Cognitive and neural processes of auditory-verbal hallucinations in schizophrenia

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PART I: INTRODUCTION

1. *Auditory-verbal hallucinations (AVH): Definition, phenomenology, and (neuro-) psychological determinants*

1.1. *Historical background and definition*

The word hallucination derives from the Latin 'hallucinare', which means 'to wander through the mind'. It is most likely that hallucinations are as old as mankind. The phenomenon has already been described during ancient times. Socrates (4th century B.C.) reportedly heard voices that guided and assisted him in making important decisions. A number of other historical figures are known to have experienced hallucinations. One of the most famous cases is probably Joan of Arc, who led the French troups against the English, guided by the divine intervention of God and the Archangel Michael, who spoke to her in voices. Ancient Chinese texts recount the power of hemp, thought to lead to "seeing of devils", when consumed in large quantities.

Although "visions" and hallucinatory phenomena are ubiquitous in medieval literature, it was not until the 19th century that the first scientific studies on hallucinations were reported. During this period the concept of "hallucinations" was introduced as a generic term, describing a host of experiences that could bear upon each of the different senses. It was the French psychiatrist Esquirol who coined the term hallucinations as we know it today. Esquirol differentiated between illusions and hallucinations, with a hallucination described as "a strong conviction of a sensory experience, when there is no external stimulus affecting the senses in a corresponding manner". An illusion on the other hand concerns a faulty interpretation of an actual external stimulus.

Despite the long standing fascination of writers and scientists with hallucinations, to this day, the very nature of the inherently elusive and subjective phenomenon complicates an encompassing description or definition, as hallucinations may take on many different forms, may occur in all sensory modalities, and may or may not be linked to mental or physical illness. Perhaps the most appropriate modern definition comes from David (2004), who states that a hallucination can be characterized as 'a sensory experience, occurring in the absence of corresponding stimulation of the relevant sensory organ". Aleman & Larøi (2008) have added to this description that a hallucination occurs during the awake state, thereby setting it apart from lucid dreams, for instance. Furthermore Aleman & Larøi (2008) add that a hallucination should have a sufficient sense of reality, such that it resembles an actual perception, and the perceiver feels he/she has no voluntary control over its occurrence.

This definition encompasses what happens when an 80 year old woman with Charles Bonnet Syndrome sees Scottish highland cattle grazing through her living room, although in reality, luckily, none are present. She can clearly perceive the animals, although no corresponding stimuli reach the retina, and she realizes they could not actually be there. The word 'corresponding' is instrumental here, since the eye *does* receive sensory input from other sources. In the case of Charles Bonnet Syndrome, hallucinations are thought to be caused by the brain 'filling in' information in a top-down manner, in the context of a loss of sensory input, due to damage to the peripheral sensory organ, i.e. the eye or optic pathways. Although sometimes disturbing, because they may interfere with daily life, these hallucinations are mostly met with indifference from the perceiver, as he or she has insight their origin. Hallucinations in mental illness present an entirely different situation. The patient with schizophrenia who hears incessant voices, commanding him to act a certain way against his own will, will frequently find this experience very disturbing, and the hallucinations may contribute to serious disability. Additionally, lack of insight into symptoms will hamper the ability to cope with them. In both described cases however, the hallucination is characterized by a perceptual 'realness', that is, the woman with Charles Bonnet Syndrome really *sees* the cows, life size and full color, and the patient with schizophrenia *hears* a voice with a particular accent, gender and tone.

From the aforementioned situational sketches it becomes clear that hallucinations represent a complex and variable phenomenon. Despite the fact that the above mentioned definition manages to outline the defining characteristics of the hallucinatory experience, setting it apart from vivid imagination of dream-like states, large differences in phenomenology exist. Importantly, these variants may be linked to divergent biological and psychological mechanisms.

1.2. *Modalities of hallucinations*

A rich literature bears evidence of the phenomenological heterogeneity of hallucinations. They can occur in all sensory modalities, and thus be of an olfactory, visual, auditory, tactile or gustatory nature. Furthermore, multimodal hallucinations have been described, where the hallucination is simultaneously expressed in different senses. Although auditory hallucinations are considered to be most prevalent, especially in psychotic disorders, evidence suggests that hallucinations in the other modalities may be underreported in the literature (Aleman & Laroi, 2008).

Auditory hallucinations may present as primitive sounds, such as whistles, tones or knocking sounds or may take on a more elaborate form, consisting of voices laughing, talking or whispering. In the case of auditory-verbal hallucinations, the perceiver will often hear his own thoughts spoken out loud, a foreign voice commenting on his actions or thoughts, or a group of voices talking about him in the third person (Nayani & David, 1996). In some cases the voices will address the voice-hearer directly and command the performance of certain actions. These commands may be relatively benign (repeatedly washing one's hands), but may also elicit socially inappropriate behavior (masturbating in public) or outright harmful and dangerous actions (jumping in front of a train) (Trower et al., 2004). A recent study conducted in a sample of 100 psychiatric patients attempted to objectively define the structure of auditory-verbal hallucinations (Stephane, Thuras, Nasrallah, & Georgopoulos, 2003). From structured interviews, twenty phenomenological variables were identified. A multi-dimensional scaling technique was applied, which revealed three underlying dimensions: (1) linguistic complexity, from low (single words), over intermediate (phrases) to high (entire conversations), (2) self-other distinction, indicating the attribution of the voice to the self (perceiving one's own inner voice out loud) or to a foreign agent (hearing someone else talking to you), and (3) spatial localization, either internal (coming from inside one's head) or external (perceiving the voice via one's ears). Within the auditory hallucinations, *musical hallucinations*, or the perception of melodies, rhythms and timbres, take up their own place. They are most prevalent in pathologies of the auditory pathway (Tanriverdi, Sayilgan, & Ozcurumez, 2001), neurological disorders (Terao & Tani, 1998), toxic effects and as side effects of antidepressant treatment (Terao, 1995). Especially women and elderly persons appear particularly prone to develop this form of auditory hallucinations (Berrios, 1990).

Visual hallucinations are reputed to occur in very divergent populations and disorders, such as acquired brain damage (Berrios & Brook, 1985), different neurodegenerative diseases (Brasic, 1998) , but also in psychiatric disorders, including schizophrenia. In the latter case, these hallucinations are typical in the so called late-onset subtype, characterized by the first emergence of symptoms during middle age, rather than adolescence. Visual hallucinations in neurodegenerative disorders are often simple in form (i.e. seeing shapes and light flashes), whereas in psychiatric conditions, they more often take on humanoid forms, and are elicited during times of stress, fatigue, loneliness or social/relational problems (Gauntlett-Gilbert & Kuipers, 2003).

Multimodal hallucinations are hallucinations affecting different sensory modalities in unison, producing an integrated, complex and holistic perception. Silbersweig et al. (1995), for instance, describe the case of a patient experiencing simultaneous auditory and visual hallucinations. He observed moving, colored scenes, consisting of rolling, bodiless heads, talking, and giving him instructions.

One category of hallucinations that deserves a separate mention, are the *hypnagogic and hypnopompic hallucinations*, referring to hallucinations that occur just before falling asleep or upon waking, respectively. Again, these hallucinations may affect any of the senses, but most typically are characterized by sensations of falling, floating, or leaving one's body, the sensation of a presence, and seeing and/or hearing people or scenes. Although they occur in the general population, i.e. in otherwise healthy individuals, there seems to be an association with sleep disorders such as narcolepsy, cataplexy, sleep paralysis and excessive daytime sleepiness (Ohayon, Priest, Caulet, & Guilleminault, 1996).

1.3. 'Clinical' versus 'non-clinical' hallucinations

Hallucinations as an intrinsically variable and ubiquitous phenomenon are associated with disorders of both psychiatric and non-psychiatric nature. Additionally, they may be elicited in otherwise healthy individuals, often under special circumstances such as sensory deprivation, isolation or bereavement. Within the clinical hallucinations (i.e. those occurring in the context of disease), typically three categories are distinguished: (1) substance induced hallucinations, (2) hallucinations in the context of neurological, neurodegenerative and sensory disorders, and (3) hallucinations in the context of psychiatric disorders.

1.3.1. Hallucinations in clinical populations

1.3.1.1. Substance induced hallucinations

A number of chemical substances, both natural and synthetic, have hallucinogenic properties. Among these are lysergic acid diethylamide (LSD), cannabis, opiates, gamma-hydroxybutyric acid (GHB), phencyclidine (PCP or 'angel dust'), amphetamines, mescaline, cocaine (Watkins, 1998), and psylocybine and psylocine-containing mushrooms ('shrooms'). Hallucinogenic substances may induce reliving of perceptual experiences one had while under the influence of the drug. These so called flashbacks may consist of visual and auditory experiences, usually lasting only a few seconds. Tactile hallucinations (e.g. a sensation of crawling bugs under the skin) are less common and mostly associated with cocaine or methamphetamine intoxications. Interestingly, the effect of the drug may differ greatly depending on the individual, the his or her emotional and physical condition, social circumstances and dosage (Asaad & Shapiro, 1986). Phenomenologically, these substance induced hallucinations can be differentiated from spontaneous hallucinations (Bentall, 2003). Visual hallucinations under intoxication often consist of rotating, pulsing or explosive perceptions of color that are enhanced with the eyes closed, or in a dark environment. Auditory hallucinations are mostly vague and unstructured, and thus quite different from for instance the 'voices' observed by a patient with schizophrenia.

Withdrawal from drugs and alcohol may also engender hallucinatory experiences. In some cases, individuals will develop an abstinence syndrome with delirium, prominently characterized by auditory, visual and tactile hallucinations. These hallucinations however are transient, lasting on average just a few days.

1.3.1.2. Hallucinations in non-psychiatric disorders

1.3.1.2.1. Neurological disorders

A number of neurological ailments, including brain tumors, epilepsy, cerebrovascular infarctions, migraine, and narcolepsy have known associations with the occurrence of different types of hallucinations (Brasic, 1998). Auditory hallucinations are often observed in epilepsy, especially when the epileptic focus originates in the temporal lobe, after resection of (part of the) temporal lobe, and in brain tumors of the temporal lobe, the diencephalon or midbrain. Visual hallucinations are more frequent in cases of viral encephalitis, vascular embolism, thrombosis, migraine, and cortical lesions in occipital or temporo-parietal regions. Olfactory and gustatory hallucinations may also result from brain tumors of the temporal lobe, epilepsy, meningiomas, and migraine attacks.

