proceedings of the National Academy of Sciences* October 1, 1993 1993;90(19):8861-8865.
10. Hurd YL, Suzuki M, Sedvall GC. D1 and D2 dopamine receptor mRNA expression in whole hemisphere sections of the human brain. *Journal of Chemical Neuroanatomy* 2001;22(1-2):127-137.
11. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.
12. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
13. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* Jul 1999;29(4):879-889.
14. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.
15. Worsley KJ, Friston KJ. Analysis of fMRI Time-Series Revisited--Again. *NeuroImage* 1995;2(3):173-181.
16. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* Jul 12 2001;412(6843):150-157.
17. Henson R, Rugg M, Friston K. The choice of basis functions in event-related fMRI. *NeuroImage 13* Mar-Apr 2001;41(Suppl 1):149.
18. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* Jan 2002;15(1):273-289.

19. Joyce JN, Janowsky A, Neve KA. Characterization and distribution of [125I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. *Journal of Pharmacology and Experimental Therapeutics* June 1, 1991 1991;257(3):1253-1263.

20. Van Hoesen GW. The parahippocampal gyrus: New observations regarding its cortical connections in the monkey. *Trends in Neurosciences* 1982;5:345-350.

21. Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci* 2000;1(1):41-50.

22. Eichenbaum H, Schoenbaum G, Young B, Bunsey M. Functional organization of the hippocampal memoryâ€‰system. *Proceedings of the National Academy of Sciences* November 26, 1996 1996;93(24):13500-13507.

23. Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123-152.

24. Wheeler ME, Petersen SE, Buckner RL. Memory's echo: Vivid remembering reactivates sensory-specific cortex. *Proceedings of the National Academy of Sciences* September 26, 2000 2000;97(20):11125-11129.

25. Kahn I, Davachi L, Wagner AD. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. *J Neurosci* Apr 28 2004;24(17):4172-4180.

26. Johnson JD, Rugg MD. Recollection and the Reinstatement of Encoding-Related Cortical Activity. *Cerebral Cortex* November 1, 2007 2007;17(11):2507-2515.

27. Brebion G, Gorman JM, Amador X, Malaspina D, Sharif Z. Source monitoring impairments in schizophrenia: characterisation and associations with positive and negative symptomatology. *Psychiatry Res* Sep 15 2002;112(1):27-39.

28. Waters FA, Badcock JC, Maybery MT, Michie PT. Inhibition in schizophrenia: association with auditory hallucinations. *Schizophr Res* Aug 1 2003;62(3):275-280.

29. Smith AT, Williams AL, Singh KD. Negative BOLD in the visual cortex: Evidence against blood stealing. *Human Brain Mapping* 2004;21(4):213-220.

30. Shmuel A, Yacoub E, Pfeuffer J, Van de Moortele P-F, Adriany G, Hu X, Ugurbil K. Sustained Negative BOLD, Blood Flow and Oxygen Consumption Response and Its Coupling to the Positive Response in the Human Brain. *Neuron* 2002;36(6):1195-1210.

31. Burgess N, Maguire EA, Spiers HJ, O'Keefe J. A Temporoparietal and Prefrontal Network for Retrieving the Spatial Context of Lifelike Events. *NeuroImage* 2001;14(2):439-453.

32. Ross RS, Slotnick SD. The Hippocampus is Preferentially Associated with Memory for Spatial Context. *Journal of Cognitive Neuroscience* 2008;20(3):432-446.

33. Woodruff CC, Johnson JD, Uncapher MR, Rugg MD. Content-specificity of the neural correlates of recollection. *Neuropsychologia* 2005;43(7):1022-1032.

34. Henson RNA, Cansino S, Herron JE, Robb WGK, Rugg MD. A familiarity signal in human anterior medial temporal cortex? *Hippocampus* 2003;13(2):301-304.

35. Weis S, Klaver P, Reul J, Elger CE, Fernandez G. Neural correlates of successful declarative memory formation and retrieval: the anatomical overlap. *Cortex* Feb 2004;40(1):200-202.

36. Hoffman RE, Anderson AW, Varanko M, Gore JC, Hampson M. Time course of regional brain activation associated with onset of auditory/verbal hallucinations. *Br J Psychiatry* Nov 2008;193(5):424-425.

37. Lennox BR, Park SB, Jones PB, Morris PG. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* Feb 20 1999;353(9153):644.

38. Shergill SS, Brammer MJ, Amaro E, Williams SCR, Murray RM, McGuire PK. Temporal course of auditory hallucinations. *The British Journal of Psychiatry* December 1, 2004 2004;185(6):516-517.

Chapter 5

Reproducibility of brain activation during auditory verbal hallucinations: an fMRI study

KMJ Diederen[1]
L Charbonnier[2]
SFW Neggers[1]
R van Lutterveld[1]
K Daalman[1]
CW Slotema[3]
RS Kahn[1]
IEC Sommer[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands
[2]Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands
[3]Parnassia Bavo Group, The Hague, the Netherlands

Manuscript submitted for publication

Abstract

Introduction

Previous studies investigated fMRI-guided repetitive Transcranial Magnetic Stimulation (rTMS) as an alternative treatment for auditory verbal hallucinations (AVH). This tailor-made treatment focuses at directing the rTMS coil to the location where hallucinatory activation is maximal, as identified with fMRI scans of individual patients. Before employing such treatment it is, however, important to determine whether brain activation during AVH is reproducible.

Methods

Thirty-three psychotic patients indicated the presence of AVH during two subsequent scan sessions. Reproducibility was measured by calculating 1) percentage overlap of activation patterns over the two sessions and 2) distance between local maxima of significantly activated clusters between both hallucination scans. These measurements were obtained in single subjects and on group-level in five regions of interest (ROIs). Scans were considered reproducible if the distance between local maxima was smaller than 2 cm, as rTMS-treatment may target an area of approximately 2-4 cm.

Results

On single subject level, percentage overlap was below 40% in all ROIs. On group-level, this was substantially higher with a percentage overlap of 98% in the most reproducible ROI. In addition, the median distance between local maxima was smaller than 2 cm for all ROIs on single-subject, as well as on group-level.

Conclusions

Based on these results, AVH-scans may be considered reproducible and hence suitable for fMRI-guided rTMS treatment.

1. Introduction

The development of functional imaging techniques capable of "symptom-capturing" (i.e., capturing the neural signature of a symptom) has enabled the start of individual tailor-made treatments of psychiatric or neurological symptoms. An example of this strategy is the focal treatment of auditory verbal hallucinations (AVH) with repetitive Transcranial Magnetic Stimulation (rTMS), in which the focus of maximum activation during the experience of AVH in individual patients is used as the target position for treatment [1-3]. In addition to rTMS, techniques such as invasive electrocortical stimulation and deep brain stimulation may be applied. A major advantage of these tailor-made treatments is that they have the potential to treat medication-resistant AVH. Although such an approach seems elegant, it is essential to determine whether brain activation during hallucinations can be detected in a reliable fashion with fMRI. This is crucial for optimal treatment as scans that are unreliable may not reflect the true substrate of interest and will therefore be less effective when used as the main source for guiding treatment.

The aim of the present study was to investigate spatial reproducibility of AVH-related brain activation. To circumvent the influence of factors that are difficult to keep constant with increased time between measurements, including arousal, medication and caffeine-intake, reproducibility was investigated between two AVH-scans acquired within the same scan session.

2. Methods

2.1. Subjects

Thirty-three psychotic patients with medication-resistant AVH were recruited from the University Medical Center Utrecht and the Parnassia Bavo Group in The Hague, the Netherlands. Patients were selected for participation from a larger group [3] if they met the following criteria: (1) the presence of two subsequent AVH scans in which (2) intermittent AVH were experienced (i.e., AVH alternated with non-AVH state), (3) at least three AVH-episodes were present per scan (4) and AVH were indicated correctly (i.e., AVH-onsets were followed by clear offsets). Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) [4] according to DSM-IV criteria by an independent psychiatrist. Demographic data of the participants is provided in table 1.

Table 1. Demographic data of the participants

		Psychotic patients (N=33)
Age (years)		Mean 39 (S.D. 10)
Age (years) at onset AVH		Mean 19 (S.D. 19)
Gender		
	Females	19
	Males	14
Handedness		
	Right-handed	26
	Not right-handed	6
Diagnosis		
	Schizophrenia	22
	Schizo-affective disorder	3
	Psychosis not otherwise specified	6
	Personality disorder not otherwise specified	1
	Borderline personality disorder	1
Medication		
	No antipsychotic medication	4
	Typical antipsychotic medication	10
	Atypical antipsychotic medication	18
	Typical and atypical antipsychotic medication	1
PANSS score		
	Total	Mean 67 (S.D. 15)
	Positive subscale	Mean 16 (S.D. 4)
	Negative subscale	Mean 18 (S.D. 5)

Abbreviations: AVH, auditory verbal hallucinations; N, number; S.D., standard deviation

2.2. Data acquisition

Participants indicated the presence of AVH by balloon-squeezes while scans were acquired continuously. Data acquisition was similar for all AVH-scans and took 8 minutes per scan. Images were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. An AVH scan consisted of a series of blood-oxygenation-level-dependent T2* weighted images over time. PRESTO-SENSE was used to acquire the T2* weighted fMRI images, optimally using parallel imaging and echo shifting to reduce acquisition time of up to 609ms/volume [5]. Eight hundred PRESTO-SENSE images were acquired per session (40 slices, TR/TE 21.75/32.4 ms, flip angle 10°, field of view 224 × 256 × 160, matrix 64 × 64 × 40, voxelsize 4 mm isotropic, acquisition time 609 ms/volume). To improve localization of functional data, a high-resolution anatomical scan was conducted in addition to the AVH-scans (TR/TE: 9.86/4.6 ms, .875 × .875 × 1 voxels, flip angle 8°, FOV 224 × 160 × 168, 160 slices).

2.3. Data analysis

Preprocessing and analyses were conducted with Statistical Parametric Mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK) and included the following steps: realignment, coregistration, spatial normalization and smoothing. Scans were analyzed on a voxel by voxel basis using multiple regression analysis with one factor coding for activation (hallucination vs nonhallucination). This model was convolved with the hemodynamic response function from SPM5 to introduce typical delays of fMRI responses and fitted to the data using general linear model estimation [6]. Data was high-pass filtered with a cutoff of 100 s. and temporal autocorrelation was modeled with an autoregressive model of the first order (AR(1)).

2.4. Selection regions of interest

Reproducibility analyses were conducted on whole brain level and within five regions of interest (ROIs). ROIs were identified with the aid of an additional fMRI experiment in which brain activation during AVH was investigated in a group of thirty psychotic patients. First, a one-sample T-test was conducted to detect clusters displaying significant activation during AVH. This analysis revealed significant activation in five brain areas comprising the left temporoparietal region, the right inferior frontal region, the middle superior frontal region and the left motor region, as well as the right cerebellum. These regions are in concordance with previous reports on brain activation during AVH [7-9] Activation of two of these areas, the motor region and cerebellum might be related to balloon-squeezes used to indicate the AVH [7]. Of each cluster, the most significant local maximum (i.e. voxel with the highest T-value) was identified and ROIs were then created by drawing 16 mm spheres centered on these local maxima. For this analysis, a threshold of P = 0.05 whole-brain false discovery rate (FDR) corrected for multiple comparisons, was used. Cluster sizes, P - values, and locations of local maxima for brain activation during AVH in this group are displayed in table 2.

Table 2. Cluster sizes, P-values and locations of local maxima for brain activation during AVH

Regions of interests (ROIs)	*MNI Coordinates*			*Z-score*	*P-value*	*Cluster size*
	X	**Y**	**Z**			
Left temporoparietal area (ITP)	-52	-24	24	3.54	0.036	63
Right inferior frontal area (rIF)	56	12	4	3.42	0.037	25
Middle superior frontal area (mSF)	0	4	52	3.39	0.038	36
Left motor area (lMA)	-36	-28	52	4.11	0.024	131
Right cerebellum (rCB)	24	-52	-24	4.07	0.024	63

Threshold: P = 0.05 whole-brain false discovery rate (FDR) corrected for multiple comparisons.
Abbreviations: MNI, Montreal Neurological Institute

2.5. Reproducibility analysis

Spatial reproducibility was measured by determining 1) Percentage overlap and 2) Euclidian distance between local maxima, between both hallucination scans. Percentage overlap '*PO*' was calculated with the Jaccard similarity coefficient [10] by dividing the number of *overlapping* voxels during AVH-scan 1 and AVH-scan 2 '*AVH*1,2' by the amount of uniquely activated voxels for both sessions '(*AVH*1 + *AVH*2) – (*AVH*1,2)' as expressed by the formula:

$$PO = \frac{(AVH1,2)}{(AVH1 + AVH2) - (AVH1,2)} * 100$$

If multiple significant local maxima could be observed within a ROI, the local maximum with the highest T-value was selected. Percentage overlap was calculated on whole brain level and within ROIs. Distance between local maxima was only calculated within ROIs.

Analyses were conducted on single subject and on group-level. On single-subject level, individuals with no significant activation in both AVH-scans were excluded from percentage overlap analysis. Subjects with no significant activation in at least one AVH-scan were excluded from the peak distance analysis. This was determined with the aid of a one sample T-test, per scan, per subject, with a threshold of P = 0.05, FDR corrected for all voxels within an ROI or on whole-brain level. The same threshold was used for reproducibility analyses.

2.6. Reproducibility criterion

As rTMS may target an area of approximately 2-4 cm, scans were considered suitable for fMRI-guided rTMS-treatment if the distance between local maxima was smaller than 2 cm [11]. For more focal treatments such as invasive electrocortical stimulation and deep brain stimulation no specific criterion was specified, however, the area that may by targeted by these techniques is expected to be in the millimeter range [12].

3. Results

3.1. Performance data

The average number of AVH was 25 (S.D. 25) for the first hallucination scan and 24 (S.D. 34) for the second hallucination scan. The average duration of a hallucination was 13 (S.D. 29) seconds in scan 1 and 17 (S.D. 41) seconds in scan 2, adding up to a mean total duration of hallucinations of 148 (S.D. 120) seconds in scan 1 and 170 (S.D. 178) seconds in scan 2.

No significant differences were found for the number of AVH (T (32) =0.41, P =0.68), the total duration of the AVH (T (32) =-1.12, P = 0.27) and the average duration of the AVH (T (32) = -1.54, p=0.14) between the two scans.

3.2. Amount of significantly activated voxels

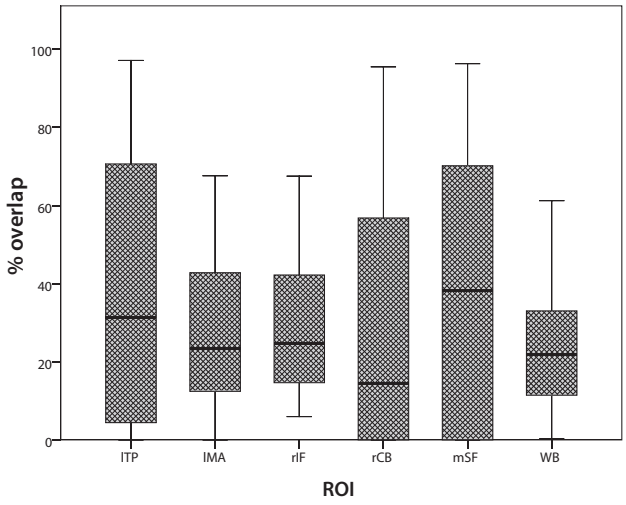
On single subject level, the median amount of significantly activated voxels was higher in the first compared to the second hallucination scan for the left temporoparietal region, the left motor area and on whole brain level. However, the right inferior frontal region, the middle superior frontal region and the right cerebellum showed more significantly activated voxels in the second scan. Except for the left temporoparietal region the number of significantly activated voxels did not differ significantly between the two scans. On group-level, all ROIs displayed a higher number of significantly activated voxels for scan 1 compared to scan 2. This was also found on whole brain level (see table 3).

Table 3. Number of voxels significantly activated in the two AVH-scans, percentage overlap and distance between local maxima for the two AVH-scans.

ROIs	*N voxels scan 1*		*N voxels scan 2*		*Statistical tests*	*Percentage overlap*		*Peak distance*	
	Median	Range	Median	Range	N voxels 1 vs N voxels 2	Median	Range	Median	Range
Single-subject									
lTP	137	9-243	74	1-240	Z=-2.930, P=0.003*	31%	0-97%	13mm	0-22mm
lMT	5006	117-14252	4831	43-16039	Z=-0.237, P=0.813	23%	0-68%	7mm	0-22mm
rIF	4774	1427-14111	5230	416-15361	Z=-0.168, P=0.866	25%	6-68%	4mm	0-19mm
mSF	111	0-242	117	0-244	Z=-0.264, P=0.792	38%	0-96%	2mm	0-23mm
rCB	70	3-237	109	11-242	Z=-1.354, P=0.176	14%	0-96%	6mm	0-17mm
WB	1313	1263.65	878	25-10342	Z=-0.884, P=0.376	22%	0-61%		
	Total		**Total**			**Total**		**Total**	
Group-level									
lTP	207		136			82%		7	
lMT	221		192			95%		18	
rIF	147		138			98%		12	
mSF	161		105			76%		13	
rCB	193		83			63%		12	
WB	7304		2560			34%			

** Significant at P < 0.05. Abbreviations: ROIs, regions of interest; N, number; lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area; rCB right cerebellum; WB, whole brain

Figure 1. Within-subject percentages overlap of the different regions of interest in AVH-scan 1 versus AVH-scan 2



Abbreviations: AVH, auditory verbal hallucinations; ROIs, regions of interest; lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area; rCB, right cerebellum; WB, whole brain.

3.3. Percentage overlap

3.3.1. Single-subject level

On single subject-level, median percentage overlap was highest for the middle superior frontal area (38%), followed by the left temporoparietal area (31%), the right inferior frontal area (25%), the left motor area (23%), whole brain (22%) and the right cerebellum (14%) (see table 3 and figure 1).

3.3.2. Group-level

On group-level, percentage overlap was 98% for the right inferior frontal area, 95% for the left motor area, 82% for the left temporoparietal area, 76% for the middle superior frontal area, 63% for the right cerebellum and 34% on whole brain level (see table 3 and figure 2).

3.4. Peak distance

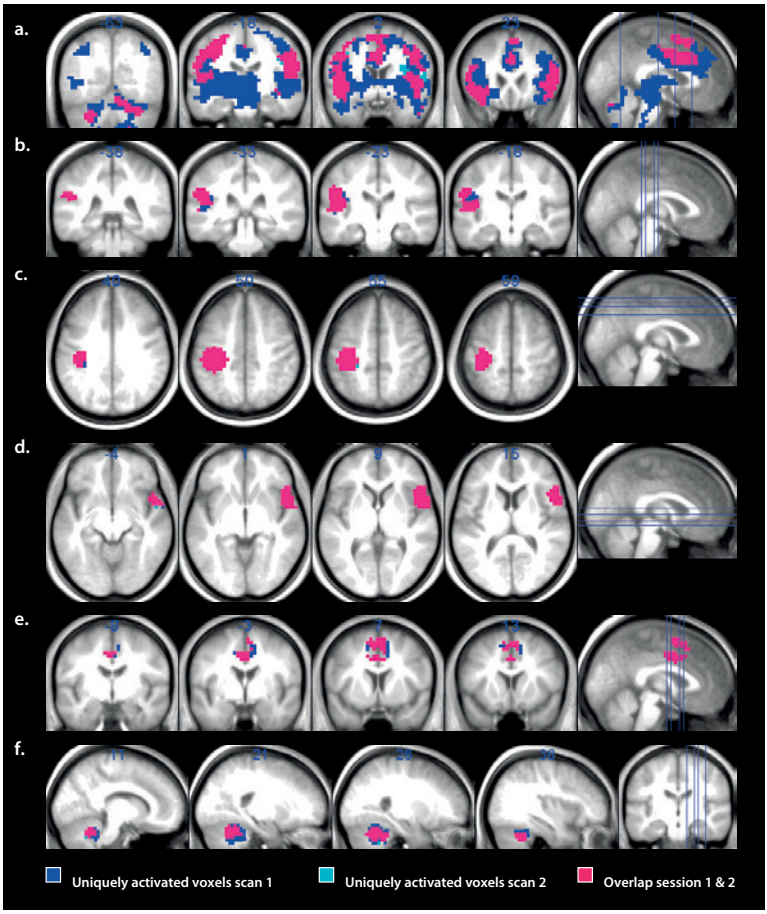
3.4.1. Single-subject level

On single-subject level, distance between local maxima was smallest for the middle superior frontal area (2mm), followed by the right inferior frontal area (4mm), the cerebellum (6mm), the left motor area (7mm) and the left temporoparietal area (13mm) (see table 3 and figure 3).

3.4.2. Group-level

On group-level, distance between local maxima was 12mm for the right inferior frontal area, 18mm for the left motor area, 7mm for the left temporoparietal area, 13mm for the middle superior frontal area and 12mm for the right cerebellum (see table 3).

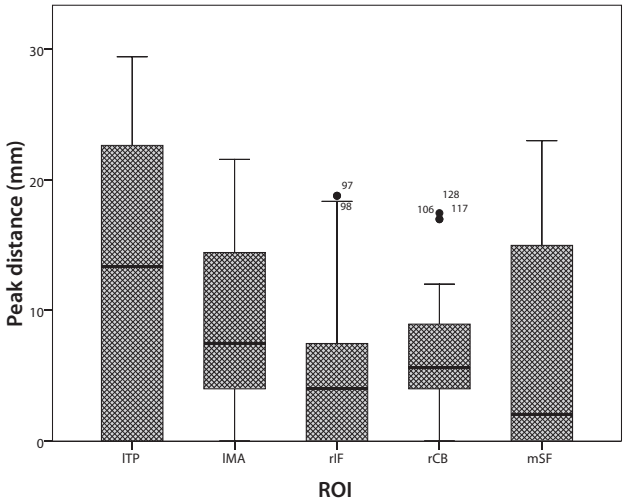
Figure 2. Brain regions significantly activated on whole brain level and within ROIs in AVH-scan 1 and AVH-scan 2 of the group-wise analysis.



a. Whole brain, b. Left temporoparietal area, c. Left motor area, d. Right inferior frontal area, e. Middle superior frontal area, f. Right cerebellum. Threshold: P = 0.05, false discovery rate corrected for multiple comparisons within ROIs or on whole-brain level

Abbreviations: AVH, auditory verbal hallucinations, ROIs, regions of interest

Figure 3. Within-subject distance between significant local maxima in AVH-scan 1 versus AVH-scan 2



Abbreviations: AVH, auditory verbal hallucinations, ROIs, regions of interest; mm, millimeter; lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area; rCB, right cerebellum

4. Discussion

This study investigated spatial reproducibility of brain activation during auditory verbal hallucinations (AVH) to evaluate whether these scans are appropriate for fMRI-guided tailor-made treatments. Reproducibility was assessed with percentage overlap and distance between local maxima as the main measurements.

On single subject level, percentage overlap was below 40% in all regions of interest (ROIs). On group-level, this was much higher with a percentage overlap of 98% in the most reproducible ROI. In addition, the median distance between local maxima was smaller than 2 cm for all ROIs on single-subject, as well as on group-level.

Based on our criterion for reproducibility these scans can be considered suitable for fMRI-guided rTMS-treatment. However, it is important to note that in the left temporoparietal area, which corresponds with the region most frequently targeted in the treatment of AVH [13], over 25% of individuals displayed a median distance of more than 2 cm (see figure 1) between local maxima. Furthermore, the median percentage overlap was below 40% in all ROIs. In addition, our measure of individual variability should be seen as a lower bound of reproducibility, as in this study reproducibility was investigated between two AVH-scans acquired within the same scan session to

circumvent the influence of factors that are difficult to keep constant with increased time between measurements, including arousal, medication and caffeine-intake.
Although we did not set criteria for more focal treatments such as invasive electrocortical stimulation and deep brain stimulation it is highly questionable if hallucination scans can be considered suitable for guiding these treatments as the areas that may be targeted by these techniques are expected to be within the millimeter range [12].

