Auditory Verbal Hallucinations

phenomenology and neurocognitive mechanisms

Kirstin Daalman

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fenomenologie en neurocognitieve mechanismen

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Prof. dr. R.S. Kahn

Voor pappa en mamma

Voor Vincent

I’m fine
but I hear those voices at night
sometimes

The Killers (Spaceman)

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General introduction

General Introduction

Auditory Verbal Hallucinations

"When I was about 16 years old and taking a walk outside, I suddenly heard a baby cry. I was distracted by the sound and started looking for this baby. I never found the baby, so I went home. In the following weeks, I kept on hearing the baby crying and a female voice that called out my name. In the following years I started hearing more voices around me, and while at first these voices were quite friendly and helpful, they later became very aggressive and threatening, frightening me. The number of voices kept growing. I didn't know where they came from; I started believing that they were deceased people, dwelling around before going to heaven or hell. Apart from hearing the voices, I also started seeing things around me. It became a whole other dimension or world that I started living in. It was hard to be in the 'regular' world, as they kept on threatening me and stealing my attention, saying things like 'That man is going to kill you' or 'We will torture you until the end'. I could not control or ignore them. Finally, after cognitive behavioral therapy and realizing that medication benefited me in making contact with other people, I learned to cope better with the voices. I now live in the real world although I still hear voices continually. I have learned to acknowledge that the voices are here, I do not fight them anymore. I have learned to live my own life instead of letting them live my life."
Christine, expert in voices.

Auditory verbal hallucinations (AVH) are best known for their occurrence in psychotic disorders. The story by Christine offers a clear example of how threatening and invalidating these voices can be in this context. Although antipsychotic medication offers a relief for the majority of these patients, in approximately 25% of them this medication remains insufficient (Shergill et al. 1998). Other treatment-options to eliminate the voices such as transcranial magnetic stimulation (TMS) are scarce and studies on their effectiveness have found inconsistent results. So while the need to find alternative treatment for AVH is strong, this is quite a challenge as the pathophysiology behind AVH still remains unknown. If we were to know where AVH originate and what brain structures or cognitive functions are involved in their formation, more specialized therapies could be developed to decrease or even eliminate AVH in patients whose lives are disturbed by them so greatly. As yet, the only therapeutic option for patients whose AVH remain despite adequate medical treatment, is learning to cope with the voices in daily life and thereby hopefully decreasing distress.

In the past decades an increasing number of studies have focused on the concept of AVH, i.e. hearing voices. They are a very heterogeneous concept, emerging in several disorders. In addition, they can be studied on many different levels (clinically, neuroimaging, electrophysiology, etc), leading to the proposal of several hypothesis concerning their origin. They are also investigated in different patient populations. Although this thesis will focus mainly on AVH in psychotic and non-psychotic individuals, this introduction will provide a more extended overview of the prevalence and phenomenology of auditory (verbal) hallucinations in other disorders. Furthermore, it will also describe several treatment options for psychotic patients who hear voices and finally it will summarize theories regarding the mechanism behind AVH. As the second aim of the research in this thesis is the investigation of neurocognitive mechanisms that may underlie the experience of AVH in psychotic patients and non-psychotic individuals, the main focus on theories concerning the origin of AVH will be in this domain.

Continuum

Many studies regarding AVH have only included psychotic patients. While AVH often occur in psychotic patients, this group also presents many confounding factors such as medication, additional symptoms such as avolition, lack of motivation and a general decline in cognitive functioning. One way to circumvent these disadvantages is to study AVH in non-psychotic and otherwise healthy individuals. In this group hallucinations occur with a lifetime prevalence of approximately 15% (for a review see Beavan et al. 2011), including individuals who hear voices once in their lifetime as well as quite frequently such as monthly, weekly or even daily. Yet, despite this, they are not disturbed in any way by these voices. These otherwise healthy individuals were furthermore able to finish their education, to found families, are medication naïve and have no history of admission to hospital, thus offering an excellent opportunity to study AVH in relative isolation.
Apart from the presence of voices in psychotic disorders and non-psychotic individuals, they can also be a symptom in several other psychiatric disorders such as borderline personality disorder or schizotypal personality disorder and post traumatic stress disorder (PTSD). In addition, AVH can be present in some somatic disorders, such as neurological disorders or hearing disorder. However, the presence of AVH in the general population (Aleman & Larøi, 2008), in otherwise healthy individuals who are not in need for care as described above, indicates that they are not necessarily a symptom or marker of a disorder. Because of this, psychotic symptoms have been proposed to lie on a continuum, ranging from rare occurrences in healthy individuals on one end, through individuals with schizotypal personality disorder, to psychotic patients with

frequent occurrence on the other end. It remains elusive however, whether AVH on both ends can indeed be viewed as similar phenomena. Some voice characteristics might be similar across this continuum, while others clearly differ. In addition to voice characteristics, other factors on both ends of the spectrum might differ, such as the biological or neurological basis or cognitive mechanisms that are involved. So although the continuum hypothesis is often described in studies, some authors remain critical about it. David (2010) suggests that we should define beforehand what results would imply continuity and discontinuity. In addition Luhrmann (2011) describes three categories within individuals experiencing AVH, with some more biologically based and others more influenced by culture. This raises the question whether both types of AVH can indeed be seen as lying on a continuum or whether a categorized view might be more appropriate.

Including both psychotic patients with AVH and non-psychotic individuals with AVH in studies allows for the comparison of AVH in these two groups. Not only can such a comparison provide information regarding the underlying mechanisms in AVH, it furthermore offers an opportunity to investigate whether these (neurocognitive) mechanisms are similar in both groups.

Auditory verbal hallucinations in different disorders and in the general population

AVH occur in several psychiatric disorders, in neurological disorders and in the general population. Although the voices can take many forms regarding for example number, loudness, frequency, gender, or emotional valence, some disorders have quite characteristic accompanying AVH, which will be described below.

Psychiatric disorders

Schizophrenia spectrum disorders

"You must die, you do not deserve to live. You must be punished. You stupid, ugly, fat pig. You must die. Everybody hates you. You do not deserve to live. Die, die, die, die!"

Characteristic for most psychotic patients is that their voices are derogatory, threatening and frightening, as described above. When these aspects of the voices are combined with a very high frequency (almost continuous) and no control, one can image that these patients suffer tremendously from their voices. The prevalence of AVH in patients with schizophrenia spectrum disorders is approximately 70% (Sartorius et al. 1986).

Borderline personality disorder

"Take that knife and cut yourself. You must be punished. You are bad, you are evil. Punish yourself! Take the knife and cut! You are bad and must punish yourself!"

In the past, AVH in borderline personality disorder were often considered as transient or misperceptions. However, a recent study by Slotema et al. (2012) shows that patients diagnosed with borderline personality disorder (BPD) experience AVH for long periods of time, with a high frequency, and high levels of ensuing distress. Hardly any differences were found in the phenomenological characteristics of AVH between psychotic patients and patients with borderline personality disorder, indicating that AVH in this patient group should not be considered as less severe. By investigating the associated distress of AVH individually, the risk of undertreatment is greatly reduced in this group. A study by Yee et al. (2005) also found that hallucinations in BPD were 'persistent, longstanding and a significant source of distress and disability'. In their study population almost 30% of the patients with BPD had a form of auditory hallucinosis.

Psychotic depression

The most prominent psychotic symptoms of a psychotic depression are delusions with topics like death, guilt, poverty or punishment. Hallucinations can also exist, most often visual hallucinations and AVH. The voices can condemn the patient for failings or sins. The hallucinations are often transitory and not very detailed.

Mania

"Yes my child, you are extraordinary. You were given this mission to spread my word. You are the connection between the divine and the earthly people".

Psychotic symptoms in a manic episode often comprise manic themes such as ideas of grandeur, inflated self esteem, power or knowledge. Patients often hear the voice of God and have the presumption that they were given a special mission on earth by Him. Prevalence of auditory hallucinations in manic-depressive patients was found to be approximately 17% in an early study (Bowman & Raymond, 1931)

Post-partum psychosis

Post-partum psychosis is possibly triggered by a rapid change in hormones after giving birth. The psychosis can include both delusions and hallucinations, and can also resemble a manic state (Sit et al. 2006). The newborn baby often plays a prominent role in the psychotic symptoms. Women can have the idea that the child must be killed and the voices may give commands to do this.

Somatic disorders

Epilepsy and migraine

"You have to visit grandma, you have to visit grandma, you have to visit grandma, you have to visit grandma, you have to visit grandma, you have to visit grandma, you have to visit grandma".

In epilepsy hallucinations are often auditory, although they can also occur in other modalities. Especially in temporal lobe epilepsy, the incidence of hallucinations is high (Torta & Keller, 1999). The AVH in epilepsy can resemble those in psychotic disorders and are often experienced as unpleasant although threats and commands are quite rare. Auditory aura, a symptom of temporal lobe epilepsy, can include auditory hallucinations (Florindo et al. 2006), both simple and complex (noises, music and (un) intelligible voices).

In migraine auditory hallucinations frequently consist of *non*verbal sounds such as single tones or a whistling sound. However, the accompanying auras in migraine are often visual, and only rarely auditory.

Dementia

Although hallucinations in dementias such as Parkinson's disease and Lewy body dementia are primarily visual, AVH can also occur and are most often accompanying the visual hallucinations as in complex hallucinations: people may see an old friend or deceased spouse and might hear these people speak to them. These AVH tend to be less distressing and frightening than in psychotic disorders. In Parkinson's disease auditory hallucinations are present in approximately 20% of patients (Fénelon & Alves, 2010). They might not always be a direct result of the disorder but rather a side-effect of dopaminergic medication.

Hearing loss (sensory deprivation)

"The itsy bitsy spider crawled up the water spout. Down came the rain, and washed the spider out. Out came the sun, and dried up all the rain. And the itsy bitsy spider, crawled up the spout again."

AVH can also occur after hearing loss, typically in the elderly and more so in women than in men (Cope & Baguley, 2009). They are known as the auditory variant of Charles Bonnet syndrome and often constitute of children's songs, nursery rhymes, or well-known poems or church songs. Although people may find that these AVH disturb their lives to some extent, they are rarely as negative or threatening as so often seen in psychosis.

Brain tumor
In some cases auditory verbal hallucinations can be the result of a brain tumor. Also after (successfully) finishing treatment for a brain tumor individuals can start hearing voices, sometimes years later (Isolan et al. 2010; Turkel et al. 2007)

Healthy individuals

"Don't worry, don't be afraid. No one will harm you. I will always protect you. If ever somebody is planning to hurt you, I will always warn you in time. You have nothing to worry about. You are safe, I'm with you".
Clearly, AVH in healthy individuals are not as distressing as in most psychiatric patients. They have been reported in a significant minority of the general population (for a review, see Beavan et al. 2011). As described above, approximately 15% of the general population reports hearing voices. This comprises individuals who hear their name called a few times in their life time as well as individuals who hear complete sentences on a fairly regular basis. On a phenomenological level, some differences between AVH in these groups were reported, mostly related to the emotional valence and associated distress (Honig et al. 1998). There is also an overlap in AVH on both ends of this continuum regarding the form of the voices, for example their location. The most distinguishing factor between non-psychotic or otherwise healthy individuals and psychotic patients is the 'need for care'. While healthy individuals experience no distress and seem in no way restricted by the voices in their functioning, the psychotic patients often require treatment in order to try and live a normal life. Luckily, several treatment options for these patients exist.

Treatment options

In the Voices Clinic of the University Medical Center Utrecht we treat psychotic patients who experience great distress due to their voices (AVH). This treatment can roughly be divided into two categories: With the help of antipsychotic medication or transcranial magnetic stimulation (TMS) we try to eliminate the voices. However, many patients that visit our clinic have been hearing voices for years despite pharmacological treatment. We therefore provide additional psychological (cognitive) therapy to try and reduce distress due to AVH in these patients. The treatment options provided in the Voices Clinic of the UMCU are described below.

Eliminating or reducing voices

Medication

Hallucinations in schizophrenia-spectrum disorders are treated with antipsychotic medication. Antipsychotic agents are usually divided into two categories: classic, or 'first generation antipsychotics' and atypical, or 'second generation antipsychotics' although this differentiation may not seem valid, as side-effects are not always different between these groups. If psychotic symptoms do not improve when using the first drug of choice (i.e. the patient is not in remission), another type can be tried, preferably one with a different receptor profile. When the second drug also fails to improve symptoms, clozapine is recommended. In several studies this antipsychotic agent proved superior over other types of antipsychotic medication (i.e. Kane et al. 1988; Chakos et al. 2001).

An important disadvantage of antipsychotic medication is its side effects. Some antipsychotics can lead to severe weight gain and sedation (for example olanzapine, quetiapine and clozapine). Other antipsychotic agents are associated with dystonia, Parkinsonism and akathisia. Unfortunately, these (often severe) side effects may lead to poor medication adherence. Despite these rather severe side-effects, most patients with schizophrenia-spectrum disorders need antipsychotic medication to achieve and maintain remission from psychosis.

Experimental treatment options, such as repetitive Transcranial Magnetic Stimulation (rTMS)

TMS has far fewer side effects than the medication described above and is thus a welcome additional candidate to induce relief from hallucinations. During TMS treatment a short strong electric pulse is send to the skull of the patient. This pulse creates a temporary yet strong magnetic field of approximately 1-3 Tesla which in turn induces a small electric pulse in the brain that can either activate or deactivate a relative small region of the outer layer of the cortex. In addition, the pulse is only able to affect the outer area of the brain, since it goes merely 1-2 cm into the brain. Because of this restricted effect, the location of the TMS has to be exact for the treatment to have any effect. In the treatment of voices, most studies target left temporoparietal cortex, as this stimulated location was found to be active during the experience of hearing voices in several previous studies. Due to strict safety guidelines (Wasserman et al. 1996), more serious side-effects such as epileptic seizures are rare. Other side effects like hearing loss or a headache can be easily prevented or resolved with the help of earplugs or aspirin, respectively.

Results regarding the efficacy vary greatly: some studies found significant improvements on hallucination severity (e.g. Hoffman et al. 1999a, 2000, 2005; Poulet et al. 2005;

Brunelin et al. 2006) while other studies fail to find a significant improvement (e.g. Fitzgerald et al. 2005; Jandl et al. 2006; Vercammen et al. 2009; Slotema et al. 2011, van Lutterveld et al. 2012). In a review by Slotema et al. (in press) a moderate effect size was found of rTMS on the severity of AVH. The treatment of AVH with rTMS is based on several parameters such as the stimulated location, the number of treatment sessions and frequency of rTMS (high or low frequency). Future research into these treatment parameters could provide a combination that is more effective compared to placebo in the treatment of medication-resistant AVH.

Reducing distress, improving quality of life

While antipsychotic treatment is still the primary form of therapy, psychotherapy is becoming a more widely accepted additional treatment. Medication is often discontinued by patients due to side-effects and lack of insight (Byerly et al. 2007; Elkis, 2007; Voruganti et al. 2008), and there are still large numbers of patients in which this antipsychotic medication does not offer enough relief. Therefore, more research on additional psychological treatment is becoming increasingly important. The most essential benefit of these psychological strategies is the reduction of distress and dysfunctional behavior as a result of the voices. While cognitive behavioural therapy (CBT) has been around for some 60 years, new strategies are still developed and tested for their efficacy.

Coping with voices protocol

The first step in helping patients to cope with their voices is starting a basic program that entails several simple and practical interventions. This method, called the 'coping with voices protocol' was developed in the Voices Clinic of the UMCU and combines various existing approaches. It aims at immediately alleviating distress and helps establish a therapeutic alliance for further treatment. First of all, it comprises psycho-education: explaining voice hearing, brain-activity and treatment options. Patients are furthermore asked to map their voices, in order to gain insight in specific situations, conditions or moments in which voices are more frequent or more distressing. Patients are also asked to try out a number of coping strategies and construe their own top 5 of most effective coping techniques in reducing distress accompanied by AVH. Another important part of the coping with voices protocol is 'healthy living', that focuses on sleep-patterns, daily activities, social contacts, physical exercise and eating habits and psycho-education on drug-use (for instance cannabis). As patients often get depressed or cope with low self-esteem due to the negative content of their voices,

they are encouraged to focus on the positive aspects of life, for instance with the help of a so called 'positive diary'. Finally, as relapse prevention, a warning protocol is made with the patient in which warning signals are described as well as actions that can be undertaken by themselves, family or friends.

Cognitive behavioral therapy (CBT)

The basic assumption in CBT is that it is not the experience of the voices itself that causes most distress, but in fact the appraisals or beliefs patients have regarding these voices. This can be illustrated with a so called ABC model: the A stands for *activating event* and thus the voice that is heard. While content of voices heard by patients is predominantly negative and derogatory, the distress that is experienced by the patients is caused by the *beliefs* the patient has concerning the voice, the ' B'. This belief in turn influences the following emotion that is experienced or action that is undertaken, the *consequence* (C). This ABC-model can be explained with the following example: imagine that you are asleep in bed and suddenly you awake because of a loud noise downstairs (activating event). What could you be thinking this loud noise is? (belief). Patients often answer that they might belief that there is a burglar in the house, trying to rob them. The consequence of this belief is then probably: feeling anxious and hide somewhere. However, another belief regarding the noise could also be possible. What if one thought: "oh, the cat has knocked over my vase again". This would probably lead to some irritation at most, but probably not the amount of anxiety that is experienced with the other belief about the burglar. This illustrates how different beliefs, based on the same activating event, can lead to different consequences (experienced emotions and actions that are undertaken). In the case of AVH, patients often have strong accompanying beliefs regarding their origin that might cause fear. For example they might think that the voices are from a secret organization that is hunting them down, or from demons that will hurt them or their loved ones. In addition, they can have beliefs about the fact that they hear voices: "I must be crazy hearing this", "I'm weak and powerless because of these voices". All these beliefs can be identified in the course of CBT and critically investigated, as they are often regarded by the patient as facts, or the 'truth'. During the course of therapy patients often find that these beliefs are untrue and unhelpful. By identifying and investigating them, they can often be adjusted and thereby decreasing or eliminating the accompanying negative and bothersome emotions. In addition to the cognitive component, the behavioral aspect of CBT involves behavioral experiments in which alternative ways to deal with situations are tested in an attempt to change one's feelings about them.

Cognitive-behavioral treatment has proven to be a useful complementary approach to psychopharmacology (Wykes et al. 2008). In addition, meta-analyses of trials with

general CBT for psychosis found effect sizes varying from small to medium (NICE 2009) and CBT for command hallucinations in particular show larger effect sizes (Trower et al. 2004). This makes CBT for hallucinations both an accepted and evidence based effective treatment.

Competitive Memory Training (COMET)

COMET is a relatively short training that can be offered to a patient on itself or within the context of CBT, it teaches to 'reexperience personal memories that are incompatible with the dominant voices; messages' (van der Gaag, 2012). A first central aim in this training is to get more emotionally detached from the voices and build self-esteem. When a patient has accomplished this, the way is paved for the second aim: creating distance from the voices, a more neutral way of dealing with them instead of engaging in/with them. In short, the training starts with establishing the theme of the voices, the negative feeling that is activated. This can be discovered with the help of a journal in which the patient writes down the content of the voices and accompanying thoughts or beliefs, emotions and actions that are evoked by it. When the patient and therapist have established the core theme of the voices with most negative emotions, the positive counter-theme can be established. This positive counter-theme has to be rehearsed by the patient in combination with the vocalization of a positive self-statement and the appropriate body-posture and facial expression. This re-living of the counter-theme has to be practiced several times a day. By doing this regularly, the accessibility of the positive network of this memory is enhanced. Therefore, after a few weeks, the positive image can be easily activated and combined with the imagined voices. Although patients find this hard at first, after several attempts, the negative feeling, evoked by the voices, is resisted and the positive image reigns: they are no longer emotionally affected by their voices.

After this stage, the patients learn to create distance from the voices. With the help of a bored or indifferent attitude towards the voices, the patient imagines that the voices diminish in sound or in vision/image. In this stage, the right posture and facial-expression are important to enhance this process.

The COMET training is offered in a protocol and can be given in eight sessions. A study regarding its efficacy found that in proved to primarily reduce depression, due to a reduction of power attribution, improvement of self-esteem, acceptance of voices and learning a less submissive attitude (van der Gaag et al. 2010, 2012)

Metacognitive Training (MCT)

As AVH are often accompanied by delusional beliefs regarding their origin, adjusting these beliefs might alleviate distress. Metacognitive training targets cognitive biases

that are an important factor in the formation and maintenance of delusions (Moritz et al. 2005). The training comprises eight modules that all start with psycho-education in which the respective bias is both normalized and explained within the context of psychosis (how this bias might enhance positive psychotic symptoms). The interactive training is usually offered in a group and the following domains are covered: attributional distortions, jumping to conclusions, bias against disconfirmatory evidence, theory of mind, overconfidence in memory and depressive cognitive patterns.
MCT resembles CBT for a great part, however an important difference is the way patients actively experience their cognitive biases with the help of exercises and tasks. A random controlled trial regarding the effectiveness of MCT showed that in patients MCT both delusion severity and conviction as well as jumping to conclusions, improved significantly more than in controls (Moritz et al. 2011).

All in all, several therapies are available that benefit most patients that hear voices. Some of these treatments are based on biological mechanisms that were found to be associated with hearing voices such as neurotransmitters (medication) or over activation in language systems (rTMS). However, cognitive theories regarding the origin of voices offer additional therapeutic possibilities (CBT, COMET and MCT), underlining the importance of this line of research.

Hypothesized models that are involved in the aetiology of AVH

Many theories have been postulated concerning the origin of AVH. Although most of them are able to explain the phenomenon of hearing voices to a large extent, not all are supported by empirical evidence in both psychotic patients with AVH *and* non-psychotic individuals with AVH. The main neurocognitive theories will be described, as well as their applicability in both AVH types.

Defective self-monitoring of inner speech

One line of theories concerning the origin of AVH comes from models stating that inner speech is not recognized as coming from one-self but are perceived as coming from an external source (Frith & Done, 1988). Self-monitoring entails signaling both your own actions and external events and being able to distinguish between them. In the case of auditory hallucinations, self-generated speech is misperceived as coming from an external source and thus experienced as a voice that is attributed to someone else. Defective self-monitoring is not related to the production of inner speech but rather

the failure to recognize that this inner speech is produces by oneself (Frith, 1992). Although this model can account for the perception of words that feel alien to the self, it does not explain the interpretation given by the individual. It also cannot explain why not every motor command ends up perceived as a hallucination. Another limitation of the self-monitoring theories is that they are not just linked to AVH but also seem to underlie several other psychotic symptoms.

Intrusive cognitions

Some studies suggest that AVH arise due to activated auditory representations that intrude into ongoing neural and cognitive processes (Badcock, 2010; Hugdahl et al. 2009). As a consequence AVH resemble intrusive cognitions: cognitions that are unwanted, uncontrollable and disrupt normal activity (Morrison, 2001, 2005). Evidence for this hypothesis comes from a study that shows a higher prevalence of intrusions in patients with schizophrenia and AVH compared to other psychiatric patients or controls (Morrison & Baker, 2000). In addition, Jones & Fernyhough (2006) found a higher amount of intrusions in healthy individuals with a high hallucination proneness compared to low hallucination proneness.

The content of the intrusions is speculated to lie in long term memory, episodic memory. Several imaging studies in which the medial temporal lobe is found to be abnormal regarding structure and functioning in schizophrenia patients with AVH provide evidence for this hypothesis (Behrendt, 2010; Jardri et al. 2011). In addition, trauma related intrusions can influence the content of AVH (Hardy et al. 2005; Scott et al. 2007) with respect to the voice of the abuser, the emotional tone of the voice or reliving episodes of the traumatic event. This suggests that neural mechanisms related to episodic memory can increase vulnerability to many hallucinatory experiences. It furthermore provides evidence for the diversity of phenomenological characteristics in AVH.
Intrusive memories are associated to AVH in both clinical and non-clinical individuals (Brébion et al. 2005, 1998; Moritz et al. 2001), underlining the similarity with regard to this aspect of the AVH mechanism.

Inhibition

In addition to intrusive cognitions, inhibition is also associated with the experience of AVH, since these irrelevant memories are not sufficiently suppressed. The term 'inhibition' is broadly used, comprising more types of processes and mechanisms. Most

evidence from studies on the involvement of inhibition in AVH points to an association between AH and *'intentional cognitive'* inhibition. Waters et al. (2006) found that the degree of inhibitory impairment was associated with the severity of AH. Moreover, the inhibitory failures were not associated with other symptoms and seem thus quite specific for the experience of AH in patients with schizophrenia. It remains unknown however whether impaired inhibition is also associated with AVH in non-psychotic individuals.

Cognitive model of the positive symptoms of psychosis

In this model Garety et al. (2001) describe two routes to the development of positive psychotic symptoms: one by cognitive and affective disturbances (including hallucinations and delusions) and the other by affective changes alone (excluding hallucinations and delusions). The cognitive disturbances entail both weakened inhibition of memories and difficulties in self-monitoring. These cognitive disturbances then lead to anomalous conscious experiences such as thoughts experienced as voices or heightened perception. It is important to note that at this point, these experiences have not yet become psychotic symptoms. Biased conscious appraisal processes are believed to be crucial for the anomalous experience to become a psychotic symptom. These appraisal processes influence the judgment that the experiences that may *feel* external, are actually externally *caused.*

The presence of cognitive biases and their influence on cognitive processes provides evidence for this hypothesis. A cognitive bias is the way in which an individual interprets his experiences, gathers information about the world and develops and maintains beliefs (So et al. 2010). Many cognitive biases are found to be related to different psychiatric disorders, among which psychosis. Allen et al. (2006) found that an externalization bias was associated with the predisposition to hallucinate in healthy subjects. And, as David (2004) claims, the externalization bias is required to assign a percept to an external source, without it an individual would merely be confused regarding the origin, it could have been something that was thought or heard.
The cognitive model by Garety et al. furthermore hypothesizes that stressful life-events and/or trauma facilitate external attribution biases and low self-esteem by their influence on the formation of negative and dysfunctional schemas. This highlights the impact of adverse experiences in addition to the cognitive and emotional (affective) influences.
The cognitive model is based on the experience of positive symptoms in the context of a psychotic disorder. It remains thus unclear to what extent these appraisals and underlying biases also play a part in the experience of non-psychotic AVH.

Top-down processing

In normal perception, bottom-up information coming from the senses, is combined with top-down information which contains previously encountered situations, prior knowledge and memories and mental imagery, leading to expectations (Behrendt, 1998). The balance between bottom-up and top-down processing can be distorted in such a way, that it is influenced to a higher degree by top-down factors. AVH are suggested to be the result of this imbalance, influenced by a stronger degree by expectations than actual perceptual input. The advantage of this theory is its ability to explain the more complex stimuli (voices) that individuals hear when exposed to noise (Margo et al. 1981; Young et al. 1987). Aberrant semantic top-down processing may play an important role in both psychotic AVH and non-psychotic AVH as it seems to be related to a higher level of hallucination proneness in healthy individuals (Vercammen & Aleman, 2010). In addition, attentional top-down processing also appears to be stronger in hallucinating patients (Aleman et al. 2003; Schneider & Wilson, 1983; Vercammen et al. 2008).

Integrated Cognitive Model of AH

The integrated model of cognitive mechanisms in auditory hallucinations (AH; Waters et al. 2012) is the most recent attempt to integrate empirical findings of cognitive mechanisms in AH in *both* clinical and non-clinical AH in a model. This model is elaborated upon previous models by Frith & Dolan (1997), Aleman et al. (2003) and Hugdahl (2009). In short, it comprises 4 stages of AH formation, source, form, content and meaning, in which specific processes are involved. Emotions can exert influence on all of these levels.

First, auditory stimuli arise from overactivation of functional networks related to language (**source**). This can be influenced by both environmental (external) and internal conditions. Impairments in signal detection lead to the perception of more ambiguous or salient signals. Possibly some of these signals like inner speech or intrusive memories are more likely to be experienced as AH, already influencing phenomenological differences between AH at this early stage.
From hereon, top-down processes influence form, content and meaning: The activated information is not properly suppressed by intentional inhibition mechanisms and becomes 'functionally autonomous' (**form**). Both expectations and hypervigilance influence the recurrence of these experiences: this in turn increases the presence of cognitive biases and reduces the threshold in accepting the signal as being real. The **content** of AVH can be influenced by several factors like expectations, mental

imagery and prior knowledge (e.g. memories) that influence perception, explaining why content is highly personalized. The **meaning** and interpretation of AH are influenced by both state and trait characteristics. Finally, as said, emotions exert their influence on all stages of this model. Phenomenological characteristics of AH may be explained by differences in severity of deficits in this model and a personalized interplay of these processes.

In conclusion, many cognitive processes are involved in the experience of AVH, each with their unique role in this complex interplay. Subtle variations in these different processes could probably account for phenomenological differences of AVH. It remains unclear to what *extent* these processes are involved in and contribute to AVH in both psychotic and non-psychotic individuals. The research in this thesis will hopefully shed more light on these remaining issues, by comparing the two AVH groups (psychotic and non-psychotic) on several (cognitive) measures.

Outline of this thesis

The first part of this thesis will focus on phenomenology of AVH and describes the healthy, non-psychotic individuals that hear voices as well as the voices themselves. The second part investigates neurocognitive factors that may be involved in the mechanism(s) behind AVH.

Phenomenology

As AVH have been described in the general population it remained unclear whether these individuals are truly free from any psychiatric symptoms. To describe this group of individuals, who hear frequent voices, the study in **chapter 2** investigates the non-psychotic individuals with AVH. They are compared to healthy non-hallucinating controls on several clinical measures in order to screen for differences that could provide clues as to why these individuals start hearing voices.

After describing the non-psychotic individuals with AVH, the next step is to describe their *voices*. In what way do AVH in non-psychotic individuals resemble AVH in psychotic patients? **Chapter 3** investigates many characteristics of voices and compares them between these two groups.