1.3.1.2.2. Neurodegenerative disorders

In recent years, in addition to the well-described cognitive deficits, researchers have become aware of the presence of non-cognitive problems in the dementias. In 1996, the International Psychogeriatric Association officially termed these problems "behavioral and psychological signs and symptoms of dementia" (Finkel, Costa, Cohen, Miller, & Sartorius, 1996). Behavioral problems included eating and sleeping disorders, agitation, aggression, abnormal vocalizations, wandering, overactivity, (sexual) disinhibition, and apathy. Symptoms in the psychological domain were described as euphoria, depression and psychotic experiences. The latter were subdivided into delusions (false ideas held with unshakable conviction), delusional misidentifications (misperceptions of oneself, other people places or objects) and hallucinations. Dementia of the Alzheimer type is characterized by a relatively high prevalence of hallucinations, with estimates ranging from 12% to 53% (Holroyd, 1996). This group of patients most often reports hallucinations in the visual modality, with simple forms or shapes predominating, although sporadically complex multimodal hallucinations are observed. Hallucinations tend to occur in the moderate to the moderately severe stages of the illness, but not in the very advanced phase. This appears to indicate that a specific deficit in cognitive and/or perceptual processes is required for the production of hallucinations, but that a severely atrophied and diseased brain no longer has the capacity to generate such phenomena.

In Lewy Body dementia, which is the second most frequent form of dementia, cognitive and motor symptoms, as well as recurring visual hallucinations are central to the illness. Given this fact, it is no surprise that the literature bears evidence of high rates of prevalence of hallucinations in these patients. For instance, (McKeith, Perry, Fairbairn, Jabeen, & Perry, 1992) observed hallucinations in 46% of patients. Hallucinations are often rich, detailed and personally relevant, as they involve family members, and personal experiences. Although visual hallucinations are most common, auditory or complex hallucinations, and even - although decidedly more rare - olfactory and tactile hallucinations have been observed. The experience can invoke highly variable affective responses that may range from amusement to fear or indifference. In general, they occur in the early phases of the disease and patients often have a certain degree of insight into their symptoms.

Hallucinations are also relatively common in Parkinson's disease. Aarsland et al. (1999) report a prevalence of 27% in a group of patients drawn from a community sample. In the group examined by (Fenelon, Mahieux, Huon, & Ziegler, 2000), 39,8% even indicated that they had experienced hallucinations in the last three months. This relatively higher rate of occurrence is probably due to the fact that the latter study also included minor forms of hallucinations, including for instance the sensation of the presence of a person or an object. When auditory, olfactory or tactile hallucinations occur in the course of Parkinson's disease, they seldom do so in isolation, but rather in association with visual hallucinations (Henderson & Mellers, 2000). Generally the experiences are quite benign, not threatening and emotionally neutral. Patients may even be amused by their hallucinations, and often retain adequate insight throughout the course of the illness. Finally, hallucinations tend to occur in the later phases of the illness.

It is possible that psychotic-like experiences are underreported in samples of patients with neurological or neurodegenerative disorders. Most studies are based on reports from informants rather than from the patients themselves, and thus should be interpreted with caution. Informants (usually close family members) may wish to protect the integrity of the patient, which may lead to behavior observed as bizarre and disturbed or indicative of mental illness being omitted from reports. Secondly, it is important to realize that although biological factors underlying the neurodegenerative process and the employment of pharmacological agents play an important part in the genesis of hallucinations, these factors are not fully explanatory. For instance, Sweet et al. (2000) compared a group of patients with Parkinson's disease and psychotic symptoms (including hallucinations) to a group of patients who did not show such symptoms. In terms of neuropathology, no differences emerged between the two groups. In addition, not all patients diagnosed with a neurodegenerative disorder develop hallucinations of other psychotic-like phenomena, which suggests that other factors in the domain of personality, cognitive and sensory deficits, and social or environmental processes must play an important role.

1.3.1.3. Hallucinations in psychiatric disorders

Hallucinations have been described in a great number of psychiatric conditions, and are therefore not limited to a specific diagnostic category. Those psychiatric disorders in which hallucinations are fairly common and well documented in the literature include schizophrenia, affective disorders (e.g. bipolar disorder), posttraumatic stress disorder, postpartum psychosis, alcoholic hallucinosis, and borderline personality disorder.

A multinational study of the World Health Organization estimated that approximately 70% of all patients meeting the diagnostic criteria for schizophrenia have hallucinations at some point during the course of the illness (Sartorius, Shapiro,

& Jablensky, 1974). Andreasen & Flaum (1991) report similar base rates for auditory hallucinations in two samples from the state of Iowa in the United States. Auditory hallucinations are the most common form among patients with schizophrenia, followed by visual hallucinations. Olfactory, gustatory or tactile hallucinations may occur, but are much less frequently reported.

Severe depression may also be accompanied by hallucinations. It has been estimated that as many as a quarter of all depressed patients may be suffering from a depression with psychotic symptoms, like delusions or hallucinations (Schatzberg & Rothschild, 1992). The hallucinations are often auditory-verbal in nature, usually transient and limited to brief utterances of single words or short phrases, expressing mood-consistent messages. A psychotically depressed subject typically hears voices that are mocking, humiliating and criticizing, and thus personally referent. They may also be ordered to make up for perceived wrongdoings by performing self-mutilating acts or even committing suicide (Watkins, 1998).

Patients with bipolar disorder may also experience hallucinations. One study reported that 47% of adult bipolar patients have had hallucinations during the course of their illness (Hammersley et al., 2003), with auditory and visual hallucinations being roughly equally prevalent. Hallucinations may occur both in the depressed and the manic phase of the disorder (Taylor & Abrams, 1975). In the manic phase, they usually consist of voices speaking directly to the subject, with the content congruent with the abnormally elevated mood.

Posttraumatic stress disorder (PTSD) is a psychiatric condition that an individual may develop as a result of exposure to a traumatic event, during which the subject's life or wellbeing was (subjectively perceived to be) in danger, and he or she suffered feelings of helplessness and intense fear. Typically symptoms involve emotional blunting, avoidance of stimuli reminiscent of the event, increased arousal and reliving of the event in the form of flashbacks. These flashbacks often take the form of auditory, visual, tactile and/or olfactory hallucinations, or a combination of these (Morrison, Frame, & Larkin, 2003). There are marked similarities between PTSD and symptoms of schizophrenia (Muenzenmaier et al., 2005). Combat veterans with PTSD are more likely to report schizophrenia-like symptoms, particularly hallucinations and paranoia, compared with those who did not develop PTSD following wartime experiences (Butler, Mueser, Sprock, & Braff, 1996; Mueser & Butler, 1987). In some cases, the hallucinations may relate to a specific event that occurred during battle.

Other trauma related psychopathology may also conjoin with hallucinations. There is evidence of a specific association between the traumatic event of childhood sexual abuse and the occurrence of auditory hallucinations, both in clinical (Read & Argyle, 1999) and non-clinical samples (Startup, 1999).

Postpartum disorders refer to a range of disturbances that women may develop shortly after giving birth, depression being the most common disorder. In some cases the postpartum disorder has psychotic features such as hallucinations, although this is quite rare, occurring in only 1-2 out of every 1000 deliveries (Kaplan & Sadock, 1981). Symptoms usually center on the woman's feelings towards the new baby, and her role as a mother. Hallucinations may take the form of voices commanding the new mother to kill or harm her child, or commenting on her competence as a mother. In contrast, some women may present with more benign forms, such as hearing their child crying.

A rare complication of chronic alcoholism is alcoholic hallucinosis, which may occur during intoxication as well as during withdrawal from alcohol. In the DSM-IV the older term has now been replaced by 'substance-induced psychotic disorder with hallucinatory features'. The syndrome is characterized by hallucinations (typically auditory, but visual and tactile hallucinations may occur), delusions, misidentification, psychomotor and affective disturbances. The hallucinatory state may be as brief as a few hours, but may also persist over the course of several months, and in some cases may take a chronic form.

Many patients diagnosed with a borderline personality disorder report hallucinations. A multiple case study of (Yee, Korner, McSwiggan, Meares, & Stevenson, 2005) reported on a total of 117 patients, of which 29.2% reported hearing voices on the Symptom Checklist 90. A closer examination of ten cases further revealed that a large majority of patients experienced the hallucinations as very distressing. They occurred with great frequency over prolonged periods, typically invoked self-harming behaviour, and had a critical content. Although the majority of hallucinations were auditory, visual and olfactory hallucinations were also reported.

1.3.2. Hallucinations in non-clinical populations

Non-clinical hallucinations are those forms of hallucinatory experiences occurring in otherwise healthy individuals, without a history of neurological or psychiatric disorder. They may manifest spontaneously, but are often associated with exceptional circumstances, such as bereavement, social isolation or sensory deprivation and particularly stressful life events.

1.3.2.1. Prevalence

A number of studies suggest that a substantive proportion of the general population have experienced or regularly experience hallucinations. Tien (1991) investigated for the first time the occurrence of hallucinations in a very comprehensive sample of 18.572 subjects from the general American public, observing a prevalence of 10% in males and 15% in females. Similar rates were found in comparable studies conducted in France (Verdoux et al., 1998) and New-Zealand (Poulton et al., 2000). Another large study (Ohayon, 2000) examined a representative sample from three different nations (the United Kingdom, Italy and Germany), by conducting telephone interviews. The investigators petitioned diverse types of hallucinations. 38.7% of the interviewees indicated that they had had at least one hallucinatory experience in their life, although the proportion of subjects having regular hallucinations was limited (2.7% having them once a week, 2.4% having multiple occurrence per week). In the Netherlands, van Os, Hanssen, Bijl & Ravelli (2000) carried out psychiatric interviews in 7.067 subjects selected randomly from the general population. 1.7% reported 'true' hallucinations, i.e. those not brought on by illness or substance (ab)use. Another 6.2% of the subjects had hallucinations considered to be non-clinically relevant, as they were not associated with any distress or discomfort.

1.3.2.2. Contextual influences

There are a number of situations particularly engendering towards hallucinations, both in clinical and non-clinical groups. States of deprivation from sleep, inadequate nourishment, lack of sensory input, as well as extreme fatigue, stress, bereavement, (sexual) abuse, life threatening situations, and religious or spiritual activities are known to be conducive to the emergence of hallucinations.

Sensory (over-)stimulation or in contrast, sensory deprivation are the most common external factors leading to hallucinations. People may report hallucinatory phenomena in situations where external stimulation is increased, such as busy crowds, or repetitive machine sounds, or decreased, such as during a long solitary sailing trip. Reduced input due to a sensory deficit may also lead to the emergence of hallucinations. Associations have been established between deafness and auditory hallucinations, especially in the elderly (David, 1999). Similarly, in the visual domain, hallucinations within a scotoma have long been recognized (Brown, 1985). Lesions of the optic tract may also result in hallucinations (Kolmel, 1985), and 10 to 30% of people who are blind experience hallucinations (Lepore, 1990). It appears that the loss of input from the external world is associated with the generation of internal perceptual experiences and that distinguishing between internally and externally derived stimulation may be hampered by a history of inadequate sensory stimulation.