This is the first study to investigate reproducibility of AVH-related brain activation. However, fMRI-reliability was previously studied in relation to motor and visual tasks, as well as during various cognitive tasks [14-20]. While percentage overlap is frequently used to investigate reproducibility, distance between local maxima is not a standard measure. Recently, Bennet and Miller [15] reviewed fMRI- reliability studies and reported an average percentage overlap, calculated with the Jaccard coefficient, of 33% when the test and retest scans took place within the same hour. This is rather similar to the percentage overlap observed in this study which ranged between 14 and 38% on single-subject level. Bennet and Miller [15] also showed that most studies observed a higher percentage overlap on group-level than on single-subject level which is in line with the findings of the current study.

4.1. Limitations

The main limitation of the metrics employed in this study, especially percentage overlap, is its dependence on the selected significance threshold [15]. In addition, the observed percentage overlap may have been influenced by differences in the total number of significantly activated voxels between the two scans. Decreases in activation from the first to the second scan have been reported by previous studies and have been suggested to result from practice effects [15]. In the present study, all ROIs showed a higher amount of significantly activated voxels in the first compared to the second scan, on group-level. This was most pronounced on whole brain level which was the area that displayed the lowest percentage overlap. However, on single subject level this pattern was less clear with some areas showing more significantly activated voxels in scan 1, while other regions showed a higher amount of significantly activated voxels in scan 2. The difference in amount of activated voxels was most pronounced in the left temporoparietal area which showed the second highest percentage overlap on single-subject level. Therefore, low percentages overlap on single subject level may not be readily interpreted to result from differences in the amount of significantly activated voxels between the two scans.
Finally, a limitation with respect to the reproducibility criterion adopted for rTMS is that the size of the area targeted by rTMS depends on a number of factors including coil

geometry and orientation. As a result, our criterion of 2 cm might be appropriate for some coils and stimulation paradigms, but not for others.

In summary, as the median distance between local maxima was smaller than 2 cm in all ROIs, these scans may be considered suitable for fMRI-guided rTMS treatment. These results should, however, be treated with caution as reproducibility was measured within one scan session and may therefore represent a lower bound of reproducibility.

References

1. Hoffman RE, Hampson M, Wu K, et al. Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. *Cerebral Cortex* November 1, 2007 2007;17(11):2733-2743.
2. Sommer IE, de Weijer AD, Daalman K, et al. Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? *Schizophr Res* Jul 2007;93(1-3):406-408.
3. Slotema CW, Blom JD, de Weijer AD, et al. Can Low-Frequency Repetitive Transcranial Magnetic Stimulation Really Relieve Medication-Resistant Auditory Verbal Hallucinations? Negative Results from a Large Randomized Controlled Trial. *Biological Psychiatry* 2011;69(5):450-456.
4. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.
5. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.
6. Worsley KJ, Friston KJ. Analysis of fMRI Time-Series Revisited--Again. *NeuroImage* 1995;2(3):173-181.
7. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.
8. Diederen KM, Daalman K, de Weijer AD, Neggers SF, van Gastel W, Blom JD, Kahn RS, Sommer IE. Auditory Hallucinations Elicit Similar Brain Activation in Psychotic and Nonpsychotic Individuals. *Schizophr Bull* Apr 28 2011.
9. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IE. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry* Apr 2010;167(4):427-435.
10. Maitra R. A re-defined and generalized percent-overlap-of-activation measure for studies of fMRI reproducibility and its use in identifying outlier activation maps. *NeuroImage* 2010;50(1):124-135.
11. Wagner T, Eden U, Fregni F, et al. Transcranial magnetic stimulation and brain atrophy: a computer-based human brain model study. *Experimental Brain Research* 2008;186(4):539-550.
12. Miglioretti DL, Boatman D. Modeling variability in cortical representations of human complex sound perception. *Experimental Brain Research* 2003;153(3):382-387.
13. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010;71(7):873-884.
14. Manoach DS, Halpern EF, Kramer TS, Chang Y, Goff DC, Rauch SL, Kennedy DN, Gollub RL. Test-Retest Reliability of a Functional MRI Working Memory Paradigm in Normal and Schizophrenic Subjects. *Am J Psychiatry* June 1, 2001 2001;158(6):955-958.
15. Bennett CM, Miller MB. How reliable are the results from functional magnetic resonance imaging? *Annals of the New York Academy of Sciences* 2010;1191(1):133-155.
16. McGonigle DJ, Howseman AM, Athwal BS, Friston KJ, Frackowiak RSJ, Holmes AP. Variability in fMRI: An Examination of Intersession Differences. *NeuroImage* 2000;11(6):708-734.
17. Rombouts SARB, Barkhof F, Hoogenraad FGC, Sprenger M, Scheltens P. Within-Subject Reproducibility of Visual Activation Patterns With Functional Magnetic Resonance Imaging Using Multislice Echo Planar Imaging. *Magnetic Resonance Imaging* 1998;16(2):105-113.
18. Tegeler C, Strother SC, Anderson JR, Kim S-G. Reproducibility of BOLD-based functional MRI obtained at 4 T. *Human Brain Mapping* 1999;7(4):267-283.

19. Zandbelt BB, Gladwin TE, Raemaekers M, van Buuren M, Neggers SF, Kahn RS, Ramsey NF, Vink M. Within-subject variation in BOLD-fMRI signal changes across repeated measurements: Quantification and implications for sample size. *NeuroImage* 2008;42(1):196-206.

20. Raemaekers M, Vink M, Zandbelt B, van Wezel RJA, Kahn RS, Ramsey NF. Test-retest reliability of fMRI activation during prosaccades and antisaccades. *NeuroImage* 2007;36(3):532-542.

Chapter 6

Auditory hallucinations elicit similar brain activation in psychotic and non-psychotic individuals

Kelly MJ Diederen[1]
Kirstin Daalman[1]
Antoin D de Weijer[1]
Sebastiaan FW Neggers[1]
Willemijn van Gastel[1]
Jan Dirk Blom[2,3]
René S Kahn[1]
Iris EC Sommer[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands
[2]Parnassia Bavo Group, The Hague, the Netherlands
[3]Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

Schizophrenia Bulletin published online April 28 2011

Abstract

Introduction

While auditory verbal hallucinations (AVH) are most characteristic for schizophrenia, they also occur in non-psychotic individuals in the absence of a psychiatric or neurological disorder and in the absence of substance abuse. At present, it is unclear if AVH in these non-psychotic individuals constitute the same phenomenon as AVH in psychotic patients. Comparing brain activation during AVH between non-psychotic and psychotic individuals could provide important clues regarding this question.

Methods

Twenty-one non-psychotic subjects with AVH and 21 matched psychotic patients indicated the presence of AVH during 3T fMRI scanning. To identify common areas of activation during the experience of AVH in both groups, a conjunction analysis was performed. In addition, a two-sample T-test was employed to discover possible differences in AVH-related activation between the groups.

Results

Several common areas of activation were observed for the psychotic and non-psychotic subjects during the experience of AVH, consisting of the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri and postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole and right cerebellum. No significant differences in AVH-related brain activation were present between the groups.

Conclusions

The presence of multiple common areas of AVH-related activation in psychotic and non-psychotic individuals, in the absence of significant differences, implicates the involvement of the same cortical network in the experience of AVH in both groups.

1. Introduction

Auditory verbal hallucinations (AVH) are common in schizophrenia patients, but also occur in other psychiatric disorders including schizotypal and borderline personality disorder, bipolar disorder and psychotic depression [1, 2]. Moreover, AVH are observed in non-psychotic individuals, in the absence of delusions, affective and negative symptoms [3-5]. These observations led to the formulation of the continuum hypothesis of psychosis, which states that symptoms observed in patients with a psychotic disorder are also apparent in non-clinical populations [6, 7]. However, it remains unclear if AVH in non-psychotic individuals are the same symptom as AVH in psychotic patients. Similarities in a number of phenomenological characteristics of AVH in psychotic and non-psychotic individuals suggest that AVH are indeed the same phenomenon in both groups [8, 9]. For instance, experienced location, loudness, reality, number of voices and personification of the AVH were shown to be similar for both groups [8, 9]. However, differences in several other AVH-characteristics may shed doubt on classifying AVH in non-psychotic individuals as 'actual' hallucinations; frequency, age of onset, emotional valence of the content, associated distress and the degree of control individuals experience over their AVH were found to differ between non-psychotic and psychotic subjects [8-10]. As both differences and similarities in phenomenological characteristics of AVH were observed in non-psychotic and psychotic individuals [8, 9] it remains unclear if AVH in non-psychotic individuals result from the same mechanism as AVH in psychotic patients. If these hallucinations are caused by comparable mechanisms in both groups, one should observe the same pattern of brain activation during AVH. Several studies investigated AVH-related brain activation in psychotic patients, primarily reporting activation of bilateral frontal and temporoparietal areas [11-14]. Thus far, only one study visualized AVH-related brain activation in non-psychotic subjects, revealing activation in bilateral frontal and temporoparietal areas as well as motor areas [15]. However, this study included only seven subjects and did not compare AVH-related brain activation in their group of non-psychotic subjects to that of psychotic patients. The aim of the present study was to identify commonalities and/or differences in brain activation during AVH between psychotic and non-psychotic individuals with AVH in samples that are large enough to enable group-wise analysis.

2. Methods

2.1. Subjects

Twenty-one non-psychotic individuals with AVH and 21 psychotic patients participated in this study. Non-psychotic subjects with AVH 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 by our group [4,9,16,17]. In short, visitors of this website filled out a questionnaire based on the Launay Slade Hallucination Scale (LSHS [18]), which is a self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals. Subjects with high scores on item 8 and 12 of the LSHS, tapping into auditory hallucinations, were invited to the University Medical Center to undergo detailed psychiatric assessment.

Psychotic patients were selected from a larger group [19] to match the healthy individuals for demographic factors, such as age, sex and handedness, but also for the total duration of the AVH, the mean duration of the AVH and the number of AVH experienced during the fMRI scans. Patients were recruited from the Department of Psychiatry, University Medical Center Utrecht and the Parnassia Bavo Group in The Hague, the Netherlands. All psychotic patients were diagnosed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History interview (CASH [20]). Ten patients were diagnosed with schizophrenia, two with schizoaffective disorder and nine with psychosis Not Otherwise Specified (NOS). The main difference between patients diagnosed with schizophrenia and schizoaffective disorder and patients diagnosed with psychosis NOS was that the first groups scored higher on items addressing negative symptoms and general psychopathology. All patients, including patients diagnosed with psychosis NOS, presented with additional positive symptoms including delusions and disorganization.

General inclusion criteria were: (1) voices should be distinct from thoughts and have a perceptual quality; (2) voices should be experienced at least once a month, (3) no chronic somatic disorder and (4) no drug use for at least one month prior to the assessment. To confirm the absence of drug use, urine samples were collected and tested for opiates, amphetamines/XTC, cocaine and cannabis. Furthermore, a number of additional scan-related inclusion criteria were used. These additional criteria were: (5) voices should be present with a frequency of at least four AVH episodes per scan (8 minutes), (6) and with a minimum total duration of fifty seconds. Finally, (7) hallucinations should be indicated correctly, i.e. each onset (balloon-squeeze) should be followed by a clear offset (balloon-release).

Additional criteria for the non-psychotic subjects consisted of (1) no psychiatric disorder other than anxiety or depressive disorder in full remission according to DSM-IV diagnostic criteria assessed by an independent psychiatrist using the CASH [20] and Structured Clinical Interview for personality Disorder (SCID-II [21]) interview and (2) no drug or alcohol abuse prior to the first AVH- experience.

In total, 42 non-psychotic individuals with AVH participated in the hallucination scans. Twenty-one of these individuals were excluded from analyses as they did not meet inclusion criteria 5 or 6. Of these twenty-one subjects seven subjects experienced no

AVH at all during the hallucination scan.

Non-psychotic subjects with AVH were not diagnosed as Psychosis NOS as they were not bothered by these AVH and showed no social or professional dysfunction. Although the non-psychotic individuals with hallucinations did not have any clinical delusions, they did score significantly higher on the Schizotypical Personality Questionnaire (SPQ [22]) than a group of matched healthy control subjects [4]. In addition, 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-IV criteria for schizotypal personality disorder. However, social capacity and affect were found to be adequate as determined by a trained psychiatrist using the CASH and the Global Assessment of Functioning (GAF [23]) scale.

Group-wise matching was used to match the group of psychotic patients to the non-psychotic individuals with AVH. After selecting the 21 non-psychotic individuals who met all inclusion criteria, we inspected our database, which contains hallucination scans of psychotic patients, in order to select a group of patients comparable to the non-psychotic individuals. Psychotic patients included in this database are described in detail in a previous study by our group [19]. For matching the following order was used: sex, handedness, age, and years of education, total duration of the hallucinations during the scans, number of hallucinations during the scans and average duration of the hallucinations during the scans. If the groups differed significantly on one of these variables, we tried minimizing these differences, being less strict with respect to one of the other variables. Unfortunately we could not adequately match the groups with respect to years of education as most patients dropped out of school as a result of the onset of psychiatric symptoms.

The groups did not differ significantly with respect to age, sex and handedness, however years of education were significantly lower for the psychotic patients. In table 1 medication use and scores on the Positive and Negative Syndrome Scale (PANSS [24]) are listed for the psychotic patients.

Table 2 provides a demographic description of all participants including the characteristics of the voices in the last three months according to the Psychotic Symptom Rating Scales [25], scores on the GAF and scores on the SPQ for the group of non-psychotic individuals with AVH. This study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

Table 1. Medication use and scores on the PANSS for the psychotic patients.

	N	*Mean (S.D.)*	*Median (range)*
Antipsychotic medication			
First generation	9		
Second generation	9		
No antipsychotic	3		
PANSS scores			
Total PANSS	19	65 (16)	67 (53)
Positive PANSS	19	17 (4)	17 (14)
Negative PANSS	19	16 (5)	15 (14)
General psychopathology	19	33 (8)	34 (25)

Abbreviations: N, number; S.D., standard deviation; PANSS, Positive and Negative Syndrome Scale

2.2. Experimental design and data acquisition

During fMRI acquisition, participants indicated the presence of AVH by balloon-squeezes.

Activation maps were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. Eight-hundred blood-oxygenation-level-dependent (BOLD) fMRI images were acquired per patient with the following parameter settings: 40 (coronal) slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224x256x160, matrix 64x64x40, 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 two directions using a commercial 8-channel SENSE headcoil [26]. Since these PRESTO SENSE images have little anatomical contrast, 40 identical scans, but with a flip angle of 27° (fa27) were acquired to improve realignment and co-registration during the preprocessing. After the functional scans a high resolution anatomical scan, with the following parameters: TR/TE: 9.86/4.6 ms, .875x.875x1 voxels, flip angle 8°, FOV 224x160x168.00, 160 slices was acquired to improve localisation of the functional data.

2.3. Data analysis

Preprocessing and data analysis was conducted with statistical parametric mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK). Preprocessing included within-subject image realignment with the mean fa27 as the reference to correct for the effects of head motion, co-registration of the mean fa27 and the T1 weighted anatomical image and spatial normalisation to a standard MNI template.

Table 2. Detailed description of the participants

	Non-psychotic subjects with AVH (n=21)				*Psychotic Patients (n=21)*				
	N	**Mean (S.D.)**	**median (range)**	**Description mean**	**N**	**Mean (S.D.)**	**median (range)**	**Description mean**	**Statistics**
Age	21	47 (13)	48 (43)		21	40 (11)	41 (41)		T(40) = 1.86, p = 0.071
Sex (male/female)	5/16				7/17				X2(1) = 0.11, p = 1
Handedness (right/ non-right)	15/6				14/7				X2(1) = 0.47, p = 0.734
Years of education	21	14 (3)	14 (11)		21	13 (2)	13 (7)		K-S Z = 1.234, 0.038*
Total AVH duration[1]	21	131 (73)	108 (225)		21	181 (96)	158 (331)		K-S Z = 0.926, p = 0.365
Average AVH duration[1]	21	9 (5)	10 (24)		21	14 (15)	10 (69)		K-S Z = 0.926, p = 0.365
Number of AVH[1]	21	17 (12)	15 (51)		21	25 (29)	13 (128)		K-S Z = 0.617, p = 0.773
AVH Frequency[2]	21	4 (1)	4 (5)	> one per day	21	5 (1)	6 (6)	(Almost) at all times	K-S Z = 2.01, p < 0.001**
AVH Duration[2]	21	2 (1)	2 (3)	Few minutes	21	3 (1)	2 (3)	An hour	K-S Z = 1.08, p = 0.046
AVH Location[2]	21	2 (1)	2 (3)	Inside head/ near ears	21	1 (1)	1 (3)	Mostly inside head.	K-S Z = 0.926, p = 0.112
AVH Intensity[2]	21	2 (1)	2 (2)	Softer than own voice	21	2 (1)	2 (3)	Volume of own voice	K-S Z = 0.617, p = 0.385
AVH Explanation origin[2]	21	3 (1)	3 (3)	> 50 % external	21	2 (1)	2 (3)	= 50 % external	K-S Z = 1.389, p = 0.017
AVH Emotional Valence[2]	21	2 (3)	0 (12)	Seldom unpleasant	21	8 (3)	9 (9)	Mostly unpleasant	K-S Z = 2.469, p < 0.001**
AVH Total Distress[2]	21	1 (1)	0 (4)	Almost no discomfort and disruption of life	21	5 (2)	6 (5)	Substantial distress/ disruption of life	K-S Z = 3,086, p < 0.001**
AVH Controllability[2]	21	1 (1)	1 (4)	Most of the time	21	3 (1)	3 (4)	Sporadically	K-S Z = 1.697, p = 0.002* *
AVH N different voices[2]	21	20 (34)	7 (99)	20.38	21	23 (39)	4 (99)	23.33	K-S Z = 1.08, p = 0.1450
AVH age onset[2]	21	22 (13)	8 (44)	15.29	21	22 (13)	21 (44)	14.28	K-S Z = 1.234, p = 0.08
GAF score	21	83 (6)	85 (25)		21	48 (11)	45 (40)		K-S Z = 3.086, p < 0.001**
SPQ total score	20	25 (13)	22 (49)		0				

[1] during scanning; [2] in the last 3 months; * significant at p<0.05; ** significant after Bonferroni correction for the number of PSYRATS items (n=10; p<0.005). Abbreviations: AVH = auditory verbal hallucinations; N, number; GAF, Global Assessment of Functioning; SPQ, Schizotypical Personality Questionnaire; S.D, standard deviation; K-S Z, Kolmorgorov-Smirnov Z

Finally, images were smoothed using an 8-mm full width at half maximum (FWHM) Gaussian kernel. To compare activation during hallucination periods to non-hallucination periods, a model was created using balloon-squeezes as hallucination onsets and time between squeezes and releases as the durations. Functional images were analysed on a voxel by voxel basis using multiple regression analysis [27] with one factor coding for activation (hallucination versus non-hallucination). This model was convolved with the standardized hemodynamic response function from SPM5 to introduce typical delays of fMRI responses, and fitted to the data using GLM estimation. To model movement artifacts the realignment parameters were entered as covariates. To identify common areas of activation for the experience of AVH in the two groups, a conjunction analysis (conjunction null [28]) was performed. For this analysis the following steps were taken. First, one sample T-tests, comparing brain activation during hallucinations (balloon-squeeze) to brain activation during baseline (no balloon-squeeze), were performed on individual fMRI-BOLD signal change maps to enable group-wise analyses for the psychotic and non-psychotic subjects, separately. Subsequently, to determine which voxels were significantly activated in both groups, one-sample T-tests of the psychotic and non-psychotic individuals were overlaid on one another.

Furthermore, to identify possible differences in brain activation during AVH between the two groups, a two-sample T-test was employed. It was hypothesized that possible differences as well as similarities in brain activation would be present in regions previously reported to be involved in the experience of AVH. To enable hypothesis-driven analyses for the conjunction analysis as well as for the two-sample T-test, a small volume correction for multiple comparisons was applied. The small volume contained regions previously reported to be involved in the experience of AVH [11-14]. These regions, comprising the bilateral inferior frontal gyri, insula, superior and middle temporal gyri (including the superior and middle temporal pole), supramarginal gyri, precentral and postcentral gyri, cerebellum, hippocampus and parahippocampal gyrus were defined using the Automated Anatomical Labeling (AAL) atlas [29]. Moreover, to identify potential similarities and differences in brain activation outside the selected regions, an additional exploratory conjunction analysis and independent samples T-test were performed, testing all grey matter voxels within the brain. All analyses were thresholded at p=0.05, False Discovery Rate (FDR [30]) corrected for all voxels within the regions of interest for the hypothesis-bases analysis and for all voxels within grey matter for the exploratory analysis. In addition, an extended threshold of 5 voxels was used.

In addition, to determine if possible differences in lateralization of language areas implicated in AVH would be present between the psychotic and non-psychotic individuals with AVH, lateralization indices were calculated on individual T-tests

and compared between the groups. For this purpose, a mask was created using the Anatomical Automatic Labeling (AAL [29]) atlas comprising the main areas where language processing is thought to be mediated and their contralateral homologues [14, 16]. Language areas consisted of the inferior frontal triangle, the insula, the middle temporal gyrus, the superior temporal gyrus, the supramarginal gyrus and the angular gyrus. Lateralization indices were defined as the difference in 'thresholded' signal intensity changes in the left versus the right hemisphere (within the selected language regions) divided by the total sum of 'thresholded' signal intensity changes. Using this method, activity measures are based on signal intensity changes in those voxels that exceed a predefined activation level, as recommended by Jansen and colleagues [31]. Differences in lateralization indices between the two groups were compared by means of a Kolmogorov-Smirnov test. Finally, to replicate the finding of a significant negative correlation between emotional valence of the AVH-content and lateralization indices within language areas by Sommer and colleagues [14], lateralization indices were correlated with the emotional valence of the content measured with the PSYRATS and tested for significance using spearman's rho.

3. Results

The hypothesis-based conjunction analysis revealed several areas that were significantly activated during the experience of AVH in both groups including the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri and postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole and right cerebellum. Except for the right cerebellum, in which no significant activation was observed, the exploratory analysis yielded activation of the same regions, albeit cluster sizes of significant voxels were smaller. Figure 1A shows the SPM(T)'s of all significant local maxima for the conjunction analysis in a priori hypothesized regions and figure 1B shows significant activation within all grey matter voxels in the brain. Table 3 shows the coordinates, T-values and cluster size of all significant local maxima for the conjunction analysis. The two-sample T-test revealed no significant difference in activation during AVH between the groups neither in a priori hypothesized regions nor in all grey matter voxels in the brain.

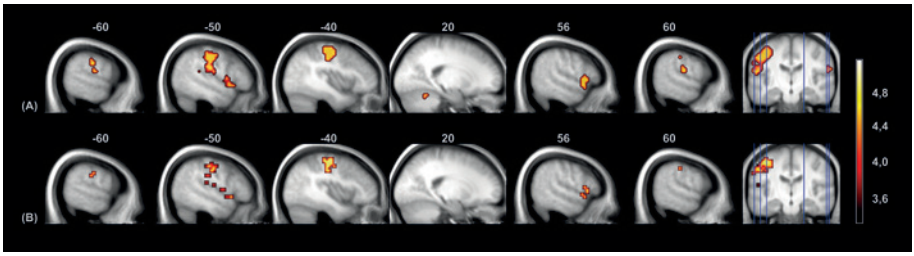
In addition, no significant difference ($p = 0.6$) in lateralization indices could be observed between the non-psychotic individuals (mean = -0.09; S.D. = 0.29; range = 1.36) and the psychotic patients (mean = -0.04; S.D. = 0.18; range = 0.67). Finally, lateralization indices of hallucinatory activation were not significantly correlated to the emotional valence of the content in either the non-psychotic (spearman's rho = 0.17, $p = 0.46$) or in the psychotic individuals (spearman's rho = 0.13, $p = 0.58$).