Neurocognitive mechanisms and AVH

Different cognitive models have tried to explain the mechanism(s) behind AVH. Most of these studies investigated cognitive functioning in hallucinating psychotic patients. Disadvantages of this study population are confounders such as additional symptoms, use of antipsychotic medication, and in some cases frequent hospitalization. Therefore the study in **chapter 4** investigates cognitive functioning in *non-psychotic* individuals, and this is compared to that of healthy controls. Impaired or aberrant functioning of the hallucinating group may provide clues for cognitive factors that are involved in the AVH-mechanism.

Another cognitive factor hypothesized to play a crucial part in the experience of AVH is overreliance on top-down processing. The study in **chapter 5** investigates and compares the influence of this cognitive phenomenon with the help of a semantic top-down task in healthy non-hallucinating controls and psychotic and non-psychotic individuals with AVH. Not only will this study provide insight in the influence of semantic top-down processing on the neurocognitive mechanism behind AVH, comparing the two AVH groups on this measure will also assess whether AVH in both groups are influenced to the same extent by it.

Apart from aberrant cognitive functioning, cognitive biases could also play a part in the vulnerability to experience AVH. These biases are prevalent in several psychiatric disorders among which psychosis. The study in **chapter 6** explores the presence of several of these biases (intentionalising, catastrophising, dichotomous thinking, jumping to conclusions and emotional reasoning) in a group of non-psychotic individuals with AVH and compares it to psychotic individuals with AVH and healthy controls. The aim is to investigate whether these biases are associated with the experience of AVH as a psychotic symptom, as these biases influence the appraisals about the voices.

Many studies so far have described the association between trauma during childhood and the experience of hallucinations later in life. It remains unclear however whether childhood trauma influences the mere presence of AVH, regardless whether this is in the context of a psychosis, or whether it mainly colors the content of these voices. If the first option were true, trauma can apparently induce a biological change that might lead to hearing voices. If trauma influences content of voices, it would mainly exert a cognitive influence. The study in **chapter 7** further explores this association between childhood trauma and the presence of AVH later in life. The prevalence of five types of childhood trauma (emotional, physical and sexual abuse and emotional and physical neglect) is compared between healthy controls and psychotic and non-psychotic individuals with AVH. In addition, this study investigates whether AVH

characteristics such as emotional valence of content, frequency or control are related to the presence of childhood trauma. Based on the results, a neurocognitive theory is offered explaining how the impact of childhood trauma on brain and cognition can lead to the experience of AVH.

Summary and general discussion

Finally, **chapter 8** provides a summary and general discussion of the findings described in this thesis.

Part I

Phenomenology

Chapter 2

Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects

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Abstract

Introduction

Epidemiological studies suggest that auditory verbal hallucinations (AVH) occur in approximately 10%-15% of the general population, of whom only a small proportion has a clinically relevant psychotic disorder. It is unclear whether these hallucinations occur as an isolated phenomenon, or if AVH in non-clinical individuals are part of a more general susceptibility to schizophrenia.

Method

For this study, 103 healthy individuals with frequent AVH were compared to 60 controls matched for sex, age and education. All participants were examined by a psychiatrist using standardized diagnostic interviews and questionnaires.

Results

The individuals with AVH did not have clinically defined delusions, disorganization, negative or catatonic symptoms, nor did they meet criteria for cluster A personality disorder. However, their global level of functioning was lower than in the controls and there was a pronounced increase on all sub-clusters of the Schizotypal Personality Questionnaire (SPQ) and the Peters Delusion Inventory (PDI), indicating a general increased schizotypal and delusional tendency in the hallucinating subjects. History of childhood trauma and family history of Axis I disorders were also more prevalent in these individuals. We showed that higher SPQ scores, lower education and higher family loading for psychiatric disorders, but not presence of AVH, were associated with lower global functioning.

Conclusions

Our data suggest that AVH in otherwise healthy individuals are not an isolated phenomenon, but part of a general vulnerability for schizophrenia.

Introduction

Auditory verbal hallucinations (AVH) are a characteristic symptom of schizophrenia (Sartorius et al. 1986). Population studies demonstrated that AVH are not specific for schizophrenia, but also occur in non-clinical subjects. For example, Tien (1991) reported a lifetime prevalence for AVH of 10% in men and 15% in women in the U.S. Similar prevalences have been reported in France (16%; Verdoux et al. 1998) and New Zealand (13%; Poulton et al. 2000). Johns et al. (2002a) found that 25% of subjects reporting hallucinations met criteria for psychosis. Little is currently known about the other 75%, i.e. individuals with AVH who are not in need of treatment. AVH in healthy subjects may exist as an isolated symptom, which would suggest that the predisposition to experience AVH can be present separately from the vulnerability to other aspects of schizophrenia. Alternatively, non-clinical subjects with AVH may have an attenuated form of schizophrenia, for instance with a paranoid tendency, sub-clinical levels of disorganization, mild negative symptoms and decreased global functioning. In that case, these subjects may share vulnerability factors with schizophrenia patients. In order to differentiate between these 2 possibilities, we investigated a substantial sample of subjects with AVH after screening for DSM-IV axis I and II pathology using standardized diagnostic interviews in all participants. 115 non-clinical subjects with AVH and 60 control subjects matched for age, sex and education were assessed for psychiatric diagnosis, Global Assessment of Functioning (GAF), family history of psychiatric disorders, schizotypal tendency, delusion proneness, personality structure and history of childhood trauma. We hypothesized that healthy individuals with AVH differ from matched controls without AVH, in particular, that they would show elevated levels of paranoid and schizotypal tendency, family history of psychiatric disorder and history of childhood trauma, and lower levels of global functioning.

Method

Subjects

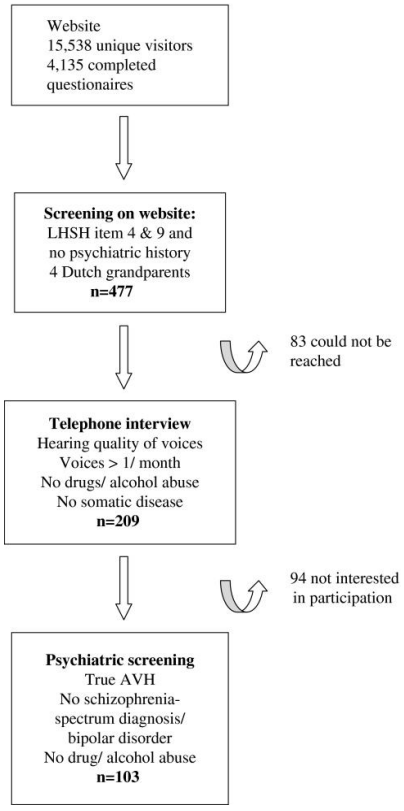
A website providing information about hearing voices was designed specifically for this study (www.verkenuwgeest.nl) and advertised by interviews on radio, television and newspapers. Visitors of this website were invited to fill out a questionnaire on AVH, based on a modified version of the Launay and Slade Hallucination Scale (LSHS; Larøi et al. 2004), a self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals.

Between March 2006 and March 2008, 15,538 subjects visited this website, of whom 4,135 completed the questionnaire. Subjects with high scores on item 4 and 9 of the LSHS (item 4: "In the past I have had the experience of hearing a person's voice and then found that there was no-one there", item 9: "I have been troubled by hearing voices in my head") were selected. Trained psychologists interviewed these

subjects by telephone. Subjects were included if they met the following inclusion criteria: (1.) voices were distinct from thoughts and had a "hearing" quality (2.) voices were experienced at least once a month (3.) no diagnosis or treatment for psychiatric disorders other than depressive or anxiety disorders in remission (4.) no alcohol or drug abuse for at least 3 months (5.) no chronic somatic disorder (6.) 18 years of age or older. (7.) 4 Dutch-born grandparents (to restrict heterogeneity for later genetic studies).
A total of 477 subjects had a summed score of at least 7 on the items 4 and 9. From these, 83 could not be reached by telephone and another 94 were not interested in participation. Several subjects were found unsuitable for inclusion: 98 did not fulfill criterion 1, 18 did not meet criterion 2, 60 did not meet criterion 3 and 9 did not meet criterion 4. The selection procedure is illustrated in figure 1.

A total of 115 individuals fulfilled all criteria and agreed to participate. Sixty control subjects who scored zero on item 4 and 9 of the LSHS and also met criteria 3-7 were recruited from the same website. Control subjects were matched for sex, age and education.
The study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the participants, written informed consent was obtained.

Figure 1. Flow diagram of the selection procedure.



Measurements

Psychiatric assessments

All individuals were assessed by a trained psychiatrist for affective and psychotic DSM-IV axis I pathology using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al. 1992). Global functioning was estimated using the GAF scale. GAF was scored as the highest level of functioning over the past year, defined by the lowest score in social, psychological or professional functioning. The presence of AVH was not interpreted as a "severe psychiatric symptom", which would have led to a maximum GAF score of 50 for all individuals with hallucinations.

To assess axis II pathology, the SCID-II interview (First et al. 1995a,b) was added to the psychiatric screening 6 months after the start of the study. The first 43 subjects with AVH were therefore not assessed with the SCID-II interview, nor were the 60 control subjects. Psychiatric disorders in family members of the participants were quantified using the Family Interview for Genetic Studies (1992). Urine samples were

obtained to screen for drug abuse (cannabis, amphetamine, cocaine, methadone and heroine). Positive screen for either of these substances led to exclusion.

Hallucinations
Characteristics of the hallucinations were assessed in an interview composed of the PSYRATS Auditory Hallucinations Rating Scale (AHRS; Haddock et al. 2001) and the LSHS.

Questionnaires
In addition to the interview, subjects filled out the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), the Peters Delusion Inventory (PDI; Peters et al. 2004), the Revised NEO Personality Inventory (NEO-PI-R; McCrae et al. 2005) and the brief version of the Childhood Trauma Questionnaire (CTQ; Bernstein et al. 2003), assessing schizotypal tendency, delusional tendency, personality structure (the "Big Five") and childhood trauma respectively.

Statistics
Scores were compared between groups with and without AVH using 2-tailed independent sample t-tests (total scores) or multivariate general linear models (GLMs), independent samples (subscores). Fisher Exact test was used to test differences in the prevalence of affective disorders and suicide attempts. Multivariate GLM with the number of family members as a covariate was used to compare family loading for psychiatric disorders and inflated type I error rate due to multiple testing. We used logistic regression with membership to the AVH or control group as dependent variable and schizotypal tendency, personality structure, childhood trauma and family loading as predictors to control for possible confounding. Due to the strong correlation between sub-scores we entered either total scores or the most significant sub-score in the regression model in order to avoid collinearity. We subsequently used linear regression with GAF score as the dependent variable and our main outcome measures as indicators to investigate the impact of these measures on global functioning. Explorative correlation analyses were performed with either Spearman's correlation or Pearson's depending on the distribution of the variables. All analyses were conducted using the statistical package for social sciences (SPSS version 12.1).

Results

Exclusions

From 115 individuals in the AVH group, 2 were excluded because they were not regarded as experiencing hallucinations. Based on the CASH interview, 5 subjects were diagnosed with schizophrenia, 2 with bipolar disorder and 3 with alcohol or drug abuse. Since we aimed to describe healthy subjects with AVH, these 12 subjects (11 percent) were excluded from further analyses. None of the controls met criteria for current psychiatric disorder. No subjects of either group had a positive urine test for illicit drugs.

Data on 103 subjects with AVH (73 females and 30 males) and 60 subjects without AVH (42 females and 18 males) were used for further analysis.

Demographic variables

Because the subjects of both groups were matched for sex, age and education, there were no significant differences between the groups on these variables. Other demographic measures were also similar between the groups: the percentage that was married or divorced, mean number of children, mean income and the percentage of subjects that had needed extra help at school (remedial teaching or coaching) or had received special education. Subjects with AVH were right-handed in only 80% of the cases compared to 87% in the controls, which was a significant difference. The mean values for these demographic variables are summarized in table 1.

Table 1. Demographic Variables of the Samples

	Subjects With AVH (n = 103)	*Subjects Without AVH (n = 60)*	*Statistic*	*P Value*
Age, y (SD)	44 (13), range = 19-64	46 (15), range = 22-60	*F* = 1.0, *df* = 153	.1
Married (%)	54	48	*F* = 0.47, *df* = 153	.49
Divorced (%)	22	33	*F* = 1.1, *df* = 153	.29
Mean number of children (SD)	1.9 (0.4)	1.7 (0.3)	*F* = 1.06, *df* = 153	.3
Mean income (€/mo)	2238.7	2213.4	*F* = 2.67, *df* = 153	.1
Years of education (SD)	13 (6)	12 (5)	*F* = 0.8, *df* = 153	.37
Extra help at school or special education (%)	45	44	*F* = 0.19, *df* = 153	.66
Hand preference (% right handed)	80	87	*F* = 11.8, *df* = 153	**.001**

Note: AVH, Auditory verbal hallucinations

Hallucinations

Individuals with AVH had experienced this symptom for a mean period of 29 years (SD 17, range 2-56). Their mean age at first experiencing voices was 14 (SD 14, range 2-57). Over the last week subjects had experienced a mean of 3.6 (SD 1.4) AVH. The mean duration of the AVH was 128 seconds (SD 153). Eighteen percent of the subjects had commenting voices and 11% had voices speaking with each other, which are considered first rank symptoms (Nordgaard et al. 2008). The majority (71%) never heard AVH with a negative content, 25% heard both positive and negative messages, while 4% experienced AVH with a negative content only. The large majority (91%) reported no disturbance of daily life by their voices, 9% experienced moderate disturbance by the AVH and none of them experienced severe disturbances. From the 103 subjects with AVH, 58% attributed the voices to an external source, mostly benevolent spirits. Sixteen percent believed that the AVH were internally generated and 27% were uncertain about the origin of the voices. Fifty-five percent reported that they could stop the AVH at inconvenient moments. Most individuals with AVH experienced hallucinations in several modalities, such as visual (lifetime prevalence: 79%), taste (lifetime prevalence 25%), olfactory (lifetime prevalence 63%) and tactile (lifetime prevalence 53%). Several subjects from the control group had also experienced hallucinations in other modalities: 50% visual, 13% taste, 39% olfactory and 22% tactile, but not in the auditory domain.

Launay Slade Hallucination Scale

The LSHS was available from all participants. The mean total score on the LSHS was 40 (SD 11) for subjects with AVH and 6 (SD 5) for controls ($t=21.0$, $df=162$, $P<.0001$). Mean scores on sub-groups of the LSHS are shown in table 2.

Table 2. Mean Scores, SD, and Statistics of the Main Outcome Measures

Measure	*Subjects With AVH (n = 103)*	*Subjects Without AVH (n = 60)*	*Statistic*	*P Value*
Hallucinatory Experiences (LSHS)				
Total score (SD)	*40.0 (11.1)*	*5.9 (4.6)*	*t* = 212, *df* = 162	***.001***
Sleep related (SD)	6.1 (2.4)	1.4 (1.8)	*F* = 147	**.001**
Vivid daydreams (SD)	7.3 (3.2)	0.9 (1.6)	*F* = 179	**.001**
Intrusive thoughts (SD)	7.3 (4.2)	1.9 (1.8)	*F* = 78	**.001**
Auditory hallucinations (SD)	7.3 (2.6)	0.1 (0.4)	*F* = 406	**.001**
Visual hallucinations (SD)	8.5 (3.6)	0.7 (1.4)	*F* = 227	**.001**
Schizotypy (SPQ)				
Total (SD)	*26 (11.0)*	*8 (6.0)*	*t = 12.8, df = 162*	***.001***
Cognitive-perceptual (SD)	15.4 (5.7)	3.7 (3.1)	*F* = 207.0	**.001**
Disorganization (SD)	5.7 (3.8)	2.2 (2.3)	*F* = 38.1	**.001**
Interpersonal (SD)	5.6 (5.0)	2.6 (2.5)	*F* = 17.5	**.001**
Personality (NEO-PI-R)				
Neuroticism (SD)	139.3 (12.2)	138.6 (8.0)	*F* = 2.286	.133
Extraversion (SD)	144.5 (10.8)	144.1 (7.1)	*F* = 1.921	.168
Openness (SD)	148.0 (11.3)	143.5 (9.2)	*F* = 5.776	**.018**
Agreeableness (SD)	148.8 (11.9)	150.4 (8.9)	*F* = 0.056	.813
Conscientiousness (SD)	155.4 (8.1)	155 (7.2)	*F* = 0.021	.885
Childhood trauma (CTQ)				
Total	*31.2 (11.1)*	*24.1 (4.4)*	*t = 5.2, df = 153*	***.001***
Emotional abuse (SD)	9.8 (4.9)	7(2.2)	*F* = 23.21	**.001**
Physical abuse (SD)	6.3 (3.3)	5.5 (1.5)	*F* = 4.18	**.043**
Sexual abuse (SD)	7.3 (4.5)	5.7 (1.3)	*F* = 9.60	**.002**
Emotional neglect (SD)	1.7 (0.8)	1.5 (0.5)	*F* = 5.56	**.020**
Physical neglect (SD)	4.7 (1.2)	4.4 (0.7)	*F* = 2.02	**.158**
Delusional Tendency (PDI)				
Preoccupation	13.6 (6.5)	3.5 (2.8)	*F* = 90	**.001**
Conviction	13.2 (7.4)	3.8 (2.8)	*F* = 84	**.001**
Distress	3.7 (4.9)	0.9 (1.1)	*F* = 15	**.001**
Family loading (FIGS)				
Total	*0.13 (0.12)*	*0.05 (0.08)*	*t = 4.6, df = 157*	***.001***
Depression (SD)	0.07 (0.09)	0.03 (0.06)	*F* = 4.14	**.02**
Psychosis (SD)	0.009 (0.02)	0.0009 (0.007)	*F* = 2.83	.06
Mania (SD)	0.005 (0.02)	0 (0)	*F* = 3.06	**.05**
Alcohol/drugs (SD)	0.04 (0.06)	0.02 (0.04)	*F* = 3.86	**.02**
Personality disorder (SD)	0.005 (0.02)	0.004 (0.002)	*F* = 0.126	.287

Note: AVH, Auditory verbal hallucinations; SPQ, Schizotypal Personality Questionnaire; LSHS, Launay and Slade Hallucination Scale; PDI, Peters Delusion Inventory; CTQ, Childhood Trauma Questionnaire; FIGS, Family Interview for Genetics Studies

Diagnosis and GAF

Axis I

Many subjects with AVH and a substantial part of the controls reported paranormal

beliefs, frequently about predestination and the existence of entities. Since these ideas are generally accepted in a large subgroup of the Western population (Ross & Joshi, 1992), they were not scored as delusions. Disorganization, catatonic or negative symptoms were absent in both groups. Twelve subjects with AVH fulfilled criteria for a single depressive episode in complete remission, 4 met criteria for recurrent depressive episodes, in full remission and one subject obtained diagnosis of dysthymia, in complete remission, the others did not meet criteria for *DSM-IV* diagnosis of psychotic or affective disorder.
In the control group, 5 met criteria for single depressive episode in complete remission, 2 for recurrent depressive episodes, in full remission and 2 subjects obtained diagnosis of dysthymia, in complete remission. The prevalence of affective disorder was similar in both groups (Fischer Exact test, P=1.0). Eleven subjects with AVH, but none of the controls ever made a suicide attempt (Fischer Exact test, P=.007).

Axis II
Complete SCID-II interviews were available from 60 subjects with AVH. There were no significant differences in age, sex, education and psychopathology between the 60 subjects who completed the SCID-II interview and the 43 who were not assessed due to the late start of the SCID-II interview, suggesting that no selection bias has occurred. From the 60 subjects with AVH who completed this interview, 2 fulfilled criteria for borderline personality disorder, 1 for histrionic personality disorder and 1 for narcissistic personality disorder.

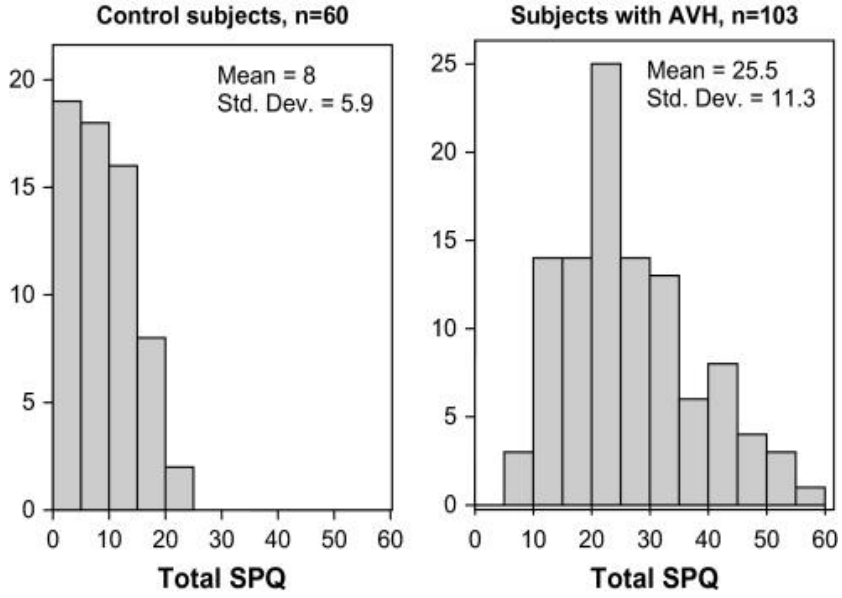
Global Assessment of Functioning
GAF scores were available from all participants. The mean GAF score was 82 (SD 7) for the subjects with AVH and 87 (SD 5) for the controls (t=-5.5, P<.001).

Family Interview for Genetic Studies
The FIGS was completed for all subjects. After controlling for the number of first and second degree family members, relatives of participants with AVH had significantly higher prevalences of depression (F=4.14, P=.018), substance abuse (F=3.9, P= .02) and mania (F=3.1, P=.05). A similar trend was present for psychosis (F=2.8, P=.06) but not for personality disorder. Data are provided in table 2.

Schizotypal Personality Questionnaire
All participants completed the SPQ. Mean score on the SPQ was 26 (SD 11) for subjects with AVH and 9 (SD 6) for controls (t=12.8, P<.0001). The increased SPQ score in the AVH group was not caused by a subgroup with extreme SPQ scores, but resulted from a general increase in SPQ score of the whole group (figure 2). Analysis of the item-clusters of the SPQ showed higher scores in subjects with AVH

for all clusters (Cognitive-Perceptual: $F_{157,3}$=207, *P*<.0001, Disorganization: $F_{157,3}$=38, *P*<.0001, Interpersonal: $F_{157,3}$=17.5, *P*<.0001). Means are shown in figure 2.

Figure 2. Frequency histograms of the total SPQ score for control subjects and for subjects with AVH.



Peters Delusion Inventory

All participants completed the PDI. Analysis of summed total scores showed higher scores for preoccupation with delusional ideas in hallucinating individuals ($F_{160,3}$= 90, *P*<.0001) than in controls. They also scored higher on conviction ($F_{160,3}$=84, *P*<.0001) and distress ($F_{160,3}$=15, *P*<.001). Means are provided in table 2.

Revised NEO Personality Inventory

Completed NEO-PI-R questionnaires were available from 94 subjects with AVH and from all controls. Analysis of the 5 clusters ("Big Five") yielded higher scores for hallucinating subjects for the cluster "Openness to Experiences" ($F_{147,5}$=5.8, *P*=.02), which was caused by higher scores on the sub-cluster "Esthetics". Mean scores for all clusters are provided in table 2.

Childhood Trauma Questionnaire

Completed CTQs were available from all control subjects and from 94 participants with AVH. Higher scores were found for the individuals with AVH on 4 of the 5 sub-clusters.

Mean scores on these sub-clusters are provided in table 2.
We found significant correlations between total trauma score and total scores on the PDI and SPQ in both groups. Within the AVH group, trauma was correlated with the SPQ- and PDI scores (r=0.39, *P*=.002) and (r=0.54, *P*<.001) respectively. In the control group these correlations were lower: 0.28 (*P*=.008) for both measures.

Combined analysis

A logistic regression model predicting presence or absence of AVH had a good fit (goodness-of-fit test, χ^2=127.4, *P*<.001) and the Nagelkerke approximation of R-squared was high: 0.80. PDI scores were removed from the model due to high correlation with SPQ scores (Pearson r=0.69, *P*<.001); inclusion would have lead to unacceptable collinearity. Table 3 shows that SPQ score was the most significant indicator of the model (*P*<0.001). Family loading for psychiatric disorders showed borderline significance (*P*=.054).

Table 3. Logistic Regression Model: Variables Prediction Presence/Absence of Auditory Verbal hallucinations

	B	*SE*	*Wald*	*Significance*
SPQ total	0.14	0.03	29.17	**.001***
Total trauma	0.04	0.05	0.64	.424
Family loading	5.99	3.10	3.73	.054
NEO-PI-R Openness	0.01	0.03	0.11	.740

Note: Neo-PI-R Revised NEO Personality Inventory.
* Significant at .05 level.

To investigate the impact of AVH and the other measures on global functioning we used a linear regression model with GAF score as outcome measure and sex, gender, education, total trauma score, NEO-personality, family loading for psychiatric disorders and SPQ as indicators. PDI scores were treated similarly as in the logistic regression. The model had a good fit (ANOVA, F= 6.3, *df*=8, *P*<.001) but limited R^2 (0.24). Family loadings for psychiatric disorders, number of years of education and SPQ scores significantly influenced global functioning, while presence of AVH did not (table 4).

Table 4. Linear Regression Model: Variables Predicting GAF Score

	B	*SE*	*t*	*Significance*
NEO-PI-R Openness	-0.05	0.057	-0.91	0.36
Family loading	-9.69	4.786	-2.03	**0.04***
Total trauma	0.03	0.057	0.43	0.67
SPQ total	-0.07	0.024	-2.95	**0.004***
Age	-0.05	0.039	-1.21	0.23
Years of education	0.59	0.218	2.70	**0.008***
Gender	0.90	1.136	0.79	0.43
AVH (present/absent)	-1.37	1.435	-0.96	0.34

Note: GAF, Global Assessment of Functioning; Neo-PI-R Revised NEO Personality Inventory; SPQ, Schizotypal Personality Questionnaire; AVH, auditory verbal hallucinations.
* Significant at P < .05 level

Discussion

This study describes a healthy group with AVH and assesses whether AVH in this group occurred as an isolated phenomenon, or was part of a subtle schizotypal tendency. The experimental group consisted of 103 individuals selected through a Web site, who had experienced AVH for a long time (mean period of 29 years) mostly since early adolescence. Apart from AVH, they also had increased prevalences of other perceptual abnormalities, such as sleep related hallucinatory experiences, visual hallucinations, vivid day dreams and intrusive thoughts. This group was contrasted to 60 individuals, matched for age, sex and education who never experienced AVH and were selected using the same procedure. After standardized psychiatric assessments for DSM-IV axis I and II pathology in face-to-face interviews by trained psychiatrists, we found that the subjects with AVH did not have clinically relevant delusions, disorganization or negative symptoms, nor did they meet criteria for schizotypal, schizoid or paranoid personality disorder. Moreover, prevalences of other personality disorders were similar to those observed in the normal population (Sperry, 2003). Despite the absence of clinical symptoms other than the hallucinations, pronounced differences between the control and the AVH group were found in non-pathologic schizotypal and delusional tendencies by means of the SPQ and the PDI respectively. In addition to high scores on positive items of the SPQ, such as perceptual abnormalities and magical thinking, subjects with AVH also scored higher on negative items and disorganization. Increased mean SPQ scores could not be attributed to a subgroup with extreme SPQ scores, but resulted from a general increase in SPQ score of the whole group with AVH. These findings suggest that in healthy individuals, who function within the normal range, the presence of AVH is associated with subclinical levels of other schizotypal phenomena. There is a strong indication that high SPQ scores are related to increased

genetic vulnerability to psychosis (Vollema et al. 2002). Indeed, the subjects with AVH also had increased family loading for psychosis, which almost reached statistical significance (*P*=.055). Family loading for other psychiatric disorders in this group was also higher than in the controls. Considering the shared genetic vulnerability to different psychiatric disorders (Maier et al. 2002), both high SPQ scores and increased rates of Axis-I disorders in relatives are suggestive for a genetic predisposition for schizophrenia in the group with AVH.

In addition to a possible genetic predisposition for psychosis, subjects with AVH had a higher prevalence of childhood trauma, indicating that environmental risk factors may also be shared between healthy subjects with AVH and those with psychosis. Although childhood trauma was still relatively uncommon in the hallucinating group as compared to prevalences in patients with schizophrenia (Andrew et al. 2008; Shevlin et al. 2007) it was statistically associated with the presence of AVH. An association between childhood trauma and AVH has consistently been reported, both in individuals who appear otherwise healthy (Andrew et al. 2008) and in clinical subjects (Shevlin et al. 2007). The total trauma score was highly correlated to SPQ and particularly to PDI scores and our data suggest that the association between trauma and presence of AVH was mainly determined by the effect on SPQ scores, suggesting that childhood trauma leads to an altered (more paranoid) perception of the world as reflected in increased SPQ and PDI scores, which in turn may confer risk to AVH. An alternative explanation is that childhood trauma is more likely in families with a (possibly genetic) predisposition to schizotypal behavior.

Analysis of the NEO-PI-R questionnaires showed that the single difference between the groups was a higher score on the item "Openness for Experiences" in the AVH group. Other studies also found an association between neuroticism and hallucinations (Young et al. 1986; Jakes & Hemsley, 1987; Barrett & Etheridge, 1994; van Os & Jones, 2001; Krabbendam et al. 2002; Delespaul et al. 2002). This discrepancy may be related to the older age of subjects included in this study. Indeed Larøi et al. (2005) found an association between hallucination-proneness and neuroticism only in the young adult sample (who were in their 20s) and not in their elderly sample. Therefore neuroticism may not play an important role later in life. A study assessing personality in unaffected parents of schizophrenia patients (Aukes et al. 2008) using the NEO-PI-R, also found an increase in the item "Openness for Experiences" only, indicating that there may be an association between psychosis proneness and this personality item.