Stress is another common eliciting factor. Evidence from case studies point to the potential for hallucinations to arise in violent and/or life threatening situations such as mining accidents (Comer, Madow, & Dixon, 1967), military operations (Belenky, 1979), and terrorist attacks (Siegel, 1984). A study (Laroi & Van der Linden, 2005a) investigating hallucinations in healthy subjects found that in approximately one fourth of the individuals reporting hallucinations, the first such experience occurred in the context of a particularly stressful life event. Loss of a loved one and the associated period of mourning may also provide a context for hallucinations. The bereaved often report seeing or hearing the deceased, and may experience a sensation of their presence. A detailed investigation in a group of 293 recently widowed women revealed that almost half had experienced hallucinations relating to the loss of their spouse. These hallucinations endured in a considerable subset of the women, such that half of the women still reported having hallucinations after ten years, and after forty years the hallucinations had persisted in approximately one third. These bereavement-induced hallucinations were more likely in elderly subjects, compared to women who were widowed at a younger age, and a long, happy marriage was a reliable predictor for their occurrence. Interestingly, most women had positive attitudes with regard to the experiences, and felt generally comforted by them during the difficult period of mourning. Subsequent research by Grimby (1993) mainly confirmed the prior findings, and added the observation that this type of hallucination is more prevalent in women then in men.

1.3.2.3. Hallucinations and the association with risk factors

Although the occurrence of hallucinations is not necessarily indicative of psychopathology, it appears that there may be link with certain risk factors for and the actual development of psychological problems. Johns et al. (2004) for instance found an association between hallucinations and neurotic traits, victimization experiences, average or below-average intelligence, alcohol dependence and the female gender. Larøi, DeFruyt, van Os, Aleman & Van der Linden (2005) examined the association between hallucination-proneness and personality structure in both young and elderly subjects. In the young sample, neuroticism was significantly associated with the presence of both auditory hallucinations and vivid daydreaming. It has often been reported that hallucinations are more prevalent in individuals with a history of (psychological) trauma, such as sexual abuse (Read & Hammersley, 2005; Read, Agar, Argyle, & Aderhold, 2003). From a number of studies it has become clear that emotional disturbances, in particular feelings of depression and anxiety, are related to hallucinations in non-clinical populations. Allen et al. (2005) for instance observed that higher levels of self-reported anxiety, self-focus and extreme responding were associated with hallucinatory predisposition. The risk for the development of psychosis in non-clinical subjects with occasional hallucinations may be mediated by depressed mood and the formation of delusional ideas (Krabbendam & van Os, 2005; Krabbendam et al., 2005; Krabbendam et al., 2004). In a Dutch study, Sommer et al. (2008a) used a public website to recruit subjects from the general population, who reported a history of auditory hallucinations. The goal was to assess whether these hallucinations occurred as an isolated phenomenon, or whether they were associated with a specific sensitivity for psychosis. Psychiatric interviews were conducted in 103 voice hearers, and the subjects filled out a number of self-report questionnaires. In addition, sixty control subjects were recruited, matched for age, education level and gender. The voice hearers could not be distinguished from the controls in terms of clinically relevant characteristics, such as delusions, disorganized, negative or catatonic symptoms, and showed no evidence of personality disorders. It was however evident that traumatic childhood experiences, and a family history of Axis I disorders were more prevalent in the group of subjects with hallucinations. The level of everyday global functioning was slightly lower in this group, and their scores on two measures of schizotypal characteristics and delusional formation were remarkably elevated. More detailed analyses revealed that these mediating variables, (i.e. schizotypal traits, lower education level, and a family history of mental illness) were particularly predictive towards reduced global functioning, rather than the presence of voices itself. This led to the conclusion that hallucinations in otherwise healthy subjects are related to a more general sensitivity for disorders in the psychosis spectrum.

Longitudinal investigations of the occurrence of 'psychotic' symptoms in pediatric populations allow the inventory of their predictive value towards the development of true psychotic disorders in later life. A number of studies have attempted to link the characteristics of hallucinations in children and adolescents to clinical variables. Interviews conducted in the Dunedin birth cohort (McGee, Williams, & Poulton, 2000) revealed that 8% of 11-year olds had occasional hallucinations. These children also scored higher on measures of anxiety and depression, as well as attention deficit/hyperactivity. Of the children showing 'strong signs of psychotic symptoms' at the age of 11, 25% had developed schizophreniform disorder at the age of 26 (Poulton et al., 2000). A Japanese study (Yoshizumi, Murase, Honjo, Kaneko, & Murakami, 2004) based on self-report scales in a sample of 761 children aged 11-12 found hallucinations in 21%. Those presenting with a combination of visual and auditory hallucinations also had increased rates of anxiety and dissociative traits. In the Netherlands, Dossche, Ferdinand, Van der Ende, Hofstra & Verhulst (2002) found a prevalence of 2% and 5% for visual and auditory hallucinations, respectively, in a sample of 914 adolescents. The presence of hallucinations was related to a score in the clinical range on the Youth Self-Report (YSR), indexing self-ratings for 20 competence and problem items paralleling those of the Child Behavior Checklist (CBCL). The study failed to find an association with the development of psychosis, but did disclose an elevated risk for affective disorders and substance abuse at follow-up eight years later. Escher, Romme, Buiks, Delespaul, & van Os (2002) followed a group of 80 children who heard voices, of which approximately half were not receiving mental health care, and collected data on hallucination characteristics, coping mechanisms, significant life events, psychopathology scores, and requests for professional (mental health) care. At the follow-up assessment after three years, 60% of the children were no longer hearing voices. Variables that contributed to the continuation of the voices included severity and frequency of the hallucinations, associated depression and anxiety, and the absence of specific triggering events in time or place. The need for professional assistance was more related to the appraisal of omnipotence and intrusiveness of the hallucinated voices, rather than the perception itself or the presence of a specific diagnosis. A recent large Australian study (Scott et al., 2009) examined the prevalence of hallucinations based on self-reports and parental assessments and additionally took into account psychosocial factors. A hallucination prevalence of 8.4% was established in this sample of adolescents. Hallucinations were more frequent in adolescents from single-parent or blended families. Adolescents who heard voices also scored significantly higher on a checklist indicating behavioral and emotional problems. Their self-reports revealed higher rates of depressed feelings and an association with prior cannabis use. The same authors recently reported follow-up data from a 21-year birth cohort study, in which psychopathology was measured at 5 and 14 years of age, using the CBCL, and at 14 using the YSR. Delusional experiences were assessed at 21 years of age with the Peters Delusion Inventory (PDI). Adolescent-onset psychopathology and continuous psychopathology throughout both childhood and adolescence strongly predicted delusional thinking in young adulthood, as was evident form the relationship between delusion-like experiences at age 21 and high CBCL scores at ages 5 and 14 and high scores on the YSR at age 14. Hallucinations at age 14 were also significantly associated with delusions. Interestingly, the general pattern of associations persisted when adjusted for previous drug use or the presence of non-affective psychoses at age 21. From these studies in children and adolescents it has become evident that a fair number of children and adolescents may have auditory-verbal hallucinations, be it regularly or sporadically. The presence of these hallucinations may be related to the development of different psychopathologic symptoms during childhood and adolescence, and later on in adult life. It is however likely that there are mediating factors in this relationship, such as (traumatic) life events which can act as triggers, and other psychosocial and environmental determinants. Importantly, in a great number of cases, the hallucinations are a transient phenomenon, and the majority of children who hear voices will have a benign outcome and will not develop a psychotic disorder. Laurens et al. (2007) furthermore suggest that in order to adequately predict the risk for psychosis, one should not only assess the presence of psychotic-like experiences, but also screen for other developmental disorders in speech, cognition, motor control, behavior and affect.

1.3.3. Conclusions form hallucinations in clinical and non-clinical populations: The continuum hypothesis

The occurrence in clinical as well as non-clinical groups suggests that hallucinations may not be nominally different from normal experiences. This line of reasoning has become known as the 'continuum hypothesis' of psychopathological symptoms, and argues that the difference between a 'clinical' and a 'non-clinical' hallucination is quantitative, rather than qualitative. Furthermore, supporters of this thesis suggest that it is not the nature of the hallucinatory experience itself which determines whether the subject becomes a psychiatric patient, but the way the subject responds to it. This view thus challenges the concept of psychiatric symptoms as discrete entities. Four assumptions underlying the continuum hypothesis may be identified:

(1) the distributional component: hallucinations should be present not only in clinical cases, but also in the general population. In addition, the hallucination

phenotype is expected to be far more prevalent than the clinical hallucination as defined by narrow medical criteria;

(2) the phenomenological component: there should be considerable inter-group similarity, as well as intra-group variability, in terms of phenomenological characteristics (degree of control, affective response, insight, rates of occurrence, etc.), resulting in considerable overlap between clinical and non-clinical groups;

(3) the developmental component: factors that are important demographical or psychosocial determinants in clinical cases (e.g. urbanicity, lower income, lower level of functioning, unemployment, single marital status, etc.) should be paralleled in non-clinical cases, which is suggestive of a general developmental mechanism underlying hallucination genesis; and

(4) the etiological component: clinical and non clinical hallucinations should have similar underlying mechanisms. These etiological determinants are to be found at the biological (e.g. genetic), psychological (e.g. cognitive deficits), and social/environmental (e.g. adverse life events).

The idea of a continuum between normality and psychopathology does not contradict the observation that hallucinations as a general phenomenon may refer to a host of heterogeneous experiences. The different types of hallucinations may consequently have diverging biological and psychological/cognitive antecedents. For instance, neuroimaging studies have revealed that hallucinations occurring in a specific modality are associated with activation in brain areas known to be involved in the processing of external sensory information in that modality. Primary and secondary auditory cortex has been found to be activated during auditory verbal hallucinations (Dierks et al., 1999; van de Ven et al., 2005) and visual hallucinations are associated with occipital activation (Ffytche et al., 1998).

The current thesis focuses on one particular type of hallucination, namely auditory-verbal hallucinations (AVH). More specifically, the main research subject will be AVH occurring in patients with schizophrenia. AVH are considered to be one of the core symptoms of the disorder and have been linked to considerable disability in the daily life of patients. In addition, in line with the continuum hypothesis, investigations in subjects from the general population, who are prone to experience hallucinations, are used as a proxy for clinical hallucinations. Studying non-clinical samples has the distinct advantage that the results are unbiased by other disease-related variables such as duration of illness, hospital admission, general cognitive decline and medication effects. However, as the continuum-hypothesis suggests, the psychological and neurobiological underpinnings of AVH may be similar in patients with schizophrenia and in people with AVH in the general population and thus informative towards the clinical variant of hallucinations. Eventually, a better understanding of the internal workings of AVH at the cognitive and neural level may lead the way towards important new avenues for therapeutic interventions.