Table 3. T-values, cluster sizes and locations of local maxima for the conjunction analysis

Clustersize	*P-value*	*T-value*	*MNI coordinates*	*Brain regions*
152	0.008	5.19	-44 -20 44	L postcentral gyrus/ supramarginal gyrus
	0.017	4.18	-52 -20 24	L precentral gyrus/ superior temporal gyrus
	0.023	3.82	-60 -24 32	L inferior parietal lobule
13	0.022	3.93	56 12 -4	R superior temporal gyrus/ inferior frontal gyrus/ insula
20	0.022	3.90	-52 8 4	L inferior frontal gyrus/ insula/ superior temporal gyrus/ superior temporal pole
7	0.025	3.65	60 -16 20	R postcentral gyrus/ supramarginal gyrus
5	0.028	3.46	20 -56 -20	R cerebellum

Thresholded at p=0.05, FDR corrected with an extended threshold of 5 voxels. Abbreviations: 'Abbreviations: AVH, auditory verbal hallucinations; MNI, Montreal Neurological Institute; L, Left; R, right; FDR, False Discovery Rate

Figure. 1. SPM(T)'s for the conjunction analysis revealing brain regions significantly activated during the experience of AVH in both psychotic and non-psychotic individuals with AVH.
(A) Areas significantly activated within a priori hypothesized regions. (B) Areas significantly activated within all gray matter voxels in the brain.



Thresholded at p=0.05 FDR corrected for multiple comparisons.
Abbreviations: SPM(T)'s, Statistical Parametric Mapping T-values; AVH, auditory verbal hallucinations; FDR, False Discovery Rate

4. Discussion

This study investigated brain activation during auditory verbal hallucinations (AVH) in 21 non-psychotic and 21 psychotic individuals. While several common areas of activation were present for the psychotic and non-psychotic subjects, no significant differences in brain activation could be observed between the groups. In addition, no significant differences in lateralization of language activity could be observed between the psychotic and non-psychotic individuals. Finally, no significant correlation was present between lateralization indices and the emotional valence of the AVH-content, in either group.

Psychotic as well as non-psychotic subjects with AVH activated the bilateral inferior frontal gyri, insula, superior temporal gyri, supramarginal gyri, postcentral gyri, left precentral gyrus, inferior parietal lobule, superior temporal pole and right cerebellum. These areas were discovered with a conjunction analysis which identifies common areas of activation by finding areas that are significantly activated in each group [28]. The result of several common areas of activation in the psychotic and non-psychotic individuals implicates involvement of the same network in the experience of AVH in both groups. However, to what extent a similar network is involved, is unclear as, during AVH, no significant differences could be observed between the groups. Future studies may aid in identifying possible differences in AVH-related brain activation between these individuals. In addition, while this study provides a first step in comparing neural processes related to AVH in psychotic and non-psychotic individuals, these results cannot explain if the same pathophysiological mechanism gives rise to AVH in psychotic and non-psychotic individuals with AVH as the resulting activation patterns may reflect a final common pathway triggered by different mechanisms. Therefore, these results cannot be used as support for, or against the continuum hypothesis of psychosis in which it is usually assumed that AVH in all individuals result from the same pathophysiological mechanism. To elucidate if AVH in different groups indeed arise from the same underlying pathology, future research should focus on comparing groups with and without a history of AVH, while they are not actively hallucinating, for instance using resting state functional connectivity or structural anatomical measures. Together with the present results such research would shed even more light on identical or different pathophysiology in both groups.

To our knowledge, this is the first study comparing brain activation during AVH between non-psychotic and psychotic individuals with AVH. In addition, as far as the authors are concerned, no studies compared brain activation during AVH between different patient groups including patients with schizotypal and borderline personality disorder, bipolar disorder and psychotic depression. As such a comparison could provide additional clues regarding similarities and differences in brain activation during AVH in different groups; future studies should focus on comparing AVH-related brain activation between patients with different diagnoses.

Activation of bilateral frontal, temporoparietal and motor areas during AVH is largely in line with previous studies in psychotic patients [11-14]. Thus far, only one study investigated brain activation during AVH in non-clinical individuals [15]. This study included seven non-clinical individuals with AVH and seven control subjects. The main difference between this study and the current study is that the current study compared AVH between psychotic and non-psychotic individuals, while Linden and colleagues compared brain

activation during AVH in non-clinical individuals to brain activation during imagery in a control group. As Linden and colleagues reported activation of fronto-temporal language areas, in the left hemisphere and their contralateral homologues and the supplementary motor area during AVH, as well as during verbal imagery, these results are for the most part in concordance with the present study.

While activation of motor areas, as observed in this study, most likely results from the employed balloon-squeeze paradigm [32], the role of bilateral frontal and temporoparietal regions in the experience of AVH is not yet clear. A number of theoretical frameworks which have been proposed to account for the experience of AVH may aid in interpreting which cognitive functions are represented by activation of these areas during AVH.
First, the most influential, contemporary, model proposes that AVH occur due to a failure to recognize self-generated inner speech [33, 34]. Consequently, left hemisphere language production and perception areas, as well as regions implicated in self-monitoring, play a crucial role in this model. Activation of left frontal and temporoparietal regions as observed during AVH have consistently been implicated in language perception and production processes [35-38], providing support for this hypothesis. However, this study provides no information regarding the self-monitoring aspect of this theory. Support for this comes from a number of studies investigating self-recognition in patients with AVH [39, 40]. In addition, this theory cannot explain activation of right hemisphere frontal and temporoparietal regions which is also observed during AVH.
A second model proposes AVH to result from the release of language activity in the right hemisphere, which is normally inhibited in the healthy brain [41]. While right hemisphere frontal and temporoparietal areas are not considered classical language regions, previous studies showed that the right hemisphere can produce so-called non-propositional or 'automatic' language, consisting of highly over learned sequences of low linguistic complexity [42, 43]. Activation of right hemisphere frontal and temporoparietal language regions is in line with this model; however, this model does not incorporate involvement of left hemisphere language regions, as observed in this study.
Furthermore, a third theory states that AVH result from aberrant activation of the primary auditory cortex [44]. As this region was not significantly activated in the current study, this study provides no support to this theory.
Finally, the fourth model hypothesizes that AVH result from spontaneous memory recollection, leading to the re-experience of previously encoded information [45, 46]. As no activation of regions implicated in memory processes was observed, this study does not support this model. However, previous studies reported involvement of the parahippocampal region, implicated in memory-processes, prior to AVH [12, 47]. Perhaps,

memory recollection preceding AVH triggers activations in language-related areas responsible for the experience of the actual AVH.

Another cognitive process likely to be involved in the experience of AVH consists of cue detection in which the AVH represent the detected cues. Previous studies showed that bilateral frontal and temporoparietal regions, observed in this study, have been implicated in the detection of salient events, providing support for the involvement of this function in AVH [48, 49].

From this discussion, it is clear that a number of cognitive processes may be involved in AVH including cue detection, language production and perception processes, memory and motor processes. Consequently, future studies should focus on disentangling which cognitive domains are involved in the experience of AVH, favourably by directly comparing AVH to a number of cognitive tasks, tapping into the aforementioned cognitive domains. An intuitive expectation is that multiple cognitive processes are involved in the experience of AVH. For instance, spontaneous memory recollection may activate language-related areas in both hemispheres, leading to the re-experience of this memory, which is subsequently detected by regions involved in the detection of salient events. Finally, self-recognition deficits may explain why this memory is not recognized as such, rendering the belief that the content of the AVH comes from an outside source. Unfortunately, investigating brain activation during AVH does not allow one to separate brain activation associated with the experience of AVH from activation involved in the genesis of this phenomenon. In addition, one should be careful in comparing brain activation during AVH to activation elicited by a cognitive task such as a language paradigm, as both vary considerably. For instance, when studying AVH, frequency, duration and content of the 'presented' stimuli differ between participants while during cognitive tasks these variables are generally held constant.

Surprisingly, we were not able to replicate earlier findings with respect to the significant correlation between lateralization of language regions during the experience of AVH and the emotional valence of the content of the voices [14]. This may be one reason that even though a significant difference in emotional valence of the voices was found between the psychotic and non-psychotic subjects no significant difference in AVH-related brain activation was observed between the two groups.

4.1. Limitations

These results should be interpreted with some caution as possible differences between the groups may not have become visible, due to for instance the fact that fMRI BOLD does not demonstrate all types of neuronal activation [50], nor does it do so at finer spatial and temporal scales. Furthermore, the moderate number of subjects may have been of influence as it was previously reported that about 25 subjects are necessary to

achieve 80% power in fMRI studies [51]. However, as not even a trend could be observed when comparing the groups, sample size would most probably have to be increased dramatically to detect significant differences between the groups. To enable a thorough comparison between the two groups, we substantially increased sensitivity for detecting (even small) differences by using a hypothesis-based approach (small volume correction) in which only voxels in regions hypothesized to be involved in AVH were tested for differences between the groups. Sensitivity was increased as this analysis dramatically decreases the number of comparisons in comparison to testing for all the voxels in the brain. Finally, a limitation of this study is that both groups were highly selected and can therefore not readily be generalized to psychotic and non-psychotic individuals in the general population.

In summary, during the experience of AVH, psychotic and non-psychotic individuals activated a common set of brain regions, implicating the involvement of the same cortical network in the experience of AVH in both groups.

References

1. Sigdwick H, Johnson A, Myers FWH, Podmore F, Sigdwick E. *Report on the Census of Hallucinations. In: Proceedings of the Society for Psychical Research. London: Kegan Paul, Trench, Trübner & Co* Vol XXVI; 1894.
2. Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, Day R. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med* Nov 1986;16(4):909-928.
3. Tien AY. Distributions of Hallucinations in the Population. *Soc Psychiatry Psychiatr Epidemiol* 1991;26:287-292.
4. Sommer IE, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MP. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. *Schizophr Bull* May 2008;36(3):633-641.
5. Johns LC, Nazroo JY, Bebbington P, Kuipers E. Occurrence of hallucinatory experiences in a community sample and ethnic variations. *Br J Psychiatry* Feb 2002;180:174-178.
6. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? *Schizophr Res* Sep 29 2000;45(1-2):11-20.
7. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* Feb 2009;39(2):179-195.
8. Honig A, Romme MA, Ensink BJ, Escher SD, Pennings MH, deVries MW. Auditory hallucinations: a comparison between patients and nonpatients. *J Nerv Ment Dis* Oct 1998;186(10):646-651.
9. Daalman K, Boks MP, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IE. The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *J Clin Psychiatry* Mar 2011;72(3):320-325.
10. David AS. Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychol Med* Dec 2010;40(12):1935-1942.
11. Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev* 2008;32(1):175-191.
12. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IE. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry* Apr 2010;167(4):427-435.
13. Jardri R, Pouchet A, Pins D, Thomas P. Cortical Activations During Auditory Verbal Hallucinations in Schizophrenia: A Coordinate-Based Meta-Analysis. *Am J Psychiatry* Oct 15 2010.
14. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.
15. Linden DE, Thornton K, Kuswanto CN, Johnston SJ, van de Ven V, Jackson MC. The Brain's Voices: Comparing Nonclinical Auditory Hallucinations and Imagery. *Cereb Cortex* Jun 7 2010.
16. Diederen KM, De Weijer AD, Daalman K, Blom JD, Neggers SF, Kahn RS, Sommer IE. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. *Brain* Dec 2010;133(Pt 12):3734-3744.
17. van Lutterveld R, Oranje B, Kemner C, et al. Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations. *Schizophr Res* Aug 2010;121(1-3):153-159.
18. Laroi F, Marczewski P, Van der Linden M. Further evidence of the multi-dimensionality of hallucinatory predisposition: factor structure of a modified version of the Launay-Slade Hallucinations Scale in a normal sample. *Eur Psychiatry* Feb 2004;19(1):15-20.

19. Slotema CW. Can low-frequency repetitive Transcranial Magnetic Stimulation really relieve medication-resistant Auditory Verbal Hallucinations? Negative results from a large Randomized Controlled Trial *Biol Psychiatry* in press.

20. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.

21. First MB, Spitzer RL, Gibbon M, Williams JBW. The Structured Clinical Interview for Dsm-Iii-R Personality-Disorders (Scid-Ii) .1. Description. *J Pers Disord* 1995;9:83-91.

22. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 1991;17(4):555-564.

23. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* Jun 1976;33(6):766-771.

24. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.

25. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* Jul 1999;29(4):879-889.

26. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.

27. Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited--again. *Neuroimage* Sep 1995;2(3):173-181.

28. Nichols T, Brett M, Andersson J, Wager T, Poline JB. Valid conjunction inference with the minimum statistic. *Neuroimage* Apr 15 2005;25(3):653-660.

29. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* Jan 2002;15(1):273-289.

30. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* Apr 2002;15(4):870-878.

31. Jansen A, Menke R, Sommer J, Forster AF, Bruchmann S, Hempleman J, Weber B, Knecht S. The assessment of hemispheric lateralization in functional MRI--robustness and reproducibility. *Neuroimage* Oct 15 2006;33(1):204-217.

32. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* Nov 2000;57(11):1033-1038.

33. Frith C. Positron emission tomography studies of frontal lobe function: relevance to psychiatric disease. *Ciba Found Symp* 1991;163:181-191; discussion 191-187.

34. Frith C, Done J. Positive symptoms of schizophrenia. *Br J Psychiatry* Apr 1989;154:569-570.

35. Price CJ. The anatomy of language: a review of 100 fMRI studies published in 2009. *Ann N Y Acad Sci* Mar 2010;1191:62-88.

36. Ferstl EC, Neumann J, Bogler C, von Cramon DY. The extended language network: a meta-analysis of neuroimaging studies on text comprehension. *Hum Brain Mapp* May 2008;29(5):581-593.

37. Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 2002;25:151-188.

38. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* Jan 2000;12(1):1-47.

39. Allen P, Aleman A, McGuire PK. Inner speech models of auditory verbal hallucinations: evidence from behavioural and neuroimaging studies. *Int Rev Psychiatry* Aug 2007;19(4):407-415.

40. Waters F, Woodward T, Allen P, Aleman A, Sommer I. Self-recognition Deficits in Schizophrenia Patients With Auditory Hallucinations: A Meta-analysis of the Literature. *Schizophr Bull* Dec 8 2010.

41. Sommer IE, Diederen KM. Language production in the non-dominant hemisphere as a potential source of auditory verbal hallucinations. *Brain* 2009;awp040-.

42. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* Aug 2005;36(8):1759-1763.

43. Van Lancker D, Cummings JL. Expletives: neurolinguistic and neurobehavioral perspectives on swearing. *Brain Res Brain Res Rev* Dec 1999;31(1):83-104.

44. Lennox BR, Park SB, Jones PB, Morris PG. Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* Feb 20 1999;353(9153):644.

45. Copolov DL, Seal ML, Maruff P, Ulusoy R, Wong MT, Tochon-Danguy HJ, Egan GF. Cortical activation associated with the experience of auditory hallucinations and perception of human speech in schizophrenia: a PET correlation study. *Psychiatry Res* Apr 1 2003;122(3):139-152.

46. Waters FA, Badcock JC, Michie PT, Maybery MT. Auditory hallucinations in schizophrenia: intrusive thoughts and forgotten memories. *Cogn Neuropsychiatry* Jan 2006;11(1):65-83.

47. Hoffman RE, Anderson AW, Varanko M, Gore JC, Hampson M. Time course of regional brain activation associated with onset of auditory/verbal hallucinations. *Br J Psychiatry* Nov 2008;193(5):424-425.

48. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. *Neuroimage* Apr 15 2010;50(3):1313-1319.

49. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* Mar 2002;3(3):201-215.

50. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* Jul 12 2001;412(6843):150-157.

51. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods* Aug 30 2002;118(2):115-128.

Part II

Trait studies

Chapter 7

Decreased language lateralization is characteristic of psychosis, not auditory hallucinations

Kelly MJ Diederen[1]
Antoin D De Weijer[1]
Kirstin Daalman[1]
Jan Dirk Blom[2,3]
Sebastiaan FW Neggers[1]
René S Kahn[1]
Iris EC Sommer[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands
[2]Parnassia Bavo Group, The Hague, the Netherlands
[3]Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

Brain (2010) 133 (12): 3734-3744

Abstract

Introduction

Decreased language lateralization is a well-replicated finding in psychotic patients. It is currently unclear, however, whether this abnormality is related to a particular symptom of psychosis or to psychosis in general. It has been argued that decreased language lateralization may be related to auditory verbal hallucinations (AVH). To elucidate this, these hallucinations should be studied in isolation.

Methods

Thirty-five patients with a psychotic disorder, 35 non-psychotic subjects with relatively isolated AVH and 35 healthy control subjects participated in this study. All subjects were scanned on a 3T magnetic resonance imaging scanner, while covertly performing a paced verbal fluency task. In order to measure performance on the task, one additional task block was presented during which subjects had to generate words overtly. In addition to calculating language lateralization indices, group-wise brain activation during verbal fluency was compared between the three groups.

Results

Task performance was nearly maximal for all groups and did not differ significantly between the groups. Compared with the healthy control subjects and non-psychotic subjects with AVH, language lateralization was significantly reduced for the patient group. In addition, the patients displayed significantly greater activity in the right precentral gyrus and left insula when compared with the healthy control subjects and the non-psychotic subjects with AVH. Furthermore, the patients showed greater activity in the right superior parietal lobule when compared with the healthy control subjects. Lateralization indices did not differ significantly between the non-psychotic subjects with AVH and the healthy control subjects. Moreover, there were no significant differences in brain activation during verbal fluency between the two non-psychotic groups.

Conclusions

As language lateralization was not significantly reduced in the non-psychotic individuals with AVH, a direct relationship between AVH and decreased language lateralization can not be established at present.

1. Introduction

Psychosis is a psychiatric syndrome with hallucinations and delusions as its core symptoms. While the biological substrate of psychosis remains elusive, a few functional brain abnormalities have consistently been reported. One of these well-replicated findings is decreased language lateralization in patients with psychosis [1, 2].

Thus far, the majority of studies on language lateralization mainly or exclusively included psychotic patients with schizophrenia [3-14]. However, schizophrenia is a complex syndrome comprising positive, negative and cognitive symptoms. It is currently unclear whether decreased left-hemispheric dominance for language is related to any particular symptom or symptom cluster of schizophrenia.

In fact, decreased language lateralization was also observed in patients with psychotic depression and psychotic mania during the performance of verbal fluency tasks [15], which suggests an association between psychosis *per se* and decreased language lateralization. Moreover, some studies reported an inverse correlation between the degree of language lateralization and the severity of AVH, thus suggesting a relation between decreased language lateralization and AVH [7, 12, 16], although it should be noted that these results are inconsistent [8, 15]. In addition, neuroimaging studies investigating brain activation during AVH in patients with psychosis showed language-related activation in various brain areas, including the bilateral, inferior frontal gyri, insula and temporoparietal language regions, which is suggestive of a relation between language dysfunction and AVH [17-24].

While the existence of a direct relationship between AVH and decreased language lateralization has been hypothesized, the presence of such a relationship must still be established. To achieve this, AVH should be studied in (relative) isolation. Previous studies have shown that AVH also occur in non-clinical subjects [25-27], in the absence of delusions and negative or cognitive symptoms and in the absence of any use of antipsychotic medication. To elucidate the existence of a direct link between decreased language lateralization and AVH, this study compared language lateralization in non-psychotic subjects with frequent AVH to healthy control subjects without AVH and to psychotic patients experiencing AVH. A verbal fluency task was used to quantify language lateralization as this task has frequently been used in previous studies [5-9, 11, 12]. It was hypothesized that psychotic, as well as non-psychotic subjects with AVH, would display decreased language lateralization in comparison to healthy control subjects.

In addition to studying language lateralization, group-wise brain activation during verbal fluency was compared between the three groups. It was hypothesized that the current study would replicate the results of previous studies that showed that patients with psychosis display functional abnormalities throughout the brain during

the performance of verbal fluency tasks. In these studies, hypoactivation was mainly observed in left hemisphere brain regions and hyperactivation in right hemisphere regions [5, 28-36].

2. Methods

2.1. Subjects

Thirty-five patients with a psychotic disorder, 35 non-psychotic subjects with AVH and 35 healthy control subjects participated in this study. Healthy control subjects and non-psychotic subjects with AVH were recruited via a website (www.verkenuwgeest.nl; 'explore your mind'). Sommer et al. [27] provide an extended description of the recruitment and selection procedure. In short, visitors of this website were invited to fill out a questionnaire based on the Launay Slade Hallucination Scale [37], a self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals. Subjects with high scores on items 8 and 12 of the Launay Slade Hallucination Scale (item 8: 'In the past, I have had the experience of a person's voice and then found that no-one was there' and item 12: 'I have been troubled by hearing voices in my head') were selected for participation in the group of subjects with AVH. Subjects with low scores on items 8 and 12 were selected as healthy control subjects. After initial selection subjects were invited to the hospital to undergo detailed psychiatric assessment. Subjects were included if they met the following inclusion criteria: (i) the absence of a psychiatric disorder other than anxiety or depressive disorder in full remission, as assessed by a psychiatrist using the Comprehensive Assessment of Symptoms and History interview (CASH) [38] and the Structured Clinical Interview for personality Disorder (SCID-II) [39]; no alcohol or drug abuse for at least 3 months prior to the assessments; (iii) no chronic somatic disorder; (iv) voices were distinct from thoughts and had a perceptual i.e. 'hearing' quality; (v) voices were experienced at least once a month; and (vi) a history of drug or alcohol abuse did not precede the first experience of voices. Although the individuals with hallucinations did not have any clinical delusions, they did score significantly higher on the Schizotypal Personality Questionnaire compared with a group of matched healthy control subjects [27, 40]. In addition, 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-IV criteria for schizotypal personality disorder. However, social capacity and affect were found to be adequate. Non-psychotic subjects with AVH were not diagnosed as 'Psychosis Not Otherwise Specified' as they were not bothered by these hallucinations and did not present with social or professional dysfunction. To confirm the absence of drug abuse, urine samples were collected and tested for opiates, amphetamines/Ecstasy, cocaine and cannabis.

In addition to the healthy control subjects and the non-psychotic subjects with AVH, 35 patients with a psychotic disorder were recruited from the Department of Psychiatry, University Medical Center Utrecht and the Parnassia Bavo Group in The Hague, the Netherlands. For these patients the following inclusion criteria were used: (i) voices had to be distinct from thoughts and have a perceptual quality; voices were experienced at least once a month; (iii) no alcohol or drugs abuse was present for at least 3 months prior to the scan; and (iv) patients did not have a chronic somatic disorder. Patients were diagnosed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History interview. DSM-IV diagnoses and medication use of the patients and a demographical description of all participants is provided in Table 1. Nine of the psychotic patients did not want to be treated with antipsychotic medication and did not meet criteria for involuntary treatment. The three groups did not differ significantly with respect to age, sex and handedness, however years of education were significantly lower for the patients with psychosis compared with the control subjects and the non-psychotic subjects with AVH. This study was approved by the Humans Ethics Committee of the University Medical Center, Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Clinical evaluation

The level of global functioning was assessed with the Global Assessment of Functioning scale (GAF) [41]. In addition, to assess if differences in characteristics of the voices were present between the non-psychotic subjects with auditory verbal hallucinations and the patients with psychosis, the Psychotic Symptom Rating Scales (PSYRATS) [42] were used. The Psychotic Symptom Rating Scales examines frequency, duration per hallucination, location (inside and/or outside the head), loudness, explanation about the origin of the AVH, emotional content (positive/negative), degree of negative content, number of positive versus negative voices, controllability, distress and the age at which subjects first experienced AVH. The variable 'emotional valence of content' was operationalized as the sum of three items from the Psychotic Symptom Rating Scales: 'amount of negative content of voices', 'degree of negative content' and 'amount of distress'. The variable 'total distress' was operationalized as the sum of two items from the Psychotic Symptom Rating Scales: 'intensity of distress' and 'disruption to life caused by voices'. Furthermore, in the patient group the Positive and Negative Syndrome Scale (PANNS) [43] was used to assess symptoms.

Univariate analysis of variance (ANOVA) was used to assess difference in global functioning. Multivariate analysis of variance (MANOVA) was used to test for differences in characteristics of the voices between the groups. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows, version 15.0. All

analyses were thresholded at $P = 0.05$. For *post hoc* testing Bonferroni correction was applied or Tukey tests were used.