Although the subjects with AVH functioned within the normal range, their mean GAF score was lower than that in controls, despite the fact that the control group was matched for sex, age and education. The difference was predominantly attributable to lower levels of occupational functioning in the hallucinating individuals.

Combined analysis of the measurements showed that schizotypal tendency was the

most significant risk factor for AVH followed by family loading for Axis I psychiatric disorders, suggesting that (genetic) vulnerability to schizophrenia (reflected in high SPQ scores and family loading for psychiatric disorders) is the main risk factor for AVH. The linear regression model showed that schizotypal tendency, family loading for psychiatric disorders and low education are associated with low global functioning, while personality, childhood trauma and presence of AVH do not predict global functioning. The finding that presence of AVH does not predict lower global functioning is in agreement with the majority of the hallucinating participants (91%) reporting minimal interference by their voices in social and occupational functioning. A possible reason why their voices were not disturbing may be that, in contrast to patients with schizophrenia (Johns et al. 2002a), voices of the healthy individuals predominantly had a positive emotional content. The difference in emotional content of AVH between clinical and non-clinical subjects has been observed previously (Honig et al. 2002; Choong et al. 2007) and indicates that emotional content constitutes an important difference between more benign hallucinations and psychopathology. Indeed the few participants from this sample who experienced AVH with a negative content had higher distress from the voices and lower global functioning (mean GAF score of 75). It could be hypothesized that not the presence of AVH per see, but rather the negative emotional content of voices and perceived distress play a role in disability.

Although the hallucinating subjects experienced 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 applied, all 103 subjects with AVH would meet criteria for Psychosis Not Otherwise Specified (NOS). The participants experienced AVH for a mean period of 29 years, thus fulfilling the criterion "persistent hallucinations", which in itself is sufficient for this classification. The fact that the hallucinating subjects were functioning normally, with a mean GAF score of 82, and not in need of treatment, indicates that the diagnosis "psychosis NOS" is clinically inappropriate. Indeed, in order to make this diagnosis, AVH should be "...associated with present distress or disability or with a significantly increased risk of suffering death, pain, ..." (page xxxi in *DSM-IV-Text Revision*). However, for many *DSM-IV* diagnoses (i.e. 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. In parallel, *International Classification of Diseases, Tenth Revision* criteria F29 for unspecified nonorganic psychosis also include "chronic hallucinatory psychosis NOS", in which dysfunction is not explicitly required. Historically the presence of persistent hallucinations has been regarded as abnormal, such that its sole presence would justify a diagnosis of psychopathology (VandenBosch, 2007). Given the current insight that AVH also occur in nonclinical subjects (Hanssen et al. 2005), it could be recommended to add the criterion "leading to significant dysfunction" in the next versions of diagnostic criteria

for Psychosis NOS.

When comparing our study to previous work (Tien, 1991; Verdoux et al. 1998; Poulton et al. 2000; Johns et al. 2002a,b; Larøi et al. 2004), the difference between this study and earlier reports on AVH in healthy subjects is that we have examined each individual in person using standardized psychiatric assessments, while other authors have used self-rating questionnaires or telephone interviews performed by trained lay-people. Some studies did use psychiatric interviews to confirm the presence of Axis I diagnosis in subjects with highest scores (Johns et al. 2002a), but except for Honig et al.(1998) who assessed 18 healthy subjects with AVH, no previous studies used psychiatric interviewing to assess the whole sample of subjects with AVH. The value of a clinical psychiatric interview should not be underestimated. In face to face contact many schizophrenia–related features such as social anxiety, affective flattening or inappropriate affect, thought and language disturbances, inappropriate or disorganised behaviour can be assessed, which may easily be missed using telephone or mail contact. To our opinion, face to face clinical interviews are the only valid method to assess presence or absence of Axis I and II disorder, especially in this group of individuals who are just above the border between full mental health and subtle psychopathology.

Limitations

The main limitation of this study is that participants are highly selected and therefore may not represent subjects with hallucinations in general, nor subjects with sub-threshold psychotic symptoms in general. We here report on subjects who accepted our invitation to participate in this study, which may have selected predominantly individuals who feel confident to speak about their voices, and may have excluded the more suspicious or shy individuals. Perhaps this is the reason why our sample was relatively old (mean age 44), while participants had been hearing voices for a mean of 29 years. If we would have been able to investigate all suitable subjects, we expect that scores on items such as paranoid tendency and social anxiety would have been higher, while global functioning may have been lower. Second, interviewing also the family members in person would have produced more reliable data on prevalences of psychiatric disorder in relatives. It should also be noted that the increase in openness scores on the NEO in the AVH group is small and the differences would render non-significant when corrected for multiple testing. A final limitation of the study is that personality was not assessed in the controls. Although this would have strengthened the findings in the AVH group, the SCID-II interview was too time consuming to score both groups.

In conclusion, our data show that while the hallucinating individuals of this sample do not fulfill criteria for Axis I or II schizophrenia spectrum disorder, they do have a general increased vulnerability to schizophrenia as reflected in increased schizotypal

and delusional tendency and increased family loading for Axis I psychiatric disorders, suggesting that the predisposition for AVH is similar or related to the predisposition for schizophrenia. While the presence of AVH per se has little impact on the level of global functioning, increased schizotypal tendency and higher family loading for Axis I disorders are responsible for the lower level of functioning in the hallucinating individuals in comparison to subjects without AVH. In future studies we aim to address the mechanisms that lead to AVH in the here described subjects, using psychological assessments, analyses of language samples, genetic linkage, functional magnetic resonance imaging, diffusion tensor imaging, and electroencephalograms.

2

Chapter 3

The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals

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Abstract

Introduction

Whereas auditory verbal hallucinations (AVH) are most characteristic for schizophrenia, their presence has frequently been described in a continuum, ranging from severely psychotic patients through schizotypal personality disorder to otherwise healthy participants. It remains unclear whether AVH at the outer borders of this spectrum are indeed the same phenomenon. Furthermore, specific characteristics of AVH may be important indicators of a psychotic disorder.

Method

To investigate differences and similarities in AVH in psychotic and non-psychotic individuals, the phenomenology of AVH in 118 psychotic outpatients was compared to that of 111 otherwise healthy individuals, both experiencing AVH at least once a month. This study was performed between September 2007 and March 2010 at the University Medical Center, Utrecht, the Netherlands. Characteristics of AVH were quantified using the Psychotic Symptoms Rating Scales Auditory Hallucinations Rating Scale.

Results

The perceived location of voices (inside/outside the head), the number of voices, loudness, and personification did not differentiate between psychotic and healthy individuals. The most prominent differences between AVH in healthy and psychotic individuals were the emotional valence of the content, the frequency of AVH, and the control subjects had over their AVH (all *P* values <.001). Age of onset of AVH was at a significantly younger age in the healthy individuals (*P*<.001). In our sample, the emotional valence of the content of AVH could accurately predict the presence of a psychotic disorder in 88% of the subjects.

Conclusions

We cannot ascertain whether AVH at the outer borders of the spectrum should be considered the same phenomenon, as there are both similarities and differences. The much younger age at onset of AVH in the healthy subjects compared to that in psychotic patients may suggest a different pathophysiology. The high predictive value of the emotional content of voices implies that inquiring after the emotional content of AVH may be a crucial step in the diagnosis of psychotic disorders in individuals hearing voices.

Introduction

Auditory verbal hallucinations (AVH) are most characteristic for schizophrenia, in which they occur in 70% of the patients (Sartorius et al. 1986). As with other psychotic symptoms, AVH have been described along a continuum of individuals, ranging from severely psychotic schizophrenia patients, to patients with schizotypal or borderline personality disorder, to individuals with infrequent hallucinatory experiences who function within the normal range (Sidgwick et al. 1894; Posey & Losch, 1983; Young et al. 1986; Tien, 1991; Barret & Etheridge, 1992; Honig et al. 1998; Van Os et al. 2000; Verdoux & Van Os, 2002; Johns et al. 2004; Allen et al. 2005; Allen et al. 2006; Barkus et al. 2007; Rössler et al. 2007; Sommer et al. 2010a). It is usually assumed that AVH in all individuals along this spectrum are the same phenomenon, and differ predominantly in terms of severity and associated dysfunction (Preti et al. 2007; Morrison et al. 2004; Fischer et al. 2004; Oertel et al. 2009). However, it is currently unclear if AVH at different parts of this continuum are phenomenologically similar or distinct (David, 2010). It could be hypothesized that AVH in healthy subjects are more similar to normal verbal thoughts, while the abnormal perceptual quality of AVH may be more pronounced in psychotic individuals. Knowledge of specific qualities characteristic for AVH in individuals with psychosis that are absent in healthy subjects with AVH would facilitate the conceptualization of the continuum hypothesis. Should AVH in healthy subjects be viewed as a symptom similar to that in schizophrenia, but experienced at a lower frequency? Or, alternatively, should AVH in healthy individuals be viewed as an intermediate between true perceptual aberration and normal verbal imagery?

In addition to the scientific consequences, clear phenomenological distinctions between AVH in psychotic and in healthy individuals may be helpful to diagnose the presence or absence of a psychotic disorder in individuals hearing voices. The current diagnostic systems, the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR), and *the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* are not very helpful for this clinical distinction, as individuals with "persistent auditory hallucinations in the absence of any other feature" are a subgroup of psychotic disorder not otherwise specified. The general criterion of the *DSM* system, that a disorder causes significant dysfunction, has to be applied strictly in order not to diagnose well functioning individuals with persistent hallucinations as being psychotic. This phenomenon may not be straightforward in every individual and some diagnostic aid derived from the phenomenology of AVH could therefore be very useful.

Several authors have tried to define characteristics of AVH specific for a psychotic disorder. Junginger & Frame (1985) hypothesized that voices perceived as being from the outer world were indicative of a psychotic disorder, while voices perceived inside the head are not. Likewise, the (delusional) attribution of voices, ie, externalizing the

voices as alien, is considered specific for patients with a psychotic disorder. Ziskind (1965) pointed out that hallucinations cannot be classified as true hallucinations when there is no lack of insight. Frequency of AVH is often used as a diagnostic tool and some suggest that this discriminates well between psychotic patients and non-psychotic individuals with AVH (Mott et al. 1965). However, most of these hypotheses lack empirical corroboration, leaving the question of their diagnostic value unanswered.

The purpose of this study is 2-fold; first, to investigate if AVH are the same phenomenon in the 2 extreme limits of the spectrum and, second, to investigate which characteristics have most prominent diagnostic value in predicting the presence or absence of a psychotic disorder.

We therefore describe, with the help of a validated standard questionnaire, the phenomenology of AVH in a large sample of healthy subjects with AVH, and compare it to that of AVH in psychotic patients.

Methods

Subjects

All participants were between 18 and 65 years of age, and they experienced persistent AVH, ie, at least once a month for over 1 year. Healthy participants with AVH were recruited and selected with the help of a Dutch Web site, called "Explore Your Mind" (www.verkenuwgeest.nl). This Web site, which is linked to several mental health and general health Web sites, provides a self-test which was the incentive for most visitors to fill-out the questionnaire.

The questionnaire on the Web site was based on the Launay and Slade Hallucination Scale (LSHS; Larøi et al. 2004); a self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals. Over 5,000 visitors have filled-out the questionnaire on the Web site. From these, subjects with high scores on items 8 ("In the past, I have had the experience of hearing a person's voice and then found that no-one was there") and 12 ("I have been troubled by voices in my head") of the LSHS were selected. Trained psychologists interviewed these respondents by telephone. Individuals were invited to participate if they met the following inclusion criteria: (1) voices were distinct from thoughts and had a perceptual quality, (2) voices were experienced at least once a month, for over 1 year (3) no diagnosis or treatment for psychiatric disorders other than depressive or anxiety disorders in complete remission, (4) no alcohol or drug abuse for at least 3 months, (5) no chronic somatic disorder.

One hundred and sixty individuals who fulfilled all criteria were invited to visit our clinic to undergo a psychiatric interview for diagnosis applying the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al. 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II; First et al. 1995a,b). Depressive and anxiety disorder in complete remission were not exclusionary criteria. A

total of 111 subjects with AVH, who did not meet criteria for a *DSM-IV* diagnosis, were included. The reason why these 111 individuals with persistent hallucinations were not diagnosed as psychosis not otherwise specified was the absence of professional, psychological, or social dysfunction. Although the healthy subjects with hallucinations did not have clinical delusions, they did have an elevated schizotypal tendency as shown with the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). The combination of hallucinations (perceptual aberrations) and magical ideation present in most healthy subjects with AVH made them score on at least 3 items on the *DSM-IV-TR* criteria for schizotypal personality disorder. However, there was no lack in social capacity, nor did these 111 subjects have inadequate or constrained affect. Other important arguments why these subjects did not meet criteria for schizotypy were that their magical beliefs were largely socially accepted (mainly spiritual ideas) and that they were functioning well. Urine samples were used to screen for cannabis, amphetamine, cocaine, methadone and heroin use, which were exclusion criteria. History of drug or alcohol abuse did not precede the first experience of voices in these healthy participants. In addition, a total of 118 outpatients with a psychotic disorder from the University Medical Centre Utrecht, who also experienced AVH at least once a month for over 1 year, were included. These patients visited our clinic for regular treatment for psychosis or, as a second opinion for intractable psychosis. In this group, clinical diagnoses were confirmed by an independent psychiatrist using the CASH interview. Ninety-one patients (77.1%) were diagnosed with schizophrenia, 4 (3.4%) with schizoaffective disorder, and 23 (19.5%) with psychosis not otherwise specified. Demographic and clinical details are shown in Table 1. Details about medication use are provided in Table 2.

Table 1. Demographic and clinical characteristics of the participants

Group	*N*	*Male (%)*	*Age (SD)*	*Age onset AVH (SD)*	*Years with AVH (SD)*
Non-patients	111	32 (29%)	41.5 (13.5)	12.4 (13.6)	28.7 (16.8)
Patients	118	71 (60%)	36.6 (10.9)	21.4 (11.7)	14.8 (12.6)

Table 2. Medication use

Antipsychotic	***Patients***	***Non-patients***
Classic antipsychotic	23 (20%)	0
Atypical antipsychotic	78 (66%)	0
No antipsychotic	17 (14%)	111 (100%)
Previous antipsychotic	13 (11%)	2 (2%)
Antidepressant		
Current antidepressant	32 (27%)	6 (5%)
Previous antidepressant	4 (3%)	18 (16%)

The mean age of both groups differed significantly (t_{227}=3.023; *P*=.003), as did sex (χ^2_1 =22.701; *P*<.001). To adjust for these differences, both variables were entered as covariates in all further analyses.

The study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the participants, written informed consent was obtained. The study was performed between September 2007 and March 2010 at the University Medical Center, Utrecht, The Netherlands.

Measurements

For the characteristics of hallucinations, we applied the PSYRATS Auditory Hallucinations Rating Scale (AHRS; Haddock et al. 1999) and 5 additional questions, written by the authors (see below).

The AHRS was used to examine the following phenomenological characteristics: frequency, duration per hallucination, perceived 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, and total distress. The variable 'emotional valence of content' was operationalized as the sum of 3 items from the AHRS: 'amount of negative content of voices', 'degree of negative content' and 'amount of distress"; ie, an ordinal variable expressing the overall burden of voices with negative content. The variable 'total distress' was operationalized as the sum of 2 items from the AHRS: 'intensity of distress', and 'disruption to life caused by voices'.

Additional questions addressed:

- Age of onset: "At which age did you first hear a voice?"
- Number of voices: "How many different voices have you heard during the past month?"
- Personification (ie, attribution to a real and familiar person): "Do the voices sound like someone you know in person?"
- Voices in third person, conversing voices ('Schneiderian hallucinations'): "Do the voices use the words "he" or "she" when they address you?"; "Do the voices speak with each other or simultaneously?"
- Specify your external explanation: "Where, in your opinion, do the voices come from?"

Statistics

Multivariate analysis of covariance (MANCOVA) was used to assess any differences in the characteristics of AVH between the two groups. The outcome measures were derived from the AHRS and the additional questions as described above. The grouping variable was the presence/absence of a psychotic disorder as addressed in the CASH interview. Sex and age were entered as covariates.

Although some of our variables are measured on an ordinal scale, fixed effects analysis of variance is robust against deviations from normality (for a detailed discussion see Lindman, 1974) particularly when differences in group sizes are small.

To investigate which AVH characteristics best predict the presence of a psychotic disorder, we used logistic regression analysis with diagnosis (patient vs nonpatient) as dependent variable, age and sex as indicators, and the AVH characteristics as binary variables. Auditory verbal hallucination characteristics were dichotomized using a median split in order to avoid potential problems from nonlinear relationships and deviations from normal distributions. The logistic regression model was optimized for explained variance and model fit using a conditional forward approach as implemented in SPSS for windows, version 15.0 (2006).

Age and sex were kept in the model to adjust for possible confounding. Sensitivity, specificity and positive predictive value were subsequently calculated. All analyses were performed using SPSS.

Results

Characteristics of AVH

The characteristics of AVH in the 2 groups are summarized in Table 3. The Willks Λ multivariate test of overall differences among groups was significant ($F_{22,204}$ = 4815.8, P<.001). A main significant effect for group was present for the variables frequency, duration, emotional valence of content, controllability, voices speaking in third person, total distress, and age of onset. The patients experienced less control, heard voices talking in the third person more frequently, were older (mean difference of 9 years) when they first heard a voice, and scored significantly higher on frequency, duration, distress and emotional valence of content than nonpatients. No differences were found for perceived location (ie, inside/outside the head), loudness, number of different voices, and personification.

Table 3. Comparison of AVH in healthy individuals and patients with description of mean scores

		Healthy individuals	*Patients*	*Healthy individuals*	*Patients*	*Statistics*	
Characteristic of AVH	Questionnaire	Description of mean	Description of mean	Mean (SD)	Mean (SD)	F (1, 225)	p-value
Frequency	Psyrats item 1	1 AVH every 3 days	1 AVH every hour	3.53 (1.26)	5.09 (1.05)	83.19	<0.001
Duration	Psyrats item 2	2-3 minutes	40 minutes	1.53 (0.73)	2.68 (1.23)	63.08	<0.001
Location	Psyrats item 3	Inside head, and further from body	Inside head, and near ears	2.21 (1.15)	2.08 (1.20)	1.25	0.265
Loudness	Psyrats item 4	Little softer than own voice	Little softer than own voice	1.81 (0.65)	1.80 (0.83)	0.29	0.594
Explanation of origin	Psyrats item 5	60% external, 40% internal	50% external	3.17 (1.13)	2.49 (1.23)	17.12	<0.001
Emotional Valence	Sum item 6, 7 and 8 Psyrats	Seldom unpleasant voices/content	Majority of voices is unpleasant and/or annoying	1.69 (3.05)	8.58 (2.70)	276.29	<0.001
Controllability	Psyrats item 11	60% of the time	20% of the time	1.77 (1.49)	3.09 (1.08)	39.07	<0.001
Number of different voices	Additional question	7.62	11.44	7.34 (17.21)	11.90 (22.34)	2.21	0.139
Total distress	Sum item 9 and 10 Psyrats	Almost no discomfort, almost no disruption daily life	Moderate to severe distress, and disruption of daily life	0.63 (1.33)	5.01 (1.83)	353.02	<0.001
Age of onset	Additional question	12.38 years old	21.36 years old	12.38 (13.59)	21.36 (11.66)	43.20	<0.001
Personification	Additional question	Some voices belong to acquaintances	Some voices belong to acquaintances	0.55 (0.70)	0.69 (0.72)	1.64	0.202
Voices speaking in 3rd person	Additional question	25%	50%	0.50 (0.66)	1.02 (0.84)	21.62	<0.001

Attribution to an external agency

Healthy individuals fostered an external explanation significantly more often than patients. Descriptions of the external explanations are shown in Table 4.

Table 4. Attribution of AVH to an external agency

	Healthy individuals	*Patients*
Number of subjects with a (predominantly) external explanation	82 (74%)	57 (48%)
Among the subjects who considered an external explanation:		
External, yet unspecific explanation	35 (43%)	11 (19%)
Spiritual explanation	47 (57%)	16 (28%)
God	-	1 (2%)
Demons/devil	-	5 (9%)
Other (living) people	-	19 (33%)
Device implanted in brain	-	5 (9%)

Predictors of a psychotic disorder based on the characteristics of AVH

A binary logistic regression model was used to investigate which characteristics best predict whether a person experiencing AVH has a psychotic disorder. The optimal model had a satisfactory fit (Hosmer and Lemeshow test, $\chi^2_8 = 13.7$, $P=.09$), and the Nagelkerke approximation of R^2 was high (0.77).

Table 5 shows the statistics of the 4 indicators in the model. Having control over the AVH for most of the time, hearing voices less than once a day, age at onset before 16 years of age, and hearing voices with a predominantly positive content are good predictors that a person does not have a psychotic illness. The sensitivity and specificity of this model were both 92% (implying that there is a 92% probability of a correct diagnosis using these characteristics).

Table 5. Logistic regression Model: AVH characteristics predicting the presence of a psychotic disorder

	B	*SE*	*Wald*	*Sign*
Control	1.020	.482	4.486	**p=0.034**
Frequency	2.134	.565	14.260	**p<0.001**
Age of onset	2.271	.527	18.566	**p<0.001**
Emotional valence of content	3.515	.523	45.214	**p<0.001**
Gender	-.445	.493	.817	p=0.366
Age	-.018	.019	.901	p=0.342

An explorative binary logistic regression was carried out with only the strongest predictor (emotional valence of content of AVH), age and sex, and group membership

(having a psychotic disorder or not) as the dependent variable. Emotional valence of content provided a better fit and substantial explained variance (Hosmer and Lemeshow test, $\chi^2_8 = 8.7$, P=.37), and the Nagelkerke approximation of R^2 was high (0.64).

Table 6 shows the statistics when only emotional valence was included in the model. There was a sensitivity of 86% and 87% specificity using only this characteristic. The positive predictive value was 88%.

Table 6. Logistic regression Model: Emotional valence of content

	B	*SE*	*Wald*	*Sign*
Emotional valence of content	3.693	0.405	83.168	**p<0.001**
Gender	-1.062	0.411	6.665	**p=0.010**
Age	-0.019	0.016	1.423	p=0.233

Discussion

A comparison was made between the phenomenological characteristics of AVH in 111 well functioning, nonpsychotic individuals and 118 psychotic patients in an attempt to determine if AVH in both groups are the same phenomenon and to reveal specific characteristics of AVH that may be helpful in establishing a correct clinical diagnosis. The most prominent difference between the groups concerned the emotional valence of the content of AVH. This feature appeared to be an important characteristic for diagnosing a psychotic disorder, as negative emotional valence of content (defined as more than half of the comments with negative content) had a positive predictive value of 88% for a psychotic disorder in this sample. Other significant differences were the higher frequency of AVH, the lower degree of control over AVH, and the later age of onset in individuals with a psychotic disorder as compared to healthy individuals with AVH. These 4 characteristics together could accurately predict the presence or absence of a psychotic disorder in 92% of the subjects in this sample. Perceived location (voices heard inside or outside the head), loudness, number of voices, and personification (attribution to a real and familiar person) were similar in both groups. In contrast to expectations, having an external explanation for AVH was not an indicator for the presence of a psychotic disorder. Patients more frequently believed that the voices originated from their own mind (internal explanation), while healthy participants were more inclined to attribute them to an external - often paranormal - source.

While the characteristics of AVH in schizophrenia patients have been well described (Nayani & David, 1996) only 1 previous study provided details about the phenomenology of AVHs in healthy subjects. Honig et al[7] examined 15 healthy subjects with AVH, and compared them to 18 patients with schizophrenia. They noted that the healthy group

experienced AVH as positive, while the patient group experienced them predominantly as negative, which was similar to our findings.

Historically, some characteristics of AVHs have been considered of particular significance for the purpose of establishing a diagnosis of psychosis. Junginger and Frame (1985) suggested that AVH in psychotic patients are more frequent, tend to be heard outside the head, and lead to an explanation of a delusional nature. In line with the first assumptions, the frequency of AVH in the patient group was higher than that in the nonpatient group. In both groups, however, the perceived location of AVH was inside as well as outside the head, while the explanation of their origin was not diagnostically predictive in the way envisaged by Junginger and Frame. Long before Junginger and Frame, Schneider (1959) considered audible thoughts, voices conversing and commenting, and voices addressing the subject in the third person as particularly relevant for a clinical diagnosis of schizophrenia. Subsequent studies investigating the specificity of these Schneiderian criteria for schizophrenia were inconsistent (Goodwin et al. 1971; David & Appleby, 1992; Peralta & Cuesta, 1999; Nordgaard et al. 2008; Ihara et al. 2009). In our study, voices talking in the third person, along with voices conversing, were indeed more prevalent in the patient group, but also occurred in 25% of the healthy individuals.

The question whether AVH constitute the same phenomenon at the two extreme ends of the spectrum cannot be answered unequivocally with the results of this study. The finding that aspects such as loudness, location and attribution are similar in both groups would imply a similar phenomenon, differing mainly in severity. It has become clear that AVH in healthy subjects are not more akin to normal verbal imagery than AVH in psychotic patients. On the other hand, the age of onset was largely different between the groups. Patients were approximately 21 years when they first experienced AVH, compared to a mean age of onset of 12 in the nonpatients. This finding might be indicative of a difference in the etiology of AVH in psychotic and nonpsychotic subjects, as the onset of AVH may be associated to aberrant synaptic connectivity[37]. Synaptic density peaks during childhood, followed by an extensive decrease of neuronal connectivity (pruning) during adolescence, to reach normal levels in adulthood (Hoffman & McGlashan, 1997). Thus, the age of onset of AVH in non-psychotic individuals coincides with maximal synaptic density. In contrast, the age of onset of AVH in psychotic patients coincides with synaptic elimination (pruning). Further research using neuroimaging techniques such as functional connectivity and diffusion tensor imaging to compare the biological basis of AVH in both groups, for example, may be helpful to clarify if hallucinations in clinical and in nonclinical individuals are the same phenomenon or not.

A limitation of this study is that the group of healthy individuals with AVH constituted a selected sample that may not be representative of the whole group of healthy subjects with AVH. It should also be noted that the predictive model we present

needs to be replicated in an independent sample, and serves the sole purpose of distinguishing between hallucinations in otherwise healthy individuals and psychotic patients. Further research is warranted to investigate whether this distinction holds for other groups as well. It should be borne in mind that the positive predictive value is highly influenced by the a priori chance. Considering the lower frequency of healthy subjects with hallucinations in clinical practice, the usefulness of this clinical distinction may be lower.

In conclusion, the most prominent differences between AVH in healthy and psychotic subjects were the negative emotional valence of content, the higher frequency, the lower degree of control, and the later age at onset in the patient group. Using these 4 characteristics, we found that 92% of the subjects in our sample could be diagnosed correctly as having a psychotic disorder or not. Negative emotional content of the hallucinations has high sensitivity and specificity (86 and 87% respectively) for the presence of a psychotic disorder.

On the basis of these results, we cannot yet conclude whether AVH in the outer borders of the spectrum should be considered the same phenomenon. It became clear that the perceived location of voices (inside/outside the head), the number of voices, loudness, personification and attribution did not differentiate between patients and nonpatients, suggesting a similar phenomenon in both groups. On the other hand, the large difference in age of onset may suggest a different pathophysiology.

Part II

Neurocognitive mechanisms

Chapter 4

Auditory verbal hallucinations and cognitive functioning in healthy individuals

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Abstract

Introduction

Auditory verbal hallucinations (AVH) are a characteristic symptom in schizophrenia, and also occur in the general, non-clinical population. In schizophrenia patients, several specific cognitive deficits, such as in speech processing, working memory, source memory, attention, inhibition, episodic memory and self-monitoring have been associated with auditory verbal hallucinations. Such associations are interesting, as they may identify specific cognitive traits that constitute a predisposition for AVH. However, it is difficult to disentangle a specific relation with AVH in patients with schizophrenia, as so many other factors can affect the performance on cognitive tests. Examining the cognitive profile of healthy individuals experiencing AVH may reveal a more direct association between AVH and aberrant cognitive functioning in a specific domain.

Methods

For the current study, performance in executive functioning, memory (both short- and long-term), processing speed, spatial ability, lexical access, abstract reasoning, language and intelligence performance was compared between 101 healthy individuals with AVH and 101 healthy controls, matched for gender, age, handedness and education.

Results

Although performance of both groups was within the normal range, not clinically impaired, significant differences between the groups were found in the verbal domain as well as in executive functioning. Performance on all other cognitive domains was similar in both groups.

Conclusions

The predisposition to experience AVH is associated with lower performance in executive functioning and aberrant language performance. This association might be related to difficulties in the inhibition of irrelevant verbal information.

Introduction

Auditory Verbal Hallucinations (AVH) are a characteristic symptom of schizophrenia but have also been described in the general population (Tien, 1991; Verdoux & Van Os, 2002). Thus far, the pathophysiology of AVH is still largely unknown. Many theories concerning the origin of AVH have been postulated of which several have implicated specific cognitive dysfunctions as the core abnormality to cause AVH. For example, Frith & Done (1988) hypothesized a failure in self-monitoring as the basic deficit in AVH whereas Vercammen et al. (2008) stated that increased top-down processing plays an important role in the vulnerability to experience AVH. In support of such cognitive deficits or traits, hypothesized to underlie AVH, a number of studies found prominent impairments in several cognitive functions such as speech processing (Hoffman et al. 1999b), working memory (Hoffman et al. 1999b), episodic memory (Berenbaum, et al. 2008), source memory (Brébion et al. 2007), attention (Berman et al. 1997), inhibition (Waters et al. 2003) and self-monitoring (Seal et al. 2004; Waters et al. 2010). However, patients with schizophrenia suffer from various other symptoms besides AVH, among which avolition, lack of motivation and a general decline in cognitive functioning. Therefore, decreased performance on specific tests is not necessarily a reflection of their tendency to hallucinate. A more specific reflection of AVH may be provided by cognitive differences that occur in non-psychotic individuals with AVH, who are free of negative symptoms and have only sub-clinical levels of positive symptoms (Sommer et al. 2010a,b). The fact that that these healthy individuals with AVH function at a normal level, were able to finish their education, are medication naïve and have no history of admission to hospital is an additional advantage. Although differences in AVH have been found between healthy individuals and psychotic patients, regarding for instance frequency and emotional content, several similarities remain: No differences were found between location of AVH, loudness, number of voices and personification (Daalman et al. 2011a). Based on these results one cannot conclude that both types of AVH are different. Furthermore, Diederen et al. (2011) found no significant differences in brain activation during the experience of AVH between healthy individuals with AVH and patients.