1.4. Auditory-verbal hallucinations in schizophrenia

1.4.1. Schizophrenia

Schizophrenia is one of the most severe psychiatric disorders. The lifetime population prevalence of schizophrenia is 1.0-1.5%, with an estimated annual incidence rate of 0.16-0.42 per 1000 persons (Jablensky, 1995). It is typically characterized by a loss of contact with reality. Schizophrenia affects the ability to think clearly, to show and experience emotions in an adaptive fashion, and to interact with others in socially appropriate ways. As a result, the individual will suffer disadvantage in performing his or her occupational and social roles in daily life. The effects are especially devastating as the disorder tends to occur fairly early in life, usually between the ages of 17 to 35, during a period of important developments in social, educational, professional and relational domains.

1.4.2. Auditory-verbal hallucinations (AVH) in schizophrenia

As can be derived from the DSM-IV criteria, and as mentioned earlier, hallucinations are a characteristic symptom of schizophrenia. It has been estimated that up to 70% of all schizophrenia patients experience hallucinations at some point during the course of their illness (WHO; Sartorius et al., 1974). Schneider (1959) defined a number of specific forms of hallucinations and delusions as most characteristic for schizophrenia. These symptoms are known as the classical 'first rank symptoms'. Hallucinations in schizophrenia are mostly auditory-verbal, and according to Schneider may be subdivided in three categories:

(1) voices with running commentary on the patient's behavior and thoughts

(2) voices conversing in the third person

(3) the patient's own thoughts spoken out loud

Although the specific form and content of the AVH may vary from one patient to the next, the assumption is that similar processes are at work at the cognitive and neural level. In the following sections, an overview will be provided of the cognitive theories on AVH. Each of these theories attempts to explain the symptom by relating it to deficits or abnormalities in normal cognitive processes, such as speech perception, attention, inner speech, self-monitoring and verbal working memory. Secondly, studies employing structural and functional neuroimaging methods in the investigation of the underlying mechanisms of AVH at the neuronal level will be reviewed. Finally, a concise description of the currently available and prevailing treatments AVH will be given.

1.4.3. Cognitive theories of AVH

1.4.3.1. Mental imagery

One of the oldest theories on AVH centered on the notion of abnormal mental imagery. The basic idea was that when mental imagery is especially vivid, or has a heightened sense of 'realness', it may be difficult to distinguish internally generated mental images from externally derived perceptions. Mintz & Alpert (1972) tested this hypothesis in a classical study. Subjects were asked to take place in a silent room, and were told that a tape with the familiar song "White Christmas" would be played at irregular intervals. In reality, the tape being played contained only noise. Compared to subjects who were not prone to hallucinations, a larger number of subjects with high scores on a hallucination proneness measure reported actually having heard the tune. Recently, a similar investigation was reported by (Knobel & Sanchez, 2009). In this case, the authors explicitly attempted to manipulate the focus of attention. Sixty-six healthy subjects were tested in the completely silent environment of a soundproofed booth, under different attentional conditions. During performance of a relatively taxing cognitive task, 10% reported some form of auditory perceptions. This rate decreased to 6% when subjects were instructed to focus their attention on visual perception (i.e. they were told there might be a change in ambient lighting), and increased to 36% in the auditory attention condition (i.e. they were told there might be a change in ambient sound). The fact that studies like these rely completely on self-report and are particularly sensitive to effects of suggestibility pleads for a cautious interpretation of the findings. Other early studies investigating the link between mental imagery and hallucinations provided conflicting evidence. Seitz & Molholm (1947) found a negative relationship between hallucinations and preferred mode of imagery, leading them to argue that schizophrenic hallucinators are relatively deficient in imagery in the modality of their hallucinations. In addition, they compared vividness of reported mental imagery in patients to that of controls and found it to be weaker in the hallucinators. An occasionally occurring vivid image in the non-preferred and weak modality could therefore be interpreted as none-self produced, and thus experienced as a hallucination. Slade (1976) employed two questionnaires measures of mental imagery and on one (the Betts Scale) schizophrenia patients were found overall to have more vivid imagery compared to controls. However, no difference could be detected between those with and without hallucinations. The other scale (the Gordon Scale of Mental Imagery Control) revealed no group differences at all. A number of other studies (Brett & Starker, 1977; Catts, Armstrong, Norcross, & McConaghy, 1980), using a very similar design failed to replicate this result. Although the findings with regard to mental imagery are discordant, studies such as these indicate that patients with schizophrenia are poor reality testers. Studies attempting to quantify this skill, or the lack thereof, have employed the so called Verbal Transformation Effect, discovered by Warren et al. (1961). The effect is elicited by playing a tape-loop of the same word or phrase, repeated at a fairly fast rate. A normal perception involves hearing phonetically related changes in the stimulus at regular intervals. An initial study (Slade, 1976) found schizophrenia patients with a history of hallucinations not to differ from controls in the frequency which they experienced stimulus transformations, but they did hear more bizarre words, phonetically less related to the original stimulus. In order to assess to what extent suggestibility rather than perceptual effects play a role in this effect, Haddock (1995) explicitly manipulated the task instructions. In one condition of the task, subjects were told they *might* observe a transformation of the stimulus, and in the highly suggestive condition, were told the stimulus *would* change form. Although no overall differences were observed between groups of hallucinating patients, psychiatric controls and healthy controls for the number of transformations or the latencies of transformations, the hallucinators reported significantly more transformations in the suggestion condition compared to the no suggestion condition. In addition, they identified a greater range of transformations. The results indicate that the auditory judgments of hallucinators are highly influenced by beliefs and expectations. Negative results from other studies however yield a mixed pattern of evidence. Catts et al. (1980) could not confirm the previous results, when comparing twelve non-hallucinating to twelve hallucinating patients, using a similar design to Slade (1976). Evans et al. (2000) tested patients with and without the propensity to hallucinate on five tasks involving the relationship between the 'inner ear' and 'inner speech', including a verbal transformation task. They found no evidence to suggest that patients with a hallucinatory predisposition are impaired or perform abnormally on any of the tests. However, as Haddock et al. (1995) suggest, the divergent results obtained from hallucinating patients may reflect the specific task demands, and especially the instructions employed in the experiments.

In order to gain insight into the nature and impact of mental imagery processes in hallucinations, more objective behavioral measures are necessary. A potential approach entails a direct comparison of performance on a perceptual version of a simple task to an imagery version of the same task (Aleman, Nieuwenstein, Bocker, & de Haan, 1999; Aleman, Nieuwenstein, Bocker, & de Haan, 2000), the underlying conception being that stronger imagery capacity will convey more sensory, contextual and semantic detail to the mental image, making it more alike to an external percept. Hypothetically this would lead to a smaller performance gap between the perceptual and the imagery version of the task. Bocker, Hijman, Kahn & de Haan (2000) compared patients with and without auditory hallucinations on two measures of auditory and visual perception and imagery. Although no group differences became apparent on the two versions of the tasks, patients with hallucinations had relatively stronger auditory imagery compared to visual imagery. A case study of a continuously hallucinating patient, reported by Aleman, de Haan, Bocker, Hijman & Kahn (2002) further illustrates enhanced imagery processing in the auditory, but not the visual modality. In a more elaborate investigation, Aleman, Bocker, Hijman, de Haan & Kahn (2003) asked subjects to form a mental image of one of two previously presented tones (a high versus a low tone). Subsequently, acoustic noise was presented, with either the imagined or the other tone embedded in the noise. Detection of the imagined tone in noise is typically enhanced, an effect known as 'imagery gain'. This measure correlated with the severity of hallucinations in a patient sample, evidencing increased 'imagery gain' with more severe hallucinations. These findings fit with the idea that hallucinations may be related to increased impact of top-down influences on (auditory) perception. Perception is not a passive process, but a reconstructive effort (Kveraga, Ghuman, & Bar, 2007). Every percept is the result of an interaction of bottom-up information, flowing through the system from the peripheral sensory organs upward to primary, secondary and association cortices, and concurrent top-down processing, consisting of internal models of the (acoustic) environment, contextual cues and general world knowledge, which generate perceptual expectations. In a similar vein, Kot & Serper (2002) investigated auditory conditioning in hallucinating and non-hallucinating schizophrenia patients by repeatedly pairing a tone (unconditioned stimulus) with a light (conditioned stimulus), until presentation of the light alone elicits the 'perception' of the tone. If top-down processes mediate the occurrence of clinical hallucinations, one would expect hallucinating patients to be more susceptible to conditioning. Consistent with the auditory sensory-conditioning model, results indicated that hallucinating patients acquire sensory-conditioned hallucinations more quickly and are more resistant to extinction than their non-hallucinating counterparts.

Thus, in the case of schizophrenia with hallucinations, there may be a distorted balance between these bottom-up and top-down processing pathways, in such a way that a relatively higher priority is assigned to top-down factors in determining the final perception (Grossberg, 2000; Behrendt, 1998), possibly giving rise to perceptions without corresponding external origin (i.e. hallucinations). This fits with a conception of perception as a fundamentally subjective and reconstructive process. (Behrendt, 1998) for instance remarks that traditionally perception is thought to be a fairly accurate internal reflection of the outside world. However, this fails to account for hallucinations and perceptions in dream-states, which have all the richness of 'true' perceptions, but no external basis. He goes on to state rather evocatively that "perception should not be seen as an introjection of external reality. Rather, it is an entirely internal production that is projected outside [...] everything that we are aware of is the mind, and what we regard as reality is nothing but an externalized part of the mind". In general, perception is internally determined by mental factors, such as appetitive and emotional drives, expectations, and current needs, and secondly, externally restricted by sensory stimulation. Within this framework, hallucinations do not differ from perception in their reliance on the activation of internal representations, as normal perceptions do not completely acquire their content from external reality either. Hallucinations differ with respect to the balance between internal and external mental conditions of the process, in that they are underconstrained by sensory input. Similarly, Grossberg (2000) suggests that learned top-down expectations are essential in normal learning and memory. These expectations produce prototypes that assist in focusing attention on the relevant feature combinations that comprise conscious perceptual experiences. Top-down expectations may modulate or sensitize target cells to respond more effectively to matched sensory information that enters the perceiving system from the bottom-up. The modulating property of top-down expectations is achieved through a balance between top-down excitation and inhibition. Phasic volitional signals can shift the balance between excitation and inhibition to favor net excitatory activation. Such a volitionally mediated shift enables top-down expectations, in the absence of supportive bottom-up inputs, to cause conscious experiences of, for example, imagery, inner speech, and dreams, and thereby to enable fantasy and planning activities to occur. If these volitional signals, which may or may not be consciously generated, become tonically hyperactive, the top-down expectations can give rise to conscious experiences in the absence of bottom-up inputs and volition. Indeed, it has been proposed that excessive top-down processing, particularly in the form of serial linguistic expectations, may lead to the generation of spontaneous perceptual experiences (Hoffman, Rapaport, Mazure, & Quinlan, 1999).