Table 1. Description of the participants

	Healthy control subjects			*Non-psychotic subjects with AVH*			Psychotic Patients			
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Statistics**
Subjects	35			35			35			
Age		41.71	14.12		44.26	13.06		43.60	11.19	F(2) =.37, P = .692
Male/ female	12/23			11/24						$\chi^2(2) = .000$, P = 1
Right-handed/ non-right-handed	29/6			29/6			29/6			$\chi^2(2) = .087$, P = 1
Main effect years of education		5.94	2.25		5.86	1.65		4.56	1.76	F(2) = 5.69, P = .005**
Post hoc tests										
Control subjects and non-psychotic subjects with AVH		5.94	2.25		5.86	1.65				P = .981
Control subjects and psychotic patients		5.94	2.25					4.56	1.76	P = .009**
Non-psychotic subjects with AVH and psychotic patients					5.86	1.65		4.56	1.76	P = .015*
Diagnosis										
Schizophrenia							26			
Schizoaffective Disorder							2			
Psychosis NOS							8			
Antipsychotic medication										
Classic antipsychotic							9			
Atypical antipsychotic							17			

* = significant at P < 0.05, ** = significant at P < 0.01. Abbreviations: AVH, auditory verbal hallucinations; Psychotic patients, patients diagnosed with a psychotic disorder based on DSM-IV criteria by an independent psychiatrist; N, number; SD, standard deviation; Psychosis NOS, psychosis not otherwise specified

2.3. Experimental task and data acquisition

While in the scanner, language activation was measured during 8 min in which a paced verbal fluency task was presented. Participants were asked to covertly generate a word starting with a letter displayed on the screen placed in front of them. Letters were presented in eight activation blocks, each block lasting 30 s. In each activation

block 10 letters were displayed at a rate of one every 3 s. The letters X, Q and C were excluded since it is relatively difficult to form words with these letters. The baseline condition consisted of a cross projected on the screen in order to correct for visual input. After the 8 min language task, one additional task block was presented, in which subjects had to generate words overtly. This block was used to measure behavioural performance of the subjects while they were in the scanner.

Activation maps were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. Eight hundred blood oxygenation level-dependent functional MRI images were acquired with the following parameter settings: 40 (coronal) slices, repetition time/echo time 21.75/32.4 ms, flip angle 10°, field of view 224 × 256 × 160, matrix 64 × 64 × 40, voxel size 4 mm isotropic. This scan sequence achieves full-brain coverage within 609 ms by combining a principles of echo shifting with a train of observations (3D-PRESTO) pulse sequence with parallel imaging [sensitivity encoding (SENSE)] in two directions [44], using a commercial 8-channel SENSE headcoil. Since these PRESTO SENSE images have little anatomical contrast, 40 identical scans, but with a flip angle of 27° rendering a better anatomical contrast were acquired to improve realignment and co-registration during the preprocessing. After the functional scans a high resolution anatomical scan was acquired to improve localization of the functional data using the following parameters: repetition time/echo time 9.86/4.6 ms, 0.875 × 0.875 × 1 voxels, flip angle 8°, field of view 224 × 160 × 168, 160 slices.

2.4. Functional magnetic resonance imaging pre-processing and analysis

Functional MRI data were analysed using statistical parametric mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK). Preprocessing included within-subject image realignment with the mean of the 40 scans with a flip angle of 27° as the reference to correct for the effects of head motion, co-registration of the mean of the 40 scans with a flip angle of 27° and the T_1-weighted anatomical image and spatial normalization to a standard Montreal Neurological Institute template. Finally, images were smoothed using an 8 mm full width at half maximum Gaussian kernel.

For the verbal fluency paradigm a model was created to contrast activity during presentation of the letter fluency versus baseline blocks. Functional images were analyzed on a voxel by voxel basis using multiple regression analysis [45] with one factor coding for activation (task versus rest).

2.5. Language lateralization

Lateralization indices were calculated on individual first level analyses. For this purpose, a mask was created using the Anatomical Automatic Labeling atlas [22, 46] comprising

the main areas where language processing is thought to be mediated as well as their contralateral homologues [22]. Language areas consisted of the bilateral inferior frontal triangle, the bilateral insula, the middle temporal gyrus, the superior temporal gyrus, the supramarginal gyrus and the angular gyrus. Lateralization indices were defined as the difference in 'thresholded' signal intensity changes in the left versus the right hemisphere (within the selected language regions) divided by the total sum of 'thresholded' signal intensity changes. Using this method, activity measures are based on signal intensity changes in those voxels that exceed a predefined activation level, as recommended by Jansen et al. [47] as a more suitable way to calculate cerebral lateralization than simple activated voxel-count hemispheric difference measures. This method yields lateralization indices between 1 (indicating strong left-hemisphere dominance) and −1 (indicating strong right-hemisphere dominance). Thresholds for calculating lateralization indices were set at $P = 0.05$, Family Wise Error corrected for all voxels within the language mask. Between-group differences in lateralization indices were assessed with an ANOVA. To explore correlations between lateralization indices and item P3 of the Positive and Negative Syndrome Scale, i.e. hallucinatory behaviour in the patient group, a Spearman correlation was calculated. Statistical analyses were performed using SPSS for Windows, version 15.0. All analyses, except for *post hoc* tests, were thresholded at $P = 0.05$. The Tukey test was used for *post hoc* testing.

2.6. Group-wise activation during verbal fluency

Group-wise activation during the verbal fluency task was assessed with a one sample *t*-test in which the three groups were combined. To test if the three groups displayed differences in brain activation during the verbal fluency task a univariate analysis of variance was specified using the full-factorial option of SPM5. For this ANOVA, one factor 'between-group' was specified with three independent levels (healthy control subjects, non-psychotic subjects with AVH and psychotic patients) with unequal variance. All analyses were thresholded at $P = 0.05$, whole-brain Family Wise Error corrected, with an extended threshold of 4 voxels. Bonferroni correction was applied for *post hoc* testing.

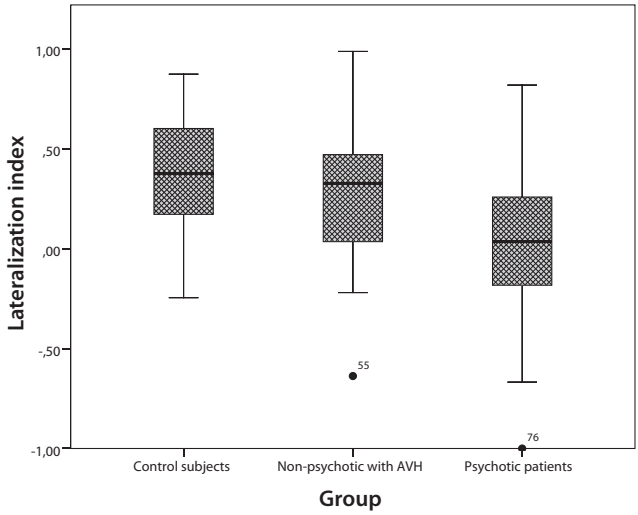
3. Results

3.1. Clinical evaluation

Thirty-two patients completed the Positive and Negative Syndrome Scale interview. This interview revealed that patients were chronically psychotic with a mean total score of 62.8 (SD 15.4) and average scores of 16.2 (SD 3.8) on the positive subscale, 16.4 (SD 4.9) on the negative subscale and 30.7 (SD 8.8) on the scale assessing general psychopathology.

Global Assessment of Functioning scores could be obtained in 34 control subjects, 34 non-psychotic subjects with AVH and in 34 patients. The between-group ANOVA with Global Assessment of Functioning scale score as the independent variable showed a main effect of group [$F(2) = 200$, $P < 0.001$]. *Post hoc* (Tukey) tests revealed that the control subjects differed significantly from the non-psychotic subjects with AVH ($P = 0.043$), the control subjects differed significantly from the patients ($P < 0.001$) and the non-psychotic subjects with AVH differed significantly from the patients ($P < 0.001$). Inspection of the mean scores indicated that, of the three groups, the patients (mean 50.22; SD 10.64) scored lowest on the Global Assessment of Functioning scale. In addition, non-psychotic subjects with AVH (mean = 82.53; SD 7.46) scored significantly lower on the Global Assessment of Functioning scale than the control subjects (mean 87.35; SD 5.80).

Figure 1. Box plots showing the lateralization indices of the healthy control subjects, the non-psychotic subjects with AVH and the patients.

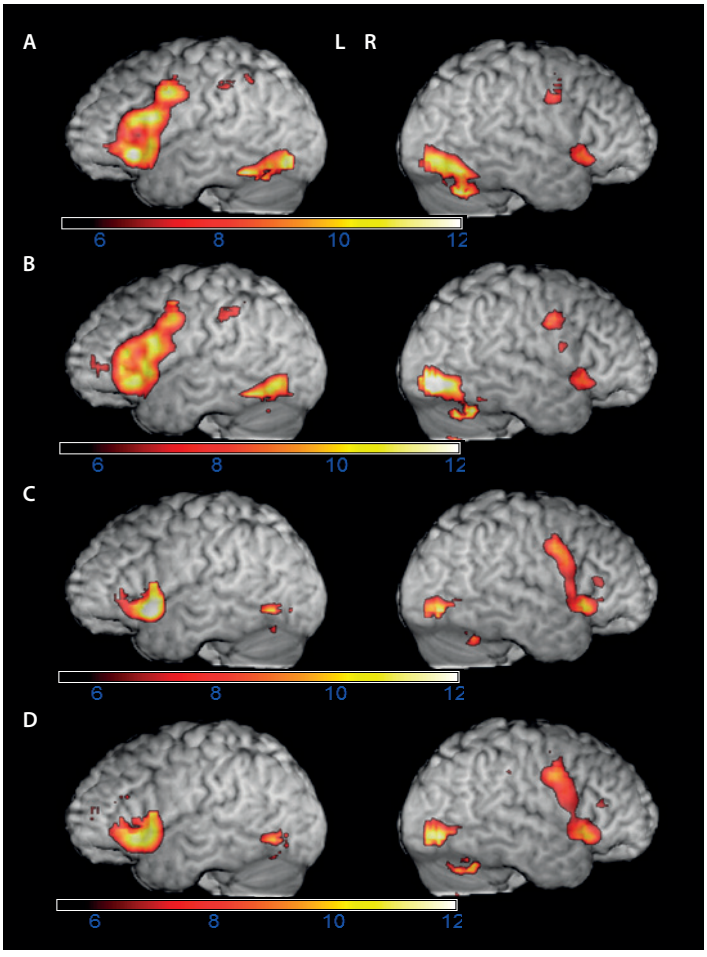


The boxes contain the middle 50% of the data. The lower and upper edges of the boxes indicate the 25th and 75th percentile of the data set. The lines in the boxes indicate the median value. The whiskers, i.e. ends of the vertical line, indicate the minimum and maximum values, unless outliers are present. Subjects 55 and 76, indicated by black dots, are non-significant outliers. Abbreviations: AVH, auditory verbal hallucinations

The between-group multivariate analysis of variance with the items of the Psychotic Symptom Rating Scales as the dependent variables revealed a significant difference between non-psychotic subjects with AVH and psychotic patients [$F(10, 259) = 22.359$, $P < 0.001$]. When the results for the dependent variables were considered separately, a significant difference was found for frequency, duration, emotional valence of content,

controllability and total distress using a Bonferroni adjusted alpha level of 0.005. Patients scored significantly higher on these items. No significant differences were found for location (i.e. inside/outside the head), loudness, number of different voices and explanation about the origin of the AVH. Means, standard deviation and statistical tests for the Psychotic Symptom Rating Scales are displayed in table 2.

Figure 2. One sample t-tests during verbal fluency.



(A) SPM t-values for the healthy control subjects (B) SPM t-values for the non-psychotic subjects with AVH (C) SPM t-values for the patients with psychosis (D) SPM t-values for the three groups collapsed.

Thresholded at P = 0.05, Family Wise Error corrected with an extended threshold of 4 voxels. Abbreviations: AVH, auditory verbal hallucinations; L, left; R, right.

Table 2. Comparison of hallucination characteristics in patients and non- psychotic subjects with AVH

	Non-psychotic subjects with AVH	*Psychotic patients*	*Non-psychotic subjects with AVH*			Psychotic patients			
AVH characteristics	**Description of mean**	**Description of mean**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Statistics**
Frequency	AVH almost every day	AVH (almost) all the time	32	3.75	1.24	30	5.37	0.81	F(1)=36.26, P < 0.001**
Duration	A few minutes	An hour	32	1.88	.87	30	2.83	1.18	F(1)=13.40, P < 0.001**
Location	Inside head, and near ears	Mostly inside head. Outside head, near ears also possible	32	2.19	1.12	30	1.93	1.05	F(1)=.85, P = 0.361
Intensity (volume)	Little softer than own voice	Same volume as own voice	32	1.88	0.55	30	2.07	.98	F(1)=.91, P = 0.343
Explanation of origin	> 50 % external	= 50 % external	32	3.16	1.02	30	2.37	1.19	F(1)=7.91, P = 0.007**
Emotional Valence	Seldom unpleasant voices/content	Majority of voices is unpleasant and/or annoying	32	1.31	2.73	30	8.93	2.43	F(1)=133.97, P < 0.001**
Total Distress	Almost no discomfort, almost no disruption of daily life	Moderate to severe distress and disruption of daily life	32	.44	1.01	30	5.30	1.70	F(1)=189.08, P < 0.001**
Controllability	>50 % of the time	Very sporadically	32	1.53	1.69	30	2.73	1.29	F(1)=9.88, P = 0.003**
N different voices (max. 100)	8.03	23.50	32	8.03	17.73	30	23.50	36.90	F(1)=4.52, P = 0.038*

* = significant at P < 0.05, ** = significant at P < 0.01. Abbreviations: AVH, auditory verbal hallucinations; Psychotic patients, patients diagnosed with a psychotic disorder based on DSM-IV criteria by an independent psychiatrist; N, number; SD, standard deviation; max., maximally.

Table 3. Cluster sizes, P-values, T-values and locations of local maxima for brain activity during verbal fluency comprising the healthy control subjects, the non-psychotic subjects with AVH and the patients with psychosis

clustersize	*P-value*	*T-value*	*MNI coordinates*		
603	<0,001	21,70	-32 24 0	Left Sub-lobar	Insula
	<0,001	18,39	-48 12 4	Left Frontal Lobe	Precentral Gyrus
	<0,001	13,20	-48 32 12	Left Frontal Lobe	Inferior Frontal Gyrus
684	<0,001	21,04	40 -80 -4	Right Occipital Lobe	Inferior Occipital Gyrus
	<0,001	16,87	-40 -68 -8	Left Temporal Lobe	Fusiform Gyrus
	<0,001	13,40	36 -60 -12	Right Cerebellum	Posterior Lobe
	<0,001	13,09	-36 -60 -24	Left Cerebellum	Anterior Lobe
	<0,001	7,33	-52 -40 4	Left Temporal Lobe	Middle Temporal Gyrus
211	<0,001	18,38	-8 16 40	Left Limbic Lobe	Cingulate Gyrus
	<0,001	18,00	4 16 44	Right Frontal Lobe	Medial Frontal Gyrus
666	<0,001	18,11	36 20 4	Right Sub-lobar	Insula
	<0,001	14,85	52 0 44	Right Frontal Lobe	Precentral Gyrus
	<0,001	12,78	44 4 28	Right Frontal Lobe	Inferior Frontal Gyrus
	<0,001	9,03	40 32 20	Right Frontal Lobe	Middle Frontal Gyrus
94	<0,001	15,10	-28 -60 48	Left Parietal Lobe	Superior Parietal Lobule
	<0,001	14,55	-32 -48 40	Left Parietal Lobe	Inferior Parietal Lobule
261	<0,001	13,85	32 -60 52	Right Parietal Lobe	Superior Parietal Lobule
	<0,001	10,90	44 -36 44	Right Parietal Lobe	Inferior Parietal Lobule
22	<0,001	12,25	-24 -4 48	Left Frontal Lobe	Middle Frontal Gyrus
14	<0,001	11,58	-48 28 28	Left Frontal Lobe	Middle Frontal Gyrus
36	<0,001	8,16	48 -32 0	Right Temporal Lobe	Superior/Middle Temporal Gyrus

Thresholded at P = 0.001, FWE corrected, with an extended threshold of 4 voxels. A threshold of P = 0.001, instead of P = 0.05 was chosen as with the latter activation consisted of one big cluster containing all local maxima. Abbreviations: AVH, auditory verbal hallucinations; Psychotic patients, patients diagnosed with a psychotic disorder based on DSM-IV criteria by an independent psychiatrist; MNI, Montreal Neurological Institute; FWE, Family Wise Error

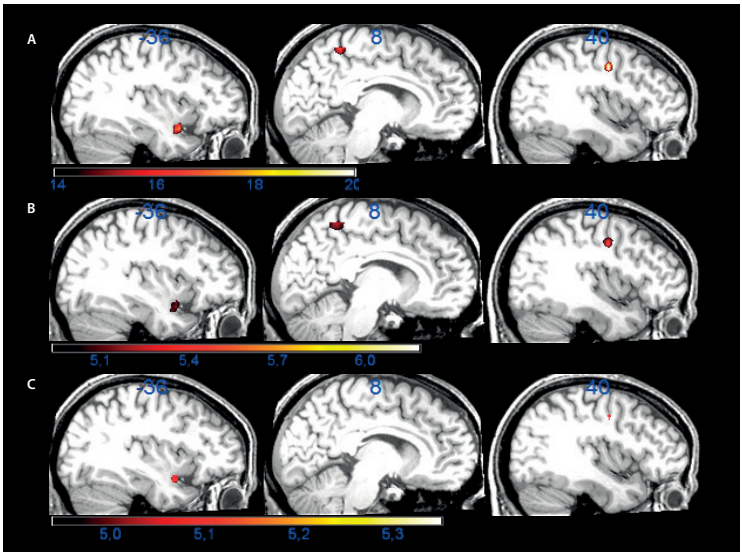
3.2. Performance

Performance on the language task was available in 22 healthy control subjects, 23 non-psychotic subjects with AVH and 31 patients with psychosis. Performance was not available in the other subjects as there was no time for an additional task block during these scans. The mean percentage correct performance was 98.9 (SD 3.1) for the healthy control subjects, 99.8 (SD 1.0) for the non-psychotic subjects with AVH and 96.8 (SD 0.4) for the patients with psychosis. There was no significant main effect for task performance ($U = 5.07$, $P = 0.08$).

3.3. Lateralization indices

The mean lateralization index was 0.35 (SD 0.29) for the healthy control subjects, 0.27 (SD 0.33) for the non-psychotic subjects with AVH and 0.02 (SD 0.38) for the patients with psychosis. The ANOVA with lateralization index as the dependent variable and group as the fixed factor revealed a significant effect for group [$F(2) = 9.33$, $P < 0.001$). *Post hoc t*-tests showed that the lateralization indices were significantly lower for the patients compared with the healthy control subjects ($P < 0.001$) as well as for the patients compared with the non-psychotic subjects with AVH ($P = 0.006$). The healthy control subjects and the non-psychotic subjects with AVH did not differ significantly ($P = 0.599$). Figure 1 shows box plots for the lateralization indices of the healthy control subjects, the non-psychotic subjects with AVH and the patients. In addition, there was no significant correlation between the score on item P3 of the Positive and Negative Syndrome Scale, i.e. hallucinatory behaviour and lateralization indices in the patients with psychosis (Spearman's $\rho = -0.090$, $P = 0.630$).

Figure 3. ANOVA with 'group' as the independent variable and 'activity during verbal fluency' as the dependent variable.



(A) SPM F-values for the main effect of between-group differences during verbal fluency (B) Post hoc SPM t-values for the psychotic patients - healthy control subjects (C) Post hoc SPM t-values for patients with psychosis - non-psychotic subjects with AVH.

Threshold: P = 0.05, Family Wise Error corrected. For post hoc testing Bonferroni correction was applied. Abbreviations: ANOVA, univariate analysis of variance; AVH, auditory verbal hallucinations; L, left; R, right.

3.4. Group-wise activation during verbal fluency

The one sample *t*-test comprising the three groups revealed activation of multiple language regions, including the bilateral inferior frontal gyri, insula, middle/superior temporal gyri and inferior parietal gyri during verbal fluency. Table 3 shows the coordinates, *t*-values and cluster size of all significantly local maxima for the three groups collapsed. Figure 2 shows SPM *t*-values of all the significant local maxima for the healthy control subjects, the non-psychotic subjects with AVH, the patients with psychosis and the three groups collapsed. The ANOVA revealed a main effect of group in the right precentral gyrus, the right superior parietal lobule and the left insula.

In addition, increased activation in the patients compared with the healthy control subjects was found in the right superior parietal lobule. No significant differences in brain activation were present when the healthy control subjects were compared with the non-psychotic subjects with AVH. Figure 3 shows the SPM *F*-values for the main effect of group differences and *post hoc* SPM *t*-values for the psychotic patients and healthy control subjects and the psychotic patients and the non-psychotic subjects with AVH. Table 4 lists the coordinates, *F*-values, *t*-values and cluster sizes for the main effect of group and the *post hoc* tests.

Table 4. Cluster sizes, P-values, F/T-values and locations of local maxima for the ANOVA with group as the independent and brain activity during verbal fluency as the dependent variable

clustersize	*P-value*	*F-value/T-value*	*MNI coordinates*		
Main effect between-group F-value					
6	0,001	19,94	40 -8 48	Right Frontal Lobe	Precentral Gyrus
6	0,003	17,59	-36 4 -12	Left Sub-lobar	Insula
8	0,006	16,79	8 -48 64	Right Parietal Lobe	Superior Parietal Lobule
5	0,013	15,86	4 -44 52	Right Parietal Lobe	Superior Parietal Lobule
Post-hoc patients – Healthy control subjects T-value					
11	<0.001	6,18	36 -8 44	Right Frontal Lobe	Precentral Gyrus
24	0,001	5,77	8 -48 64	Right Parietal Lobe	Superior Parietal Lobule
7	0,001	5,68	24 -44 64	Right Parietal Lobe	Superior Parietal Lobule
5	0,002	5,49	-36 4 -8	Left Sub-lobar	Insula
Post-hoc patients – Non-psychotic subjects with AVH T-value					
5	0,003	5,35	-36 0 -12	Left Sub-lobar	Insula
4	0,004	5,32	40 -8 48	Right Frontal Lobe	Precentral Gyrus

Main effect between-group thresholded at P = 0.05, FWE corrected, with an extended threshold of 4 voxels, Post-hoc tests thresholded at P = 0.0167, FWE corrected, with an extended threshold of 4 voxels.
Abbreviations: ANOVA, univariate analysis of variance; AVH, auditory verbal hallucinations; MNI, Montreal Neurological Institute; FWE, Family Wise Error

4. Discussion

This study focused on comparing language lateralization between patients with psychosis, non-psychotic subjects with auditory verbal hallucinations (AVH) and healthy control subjects. As a number of previous studies suggested a direct link between AVH and decreased language lateralization, this study investigated language lateralization in non-psychotic subjects who experience AVH in relative isolation. Non-psychotic individuals with AVH were considered to hold an intermediate position on an AVH continuum, with healthy individuals at one end and individuals with a psychotic disorder at the other. Being an intermediate on this continuum, these individuals are expected to be affected to some extent as expressed by the presence of sub-clinical levels of suspicion, formal thought disorder, a tendency for magical ideation and a somewhat lower Global Assessment of Functioning scale score. It was hypothesized that patients with psychosis as well as non-psychotic subjects with AVH would display decreased language lateralization in comparison to healthy control subjects. Contrary to this hypothesis, non-psychotic subjects with AVH did not show decreased language lateralization in comparison to the healthy control subjects. In contrast, lateralization was significantly reduced for the patients with psychosis in comparison to both the non-psychotic subjects with AVH and the healthy control subjects. Reduced left-hemispheric dominance for language in patients with psychosis is in line with previous studies [3-14]. The absence of decreased language lateralization in non-psychotic subjects with AVH argues against a direct relation between decreased language lateralization and AVH. As decreased language lateralization is not only present in psychotic patients with schizophrenia, but also in patients with psychotic depression and psychotic mania [15], this abnormality is presumably related to psychosis in general. Moreover, decreased language lateralization was also observed in non-psychotic monozygotic twins with schizophrenic co-twins, as well as in subjects at high genetic risk for psychosis [9, 48], which might indicate that this abnormality is a trait, i.e. a genetic predisposition, for psychosis. Speculating on these results, non-psychotic individuals with AVH may share their predisposition to hallucinate with psychotic patients, but may lack other psychosis-related factors such as decreased language lateralization. Furthermore, differences in language lateralization between the patients with psychosis and the non-psychotic subjects with AVH may be related to different characteristics of the voices in these groups. Voices in the non-psychotic subjects with AVH differed from the voices in the psychotic patients with respect to frequency, duration, emotional valence of content, controllability and total distress experienced by the voices. This is in concordance with a previous study in which over 100 non-psychotic subjects with AVH were compared with patients with psychosis [49].