In order to measure cognitive functioning in non-psychotic individuals with AVH, a group of 101 persons with AVH who were screened for axis I or II pathology was compared to a matched control group with a battery of neuropsychological tests. These tests focus primarily on cognitive domains that were previously found to be affected in patients with a psychotic disorder experiencing AVH. The most important cognitive domains in that perspective were included: memory, language, executive functioning, processing speed, spatial ability, verbal and non-verbal reasoning.

The aim of the present study was to establish a cognitive profile of healthy individuals with AVH. Compared to healthy individuals without AVH, this group might show deviant cognitive performance. These cognitive differences will then provide clues for

a potential cognitive mechanism that could underlie AVH since these individuals are otherwise healthy.

Method

Participants

A total of 101 healthy individuals with AVH were compared to 101 healthy individuals without AVH. Hallucinating individuals that were free of a DSM-IV diagnosis, as assessed by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al. 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II, First et al. 1995a,b), were included. Depressive disorder in complete remission was not an exclusionary criterion. Urine samples were used to screen for cannabis, amphetamine, cocaine, methadone or heroine abuse, which was an exclusion criterion. Additional exclusion criteria for both groups were alcohol abuse and IQ below 80.

For the healthy individuals with AVH, the minimum frequency to experience AVH was once every three months and the minimum duration since onset of AVH was one year. Both healthy controls and healthy individuals with AVH were recruited with the help of a Dutch website called 'explore your mind' (www.verkenuwgeest.nl). For more details about selection and assessment procedure see previous studies by our group (Sommer et al. 2010a,b; Daalman et al. 2011a). The control group was matched for gender, age, handedness and education and did not differ significantly on these variables, as shown in Table 1. All participants had four Dutch grandparents. The study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the participants, written informed consent was obtained.

Table 1. Demographic characteristics of the participants: healthy individuals with AVH and healthy controls.

Group	*Individuals with AVH*	*Controls*	*Difference (significance)*
n	101	101	
Male (%)	33.7	29.7	χ^2=.366 (P=0.545)
Right handed (%)	78.2	84.2	χ^2=1.167 (P=0.280)
Mean age (s.d.)	43.78 (12.50)	43.30 (14.23)	t=.257 (P=0.797)
Mean years of education (s.d.)	13.39 (2.18)	13.76 (2.40)	t=-1.17 (P=0.245)

Phenomenology of AVH in healthy individuals

To establish the phenomenological characteristics of AVH, the PSYRATS Auditory Hallucination Rating Scale (AHRS, Haddock et al. 1999) was administered. This questionnaire describes 11 characteristics of AVH. Each item of this scale is evaluated on a 5-point Likert Scale ranging from 0 to 4. For the use of this questionnaire in healthy individuals, the range of the frequency scale is extended to 0-6 (also covering options 'at least once every month' and 'at least once every three months' since AVH are experienced less often than once a week (the original minimum score of this item). This questionnaire was administered by trained psychologists.

Due to high correlations between several of these items, two new variables were computed (see also Daalman et al. 2011a). The variable 'emotional valence of content' was operationalized as the sum of three items from the AHRS: 'amount of negative content of voices', 'degree of negative content' and 'amount of distress"; i.e. an ordinal variable expressing overall burden of voices with negative content. The variable 'total distress' was operationalized as the sum of two items from the AHRS: 'intensity of distress', and 'disruption to life caused by voices'. As a result, the following items were used in this study: frequency, duration, location, loudness, beliefs re-origin of voices, controllability, emotional valence of content and total distress.

Measures

Neuropsychological assessments

The neuropsychological tests used in this study cover the domains in which impaired functioning in psychotic patients with AVH is found, and are thus candidates for examining the relationship between AVH in healthy individuals and cognitive functioning (Table 2).

Tests were administered in a fixed order and all examiners were extensively trained and supervised in the use of the tests. To rule out language deficits (aphasia, language expression and comprehension difficulties), the Boston naming task (Kaplan et al. 1983) and Tokentest (De Renzi & Vignolo, 1962) were administered. Participants who showed impaired language functioning, as measured by these tasks, were excluded.

Table 2. Description of neuropsychological tests and measured domains.

Task	*Measured domain*
Stroop Colour-Word Task (Stroop, 1935)	Executive functioning: response inhibition and selective attention (time card 3 – time card 2)
Card 1: Subject is asked to read names of colours	Processing speed (time card 1, time card 2)
Card 2: Subject is asked to name colour of ink	
Card 3: Subject is asked to name colour of ink while written word states different colour	
Backward Digit Span-task, WAIS III subtask (Wechsler, 1997)	Verbal Working Memory
Numbers are presented and subject has to repeat them backwards. Sequence of numbers increases after two trials	Executive functioning and verbal working memory, requiring executive manipulation of verbal presented stimuli
Forward Digit span, WAIS III subtask (Wechsler, 1997)	Attention span
Numbers are presented and subject has to repeat them in same order. Sequence of numbers increases after two trials	
California Verbal Learning Test (CVLT, Delis et al. 1987) (Dutch version: VLGT, Mulder et al. 1996)	Long-term verbal memory
Recall of list of words after 25 minutes. Words can be grouped into categories	
Complex Figure of Rey-Ostherrieth (Rey-O, Knight & Kaplan, 2003)	Spatial ability
Subject has to copy a complex figure. After 25 minutes, subject is asked to draw this figure again from memory	Non-verbal long-term memory (recall after 25 minutes)
Vocabulary test, WAIS III subtask (Wechsler, 1997)	Lexical access
Subject is asked to give the definition of words	
Similarities test, WAIS III subtask (Wechsler, 1997)	(Verbal) abstract reasoning
Subject is asked to state the similarity between two concepts	
Dutch version of the controlled oral word association test, COWAT (Lezak et al. 2004)	Executive functioning
Subject is asked to name as many words within one minute, starting with a specific letter	Phonemic fluency (letters N and A, each 1 minute), verbal retrieval and recall, self-monitoring, self-initiation
Semantic Fluency (Lezak et al. 2004)	Semantic memory
Subject is asked to name as many items from a category within two minutes	Categorical fluency (animals and occupations, each 2 minutes). Verbal retrieval and recall, self monitoring, Semantic associations in the lexicon
National Reading Test for Adults (NART, Crawford et al. 1989; Blair & Spreen, 1989).: Dutch adaptation NLV, Schmand et al. 1992)	Verbal IQ
Subject is asked to read aloud a list of words with irregular pronunciation	
Raven's Advanced progressive Matrices (Raven et al. 1998)	Non-verbal IQ and abstract reasoning
Subject has to choose which pattern is missing from the overall matrix on the page. With increasing difficulty after each item	

Statistical analyses

Between-group comparison on the above described cognitive measures was achieved through multivariate analysis of variance (MANOVA), applying a General Linear Model. The independent variable was group (experiencing AVH or not i.e. controls) and the dependent variables were the raw scores on the fourteen cognitive tasks as described above. The Step-Up Hochberg correction was used to adjust P-values because of multiple testing (Westfall & Young, 1993; Benjamini & Hochberg, 1995). All data were analyzed with the Statistical package for the Social Sciences (SPSS, 2006).

Results

Table 3 describes how often AVH were experienced in the healthy individuals. Table 4 provides more information about the phenomenology of AVH in this group.

Table 3. Frequency of AVH.

Frequency of AVH	*Percentage*	*Frequency (N=101)*
At least once every 3 months	3.0	6
At least once a month	11.4	23
At least once a week	17.3	35
At least daily	11.4	23
At least once per hour	4.5	9
Continuous	2.5	5

Table 4. Characteristics of AVH in the healthy individuals.

Characteristic of Auditory Verbal Hallucinations	*Mean (s.d.)*	*Description of closest anchor*
Age at onset	14.5 (14.3)	Mean age of onset voices is 14.5 years old
Frequency (0-6)	3.31 (1.2)	At least once a week
Duration (0-4)	1.47 (0.65)	A few seconds
Location (0-4)	2.41 (1.18)	Voices outside the head. Inside the head may also be present
Loudness (0-4)	1.91 (0.60)	About same loudness as own voice
Beliefs of re-origin (0-4)	3.04 (1.09)	Holds ≥ 50% conviction (but < 100%) that voices originate from external causes
Controllability (0-4)	2.00 (1.6)	Some control over their voices, approximately half of the time
Emotional Valence (0-12)	1.25 (2.53)	Hardly any negative content
Total Distress (0-8)	0.51 (1.38)	No distress due to voices

As expected, individuals of both groups performed the tests within the normal range, when compared to the norm reference scores of each test. There was a statistically

significant difference between the groups on the combined dependent variables: $F(14,187) = 3.65$, $P<0.001$; Pillai's Trace 0.22. When the results for the dependent variables were considered separately (Table 5), the individuals experiencing AVH were more sensitive to distraction as reflected in lower performance on the Stroop interference measure, had a lower verbal working memory capacity (reflected in lower Digit-span backward performance), underperformed, compared to controls, on a task for vocabulary (Vocabulary test, WAIS III subtask) and for judging verbal similarities (Similarities test, WAIS III subtask). In addition the individuals with AVH performed slightly lower on the NART, an estimate of verbal intelligence. No differences were found on tasks tapping verbal and nonverbal memory, attention span, nor on verbal fluencies. The level of nonverbal reasoning and non-verbal IQ was also similar in both groups.

Table 5. Comparison of cognitive measures in healthy individuals experiencing AVH and controls.

Measures	*AVH (n=101) Mean (s.d.)*	*Controls (n=101) Mean (s.d.)*	*F(1,200), P-value*
Executive function and working memory			
Stroop interference	35.42 (19.66)	28.98 (12.95)	7.55 (0.007*)
Digit-span backward	6.35 (2.06)	7.13 (2.01)	7.46 (0.007*)
Attention			
Digit-span forward	8.75 (1.67)	9.17 (1.88)	2.77 (0.098)
Memory			
CVLT delayed recall	12.45 (2.82)	12.31 (2.56)	0.13 (0.715)
Rey-O delayed recall	19.72 (6.73)	19.41 (6.32)	0.12 (0.731)
Processing speed			
Stroop card 1	46.41 (7.75)	44.96 (7.79)	1.75 (0.188)
Stroop card 2	57.96 (10.66)	56.54 (10.60)	0.90 (0.345)
Spatial ability			
Rey-O copy	32.71 (3.46)	32.74 (2.89)	0.00 (0.947)
Lexical access and abstract reasoning			
Vocabulary test	47.43 (10.83)	53.75 (6.52)	25.29 (< 0.0005*)
Similarities test	26.28 (4.33)	28.01 (3.66)	9.44 (0.002*)
Verbal Fluency			
Letter Fluency total	28.87 (9.02)	28.77 (8.58)	0.01 (0.936)
Semantic Fluency total	71.72 (16.43)	68.99 (14.91)	1.53 (0.217)
Intelligence Correlates			
Raven's matrices	9.14 (2.14)	9.27 (2.18)	0.18 (0.673)
National adult reading test	84.12 (10.07)	89.37 (7.36)	17.87 (<0.0005*)

* Significant after Step-Up Hochberg correction for multiple testing

Discussion

We compared cognitive functioning in various domains between 101 non-psychotic individuals with auditory verbal hallucinations (AVH) and 101 healthy controls matched for age, gender, handedness and education. As expected, task performance of both groups was within the non-pathological range, both groups scored within the top 50% to 25% on all the tests.

The cognitive profile of healthy individuals experiencing AVH was largely similar to that of healthy controls without AVH. However, they underperformed on several domains compared to the controls. Healthy individuals with AVH showed poorer performance on verbal distractibility, inhibition (Stroop interferences), verbal working memory and on tasks tapping lexical access and reasoning (WAIS backward digit-span, vocabulary and similarities, respectively). Thus, it appears that a specific combination of decreased executive functioning, consisting of verbal inhibition, distractibility and verbal working memory in particular, and a reduced level of verbal intellectual performance is associated with the tendency to hallucinate in the auditory verbal domain.

Although the groups were matched for total years of education and also had similar levels of nonverbal abstract reasoning (nonverbal intelligence estimate), individuals with AVH had significantly lower scores on a verbal estimate for level of intellectual functioning (NART). Lower scores in the AVH group on the vocabulary test and the similarities test may be related to this lower verbal intelligence, since the NART scores correlate highly with WAIS-R Verbal-IQ as well as with WAIS-R Vocabulary scores (Carswell et al. 1997; Uttl, 2002). Interestingly, no difference between both groups was found on phonological and semantic verbal fluency tasks. However, these tasks also assess the ability to generate concepts and to associate which is, apparently, similar in both groups.

Speculating, this reduced inhibition and increased distractibility in the verbal domain could render individuals less apt to inhibit irrelevant verbal information. Decreased inhibition could prevent them from focusing on the appropriate information, resulting in reduced performance on executive tasks within the verbal domain. In support of this hypothesis, healthy individuals with AVH were found to have increased levels of positive formal thought disorder as compared to controls without AVH, including peculiar word and sentence usage and peculiar logic (Sommer et al. 2010b). Possibly, irrelevant verbal associations which are not adequately inhibited may not be recognized as self-generated and, as such, be attributed to an external source, resulting in an auditory verbal hallucination.

To our knowledge, this is the only study assessing cognitive performance in healthy individuals with AVH. However, other groups have assessed cognitive functioning in related groups, such as healthy individuals with an increased tendency to experience hallucinations, healthy siblings of patients with schizophrenia, individuals at increased

genetic risk to develop psychosis and individuals with schizotypal traits. Individuals with high scores on the Launay Slade Hallucination Scale, and thus with a high predisposition to hallucinate were found to have poorer intentional inhibition of memories (Paulik et al. 2007). This is in line with our finding that the presence of AVH is associated with aberrant inhibition. As these individuals were not extensively screened to investigate their hallucinations, it remains unclear whether their experience can be truly classified as, for example, an AVH and whether they have experienced this once or more frequently. Sibling studies show deficits in most cognitive domains, including executive functions, attention, (working) memory, spatial ability, language and performance speed (Snitz et al. 2006; Kuha et al. 2007). For individuals at high genetic risk for psychosis this profile is somewhat similar albeit less extensive: poorer performance on executive function, on global intellectual function, on learning and memory (Byrne et al. 2003). These observed cognitive deficits in siblings and high-risk individuals can be related to the genetic predisposition for schizophrenia in general, rather than to AVH specifically, since there were no differences in spatial ability, processing speed and (working) memory in our sample. Healthy individuals with AVH have significantly higher scores on the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) (Sommer et al. 2010a), situating them on a continuum somewhere between healthy controls on one end and individuals with schizotypal personality disorder at the other. While they did experience perceptual abnormalities and some degree of suspicion, their social abilities were generally good and they functioned both socially and professionally within the normal range. Studies on cognitive functioning in individuals with schizotypal traits, as measured by the SPQ, may therefore show partial overlap with our results. With respect to verbal subtasks of the WAIS-R, poorer cognitive performance was found in healthy individuals with high scores on the SPQ (Noguchi et al. 2008). Executive working memory was also found to be lower (Matheson & Langdon, 2008) in the subjects with schizotypal traits, but not executive functioning (Noguchi et al. 2008). In the latter study a relationship between schizotypal traits and an inductive reasoning component of IQ was found, whereas in our study, this domain appears unaffected. Decreased 'cognitive inhibition' is also often found in individuals with high schizotypy (Beech et al. 1989; Peters et al. 1994; Moritz & Mass, 1997). The fact that our healthy individuals with AVH show cognitive deviations that partly fit these findings of individuals with high schizotypal traits comes as no surprise since these two groups show considerable overlap in features of perceptual abnormalities and the tendency to suspicion.

Our results should be interpreted with caution as they provide no information with respect to causality. It could be hypothesized that aberrant verbal and executive functioning underlies the predisposition to hallucinate, but alternatively the experience of AVH may lower performance on these specific tasks. As most participants did not experience AVH during cognitive testing, the first explanation appears stronger,

although the second cannot be ruled out. Another limitation is that the individuals that participated in this study are a highly selected group as only participants who were willing to visit us, and in the case of the healthy individuals with AVH, who were willing to talk openly about their AVH, could be included. This might also be the reason for the overrepresentation of women in the sample, although auditory hallucinations are more prevalent in women than in men (Rector & Seeman, 1992).
In conclusion, while their cognitive performance is within the normal range and thus not clinically impaired, healthy individuals experiencing AVH do show reduced levels of executive functioning and verbal (intellectual) performance. This deviation compared to individuals without AVH suggests that experiencing AVH is directly associated with difficulties in the inhibition of irrelevant verbal information.

4

Chapter 5

The influence of semantic top-down processing in auditory verbal hallucinations

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Abstract

Background

Auditory verbal hallucinations (AVH) are one of the most prominent symptoms of schizophrenia, but have also been reported in the general population. Several cognitive models have tried to elucidate the mechanism behind auditory verbal hallucinations, among which a top-down model. According to this model, perception is biased towards top-down information (e.g. expectations), reducing the influence of bottom-up information coming from the sense organs. This bias predisposes to false perceptions, i.e., hallucinations.

Methods

The current study investigated this hypothesis in non-psychotic individuals with frequent AVH, psychotic patients with AVH and healthy control subjects by applying a semantic top-down task. In this task, top-down processes are manipulated through the semantic context of a sentence. In addition, the association between hallucination proneness and semantic top-down errors was investigated.

Results

Non-psychotic individuals with AVH made significantly more top-down errors compared to healthy controls, while overall accuracy was similar. The number of top-down errors, corrected for overall accuracy, in the patient group was in between those of the other two groups and did not differ significantly from either the non-psychotic individuals with AVH or the healthy controls. The severity of hallucination proneness correlated with the number of top-down errors.

Discussion

These findings confirm that non-psychotic individuals with AVH are stronger influenced by top-down processing (i.e., perceptual expectations) than healthy controls. In contrast, our data suggest that in psychotic patients semantic expectations do not play a role in the etiology of AVH. This finding may point towards different cognitive mechanisms for pathological and nonpathological hallucinations.

Introduction

Auditory verbal hallucinations (AVH) are among the most prominent symptoms of schizophrenia, but have also been reported in other psychiatric disorders as well as in a significant minority of the general population (for a review, see Beavan et al. 2011, Aleman & Larøi, 2008). AVH have been suggested to lie on a continuum (Verdoux & van Os, 2002), ranging from non-psychotic and otherwise healthy individuals with AVH on one end to psychotic patients on the other. On the phenomenological level, some differences between AVH in these groups were reported, mostly related to the emotional valence and associated distress (Daalman et al. 2011a), but there is also a substantial overlap in AVH on both ends of this continuum: loudness, number of voices, personification and location of voices were rather similar.

On the neurobiological level, brain activation during AVH measured with fMRI was found to be similar in non-psychotic and psychotic individuals (Diederen et al. 2011). However, increased striatal dopamine, known to play a key role in AVH in psychosis, was absent in non-psychotic individuals with frequent AVH (Howes et al. 2012). It so far remains unclear if similar or different processes underlie hallucinations at either ends of the continuum.

Different cognitive models have tried to explain the mechanism(s) behind AVH. A possible mechanism accounting for the vulnerability to hallucinate is increased reliance on top-down processing. In normal perception, bottom-up information coming from the senses is combined with top-down information which regards implicit prior knowledge based on previously encountered situations, leading to perceptual expectations (Behrendt, 1998; Meyer, 2011). The balance between bottom-up and top-down processing can be distorted in such a way, that it is influenced to a higher degree by top-down factors, which may trigger perceptual experiences in the absence of corresponding external stimulation, i.e. hallucinations (Behrendt, 1998; Grossberg, 2000).

The aim of this study was to investigate whether both psychotic and non-psychotic individuals with AVH indeed make more top-down errors, compared to healthy controls. A previous study revealed an increased number of top-down errors in university students selected for hallucination-proneness compared to students without a proneness towards hallucination (Vercammen & Aleman, 2010). That is, subjects with higher levels of hallucination proneness were more likely to report hearing a word that fitted the sentence context, when it was not actually presented. The present study investigated whether such a finding would extend to a sample of people from the general population who experience AVH and to patients with schizophrenia and AVH. Investigating this effect in non-psychotic individuals with AVH as well as in patients with AVH would provide further evidence for the top-down model in AVH. To this end, three groups of participants were included: 40 healthy control subjects, 40 non-psychotic individuals with AVH and 40 psychotic patients with AVH. Patients

are hypothesized to make more top-down errors than non-psychotic individuals with AVH, since they experience AVH more frequently (Daalman et al. 2011a). In addition, the Launay-Slade Hallucination Scale (LSHS; Larøi et al. 2004) was used to measure whether hallucination proneness would be associated with more top-down errors in the non-psychotic groups. For the patient group, the association between number of top-down errors and hallucinatory behaviour (item P3 of the Positive and Negative Syndrome Scale; PANSS, Kay et al. 1987) was determined.

Methods

Participants

A total of 120 participants were included: 40 psychotic patients with AVH, 40 non-psychotic individuals with AVH and 40 non-hallucinating control subjects. The healthy control subjects and non-psychotic individuals with AVH did not meet criteria for a DSM-IV diagnosis, as assessed by an independent psychiatrist with the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al. 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II) (First et al. 1995a,b). Depressive disorder in complete remission was not an exclusionary criterion. Additional exclusion criteria for all groups were alcohol abuse and drug abuse. For the non-psychotic individuals and psychotic patients with AVH, the minimum frequency to experience AVH was once a month and the minimum duration since onset of AVH was one year.

Both the non-psychotic individuals with AVH and the healthy controls were recruited with the help of a Dutch website called 'explore your mind' (www.verkenuwgeest.nl). An extended description of the recruitment and selection procedure is provided in prior studies by our group (Daalman et al. 2011a; de Weijer et al. 2011; Diederen et al. 2010a, 2011; Sommer et al. 2010a,b; van Lutterveld et al. 2010).

The outpatients with a psychotic disorder were recruited from the University Medical Centre Utrecht. These patients visited our clinic for regular treatment for psychosis. In this group, clinical diagnoses were confirmed by an independent psychiatrist using the CASH interview. Twenty-five patients (62.5%) were diagnosed with paranoid schizophrenia, 6 (15%) with schizoaffective disorder, and 9 (22.5%) with psychosis not otherwise specified. Demographic and clinical details are shown in table 1; the three groups were matched for gender and total years of education but differed on age. For a detailed overview of medication use in the three groups, see Supplementary table 1.

The 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. Demographic characteristics of the participants: psychotic patients, non-psychotic individuals with AVH and healthy control subjects.

Group	*Patients with AVH*	*Non-psychotic individuals with AVH*	*Healthy controls*	*Difference (significance)*
n	40	40	40	
Male (%)	21 (52.5%)	17 (40%)	18 (45%)	χ^2=0.871; df=2; p=0.647
Mean age (s.d.)	37.60 (12.17)	47.63 (10.48)	45 (14.87)	F=6.77; df=2; p<0.01
Total years of education (s.d.)	13.15 (2.60)	13.75 (2.12)	13.60 (2.37)	χ^2=1.677; df=2; p=0.432

Measurements

Experimental tasks

Hearing task

To ensure proper hearing, a test was developed in which tones of various frequencies were presented (300 Hz, 500 Hz, 700 Hz, 900 Hz and 1100 Hz) at 65 dB. Participants were asked to press a response button when a tone was presented. After completing the test, the results were immediately calculated before proceeding to the semantic task. In case of an accuracy score below 75 percent, the experiment was aborted, since the performance on the top-down task would be influenced too much by a hearing deficiency. No participants had to be excluded because of this criterion.

Semantic expectation task

The semantic expectation (top-down processing) task was previously used by Vercammen & Aleman (2010). The task contained 150 Dutch sentences, in which the last word was masked by noise (N=100), or the last word was replaced by noise (N=50). Of the 100 masked stimuli, 50 ended with a word which was to be expected given the context of the sentence (e.g. The sailor sells his **boat**), whereas the other 50 of the sentences ended in an unpredictable manner (e.g. The sailor sells his **chair**). The participants were seated in front of a computer and listened to the task through headphones. After hearing a sentence, participants were asked to indicate with a button response whether they heard a word during the noise, and if so, to type in which word they had heard. In case of doubt, the participants were given the option of stating he or she had heard a word but that they were unsure about the answer. This way, participants were discouraged to guess and instead, only to report words they actually perceived.

Consequently five types of responses were possible: correct; missing (hearing only noise when in fact a word was presented); unsure (hearing a word but not knowing which); top-down (hearing a word that was predictable when in fact an unpredictable word or noise was presented); confabulation (hearing an incorrect word that was not

predicted).
Responses on the task were all scored by two raters, both blind for condition/type of participant. To investigate whether patients would give more idiosyncratic responses (that did not fit in the sentence but were also not expected and would thus not count as a top-down error but could be due nevertheless to aberrant top-down processing) responses were also rated on "strangeness" on a 5-point scale (see supplementary material).

Questionnaires

Hallucination proneness

Participants filled out a modified version of the Launay-Slade Hallucination Scale (LSHS; Larøi et al. 2004), a 16-item self-report questionnaire designed to quantify the tendency to hallucinate in healthy individuals. It has been proven to be reliable in both clinical and nonclinical populations (Bentall & Slade, 1984; Larøi et al. 2004; Levitan et al. 1995). Two patients did not fill out this questionnaire.
For the patient group, hallucinatory behaviour was measured with item P3 (amount of hallucinatory behavior) of the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). Although the PANSS assesses hallucinations in all modalities, the *auditory* hallucinations in the patient group were that frequent and severe that the score on this item was mainly influenced by these AVH (leading to a minimum score of 4).

Auditory Verbal Hallucinations

To describe phenomenological characteristics of AVH in the psychotic patients and the non-psychotic individuals, the PSYRATS Auditory Hallucination Rating Scale (AHRS) (Haddock et al. 1999) was administered. This questionnaire consists of 11 items that describe the AVH with the help of a Likert scale (0-4). For the use of this questionnaire in non-psychotic individuals, the range of the frequency scale is extended to 0-6 (also covering options 'at least once every month' and 'at least once every three months' since AVH are experienced less often than once a week (the original minimum score of this item). This questionnaire was administered by trained psychologists. Due to high correlations between several of these items, two new variables were computed: The variable 'emotional valence of content' was operationalized as the sum of three items from the AHRS: 'amount of negative content of voices', 'degree of negative content' and 'amount of distress"; i.e. an ordinal variable expressing overall burden of voices with negative content. The variable 'total distress' was operationalized as the sum of two items from the AHRS: 'intensity of distress', and 'disruption to life caused by voices'. As a result, the following items were used in this study: frequency, duration, location, loudness, beliefs re-origin of voices, controllability, emotional valence of content and total distress.

Statistical Analyses

The primary analysis concerned the question whether the three groups differ on the number of top-down errors made in the semantic task, while correcting for overall accuracy. An ANCOVA was performed, with the number of correct answers as a covariate to ensure that overall test performance has not biased the results. Age was associated with group membership and was therefore also entered as a covariate in this analysis. Pairwise comparisons, Bonferroni corrected for multiple testing, were used to explore between-group differences.

Furthermore, to test whether the score on the Launay-Slade Hallucination Scale is positively correlated with the number of top-down errors in the non-psychotic groups, a Spearman's rank or Pearson's correlation coefficient was calculated, depending on the distribution of the variables. In the psychotic patients, we calculated a Spearman's rank or Pearson's correlation coefficient for the number of top-down errors and the score on item P3 (amount of hallucinatory behavior) of the PANSS, depending on the distribution of the variables.

All data were analyzed with the Statistical package for the Social Sciences (SPSS, version 15.0).

Results

Description of AVH characteristics

Table 2 illustrates the characteristics of the voices in both AVH groups based on the PSYRATS items. Mean scores are provided as well as a description of its closest anchor in the questionnaire.

Top-down errors corrected for overall accuracy

The total of top-down errors showed a significant main effect for group, after correcting for overall task accuracy (correct answers) and age ($F_{2,117}$=3.549, *P*=0.032). Mean number of top-down errors in the healthy controls was 10.55 (SD 8.29), in the non-psychotic individuals with AVH 16.75 (SD 12.13) and in the psychotic patients with AVH 12.68 (SD 8.70). Pairwise comparisons (significant at 0.05 level, Bonferroni adjusted) showed that the non-psychotic individuals with AVH differed significantly from the healthy controls ($F_{1,78}$= 5.700, *P*<0.027). No difference was observed between non-psychotic individuals with AVH and psychotic patients ($F_{1,78}$= 3.386, *P*=.448), and between psychotic patients and healthy controls ($F_{1,78}$= 2.314, *P*=.944).

For an overview of the errors that were made during the task in the three groups, means and standard deviations see Supplementary table 2. Also described in the supplementary results is a secondary analysis concerning idiosyncratic answers that were given in the three groups, on which the groups did not differ.