1.4.3.2. Deficits in speech perception

AVH are by definition speech perceptions that are erroneously perceived in the absence of speech input. It is therefore understandable that a considerable number of investigations have focused on the integrity of perceptual processes in hallucinating individuals. In contrast to the top-down account of AVH, this approach assumes that deficits occur in the bottom-up processing pathway. Ample evidence from neurology and psychology supports the occurrence of hallucinations in association with sensory impairment and deprivation. For example, acquired deafness in old age has been associated with the emergence of AVH. Thewissen et al. (2009) prospectively investigated the onset of hallucinations and delusions in a general community sample. Of the subjects with deafness or hearing impairment at baseline, 10.1% displayed psychotic symptoms at follow-up, compared to only 2.9% in hearing subjects. Hallucinations arising from various forms of sensory impairments have been termed 'release' hallucinations. A lesion to cortical areas may cause loss of inhibition in other cortical areas, resulting in the release of cortical activity and subsequent hallucinatory perceptions.

The evidence for sensory impairments in schizophrenia is however mixed. On the one hand, schizophrenia patients as a group do show sensory abnormalities, both in the auditory and visual domains (David, Malmberg, Lewis, Brandt, & Allebeck, 1995). In accordance with the prominent linguistic problems in schizophrenia, sensory deficits may be more pronounced in the language domain. Hoffman, Rapaport, Mazure & Quinlann (1999) observed a performance deficit in hallucinating patients, compared to non-hallucinating patients on a masked speech tracking task, using different levels of superimposed phonetic noise. The task requires subjects to immediately repeat the speech stimuli, as they are listening to the auditory stream. Additionally, a sentence repetition task and an auditory continuous performance task were used to assess verbal working memory and non-language attentional processes. Results supported the hypothesis that hallucinated voices arise from disrupted speech perception and verbal working memory system rather than from non-language cognitive deficits. The fact that this deficit occurs at the level of linguistic processes, and not in more basic perceptual domains was confirmed in a study that tested 30 patients with schizophrenia and 32 controls subjects on verbal serial position tasks on the one hand and tone serial position tasks on the other hand (Stevens, Donegan, Anderson, Goldman-Rakic, & Wexler, 2000) Groups were matched on auditory acuity, such that performance deficits could not be ascribed to basic sensory differences. Remarkably, patients performed worse on all verbal tasks, but did not differ from controls on the tasks employing tones. McKay, Headlam & Copolov (2000) used a comprehensive battery of auditory tests in order to assess whether auditory hallucinations are associated with abnormalities in central auditory processing. Three groups of subjects were tested: 22 patients with psychosis and a recent history of auditory hallucinations, 16 patients with psychosis but no history of auditory hallucinations, and 22 normal subjects. The auditory assessments included auditory brainstem response, monotic and dichotic speech perception tests, and non-speech perceptual tests. There were no group differences on tests that were sensitive to low brainstem function. However, patients in general performed worse than controls on tests sensitive to higher brain stem and cortical function. Hallucinating patients differed from their non-hallucinating counterparts on particularly on a number of speech perception tests, e.g. filtered speech perception and dichotic listening tasks, on which stimuli are presented to both ears simultaneously, and attention should be directed to one ear. Hallucinating subjects performed worse than controls when stimuli presented in the left ear had to be reported. The authors concluded that AVH may be associated with dysfunctions in interhemispheric transfer or language processing of the right hemisphere, but that the deficit observed in hallucinating patients probably represents a greater degree of the same kind of language abnormalities seen schizophrenia patients in general. Other studies utilizing the dichotic listening paradigm have likewise observed performance deficits in patients with AVH (for a review, see Hugdahl et al., 2007). In the Bergen dichotic listening paradigm (Tervaniemi & Hugdahl, 2003), the subject is presented with two consonant–vowel syllables simultaneously, one in each ear, and required to report the syllable identified best on each trial. The instruction emphasizes that the subject should provide only the syllable identified best on each trial. The idea is that this taps into an initial perceptual process and avoids confounding with memory. Moreover, the subject is not told that there are two different syllables on each trial, and is encouraged to "not to try to remember, or think about the stimulus, but just report what you initially hear". Healthy controls typically show a right-ear-advantage (REA) in this paradigm. The neuroanatomical model suggested by Kimura (1961) is often advanced in explaining the REA, as it states that the contralateral auditory neural pathway is more preponderant than the ipsilateral one, and that the left hemisphere is dominant for speech perception. This should favor processing of the right ear stimulus because it has direct access through the contralateral auditory pathways to the speech processing areas in the left temporal lobe. As a group, patients with AVH show a reduced REA, and an inverse relationship exists between AVH severity and right ear performance, supporting the idea that hallucinations interfere with the perception of external speech stimuli, localized to the left temporal lobe. What is not clear from these results is whether this is caused by a direct interference by "active voices" or that the presence of AVH over a long time is associated with neuronal pathology at the level of the left peri-Sylvian region.

Decision processes higher up in the processing stream may also affect speech perception ability. In a number of studies, a positive response bias was observed in patients with AVH, when reporting the detection of stimuli. Bentall and Slade (1985) constructed a task based on Signal Detection Theory (SDT), in which the word "who" had to be detected against a background of acoustic noise. On half of the trials only noise was presented. SDT allows the dissociation between perceptual sensitivity, i.e. the general efficiency of the perceptual system, and response bias, i.e. the individual's private criterion for deciding that a perceived event is an actual stimulus. Two non-clinical groups, consisting of hallucination prone subjects and non-hallucination prone subjects, as well as groups of schizophrenia patients with and without AVH completed the task. Hallucinators did not differ from non-hallucinators in terms of perceptual sensitivity. In contrast, hallucinators were more likely to indicate they observed the word in noise, when it was not present (i.e. a false alarm). Thus, it seems that the predisposition for hallucinations relates to changes in the perceptual criterion for speech stimuli. In opposition to the idea of a speech perception deficit, one could even posit that this response bias may actually lead to improved detection of stimuli under ambiguous circumstances, as it is characterized by a willingness to err on the side of false positives. Theoretically, the number of missed stimuli will decrease, as the decision criterion shifts (Dolgov & McBeath, 2005).

1.4.3.3. Meta-cognitive control processes

Metacognition means "thinking about thinking", or in other words, reflections about your own thought processes. This metacognitive attitudes and beliefs may be implicit, that is, the subject is not necessarily consciously aware of them. Recent cognitive models of hallucinations have focused on potential deficits in these processes, particularly in the attribution of internally generated experiences. The most prominent theories relate AVH to misattribution of inner speech, and problems with monitoring the source of mental events.

1.4.3.3.1. Misattributed inner speech

Inner speech refers to the "inner voice", which is a common human cognitive process that enables the regulation of behavior and emotions. It typically involves commenting to oneself about what is happening or issuing instructions about what to do. The idea that AVH occur when an individual misattributes this inner speech to an external source has considerable intuitive appeal, and in the literature a certain consensus exists in support of this view. In support of this theory, subvocal activation of the speech muscles has been observed during hallucinations, similar to the subvocalization present during normal inner speech in healthy adults (Gould, 1948; Gould, 1949). Similarly, some studies have found that verbal tasks that block subvocalization also inhibit the occurrence of AVH (Gallagher, Dinan, & Baker, 1994). It is hypothesized that a breakdown in the monitoring of inner speech production is responsible for its misattribution to an external source. Frith (1987; 1989) formulated a theory of alien control symptoms in schizophrenia, explaining them in terms of failure in monitoring the intention to act. Deficits in self-monitoring may cause overt actions or mental actions to become isolated from the volitional signal. Applied to AVH, if one fails to recognize the intention associated with one's inner speech, this would lead to the interpretation of the inner voice as an external one. This proposition is largely based on Feinberg's (1978) idea that schizophrenia is associated with deficits in the efference-copy/corollary discharge system. Briefly, each action a person makes is assumed to be accompanied by an 'efference copy' of the action, which sends a signal to the sensory cortex. Here, a corollary discharge is produced, which primes the cortex for the impending sensory consequences of the action. This signals to the person that the sensations are linked to a self-generated act. During talking, for instance, the plan to speak sends an efferent signal to the auditory cortex, where it becomes a corollary discharge. Almost simultaneously, speech is initiated, and the sound reaches the auditory cortex. In the normal situation, an internal monitor matches the afferent input to the corollary discharge, and the sensory experience is reduced in its impact. In schizophrenia however, it is presumed that this efference copy does not produce a timely corollary discharge, which complicates the distinction between internal and external perceptual events. If this corollary discharge process fails during inner speech, a self-generated inner dialogue may be experience as coming from a non-self source.

1.4.3.3.2. Reality discrimination and reality monitoring

Richard Bentall (1990) introduced an influential model that explains hallucinations in terms of a disruption in reality discrimination and/or monitoring, i.e. the ability to distinguish real from imagined events. Reality discrimination refers to the on-line judgment of whether an ongoing experience internally generated or is coming from an external (i.e. non-self) source. Reality monitoring then refers to memories regarding the internal or external source of an event. The theory suggests that hallucinating individuals have specific externalizing bias, or the tendency to attribute their thoughts to an external source. This idea is obviously in accordance with the general idea underlying other theories of AVH, e.g. the inner speech model. A major advantage of this approach lies in the fact that it is based on a body of experimental work with a paradigm tapping into the more general ability of "source monitoring" (Johnson, Hashtroudi, & Lindsay, 1993). Source monitoring refers to the ability to discriminate different sources of information, e.g. whether you read something in the newspaper, or heard the story from a friend. Reality discrimination and monitoring can be seen as a subset of source monitoring processes, specifically relating to the internal/external distinction. In a typical source monitoring paradigm subjects are given a list of words to remember. During the encoding phase, half of the words will be read by the experimenter, and half by the subject herself. In the test phase, the subject has to indicate for each given word, whether it was self generated or read aloud by the experimenter, or whether it is a new distractor word. According to Bentall's hypothesis, patients with hallucinations should make more errors indicating a self-generated word was spoken by the experimenter. A number of studies have found corroborating evidence (Bentall, Baker, & Havers, 1991; Morrison & Haddock, 1997; Brebion et al., 2000). Evidence of disturbances in reality monitoring in non-clinical participants was reported by Larøi, Van der Linden & Marcewski (2004). For every presented word, the subject was required to associate another word. Interestingly, the stimuli were varied in terms of emotional valence, and cognitive effort. High cognitive effort words were those for which longer latencies were required in finding an associate. After a delay, a series of stimuli was presented, including those generated by the experimenter, the associate words provided by the subject, and distractor words, and the subject was asked to identify the source of each word. Hallucination prone subjects made more errors for self-generated items, and this pattern of results was particularly marked in the high cognitive effort and emotionally charged material. This suggests that hallucination prone subjects have a deficit in the use of meta-cognitive cues, such as cognitive effort (typically, one is more likely to accept an experience as self-generated when it is associated with a memory of the cognitive effort associated with the production of the event), and the effect of emotion on cognitive processes.