They reported that voices in patients with psychosis differ from voices in non-psychotic subjects with AVH with respect to the emotional valence of the content, the frequency of AVH, the degree of control subjects had over their AVH and the age at which subjects heard voices for the first time. However, other characteristics such as voices heard inside or outside the head, loudness and number of voices were similar for both groups.

In addition to comparing language lateralization between the psychotic patients, the non-psychotic subjects with AVH and the healthy control subjects, group-wise brain activation during verbal fluency was compared between the three groups. No significant differences in brain activation were observed between non-psychotic subjects with AVH and healthy control subjects. However, the patients differed significantly from both the healthy control subjects and the non-psychotic subjects with AVH. In comparison to both groups, patients with psychosis displayed increased activation in the right precentral gyrus and left insula during the verbal fluency task. In addition, as compared with the healthy control subjects, the patients showed increased activation in the right superior parietal lobule. Hyperactivation in the left insula, as observed in the present study, in not in concordance with previous studies that mainly reported hypoactivation in left hemisphere brain regions [5, 28-36]. Hyperactivation in the right precentral gyrus and superior parietal lobule is partly in agreement with previous studies [29, 32], but not with others that primarily reported hypoactivations in left-hemisphere brain regions [30, 34, 36]. It has been suggested that task performance can be a confounding factor because poorly performing patients may not generate sufficient words in a verbal fluency task, which will typically result in a bias towards reduced language-related left-frontal activity [28]. When patients are matched for performance, however, no hypoactivation is observed [8, 11, 28].

Interestingly, both the right precentral gyrus and superior parietal lobule, showing significant differences in the patients with psychosis, are not considered to be classic language areas. The right precentral gyrus has primarily been implicated in motor function and the right superior parietal lobule in visuomotor and attention processes [50, 51]. Yet, a review by Vigneau and colleagues [52] showed that activation of the precentral gyrus is frequently reported during verbal fluency and other phonological language tasks. Perhaps activation of this region is related to motor processes involved in language production, such as articulation.

4.1. Limitations

A limitation of the present study is that the usage of antipsychotic medication by many of the patients may have influenced the results. Although Weiss et al. [12] and Razafimandimby et al. [14] showed that reduced language lateralization was also present

in unmedicated patients with schizophrenia, the exact effects of these agents on brain activation during verbal fluency tasks remains unclear.
Another limitation is that performance was not measured in all subjects. However, performance was measured in most (31/35) of the patients with psychosis, in which low performance might have constituted a problem. In addition, while no significant difference in performance was present between the three groups, performance differed on trend level, which may have influenced the results. As the difference was not significant, performance was not entered as a covariate in the analyses. Also, due to the relative simplicity of the task, possible differences in performance between the groups may not have been visible. Finally, a limitation of the applied method for the calculation of lateralization indices is that the chosen significance level could have exerted an influence on the results. However, after calculating lateralization indices using different thresholds ($t = 2$ and $t = 4$), the differences between the three groups remained stable i.e. the patients differed significantly from both the healthy control subjects and the non-psychotic with AVH, while the latter two groups did not differ significantly from one another.

In summary, no decrease in language lateralization was present in non-psychotic subjects with AVH, while patients with psychosis showed decreased language lateralization compared with the healthy control subjects and the non-psychotic subjects with AVH. A direct relationship between AVH and decreased language lateralization can therefore not be established.

References

1. Li X, Branch CA, DeLisi LE. Language pathway abnormalities in schizophrenia: a review of fMRI and other imaging studies. *Curr Opin Psychiatry* Mar 2009;22(2):131-139.
2. Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A. Handedness, language lateralisation and anatomical asymmetry in schizophrenia. *The British Journal of Psychiatry* April 1, 2001 2001;178(4):344-351.
3. Bruder G, Rabinowicz E, Towey J, Brown A, Kaufmann CA, Amador X, Malaspina D, Gorman JM. Smaller right ear (left hemisphere) advantage for dichotic fused words in patients with schizophrenia. *Am J Psychiatry* June 1, 1995 1995;152(6):932-935.
4. Løberg E-M, Hugdahl K, Green MF. Hemispheric asymmetry in schizophrenia: a "dual deficits" model. *Biological Psychiatry* 1999;45(1):76-81.
5. Artiges E, Martinot JL, Verdys M, Attar-Levy D, Mazoyer B, Tzourio N, Giraud MJ, Paillere-Martinot ML. Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophr Bull* 2000;26(3):709-721.
6. Crow TJ. Invited commentary on: Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. *The British Journal of Psychiatry* January 1, 2000 2000;176(1):61-63.
7. Sommer IE, Ramsey NF, Kahn RS. Language lateralization in schizophrenia, an fMRI study. *Schizophr Res* Oct 1 2001;52(1-2):57-67.
8. Sommer IE, Ramsey NF, Mandl RC, Kahn RS. Language lateralization in female patients with schizophrenia: an fMRI study. *Schizophr Res* Apr 1 2003;60(2-3):183-190.
9. Sommer IEC, Ramsey NF, Mandl RCW, Van Oel CJ, Kahn ReS. Language activation in monozygotic twins discordant for schizophrenia. *The British Journal of Psychiatry* February 1, 2004 2004;184(2):128-135.
10. Kircher TT, Liddle PF, Brammer MJ, Williams SC, Murray RM, McGuire PK. Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. *Psychol Med* Apr 2002;32(3):439-449.
11. Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Brinkhoff C, Kremser C, Felber S, Fleischhacker WW. Brain activation patterns during a verbal fluency test-a functional MRI study in healthy volunteers and patients with schizophrenia. *Schizophr Res* Oct 1 2004;70(2-3):287-291.
12. Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Felber S, Fleischhacker WW. Language lateralization in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. *Psychiatry Res* Mar 31 2006;146(2):185-190.
13. Dollfus S, Razafimandimby A, Delamillieure P, Brazo P, Joliot M, Mazoyer B, Tzourio-Mazoyer N. Atypical hemispheric specialization for language in right-handed schizophrenia patients. *Biological Psychiatry* 2005;57(9):1020-1028.
14. Razafimandimby A, Maiza O, Herve PY, et al. Stability of functional language lateralization over time in schizophrenia patients. *Schizophr Res* Aug 2007;94(1-3):197-206.
15. Sommer IE, Vd Veer AJ, Wijkstra J, Boks MP, Kahn RS. Comparing language lateralization in psychotic mania and psychotic depression to schizophrenia; a functional MRI study. *Schizophr Res* Jan 2007;89(1-3):364-365.
16. Levitan C, Ward PB, Catts SV. Superior temporal gyral volumes and laterality correlates of auditory hallucinations in schizophrenia. *Biological Psychiatry* 1999;46(7):955-962.
17. McGuire PK, Murray RM, Shah GMS. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *The Lancet* 1993;342(8873):703-706.
18. Dierks T, Linden DEJ, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W. Activation of Heschl's Gyrus during Auditory Hallucinations. *Neuron* 1999;22(3):615-621.

19. Shergill SS, Brammer MJ, Williams SC, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* Nov 2000;57(11):1033-1038.

20. van de Ven VG, Formisano E, Röder CH, et al. The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *NeuroImage* 2005;27(3):644-655.

21. Hoffman RE, Hampson M, Wu K, et al. Probing the Pathophysiology of Auditory/Verbal Hallucinations by Combining Functional Magnetic Resonance Imaging and Transcranial Magnetic Stimulation. *Cerebral Cortex* November 1, 2007 2007;17(11):2733-2743.

22. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.

23. Sommer IEC, Slotema CW, de Weijer AD, et al. Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? *Schizophrenia Research* 2007;93(1-3):406-408.

24. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IE. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry* Apr 2010;167(4):427-435.

25. Tien AY. Distributions of Hallucinations in the Population. *Soc Psychiatry Psychiatr Epidemiol* 1991;26:287-292.

26. Johns LC, Nazroo JY, Bebbington P, Kuipers E. Occurrence of hallucinatory experiences in a community sample and ethnic variations. *Br J Psychiatry* Feb 2002;180:174-178.

27. Sommer IE, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MP. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. *Schizophr Bull* May 2008;36(3):633-641.

28. Frith CD, Friston KJ, Herold S, et al. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry* Sep 1995;167(3):343-349.

29. Spence SA, Liddle PF, Stefan MD, et al. Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *Br J Psychiatry* Jan 2000;176:52-60.

30. Boksman K, Théberge J, Williamson P, et al. A 4.0-T fMRI study of brain connectivity during word fluency in first-episode schizophrenia. *Schizophrenia Research* 2005;75(2-3):247-263.

31. Yurgelun-Todd DA, Waternaux CM, Cohen BM, Gruber SA, English CD, Renshaw PF. Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. *Am J Psychiatry* February 1, 1996 1996;153(2):200-205.

32. Costafreda SG, Fu CHY, Picchioni M, et al. Increased inferior frontal activation during word generation: A marker of genetic risk for schizophrenia but not bipolar disorder? *Human Brain Mapping* 2009;30(10):3287-3298.

33. Curtis VA, Bullmore ET, Brammer MJ, et al. Attenuated Frontal Activation During a Verbal Fluency Task in Patients With Schizophrenia. *Am J Psychiatry* August 1, 1998 1998;155(8):1056-1063.

34. Jones HM, Brammer MJ, O'Toole M, et al. Cortical effects of quetiapine in first-episode schizophrenia: A preliminary functional magnetic resonance imaging study. *Biological Psychiatry* 2004;56(12):938-942.

35. Schaufelberger M, Senhorini MCT, Barreiros MA, et al. Frontal and anterior cingulate activation during overt verbal fluency in patients with first episode psychosis. *Revista Brasileira de Psiquiatria* 2005;27:228-232.

36. Fu CHY, Suckling J, Williams SCR, Andrew CM, Vythelingum GN, McGuire PK. Effects of Psychotic State and Task Demand on Prefrontal Function in Schizophrenia: An fMRI Study of Overt Verbal Fluency. *Am J Psychiatry* March 1, 2005 2005;162(3):485-494.

37. Laroi F, Marczewski P, Van der Linden M. Further evidence of the multi-dimensionality of hallucinatory predisposition: factor structure of a modified version of the Launay-Slade Hallucinations Scale in a normal sample. *Eur Psychiatry* Feb 2004;19(1):15-20.

38. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.

39. First MB, Spitzer RL, Gibbon M, Williams JBW. The Structured Clinical Interview for Dsm-Iii-R Personality-Disorders (Scid-Ii) .1. Description. *J Pers Disord* 1995;9:83-91.

40. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 1991;17(4):555-564.

41. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment Scale: A Procedure for Measuring Overall Severity of Psychiatric Disturbance. *Arch Gen Psychiatry* June 1, 1976 1976;33(6):766-771.

42. Haddock G, McCarron J, Tarrier N, Faragher EB. Scales to measure dimensions of hallucinations and delusions: the psychotic symptom rating scales (PSYRATS). *Psychol Med* Jul 1999;29(4):879-889.

43. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.

44. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.

45. Worsley KJ, Friston KJ. Analysis of fMRI Time-Series Revisited--Again. *NeuroImage* 1995;2(3):173-181.

46. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* Jan 2002;15(1):273-289.

47. Jansen A, Menke R, Sommer J, Förster AF, Bruchmann S, Hempleman J, Weber B, Knecht S. The assessment of hemispheric lateralization in functional MRI--Robustness and reproducibility. *NeuroImage* 2006;33(1):204-217.

48. Bhojraj TS, Francis AN, Rajarethinam R, et al. Verbal fluency deficits and altered lateralization of language brain areas in individuals genetically predisposed to schizophrenia. *Schizophr Res* Dec 2009;115(2-3):202-208.

49. Daalman K, Boks MP, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IE. The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *J Clin Psychiatry* Mar 2011;72(3):320-325.

50. Corbetta M, Akbudak E, Conturo TE, et al. A Common Network of Functional Areas for Attention and Eye Movements. *Neuron* 1998;21(4):761-773.

51. Culham JC, Kanwisher NG. Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology* 2001;11(2):157-163.

52. Vigneau M, Beaucousin V, Hervé PY, Duffau H, Crivello F, Houdé O, Mazoyer B, Tzourio-Mazoyer N. Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. *NeuroImage* 2006;30(4):1414-1432.

Chapter 8

Aberrant resting state connectivity in non-psychotic individuals with auditory hallucinations

KMJ Diederen[1]
SFW Neggers[1]
AD de Weijer[1]
R van Lutterveld[1]
K Daalman[1]
RS Kahn[1]
IEC Sommer[1]

[1]Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Utrecht, the Netherlands

Manuscript submitted for publication

Abstract

Introduction

Whereas auditory verbal hallucinations (AVH) are a core symptom of schizophrenia, they also occur in non-psychotic individuals, in the absence of other psychotic symptoms, cognitive dysfunction and negative symptoms. Although AVH have been hypothesized to result from deviant integration of frontal, parahippocampal and temporoparietal brain areas, a direct link between dysfunctional connectivity and AVH has, thus far, not been established. To elucidate if hallucinations are indeed related to deviant connectivity, AVH should be studied in isolation, i.e. in non-psychotic individuals with AVH.

Methods

Resting state connectivity was investigated in 25 non-psychotic subjects with AVH and 25 matched control subjects using seed regression analysis with the left (1) and right (2) inferior frontal, left (3) and right (4) temporoparietal, and the (5) left parahippocampal area as the seed regions. To correct for cardiorespiratory pulsatility rhythms in the fMRI data, heartbeat and respiration were monitored during scanning and the fMRI data was corrected for these rhythms using RETROICOR.

Results

In non-psychotic individuals with AVH the left temporoparietal seed displayed increased connectivity with the right superior temporal region and decreased connectivity with the right inferior frontal region, in comparison with the control group. In addition, non-psychotic subjects showed increased connectivity between the left parahippocampal seed and the left inferior frontal gyrus.

Conclusions

These findings provide support for the hypothesis that AVH result from dysfunctional connectivity of frontal, parahippocampal and temporoparietal regions.

1. Introduction

Auditory verbal hallucinations (AVH) constitute a core symptom of schizophrenia and can be highly distressing [1]. Although the precise neurobiological mechanism of AVH remains largely unknown, previous studies revealed AVH-related activation in frontal, parahippocampal and temporoparietal regions [2-5]. The involvement of frontal and temporoparietal regions has been interpreted to reflect language production and perception processes, while parahippocampal activation presumably represents the role of memory processes in the experience of AVH. Dysfunctional connectivity of frontal and temporoparietal areas involved in AVH is frequently hypothesized to play a crucial role in the genesis of these hallucinations, through dysfunction of the 'corollary discharge' mechanism. In healthy subjects a corollary discharge signal is thought to be sent from language production to language perception areas, to tag the perception as self-generated. In individuals with AVH, dysfunction of the corollary discharge may lead to verbal thoughts acquiring a perceptual quality and being misattributed to an external source [6-8].

Alternatively, these hallucinations were proposed to result from the re-experience of verbal memories which may be instantiated by aberrant connectivity of frontal speech-related areas and the parahippocampal gyrus [9, 10].

A number of previous studies investigated if AVH are indeed related to dysfunctional connectivity and studied task-related or resting state connectivity. A major advantage of resting state studies is that the results are unlikely to be influenced by differences in performance between participant groups. Resting state studies in schizophrenia patients with AVH reported deviant integration of frontal, temporoparietal and subcortical regions [11-15]. However, results are inconsistent as some studies found reduced connectivity, while others reported increased connectivity. In addition, the exact loci of aberrant connectivity varied among studies.

This variation in findings could result from a number of factors. First, the mere presence of AVH episodes during scanning could have influenced results as most studies did not exclude patients with active AVH, or did not report if AVH were present during scanning [13, 14, 16]. In addition, previous studies did not correct for cardiorespiratory processes which may have confounded the result, as they are present throughout the brain in a similar phase locked fashion, thus potentially leading to artificially increased correlation strengths [15, 17-20]. Finally, most studies included patients with schizophrenia who present with a broad range of other symptoms which may have influenced resting state connectivity. Finally, the majority of these patients used antipsychotic medication which may have further confounded results [21].

To elucidate if AVH are indeed related to dysfunctional connectivity, these hallucinations should be studied in isolation. Interestingly, previous studies showed that AVH also

occur in non-psychotic subjects, in the absence of delusions and negative symptoms, thus providing an opportunity to investigate a more isolated form of AVH [22, 23]. An additional advantage is that these individuals do not use psychoactive medication and have not been subject to hospitalization.

In this study we investigated resting state connectivity in 25 non-psychotic individuals with AVH. As AVH were hypothesized to result from deviant integration of frontal, parahippocampal and bilateral temporoparietal regions these areas provided an intuitive starting point for investigating resting state connectivity in non-psychotic individuals. Bilateral frontal and temporoparietal seeds were defined by drawing six mm spheres centred on loci of maximum hallucinatory activation in a separate group of non-psychotic individuals. The parahippocampal seed was based on a previous study by our group in which we showed that AVH were preceded by consistent deactivation of this area [9]. To circumvent contamination of the functional connectivity estimates by signals arising from 'active' AVH episodes occurring during scanning, individuals experiencing AVH during scanning were excluded from analysis. To allow for postprocessing corrections of the fMRI data for cardiorespiratory rhythms, heartbeat and respiration were monitored during scanning.

2. Methods

2.1. Subjects

Thirty-seven non-psychotic individuals with AVH and forty-four healthy control subjects 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 by our group [4, 23-26]. In short, visitors of this website filled out a questionnaire based on the Launay Slade Hallucination Scale (LSHS) [27], a self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals. Subjects with high scores on item 8 and 12 of the LSHS, tapping into auditory hallucinations, were selected for participation in the group of subjects with AVH. Subjects with low scores on items 8 and 12 were selected as healthy control subjects. After initial selection subjects were invited to the hospital to undergo detailed psychiatric assessment.

Subjects were selected for further participation if they met the following inclusion criteria: (1) the absence of any axis I psychiatric disorder other than anxiety or depressive disorder in full remission, as assessed by a psychiatrist using the Comprehensive Assessment of Symptoms and History interview (CASH) [28] ; (2) no chronic somatic disorder; and (3) no 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/ecstasy, cocaine and cannabis. Additional inclusion criteria

for the non-psychotic individuals with AVH consisted of (4) voices were distinct from thoughts and had a perceptual quality; (5) voices occurred at least once a week; (6) drug or alcohol abuse did not precede the first experience of AVH; and (7) the absence of AVH during the resting state scan. To assess schizotypy all subjects were required to fill-out the Schizotypical Personality Questionnaire (SPQ) [29]. This study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Data acquisition

Resting state fMRI scans were acquired while participants kept their eyes closed but stayed awake. During scan acquisition, cardiorespiratory (CR) [15] processes were monitored by affixing four electrocardiogram electrodes to the subjects' chest and by placing a respiration band at the level of the abdomen. The measured CR data consisted of a heart beat signal with a trigger marking times at which an R-peak was detected, and a respiratory signal measuring the expansion of the respiration band [15, 30]. Following acquisition of the resting state scan participants were asked if they had experienced hallucinations. Subjects experiencing AVH during scanning were excluded from analyses.

FMRI time series data was obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. Six-hundred blood-oxygenation-level-dependent (BOLD) fMRI images were acquired per patient with the following parameter settings: 40 (coronal) slices, TR/TE 21.75/32.4 ms, flip angle 10°, FOV 224x256x160, matrix 64x64x40, 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 two directions using a commercial 8-channel SENSE headcoil [31]. Since these PRESTO SENSE images have little anatomical contrast, 40 identical scans, but with a flip angle of 27° (fa27) were acquired to improve realignment and co-registration during preprocessing. After the functional scans a high resolution anatomical scan, with the following parameters: TR/TE: 9.86/4.6 ms, .875x.875x1 voxels, flip angle 8°, FOV 224x160x168.00, 160 slices was acquired to improve localisation of the functional data.

2.3. Data preprocessing

Preprocessing and data analysis were conducted using Statistical Parametric Mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK). First, within-subject image realignment with the mean fa27 as the reference was used to correct for the effects of head motion. Subsequently, the T1-weighted anatomical image was

coregistered to the mean fa27. Using unified segmentation the structural scan was then segmented, followed by estimation of normalization parameters which were subsequently used to register all scans (T1 and fMRI) to the Montreal Neurological Institute (MNI) template as present in SPM5. Finally, images were smoothed using an 8-mm full width at half maximum Gaussian kernel.

2.4. Seed selection

To identify seed regions for seed regression analysis, we used data from a separate fMRI study published earlier in which 21 non-psychotic individuals indicated the presence of AVH during scanning [4]. Six of these 21 subjects also participated in the current study (for a detailed description see Diederen et al. [4]). At the group level, clusters of significant activity during the experience of AVH in the left (1) and right (2) inferior frontal gyri, the left (3) and right (4) temporoparietal area and the left (5) parahippocampal region were selected as seed regions. First, a frontal and temporoparietal seed were selected in the left hemisphere (figure 1). Subsequently, seeds in the right hemisphere were chosen based on the locations of significant activation that corresponded best with the seeds in the left hemisphere (figure 1). As this separate fMRI experiment revealed no significant AVH-related activation in the parahippocampal area, coordinates from a previous study by our group in which significant signal changes were observed to precede AVH were used to create a parahippocampal seed [9]. Seed regions are shown in figure 1.

2.5. Data analysis

After preprocessing, fMRI time courses were extracted for all voxels in a seed for each subject. Next, the first eigenvariate of the voxel timeseries contained in each seed was calculated and entered as a covariate of interest in a whole-brain regression analysis [32-34]. Per seed a regression analysis was conducted resulting in 5 analyses per subject, i.e. one for each seed. The above approach is generally referred to as seed-based resting state fMRI, or functional connectivity [35-37].

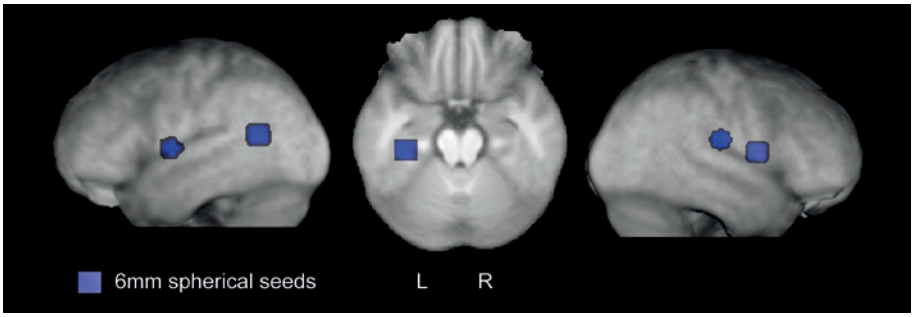
FMRI time series can be dramatically contaminated by a number of (non-white) noise factors including head movement induced image noise and cardiorespiratory noise. Such signals may induce spurious correlations in a seed-based analysis, as these global signals often occur similarly in regions throughout the brain. To correct for these confounding factors, a number of covariates of no interest were included in the model [38]. First, the average white matter and cerebrospinalfluid (CSF) signals were used as covariates of no interest as these tissues may carry physiological fluctuations that are similar to those affecting gray matter, while containing little contribution from

neural activity [39]. Average white matter and CSF signal was obtained by extracting the average signal per time point of two additional 6 mm spheres which were placed in white matter (MNI coordinates 0 28 5) and CSF (MNI coordinates -4 13 9). The global signal was not entered as a covariate in the analysis as is was recently shown that this may induce spurious negative correlations [30]. Secondly, the realignment parameters, consisting of six parameter rigid body transformations (3 translations and 3 rotations) were entered to model movement artefacts. Finally, cardiorespiratory processes were corrected for using the Retrospective Image Correction for physiological motion effects (RETROICOR) [15]. RETROICOR is a retrospective image-based correction technique that extracts cardiac- and respiratory-related noise effects from the MR signal by assigning cardiac and respiratory phases to each image in a time series. The CR noise is then modeled as the linear combination of a set of sinusoid functions which can be used to correct for this noise. In the current study, CR noise was modeled using 10 sinusoid functions for cardiac noise and 10 for respiratory noise, which were entered as covariates of no interest in the analysis. Furthermore, data was high-pass filtered with a cut-off of 100 s. to remove non-global low-frequency noise.