Table 2: Characteristics of AVH in 40 healthy individuals with AVH and 40 patients with psychosis

	Patients Mean (SD)	*Description of closest anchor*	*Non-psychotic individuals with AVH Mean (SD)*	*Description of closest anchor*
Frequency (0-6)	5.15 (0.89)	Voices at least once an hour	3.65 (0.98)	Voices at least once a day
Duration (0-4)	2.73 (1.20)	Voices last for at least one hour	1.53 (0.68)	Voices last for several minutes
Location (0-4)	2.08 (1.00)	Outside head, close to ears and inside head	2.35 (1.27)	Outside head, close to ears and inside head
Loudness (0-4)	1.95 (0.85)	Same loudness as own voice	1.95 (0.50)	Same loudness as own voice
Beliefs origin (0-4)	2.35 (1.12)	<50% conviction that voices have external cause	3.03 (1.10)	≥50% conviction that voices have external cause
Controllability (0-4)	3.13 (1.02)	Occasional control over voices	2.03 (1.63)	Half of the time control over voices
Emotional Valence of content (0-12)	8.88 (2.64)	Most of the voices are negative and unpleasant	1.15 (2.28)	Hardly any voices are negative or unpleasant
Total Distress (0-8)	4.78 (1.70)	Voices cause considerable distress	0.43 (1.22)	Voices cause no distress
Age of onset	19.83 years old (11.05)		14.40 years old (15.04)	

Hallucination Proneness & Top-down errors in nonpsychotic groups

The means of the total score on the Launay Slade Hallucination scale per group are: healthy controls 6.03 (SD 5.15), non-psychotic individuals with AVH 40.43 (SD 12.15) and psychotic patients with AVH 36.08 (SD 12.71). However, as this questionnaire was designed to screen for hallucination proneness in healthy individuals, patients' scores were obtained purely for descriptive purposes and not entered in the analysis. The number of top-down errors significantly correlated with the total score on the LSHS in the non-psychotic individuals with AVH and healthy controls (r=.349, $P<0.01$)

Hallucinatory behavior & Top-down errors in psychotic patients

The number of top-down errors did not correlate significantly with the amount of hallucinatory behavior (item P3 of the PANSS) in patients (r=.027, $P=.866$).

Discussion

The aim of this study was to compare the influence of top-down processing between hallucinating individuals with and without a clinical psychotic disorder and healthy controls. Non-psychotic individuals with auditory verbal hallucinations (AVH) made significantly more top-down errors than healthy controls. Psychotic patients obtained intermediate scores which were not significantly different from either group. The total score on the LSHS questionnaire in the two non-psychotic groups was associated with the number of top-down errors that are made: the higher the hallucinations proneness, the more top-down errors were made. When investigating the association between top-down errors and the severity of hallucinatory behavior in psychotic patients, no significant association was found.

Our results corroborate and extend the findings reported by Vercammen & Aleman (2010), who observed more top-down errors using the same semantic expectation task in undergraduates with high scores on the LSHS compared to undergraduates with low scores. Speculatively, one could argue that attentional top-down processes only play a pivotal role in the generation of AVH in the non-psychotic individuals and not in the patient group. This may suggest different cognitive mechanisms for pathological and nonpathological hallucinations and may thus point to a more categorical view on hallucinations. Indeed, whereas researchers are increasingly using a continuum to describe psychotic phenomena such as AVH, David (2010) recently advocated a critical view on the use of such a continuum. Although the hypothesis of a continuum in hallucinatory experiences across the general population has received strong empirical support, it remains unclear whether it can acknowledge the pathological or disruptive nature of hallucinations in a clinical context. David suggests that we should define beforehand what results would imply continuity and discontinuity. In addition, Luhrmann (2011) describes three fundamentally different patterns (categories) within individuals experiencing AVH. He states that AVH in psychosis are quite universal and therefore least influenced by culture, other types of AVH are more shaped by expectations and culture. He suggests that 'cultural ideas and practices can affect mental experience so deeply that they lead to override of ordinary sense perception'. In other words, perhaps AVH can be viewed in the light of a hierarchical model: a biological basis determines if hallucinations can arise, next cognitive factors determine whether this experience is perceived as a hallucination. This raises the question whether both types of AVH can indeed be viewed as similar phenomena. Although substantial overlap is found on clinical and neuroimaging measures, the etiology of AVH is complex, making it likely that different cognitive processes play parts in this phenomenon. A different age of onset in both groups (Daalman et al. 2011a) supports this hypothesis. In addition, the absence of increased striatal dopamine turn-over in non-psychotic individuals with AVH (Howes et al. 2012) confirms the idea of different underlying mechanisms. While increased striatal dopamine turn-over may be

an important biological factor in hallucinations in psychosis (Kapur, 2003) cognitive factors, such as strong expectations, may be the main contributing factor in non-psychotic individuals with AVH.

Indeed, Vercammen & Aleman (2010) also found that increased reliance on top-down processes is present in individuals with a high degree of hallucination proneness. However, other studies suggested that attentional top-down processing may be stronger in hallucinating *patients* compared to non-hallucinating patients (Aleman et al. 2003; Schneider & Wilson, 1983; Vercammen al. 2008). However, the experimental tasks used in these studies were not based on semantic expectations, but on signal detection. One could argue that patients maybe did have stronger top-down processing in our task, but that they gave idiosyncratic responses due to aberrant semantic processing. For example, Hoffman et al. (1999b) showed that patients with AVH confabulate numerous words after being presented with multiple speech streams ("speaker babble") that have been intermingled and are hence unintelligible. We could not confirm this in the present semantic expectation task, however, as patients did not respond with "stranger" words than the other groups.

The current finding of increased top-down processing in non-psychotic individuals with AVH is consistent with studies suggesting enhanced perceptual attention in hallucination-prone subjects. For example, Van Lutterveld et al. (2010) found that non-psychotic individuals with AVH score higher than healthy controls on measures of effortful attention, which can also be viewed as a measure of top-down processing In addition, using fMRI, Lewis-Hanna et al. (2011) found enhanced cortical effects of auditory stimulation and auditory attention in healthy individuals prone to auditory hallucinations during partial wakefulness. Finally, Daalman et al. (2011b) reported that non-psychotic individuals with AVH showed aberrant inhibition compared to healthy controls as measured with standard cognitive tasks, and too much top-down processing can be viewed as having insufficient inhibition.

Limitations:

The absence of increased top-down processing in patients may be associated with specific task characteristics. The stimuli applied in the present study were neutral sentences, with no distinct positive or negative emotional valence. Psychotic patients hear predominantly negative voices whereas non-psychotic individuals with AVH hear primarily positive or neutral voices (Daalman et al. 2011a). Possibly, stimulus material with a more negative content could have led to a higher number of top-down errors in the patient group. Indeed, Morrison & Haddock (1997) found that emotional valence of a source monitoring task affects external attributions in hallucinating and not in non-hallucinating control groups. Another task-related explanation for the lack of deviant top-down processing in patients is that the top-down task used in this study might be too difficult for the psychotic population, although total years of education is *not* significantly different in the three groups. Possibly, cognitive decline that is

associated with psychosis might have influenced task performance. However, the analysis included overall accuracy (number of correct responses) as a covariate. In addition, medication might have influenced task-performance. Most patients and only a few non-psychotic individuals and controls used psychoactive medication; as such the effects might be most prominent in the patient-group. One could argue that this might have normalized their amount of top-down processing and explain why no significant difference in top-down errors was found between the psychotic patients and healthy control subjects. If this were the case, hallucinations in both psychotic and non-psychotic individuals could be explained by similar cognitive mechanisms. However, if medication would have influenced the attentional top-down processes it would also have affected the hallucinations, yet all psychotic patients still experienced frequent AVH. For future research, we recommend including a group of psychotic patients without AVH. Comparing performance of this group with the AVH group could more specifically clarify the role of semantic top-down processing in the experience of AVH.

In conclusion, the current results suggest that top-down processing may be associated with the experience of AVH in non-psychotic individuals, but it does not seem an important factor in psychotic patients with hallucinations. Other cognitive and neurobiological processes may underlie AVH in psychotic patients. We should therefore more critically investigate the use of the continuum hypothesis in psychosis.

Supplementary methods

Medication information in the three groups

Detailed information regarding medication use is provided in supplementary table 1.

Supplementary table 1: Average dosage of all medication used in the three groups.

	Medication	*N*	*Average daily dosage in mg*
Healthy controls	No medication	39	
	Antipsychotic	0	
	Antidepressant		
	- paroxetine	1	Dosage unknown
	Calming	0	
	Other	0	
Non-psychotic AVH	No medication	38	
	Antipsychotic		
	- quetiapine	1	500
	Antidepressant		
	- venlafaxine	1	300
	- sertraline		100
		0	
	Calming		
		0	
	Other		
Patients AVH	No medication	7	
	Antipsychotic		
	- clozapine	18	462.5
	- aripiprazol	4	22.5 (1 person dosage unknown)
	- risperidon	1	4
	- olanzapine	3	19.2
	- quetiapine	8	468.75
	- flupentixol	1	100
	- pimozide	2	4
	- penfluridol	1	40 (2 times a week)
	Antidepressant		
	- amitriptyline	2	125
	- clomipramine	2	162.5
	- nortriptyline	1	150
	- mirtazapine	1	30
	- citalopram	1	25
	- fluoxetine	2	40
	- venlafaxine	2	56.3
	- venlafaxine SR	1	225
	- sertraline	1	200
	- fluvoxamine	1	50
	- paroxetine	3	33.3
	- agomelatine	1	Dosage unknown
	Calming		
	- clorazepate	1	20
	- lorazepam	1	20
	- diazepam	1	2
	- temazepam	1	20
	- lormetazepam	2	2
	- clonazepam	1	4
	- propanolo	1	40
	- zopiclon	1	7.5
	Other		
	- lithium	2	700
	- akineton	1	2
	- valproic acid	1	1500

Supplementary results

Distribution of errors between the three groups

For an overview of the errors that were made during the task in the three groups, means and standard deviations are presented in supplementary table 2.

Supplementary table 2: Mean number of different responses made by the three groups during the semantic top-down task.

	Healthy Controls	*Non-psychotic AVH*	*Patients AVH*	*df (2)*	*P*
Top-Down, Mean (SD)	10.55 (8.29)	16.75 (12.13)	12.68 (8.70)	F = 4.084	.019
Confabulation, Mean (SD)	2.40 (2.42)	4.30 (4.20)	3.03 (4.05)	χ^2 = 3.883	.143
Missing, Mean (SD)	12.43 (19.42)	7.05 (10.19)	24.05 (22.57)	χ^2 = 14.289	.001*
Unsure, Mean (SD)	31.55 (19.96)	29.73 (18.49)	23.13 (20.65)	χ^2 = 3.857	.145
Correct, Mean (SD)	93.08 (11.74)	92.18 (10.55)	87.13 (11.22)	F = 3.290	.041

* = significant after Bonferroni correction for multiple testing ($p<0.01$)

Idiosyncratic answers

The fact that no significant difference was found in top-down errors between the psychotic patients with AVH and healthy controls could be explained by strangeness of the answers given by patients. For example, Hoffman et al. (1999b) reported that hallucinating patients hear more bizarre and unrelated words in a masked speech tracking task. Patients might have given answers that were idiosyncratic and therefore not scored as top-down errors. If this were the case, they might have increased top-down processing but this is then more closely related to their own internal (and sometimes bizarre) perception than the actual perceptual reality. To investigate this in our sample, confabulations were scored as 'idiosyncratic' when they were found to be unusual in both a semantic and phonological way. A word that did not fit will in the sentence with respect to its meaning was scored 'semantically unusual'. A word that did not resemble the sound of the presented word was scored 'phonological unusual'. The three groups were compared with an explorative nonparametric Kruskal-Wallis test since the data on this variable were not normally distributed. No significant difference was found between the three groups (χ^2= .418; *P*=.811).

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Chapter 6

Cognitive biases and auditory verbal hallucinations in psychotic and non-psychotic individuals

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Abstract

Background

Several cognitive biases are prevalent in psychotic patients. It remains unclear whether these biases differ between psychotic patients and non-psychotic individuals with auditory verbal hallucinations (AVH).

Methods

The presence of cognitive biases was compared between 72 healthy controls, 72 non-psychotic individuals with AVH and 72 psychotic patients with AVH using the Cognitive Biases Questionnaire for psychosis (CBQp), which assesses the five biases of 'intentionalising', 'jumping to conclusions', 'catastrophising', 'dichotomous thinking', and 'emotional reasoning' in vignettes characterised by two themes, 'threatening events' and 'anomalous perceptions'.

Results

Non-psychotic individuals with AVH scored intermediately on the total CBQp between healthy controls and psychotic patients. However their profile on individual cognitive biases closely resembled healthy controls on four out of the five biases. The only exception was emotional reasoning, on which their scores were comparable to those of psychotic patients. Healthy voice-hearers demonstrated fewer biases on the 'threatening events' vignettes than the psychotic patients, but had equal scores on the 'anomalous perceptions' theme. Cognitive biases were related to emotional characteristics of voices in the patient group only.

Conclusions

Most cognitive biases that are prevalent in psychosis and associated with distressing voices are absent in healthy voice-hearers. The absence of these biases might prevent the formation of malign appraisals and delusions in these individuals.

Introduction

Although auditory verbal hallucinations (AVH) are a characteristic symptom of psychotic disorders, they are also found in healthy individuals in the general population (Tien, 1991). Therefore, AVH have been proposed to form a continuum, ranging from rare occurrences in otherwise healthy individuals at one end, through individuals high on 'schizotypal' traits, to psychotic patients with frequent occurrence at the other end (Larøi et al. 2012). While AVH in these groups show considerable overlap (Daalman et al. 2011a; Diederen et al. 2011), it remains unclear why some individuals remain healthy while others make the transition to psychosis. Cognitive models of psychosis suggest that it is not solely the presence of anomalous experiences, for example AVH, which lead to full-blown psychotic symptoms, but rather the appraisals that individuals hold about these experiences (Morrison, 2001; Garety et al. 2001, 2007). For example, an AVH might be considered as a phenomenon originating from one's own brain, as a message coming from the spirit of a deceased grandparent, or it might be perceived as an evil force from another dimension. Since appraisals may differ between individuals with AVH, some might render a person more vulnerable to develop psychosis and a 'need-for-care' (van Os et al. 2009).

Cognitive biases have been proposed to be instrumental in shaping these appraisals. A cognitive bias is a way in which an individual habitually interprets his experiences, gathers information about the world and develops and maintains beliefs. For example, the typical 'Beckian' bias of 'dichotomous thinking' leads to an absolute or black and white view of things: When a small mistake is made, someone might judge themselves as totally useless and worthless. There is now a large body of work demonstrating that cognitive biases play a key role in the formation and maintenance of delusions (see So et al. 2010, for a review), but few studies have investigated their role in AVH, or more precisely, the beliefs people hold about their voices. It remains unclear whether cognitive biases differ between individuals experiencing AVH with and without a 'need-for-care'. Ascertaining the extent to which cognitive biases are present in non-psychotic individuals with AVH may further clarify the relationship between biases, appraisals about voices and the transition to psychosis, as proposed by cognitive models of positive symptoms. Potentially the absence of cognitive biases in the non-psychotic group may prevent the formation of malign appraisals, in turn reducing the chances that hearing voices becomes problematic for the individual and leads to a 'need-for-care'.

The Cognitive Biases Questionnaire for psychosis (CBQp) was recently developed to assess cognitive biases in psychotic patients (Peters et al. 2010). Five types of cognitive biases, all believed to be important in psychosis, were incorporated in the questionnaire: jumping to conclusions, intentionalising, catastrophising, emotional reasoning and dichotomous thinking. The aim of this study was to compare the presence of cognitive biases with the CBQp in three groups: non-psychotic individuals

who experience AVH, psychotic patients with AVH, and healthy controls. Based on the cognitive model of psychosis, we hypothesized that the non-psychotic individuals with AVH would not show the cognitive biases that are characteristic of psychosis.

Method

Participants

A total of 72 non-psychotic participants with AVH, 72 psychotic patients with AVH, and 72 healthy controls without AVH, were included. The non-psychotic participants with AVH did not meet criteria for a DSM-IV diagnosis, as defined by a psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al. 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II; First et al. 1995a,b). Depressive disorder in complete remission was not an exclusion criterion. Additional exclusion criteria for all groups were alcohol and drug abuse.

For the non-psychotic participants with AVH, the minimum frequency to experience AVH was once every three months and the minimum duration since onset of AVH was one year.

Both the controls and non-psychotic individuals with AVH were recruited with the help of a Dutch website called 'explore your mind' (www.verkenuwgeest.nl) and selected on basis of respectively low and high scores in the items of the Launay and Slade Hallucinations scale (LSHS; Larøi et al. 2004) tapping into auditory verbal hallucinations. For more details about the selection and assessment procedure see Sommer et al. (2010a) and Daalman et al. (2011a).

The patients with a psychotic disorder were all outpatients from the Voices Clinic of the University Medical Centre Utrecht. These patients visited our clinic for regular treatment for psychosis or as a second opinion for intractable psychosis. In this group, clinical diagnoses were confirmed by an independent psychiatrist using the CASH interview. Forty-two patients (58.3%) were diagnosed with paranoid schizophrenia, 18 (25%) with psychosis not otherwise specified, 10 (13.9%) with schizo-affective disorder and 2 (2.8%) with disorganized schizophrenia. Demographic details are provided in table 1.

The study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the participants, written informed consent was obtained.

Table 1: Demographic characteristics of the participants: psychotic patients with AVH, non-psychotic individuals with AVH and healthy controls.

Group	*Psychotic patients with AVH*	*Non-psychotic individuals with AVH*	*Healthy controls*	*Difference (significance)*
n	72	72	72	
Male (%)	33 (45.8%)	22 (30.6%)	20 (27.8%)	χ^2= 6.01; df=2; p=.050
Female (%)	39 (54.2%)	50 (69.4%)	52 (72.2%)	
Mean age (s.d.)	39.71 (11.9)	47.58 (11.2)	45.13 (14.5)	F= 7.38; p=.001
Mean years of education (s.d.)	12.85 (2.6)	13.25 (2.3)	13.99 (2.4)	F= 3.94; p=.021
Married/living together (%)	20 (27.8%)	43 (59.7%)	43 (59.7%)	χ^2= 19.60; df=2; p<.001
Divorced (%)	10 (13.9%)	29 (40.3%)	11 (15.3%)	χ^2= 17.85; df=2; p<.001
Ethnicity				
Caucasian	69 (95.8%)	71 (98.6%)	72 (100%)	χ^2= 3.57; df=2; p=.168
Other	3 (4.2%)	1 (1.4%)	-	
- Asian	-	1 (1.4%)	-	
- Arabic	2 (2.8%)	-	-	
- African American	1 (1.4%)	-	-	

Measurements

The Cognitive Biases Questionnaire for psychosis (CBQp) was developed by Peters et al. (2010) to assess cognitive biases in patients with a psychotic disorder. It consists of thirty vignettes that can be grouped under two themes: 'anomalous perception' (e.g., "*Imagine that you are walking down the street when you hear your name being called, but when you look around you don't see anybody*") and 'threatening events' (e.g., "*Imagine you receive a letter and you notice it is not sealed*"), and assess five types of cognitive biases: 'intentionalising', 'catastrophising', 'dichotomous thinking', 'jumping to conclusions' and 'emotional reasoning'. There are three vignettes per bias for each theme (six vignettes per bias in total). Each vignette is rated on a 3-point scale ranging from 1 to 3 (1 = absence of bias; 2 = presence of bias with some qualification; and 3 = presence of bias). The maximum total score for each theme is 45, with a total overall score of 90. The minimum total overall score is 30. The scale has good psychometric properties, both internal consistency and test-retest reliability are high (Peters et al. 2010). In addition to the total score, all subscales as well as both themes were compared between the three groups.
For this study, a Dutch translation by De Hert, Lacluyse & Valmaggia was used.

The PSYRATS Auditory Hallucination Rating Scale (AHRS; Haddock et al. 1999) was used to map the phenomenological characteristics of the AVH. This questionnaire describes 11 characteristics of AVH. Each item is evaluated on a 5-point Likert Scale ranging from 0 to 4. For the use of this questionnaire in non-psychotic individuals, the range of the frequency scale is extended to 0-6 (also covering options 'at least once

every month' and 'at least once every three months' since AVH are experienced less often than once a week, the original minimum score of this item). This questionnaire was administered by trained psychologists.
The items of the PSYRATS AHRS can be extrapolated into three dimensional subscales (Haddock et al. 1999; Morrison et al. 2004): 1. An emotional characteristics factor (i.e. amount and intensity of distress, amount and degree of negative content items); 2. A physical characteristics factor (i.e. descriptions of the voice: items frequency, duration, location and loudness); 3. A cognitive interpretation factor (i.e. beliefs regarding the origin and attributions of control: items origin, disruption and control).

Statistics

The primary outcome measure was the total score on the CBQp. Between-group comparison (i.e., psychotic patients with AVH, non-psychotic individuals with AVH, and controls) of this measure was achieved through univariate analysis of covariance (ANCOVA), applying a General Linear Model procedure. In addition, the five cognitive biases subscales of the CBQp (intentionalising, catastrophising, dichotomous thinking, jumping to conclusions and emotional reasoning) as well as both themes (anomalous perceptions & threatening events) were analyzed in multivariate analysis of covariance, to gain more insight into possible differences between the three groups. Age was entered as a covariate since this variable differed significantly between the three groups and was related to both intentionalising (r= -.195, p=.004) and catastrophising (r= -.234, p=.001). Gender, total years of education, divorced and ethnicity were not associated with the CBQp total score or the subscales. In addition, 'married' was related to the total CBQp score (r=-.183, p=.007) but we did not include this variable as a covariate as the fact that psychotic patients are less often married is intrinsic to group status and correcting for this would remove part of the actual difference between the three groups (Miller & Chapman 2001).
Spearman correlations were calculated between the total score of the CBQp, the five cognitive biases and the three subscales of the PSYRATS to explore possible associations in the two AVH groups separately.

Missing values

In the complete sample of 216 participants, four items of the CBQp were missing. This could affect the power of statistical analyses if participants with incomplete data are excluded. In addition, complete-case analysis will give biased results because non-response to a particular question is usually not completely at random (van der Heijden et al. 2006). We therefore used a multiple imputation procedure based on linear regression to estimate these values based on the other observed variables.
All data were analyzed with the Statistical package for the Social Sciences.

Results

Description of AVH characteristics

Table 2 illustrates the characteristics of the voices in both AVH groups and the total scores on the three subscales of the PSYRATS. Mean scores are given as well as the description of its closest anchor.

Table 2: Characteristics of AVH in non-psychotic individuals and psychotic patients.

	Patients *Mean (SD)*	*Description of closest anchor*	*Non-psychotic individuals* *Mean (SD)*	*Description of closest anchor*
Frequency (0-6)	5.07 (0.92)	Voices at least once an hour	3.47 (1.28)	Voices at leas once a week
Duration (0-4)	2.69 (1.21)	Voices last for at least one hour	1.63 (0.80)	Voices last for several minutes
Location (0-4)	2.13 (1.16)	Outside head, close to ears and inside head	2.38 (1.23)	Outside head, close to ears and inside head
Loudness (0-4)	2.04 (0.84)	Same loudness as own voice	1.9 (0.56)	Same loudness as own voice
Beliefs origin (0-4)	2.25 (1.22)	<50% conviction that voices have external cause	3.01 (1.07)	≥50% conviction that voices have external cause
Amount negative content (0-4)	2.96 (1.08)	Majority voices is unpleasant or negative	0.38 (0.90)	No unpleasant content
Degree negative content (0-4)	2.96 (1.01)	Personal verbal abuse relating to self concept	0.39 (0.93)	Not unpleasant or negative
Amount distress (0-4)	3.04 (1.0)	Majority of voices is distressing	0.46 (0.92)	Voices not distressing at all
Intensity distress (0-4)	2.53 (0.80)	Voices are very distressing	0.26 (0.61)	Voices not distressing at all
Disruption life (0-4)	2.36 (0.95)	Moderate amount of disruption	0.21 (0.60)	No disruption to life
Controllability (0-4)	3.15 (1.11)	Occasional control over voices	2.03 (1.66)	Majority of occasions control over voices
Emotional subscale	11.49 (3.20)		1.49 (3.09)	
Physical subscale	11.99 (2.64)		9.38 (1.95)	
Cognitive subscale	7.76 (2.26)		5.25 (1.86)	

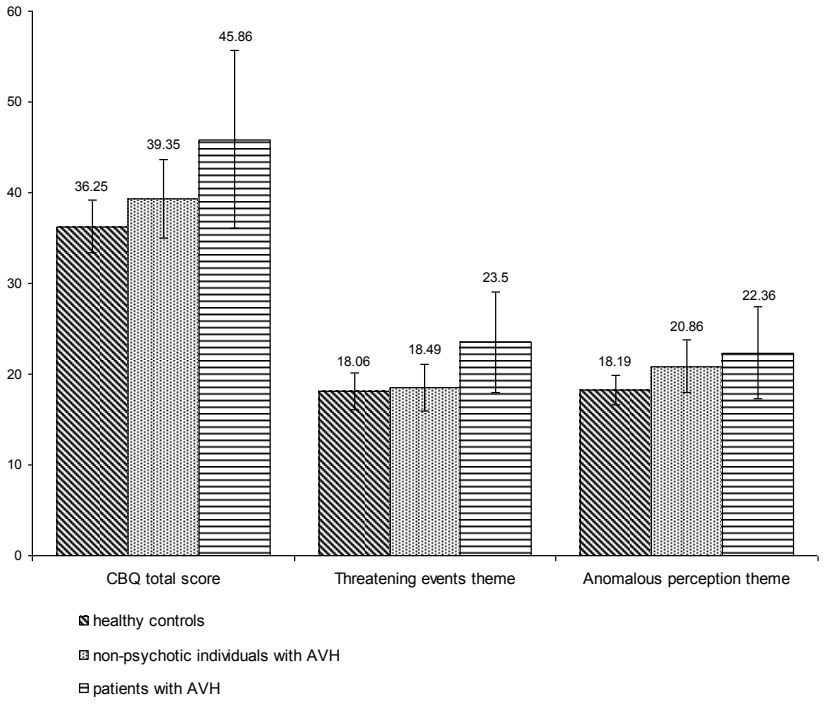
Differences in cognitive biases between the three groups

Total score of the CBQp

The total score of the CBQp differed significantly between the groups ($F_{2,213}$=37.510, p<.001). Pairwise comparisons showed that the healthy controls scored significantly lower than both the non-psychotic individuals with AVH ($F_{1,142}$= 3.242, p=0.008) and the psychotic patients with AVH ($F_{1,142}$= 9.292, p<0.001). The psychotic patients with AVH and non-psychotic individuals with AVH also differed significantly from each other ($F_{1,142}$= 6.049, p<0.001), with lower scores in the non-psychotic group. We used Bonferroni correction to take into account the fact that we performed three different tests and therefore applied a p-value of .05/3= .017 as the type-I error rate.

The mean total scores on the CBQp are illustrated in Figure 1, including standard deviation per group.

Figure 1: total score on the CBQp, on the threatening events theme and on the anomalous perception theme in the three groups



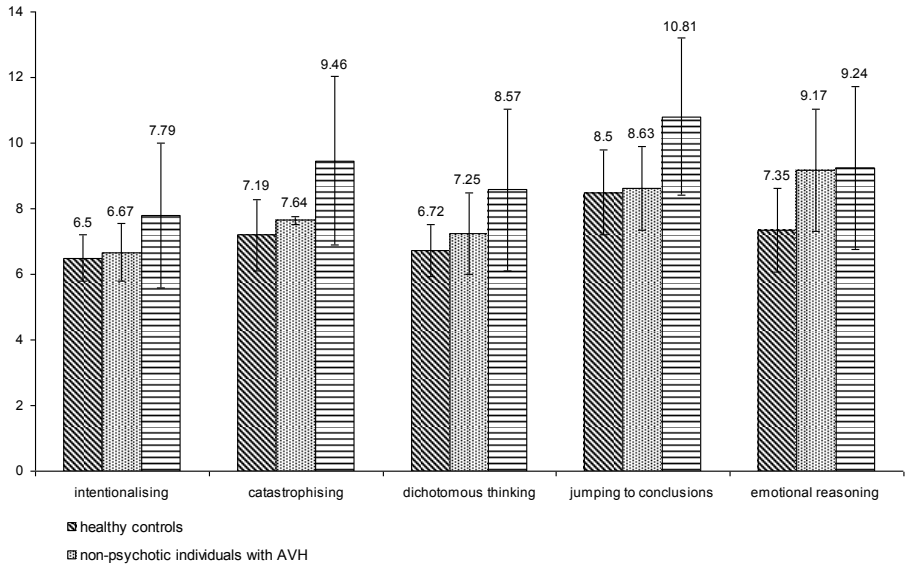
Cognitive biases independently

There was a statistically significant difference between the three groups on the combined dependent variables: $F_{10,418}$ = 11,947, p<0.001; Pillai's Trace 0.44, after correcting for age. When the results for the dependent variables were considered separately the three groups differed significantly on all subscales of the CBQp after correction for multiple testing (.05/5=.01): Intentionalising ($F_{2,213}$=14.319, p<.001), Catastrophising ($F_{2,213}$=28.062, p<.001), Dichotomous Thinking ($F_{2,213}$=20.743, p<.001), Jumping to Conclusions ($F_{2,213}$=36.260, p<.001) and Emotional Reasoning ($F_{2,213}$=21.893, p<.001).

Closer inspection of the cognitive biases with post-hoc Bonferroni-corrected t-tests reveals that healthy controls and non-psychotic individuals with AVH scored significantly lower than patients with AVH on the subscales intentionalising ($F_{1,142}$= 1.216, p<0.001 and $F_{1,142}$= 0.995, p<0.001, resp.), catastrophising ($F_{1,142}$= 2.143, p<0.001 and $F_{1,142}$= 1.643, p<0.001, resp.), dichotomous thinking ($F_{1,142}$= 1.764, p<0.001 and $F_{1,142}$=

1.198, $p<0.001$, resp.) and jumping to conclusions ($F_{1,142}= 2.270$, $p<0.001$ and $F_{1,142}= 2.130$, $p<0.001$, resp.), but did not differ significantly from each other. However, on emotional reasoning the healthy controls scored significantly lower than both healthy individuals and patients with AVH ($F_{1,142}= 1.815$, $p<0.001$ and $F_{1,142}= 1.898$, $p<0.001$ resp.), which did not differ from each other. The mean scores of the cognitive biases and their standard deviations are presented in Figure 2.