However, not all studies have been able to endorse the specific link between hallucinations and source monitoring deficits. For instance, Keefe et al. (1999; 2002) report that patients without hallucinations, but with other positive symptoms, make the same errors. Costafreda et al. (2008) also found that external misattributions were more common than self-misattributions, especially for negatively valenced material, and that the bias was greater for patients with active positive symptoms relative to patients in remission. However, this association held up for both patients with hallucinations and delusions, and thus argues against the specificity of source monitoring deficits to the hallucination process. Another issue plaguing this theory is the fact that phenomenologically, the perceived voices are not necessarily externalised by hallucinating patients. A number of studies indicate that patients often experience their voices as coming from "inside their head". In addition, some patients have difficulty distinguishing their own thoughts from their verbal hallucinations. Or, in other words, a subjective perceptual event does not need to be externalized in order to qualify as a hallucination.

1.4.4. Neuroimaging of hallucinations

Are there observable alterations or deficits in the brain of an individual who hears voices when no one is speaking? Which brain areas are involved in the experience of hallucinations? With the use of modern imaging techniques, such as Positron Emission Tomography (PET) and (functional) Magnetic resonance Imaging (fMRI) researchers have attempted to answer these questions. Allen et al. (2008) provide an exhaustive review of structural and function imaging studies investigating the neural substrates of AVH. Here, we provide a brief summary of activation studies, which probe the immediate neural activity associated with the occurrence of AVH, cognitive interference studies, investigating the neural basis of cognitive processes involved in AVH, and studies mapping brain changes in terms of structure and connectivity.

1.4.4.1. Structural neuroimaging

The aim of these studies is to link structural changes in brain morphology to the presence and/or severity of AVH. In contrast to hallucinations caused by a specific pathological process, such as a tumor, hallucinations in psychiatric disorders are generally not observable in terms of consistent and evident brain changes at the individual level. However, when brain scans from larger samples of schizophrenia patients with AVH are averaged and compared with brain scans obtained from psychiatric controls and/or healthy subjects, structural alterations may be observed. Another option is a correlations approach, in which the relationship between symptom severity and neurobiological measures (e.g. volumes of particular brain regions) is explored.

The first study comparing hallucinating schizophrenia patients with healthy controls revealed that patients had larger lateral ventricles, as well as reduced volume in the superior temporal gyrus (STG). In addition, the severity of AVH was negatively correlated with left STG volume, an area important for speech processing (Barta, Pearlson, Powers, Richards, & Tune, 1990). A number of other studies support this latter finding, and also report a link between STG volume and hallucinations severity (Flaum et al., 1995; Onitsuka et al., 2004). Structural changes in non-sensory brain regions have been reported in studies using advanced, automated techniques for the assessment of brain volumes (e.g. Voxel-Based Morphometry; VBM). Neckelmann et al. (2006) confirmed the association of AVH with the left STG, and in addition were able to link AVH to gray matter volume in the thalamus and cerebellum. Shapleske, Rossell, Simmons, David & Woodruff (2001) assessed the length of the Sylvian Fissure (SF) and the Planum Temporal (PT) volume in schizophrenia patients, and calculated both absolute measures and degree of lateralization. Although no asymmetry differences were observed between groups of patients with and without AVH and healthy controls, hallucination severity was correlated with greater leftward asymmetry of the PT. This relationship does not seem very specific however, as thought disorder also correlated with the asymmetry measure. A later study (Shapleske et al., 2002) did reveal a reduction of grey matter tissue in localized areas in the brains of schizophrenia patients. There were also reductions in white-matter tissue, extending along much of the large anterior-posterior frontal tracts in the right hemisphere. Small regions of increased grey matter were also noted in the right inferior parietal lobe. When specifically contrasting patient groups with and without AVH, a single region of reduced grey-matter tissue was identified, affecting the left insula and adjacent temporal lobe. Most of these studies have relatively small sample sizes and divergent findings may be due to differences in methodology and sample characteristics. In order to overcome the limitations of conventional volumetric methods, Gaser et al. (2004) used deformation-based morphometry (DBM), a novel automated whole-brain morphometric technique, to assess local gray and white matter deficits in structural magnetic resonance images in a large sample of 85 schizophrenia patients. They found severity of auditory hallucinations to be significantly correlated with volume loss in the left transverse temporal gyrus of Heschl (i.e. the primary auditory cortex) and left inferior supramarginal gyrus, as well as middle/inferior right prefrontal gyri. These structural deficits in a distributed fronto-temporal network appeared to be specific to auditory hallucinations which suggests that AVH may be associated with alterations in interconnected brain regions involved in the processing of auditory and linguistic information. Changes in speech processing areas could possibly lead to a loss of inhibition of inner speech. The volume loss in the prefrontal cortex potentially explains reduced volitional control over inner speech and auditory perception processes. Sumich et al. (2005) partially confirmed these findings.

Stephane, Barton & Boutros (2001) conducted a review of studies investigating hallucinations and changes in speech processing areas. The authors warn against far-reaching conclusions based on the available literature, as not all studies were able to confirm the link between AVH and structural deficits in auditory regions (e.g. (DeLisi, Hoff, Neale, & Kushner, 1994; Havermans et al., 1999)). Although older MRI studies have produced rather diverging results, recent, and methodologically more advanced studies seem to be more in agreement. Eight studies report volumetric reductions of the left temporal region, in association with AVH, whereas three failed to find a link. One study actually observed in increase in frontal and temporal gray and white matter (Shin et al., 2005). The patient group in this study was quite atypical however, as it consisted of young, unmedicated patients during a first psychotic break.

Periventricular and ventricular changes were found in four of these studies. In all, it appears that the most consistent finding in hallucinating patients is a reduction in left STG volume. This concurs with lesion studies, which indicate that the localization of the lesion is expected to match the specific modality of the hallucination, i.e. language-related brain regions in the case of AVH.

1.4.4.2. Functional neuroimaging

PET, fMRI and other functional neuroimaging methods are used to quantify and image changes in cerebral blood flow, metabolism and neurotransmission. With regard to the study of AVH two prevailing approaches can be distinguished.

The first category of experiments can be described as "activation studies". These studies are designed to measure AVH-related activity at the moment they occur. Either patients are scanned once during the active symptomatic phase and some time later when the symptoms have remitted, or, patients are scanned in a single imaging session, and simply asked to indicate (e.g. by means of a button press) the duration of the periods he or she is having a hallucination. In some instances concurrent auditory stimuli are presented, in order to assess conflicts between internal and external "auditory" information.

The second category of studies are so called "cognitive interference" studies. Typically, groups of subjects with and without a (history of) hallucinations are compared in terms of behavioral performance and cerebral activity on a cognitive task. A particular task is chosen because it is thought to tap into specific cognitive processes underlying AVH (e.g. reality monitoring, inner speech processing, etc.). Both types of studies (activation studies and interferences studies) will be discussed in more detail hereafter.

1.4.4.2.1. Activation studies

In the first study of its kind, McGuire, Shah & Murray (1993) scanned 13 patients with schizophrenia during a period in which they had active positive symptoms, including AVH. The same protocol was repeated in each of the patients, upon remission of the symptoms. A comparison of these scans revealed increased activity in the left inferior frontal gyrus, i.e. Broca's area, during the hallucinatory phase. This region has long been known to be involved in speech production. Additionally, but to a lesser extent, activity was observed in the left temporal cortex, which is important for speech perception, and the anterior cingulate gyrus, which controls attentional processes. Using the same general design, but a different imaging technique (SPECT), Suzuki, Yuasa, Minabe, Murata & Kurachi (1993) confirmed part of the latter findings, also observing left temporal cortex activation in 5 patients with AVH. Reporting data from a similarly small sample, Silbersweig et al. (1995) demonstrate AVH related activity in a much more distributed network of subcortical nuclei (thalamic, striatal), limbic structures (especially hippocampus), and paralimbic regions (parahippocampal and cingulate gyri, as well as orbitofrontal cortex). They also report a case study of a unique, drug-naive patient who had both visual and auditory hallucinations. This patient showed activity in visual and auditory/linguistic association cortices as part of a distributed cortical-subcortical network. Based on these findings, the authors suggested that activity in deep brain structures may generate or modulate hallucinations, whereas the particular neocortical regions entrained in individual patients may affect the specific perceptual content. Lennox, Park, Jones & Morris (1999) performed the first activation study with fMRI. They describe a single case of a patient with intermittent AVH. On average his AVH episodes lasted 26 seconds and were followed by hallucination free periods of approximately the same duration. The patient was asked to press a button when the hallucination started, and release it when the voices subsided. A comparison of these short AVH epochs revealed increased activity in the right middle temporal gyrus during AVH. In a follow-up study (Lennox, Park, Medley, Morris, & Jones, 2000) with four subjects, cerebral activation associated with auditory hallucinations was again mapped with fMRI. Group analysis demonstrated shared areas of activation in right and left superior temporal gyri, left inferior parietal cortex and left middle frontal gyrus. When the data were examined on an individual basis, the temporal and prefrontal cortices were activated during AVH in all four subjects. These findings support the theory that AVH reflect abnormal activation of normal auditory pathways. This conclusion was further supported by another fMRI study (Dierks et al., 1999), which, interestingly, found AVH-related activation of the primary auditory cortex in three patients. In healthy subjects, inner speech or auditory imagery does not activate primary sensory areas. The possibility exists that in patients with AVH, there are abnormal feedback projections from higher order processing regions to primary auditory cortex, leading to concomitant activity, and the subjective experience of a "real" auditory stimulus with definitive perceptual characteristics. The case study describing a patient with AVH, that subsided when external sounds were presented again implicated primary auditory cortex in the process of AVH. Van de Ven et al. (2005) argued that the self-report method used in previous studies may not be sensitive enough to capture all neurophysiological signals related to hallucinations. They employed spatial independent component analysis (sICA) to extract the activity patterns associated with AVH in six patients. SICA decomposes the functional data set into a set of spatial maps without the use of any input function. Bilateral auditory cortex activity, including Heschl's gyrus, was seen during hallucinations of one patient, and unilateral auditory cortex activity in two more patients. The associated time courses showed a large variability in the shape, amplitude, and time of onset relative to the self-reports. This latter fact may have contributed to the somewhat divergent results among the self-report based studies. Additionally, when the subject is required to actively monitor for the presence of AVH and press a button when they occur, the resulting brain activity probably does not only reflect true AVH processes, but other (meta-)cognitive activity as well (e.g. sustained attention and vigilance, self-monitoring, response selection, and motor activity). Shergill, Brammer, Williams, Murray & McGuire (2000) attempted to bypass this methodological flaw by using a novel fMRI method that permitted the measurement of spontaneous neural activity without requiring subjects to signal when hallucinations occurred. Approximately 50 individual scans were acquired at unpredictable intervals in six patients while they were intermittently hallucinating. Immediately after each scan, subjects reported whether they had been hallucinating at that instant. AVH were associated with activation in the inferior frontal/insular, anterior cingulate, and temporal cortex bilaterally, with greater responses on the right. The right thalamus and inferior colliculus, and the left hippocampus and parahippocampal cortex were activated as well. The authors concluded that AVH appear to be mediated by a distributed network of cortical and subcortical area and that prior neuroimaging studies may have identified different components of this network. One interesting aspect of this study was that it also provided information on the temporal course of AVH. Activity in the left frontal and right middle temporal cortex preceded the start of the AVH, whereas the superior temporal gyri and insula responded during AVH. This finding is consistent with the hypothesis that cortical areas associated with inner speech production become activated before speech perception areas are recruited. The most recent, and largest study to date, investigating on-line AVH activity in intermittent hallucinators was reported by Sommer et al. (2008b). Cerebral activation was measured using fMRI in 24 psychotic patients while they experienced AVH in the scanner and, in another session, while they silently generated words. Group analysis for AVH revealed activation in the right homologue of Broca's area, bilateral insula, bilateral supramarginal gyri and right superior temporal gyrus. The word generation task on the other hand yielded activation in the typical left hemisphere language areas (Broca's and Wernicke's area) and to a lesser degree their right-sided homologues, as well as the bilateral insula and anterior cingulate gyri. The lateralization of AVH-related activity did not correlate with language lateralization, but rather with the degree to which the content of the hallucinations had a negative emotional valence. These findings appear to indicate that the main difference between the neural processes of AVH and normal inner speech is the lateralization of activity. AVH predominantly engage the right inferior frontal region, which may also account for the low semantic complexity and negative emotional content typically associated with AVH.