Following analysis, individual T-maps were created for the covariates of interest and converted to R maps, which represent the correlation coefficient of the timeseries signal in each voxel with the signal from the seed regions. Correlation coefficients were subsequently Z-transformed and entered in five separate (i.e. one for each seed) random-effects two-sample T-tests to enable comparisons between groups. These tests comprised the main outcome measure of this study.

As it was hypothesized that aberrant connectivity in the non-psychotic individuals with AVH would be present between frontal, temporoparietal and parahippocampal regions, a small volume correction (SVC) for multiple comparisons was applied using one region of interest (ROI). The ROI contained all voxels within a sphere with a diameter of 24 instead of 6 mm centred on all seed regions, to account for potential differences in the exact location of regions involved in AVH between the present group of non-psychotic individuals with AVH and the group described by Diederen et al. [4]. Such a difference is likely as Ojemann [40] reported a high intersubject variability in the location of frontal and temporoparietal language areas in the brain. Analyses were thresholded at P=0.05 false discovery rate (FDR) corrected for al voxels within the ROI, with an extended threshold of 5 voxels.

Figure 1. Seed regions used in the seed regression analysis



Seeds: (1) left inferior frontal gyrus (-48 0 12), (2) right inferior frontal gyrus (60 8 12), (3) left temporoparietal region (-60 -56 20), (4) right temporoparietal region (56 -16 20), and (5) left parahippocampal region (-36 -24 -1). Abbreviations: L, left; R, right

3. Results

3.1. Exclusions

After scanning, 12 non-psychotic individuals with AVH and 13 control subjects were found unsuitable for inclusion, resulting in 25 scans of non-psychotic subjects with AVH and 31 scans of healthy control subjects. Nine of the 12 excluded non-psychotic subjects were excluded as they had experienced AVH during the resting state, while three were excluded as a result of the poor quality of the obtained cardiorespiratory (CR) data. Poor quality of CR also resulted in the exclusion of thirteen control subjects. Twenty-five of the 31 control subjects were then selected to enable a good match with the non-psychotic individuals with AVH. Data on these 25 non-psychotic individuals with AVH and 25 healthy control subjects were then used for further analyses.

3.2. Demographic variables

The groups did not differ significantly with respect to age, sex, handedness and years of education, however the non-psychotic individuals with AVH scored significantly higher on the SPQ. Table 1 provides a demographic description of the participants, including SPQ scores.

3.3. Left temporoparietal seed

The left temporoparietal seed showed significantly increased connectivity with the right superior temporal, and the right inferior frontal region in the non-psychotic individuals. Inspection of the average R-values of the right superior temporal gyrus revealed an average correlation coefficient of 0.02 (S.D. = 0.12) in the healthy control

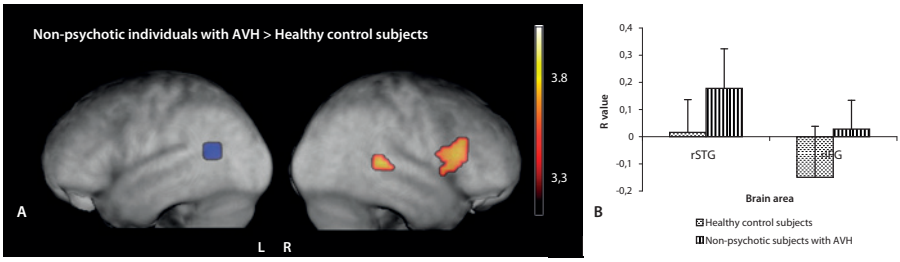
subjects and 0.18 (S.D. = 0.15) in the non-psychotic individuals with AVH. For the right inferior frontal gyrus, the healthy controls showed a negative correlation with the left temporoparietal region (mean R = -0.15; S.D. = 0.19) which was absent in the non-psychotic individuals with AVH (mean R = 0.03; S.D. = 0.11). Figure 2 shows the SPM(T)'s and average R-values of the clusters displaying significantly increased connectivity with the left temporoparietal seed in the non-psychotic individuals with AVH. Coordinates, T-values and cluster sizes of these regions are listed in table 2.

Table 1. Demographic description of all participants.

	Healthy control subjects (N=25)		*Non-psychotic subjects with AVH (N=25)*		
	N	**Mean (S.D.)**	**N**	**Mean (S.D.)**	**Statistics**
Age	25	39.8 (15.9)	25	41.6 (13.5)	K-S Z = 0.85, P = 0.47
Sex (male/female)	7/18		7/18		X2(1) = 0.11, P = 1
Handedness (right/ non-right)	19/6		18/6		X2(1) = 0.11, P = 1
Years of education	25	14.0 (2.4)	25	13.5 (2.0)	K-S Z = 0.57, P = 0.91
SPQ total score	24	7.5 (6.1)	25	29.6 (10.6)	T(38.46) = -8,95, P < 0.001**

** Significant at P < 0.001. Abbreviations: AVH, auditory verbal hallucinations; N, number; S.D., standard deviation; K-S Z, Kolmorgorov-Smirnov Z; SPQ, Schizotypical Personality Questionnaire.

Figure 2. (A) SPM(T)'s revealing significantly increased connectivity with the left temporoparietal seed in non-psychotic subjects with AVH. (B) Average R-values of clusters showing significantly increased connectivity with the left temporoparietal seed in non-psychotic subjects with AVH.



The left temporoparietal seed is shown in blue. Results from random-effects two sample T-tests on Z-transformed correlation coefficients. Thresholded at P = .05 FDR corrected for multiple comparisons within the a priori hypothesized regions with an extend threshold of 5 voxels. Abbreviations: AVH, auditory verbal hallucinations; L, left; R, right; rSTG, right superior temporal gyrus; rIFG, right inferior frontal gyrus; SPM(T)'s, Statistical Parametric Mapping T-values; FDR, False Discovery Rate.

Table 2. T-values, cluster sizes, and locations of local maxima for the two sample T-test with the left temporoparietal region as the seed region.

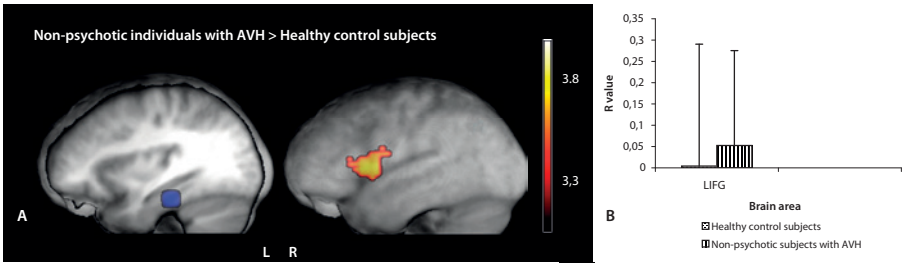
Cluster size	*P Value*	*T Value*	*MNI Coordinates*	
8	0,034	4,23	44 -32 8	Right superior temporal gyrus
36	0,034	4,05	48 24 16	Right inferior frontal gyrus

Results from random-effects two sample T-tests on Z-transformed correlation coefficients. Thresholded at P = 0.05, FDR corrected for multiple comparisons with an extended threshold of 5 voxels. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right; FDR, False Discovery Rate.

3.4. Left parahippocampal seed

The left parahippocampal gyrus displayed significantly increased connectivity with the left inferior frontal region in the non-psychotic individuals with AVH. Although the non-psychotic individuals displayed a small positive correlation between the left parahippocampal region and the left inferior frontal gyrus (mean R = 0.05; S.D. = 0.22) this was absent in the healthy control subjects (mean R = 0.00; S.D. = 0.05). Figure 3 shows the SPM(T)'s and average R-value of the voxels displaying significantly increased connectivity with the left parahippocampal seed in the non-psychotic individuals with AVH. Coordinates, T-values and cluster sizes are listed in table 3.

Figure 3. (A) SPM(T)'s revealing significantly increased connectivity with the left parahippocampal seed in the non-psychotic subjects with AVH. (B) Average R-values of the cluster showing significantly increased connectivity with the left parahippocampal seed in the non-psychotic subjects with AVH.



The left parahippocampal seed is shown in blue. Results from random-effects two sample T-tests on Z-transformed correlation coefficients. Thresholded at P = 0.05 FDR corrected for multiple comparisons within the a priori hypothesized regions with an extended threshold of 5 voxels. Abbreviations: AVH, auditory verbal hallucinations; L, left; R, right; LIFG, left inferior frontal gyrus; SPM(T)'s, Statistical Parametric Mapping T-values; FDR, False Discovery Rate.

3.5. Right temporoparietal and bilateral inferior frontal seeds

No significant differences in connectivity between the right temporoparietal and the left and right inferior frontal seeds on the one hand and voxels within the a priori

hypothesized regions on the other hand could be observed between the healthy control group and the group of non-psychotic individuals with AVH.

Table 3. T-values, cluster sizes, and locations of local maxima for the two sample T-test with the left parahippocampal region as the seed region.

Cluster size	*P Value*	*T Value*	*MNI Coordinates*	
59	0,029	3,81	-44 16 12	Left inferior frontal gyrus
	0,029	3,97	-44 4 8	Left insula/ precentral gyrus

Results from random-effects two sample T-tests on Z-transformed correlation coefficients.Thresholded at P = 0.05, FDR corrected with an extended threshold of 5 voxels. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right; FDR, False Discovery Rate.

4. Discussion

This study compared resting state connectivity between 25 non-psychotic individuals with auditory verbal hallucinations (AVH) and 25 healthy control subjects using seed regression analysis. In the non-psychotic individuals, the left temporoparietal seed showed increased connectivity with the right superior temporal and the right inferior frontal region. Increased connectivity with the latter region resulted from a negative correlation in the control subjects which was absent in the subjects with AVH. A marginally increased connectivity in the non-psychotic individuals was also observed between the left parahippocampal and the left inferior frontal gyrus. No significant differences in connectivity were found for the right temporoparietal and bilateral inferior frontal areas as the seed regions.

4.1. Left temporoparietal seed

Activity of frontal and temporoparietal regions during the experience of AVH is often signified to mean that these hallucinations result from self-produced inner speech [3, 41-43]. This inner speech is hypothesized to be misattributed to an external source as a result of deviant integration of language production areas in the frontal lobes and perception areas in the temporoparietal region. The present finding of aberrant connectivity between the left temporoparietal and the right inferior frontal area in the non-psychotic individuals with AVH may be interpreted within this framework. However, in the current study an interhemispheric instead of intrahemispheric difference in connectivity was found, which seems at odds with this theory. It should, however, be noted that while the right inferior frontal area is not considered a classic language area, previous studies showed that the right hemisphere can produce so-called non-propositional or "automatic" language, consisting of highly over learned

sequences of low linguistic complexity [44, 45]. As a result, dysfunctional connectivity may arise from aberrant integration of language production areas in the right hemisphere and language perception areas in the left hemisphere. An important argument against this reasoning is, however, that there is no evidence for a direct, i.e. contralateral, anatomical connection between these areas. Integration of these areas may, however, be enabled through involvement of a third region such as the left inferior frontal gyrus or the right temporoparietal region. Yet, in this scenario we should have observed dysfunctional connectivity between the right inferior frontal and the left inferior frontal or the right temporoparietal area. Dysfunctional connectivity with one of these areas may, however, not have become significant in the present study. As the left temporoparietal region also displayed aberrant connectivity with the right temporal region, one may speculate that the right temporoparietal region is the intermediate for increased signalling between the right inferior frontal gyrus and the left temporoparietal region in subjects with AVH.

4.2. Left parahippocampal seed

Increased functional connectivity was also observed between the left parahippocampal area and the left inferior frontal gyrus in the non-psychotic individuals with AVH. As the parahippocampal region fulfils a prominent role in memory processes, and the left inferior frontal gyrus contains the location of Broca's speech production area, increased connectivity of these areas may reflect a deficit in memory-induced language production [46]. This is in concordance with the view that AVH result from spontaneous memory recollection which triggers activation in language-related areas responsible for the experience of AVH [10, 47].

Based on these findings it is conceivable that AVH do not result from a single deficit, but rather from the integration of multiple deficits. Speculating on this, a hallucination may originate from spontaneous recollection of a memory fragment which is re-experienced through parahippocampal-induced re-activation of language production areas. Due to dysfunction of the corollary discharge mechanism, language perception areas are subsequently not informed that the percept is self-generated, presumably leading to the audible aspect of the AVH [48].

4.3. Comparison to previous studies

This is the first study to investigate resting state functional connectivity in a group of non-psychotic individuals with AVH. However, a number of studies investigated resting state connectivity in relation to AVH in schizophrenia patients [12-14, 16]. The present study is partly in line with these studies as Vercammen et al. [16] observed aberrant connectivity between the left temporoparietal junction and the right inferior frontal gyrus and

Gavrilescu et al. [12] reported deviant interhemispheric connectivity between bilateral temporoparietal areas. However, these studies reported reduced connectivity, while increased connectivity was observed in the present study. Furthermore, Rotarska-Jagiela et al. [13] showed that severity of hallucinations negatively correlated with functional connectivity of fronto-temporal and auditory networks in schizophrenia. Finally, Hoffman et al. [14] reported increased connectivity between Wernicke's area in the temporoparietal region and a large subcortical region which is not in line with the present study.

However, as all of these studies included patients with schizophrenia, which is a complex syndrome comprising positive, negative and cognitive symptoms, observed dysfunctions in connectivity may well be related to other symptoms of schizophrenia as well as to the general cognitive decline. In addition, the majority of schizophrenia patients use antipsychotic medication which may have substantially impacted on the results. Furthermore, most studies did not exclude patients with active AVH from analyses or did not report if AVH were present during scanning [11, 13, 14], which may have further confounded the results. Finally, these studies did not correct for cardiorespiratory rythms, known to contaminate resting state connectivity analyses [15, 17-20] as they usually occur globally throughout the brain, thus potentially influencing temporal correlation patterns between brain areas.

4.4. Limitations

The main limitation of this study is that although aberrant connectivity was observed between the left temporoparietal region and the right superior temporal region as well as with the right inferior frontal region the exact sites of these latter regions do not correspond with the right temporoparietal and inferior frontal seed regions we defined a priori. Although this discrepancy limits the present result, this may be due to high inter individual differences in the exact location of brain regions observed in AVH [40]. In line with this reasoning it would be expected that significant activation during AVH in the present group of subjects differs somewhat with respect to the exact location of frontal and temporoparietal regions compared to the group on which the seed regions were based [4]. In relation to this, a second limitation of this study is that while the left temporoparietal seed showed aberrant connectivity with the right temporoparietal and the right inferior frontal region, no significant differences in connectivity with the temporoparietal region (the current seed) between the groups were observed when the right temporoparietal and inferior frontal regions were used as seed regions, i.e. when the logic of the current analysis is reversed. This discrepancy in findings was also observed for the left parahippocampal and the left inferior frontal area as the seed regions. This might also result from differences in the exact location of frontal, and

temporoparietal regions involved in AVH between the present group of non-psychotic subjects with AVH and the group described by Diederen et al. [4, 40].
Another limitation is that as areas displaying aberrant connectivity in the non-psychotic individuals correspond largely with brain areas involved in the experience of AVH [4] increased resting state connectivity of these areas could result from sustained activation of these regions after the occurrence of a hallucination. However, since the non-psychotic individuals included in this study experienced AVH with an average frequency of once every week, this is unlikely. In addition, a limitation of the current study is that the method used provides no information on the directionality of connectivity.

These findings provide support for the hypothesis that AVH result from dysfunctional connectivity of frontal, parahippocampal and temporoparietal regions.

References

1. Nayani TH, David AS. The auditory hallucination: a phenomenological survey. *Psychol Med* Jan 1996;26(1):177-189.
2. Kuhn S, Gallinat J. Quantitative Meta-Analysis on State and Trait Aspects of Auditory Verbal Hallucinations in Schizophrenia. *Schizophr Bull* Dec 22 2010.
3. Sommer IE, Diederen KM, Blom JD, et al. Auditory verbal hallucinations predominantly activate the right inferior frontal area. *Brain* Dec 2008;131(Pt 12):3169-3177.
4. Diederen KM, Daalman K, de Weijer AD, Neggers SF, van Gastel W, Blom JD, Kahn RS, Sommer IE. Auditory Hallucinations Elicit Similar Brain Activation in Psychotic and Nonpsychotic Individuals. *Schizophr Bull* Apr 28 2011.
5. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry* Jan 2010;168(1):73-81.
6. Frith CD, Friston KJ, Herold S, et al. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry* Sep 1995;167(3):343-349.
7. Spence SA, Liddle PF, Stefan MD, et al. Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *Br J Psychiatry* Jan 2000;176:52-60.
8. Ford JM, Roach BJ, Faustman WO, Mathalon DH. Synch Before You Speak: Auditory Hallucinations in Schizophrenia. *Am J Psychiatry* March 1, 2007 2007;164(3):458-466.
9. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, Sommer IE. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *Am J Psychiatry* Apr 2010;167(4):427-435.
10. Copolov DL, Seal ML, Maruff P, Ulusoy R, Wong MT, Tochon-Danguy HJ, Egan GF. Cortical activation associated with the experience of auditory hallucinations and perception of human speech in schizophrenia: a PET correlation study. *Psychiatry Res* Apr 1 2003;122(3):139-152.
11. Vercammen A, Knegtering H, den Boer JA, Liemburg EJ, Aleman A. Auditory Hallucinations in Schizophrenia Are Associated with Reduced Functional Connectivity of the Temporo-Parietal Area. *Biological Psychiatry* 2010;67(10):912-918.
12. Gavrilescu M, Rossell S, Stuart GW, et al. Reduced connectivity of the auditory cortex in patients with auditory hallucinations: a resting state functional magnetic resonance imaging study. *Psychol Med* Jul 2010;40(7):1149-1158.
13. Rotarska-Jagiela A, van de Ven V, Oertel-Knochel V, Uhlhaas PJ, Vogeley K, Linden DE. Resting-state functional network correlates of psychotic symptoms in schizophrenia. *Schizophr Res* Mar 2010;117(1):21-30.
14. Hoffman RE, Fernandez T, Pittman B, Hampson M. Elevated functional connectivity along a corticostriatal loop and the mechanism of auditory/verbal hallucinations in patients with schizophrenia. *Biol Psychiatry* Mar 1 2010;69(5):407-414.
15. Glover GH, Li T-Q, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magnetic Resonance in Medicine* 2000;44(1):162-167.
16. Vercammen A, Knegtering H, Liemburg EJ, den Boer JA, Aleman A. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. *J Psychiatr Res* Aug 2010;44(11):725-731.
17. Dagli MS, Ingeholm JE, Haxby JV. Localization of Cardiac-Induced Signal Change in fMRI. *NeuroImage* 1999;9(4):407-415.
18. Noll DC, Schneider W. Theory, simulation, and compensation of physiological motion artifacts in functional MRI. Paper presented at: Image Processing, 1994. Proceedings. ICIP-94., IEEE International Conference; 13-16 Nov 1994, 1994.

19. Glover GH, Lee AT. Motion Artifacts in fMRI: Comparison of 2DFT with PR and Spiral Scan Methods. *Magnetic Resonance in Medicine* 1995;33(5):624-635.

20. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *NeuroImage* 2006;31(4):1536-1548.

21. Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proc Natl Acad Sci U S A* Nov 9 1999;96(23):13432-13437.

22. Tien AY. Distributions of Hallucinations in the Population. *Soc Psychiatry Psychiatr Epidemiol* 1991;26:287-292.

23. Sommer IE, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, Boks MP. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. *Schizophr Bull* May 2008;36(3):633-641.

24. Daalman K, Boks MP, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IE. The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *J Clin Psychiatry* Mar 2011;72(3):320-325.

25. Diederen KM, De Weijer AD, Daalman K, Blom JD, Neggers SF, Kahn RS, Sommer IE. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. *Brain* Dec 2010;133(Pt 12):3734-3744.

26. van Lutterveld R, Oranje B, Kemner C, et al. Increased psychophysiological parameters of attention in non-psychotic individuals with auditory verbal hallucinations. *Schizophr Res* Aug 2010;121(1-3):153-159.

27. Laroi F, Marczewski P, Van der Linden M. Further evidence of the multi-dimensionality of hallucinatory predisposition: factor structure of a modified version of the Launay-Slade Hallucinations Scale in a normal sample. *Eur Psychiatry* Feb 2004;19(1):15-20.

28. Andreasen NC, Flaum M, Arndt S. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. *Arch Gen Psychiatry* Aug 1992;49(8):615-623.

29. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull* 1991;17(4):555-564.

30. van Buuren M, Gladwin TE, Zandbelt BB, van den Heuvel M, Ramsey NF, Kahn RS, Vink M. Cardiorespiratory effects on default-mode network activity as measured with fMRI. *Human Brain Mapping* 2009;30(9):3031-3042.

31. Neggers SF, Hermans EJ, Ramsey NF. Enhanced sensitivity with fast three-dimensional blood-oxygen-level-dependent functional MRI: comparison of SENSE-PRESTO and 2D-EPI at 3 T. *NMR Biomed* Aug 2008;21(7):663-676.

32. Boly M, Tshibanda L, Vanhaudenhuyse A, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping* 2009;30(8):2393-2400.

33. van Marle HJF, Hermans EJ, Qin S, Fernández G. Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *NeuroImage* 2010;53(1):348-354.

34. O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and Overlapping Functional Zones in the Cerebellum Defined by Resting State Functional Connectivity. *Cerebral Cortex* April 1, 2010 2010;20(4):953-965.

35. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences* January 7, 2003 2003;100(1):253-258.

36. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America* July 5, 2005 2005;102(27):9673-9678.

37. Cole DM, Smith SM, Beckmann CF. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Front Syst Neurosci* 2010;4:8.

38. Lund TE, Madsen KH, Sidaros K, Luo W-L, Nichols TE. Non-white noise in fMRI: Does modelling have an impact? *NeuroImage* 2006;29(1):54-66.

39. Chang C, Glover GH. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *NeuroImage* 2009;47(4):1448-1459.

40. Ojemann GA. Cortical organization of language. *J Neurosci* Aug 1991;11(8):2281-2287.

41. Shergill SS, Brammer MJ, Amaro E, Williams SCR, Murray RM, McGuire PK. Temporal course of auditory hallucinations. *The British Journal of Psychiatry* December 1, 2004 2004;185(6):516-517.

42. Sommer IE, Diederen KM. Language production in the non-dominant hemisphere as a potential source of auditory verbal hallucinations. *Brain* 2009.

43. McGuire PK, Murray RM, Shah GMS. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *The Lancet* 1993;342(8873):703-706.

44. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* Aug 2005;36(8):1759-1763.

45. Van Lancker D, Cummings JL. Expletives: neurolinguistic and neurobehavioral perspectives on swearing. *Brain Res Brain Res Rev* Dec 1999;31(1):83-104.

46. Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123-152.

47. Waters FA, Badcock JC, Michie PT, Maybery MT. Auditory hallucinations in schizophrenia: intrusive thoughts and forgotten memories. *Cogn Neuropsychiatry* Jan 2006;11(1):65-83.

48. Sommer IE, Selten JP, Diederen KM, Blom JD. Dissecting auditory verbal hallucinations into two components: audibility (Gedankenlautwerden) and alienation (thought insertion). *Psychopathology* 2010;43(2):137-140.