Figure 2: CBQp scores of the three groups on the five cognitive bias subscales



Themes of the CBQp

There was a statistically significant difference between the groups on the combined dependent variables: $F_{4,424} = 26.065$, $p<0.001$; Pillai's Trace 0.395, after correcting for age. When the results for the dependent variables were considered separately the three groups differed significantly on both themes after correction for multiple testing. The total score on threatening events showed a significant main effect for group, after correcting for age ($F_{2,213} = 41.80$, $p<0.001$). Mean scores on the threatening events theme and their standard deviations are presented in Figure 1. Pairwise comparisons (significant at 0.025 level, Bonferroni adjusted for two tests) showed that the psychotic patients with AVH scored significantly higher than both the healthy controls ($F_{1,142}= 5.23$, $p<0.001$) and the non-psychotic individuals with AVH ($F_{1,142}= 4.69$, $p<0.001$). No difference was observed between non-psychotic individuals with AVH and healthy controls ($F_{1,142}= 0.53$, $p=1.000$).

The total score on anomalous perception also showed a significant main effect for group, after correcting for age ($F_{2,213}$ = 24.98, p<0.001). Mean scores and standard deviations on the anomalous perception theme are presented in Figure 1. Pairwise comparisons (significant at 0.025 level, Bonferroni adjusted for two tests) showed that the healthy controls scored significantly lower than both the non-psychotic individuals with AVH ($F_{1,142}$= 2.712, p<0.001) and the psychotic patients with AVH ($F_{1,142}$= 4.067, p<0.001). No difference was observed between non-psychotic individuals with AVH and psychotic patients with AVH ($F_{1,142}$= 1.355, p=0.075).

Relationships between AVH characteristics and cognitive biases

To explore possible associations between individual biases and characteristics of AVH, Spearman correlations were calculated between the five biases and the three subscales of the PSYRATS AHRS. The two AVH groups differed on the biases, and were therefore analyzed separately.

There were no significant associations in the non-psychotic individuals with AVH, apart from between the PSYRATS AHRS 'Cognitive' subscale and Intentionalising (after a Bonferroni correction for multiple testing: .05/36=.0014; p<0.0014).

In contrast, in the psychotic patients with AVH, significant associations were found between the PSYRATS AHRS 'Emotional' subscale and the biases Intentionalising, Jumping to Conclusions, Emotional Reasoning as well as the total score on the CBQp (after a Bonferroni correction for multiple testing: .05/36=.0014; p<0.0014). The Spearman correlation coefficients are presented in table 3 for both non-psychotic individuals with AVH and psychotic patients with AVH.

Table 3: Spearman correlations between Cognitive biases and AVH subscales in non-psychotic and psychotic individuals with AVH

	Emotional (P)	*Physical (P)*	*Cognitive (P)*
Non-psychotic individuals			
CBQ total	.162	-.089	.293
Intentionalising	.173	-.124	.380*
Catastrophising	.112	-.080	.192
Dichotomous Thinking	.153	.088	.205
Jumping to Conclusions	.231	.058	.117
Emotional Reasoning	-.050	-.156	.181
Psychotic individuals			
CBQ total	.410*	.301	.248
Intentionalising	.371*	.244	.233
Catastrophising	.294	.295	.258
Dichotomous Thinking	.206	.175	.239
Jumping to Conclusions	.388*	.191	.230
Emotional Reasoning	.396*	.266	.124

* significant at p<.0014

Discussion

This study investigated the potential differences in presence of cognitive biases in non-psychotic and psychotic individuals with AVH. Non-psychotic individuals with AVH obtained intermediate total scores between controls and psychotic patients on the Cognitive Biases Questionnaire for psychosis (CBQp), measuring several cognitive biases that are prevalent in psychosis. While at first glance these results might be interpreted as reflecting the non-psychotic individuals with AVH lying half way on a psychosis continuum, further analyses of the CBQp subscales showed that the non-psychotic voice hearers had the same profile as the healthy controls on four out of the five cognitive biases, differing significantly from the controls only on 'emotional reasoning', which accounted for most of the difference between these two groups on the total CBQp score. Only on emotional reasoning were the scores of non-psychotic individuals with AVH comparable to those of psychotic patients with AVH. This cognitive bias, i.e., reasoning based on emotions, feeling or instinct instead of logic, therefore is the only bias that appears to be related to the presence of AVH, rather than to a 'need for care'. The emotional reasoning bias is perhaps the least psychosis specific, and is not only highly prevalent in other psychiatric disorders, such as anxiety disorders (Clark, 1999), but also likely to be the most culturally accepted of the five biases assessed by the CBQp. The remaining biases, namely intentionalising, catastrophising, dichotomous thinking and jumping to conclusions, were all significantly higher in the psychotic group, suggesting that the absence of these biases in non-psychotic individuals with AVH might have contributed to preventing them from developing a 'need-for-care', as proposed by cognitive models of psychosis (Morrison, 2001; Garety et al. 2001, 2007).

The findings comparing the groups on the two themes of the case vignettes of the CBQp ('Anomalous Perceptions' and 'Threatening Events') were intriguing. Both non-psychotic individuals and psychotic patients with AVH scored higher than healthy controls on the scores on 'Anomalous Perceptions': Biases were therefore more pronounced in the AVH-groups when they were presented in the context of this theme. However, non-psychotic individuals with AVH and healthy controls scored lower than the psychotic patients on the theme 'Threatening Events': non-psychotic individuals with AVH have comparable low scores to controls when biases were presented in the context of threatening events. Indeed, non-psychotic individuals with AVH often hold appraisals about their voices that are non-threatening (e.g., they often have spiritual explanations). These results are in line with previous findings that paranoid (but not necessarily external) appraisals differentiate individuals with psychotic experiences with and without a 'need for care' (Brett et al. 2007; Lovatt et al. 2010), and that non-psychotic voice hearers do not show delusional symptoms (Sommer et al. 2010a). Similarly, Lawrence & Peters (2004) found that reasoning biases were limited to people who reported a belief in, rather than experience of, paranormal phenomena.

Cognitive Biases and AVH factors

In the psychotic patients, but not the healthy voice-hearers, several cognitive biases (Intentionalising, Dichotomous Thinking and Emotional Reasoning), as well as the CBQ total score, were specifically related to the emotional characteristics of AVH, as measured with the PSYRATS. In other words, the presence of cognitive biases goes hand in hand with distressing voices with predominantly negative content. Cognitive models of psychosis would propose that the biased appraisals either cause, or at least act as a maintaining factor for, the resulting distress. However it cannot be determined from these data whether the reasoning biases drive the distress, or whether negative, distressing content leads to a higher likelihood of interpreting events in a biased way.

Clinical implications

The assessment of cognitive biases in individuals with AVH may shed more light on individuals' vulnerability to make the transition to full-blown psychosis. Furthermore it can help identify the tendency to make unhelpful appraisals, which can then be targeted in cognitive behavioural therapy (CBT) and in turn alleviate accompanying distress. New adjunctive interventions to CBT have also recently been developed to target reasoning processes specifically, for instance, Metacognitive Training (MCT; Moritz & Woodward, 2007; Moritz et al. 2011) or the Maudsley Review Training Programme (Waller et al. 2011) which focuses specifically on 'Jumping to Conclusions' and belief flexibility. The results of this study support this recent trend in focusing explicitly on cognitive and reasoning biases, rather than the anomalous experiences themselves.

Limitations

The non-psychotic individuals with AVH and controls in our study were recruited with the help of a website. This could have led to a selection bias, as suspicious individuals may not have completed the questionnaires on the website or rejected our invitation to visit our research ward.

In conclusion, most cognitive biases that are associated with psychosis, particularly with themes of threatening events, were absent in non-psychotic individuals with AVH, with the exception of emotional reasoning. Cognitive biases were related to the emotional characteristics of voices in the psychotic patients. The absence of cognitive biases may prevent the formation of malign appraisals and delusions in non-psychotic voice hearers, keeping them on the safe end of a psychosis continuum.

Chapter 7

Childhood trauma and auditory verbal hallucinations

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Abstract

Background

Hallucinations have consistently been associated with traumatic experiences during childhood. This association appears strongest between *physical* and *sexual* abuse and auditory verbal hallucinations (AVH). It remains unclear whether traumatic experiences mainly colour the content of AVH or whether childhood trauma triggers the vulnerability to experience hallucinations in general. In order to investigate the association between hallucinations, childhood trauma and emotional content of hallucinations, experienced trauma and phenomenology of AVH was investigated in non-psychotic and individuals with a psychotic disorder who hear voices.

Methods

127 non-psychotic individuals with frequent AVH, 124 healthy controls and 100 psychotic patients with AVH were assessed for childhood trauma. Prevalence of childhood trauma was compared between groups and the relation between characteristics of voices, especially emotional valence of content and childhood trauma was investigated.

Results

Both non-psychotic individuals with AVH and patients with a psychotic disorder and AVH experienced more sexual and emotional abuse compared to the healthy controls. No difference in the prevalence of traumatic experiences could be observed between the two groups experiencing AVH. In addition, no type of childhood trauma could distinguish between positive or negative emotional valence of the voices and associated distress. No correlations were found between sexual abuse and emotional abuse and other AVH characteristics.

Conclusions

These results suggest that sexual and emotional trauma during childhood render a person more vulnerable to experience AVH in general, which can be either positive voices without associated distress or negative voices as part of a psychotic disorder.

Introduction

Auditory verbal hallucinations (AVH) are not only a characteristic symptom of psychotic disorders; they also occur in the general population with a prevalence of approximately 15% (for a review see Beavan et al. 2011). This includes individuals who report to hear voices quite regularly as well as individuals who report hearing a voice at least once in their lifetime. Several phenomenological details of AVH, such as location, loudness and personification are similar in individuals with and without psychosis who hallucinate. However, differences have been found in the emotional valence of the content, which can be quite the opposite in these two groups (Daalman et al. 2011a; Honig et al. 1998). For example: "We will get you and then kill you, you cannot escape us" as opposed to "Don't be afraid, I'm always there to watch over you. Nothing will ever happen to you". Both sentences are examples of AVH, the first is from a patient with a psychotic illness and the second from a non-psychotic individual experiencing frequent AVH.

It has consistently been shown that individuals with hallucinations more frequently experienced traumas during childhood (for a review: Read, 1997; Famularo et al. 1992; Sansonnet-Hayden et al. 1987; Ross et al. 1994). Sometimes the content of voices is directly related to the trauma, for example when people hear the voice of their former abuser. The relationship between childhood abuse and hallucinations seems strongest for *physical* abuse and *sexual* abuse and specifically relates to hallucinated *voices* (Janssen et al 2004; Hammersley et al. 2003; Ensink 1992). Individuals who report hearing voices have more frequently experienced childhood traumas. This suggests that there might be a relationship between severity of trauma and an increased risk for a psychotic disorder later in life (Janssen et al. 2004). Several models have been proposed to explain how trauma during childhood might lead to psychotic symptoms later in life. For instance, the traumagenic neurodevelopmental (TN) model, which combines social, psychological and biological factors (Walker & DiForio, 1997; Read et al. 2001; Heim et al. 2000), suggests that prolonged exposure to stressors leads to a chronic heightened glucocorticoid release. This could cause permanent changes in the hypothalamic-pituitary-adrenal (HPA) axis which in turn may induce increased striatal dopamine turn-over, rendering a person more vulnerable for positive psychotic symptoms. As an alterative to the TN model, cognitive explanations state that traumatic experiences enhance negative or maladaptive schematic models of the self, of others and the world. This in turn renders a person more vulnerable to negative schemas about social humiliation or subordination, which may influence the content of, or attitude towards AVH (Birchwood et al. 2000). A third possibility is offered by Garety et al. (2001), who define a central role for cognitive disturbances, leading to external appraisal errors. They hypothesized that childhood trauma affects the appraisal of internal experiences as coming from an external agent. As the abovementioned theories all describe how psychotic symptoms can arise, it remains unclear whether

these are also applicable in non-psychotic individuals who experience AVH.
A previous study (Andrew et al. 2008) showed a high-incidence of childhood trauma in both psychiatric (N=22) and non-psychiatric individuals who experience AVH (N=21). While the psychiatric individuals with AVH considered their voices predominantly as malevolent and distressing, the non-psychiatric individuals with AVH viewed them as benevolent and hardly stressful. Interestingly, the psychiatric individuals experienced significantly more childhood sexual abuse than the non-psychiatric group.
As specific types of childhood trauma (sexual abuse and physical abuse) are considered to be risk factors for hallucinations, especially AVH, traumatic experiences during childhood may not be related to the presence of AVH itself, but more to the emotional content of AVH (hearing positive or negative voices). Indeed, content or theme of hallucinations can often be related to the experienced trauma (Read & Argyle, 1999; Hardy et al. 2005). Moreover, McCarthy-Jones (2011) suggests in his review that childhood sexual abuse may even be a risk factor for hearing specific types of voices (e.g., command hallucinations). The specific relation to hallucinated *voices* could imply that experienced traumas are relived during hallucinations. Trauma may therefore colour the content of hallucinations, rather than trigger the phenomenon per se.
In order to investigate this we will compare prevalence of childhood trauma in individuals with voices with a positive or neutral emotional content (most of them are non-psychotic) and in individuals who experience AVH with a negative emotional content (mainly patients with a psychotic disorder). In addition we will investigate the association between the childhood traumas that were found to differ between groups and AVH characteristics, such as frequency, location and controllability. We included three groups, each with a substantial number of subjects: non-psychotic individuals who experience frequent AVH (N=127), patients with a psychotic disorder experiencing frequent AVH (N=100) as well as healthy control subjects without AVH (N=124) and assessed 5 different types of childhood trauma using the Childhood Trauma Questionnaire – Short form (CTQ-SF). Comparing these three groups will provide information about the association between childhood trauma and AVH: is there a relation between trauma and all sorts of AVH, or is this relation only apparent for voices with an abusive or negative content?

Method

Participants

One-hundred patients with a psychotic disorder were included, as well as 127 non-psychotic subjects with AVH and 124 healthy control subjects without AVH. The non-psychotic subjects with AVH and healthy controls without AVH did not meet criteria for a DSM-IV diagnosis, as assessed with the Comprehensive Assessment of

Symptoms and History (CASH) interview (Andreasen et al. 1992) and the Structured Clinical Interview for Personality Disorder (SCID-II) (First et al. 1995a,b). Depressive disorder in complete remission was not an exclusionary criterion. Exclusion criteria for all groups were alcohol abuse and drug abuse. The healthy controls and non-psychotic subjects with AVH were screened for alcohol abuse (more than 20 units per week) and drug abuse (using cannabis more than once a month and/or the use of other illicit substances) by telephone and later with the help of urine samples, a total of 10 individuals in these groups were excluded for this reason. In the patient group alcohol and drug abuse was screened for by the independent psychiatrist with the help of the CASH interview. No patients were excluded. For the non-psychotic subjects with AVH, the minimum frequency to experience AVH was once a month and the minimum duration since onset of AVH was one year. Both the non-psychotic individuals with AVH and the healthy controls were recruited with the help of a Dutch Web site called 'explore your mind' (www.verkenuwgeest.nl). An extended description of the recruitment and selection procedure is provided in prior studies of our group (van Lutterveld et al. 2010; Sommer et al. 2010a; Daalman et al. 2011a; Diederen et al. 2010a, 2011; de Weijer et al. 2011).

A total of 100 outpatients with a psychotic disorder from the University Medical Centre Utrecht were included. These patients visited our clinic for regular treatment of psychosis or as a second opinion for refractory psychosis. In this group, clinical diagnoses were confirmed by an independent psychiatrist using the CASH interview. Fifty-nine patients (59%) were diagnosed with paranoid schizophrenia, 14 (14%) with schizoaffective disorder, 2 (2%) with disorganized schizophrenia, 1 (1%) with catatonic schizophrenia and 24 (24%) with psychosis not otherwise specified. Demographic details are shown in Table 1; the three groups were matched for gender but differed on age.

The 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.

Questionnaires

Childhood trauma was assessed with the help of the Childhood Trauma Questionnaire – Short form (CTQ-SF) (Bernstein et al. 2003). This 25-item version was derived from the original 70 item CTQ (Bernstein & Fink, 1998; Bernstein et al., 1994). Cut-off scores for 'moderate to severe' exposure were used to classify the occurrence (presence or absence) of a specific trauma in the three groups (emotional abuse ≥ 13; physical abuse ≥ 10; sexual abuse ≥ 8; emotional neglect ≥ 15; physical neglect ≥ 10). Scores above this cut-off score correspond with rating most traumatic experiences of that specific trauma as "often true". The short form of the CTQ demonstrated good criterion-related validity in s subsample of adolescents and appeared to be viable

across diverse populations (Bernstein et al. 2003).

Table 1. Demographic characteristics of the participants: healthy control subjects, non-psychotic individuals with AVH and patients with a psychotic disorder and AVH.

Group	*Healthy controls*	*Non-psychotic individuals with AVH*	*Psychotic patients with AVH*	*Difference (significance)*
Male (%) N	40 (32.3%) 124	41 (32.3%) 127	44 (44%) 100	χ^2=4.29; df= 2; *p*=.117
Mean age (s.d.) N	43.06 (14.39) 124	42.41 (12.63) 127	38.02 (11. 49) 100	F=4.79; df=2; *p*=.009
Total years education N	14.02 (2.32) 123	13.23 (2.19) 126	12.70 95	F=98.45; df=2; *p*<.001
Mean gross income No information < € 1264,- > € 1264, < € 2458,- > € 2458,- No income N	 5 25 41 40 2 113	 11 22 36 37 1 107	 4 61 20 6 1 92	χ^2=65.62; df= 8; *p*<.001
Married N	60.16% 123	53.54% 127	25.51% 98	χ^2=28.71; df= 2; *p*<.001
Divorced N	21.14% 123	33.86% 127	13.40% 97	χ^2=13.41; df= 2; *p*=.001
Lifetime depression N	18.33% 120	43.55% 124	75% 92	χ^2=70.21; df= 2; *p*<.001

To establish the phenomenological characteristics of AVH, the PSYRATS Auditory Hallucination Rating Scale (AHRS) (Haddock et al. 1999) was administered. This questionnaire consists of 11 items that describe the AVH with the help of a Likert scale (0-4). For the use of this questionnaire in non-psychotic individuals, the range of the frequency scale was extended to 0-6 (also covering options 'at least every three months' and 'at least once every month', next to 'at least once a week', 'at least once a day', 'at least once a hour' and 'continuously', since AVH were experienced less often than once a week (the original minimum score of this item). This questionnaire was administered by trained psychologists. Due to high correlations between several of these items, two new variables were computed: The variable 'emotional valence of content' was operationalized as the sum of three items from the AHRS: 'amount of negative content of voices', 'degree of negative content' and 'amount of distress"; i.e. an ordinal variable expressing overall burden of voices with negative content. The variable 'total distress' was operationalized as the sum of two items from the AHRS: 'intensity of distress', and 'disruption to life caused by voices'. As a result, the following items were used in this study: frequency, duration, location, loudness, beliefs re-origin of voices, controllability, emotional valence of content and total distress.

Statistical Analyses

First, for an overview of the data, the prevalence of the different childhood traumas was calculated for the three groups and compared with χ^2 tests.

To investigate which childhood trauma subtypes were associated with group membership (healthy controls, non-psychotic individuals with AVH, patients with a psychotic disorder and AVH), a stepwise multinomial logistic regression analysis was performed. Predictors were the five types of childhood trauma as measured with the CTQ-SF (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect). The dependent variable was group membership. The choice for a multinomial logistic regression was based on the fact that the three levels of the dependent variable were not necessarily ordered. Age was associated with group membership and with one of the childhood trauma's (emotional neglect, $\chi^2(49, N = 351) = 78.03$, $p=.005$) and was therefore entered as a covariate in this analysis. In addition, gender appeared to be associated with sexual abuse ($\chi^2(1, N = 351) = 7.223$, $p=.007$) and emotional neglect ($\chi^2(1, N = 351) = 3.887$, $p=.049$). Both childhood traumas are found to be more prevalent in women. Therefore, gender was entered as a covariate in the regression analysis.

A logistic regression analysis was performed to investigate which childhood traumas best predict the emotional valence of the voices. Emotional valence of content was used as dependent variable and the (presence of) childhood traumas as predictor variables. Emotional valence of content was dichotomized using a median split.

To establish whether characteristics of AVH were associated with childhood trauma, correlation coefficients were calculated between the childhood traumas that were found to predict group-membership and AVH characteristics from the PSYRATS (frequency, duration, location, loudness, beliefs re-origin of voices and controllability, as well as the computed variables 'emotional valence of content' and 'total distress' of AVH). Since this data was not normally distributed, non-parametric Spearman correlations were used.

Results

Description of AVH characteristics

Table 2 illustrates the characteristics of the voices in both AVH groups based on the PSYRATS items. Mean scores are provided as well as a description of its closest anchor in the questionnaire.

Table 2. Characteristics of AVH in 127 non-psychotic individuals with AVH and 100 patients with a psychotic disorder and AVH.

	Patients with psychotic disorder and AVH Mean (SD)	*Description of closest anchor*	*Non-psychotic individuals with AVH Mean (SD)*	*Description of closest anchor*
Frequency (0-6)	5.05 (1.05)	Voices at least once per hour	3.61 (1.19)	Voices at least once a day
Duration (0-4)	2.82 (1.21)	Voices last for at least one hour	1.54 (0.78)	Voices last for several minutes
Location (0-4)	2.13 (1.21)	Outside head, close to ears and inside head	2.28 (1.18)	Outside head, close to ears and inside head
Loudness (0-4)	2.00 (0.88)	Same loudness as own voice	1.87 (0.62)	Same loudness as own voice
Beliefs origin (0-4)	2.43 (1.22)	<50% conviction that voices have external cause	3.03 (1.13)	≥50% conviction that voices have external cause
Controllability (0-4)	3.02 (1.19)	Occasional control over voices	2.02 (1.57)	Half of the time control over voices
Emotional Valence of content (0-12)	8.73 (2.98)	Most of the voices are negative and unpleasant	1.72 (3.04)	Hardly any voices are negative or unpleasant
Total Distress (0-8)	4.64 (1.94)	Voices cause considerable distress	0.70 (1.50)	Voices cause no distress
Age of onset	22.64 years old (12.22)		13.62 years old (14.13)	
Number of years hearing voices	For 14.93 years (12.35)		For 28.36 years (16.52)	

Prevalence of childhood trauma

The prevalence of childhood trauma in the three groups was described and compared with the help of χ^2 tests in Table 3. After correcting for multiple testing, childhood physical abuse, sexual abuse and emotional abuse as well as emotional neglect differed significantly between the three groups.

Table 3. Prevalence of childhood trauma per group.

Childhood trauma	*Healthy controls N=124*	*Non-psychotic AVH N=127*	*Odds ratio Non-psychotic AVH vs controls*	*Patients AVH N=100*	*Odds ratio Patients AVH vs controls*	*Pearson χ^2 df (2)*	*p*
	N total %	**N total %**		**N total %**			
Physical abuse	2 1.6%	18 14.3%	8.79	12 12.0%	7.44	13.46	0.001*
Sexual abuse	12 9.7%	38 29.9%	3.09	32 32.0%	3.31	20.19	< 0.001*
Emotional neglect	21 16.9%	45 35.4%	2.09	23 23.0%	1.36	11.75	0.003*
Physical neglect	13 10.5%	28 22.0%	2.10	19 19.0%	1.81	6.28	0.043
Emotional abuse	6 4.8%	40 31.7%	6.51	27 27.0%	5.58	30.61	< 0.001*

* = significant after Bonferroni correction for multiple testing (p<0.01)

More specifically and after correcting for multiple testing, the two AVH groups did not differ significantly from each other regarding the prevalence of the five childhood traumas. The healthy controls and the non-psychotic individuals differed significantly from each other on physical abuse (U = 6822, z = -3.685, p <.001*),* sexual abuse (U = 6280, z = -4.007, p <.001*)*, emotional neglect (U = 6417.5, z = -3.322, p = .001*)* and emotional abuse (U = 5710, z = -5.479, p <.001*).* The healthy controls and patients with a psychotic disorder differed significantly from each other on physical abuse (U = 5556, z = -3.186, p =.001*),* sexual abuse (U = 4816, z = -4.171, p <.001*)* and emotional abuse (U = 4826, z = -4.642, p <.001*).*

Differences in childhood trauma between the three groups

A stepwise multinomial regression analysis was used to investigate which childhood traumas best predict whether a person belongs to the "healthy control", the "non-psychotic individual with AVH" or the "patient with a psychotic disorder and AVH" group. The indicators of the model were 5 types of childhood trauma (sexual, emotional and physical abuse, emotional and physical neglect). Covariates were gender and age. The optimal model included only sexual abuse and emotional abuse as predictors ($\chi^2(2, N = 351) = 62.39$, $p<.001$). The predictive value of 18.4% of this model can be considered low (The Nagelkerke Pseudo R^2 for the regression model was 0.184). Likelihood Ratio tests indicate that there is a difference between the three groups regarding sexual abuse ($\chi^2(2, N = 351) = 10.87$, $p=.004$) and emotional abuse ($\chi^2(2, N = 351) = 24.26$, $p<.001$). Table 4 shows the statistics of the two significant indicators and covariates in the model.

Non-psychotic individuals and patients with a psychotic disorder and AVH were compared to healthy control subjects, the reference category. Both AVH groups were significantly more likely to report having experienced sexual and emotional abuse compared to these healthy controls.
Odds ratios are also presented in table 4. Compared to non-hallucinating controls, both non-psychotic individuals with AVH as well as patients with a psychotic disorder and AVH have a greater chance to have suffered from sexual abuse (2.51 and 3.57 respectively) and emotional abuse (7.3 and 5.65 respectively) during childhood.

Table 4. Multinomial regression model: sexual and emotional abuse, control subjects is reference category.

	B	*SE*	*Odds ratio*	*Wald*	*p*
Non-psychotic individuals with AVH					
Sexual abuse	0.922	0.391	2.51	5.578	0.018
Emotional abuse	1.986	0.474	7.3	17.551	<0.001
Psychotic patients with AVH					
Sexual abuse	1.273	0.406	3.57	9.837	0.002
Emotional abuse	1.731	0.502	5.65	11.913	0.001
Gender	0.754	0.300	0.47	6.313	0.012
Age	0.034	0.011	1.04	9.581	0.002

Predictors of the emotional valence based on the childhood traumas

A binary logistic regression model was used to investigate which childhood traumas best predict whether a person experiences AVH with a predominantly positive or negative emotional valence. The outcome variable (emotional valence of content) was dichotomised using a median split. The median of emotional valence of content was 4 (content of voices has partly a negative emotional valence). The optimal model had a poor predictive power (Hosmer and Lemeshow test, $\chi^2(5, N = 351) = 2.998$, $p=.70$), and the Nagelkerke approximation of R^2 was relatively low: 0.018), indicating that no childhood trauma was able to distinguish between positive or negative emotional valence of the hallucinated voices.

Relation between AVH characteristics and trauma

No significant relationships were found between sexual abuse and emotional abuse and AVH characteristics such as frequency, duration, location, loudness, beliefs about their origin, controllability, emotional valence of content and total associated distress (after a Bonferroni correction for multiple testing ($p<0.0028$). The Spearman correlation coefficients are presented in table 5, below the correlation coefficient the significance is given.

Table 5. Spearman correlation coefficients between sexual and emotional abuse, and AVH characteristics as measured with the PSYRATS.

	Sexual Abuse	*Emotional Abuse*
Frequency	-.051	.008
	.440	.909
Duration	-.027	.037
	.690	.576
Location	.026	-.054
	.695	.421
Loudness	-.010	.093
	.882	.165
Beliefs origin	.000	-.011
	.999	.865
Controllability	-.053	.040
	.431	.553
Emotional Valence of content	.088	.099
	.188	.139
Total Distress	-.023	-.017
	.732	.805

Discussion

The aim of this study was to clarify the relation between childhood trauma and auditory verbal hallucinations (AVH): Is childhood trauma related to experiencing AVH in relative isolation, or to the presence of predominantly negative AVH as often seen in patients with a psychotic disorder? We found that non-psychotic individuals with AVH and patients with a psychotic disorder and AVH both report having experienced more sexual and emotional abuse during childhood compared to healthy controls. Odd ratios were 2.5 and 3.5 regarding sexual abuse, and 7.3 and 5.7 regarding emotional abuse. Therefore, emotional abuse and sexual abuse in childhood appear to be related to the presence of AVH in general and *not* to the presence or absence of a psychotic disorder or to the negative emotional content of the voices. No significant difference in the prevalence of childhood traumas was found between the two groups experiencing AVH.

In addition, none of the childhood traumas could provide significant predictive value for the emotional content of voices. Moreover, no correlations were found between sexual and emotional abuse during childhood and specific phenomenological characteristics of AVH. Thus, trauma may be able to trigger both negative and positive voices, either in the absence or in the presence of a psychotic disorder. This suggests that childhood trauma renders the brain vulnerable to experience AVH, rather than just providing the content of these voices.

A cognitive model explaining the influence of childhood trauma on the presence of AVH is described by Garety et al. (2001). In this model a central role is defined for cognitive

disturbances, leading to external appraisal errors. They hypothesized that childhood trauma affects the appraisal of internal experiences as arising from an outside agent. Indeed, an external attributional bias was found to be associated with the presence of auditory hallucinations in patients (Morrison & Haddock, 1997), but this has not been tested yet in non-psychotic individuals with AVH. In addition, the association between this cognitive bias and presence of trauma has, to our knowledge, not been investigated so far.