In sum, some variability exists in the particular brain regions identified by the different activation studies. It is likely that AVH recruit a distributed network of cortical and subcortical structures. Through methodological and sample variations, different studies may have exposed separate individual parts of this network. Some studies report activity in speech production areas, and others in speech perception areas, a minority including the primary auditory cortex. Most studies however do find that the temporal cortex, in particular the posterior superior and middle parts, is involved when subjects perceive hallucinated voices.

1.4.4.2.2. Cognitive interference studies

The rationale behind cognitive interference is that a decreased neural response to external (auditory-verbal) stimulation in hallucinating patients, compared to non-hallucinating patients, indicates that the same neurophysiological resources are addressed by the perception of hallucinations and by the perception of external ("real") stimuli. In its most simple version, external stimuli are presented in the same modality as the hallucinations experienced by the patient. David et al. (1996) studied one patient with AVH, and measured cortical activation in response to periodic exogenous auditory and visual stimulation. Functional brain images were obtained in each condition, both while the patient was on and off antipsychotic drugs. The response of the temporal cortex to exogenous speech stimuli was markedly reduced when the patient was experiencing hallucinating voices, regardless of medication. Visual cortical activation, however, was unaffected. This suggests that hallucinations coincide with activation of the sensory and association cortex, specific to the modality of the experience. Woodruff et al. (1997) confirmed these findings in a larger sample with different groups of subjects: eight currently asymptomatic patients with schizophrenia and a history of auditory hallucinations (trait-positive); seven patients without such a history (trait-negative); and eight healthy volunteers. In addition, seven patients with schizophrenia were examined on two occasions: while they were experiencing severe AVH and again after the AVH had remitted. Neural responses to external speech were diminished in the left superior temporal gyrus, but increased in the right middle temporal gyrus in the combined schizophrenia groups relative to the healthy controls. Thus, the trait-positive and trait-negative patients did not appear to differ in terms of brain response to external auditory stimuli. However, comparing patients in the hallucinatory state, to the remitted state, revealed that the neural response to external speech was reduced in the temporal cortex, especially the right middle temporal gyrus. These results suggest that speech perception may be abnormal in all schizophrenia patients, regardless of the predisposition towards hallucinations, but that the active hallucinatory state is particularly associated with reduced responsivity in temporal cortical regions, which normally process external speech. A more recent study (Plaze et al., 2006) also tested the hypothesis of an inverse relationship between the clinical severity of hallucinations and local brain activity during external speech processing. Fifteen right-handed patients with schizophrenia and daily AVH were studied with event-related fMRI while listening to spoken sentences. AVH severity indeed showed a negative correlation with activity in the left temporal superior cortex when patients were listening to sentences as opposed to silence, again supporting the idea regarding neurophysiological competition between AVH and external speech processing. There is also some evidence that not only perceptual areas show aberrant response patterns to external stimulation. Copolov et al. (2003) used PET to scan hallucinating, non-hallucinating patients and as healthy controls. Perception of externally speech was associated with a consistent pattern of extensive bilateral auditory cortex activation in non-hallucinating patients and healthy controls. Hallucinating participants also activated bilateral auditory cortex, but in addition showed activation in left limbic regions, right medial frontal and right prefrontal regions. The authors contend that this pattern of neural responses is consistent with the idea that AVH represent the activation of mis-remembered episodic memories of speech.

The above mentioned studies provide evidence in support of the idea that AVH are not simply externalized thoughts, but that they possess "sensory" qualities, as they activate brain areas involved in auditory perception. It is however unclear which processes are involved in the production of these aberrant perceptions. A number of studies have attempted to clarify this issue, by employing specific tasks that engage cognitive processes thought to be involved in AVH. These studies are designed to investigate the neural correlates of processes such as auditory imagery, inner speech, and self/source monitoring. In a PET study by McGuire et al. (1995) volunteers were asked to imagine speaking particular sentences in their own voice (inner speech task). Secondly, they were asked to imagine sentences spoken in another person's voice (verbal imagery task), which is thought to engage inner speech monitoring processes to a larger extent. The latter task was associated with reduced activation in the left medial temporal gyrus and the rostral supplementary motor area in patients with AVH, compared to non-hallucinating patients and controls. The authors concluded that a predisposition to AVH is associated with a failure to activate areas implicated in the normal monitoring of inner speech. In an analogous study using fMRI Shergill et al. (2001) schizophrenia patients with a history of prominent auditory hallucinations and a healthy control group were scanned while either generating inner speech or imagining external speech. Inner speech generation revealed no differences between the groups, but during verbal imagery patients with AVH did show an attenuated response in a distributed network of cortical and subcortical areas, including the posterior cerebellar cortex, hippocampi, lenticular nuclei, right thalamus, temporal cortex and left nucleus accumbens. These results were consistent with previous findings of reduced recruitment of inner speech monitoring regions, but suggested that a more distributed network may be involved. The same authors further investigated inner speech processing using a parametric design (Shergill et al., 2003). Subjects were trained to vary the rate of inner speech generation. When the rate of inner speech is increased, monitoring demands are thought to increase. Patients with schizophrenia and a history of prominent AVH showed a relatively attenuated response in the right temporal, parietal, parahippocampal and cerebellar cortex, compared to healthy controls, with increasing rate of inner speech. These findings were again interpreted as evidence for defective self-monitoring of inner-speech in patients experiencing hallucinations.

A small number of studies have directly addressed neural correlates of explicit source monitoring. McGuire, Silbersweig & Frith (1996) implemented a verbal self-monitoring task in a PET study with healthy volunteers. In the first condition volunteers were shown words and asked to read them aloud. In a second condition volunteers read the word silently, and the auditory feedback consisted of another person's voice. On half of all the trials the speech that the volunteers heard was distorted by elevating the pitch. The speaker's own distorted speech led to a bilateral activation of the lateral temporal cortex, with greater responses on the right. A similar pattern of activity was evident when the word they heard was spoken by someone else. These data suggest self generated and external speech are processed in similar regions of the temporal cortex. A subsequent fMRI study using the same task in a healthy control group confirmed these results (Fu et al., 2006). Furthermore, in this study the use of an event related design allowed correct and misattributed source judgments trials to be isolated and analyzed separately. Correct source attributions for self-speech were associated with greater temporal activation than misattributions, which supports the idea that a mismatch between expected (signaled via a feed forward signal and leading to a corollary discharge) and perceived auditory feedback leads to greater temporal activation. Allen et al. (2007) studied the neural correlates of source misattribution in patients with and without AVH, compared to healthy controls. All subjects underwent fMRI, while listening to pre-recorded words. The source (self/non-self) and acoustic quality (undistorted/distorted) of the auditory feedback were varied across trials. The hallucinating group made more external misattributions and showed altered activation in the superior temporal gyrus and anterior cingulate compared to both other groups. The authors suggest that these abnormal neural responses may be related to impairments in the explicit evaluation of ambiguous auditory verbal stimuli.

Few studies have paid particular attention to the content of the stimuli used in inner speech or self-monitoring experiments. However, hallucinations in psychotic disorders often have a distinct affective component, which suggests that it is pertinent to assess changes in the neuronal systems involved in emotion processing. A study by Sanjuan et al. (2007) evaluated neural responses to neutral and emotional words spoken by an actor, with affective prosody. The auditory paradigm was based on the most frequent words reported by psychotic patients with AVH. Cerebral activation was assessed with fMRI in 11 patients with schizophrenia with persistent hallucinations and 10 healthy subjects. Compared to controls, increased activity of the frontal lobe, temporal cortex, insula, cingulate, and amygdala (mainly right side) was observed in patients when listening to emotional words. These findings are consistent with other studies (Aleman & Kahn, 2005) suggesting a relevant role for emotional response in the pathogenesis of AVH.

1.4.4.2.3. Alterations in lateralization

There is a long-standing hypothesis regarding the etiology of schizophrenia, which posits that reduced language lateralization is responsible for a number of typical symptoms, including AVH. A major proponent of this view, Crow (1998) argues that symptoms of schizophrenia can be understood as a failure to establish language dominance in one hemisphere, with consequent disruption of the mechanisms that allow the speaker to distinguish thoughts from speech output. Several authors have asserted that AVH may arise from aberrant activation in the right hemisphere (Olin, 1999), a hypothesis that dates back to an influential book by Julian Jaynes (1979), "The origin of consciousness in the breakdown of the bicameral mind". Jaynes contended that in ancient times human behavior was controlled by a "bicameral mind", consisting of the left hemisphere as the site for speech, and the right hemisphere, which mediated supernatural voices of gods and demons (i.e. hallucinations). Over the course of human evolution the hemispheres became integrated, but the bicameral mind would still be reflected in mental disorders such as schizophrenia. Although some studies have observed either bilateral or right hemisphere activation during AVH (Lennox et al., 2000; Shergill, Brammer, Williams, Murray, & McGuire, 2000; Sommer et al., 2008b), many studies implicate typical left hemisphere language areas in AVH, which argues against Jaynes' hypothesis.