Chapter 9

Summary and general discussion

The research presented in this thesis aimed at providing more insight into the pathophysiology of auditory verbal hallucinations (AVH). The first part of this thesis consists of *state* studies which aim at capturing the neural signature of AVH. The second part described *trait* studies which focus at comparing brain activation between individuals with and without AVH. The rational of these *trait* studies is that differences in brain activation between hallucinating and non-hallucinating subjects may reveal specific mechanisms predisposing a person to experience AVH.

1. Part I: State studies

The studies described in part one of this thesis investigated the *state* of AVH as identifying which regions come into play during AVH could provide a first step in elucidating the neurobiological origin of this symptom. While brain activation during AVH has been investigated by previous studies, results of these studies are questionable due to small sample sizes and liberal thresholds for significance. The main goal of the study described in **chapter 2** was therefore to investigate brain activation during AVH in a substantial number of individuals. The second aim of this study was to compare the observed pattern of activation to brain activation during silent language production. The main finding was that AVH activated an extended network of regions including the right homologue of Broca's area (inferior frontal gyrus), the bilateral insula, bilateral supramarginal gyri and right superior temporal gyrus. This pattern of activation showed considerable overlap with regions activated during the language production task. However, language production mainly activated left hemisphere language regions, while AVH were related to activation of the contralateral homologues of these regions, especially the insula and the right inferior frontal gyrus. Although these regions are not considered classic language regions, they have been shown to possess some basic capacity for language consisting of 'automatic' language which includes highly overlearned sequences such as swearwords or words of abuse, typically with a negative emotional content [1, 2]. As AVH in psychotic patients often consist of single words or truncated sentences [3] and have a predominantly negative emotional content [4], is was concluded that these hallucinations may result from inner speech produced by the right hemisphere.

This finding was further elaborated upon in the study described in **chapter 3**. Here it was posed that 'normal' inhibition of right hemisphere language regions by the left hemisphere is dysfunctional in individuals with AVH, resulting in inappropriate activation of these right hemisphere regions. This dysfunctional inhibition was proposed to arise from decreased left cerebral dominance for language in subjects presenting with AVH.

Although functional imaging of brain activity during hallucinations may aid in understanding which regions are involved in the experience of AVH, it cannot explain how and where these experiences originate in the brain. Because auditory hallucinations arise without an external source (i.e., the experience of an actual voice) it was reasoned that they are triggered internally. An intuitive way to identify such an internal trigger consists of investigating brain activation in the time period preceding the hallucinations. Therefore, the study described in **chapter 4** investigated brain activation in the six seconds prior to AVH in fifteen psychotic patients. The main finding of this study was that the experience of AVH was consistently preceded by deactivation of the parahippocampal gyrus.

The parahippocampal gyrus has been hypothesized to play a central role in memory recollection, as it receives perceptual information from association cortices, such as the language areas, and forwards this information to the hippocampus in order to be 'recognized.' This perceptual information is then passed back to the parahippocampal gyrus from where it is redistributed to the association cortices involved in the original perception [5-8]. Activation of association areas is then hypothesized to be responsible for the re-experience of the retrieved memory. In the case of AVH, spontaneous memory retrieval may lead to parahippocampal-induced activation of language areas responsible for the experience of the hallucinations. This is in line with the observed activation of language areas during the experience of AVH.

In this model, an enhanced redistribution function of the parahippocampal gyrus, possibly mediated by increased dopaminergic signalling, may lead to erroneous activation of association cortices and hence to incorrect recognition. This incorrect recognition may consist of memory fragments of which the context cues are missing. When context cues such as the source of a memory are absent a memory fragment may not be recognized as an actual memory, but instead as coming from an outside source [9]. As such, AVH may be triggered by spontaneous memory retrieval which is not recognized as self-produced.

A missing link in this model is, however, that the perceptual aspect of AVH (i.e. individuals *hear* voices) is not accounted for. Sommer et al. [10] termed this perceptual aspect *audibility* and hypothesized it to result from a dysfunction of the corollary discharge mechanism [11]. According to this model, language production in the healthy brain is accompanied by an efferent copy (i.e. the corollary discharge) of the formed speech which is send to language perception areas to signal that the language percept is self-generated. Support for the presence of such a feed-forward system in humans is provided by a study which showed that healthy subjects suppressed auditory perception areas during self-generated speech. In schizophrenia patients this suppression was decreased [11, 12].

Activation of language production and perception areas observed during the experience of AVH can be interpreted in line with this hypothesis. However, a dysfunctional corollary discharge mechanism within the language system would be expected to manifest as aberrant connectivity of language production and perception regions.

Symptom-capture studies may not only provide a starting point for elucidating the origin of AVH, they could also be of aid in developing tailor-made treatments for these hallucinations. Examples of this strategy are the focal treatment of AVH with repetitive Transcranial Magnetic Stimulation (rTMS) or with invasive electrocortical stimulation, in which the focus of maximum activation during AVH in individual patients is used as the target position for treatment. In order to apply such a treatment it is, however, important to determine whether brain activation during AVH can be reliably detected with fMRI. With this aim, the study described in **chapter 5** investigated spatial reproducibility of AVH-related activation between two subsequent scan sessions in thirty-three psychotic patients. The main finding of this study was that the median distance between local maxima of significant activation was smaller than 2 cm for frontal, temporoparietal as well as motor regions. As rTMS may target an area of approximately 2-4 cm [13], these scans were considered suitable for fMRI-guided rTMS treatment. For stimulation techniques that require a finer spatial resolution (i.e. in mm) such as invasive electrocortical stimulation these scans may be less suitable. These results should, however, be treated with caution as reproducibility was measured within one scan session and may therefore represent a lower bound of reliability.

The studies described in the previous chapters all revealed activation within a network of frontal and temporoparietal language regions during the *state* of AVH. It is, however, unclear if a similar pattern of activation during AVH can also be observed in other individuals presenting with these hallucinations. This is of major importance as a comparison of brain activation during AVH between different groups of individuals may provide a first clue regarding similar or differential mechanisms of the origin of these hallucinations in different groups. If these hallucinations are caused by comparable mechanisms in different groups, one should observe the same pattern of brain activation during AVH. To elucidate if AVH in psychotic and non-psychotic individuals are indeed related to similar patterns of brain activation, the study described in **chapter 6** compared AVH-related brain activation between 21 psychotic and 21 non-psychotic, i.e. healthy, individuals with AVH. The main finding of this study was that psychotic and non-psychotic individuals displayed several common areas of activation during the experience of AVH, in the absence of any significant differences. Although

these results cannot explain if the exact same pathophysiological mechanism gives rise to AVH in these individuals, they provide a first clue with respect to similar mechanisms. To further elucidate this, groups with and without a history of AVH should be compared, while they are not actively hallucinating, i.e. in *trait* studies.

The absence of significant differences in brain activation during AVH between psychotic and non-psychotic individuals is somewhat unexpected as it was previously shown that these groups differ with respect to a number of phenomenological aspects of the AVH [14]. Elucidating how specific AVH-characteristics are associated with brain activation during the *state* of AVH should therefore be a goal of future studies.

In addition, to obtain additional clues regarding similarities and differences in brain activation during AVH in different groups, future studies should aim at investigating AVH-related brain activation in patients with schizotypal and borderline personality disorder, bipolar disorder, psychotic depression and individuals with a neurological or neurodevelopmental disorder.

2. Part II : Trait studies

The first *trait* study aimed at testing an influential hypothesis on the origin of AVH. According to this hypothesis, AVH result from decreased left cerebral dominance for language, i.e. language lateralization, which is a well-replicated finding in schizophrenia patients. It is, thus far, unclear if this abnormality is indeed related to AVH or to another symptom of schizophrenia, or schizophrenia in general. To elucidate this, the study described in **chapter 7** investigated language lateralization in 35 non-psychotic individuals with AVH as these subjects experience AVH in isolation, i.e. in the absence of delusions, negative and cognitive symptoms, hospitalization and medication use. The main finding of this study was that decreased language lateralization could not be observed in the non-psychotic individuals with AVH. It is therefore not likely that these hallucinations result from decreased cerebral dominance for language.

Another influential theory on AVH proposes that these hallucinations result from dysfunctional connectivity of frontal, parahippocampal and temporoparietal brain areas. While dysfunctional connectivity has been observed in schizophrenia patients, a direct link between aberrant connectivity and AVH has, thus far, not been established. To elucidate if these hallucinations are indeed related to aberrant integration, the study presented in **chapter 8** investigated resting state connectivity in 25 non-psychotic subjects with AVH as these subjects experience AVH in relative isolation.

The main findings of this study were that non-psychotic individuals displayed aberrant connectivity between the right inferior frontal gyrus and the left temporoparietal region as well as between the left parahippocampal and the inferior frontal region.
A potential explanation for these results is that aberrant frontal-parahippocampal connectivity represents dysfunctions in verbal memory retrieval, while dysfunctional frontal-temporoparietal connectivity is related to malfunctioning of the corollary discharge mechanism.

3. Methodological considerations

When interpreting the findings from the studies presented in this thesis a number of methodological limitations should be considered. First, a general limitation of using functional MRI is that this technique provides an indirect and relative measure of brain activation. As a result, the findings obtained with this technique are highly dependent on a number of factors including task design, scan technique, preprocessing steps and selected statistical analysis. Furthermore, brain activation as investigated with fMRI is contaminated by a number of (non-white) noise factors such as cardiac, respiratory and low-frequency noise which it is difficult to correct for. Moreover, head movement during scanning strongly influences the acquired data. It is, however, possible to partially overcome these factors by using a task design with an adequate control condition, applying a reproducible scan technique, include a substantial number of subjects (i.e. at least 20) and control for movement and cardiorespiratory processes.
Although the studies described in this thesis aimed at controlling optimally for these factors, some of these factors are very challenging to control for when investigating brain activation during AVH. For instance, designing an adequate control condition for AVH (i.e. with the aim of investigating a particular aspect of AVH), poses a major problem as designing such a condition requires a conclusive understanding of the neurocognitive processes involved in AVH. To circumvent this, one might choose to solely control for motor activation related to the balloon-squeezes used to indicate the AVH. Still, a problem with this approach is that the design used to study AVH included a paced motor response which is difficult to control for as the nature of the cue for these balloon-squeezes, i.e. AVH, is unclear. Therefore, random balloon-squeezes were used to correct for motor activation in the study described in chapter 4.
A second difficulty with respect to investigating fMRI-guided brain activation during AVH is that the presence of AVH may be substantially influenced by the scan-environment. For instance, some participants report a sudden absence of AVH when they are in the scanner, while others start presenting with continuous AVH.

Another general limitation when investigating AVH is that results are dependent on introspective reports of participants. As a result it is not feasible to investigate the reliability of subject responses. Furthermore, a difficulty with studying AVH is that these hallucinations represent a very diverse phenomenon in which a number of hallucination-characteristics such as AVH-content, frequency, number of voices etc. may differ among participants. In relation to this, one may argue if AVH with (partially) different characteristics, such as observed in non-psychotic individuals with AVH, indeed represent the same symptom.
If these hallucinations do not represent the same symptom in both groups, the approach of investigating non-psychotic individuals as a more isolated model for studying AVH as observed in psychotic patients, is not appropriate.

A further methodological consideration that should be mentioned is that both psychotic and non-psychotic individuals with AVH participating in these studies represent highly-selected groups and can therefore not readily be generalized to psychotic and non-psychotic individuals in the general population. Non-psychotic participants were recruited via a website on which they filled out a questionnaire tapping into hallucinations. Subjects with high scores on these items were invited to the hospital to undergo further screening for participation. This approach may have predominantly selected individuals who feel confident to speak about their voices and may have excluded the more suspicious or shy individuals.
Psychotic patients participating in these studies mainly considered of individuals who presented with chronic, medication-resistant AVH and are therefore not comparable to, for instance, first-episode schizophrenia patients.

Finally, one may wonder if the non-psychotic subjects with AVH included in some of these studies can indeed be considered to be 'non-psychotic' or healthy. Although these individuals experience little discomfort from the AVH, and their AVH may be characterized as "benign," the absence of a major psychiatric diagnosis in these individuals can be disputed. When strict DSM-IV criteria for axis I were to be applied to these subjects, they would meet criteria for psychosis not otherwise specified (NOS) as they all fulfilled the criterion "persistent hallucinations," which in itself is sufficient for this classification. However, for many DSM-IV diagnoses (ie, schizophrenia, substance abuse, personality disorder, and anxiety disorders), an explicit diagnostic criterion is that symptoms have to lead to dysfunction, while psychosis NOS lacks this criterion. If this criterion was applied to AVH, the non-psychotic individuals included in this thesis, would indeed be considered healthy.

For the current studies it is, however, not a major issue if these individuals can be concluded to be healthy or not as the main rationale for including these subjects was that they experience AVH in relative isolation.

In summary, when the findings from this thesis are integrated it may be speculated that language activation during AVH is triggered by spontaneous memory recollection which is not recognized as self-generated. The perceptual aspect of AVH may subsequently arise from aberrant connectivity of language production and perception regions as observed during resting state. Further investigation of this hypothesis is, however, warranted.

References

1. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, Heiss WD. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke* Aug 2005;36(8):1759-1763.
2. Van Lancker D, Cummings JL. Expletives: neurolinguistic and neurobehavioral perspectives on swearing. *Brain Res Brain Res Rev* Dec 1999;31(1):83-104.
3. Stephane M, Thuras P, Nasrallah H, Georgopoulos AP. The internal structure of the phenomenology of auditory verbal hallucinations. *Schizophr Res* Jun 1 2003;61(2-3):185-193.
4. Copolov D, Trauer T, Mackinnon A. On the non-significance of internal versus external auditory hallucinations. *Schizophr Res* Jul 1 2004;69(1):1-6.
5. Van Hoesen GW. The parahippocampal gyrus: New observations regarding its cortical connections in the monkey. *Trends in Neurosciences* 1982;5:345-350.
6. Eichenbaum H. A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci* 2000;1(1):41-50.
7. Eichenbaum H, Schoenbaum G, Young B, Bunsey M. Functional organization of the hippocampal memoryâ€‰system. *Proceedings of the National Academy of Sciences* November 26, 1996 1996;93(24):13500-13507.
8. Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 2007;30:123-152.
9. Waters FA, Badcock JC, Michie PT, Maybery MT. Auditory hallucinations in schizophrenia: intrusive thoughts and forgotten memories. *Cogn Neuropsychiatry* Jan 2006;11(1):65-83.
10. Sommer IE, Selten JP, Diederen KM, Blom JD. Dissecting auditory verbal hallucinations into two components: audibility (Gedankenlautwerden) and alienation (thought insertion). *Psychopathology* 2010;43(2):137-140.
11. Heinks-Maldonado TH, Mathalon DH, Houde JF, Gray M, Faustman WO, Ford JM. Relationship of Imprecise Corollary Discharge in Schizophrenia to Auditory Hallucinations. *Arch Gen Psychiatry* March 1, 2007 2007;64(3):286-296.
12. Ford JM, Mathalon DH, Whitfield S, Faustman WO, Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol Psychiatry* Mar 15 2002;51(6):485-492.
13. Wagner T, Eden U, Fregni F, et al. Transcranial magnetic stimulation and brain atrophy: a computer-based human brain model study. *Experimental Brain Research* 2008;186(4):539-550.
14. Daalman K, Boks MP, Diederen KM, de Weijer AD, Blom JD, Kahn RS, Sommer IE. The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. *J Clin Psychiatry* Mar 2011;72(3):320-325.

Chapter 10

Nederlandse samenvatting

Bijzonder zintuiglijke ervaringen of paranormaal begaafd; in niet-westerse samenlevingen worden auditieve verbale hallucinaties of 'stemmen' vaak gezien als een teken van spiritualiteit. Dit in tegenstelling tot de westerse wereld waarin ze al snel als onderdeel van een ziekte gezien worden. Stemmen komen inderdaad vaak voor in personen met een neurologische of psychiatrische stoornis, maar worden ook wel geobserveerd in gezonde mensen zoals Karin. Karin hoort zolang ze zich kan herinneren stemmen. De stemmen geven haar advies, stellen haar gerust en waarschuwen haar in geval van gevaar. Hoewel gezonde personen vaak vriendelijke stemmen horen zijn deze bij patiënten vaak veel minder positief. Neem nu Willem die op zijn 26ste gediagnosticeerd werd met schizofrenie. Willem hoort sinds vijf jaar stemmen die hem overal volgen. Ze geven hem opdrachten en hij weet zeker dat ze van een organisatie komen die hem in de gaten houdt.

Willem is een typisch voorbeeld van een schizofreniepatiënt die veel last van zijn stemmen heeft. Stemmen komen voor in zo'n 70% van de patiënten met schizofrenie. Dit is veel hoger dan in gezonde personen waarin de prevalentie tussen de 1,5 en 16% ligt, afhankelijk van factoren als geslacht, etniciteit en maatschappelijke situatie. Patiënten met schizofrenie worden meestal behandeld met antipsychotische medicatie welke goed aanslaat in het merendeel (75%) van de patiënten. Het overige kwart is helaas niet gebaat bij deze medicatie. Veel onderzoek richt zich op het ontrafelen van de oorzaak van auditieve verbale hallucinaties omdat extra kennis kan helpen bij het ontwikkelen van nieuwe behandelmethoden voor deze hallucinaties.

Het onderzoek beschreven in dit proefschrift richtte zich op het in kaart brengen van de neurale en cognitieve basis van auditieve verbale hallucinaties aan de hand van functionele MRI. Het eerste deel van dit proefschrift, hoofdstuk 2 t/m 6, bestaat uit zogenaamde state studies die zich richten zich op het in kaart brengen van hersenactiviteit tijdens het horen van stemmen. In het tweede deel, hoofdstuk 7 en 8, komen trait studies aan bod. Trait studies hebben tot doel verschillen in hersenactiviteit tussen personen met en personen zonder auditieve verbale hallucinaties op te sporen. Het idee van deze trait studies is dat verschillen in hersenactiviteit tussen hallucinerende en niet hallucinerende mensen mechanismen bloot kunnen leggen die kunnen verklaren waarom sommige personen aanleg hebben voor auditieve verbale hallucinaties en anderen niet.

1. State studies

In de eerste state studie, beschreven in **hoofdstuk 2**, werd aan 24 psychotische patiënten gevraagd om aan te geven wanneer ze stemmen hoorden, terwijl er fMRI

scans gemaakt werden. Hiernaast werd aan dezelfde groep patiënten gevraagd om na de hallucinatiescan een taaltaak uit te voeren. Doel was om te achterhalen welke hersengebieden actief werden tijdens auditieve verbale hallucinaties en in hoeverre deze gebieden overeenkwamen met hersengebieden die activeerden tijdens normale taalproductie. Enige overlap tussen auditieve verbale hallucinaties en taal werd verwacht aangezien auditieve verbale hallucinaties uit woorden en zinnen bestaan en eerdere studies activiteit in deze gebieden rapporteerden. Eerder onderzoek werkte echter alleen met kleine patiëntengroepen waardoor er getwijfeld kan worden aan de betrouwbaarheid van deze resultaten.
Deze studie liet zien dat hersengebieden die betrokken zijn bij auditieve verbale hallucinaties (de rechter inferieure frontale en superieure temporale gyrus, de bilaterale insula en supramarginale gyrus) maar deels overeenkomen met gebieden die activeren tijdens taalproductie. Taalproductie activeerde voornamelijk delen in de linker hersenhelft, terwijl auditieve verbale hallucinaties geassocieerd waren met activiteit van gelijksoortige gebieden in de rechter hersenhelft, de zogenaamde homologen van de taalgebieden. Hoewel deze homologen niet beschouwd worden als 'klassieke' taalgebieden hebben eerdere studies uitgewezen dat zij toch een beperkte capaciteit voor taal bezitten. Zo zijn ze betrokken bij de vorming van zogenaamde automatische taal zoals simpele zinnen met een voornamelijk negatieve inhoud. Het is opvallend dat deze automatische taal veel wegheeft van de hallucinaties die patiënten ervaren. Dit maakt het aannemelijk dat stemmen in psychotische patiënten gevormd worden in de rechter hersenhelft.

Hoofdstuk 3 bevat een verdere bespreking van deze resultaten. Deze studie richtte zich op het formuleren van een model dat kan verklaren waarom activiteit van taalgebieden in de rechter hersenhelft opspeelt bij personen die stemmen horen, maar niet of in mindere mate in personen die geen stemmen horen. Een mogelijke verklaring is dat de taalgebieden in de rechter hersenhelft onvoldoende of niet worden geremd door linker taalgebieden in personen die stemmen horen. Deze afwijkende remming kan leiden tot verhoogde activiteit van taalgebieden in de rechter hersenhelft.

De volgende stap bestond uit het opsporen hoe activiteit van taalgebieden tijdens auditieve verbale hallucinaties aangezet wordt. In de studie, beschreven in **hoofdstuk 4**, werd daarom gekeken naar veranderingen in hersenactiviteit in de zes seconden voorafgaand aan auditieve verbale hallucinaties. Uit de resultaten bleek dat vlak voor iemand hallucineerde er een verandering in activiteit optrad in de linker parahippocampale gyrus. Eerder onderzoek wijst uit dat dit gebied een belangrijke rol vervult bij het herinneren. Dit zou kunnen betekenen dat auditieve verbale hallucinaties 'aangezet' worden vanuit het geheugen. Eerder onderzoek liet ook zien dat wanneer

mensen zich iets herinneren er vermoedelijk een seintje van de parahippocampale gyrus naar zogenaamde associatiegebieden, zoals de taalgebieden, gestuurd wordt om deze herinnering te kunnen herbeleven. Een spontane herinnering, voorafgaand aan het horen van stemmen, kan daardoor leiden tot activiteit van taalgebieden welke verantwoordelijk is voor de herbeleving van de herinnering. Dat de herinneringen zich manifesteren als stemmen en niet als herinneringen herkend worden, kan mogelijk worden verklaard door het ontbreken van bepaalde stukjes van die herinnering. Wat helaas niet kan worden verklaard vanuit dit model is het perceptuele, of gehoorsaspect, van auditieve verbale hallucinaties.

De studie beschreven in **hoofdstuk 5** richtte zich op het onderzoeken van de betrouwbaarheid van fMRI voor het in beeld brengen van hersenactiviteit tijdens auditieve verbale hallucinaties. Het is van belang om deze betrouwbaarheid te onderzoeken aangezien fMRI scans soms gebruikt worden bij experimentele behandelingen. Een voorbeeld van zo'n behandeling is repetitieve Transcraniële Magnetische Stimulatie (rTMS) waarbij hersenactiviteit in gebieden betrokken bij auditieve verbale hallucinaties gericht afgeremd kan worden. Deze gebieden worden per patiënt opgespoord met fMRI. Voor deze studie werden daarom twee hallucinatiescans gemaakt van 33 patiënten. Gekeken werd hoe groot de afstand was tussen geactiveerde gebieden in de twee hallucinatiescans. Bij de meeste patiënten was deze kleiner dan 2 cm. Omdat rTMS een gebied kan beïnvloeden van ongeveer 2-4 cm kunnen we stellen dat deze scans betrouwbaar zijn voor gebruik bij deze behandeling.

Hoewel auditieve verbale hallucinaties ook voorkomen in gezonde personen is het tot nu toe onduidelijk of stemmen in gezonde personen en personen met een neurologische of psychiatrische stoornis als hetzelfde fenomeen beschouwd kunnen worden. Als auditieve verbale hallucinaties in verschillende groepen inderdaad hetzelfde symptoom betreffen, is te verwachten dat hersenactiviteit tijdens deze hallucinaties ook vergelijkbaar is bij verschillende groepen. Het doel van de studie, beschreven in **hoofdstuk 6**, was daarom om hersenactiviteit tijdens auditieve verbale hallucinaties te vergelijken tussen 21 psychotische en 21 gezonde personen die stemmen horen.
Deze studie liet zien dat psychotische en gezonde personen een groot aantal dezelfde gebieden activeren tijdens auditieve verbale hallucinaties. Dit is een eerste aanwijzing dat deze hallucinaties mogelijk hetzelfde fenomeen betreffen in gezonde en psychotische personen. Opmerkelijk is wel dat verschillen in karakteristieken van de auditieve verbale hallucinaties, zoals frequentie, controle over de hallucinaties en de

inhoud van de stemmen, tussen psychotische en gezonde mensen, niet geassocieerd lijken te zijn met verschillen in hersenactiviteit. Het blootleggen van een mogelijke associatie tussen hersenactiviteit en specifieke kenmerken van auditieve verbale hallucinaties is dan ook een belangrijk doel voor vervolgstudies.