As an alterative to this cognitive model a biological mechanism targeting memory-related structures such as the hippocampus and parahippocampal gyrus may be at work. The hippocampus mediates, among others, responses to stress and the return of the brain to prestress levels (Read et al. 2001). High degrees of stress however, can permanently reduce the reactivity of the hippocampus (Walker & DiForio, 1997), leading to a hyperarousal state (Perry, 1994). As such, distress due to sexual or emotional abuse during childhood will cause the release of stress hormones, such as cortisol. These stress hormones alter connections between the hippocampus and other structures (Leuner et al. 2010), possibly the parahippocampal gyrus. The parahippocampal gyri integrate and transfer information to the hippocampus (Bauer et al. 2007). Speculating, traumatic stress may interfere with the flow of information due to altered connectivity between these two structures. Consequently, information from memory may be activated and generate a hallucinatory experience. Evidence for parahippocampal and hippocampal involvement in hallucinations comes from MRI studies: Pronounced deactivation in the left parahippocampal gyrus has been found to precede AVH in patients with a psychotic disorder (Hoffman et al. 2008; Diederen et al. 2010a), and activity in this structure and the hippocampus has also been related to the presence of AVH itself (Jardri et al. 2011). Moreover, *during* childhood, different brain structures seem to have their own unique sensitive periods in which sexual abuse has a different impact (Andersen et al. 2008), among which the hippocampus. Possibly, trauma during specific periods in childhood might lead to more prominent changes due to these developmental effects. Indeed, the neurocognitive model described above might be further refined when considering these age-specific events. Hypothesizing on the different models described above, trauma-induced biological changes may lead to cognitive aberrations, which induce anomalous perceptual experiences such as AVH. Indeed, dissociative tendencies were found to be a mediating factor in the relationship between childhood trauma and hallucination-proneness (Varese et al. 2011). Although a clear cognitive mechanism from dissociation to hallucinations remains elusive, recent studies suggest that cognitive inhibition is associated with dissociation. This fits well with other evidence that deficits in inhibition are associated with auditory hallucinations in patients (Waters et al. 2003; Badcock et al. 2005), and aberrant inhibition that is associated with AVH in non-psychotic individuals (Daalman et al. 2011b).

Previous studies have proposed pathways as to how trauma during childhood might lead to *psychosis* later in life, such as the traumagenic neurodevelopmental (TN) model (Walker & DiForio, 1997; Read et al. 2001; Heim et al. 2000) and a cognitive explanation regarding negative or maladaptive schematic models of the self, of others and the world (Birchwood et al. 2000). However, these theories are not supported by our data, as we found increased prevalence of childhood trauma also in individuals who experience voices with a positive emotional content, in the absence of psychosis. Non-psychotic individuals with AVH and individuals with a psychotic disorder and AVH clearly differ on emotional *content* of AVH (Daalman et al. 2011a). However, a possibility is that the *theme* 'danger' may be present in both non-psychotic and psychotic individuals with AVH. The way this theme is expressed differs and might influence associated distress: Non-psychotic individuals frequently hear reassuring and encouraging messages in situations of danger (for instance, "he will be okay, don't worry" or "I will warn you if there's danger"), while patients may hear threats (for instance, "that man is going to kill you" or "you do not deserve to live"). Indeed, the fact that emotional content of AVH is apparently not influenced by childhood trauma partly fits the findings of Hardy et al. (2005). They found no association between theme and content of AVH and trauma in 42.5% of the patients in their study. In almost half of the patients (45%), the theme of the hallucinations was influenced by the experienced trauma and only in a small subgroup of patients both theme and *content* of the hallucinations were related to trauma (12.5%).

In previous studies, physical abuse during childhood has also been linked to psychosis later in life (for a review see: Read et al. 2005). However, in the current study, no predictive value for the presence of AVH was found for childhood physical abuse. In our samples, the prevalence of physical abuse was also higher in the hallucinating groups as compared to the non-hallucinating individuals, but high correlations with a range of .32 and .50 with the other significant childhood traumas prevented physical abuse to contribute significantly to our model.

Limitations

As with other studies using self-report measures, underreporting remains a possibility since abuse, and in particular sexual abuse, might be susceptible to social desirability: it is denied or kept silent due to shame or feelings of guilt (Graham, 1996; Goldman & Padayachi, 2000). Moreover, patients with a psychotic disorder might be more vulnerable to a recall bias, due to other symptoms such as delusions or cognitive impairment. However, two studies demonstrated that patients with psychotic disorders give an accurate history of abuse when interviewed (Read & Fraser 1998; Read & Argyle, 1999). In addition, patients with schizophrenia are able to accurately report information on their premorbid functioning compared to healthy controls (Brill et al. 2007). Furthermore, since age of onset of AVH in the group of non-psychotic

individuals is 13.6 years of age, there is a possibility that the childhood trauma might have happened after this age in some individuals, which makes it unlikely that it has been a triggering factor. This limits a causal interference regarding the influence of sexual and emotional childhood trauma to the psychotic group only, since patients were on average 22.6 years of age when they started hearing voices. Information regarding the age at which the abuse took place might have provided the opportunity to correct for this. In addition, traumatic experiences might have age-specific effects during childhood on beliefs about voices (Offen et al. 2003) and brain development (Andersen et al. 2008). Possibly, the non-psychotic individuals with AVH might have experienced abuse in a different stadium during childhood than patients with a psychotic disorder and AVH, explaining the more malevolent beliefs and/or content in the latter group.

Other factors that might explain the difference in emotional valence of AVH in both groups while prevalence of abuse is similar are the specific circumstances and conditions of the abuse and abuse *after* childhood. In his review, McCarthy-Jones (2011) suggests that whether individuals are more likely to develop psychiatric symptoms depends not only on the abuse itself but also specific circumstances such as relation to the perpetrator, support from others or punishment for the abuse. In addition, the content of AVH might change from benevolent to malevolent due to trauma, also in adulthood (Jones, 2010). Patients with a psychotic disorder and AVH may have experienced more traumas *after* childhood compared to the non-psychotic individuals with AVH.

In conclusion, both non-psychotic individuals with AVH and patients with a psychotic disorder and AVH experienced more childhood sexual and emotional abuse compared to healthy non-hallucinating controls. The presence of these childhood traumas is not associated with the presence of psychosis nor with the emotional content or other characteristics of AVH. This suggests a direct relationship between childhood trauma and the vulnerability to experience AVH.

Chapter 8

Summary and general discussion

Summary and general discussion

What have these studies about auditory verbal hallucinations (AVH), their phenomenology and neurocognitive mechanisms brought us? This chapter summarizes the main findings of the research described in this thesis. In addition, the implications for cognitive theories and the continuum hypothesis in relation to AVH are discussed, as well as therapeutic implications, methodological considerations and future directions.

Phenomenology

Although AVH are known to occur in the general population, at present little is known about the group that hears voices quite regularly (at least once a month) but is not in need of care. To shed more light on this group, the study presented in **chapter 2** explored non-psychotic and otherwise healthy individuals with AVH. No psychopathology could be found when screened for axis I and II disorders, but these individuals did score higher on several clinical measures for magical ideation, schizotypal personality characteristics, family loading for axis I psychiatric disorders and childhood trauma when compared to healthy non-hallucinating controls. The non-psychotic individuals with AVH furthermore had lower global functioning scores than the healthy controls. This lower level of functioning was not due to the presence of AVH, but to the increased schizotypal tendency and higher psychiatric family loading. These results suggest that the predisposition to hear voices is related to the predisposition for schizophrenia. Indeed, another study found increased levels of positive formal thought disorder in non-psychotic individuals, comparable to patients with schizophrenia (Sommer et al. 2010b), suggesting an, at least partly, shared biological mechanism.

After describing the non-psychotic individuals with AVH, **chapter 3** described the *voices* they hear. In what way are the voices of non-psychotic individuals similar to the voices that psychotic patients hear and (how) do they differ? Several characteristics, mostly relating to the form of the voices, were similar in these two groups: loudness, location, personification and number of voices. Other characteristics differed significantly: frequency, duration, controllability, emotional valence and the distress caused by the voices are quite the opposite in both groups. Furthermore, emotional valence of content alone could predict the presence of a psychotic disorder in 88% of the participants, pointing out that clinicians should inquire after the content of the voices and preferably more voice-characteristics before considering the diagnosis of a psychotic disorder.

An interesting finding was a difference in age of onset. While psychotic patients start hearing voices when they are approximately 21 years old, the non-psychotic individuals started to hear voices at on average 12 years of age. This might indicate a different mechanism of origin in the two groups.

In conclusion, although the non-psychotic individuals with AVH might have an increased vulnerability for schizophrenia, they are not disturbed by their sub-clinical symptoms. While some may claim that these individuals have to be diagnosed with psychosis not otherwise specified due to their frequent hallucinations, this seems quite inappropriate since they function well both socially and occupationally. Indeed, their voices did not cause any distress and differed furthermore on several stress-related characteristics when compared to the voices that psychotic patients hear. Nevertheless, some characteristics were quite similar and taken together with the fact that these non-psychotic individuals with AVH are not burdened by any other clinical symptoms, they seem an ideal group to investigate the origin of these voices in, free from confounding factors such as medication use and cognitive dysfunction.

Neurocognitive mechanisms

Cognitive function and AVH

Schizophrenia patients with AVH show impairments on most cognitive domains. However, this patient group presents with a number of confounding factors such as antipsychotic medication, unfinished education, hospitalisation and last but not least, addition symptoms that can all influence test results. To further investigate the cognitive mechanism behind AVH, the non-psychotic individuals with AVH were subjected to a number of cognitive tests in the study described in **chapter 4**. Investigating the cognitive performance in non-psychotic individuals with AVH and comparing them to healthy controls, provided a clearer picture of the cognitive domains that might be involved in the experience of AVH. As expected, all individuals scored within the normal range when compared to norm-scores. However, the non-psychotic individuals did show poorer performance when compared to controls on verbal distractibility, inhibition, verbal working memory and on tasks tapping lexical access and reasoning. It appears therefore that a specific combination of decreased executive functioning, verbal working memory and a reduced level of verbal intellectual performance is associated with the tendency to experience auditory verbal hallucinations.

Possibly, the reduced inhibition and increasing distractibility in the verbal domain could render individuals less apt to inhibit irrelevant verbal information. These irrelevant verbal associations that are not adequately inhibited may not be recognized as self-generated and, as such, be attributed to an external source, resulting in an auditory

verbal hallucination.

Semantic top-down processing and AVH

A prominent cognitive theory concerning the origin of AVH entails top-down processing. This theory suggests that during perception more priority or weight is given to top-down factors, such as prior knowledge and expectations, compared to bottom-up information coming from the senses. This phenomenon has already been described in hallucination-prone individuals. Although scoring high on a measure for hallucination proneness, this group has not been screened for the actual presence of AVH or their frequency. The study in **chapter 5** explored the role of semantic top-down processing in non-psychotic individuals as well as psychotic patients, both with frequent AVH and in healthy controls. While non-psychotic individuals with AVH made significantly more top-down errors on the experimental task than the controls, patients scored in between healthy controls and non-psychotic individuals with AVH and did not differ significantly from either group. Furthermore, while the degree of top-down processing is related to the measure of hallucination proneness in the healthy individuals with and without AVH, it is not related to the hallucination-severity score in patients. These results suggest different involvement of the cognitive factor 'semantic top-down processing' in the two AVH groups.

Cognitive biases and AVH

As cognitive processes involved in AVH might differ between non-psychotic individuals and patients with AVH, we elaborated our study on this topic. The cognitive model of Garety et al. (2001) describes the role of cognitive dysfunction in the formation of AVH in the context of a psychotic disorder. This cognitive dysfunction can be viewed as a broad concept, including both aberrant or impaired cognitive functioning and the presence of cognitive biases. **Chapter 6** explored cognitive biases and their relationship with AVH with the help of the cognitive biases questionnaire for psychosis (CBQp). The CBQp assesses the presence of 5 cognitive biases that are often found in patients with a psychotic disorder. This was not only investigated in these psychotic patients, but also in non-psychotic individuals with AVH and healthy controls. The total score on the CBQp of non-psychotic individuals with AVH was in between those of psychotic patients with AVH and healthy controls and differed significantly from both. Although this would fit nicely with the continuum hypothesis of psychosis, closer inspection of the subscales showed that non-psychotic individuals with AVH closely resembled the healthy controls on almost all subscales. Emotional reasoning was the only cognitive bias on which both hallucinating groups had comparable scores. As such, the cognitive biases appear to be more related to the presence of psychosis in general. Moreover, the *absence* of these biases in non-psychotic individuals with AVH might have prevented the formation of malign appraisals and delusions in the context

of a psychotic disorder.

Childhood trauma and AVH

In addition to the impact of the cognitive factors on AVH as described in the previous chapters, **chapter 7** aimed to explore the role childhood trauma has on the presence and characteristics of AVH. Does the experience of trauma during childhood lead to the presence of AVH as a symptom, or can trauma influence and colour the content of these voices? When the prevalence of childhood trauma in non-hallucinating controls, non-psychotic individuals with AVH and psychotic patients with AVH was compared it appeared that both hallucinating groups experienced significantly more emotional and sexual abuse during childhood. No difference in the prevalence of these traumas was found between the psychotic and non-psychotic AVH groups. In addition, none of the childhood traumas could predict the emotional valence of content of the voices. Furthermore, no associations were found between these childhood traumas and other AVH characteristics. This suggests that childhood trauma renders the brain vulnerable to experience AVH either in the absence or in the presence of a psychotic disorder, rather than providing content for these voices.

A hypothesis explaining the route from childhood trauma to the presence of AVH suggests a central role for the hippocampus, focusing on the influence of memories. Due to high levels of stress following childhood abuse, connections and consequently information-flow between the hippocampus and other structures such as the parahippocampus might be altered. Information from memory may be activated to generate a hallucinatory experience. MRI studies offer evidence for hippocampal activity during AVH (Jardri et al. 2011) and parahippocampal deactivation preceding AVH (Hoffman et al. 2008; Diederen et al. 2010b). Hypothesizing, trauma-induced biological changes may lead to cognitive aberrations, which induce anomalous perceptual experiences like AVH. As dissociative tendencies were found to be a mediating factor in the relation between childhood trauma and AVH (Varese et al. 2011), cognitive inhibition, which has been linked to dissociation, might be involved in the cognitive mechanism behind AVH. This is supported both in patients with AVH (Waters et al. 2003; Badcock et al. 2005) as well as healthy individuals with AVH (**chapter 4**).

Exploring cognitive factors in AVH

Elaborating on the cognitive factors that could contribute to the experience of hearing voices, the studies described in this thesis found AVH to be related to poorer inhibition and working memory within the verbal domain, and increased top-down

functioning in non-psychotic individuals with AVH and the presence of cognitive biases predominantly in psychotic patients. Memory-related structures such as the hippocampus or parahippocampus may also be associated with the aetiology of AVH since a high prevalence childhood trauma was linked to the presence of AVH.

Speculating, when a large amount of verbal information is present, whether coming from memory or from perception, non-psychotic individuals with AVH seem less able to inhibit irrelevant information and focus on task-related information. Furthermore, their expectations, previous knowledge and cognitive biases appear to colour the content of the AVH and additionally influence the meaning and appraisals that are given.

These factors that were found to be associated with AVH in non-psychotic individuals have all been mentioned in theories regarding the aetiology of AVH. The most recent model by Waters et al. (2012) integrates most of these previous stated theories and is furthermore supposed to be able to explain differences in phenomenology of auditory hallucinations between clinical and non-clinical groups. Waters et al. assume in their model that AVH in both groups are comparable in their underlying cognitive mechanisms, but the data presented in this thesis questions whether this is really the case.

Differences between AVH in non-psychotic individuals and psychotic patients such as age at onset, emotional valence, frequency (**chapter 3**), involvement of semantic top-down processes (**chapter 5**) and presence of cognitive biases (**chapter 6**) suggest that underlying mechanisms are **not** completely similar and in fact differ on rather fundamental aspects. Furthermore, while deficits in inhibition may play an important part in psychotic patients (Badcock et al. 2005), in non-psychotic individuals with AVH inhibition is merely aberrant, not at all clinically impaired (**chapter 4**). In addition, increased striatal dopamine production (as measured with F-DOPA PET scans), known to play a key role in psychotic symptoms (Howes et al. 2009), was absent in non-psychotic individuals with frequent AVH (Howes et al. 2012). Finally, van Lutterveld et al. (2010) found that non-psychotic individuals with AVH score higher on measures of effortful attention compared to controls, while psychotic patients perform worse on this measure.

On the other hand, similar brain activation during AVH in non-psychotic and psychotic individuals was found (Diederen et al. 2011) and the prevalence of childhood trauma was also comparable in these two groups (**chapter 7**). These similarities could be explained by making a distinction between biological and cognitive factors in the generation in AVH. This contrasts with most cognitive models (Garety et al. 2001; Waters et al. 2012), which focus primarily on cognitive dysfunction. While this may be the case in psychotic patients, when taking non-psychotic individuals into account cognitive dysfunction alone cannot explain the presence of AVH since this is relatively intact. Possibly the biological basis for AVH and thereby cognitive aberrations in

the non-psychotic group are not impaired 'enough' for the experience to become a clinically psychotic symptom.

Refining the continuum hypothesis

This apparent continuum of cognitive functioning, ranging from intact through aberrant to impaired cognitive functioning fits well with the most recent variation of the continuum hypothesis of psychosis by van Os et al. (2010). This hypothesis describes the phenotype of psychosis in both the general population and clinical populations. It comprises not only the psychotic dimension (i.e. hallucinations and delusions) but also affective dysregulation (i.e. anxiety, depression), negative symptoms and cognitive alterations, which are all characteristics of a general psychotic syndrome. Low expression of each of the dimensions is representative of the general population, and thus constitutes an extended phenotype. However, when severity on a dimension increases it becomes more likely that an individual also has additional symptoms (higher expression on other dimensions). This would make it more likely that this person has a clinical phenotype. Several symptoms in the clinical phenotype would lead to help-seeking behaviour and/or dysfunction and thus to the detection of these individuals by psychiatric services.

With regard to the applicability of the continuum hypothesis, it remains unclear whether symptoms on both ends can be considered similar. Questionnaires that are usually applied to detect the prevalence of psychotic symptoms in the general population merely rate the presence or frequency of psychotic symptoms, without enquiring after their phenomenological characteristics. Therefore, this cohort of non-psychotic individuals with AVH provides an excellent opportunity to further refine this continuum hypothesis, not only with respect to the phenomenological characteristics but also by assessing the underlying neural and cognitive factors of AVH.
Speculating, the biological basis for AVH (genetic predisposition and factors influencing brain development early in life, for example childhood trauma) is dominant in psychotic patients, comprising all domains described by van Os et al. (2010) and thereby limiting their functioning in many ways. As such, little room may be left for (intact) cognitive processes to play a part in the generation of AVH. Across the continuum, where the non-psychotic individuals with only non-clinical symptoms lie, this biological influence is weaker (as reflected for example in normal striatal dopamine turnover). Their psychotic symptoms are less severe, affective dysregulation plays a lesser role when compared to patients and their cognitive alterations are not of clinical significance. This gives these intact cognitive processes, such as effortful attention or semantic

top-down processing, more opportunity to exert their influence and thereby possibly shaping the phenomenology or experience of AVH. This is reflected by the different involvement of these cognitive factors in non-psychotic individuals compared to patients. Furthermore, this relatively intact instead of impaired cognitive functioning may be considered a protective factor.

Therapeutic implications

In the context of psychosis, where first choice of treatment is anti-psychotic medication, patients may benefit from the additional cognitive interventions as described in chapter 1. Impaired cognitive performance may be improved or compensated for by these cognitive strategies: Metacognitive training (MCT) for example may help an individual recognise and correct existing cognitive biases (Moritz et al. 2011), cognitive behavioural therapy (CBT) may adjust faulty appraisals of the voices that lead to secondary distress, and competitive memory training (COMET) may facilitate the activation of positive memories to compensate for the negative self-evaluations triggered by the voices (van der Gaag et al. 2012). In addition, cognitive remediation therapy for schizophrenia is "a behavioral training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization" (Wykes et al. 2011). This can be done by practising a variety of cognitive skills such as teaching (or facilitating learning of) new efficient information processing strategies (Wykes et al. 2007).

Finally, as hearing voices is not necessarily a symptom of a psychotic illness, clinicians should inquire after the characteristics of these voices. A predominantly positive or neutral emotional content, low frequent occurrence, having some degree of control over the voices and an age of onset in childhood are all predictors for the *absence* of a psychotic disorder. Although an individual may be a little disturbed when first hearing voices, prescribing anti-psychotic medication is *not* desirable when the AVH are not part of a psychotic illness and do not influence social or occupational functioning. Instead, such an individual may benefit from psycho-education and if necessary some additional sessions of CBT.

Methodological considerations

In contrast to the non-psychotic individuals with AVH that hear voices on average

once a week, the frequency of AVH in the psychotic group is high, hearing voices almost continuously. As such, studies should consider the presence of AVH *during* studies, as frequent AVH (especially present in patients), may alter or further impair functioning on cognitive tasks. Apart from this, other methodological issues should be taken into account. The subjects that were included in the studies in this thesis are all (more or less) selected groups. The healthy (non-hallucinating) controls and non-psychotic individuals with AVH were recruited with the help of a website (www.verkenuwgeest.nl) and may therefore not be representative of the general population. They were individuals that found the website and chose to participate in the study. In the case of the non-psychotic individuals, only those who were willing to talk openly about their voices could be included. It is therefore likely that individuals who were suspicious, shy or anxious were underrepresented in this group. The psychotic patients all visited our voices clinic or participated in other studies. Many of them are medication resistant patients, and may therefore be not comparable to patients with a 1st episode psychosis.

With respect to the studies that involved questionnaires regarding the voices, childhood trauma or cognitive biases, the presence of several biases should be considered. A self-report bias might have caused some individuals to worsen their symptoms as a cry for help. Others might have minimized their complaints to prove that they do not need help. In the case of the non-psychotic individuals with AVH, some may have been afraid of the stigma that 'hearing voices' accompanies. As this phenomenon is often judged as a sign of mental illness, some may therefore have denied complaints or other symptoms. In addition, socially desirable answers may have been given and, in the case of childhood trauma, shame or guilt may have prevented individuals to answer the questions truthfully or correctly.

Future directions

To what degree are AVH in psychotic patients similar or different to AVH in other psychiatric disorders or neurological disorders such as epilepsy, dementia or individuals with hearing loss? As auditory (verbal) hallucinations are prevalent in several other groups besides non-psychotic individuals and psychotic patients, much more research is warranted.

In addition to a phenomenological field of research, describing the characteristics of the voices, underlying biological and cognitive mechanisms could be investigated in all these populations. This can be done with different methods, such as cognitive tasks and neuroimaging techniques to further clarify brain structures that are involved in

this complex interplay. Different involvement of brain structures may further explain phenomenological differences between voices in different populations as suggested by Waters et al. (2012).

Conclusion

Although cognitive factors are suggested to play an essential part in the aetiology of AVH in both non-psychotic individuals and psychotic patients, the extent to which they are associated with AVH may differ between these groups. Relative intact cognitive functioning instead of cognitive impairment may even have served as a protective factor in the non-psychotic individuals, and prevented them to progress further along the continuum to the help-seeking minority with the clinical phenotype.
All in all, many factors are involved in the complex interplay that results in hearing voices. Therefore, much more research is necessary on this symptom, also in other patient groups. Hopefully the exact pathophysiology will be revealed in the near future, resulting in treatment options that can relieve the burden of hearing voices in so many, and offering them a highly improved quality of life.

Chapter 9

Nederlandse samenvatting

"Toen ik ongeveer 16 jaar was en buiten liep hoorde ik ineens een baby huilen. Ik schrok een beetje en ging de baby zoeken. Ik kon hem niet vinden. In de weken daarna bleef ik af en toe de baby horen en daarnaast ook een vrouwenstem die mijn naam riep. In de loop van de jaren kwamen er meer stemmen bij. In het begin waren ze vriendelijk en hielpen ze me, maar daarna werden ze vervelend en dreigend. Ik werd er bang van. Het werden er meer en meer en ik had geen idee waar ze vandaan kwamen. Misschien waren het overleden mensen, die om me heen dwaalden voordat ze naar de hemel of de hel verder gingen.
Naast de stemmen zag ik ook dingen, het was alsof ik in een hele andere dimensie leefde. Soms was het moeilijk om in de 'echte' wereld te blijven, want ik hoorde steeds maar boodschappen als "die man gaat je vermoorden" of "we blijven je kwellen". Ik had er geen controle over en kon het niet negeren. Na een paar jaar cognitieve gedragstherapie en nadat ik me realiseerde dat medicatie me hielp om meer in contact met andere mensen te staan, leerde ik beter met de stemmen omgaan. Hoewel ik nog steeds continu stemmen hoor, leef ik nu in de 'echte' wereld. Ik erken dat de stemmen er zijn, maar ik vecht er niet meer tegen. Ik leef mijn eigen leven zoals ik dat zelf wil en laat me niet meer leven door de stemmen".
Christine, expert in stemmen horen.

Het horen van stemmen is het meest bekend in het kader van psychotische stoornissen. Het verhaal van Christine beschrijft hoe bedreigend en beperkend de stemmen kunnen zijn. Hoewel een groot deel van de mensen met stemmen in het kader van een psychose baat hebben bij antipsychotische medicatie, helpt dit niet voldoende bij zo'n 25%. Er is dus duidelijk vraag naar behandelalternatieven bij auditieve verbale hallucinaties (AVH). Dit blijft echter een uitdaging aangezien we nog steeds niet weten welke mechanismen hieraan ten grondslag liggen. Als we zouden weten waar AVH in de hersenen ontstaan en welke hersenstructuren en cognitieve functies betrokken zijn, zouden gespecialiseerdere behandelingen ontwikkeld kunnen worden. Dit zou dan bij een velen de stemmen kunnen verminderen en hopelijk zelfs doen verdwijnen, resulterende in een hogere kwaliteit van leven.
Tot nu toe is de enige optie voor mensen die last hebben van stemmen en niet reageren op antipsychotica het leren omgaan met stemmen. Dit kan met behulp van bijvoorbeeld cognitieve gedragstherapie, zoals Christine uit het voorbeeld heeft gedaan en waar ze veel baat bij heeft. De stemmen zijn er nog wel, maar door de gedachten erover en interpretatie ervan kritisch te onderzoeken en bij te stellen, kun je met minder angst en stress door het leven.

Stemmen horen komt voor in verschillende ziektebeelden en daarnaast ook in de algemene populatie. Het horen van stemmen is niet noodzakelijkerwijs een symptoom van een stoornis. Dit heeft ertoe geleid dat steeds meer onderzoekers de aanwezigheid

van psychotische symptomen zien als een continuüm. Op het ene eind liggen zeldzame waarnemingen in gezonde personen, en via patiënten met schizotypische persoonlijkheidsstoornis loopt dit continuüm naar psychotische patiënten met frequente psychotische symptomen aan het andere eind.
Het onderzoek in dit proefschrift richt zich vooral op het horen van stemmen in het kader van een psychotische stoornis en daarnaast in gezonde personen zonder psychotische stoornis. Door deze twee groepen te onderzoeken kunnen we niet alleen de stemmen zelf vergelijken maar geeft het ook informatie over de onderliggende mechanismen. Daarnaast kunnen we hierdoor onderzoeken of deze neurocognitieve mechanismen gelijk zijn in de twee groepen.

Het eerste deel van dit proefschrift richt zich op de fenomenologie van de stemmen. Het beschrijft de niet-psychotische personen met AVH en daarnaast de stemmen die ze horen. Het tweede deel onderzoekt neurocognitieve factoren die betrokken zouden kunnen zijn bij het mechanisme achter AVH.

Fenomenologie

Hoewel stemmen horen vrij veel voorkomt in de algemene populatie is er weinig bekend over de groep mensen die regelmatig stemmen hoort maar desondanks geen behandeling hiervoor nodig heeft. **Hoofdstuk 2** beschrijft daarom deze groep mensen met AVH *zonder* psychotische stoornis. Er wordt geen psychopathologie gevonden maar deze personen scoren wel hoger op bepaalde klinische maten voor magisch denken, schizotypische persoonlijkheidskarakteristieken, familiaire belasting voor psychiatrische stoornissen en trauma tijdens de kindertijd, wanneer ze vergeleken worden met niet-hallucinerende controleproefpersonen. Daarnaast hadden de niet-psychotische personen met AVH een lager globaal functioneren dan de controles. Dit lager niveau van functioneren kwam niet voort uit de aanwezigheid van de stemmen, maar door de verhoogde neiging tot schizotypy en de hogere psychiatrische kwetsbaarheid in de familie. Deze resultaten suggereren dat de aanleg om stemmen te horen gerelateerd is aan de aanleg om schizofrenie te ontwikkelen. Een andere studie vond een verhoogde mate van positieve formele denkstoornissen in de groep niet-psychotische personen, vergelijkbaar met patiënten met schizofrenie (Sommer et al. 2010). Dit wijst erop dat er mogelijk een gedeeld biologisch mechanisme aan ten grondslag ligt.

Na het beschrijven van de groep niet-psychotische personen met stemmen, beschrijft **hoofdstuk 3** de stemmen die zij horen. In welk opzicht zijn deze stemmen vergelijkbaar met stemmen in het kader van een psychose en in welk opzicht verschillen ze? Een

aantal karakteristieken die met name gerelateerd zijn aan de vorm van de stemmen waren gelijk in beide groepen. Bijvoorbeeld de luidheid van de stemmen, de plaats waar ze gehoord worden (buiten of binnen het hoofd), de personificatie (klinkt de stem als van een bekende) en het aantal stemmen dat iemand hoort. Andere karakteristieken waren verschillend: hoe vaak stemmen worden gehoord, hoe lang ze spreken, de mate van controle over de stemmen, de emotionele lading van de stemmen en de spanning en stress die ermee gepaard gaat. Deze kenmerken zijn juist vrij tegengesteld in beide groepen.
Daarnaast werd gevonden dat alleen al de emotionele waarde van de inhoud van de stemmen voor 88% kon voorspellen of er sprake was van een psychotische stoornis in deze groep deelnemers. Deze resultaten laten zien dat het belangrijk is dat een behandelaar gedetailleerde vragen stelt over de stemmen voordat er een diagnose van een psychotische stoornis gegeven wordt.
Een interessante bevinding was daarnaast het verschil in de leeftijd waarop de stemmen ontstonden. De patiënten met een psychotische stoornis waren gemiddeld 21 jaar oud toen ze stemmen gingen horen terwijl de niet-psychotische personen al ongeveer op hun 12e stemmen hoorden. Dit zou kunnen wijzen op een verschillend ontstaansmechanisme in de twee groepen.
Uit bovenstaande resultaten blijkt dat de niet-psychotische personen met stemmen niet gehinderd worden door hun subklinische symptomen, ondanks dat ze een verhoogde kwetsbaarheid voor schizofrenie lijken te hebben. Hoewel iemand de diagnose 'psychose niet anderszins omschreven' zou kunnen overwegen bij deze niet-psychotische personen met frequente stemmen, is dit niet gepast aangezien deze personen normaal functioneren, zowel sociaal als beroepsmatig. De stemmen veroorzaken geen hinder of last en verschillen daarnaast op stress-gerelateerde karakteristieken wanneer ze vergeleken worden met de stemmen in het kader van een psychotische stoornis. Desalniettemin zijn een aantal karakteristieken van de stemmen ook vergelijkbaar tussen de twee groepen, wat maakt dat de groep niet-psychotische personen een ideale populatie is om stemmen in te onderzoeken, vrij van andere symptomen en zonder medicatiegebruik.

Neurocognitieve mechanismen

Cognitief functioneren en AVH

Patiënten met schizofrenie laten verstoord functioneren zien op de meeste cognitieve domeinen, zoals bijvoorbeeld aandacht, geheugen, verwerkingssnelheid of executief functioneren. Het nadeel aan onderzoek in deze groep is de aanwezigheid van factoren als antipsychotische medicatie, een opleiding die vaak niet wordt afgerond, psychiatrische opnames en vooral ook andere symptomen en klachten passend bij

schizofrenie die testresultaten kunnen beïnvloeden. Om cognitieve mechanismen van AVH te onderzoeken, hebben we een aantal cognitieve tests afgenomen bij niet-psychotische personen met AVH in de studie die in **hoofdstuk 4** beschreven wordt. Wanneer je het cognitief functioneren van niet-psychotische personen met AVH onderzoekt en vergelijkt met gezonde controles geeft het een helderder beeld van de cognitieve domeinen die betrokken kunnen zijn bij het horen van stemmen.
Zoals verwacht scoorden alle proefpersonen binnen de norm. De niet-psychotische personen met AVH scoorden echter wel slechter dan controles op taken die verbale afleidbaarheid, inhibitie en verbaal werkgeheugen in kaart brengen en op taken die beroep doen op woordenschat en verbaal redeneren. Het lijkt erop dat een specifieke combinatie van verminderd executief functioneren, verbaal werkgeheugen en een verminderd niveau van intellectueel functioneren geassocieerd zijn met het horen van stemmen.
Mogelijk zorgen een verminderde inhibitie en verhoogde afleidbaarheid in het verbale domein ervoor dat deze personen minder goed zijn in het onderdrukken van irrelevante verbale informatie. Deze irrelevante verbale associaties die niet voldoende onderdrukt worden, worden vervolgens mogelijk niet herkend als afkomstig van de persoon zelf en toegekend aan een externe bron. Dit leidt dan tot een auditieve verbale hallucinatie.

Semantische topdown verwerking en AVH

Een belangrijke theorie over het ontstaan van AVH gaat over topdown verwerking. Aan topdown factoren, zoals bestaande kennis en verwachtingen, wordt tijdens de waarneming meer waarde toegekend vergeleken met de bottom-up informatie die via de zintuigen binnenkomt. Dit fenomeen is al eerder beschreven in personen met een *neiging* tot hallucineren. Hoewel deze personen hoog scoren op een maat die neiging tot hallucineren meet, zijn ze niet gescreend op de daadwerkelijke aanwezigheid van stemmen of de frequentie hiervan. De studie in **hoofdstuk 5** onderzoekt de rol van semantische topdown verwerking in niet-psychotische personen en patiënten met een psychotische stoornis, beide met frequente AVH, en in gezonde controles.
De niet-psychotische personen maakten significant meer topdown fouten op de experimentele taak dan de controles. De patiënten hadden scores tussen de niet-psychotische personen en controles in, maar verschilden niet significant van beide groepen. Daarnaast bleek de mate van topdown verwerking wel gerelateerd aan een hoge mate van neiging tot hallucineren in de gezonde personen met en zonder stemmen, en niet aan de ernst van de hallucinaties in patiënten. Deze resultaten suggereren dat de cognitieve factor 'semantische topdown verwerking' in verschillende mate betrokken is bij stemmen horen in de twee AVH groepen.

Denkfouten en AVH

Omdat cognitieve processen betrokken bij AVH kunnen verschillen tussen niet-

psychotische personen en patiënten met een psychotische stoornis, hebben we het onderzoek op dit onderwerp uitgebreid. Cognitieve modellen (bv. van Garety et al. 2001) beschrijven de rol van cognitief disfunctioneren in het ontstaan van AVH in de context van een psychotische stoornis. Dit disfunctioneren kan gezien worden als een breed concept dat zowel afwijkend of verstoord functioneren beslaat alsmede de aanwezigheid van denkfouten. **Hoofdstuk 6** onderzoekt de aanwezigheid van denkfouten en de relatie hiervan met AVH met behulp van de 'cognitive biases questionnaire voor psychose' (CBQp). Deze vragenlijst meet de aanwezigheid van 5 denkfouten die vaak aanwezig zijn bij patiënten met een psychotische stoornis, te weten: opzet zien in acties van anderen, rampdenken, zwart-wit denken, overhaast conclusies trekken en emotioneel redeneren. Dit werd niet alleen onderzocht in patiënten met een psychotische stoornis, maar ook in niet-psychotische personen met AVH en gezonde controles.

De totale score op de CBQp van niet-psychotische personen zat tussen die van de psychotische patiënten en gezonde controles in en verschilde significant van beide. Hoewel dit goed zou passen bij een continuüm hypothese van AVH, blijkt dit minder duidelijk het geval wanneer de sub-schalen apart werden vergeleken. De niet-psychotische personen scoren hetzelfde als de controles op bijna alle sub-schalen. Alleen de denkfout emotioneel redeneren was in vergelijkbare mate aanwezig in beide hallucinerende groepen.

Het lijkt er dus op dat de aanwezigheid van deze denkfouten meer gerelateerd is aan de aanwezigheid van een psychotische stoornis dan aan het horen van stemmen. Sterker nog, de afwezigheid van deze denkfouten zou er voor gezorgd kunnen hebben dat de niet-psychotische personen kwaadwillende interpretaties hebben gevormd met betrekking tot de stemmen en wanen hebben ontwikkeld in de context van een psychose.

Trauma tijdens de kindertijd en AVH

Naast de invloed van cognitieve factoren op stemmen horen, zoals beschreven in de voorgaande hoofdstukken, onderzoekt de studie in **hoofdstuk 7** de rol die trauma tijdens de kindertijd heeft op het horen van stemmen. Leidt het meemaken van trauma in de kindertijd tot het horen van stemmen, en/of heeft het daarnaast invloed op de inhoud van deze stemmen? De prevalentie van trauma tijdens de kindertijd is in deze studie vergeleken tussen gezonde controles, niet-psychotische personen met AVH en patiënten met een psychotische stoornis en AVH. Het blijkt dat allebei de hallucinerende groepen significant vaker emotioneel en seksueel misbruik tijdens de kindertijd hebben meegemaakt dan controles. Tussen de twee AVH-groepen is geen verschil gevonden met betrekking tot deze twee trauma's. Daarnaast bleek dat geen enkel soort trauma tijdens de kindertijd de emotionele lading van de stemmen kon voorspellen. Er werden ook geen relaties gevonden tussen deze trauma's in de

kindertijd en andere karakteristieken van de stemmen. Dit suggereert dat trauma tijdens de kindertijd de hersenen kwetsbaarder maakt om stemmen te horen, of dit nu wel of niet in de context van een psychotische stoornis is, en dus *niet* specifiek zorgt voor de inhoud van deze stemmen.
Een mogelijke route van trauma tijdens de kindertijd naar het horen van stemmen beschrijft een belangrijke rol voor de hippocampus en de invloed van herinneringen. MRI-studies vonden al activiteit in de hippocampus tijdens het horen van stemmen (Jardri et al. 2011) en deactivatie van de parahippocampus voorafgaand aan stemmen horen (Hoffman et al. 2008; Diederen et al. 2010). Mogelijk zorgt het trauma in de kindertijd voor biologische veranderingen in de hersenen, dit leidt tot cognitieve afwijkingen die voor abnormale perceptuele ervaringen zorgen zoals AVH. Dissociatieve neigingen lijken een mediërende factor te zijn tussen trauma tijdens de kindertijd en AVH (Varese et al. 2011). Dit wijst erop dat cognitieve inhibitie, al eerder gelinkt aan dissociatie, betrokken is bij het mechanisme achter stemmen horen. Dat inhibitie een rol speelt bij stemmen is al gevonden in patiënten met AVH (Waters et al. 2003; Badcock et al. 2005) en ook in niet-psychotische personen met AVH (**hoofdstuk 4**).

De rol van cognitieve factoren in AVH

De studies in dit proefschrift laten zien dat het horen van stemmen gerelateerd is aan verminderde inhibitie en werkgeheugen in het verbale domein, en toegenomen semantische topdown verwerking in niet-psychotische personen en aan de aanwezigheid van denkfouten in patiënten. Hersenenstructuren die betrokken zijn bij het geheugen, zoals de hippocampus en parahippocampus zijn mogelijk ook betrokken bij de etiologie van stemmen horen aangezien een hogere prevalentie van trauma in de kindertijd gerelateerd is aan de aanwezigheid van AVH.
Speculatief zou je kunnen stellen dat wanneer een grote hoeveelheid verbale informatie aanwezig is, of dit nu uit het geheugen komt of de waarneming, de niet-psychotische personen met AVH minder goed zijn in zowel het onderdrukken van de irrelevante informatie als het focussen op de informatie die belangrijk is voor het uitvoeren van een taak. Daarnaast lijken verwachtingen, bestaande kennis en denkfouten de inhoud van de stemmen te kleuren en beïnvloeden ze op deze manier ook de betekenis die aan de stemmen wordt gegeven.
Deze factoren, die betrokken lijken te zijn bij AVH in niet-psychotische personen, zijn allen al eerder beschreven in theorieën omtrent de etiologie van AVH. Het meest recente model van Waters et al. (2012) integreert de meeste van deze theorieën en zou daarnaast ook fenomenologische verschillen in AVH kunnen verklaren tussen klinische en niet-klinische groepen. Ze gaan er echter in dit model vanuit dat AVH in beide

groepen vergelijkbaar zijn in hun onderliggende mechanismen, maar op basis van de onderzoeken in dit proefschrift kan getwijfeld worden of dit daadwerkelijk wel het geval is. Verschillen in AVH tussen niet-psychotische personen en psychotische patiënten zoals ontstaansleeftijd, emotionele lading, frequentie (**hoofdstuk 3**), betrokkenheid van semantische topdown verwerking (**hoofdstuk 5**) en de aanwezigheid van denkfouten (**hoofdstuk 6**) suggereren dat de onderliggende mechanismen **niet** geheel hetzelfde zijn en juist op fundamentele gebieden verschillen. Daarnaast speelt een verstoorde inhibitie een grote rol in psychotische patiënten met stemmen (Badcock et al. 2005), terwijl in niet-psychotische personen met AVH dit slechts afwijkend is, niet klinisch verstoord (**hoofdstuk 4**). Verder werd er geen verhoogde dopamine productie in het striatum gevonden in de niet-psychotische personen met AVH (Howes et al. 2012), terwijl dit bij psychotische patiënten wel wordt gevonden en een grote rol speelt in hun psychotische symptomen (Howes et al. 2009). Tenslotte hebben van Lutterveld et al. (2010) gevonden dat niet-psychotische personen met AVH hoger scoren op een taak die bewuste auditieve aandacht meet, terwijl patiënten met een psychose juist consequent slechter scoren op deze taken.

Aan de andere kant is er wel vergelijkbare hersenactiviteit gevonden tijdens het horen van stemmen bij niet-psychotische en psychotische personen (Diederen et al. 2011) en is de prevalentie van trauma tijdens de kindertijd ook gelijk in deze twee groepen (**hoofdstuk 7**). Deze overeenkomsten zouden verklaard kunnen worden door een onderscheid te maken tussen biologische en cognitieve factoren in het ontstaan van AVH. Dit contrasteert met de meeste cognitieve modellen (Garety et al. 2001; Waters et al. 2012) die met name focussen op cognitief disfunctioneren. Hoewel dit inderdaad bij psychotische patiënten het geval is, kan het niet de aanwezigheid van AVH in de niet-psychotische personen met AVH verklaren aangezien hun cognitief functioneren relatief intact is. Mogelijk zijn de biologische basis voor AVH en de bijbehorende cognitieve afwijkingen in de niet-psychotische groep niet verstoord 'genoeg' om de ervaring van stemmen horen tot een klinisch psychotisch symptoom te maken.

Een verfijning van de continuüm hypothese

Dit ogenschijnlijke continuüm van cognitief functioneren, dat van intact functioneren, via afwijkend functioneren, naar verstoord functioneren loopt, past mooi bij een van de meest recente variaties op de continuüm hypothese van psychose door van Os et al. (2010). Deze hypothese beschrijft het fenotype van psychose in zowel de algemene bevolking en in klinische populaties. Het omvat niet alleen de psychotische dimensie (met bijvoorbeeld hallucinaties en wanen) maar ook affectieve disregulatie (bijvoorbeeld angst of depressie), negatieve symptomen en cognitieve veranderingen, die allemaal

karakteristiek zijn voor een algemeen psychotisch syndroom. Lage expressie op elk van de dimensies is representatief voor de algemene bevolking, en staat dus voor het uitgebreide fenotype. Maar wanneer de ernst op een van de dimensies toeneemt, wordt het waarschijnlijker dat die persoon ook andere symptomen heeft (dus hogere expressies op de andere dimensies). Dit vergroot de kans dat degene een klinisch fenotype heeft. Meerdere symptomen in het klinische fenotype leiden tot het zoeken van hulp en/of tot disfunctioneren en zo tot de detectie van deze personen door de psychiatrische instellingen.

Met betrekking tot de toepasbaarheid van deze continuüm hypothese blijft het onduidelijk of de symptomen op de uiteinden van dit continuüm als gelijk kunnen worden beschouwd. Vragenlijsten die normaal gesproken worden afgenomen om de prevalentie van psychotische symptomen in de algemene bevolking te onderzoeken scoren alleen de aan- of afwezigheid of frequentie van deze symptomen, zonder verder fenomenologische karakteristieken uit te vragen. Dit cohort van niet-psychotische personen met AVH brengt daarom de unieke kans met zich mee om de continuüm hypothese verder te verfijnen, niet alleen met betrekking tot de fenomenologische karakteristieken maar ook door de onderliggende neurale en cognitieve factoren in kaart te brengen.
De biologische basis voor AVH (genetische kwetsbaarheid en factoren die de ontwikkeling van de hersenen vroeg in het leven kunnen beïnvloeden zoals trauma tijdens de kindertijd) is mogelijk dominant in psychotische patiënten, en beslaat alle gebieden die beschreven worden door van Os et al. (2010) waardoor het functioneren van deze patiënten flink beperkt wordt. Hierdoor is er weinig ruimte voor (intacte) cognitieve processen om een rol te spelen in het ontstaan van AVH. Aan de andere kant van het continuüm, waar de niet-psychotische personen met alleen niet-klinische 'symptomen' zich bevinden is deze biologische invloed zwakker (aangetoond door bijvoorbeeld de normale dopamineproductie). De psychotische symptomen zijn niet ernstig, affectieve disregulatie speelt een kleinere rol vergeleken met patiënten en de cognitieve veranderingen zijn niet klinisch significant. Hierdoor hebben intacte cognitieve processen zoals bewuste auditieve aandacht en semantische topdown verwerking meer de kans om hun invloed uit te oefenen en mogelijk de fenomenologie van de stemmen te beïnvloeden. Dit wordt weerspiegeld door de verschillende betrokkenheid van deze cognitieve factoren in de niet-psychotische personen vergeleken met de patiënten. Dit relatief intact in plaats verstoord cognitief functioneren zou gezien kunnen worden als een beschermende factor.

Therapeutische implicaties

In de context van een psychose, waar de eerste behandelkeus antipsychotische medicatie is, kunnen patiënten veel baat hebben bij aanvullende cognitieve interventies. Verstoord cognitief functioneren kan verbeterd of gecompenseerd worden door deze cognitieve strategieën: Metacognitieve training (MCT) zou bijvoorbeeld iemand kunnen helpen om bestaande denkfouten te herkennen en te corrigeren (Moritz et al. 2011), cognitieve gedragstherapie (CGT) zou onjuiste stressvolle interpretaties van de stemmen kunnen onderzoeken en aanpassen en competitive memory training (COMET) zou kunnen helpen in het makkelijker ophalen van positieve herinneringen om de negatieve zelf-evaluaties die geactiveerd worden door de stemmen te compenseren (van der Gaag et al. 2012). Daarnaast is er nog cognitieve remediatietherapie voor schizofrenie, een interventie die gebaseerd is op een gedragstraining en als doel heeft om cognitieve processen (aandacht, geheugen, executief functioneren, sociale cognitie of metacognitie) langdurig en generaliseerbaar te verbeteren (Wykes et al. 2011). Dit kan worden gedaan door een aantal cognitieve vaardigheden te oefenen zoals het leren van nieuwe efficiënte informatieverwerkings-strategieën (Wykes et al. 2007).

Omdat het horen van stemmen niet noodzakelijkerwijs een symptoom is van een psychotische stoornis, is het voor een behandelaar belangrijk om meer karakteristieken van de stemmen uit te vragen. Een voornamelijk positieve of neutrale inhoud, lage frequentie, controle over de stemmen en een ontstaansleeftijd in de kindertijd zijn allen voorspellers van de *afwezigheid* van een psychotische stoornis. Hoewel iemand even in de war kan zijn wanneer voor het eerst stemmen worden gehoord, is het voorschrijven van anti psychotische medicatie niet wenselijk wanneer er geen sprake is van een psychotische stoornis en het sociaal en beroepsmatige functioneren niet beïnvloeden. In plaats daarvan kan iemand gebaat zijn bij psycho-educatie en zo nodig aanvullende sessies cognitieve gedragstherapie.

Richtingen voor toekomstig onderzoek

In welke mate zijn AVH in psychotische patiënten gelijk of verschillend aan die in andere psychiatrische of neurologische aandoeningen zoals epilepsie, dementie of personen met gehoorverlies? Aangezien auditieve (verbale) hallucinaties voorkomen in een aantal andere groepen buiten de niet-psychotische personen en psychotische patiënten, is er nog verder onderzoek noodzakelijk.
Naast een fenomenologische lijn van onderzoek, dat de karakteristieken van deze

stemmen beschrijft, kunnen ook onderliggende biologische en cognitieve mechanismen in deze populaties onderzocht worden. Dit kan op verschillende manieren gedaan worden, zoals met cognitieve taken of neuroimaging technieken, om zo te ontdekken welke hersenstructuren nog verder betrokken zijn bij dit complexe samenspel dat leidt tot het horen van stemmen. Een verschil in betrokkenheid van hersenstructuren zou mogelijk fenomenologische verschillen tussen stemmen in de verschillende groepen kunnen verklaren zoals al werd geopperd door Waters et al. (2012).

Conclusie

Hoewel verondersteld wordt dat cognitieve factoren een essentiële rol spelen in de etiologie van AVH in zowel niet-psychotische personen als psychotische patiënten, verschilt de mate waarin ze betrokken zijn bij AVH tussen deze twee groepen. Een relatief intact cognitief functioneren in plaats van cognitieve verslechtering kan zelfs een beschermende factor geweest zijn in de niet-psychotische personen, waardoor ze niet verder naar de hulpzoekende klinische minderheid zijn geschoven op het continuüm.

Concluderend kan gesteld worden dat er veel factoren betrokken zijn bij het complexe samenspel van factoren dat leidt tot stemmen horen. Er is dus nog veel verder onderzoek nodig, ook in andere patiëntgroepen. Hopelijk wordt in de nabije toekomst het fenomeen stemmen horen ontrafelt, waardoor er nieuwe behandelopties ontstaan die de last van het stemmen horen kunnen verlichten, en zo velen een betere kwaliteit van leven kunnen geven.

9

Chapter 10

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Chapter 11

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Chapter 12

List of Publications

Peer-reviewed journals

Articles marked with an asterix (*) relate to the work described in this thesis.

van Lutterveld R, Hillebrand A, Diederen KMJ, Daalman K , Kahn RS, Stam CJ, Sommer IEC (2012). Oscillatory cortical network involved in auditory verbal hallucinations. *PLoS ONE*. 2012;7(7):e41149. Epub 2012 Jul 23

* Daalman K, Sommer IEC, Derks EM, Peters E. Cognitive biases and Auditory Verbal Hallucinations in psychotic and non-psychotic individuals. *Psychological Medicine*, manuscript submitted

* Daalman K, Verkooijen S, Derks EM, Aleman A, Sommer IEC (2012). The influence of semantic top-down processing in Auditory Verbal Hallucinations. *Schizophrenia Research*, 139 (1-3), 82-86

* Daalman K, Diederen KMJ, Derks EM, van Lutterveld R, Kahn RS, Sommer IEC (2012). Childhood trauma and auditory verbal hallucinations. *Psychological Medicine*, 2012 Apr 16:1-10. [Epub ahead of print]

Slotema CW, Daalman K, Blom JD, Diederen KMJ, Hoek HW, Sommer IEC (2012). Auditory verbal hallucinations in patients with borderline personality disorder are similar to those in Schizophrenia. *Psychological Medicine* 2012 Feb 16:1-6. [Epub ahead of print]

Howes OD, Shotbolt P, Bloomfield M, Daalman K, Demjaha A, Diederen KMJ, Ibrahim K, Kim E, McGuire P, Kahn RS, Sommer IEC (2012). Dopaminergic function in the psychosis spectrum: an [18F]-DOPA imaging study in healthy individuals with auditory hallucinations. *Schizophrenia Bulletin*. 2012 Jan 26. [Epub ahead of print]

Gaag M van der, Oosterhout B van, Daalman K, Sommer IEC (2012). Initial evaluation of the effects of Competitive Memory Training (COMET) on depression in schizophrenia-spectrum patients with persistent auditory verbal hallucinations: a randomized controlled trial. *British Journal of Clinical Psychology* 51(2),158-171

* Daalman K, van Zandvoort M, Bootsman F, Boks MPM, Kahn RS, Sommer IEC (2011). Auditory verbal hallucinations and cognitive functioning in healthy individuals. *Schizophrenia Research*, 132, 203-207

Diederen KMJ, Daalman K, De Weijer AD, Neggers SF, Van Gastel W, Blom JD, Kahn RS, Sommer IEC (2011). Auditory hallucinations elicit similar brain activation in psychotic and nonpsychotic individuals. *Schizophrenia Bulletin*, Apr 28. [Epub ahead of print]

* Daalman K, Boks MPM, Diederen KMJ, de Weijer AD, Blom JD, Kahn RS, Sommer IEC (2011). The same or different? A phenomenological comparison of Auditory Verbal Hallucinations in healthy and psychotic individuals. *Journal of Clinical Psychiatry* 72(3), 320-325

Slotema CW, Blom JD, De Weijer AD, Diederen KMJ, Goekoop R, Looijestijn J, Daalman K, Rijkaart AM, Kahn RS, Hoek HW, Sommer IEC (2011). Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biological Psychiatry,* 69(5), 450-456

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

Sommer IEC, Derwort AMC, Daalman K, de Weijer AD, Liddle PF, Boks MPM (2010). Formal thought disorder in non-clinical individuals with auditory verbal hallucinations. *Schizophrenia Research*, 118, 140-145

Daalman K, Sommer IEC (2010). Na 10 jaar eindelijk minder last van stemmen. *Dth*, Vol 30, 5-16

Diederen KMJ, Neggers SFW, Daalman K, Blom JD, Kahn RS, Sommer IE (2010). Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. *American Journal of Psychiatry*, 167(4), 427-435

* Sommer IEC, Daalman K, Rietkerk T, Diederen KMJ, Bakker S, Wijkstra J, Boks MPM (2010). Healthy individuals with auditory verbal hallucinations; who are they? *Schizophrenia Bulletin*, 36(3), 633-641

Sommer IEC, Diederen KMJ, Blom JD, Willems A, Kushan L, Slotema CW, Boks MPM, Daalman K, Hoek HW, Neggers SFW and Kahn RS (2008). Auditory Verbal Hallucinations predominantly activate the Right Inferior Frontal Area. *Brain*, 131(Pt 12), 3169-3177

Daalman K, Sommer I (2008). De stemmenpolikliniek: resultaten nieuwe aanpak. *Tijdschrift voor Neuropsychiatrie en Gedragsneurologie,* 7(4), 89-93

Sommer IE, Slotema CW, de Weijer AD, Blom JD, Daalman K, Neggers SF, Somers M, Hoek HW, Aleman A, Kahn RS (2007). Can fMRI-guidance improve the efficacy of rTMS treatment for auditory verbal hallucinations? *Schizophrenia Research,* 93(1-3), 406-408

Book chapters

IEC Sommer and K Daalman. COMET training (chapter 15).*Stemmen horen* by Iris Sommer, Balans uitgeverij 2011, ISBN-9789460033018

WA van Gastel and K Daalman. Groundwork for the treatment of voices: Introducing the Coping-With-Voices Protocol- (chapter 27). *Hallucinations. Research and Practice* edited by JD Blom en IEC Sommer, Springer, New York, New York 2012

Conference abstracts

K Daalman, KMJ Diederen, EM Derks, R van Lutterveld, RS Kahn, IEC Sommer. Childhood trauma and auditory verbal hallucinations. Oral presentation and poster presentation at the Schizophrenia International Research Society conference, Florence, Italy 2012

K Daalman, F Bootsman. Auditory Verbal Hallucinations and cognitive functioning in healthy individuals. Oral presentation at the International Congress on Schizophrenia Research, Colorado, USA 2011

K Daalman, MPM Boks, KMJ Diederen, AD de Weijer, JD Blom, RS Kahn, IEC Sommer. Same or different? Auditory verbal hallucinations in healthy and psychotic individuals. Poster presentation at the Schizophrenia International Research Society conference, Florence, Italy 2010

Chapter 13

Curriculum Vitae

Kirstin Daalman was born in Heerlen, the Netherlands on January 18, 1982. She completed her pre-university education (VWO) at the Eijkhagen College in Landgraaf in 1999 before starting her Psychology study at Utrecht University the same year. She obtained her first master's degree in Applied Cognitive Psychology. After this she obtained her second master's degree in Neuropsychology, including an internship at the Department of Psychiatry at the University Medical Center Utrecht under supervision of dr. Ron Hijman and additional courses in Clinical and Health psychology. Thereafter she started working at the University Medical Center Utrecht under the supervision of Prof. dr. Iris Sommer, coordinating a pilot study on the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) treatment for auditory verbal hallucinations (AVH). This project created the basis for coordinating all running studies on AVH, in addition to coordinating other studies at the department of Psychiatry. For the research in this thesis, her work as research-coordinator was combined with a position of a part-time PhD-student in 2008 under supervision of Prof. dr. Iris Sommer and Prof. dr. René Kahn. She started working at the Voices Clinic of the University Medical Center Utrecht in September 2007 to combine her scientific knowledge with clinical experience of AVH, treating patients with frequent voices.

Kirstin Daalman werd geboren te Heerlen op 18 januari 1982. Ze behaalde haar VWO diploma aan het Eijkhagen College te Landgraaf in 1999, waarna ze psychologie ging studeren aan de Universiteit Utrecht. Als eerste haalde ze haar doctoraal in Cognitieve Ergonomie (toegepaste cognitieve psychologie), waarna ze haar doctoraal in Neuropsychologie behaalde. Voor deze laatste studierichting deed ze haar klinische stage op de afdeling psychiatrie van het Universitair Medisch Centrum Utrecht onder supervisie van dr. Ron Hijman. Na het verplichte opleidingsprogramma van Neuropsychologie volgde ze nog aanvullende cursussen van Klinische en Gezondheidspsychologie. Ook kreeg ze hiernaast de mogelijkheid om in het UMCU een studie te coördineren naar de effectiviteit van repetitieve transcraniële magnetische stimulatie (rTMS) onder supervisie van Prof. dr. Iris Sommer. Na het behalen van haar doctoraal in Neuropsychologie was ze werkzaam als onderzoekscoördinator op de afdeling psychiatrie van het UMCU. Eind 2008 startte ze met haar promotietraject naar auditieve verbale hallucinaties (AVH) bij deze afdeling onder supervisie van Prof. dr. Iris Sommer en Prof. dr. René Kahn. Haar onderzoekskennis over AVH werd aangevuld met klinische ervaring doordat ze vanaf september 2007 als psycholoog werkzaam is op de Stemmenpoli van het UMC. Hier behandelt ze patiënten die frequent stemmen horen en helpt ze hen er minder last van te ervaren in het dagelijks leven.


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GEORGE NUTTALL CLOSE


DENIM COLLECTI
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Uitgang