2. Trait studies

De studies beschreven in hoofdstuk 7 en 8 van dit proefschrift richtten zich op het testen van twee invloedrijke theorieën die trachten het ontstaan van auditieve verbale hallucinaties te verklaren. Volgens de eerste theorie zijn de stemmen het gevolg van een verlaagde specialisatie van de linker hersenhelft voor taal. Verlaagde taallateralisatie (de verhouding tussen taalactiviteit in de linker en rechter hersenhelft) is inderdaad vaak gevonden in patiënten met schizofrenie. Tot nu toe is het echter onduidelijk of deze afwijking inderdaad gerelateerd is aan auditieve verbale hallucinaties of aan een ander symptoom van schizofrenie. Om dit uit te zoeken onderzocht de studie beschreven in **hoofdstuk 7** taallateralisatie in 35 gezonde stemmenhoorders, 35 psychotische patiënten en 35 controle proefpersonen. Aangezien gezonde stemmenhoorders geen last hebben van wanen, negatieve en cognitieve symptomen en geen medicijnen gebruiken, zijn ze een goed model om deze hallucinaties in relatieve isolatie te bestuderen. Het meest opvallende resultaat van deze studie was dat taallateralisatie niet significant verlaagd was in gezonde personen die stemmen horen. Het is daarom niet waarschijnlijk dat deze hallucinaties het gevolg zijn van een verlaagde dominantie van de linker hersenhelft voor taal.

Een andere invloedrijke theorie stelt dat auditieve verbale hallucinaties het gevolg zijn van een afwijkende samenwerking tussen taal- en geheugengebieden in de hersenen. Hoewel verstoorde connectiviteit geobserveerd is in schizofrenie patiënten is er tot nu toe geen directe link gevonden tussen afwijkende connectiviteit en auditieve verbale hallucinaties. Om vast te kunnen stellen of deze hallucinaties inderdaad gelinkt zijn aan afwijkende samenhang, richtte de studie beschreven in **hoofdstuk 8** zich op het onderzoeken van connectiviteit tussen taal- en geheugengebieden in 21 gezonde personen met auditieve verbale hallucinaties. Gezonde personen met auditieve verbale hallucinaties lieten afwijkende samenwerking zien tussen taalproductie en taalwaarnemingsgebieden. Dit zou erop kunnen wijzen dat gebieden in de hersenen die betrokken zijn bij taalwaarneming niet geïnformeerd zijn dat de taal door de persoon zelf gevormd is. Hierdoor zouden eigen gedachten gehoord kunnen worden. Hiernaast werd afwijkende communicatie gevonden tussen taalproductie- en geheugengebieden wat erop kan wijzen dat de hallucinaties aangezet worden door het geheugen.

3. Conclusie

De resultaten van de studies beschreven in dit proefschrift wijzen naar een aantal fenomenen gerelateerd aan auditieve verbale hallucinaties. Taalactiviteit, die tijdens auditieve verbale hallucinaties geobserveerd kan worden, wordt waarschijnlijk getriggerd door spontane herinneringen die niet als dusdanig herkend worden. Het feit dat de hallucinaties *gehoord* worden zou veroorzaakt kunnen worden door een verstoorde connectiviteit van taalproductie en – perceptie gebieden in de hersenen. Verlaagde taallateralisatie is anderzijds waarschijnlijk niet geassocieerd met deze hallucinaties.

Chapter 11

Dankwoord

De laatste vijf jaar heb ik een ontelbaar aantal e-mails, telefoontjes en meetings afgesloten met een woord van dank. Aan supervisors, mede-promovendi en vrienden. Dit illustreert sterk hoeveel mensen bij hebben gedragen aan het tot stand komen van dit proefschrift. Zonder hen was het er niet geweest.

In de eerste plaats gaat mijn dank uit naar mijn (co)promotoren Iris Sommer, Rene Kahn en Bas Neggers. Iris, jouw enthousiasme en veelvuldigheid aan ideeën motiveerde en inspireerde me vanaf de eerste minuut. Had ik nog geen idee hoe ik mijn onderzoek verder uit wilde werken, had jij alweer vijf ambitieuze plannen bedacht waaruit ik maar hoefde te kiezen. En als ik ze eigenwijs van de hand wees, wist jij me weer te helpen mijn eigen plannen verder uit te werken. Je hebt me de kans gegeven in een fantastische groep te werken, zelfstandig projecten te runnen en wat van de klinische praktijk te leren. Ik heb bewondering voor je kennis, vindingrijkheid en kijk op hoe ons onderzoeksveld zich zou moeten ontwikkelen. Hopelijk wordt ik ooit half zo'n goede onderzoeker als jij!
Bas, aan het begin van mijn promotietraject raakte ik onder de indruk van je snelle geest. Dit leidde er nog weleens toe dat mijn hoofd tolde en ik het idee had dat je in formules sprak. Gelukkig ging dat snel beter en hielp je me om in heldere termen to the point the komen. Ik heb ontzettend veel geleerd van je expertise op het gebied van fMRI, matlab en methodologie. Dank ook voor al je goede adviezen als ik weer eens ergens over twijfelde. Je had altijd mijn belang voorop. Zelfs toen ik je met de fiets aanreed zat je nog in over mijn gesneuvelde horloge.
Rene, hoewel wij minder contact momenten hadden, wist je bij onze meetings direct de rode draad te vinden die ik met mijn focus op detail soms uit het oog verloor. Dank voor je eerlijke mening en het meedenken over studies, subsidiemogelijkheden en toekomstplannen. Hoewel je me weleens eigenwijs noemde, heb ik erg veel geleerd van je kennis en inzicht in de wetenschappelijke wereld.

Met de sfeer op de afdeling psychiatrie zat het altijd goed. Die kwam voor een groot deel van de mede-promovendi bij stemmingsstoornissen en in het bijzonder Kirstin, Remko, Antoin, Willemijn, Thomas R., Lucija en Annabel. Het zit wel goed met die secundaire arbeidsvoorwaarden! Kirstin (KD2), zonder jou geen efficiënt gerunde spectrumgroep, taartvrijdagen, Primark-shopdagen, Oprah advies, Pub quizzen (Go Red Scientists!) en theespreukvergelijk. Wie zegt dat onderzoekers nerds zijn? Dank voor al je hulp met moeilijke mails, prioriteiten stellen en keuzes maken. Antoin, van transformerliefhebber tot Gelderse carnavalstijger. Als de radio hard ging met eighties en nineties hits, happy hardcore of Frans Duijts werd het pas echt gezellig. Wat waren de socials op congressen en summer schools leuk met jou. Knoop je hemd open en

ga los! Ik wil je ook bedanken voor je kritische blik, hulp met scannen en je eeuwige wetenschap relativerende humor. Je hield je goed staande tussen al die vrouwen op de afdeling. Remko, jij ging graag los over dat gebrek aan mannen en had binnen een jaar onze hele groep ingelicht over jouw 'onderzoek' naar man/vrouw verschillen. Dankzij jou weet ik nu dat ik een typische '6' ben, kwadrant 2 prioriteit moet geven en komma's zetten niet mijn grootste talent is. Het was altijd gezellig: tafeltennissen, recepten uitwisselen (hoe zit dat nou met dat man/vrouw verschil?) en vooral de borrels. Nog eens *stappen* of *statten* of wil je liever *je eigen ding doen*? Veel dank voor de goede discussies, adviezen en hulp bij het een miljoen keer nakijken van mijn manuscripten. Thomas R., de onderzoekswereld was het misschien niet voor jou, maar jouw inspanningen legden de basis voor het werven van een hele groep gezonde stemmenhoorders. Dank ook voor je gezelligheid en hulp bij mijn kennismaking met onderzoek.
Lucija, jij was mijn eerste stagiair en als bewijs dat ik er toch wel iets van bakte, besloot je een jaar later weer stage bij me te komen lopen. Blijkbaar deed ik het toch niet helemaal goed want na die tweede stage twijfelde je of je wel het onderzoek in wilde. Gelukkig ben je tot 'inkeer' gekomen. Anne W., Anouk N., Merel, Marleen, Carlijn, Lisette, Natanja, Romy en Sanne K., ik wil ook jullie bedanken voor al jullie enthousiasme, hulp en harde werk tijdens jullie stages. Zonder jullie waren mijn studies heel wat minder soepel en snel verlopen. Succes met afstuderen, promoveren of het bewandelen van andere carrièrepaden.
Ook de andere spectrumstagairs, onderzoeksassistenten Anne Lotte, Marieke B., Sanne V. en Lotte, de psychiaters en arts-assistenten Jaap, Marco, Steven, Chris, Metten, Elemi, Annet, Lot en Wanda wil ik bedanken voor de fijn sfeer op onze afdeling.

Verder wil ik de volgende mensen binnen het UMC bedanken. Julia voor de hulp bij het geven van psycho-educatie en begeleiden van patiënten, Inge W., Anne Lotte, Rene M., Anouk M. en Esben voor de hulp bij organisatorische zaken en het opzetten van MRS en ASL scans voor Optimise. Marian J., Hilleke, Rene K., Iris en Bas voor het schrijven van aanbevelingsbrieven voor subsidies. Yumas en Vincent voor het onderhouden en verrijken van onze data en rekenservers en Emmy, Elly, Jeanette, Tania, Maria, Linda (succes met je nieuwe baan) en Karin voor alle hulp bij het maken van brieven, faxen, inscannen en andere organisatorische kwesties.

Mijn mede-imaging promovendi, post-docs, senior onderzoekers en (ex)bewoners van de verschillende kantoortuinen wil ik bedanken voor de vele discussies, feedback op mijn onderzoek en gezelligheid op congressen en natuurlijk de borrels. Mariet (wat was de HBM2010 leuk), Tjerk (bij wie moet ik straks om HBO serie advies vragen?), Bram

(dank voor je hulp bij onze reliability & detectie studies), Janna (dank voor je resting state tips), Janna-Marie (dank voor de reward-taak tour), Cedric ('JAAP'), Neeltje (dank voor het regelen van de scanplanning), Mirjam (succes in Nijmegen), Florian (tja als mijn paranimf je als man kiest. Succes verzekerd!), Martijn M., Peter (samen patiënten scannen was hilarisch), Dora (dank voor de thee en wandeldates), Dienke (dank voor het scannen), Sanne R., Thalia, Sven, Marc, Inge S., Tamar, Marieke L., Patrick, Sarai, Esther, Mireille, Gayane, Mitzi, Anna, Erika, Marijn, Matthijs V., Matthijs B., Martijn H., Thomas S., Juliette, Rosanne, Muriel en eenieder die ik vergeten ben.

Tevens wil ik hierbij de leden van de beoordelingscommissie Hilleke Hulshoff Pol, Sarah Durston, Nick Ramsey, Frans Verstraten en Andre Aleman hartelijk danken voor het lezen en beoordelen van het manuscript van mijn proefschrift.

Naast UMCers is dit onderzoek voor een groot deel tot stand gekomen met hulp van onze collega's van de Parnassia Bavo Groep in Den Haag. Dank aan Jan Dirk Blom, Karin Slotema, Rutger Goekoop, Jasper Looienstijn, Anne-Marije Rijkaart, Audrey Fennema en Wijbrand Hoek voor de samenwerking.

Ik wil ook een woord van dank richten aan onze proefpersonen en patiënten. Jullie bereidheid om te spreken over zoiets persoonlijks als stemmen horen, maakte dit onderzoek mogelijk.

Lennert, ik wil je hartelijk bedanken voor het poseren voor de kaft van dit proefschrift. Als ik ooit iets terug kan doen? Willemijn, dank voor de fotoshoot, Theo voor het helpen bij het concept en de kleurstelling voor de kaft en Robin voor de photoshop hulp.

Willemijn S., Yael en Hanneke, mede-promovendi buiten de afdeling psychiatrie. Willemijn en Yael, ik wil jullie bedanken voor de gezellige dates waarin ik wetenschap eens vanuit een andere hoek kon bekijken en waarin we zowel wetenschappelijke als niet-wetenschappelijk toekomstplannen konden bespreken. Hopelijk doen we dat nog vaak!
Hanneke, wat was het heerlijk om met jou (en Willemijn G.) over de hobbels van de wetenschap te praten. Om de subsidiemolen samen te doorlopen en alles lekker te kunnen relativeren.

Lieve paranimfen Anne en Willemijn onze beider vriendschappen begonnen als kamer/ huisgenoten. Anne, hoewel we allebei gruwelijk dominant en het chronisch oneens kunnen zijn over zoiets onnozels als de grootte van champignons ben ik blij

dat we zo'n goede vrienden zijn. Met je gezelligheid, kritiek en coaching was je steeds een enorme steun. Ik zie er erg naar uit om weer lekker mutserig wijn met jou te drinken.
Willemijn G., toen ik je leerde kennen was ik aangenaam verrast door je enthousiasme en geloof in de goede kant van mensen. Hoewel mijn vorige kamergenote potten pindakaas leek te verzamelen, vulde jij onze kamer direct met lekkere theetjes, foto's, posters en kaartjes met allerlei boodschappen. Je knutselde bedankjes in elkaar, gaf me souvenirs na je vakantie en had soms een kleine attentie. Veel belangrijker was je immer luisterend oor en goede adviezen bij zowel werk als privédingen. Lieve paranimfen, ik ben blij dat jullie straks ook achter me staan.

Gelukkig zijn er ook heel wat mensen die niet door de wetenschapskoorts overgenomen zijn! Lieve niet-onderzoeks vrienden en familie dank jullie voor alle steun, interesse en geduld in de afgelopen jaren. Sas, Win en Nico, onze damesdates bestaan altijd uit heerlijk relaxte dagjes waarbij ik helemaal bij kan komen. Veer en Matthijs, jullie weten hoe je van het leven moet genieten. Zonder jullie is geen festival compleet. Wout, dat sparren blijven we doen! Roy, jouw compleet eigen kijk op de wereld blijft me fascineren. Jeroen, je vriendschap met Bram heeft je tot onderdeel van de inboedel omgetoverd. Je zelfverkozen rol als scheidsrechter was een welkome afwisseling na lange UMC dagen.

Mia, Theo, Rachel, Mark en Mees, ik voel me altijd thuis bij jullie. Dank voor jullie gezelligheid en nooit aflatende interesse in mijn onderzoek.

Robin en Carinja, bij jullie kan ik altijd helemaal ontspannen!

Lieve pap en mam. Hoewel jullie je soms niet kunnen vinden in mijn keuzes steunen jullie me altijd. Dank voor het vertrouwen en de basis die jullie me hebben meegegeven.

Bram, hoe kan zo'n babbelkous nu een vriend vinden bij wie ze geen woorden nodig heeft? Dank voor je liefde en onuitputtelijke geloof in mij. Dankzij jou durf ik steeds aan nieuwe dingen te beginnen. Wat wordt het deze keer? Afrika, de V.S. of toch weer Rio?

Chapter 12

List of Publications

1. Peer-reviewed journals

KMJ Diederen, K Daalman, AD de Weijer, SFW Neggers, W van Gastel, JD Blom, RS Kahn and IEC Sommer. Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. Schizophrenia Bulletin published online April 28 2011

KMJ Diederen, AD de Weijer, K Daalman, JD Blom, SFW Neggers, RS Kahn and IEC Sommer. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. Brain 2010, 133 (12): 3734-3744

KMJ Diederen, SFW Neggers, K Daalman, JD Blom, R Goekoop, RS Kahn and IEC Sommer. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. American Journal of Psychiatry 2010, 167:427-435

IEC Sommer and KMJ Diederen. Language production in the non-dominant hemisphere as a potential source of auditory verbal hallucinations. Brain (2009) 132 (10): e124

IEC Sommer, KMJ Diederen, JD Blom, AE Willems, L Kushan, CW Slotema, MPM Boks, K Daalman, W Hoek, SFW Neggers and RS Kahn. Auditory verbal hallucinations predominantly activate the right inferior frontal area. Brain 2008, 131 (12): 3169-3177

AD de Weijer, SFW Neggers, KMJ Diederen, R Mandl, RS Kahn, HE Hulshoff Pol and Iris EC Sommer. Aberrations in the arcuate fasciculus are associated with auditory verbalhallucinations in psychotic and in non-psychotic individuals. Human Brain Mapping in press

AD de Weijer, RC Mandl, KMJ Diederen, SFW Neggers, RS Kahn, HE Hulshoff Pol and IEC Sommer. Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. Schizophrenia Research published online June 3 2011

K Daalman, MPM Boks, KMJ Diederen, AD de Weijer, JD Blom, RS Kahn and IEC Sommer. Are auditory verbal hallucinations in healthy and psychotic individuals the same or different? Journal of Clinical Psychiatry 2011, 72: 320-325

JD Blom, J Looijestijn, R Goekoop, KMJ Diederen, AM Rijkaart, CW Slotema and IEC Sommer. Treatment of Alice in Wonderland syndrome and verbal auditory hallucinations using repetitive transcranial magnetic stimulation. A case report with fMRI findings. Psychopathology 2011, 44: 337-344

M Somers, SFW Neggers, KMJ Diederen, MPM Boks, RS Kahn and IEC Sommer. The measurement of language lateralization with functional Transcranial Doppler and functional MRI. A critical evaluation. Frontiers in Human Neuroscience 2011, 5: 31

CW Slotema, JD Blom, AD de Weijer, KMJ Diederen, R Goekoop, J Looijestijn, K Daalman, AM Rijkaart, RS Kahn, HW Hoek and IEC Sommer. Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial**.** Biological Psychiatry 2011, 69: 450-456

IEC Sommer, K Daalman, T Rietkerk, KMJ Diederen, S Bakker, J Wijkstra and MPM Boks. Healthy individuals with auditory verbal hallucinations; who are they? Schizophrenia Bulletin 2010, 36 (6): 633-641

IEC Sommer, JP Selten, KMJ Diederen and JD Blom. Dissecting auditory verbal hallucinations into two components: audibility (gedankenlautwerden) and alienation (thought insertion). Psychopathology 2010, 43:137-140

2. Submitted manuscripts

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

KMJ Diederen, SFW Neggers, AD de Weijer, R van Lutterveld, K Daalman, RS Kahn and IEC Sommer. Aberrant resting state connectivity in non-psychotic individuals with auditory hallucinations.

J Looijestijn, KMJ Diederen, R Goekoop, IEC Sommer, K Daalman, RS Kahn, HW Hoek and JD Blom. Out of our minds: the auditory 'where' pathway projects hallucinated voices into external auditory space.

IEC Sommer, M Clos, AL Meijering, KMJ Diederen and SB Eickhoff. Where the voices come from: Functional connectivity in patients with chronic hallucinations.

R van Lutterveld, A Hillebrand, KMJ Diederen, K Daalman, RS Kahn, CJ Stam and IEC Sommer. Decrease in theta-band power in the hippocampus during the onset of auditory verbal hallucinations.

3. Book chapters

KMJ Diederen and IEC Sommer. Auditory verbal hallucinations and language lateralization (chapter 11). Language Lateralization and Psychosis, edited by IEC Sommer and RS Kahn, Cambridge University Press 2009

KMJ Diederen and IEC Sommer. Auditory verbal hallucinations. Hallucinations. Research and Practice, edited by JD Blom and IEC Sommer, Springer, New York, New York. - To be published in January 2012

4. Conference abstracts

KMJ Diederen, AD de Weijer, K Daalman, SFW Neggers, RS Kahn and IEC Sommer. No deviant activation during verbal fluency in non-psychotic subjects with auditory hallucinations. Poster presentation at the Organization for Human Brain Mapping conference, Barcelona, Spain 2010

KMJ Diederen, SFW Neggers, K Daalman, AD de Weijer, RS Kahn and IEC Sommer. Language activation in psychotic and non- psychotic individuals with auditory verbal hallucinations. Poster presentation at the Schizophrenia International Research Society conference, Florence, Italy 2010

KMJ Diederen, AD de Weijer, K Daalman, SFW Neggers, RS Kahn and IEC Sommer. No deviant activation during verbal fluency in non-psychotic subjects with auditory hallucinations. Poster presentation at the Forum of European Neuroscience conference, Amsterdam, the Netherlands 2010

KMJ Diederen. Hersenactiviteit tijdens en voorafgaand aan auditief verbale hallucinaties. Oral presentation at the Spring Psychiatry Conference, Maastricht, the Netherlands 2010

KMJ Diederen. Brain activation and auditory verbal hallucinations. Oral presentation at the conference Joliot, Lille, France 2010

KMJ Diederen and IEC Sommer. Cerebral activity before and during auditory verbal hallucinations. Oral presentation at the World Federation of Societies of Biological Psychiatry, Paris, France 2009

KMJ Diederen. The temporal course of auditory verbal hallucinations: an fMRI study. Oral presentation at the Spring Psychiatry Conference, Amsterdam, the Netherlands 2008

KMJ Diederen, IEC Sommer, JD Blom, R Goekoop, M Wildeman, M Boks, B Neggers and RS Kahn. Brain activity preceding the experience of auditory verbal hallucinations. Poster presentation at the Organization for Human Brain Mapping conference, Melbourne, Australia 2008

IEC Sommer, KMJ Diederen, JD Blom, L Kushan, K Slotema, MPM Boks, K Daalman, HW Hoek, SFW Neggers and RS Kahn. Comparing auditory verbal hallucinations to inner speech in schizophrenia: an fMRI study. Poster presentation at the Organization for Human Brain Mapping conference, Melbourne, Australia 2008

Chapter 13

Curriculum Vitae

Kelly Maria Johanna Diederen was born on October 27 1983 in Heerlen the Netherlands. She graduated from high-school (Eijkhagen College in Landgraaf) in 2001 after which she started a Bachelor's degree program in Neuro- and Rehabilitation Psychology at the Radboud University Nijmegen. After obtaining her Bachelor's degree she was accepted into the Cognitive Neuroscience Research Master program of the Radboud University Nijmegen. She obtained her degree in Cognitive Neuroscience after completing an internship at the Department of Psychiatry at the University Medical Center Utrecht under supervision of Prof. dr. Iris Sommer. During this internship she investigated language lateralization and functional connectivity using functional MRI in individuals with auditory verbal hallucinations. This internship created the basis for her subsequent PhD-candidacy into the neural basis of auditory verbal hallucinations. She started her PhD candidacy at October 2006 at the University Medical Center Utrecht under supervision of Prof. dr. Iris Sommer, Prof. dr. Rene Kahn and dr. Bas Neggers.
In January 2012 Kelly will become a post-doctoral researcher at the group of Prof. dr. Wolfram Schultz at the University of Cambridge where she will investigate the neural correlates of reward.

Kelly Maria Johanna Diederen werd geboren op 27 oktober 1983 te Heerlen. Ze behaalde in 2001 haar VWO diploma aan het Eijkhagen College in Landgraaf. In datzelfde jaar begon ze aan de opleiding psychologie aan de Radboud Universiteit Nijmegen waarbij ze zich specialiseerde in de richting neuro- en revalidatiepsychologie. Na het behalen van haar Bachelor titel werd ze toegelaten tot de onderzoeksmaster Cognitive Neuroscience aan de Radboud Universiteit Nijmegen. Tijdens deze master liep ze een stage bij de afdeling volwassenen psychiatrie van het UMC Utrecht onder leiding van Prof. dr. Iris Sommer. Tijdens deze stage onderzocht ze taallateralisatie en functionele connectiteit met behulp van functionele MRI in personen die stemmen horen. Deze stage legde de basis voor haar hieropvolgende promotietraject naar het neurale correlaat van stemmen horen. In Oktober 2006 begon zij aan haar promotietraject bij de afdeling volwassen psychiatrie van het UMC Utrecht onder supervisie van Prof. dr. Iris Sommer, Prof. dr. Rene Kahn en dr. Bas Neggers.
Vanaf january 2012 zal Kelly werkzaam zijn als post-doctorale onderzoeker in de groep van Prof. dr. Wolfram Schultz aan de Universiteit van Cambrigde waar zij zich zal richten op de neurale correlaten van beloning.