However, lateralization of language functions, does appear to be abnormal in schizophrenia (see Sommer, Ramsey, Aleman, Bouma, & Kahn, 2001, for a meta-analysis), and a specific link to AVH has been observed as well. Severity of AVH shows a negative correlation with language lateralization (Sommer, Ramsey, & Kahn, 2001). Consistent with this, a study by Weiss et al. (2006) has also implicated aberrant asymmetry in AVH. During performance of a verbal fluency task, patients with schizophrenia showed reduced language lateralization in the frontal cortex, due to a more bilateral activation of Broca's area compared to primarily left hemisphere activation in healthy controls. The decrease in lateralization was correlated with the severity of AVH. Stephane et al. (2006) used PET to scan eight patients with AVH , ten patients without AVH, and twelve healthy controls under different conditions: reading aloud English nouns and passively looking at English nouns. Reading aloud, compared to passive viewing was characterized by a reversed laterality index for the supplementary motor area in the group of patients with AVH. The authors suggest that this abnormal lateralization of brain activity may account for the failure to attribute speech generated by one's own brain to one's self. Angrilli et al. (2009)

tested twelve schizophrenic patients treated with low levels of neuroleptics and twelve matched healthy controls in an Event-Related Potential (ERP) study. Subjects were required to match pairs of words in three tasks: phonological, semantic judgment and word recognition. Slow evoked potentials were recorded from 26 scalp electrodes, and a laterality index was computed for anterior and posterior regions during the inter stimulus interval. During phonological processing individuals with schizophrenia failed to achieve the left hemispheric dominance in anterior brain regions consistently observed in healthy controls. This study suggests that the deficit of lateralization in the schizophrenic brain is specific for the phonological component of language. This loss of hemispheric dominance would explain typical symptoms, e.g. when an individual's own thoughts are perceived as an external intruding voice.

1.4.4.2.4. Studies on anatomical and functional connectivity

Although a number of neuroimaging studies have taken a localized approach to AVH, attempting to link the occurrence of hallucinations to abnormal activity in particular brain regions (e.g. superior temporal cortices involved in speech perception), recent models of schizophrenia favor a conception of the disorder in terms of a failure to integrate activity across distributed neural circuits (Andreasen et al., 1999; Stephan, Baldeweg, & Friston, 2006; Stephan, Friston, & Frith, 2009; Zhou et al., 2008; Liang et al., 2006). McGlashan & Hoffman (2000) for instance, formulated a pathophysiological model referred to as 'developmentally reduced synaptic connectivity'. This model posits that schizophrenia arises from critically reduced synaptic connectedness as a result from developmental disturbances of synaptogenesis during gestation and early childhood, and a failure in synaptic pruning during adolescence.

Advances in neuroimaging methods now allow detailed imaging of white matter tracts connecting spatially distinct brain regions, e.g. by means of Diffusion Tensor Imaging (DTI). DTI assesses the directionality of water diffusion (anisotropy), which is restricted by boundaries such as white matter fibers. Reduced anisotropy implies a loss of white matter integrity. Hubl et al. (2004) investigated integrity of white matter tracts in the brains of schizophrenia patients with and without AVH and a healthy control group. Patients with AVH had significantly higher anisotropy values relative to both control groups in the lateral temporo-parietal section of the arcuate fasciculus. This white matter tract connects frontal language production areas (e.g. Broca's area) with temporal auditory perception areas. The authors speculate that enhanced connectivity between these areas in patients with hallucinations may lead to dysfunctional coactivation of brain regions involved in acoustical processing of external stimuli. Another DTI study (Shergill et al., 2007) assessed integrity of the major white matter fasciculi connecting frontal, temporal and parietal cortices, as well as the corpus callosum which connects the two hemispheres. Across the entire group of patients there was reduced anisotropy in regions corresponding to the longitudinal fasciculi bilaterally and in the genu of the corpus callosum. However, within the group experiencing AVH, the propensity to hallucinate was related to relatively increased anisotropy in the superior longitudinal fasciculi and in the anterior cingulum, leading to the conclusion that schizophrenia is associated with altered white matter integrity in the tracts connecting the frontal cortex with the temporal and parietal cortices and with the contralateral frontal and temporal lobes. The severity of these changes may vary with the pattern of symptoms associated with the disorder.

Seok et al. (2007) obtained DTI scans and structural MRI scans from schizophrenia patients with and without AVH, and a healthy control group. The three groups were compared on fractional anisotropy derived from DTI as well as white matter density derived from structural MRIs. In both the hallucinating and non-hallucinating groups, anisotropy of the white matter regions was significantly decreased in the left superior longitudinal fasciculus, whereas white matter density was significantly increased in the left inferior longitudinal fasciculus. AVH severity correlated positively with the mean anisotropy value of the left frontal part of the superior longitudinal fasciculus in the hallucinating patient group. The findings show that white matter changes were mainly observed in the frontal and temporal areas, suggesting that disconnectivity in the left fronto-temporal area may contribute to the pathophysiology of schizophrenia. Pathologic white matter changes in this region may also be an important step in the development of auditory hallucinations in schizophrenia. A study by Lee et al. (2009) conducted the first investigation of altered structural integrity in gray and white matter of the superior temporal gyrus (STG) in patients with chronic schizophrenia compared with healthy controls. MRIs and DTI were acquired in the two groups of subjects. Mean diffusivity and fractional anisotropy were measured within STG and correlational analyses were conducted to assess possible associations between DTI and clinical measures. Compared with controls, patients demonstrated reduced volume in bilateral STG gray matter, but not in white matter. For DTI measures, patients showed increased mean diffusivity, in bilateral STG gray matter, and in left STG white matter. In addition, mean diffusivity in left STG white matter was significantly correlated with auditory hallucinations and attentional impairments in patients. These findings suggest a disruption of tissue integrity in STG gray and white matter in schizophrenia. In addition, increased water diffusivity in left STG, which was associated with auditory hallucinations and attentional impairments, suggests the possibility of a disconnection among auditory/language processing regions.

In addition to DTI studies, which describe anatomical connectivity, a number of reports are available on functional and effective connectivity, derived from fMRI data. Functional connectivity refers to covariation of neural responses over time between spatial remote brain regions, without making inferences with regard to the direction of the effect (Friston, Frith, Liddle, & Frackowiak, 1993). Studies of effective connectivity on the other hand aim to indicate the contributory influence of each region on another (Friston, Frith, Fletcher, Liddle, & Frackowiak, 1996; Bullmore et al., 2000). Schizophrenia with AVH appears to be characterized particularly by a disintegration of fronto-temporal connections. Disturbances in connectivity have been reported during a sentence completion task (Lawrie et al., 2002), in association with misattributions of speech stimuli (Mechelli et al., 2007), and during verbal working memory (Hashimoto, Lee, Preus, McCarley, & Wible, 2009). Recently, abnormal patterns of connectivity have also been observed in schizophrenia patients during the resting state (Zhou et al., 2008; Liu et al., 2006; Liang et al., 2006). This default mode of the brain is considered to reveal intrinsic activity involving self-referenced processing. It has been suggested that this intrinsic activity may be at least as important as evoked activity in terms of overall brain function (Raichle & Gusnard, 2005). However, it is unclear whether specific changes in the resting state can be linked to particular symptoms.

AVH are inherently complex, involving perceptual, attentional, cognitive control, affective and memory processes, and accordingly recruit a distributed network of brain regions. Further development of methods for the investigation of structural and functional integration of language, emotion and attention networks will therefore be crucial to the understanding of the neural substrate of this intriguing phenomenon. Specifically, the combination of different imaging methodologies in the same subjects could be informative. For instance, the higher temporal resolution of EEG could shed some light the sequence of processes involved in the production of AVH, whereas fMRI measured concurrently could clarify the spatial origin.

1.4.5. Treatment of AVH

A number of treatments are available for the management of AVH. At this time, the primary treatment usually consists of pharmacological intervention. Antipsychotics (also known as 'neuroleptic drugs', literally meaning 'to take hold of one's nerves') are a group of psychoactive compounds that are largely effective in treating acute psychosis, and preventing relapse. The first antipsychotic drugs were happened upon largely by chance and were subsequently tested empirically for their effectiveness. Chlorpromazine, the first antipsychotic, was originally intended as a surgical anesthetic. It was used in psychiatric patients because of its powerful calming effect. Over time, a wide range of compounds have been developed. The first generation of drugs, now known as "typical" antipsychotics, was discovered in the 1950s. Most of the drugs in the second generation, now known as "atypical" antipsychotics, have been developed more recently. However, the first atypical anti-psychotic, clozapine, was actually discovered in the 1950s, but introduced clinically in the 1970s. Both classes of medication tend to block dopamine D2 receptors in the brain, but antipsychotic drugs encompass a wide range of receptor targets, and the newer drugs tend to have more diverse receptor profiles, additionally targeting serotonergic and/or GABA-ergic neurotransmission. Compared to the typical drugs, the second generation antipsychotics are reported to be more efficient in the treatment of negative symptoms, and seem to cause fewer undesired side effects (Stip, 2000), but do not necessarily lead to better management of positive symptoms. A third generation of antipsychotics has now seen the light, with the production of aripiprazole, which is a partial D2-agonist. At low dopamine levels, a partial agonist will stimulate dopamine receptors, and at high dopamine levels a partial agonist will inhibit dopamine receptors, which may serve to stabilize the dopamine imbalance associated with schizophrenia (Stahl, 2001a; 2001b).

Pharmacotherapy has its limitations, as it was shown that in a significant number of patients symptoms persist to a certain extent. It has been estimated that between 10% and 60% of patients who adhere to treatment continue to experience psychotic symptoms (Curson, Patel, Liddle, & Barnes, 1988). In hallucinations, evidence suggest that in 25 to 50% of cases, the symptoms are not managed fully, even in face of adequate levels of medication (Pantelis & Barnes, 1996). Furthermore, pharmacotherapy is complicated by non-compliance. A meta-analysis of studies examining medication non-adherence in patients with schizophrenia reported a rates of 41% to 50% (Lacro, Dunn, Dolder, Leckband, & Jeste, 2002). One of the reasons for this non-compliance is the association of antipsychotics with important and potentially grave side effects, including weight gain and diabetes, agranulocytosis (an acute condition involving potentially lethal leucopenia associated with clozapine), extrapyramidal reactions, such as tardive dyskinesia (involuntary, repetitive movements), Parkinsonian symptoms, tachycardia and hypotension, and a decreased subjective wellbeing. All of this suggests that adjunctive treatments are warranted in the management of psychotic symptoms.

Transcranial magnetic stimulation (TMS), in particular repetitive TMS potentially provides such an additional treatment strategy for patients with medication resistant hallucinations. In TMS, a magnetic field is generated by a very short current pulse sent through a coil of wire. The stimulator coil is placed over a certain scalp position, and the magnetic field passes unimpeded through the skull, inducing a current in the underlying brain tissue, which results in neuronal membrane depolarization and neural activation (Pascual-Leone, Davey, Rothwell, Wassermann, & Puri, 2002).

Repetitive TMS then refers to the application of series of pulses at particular frequencies. At a frequency of 1 Hz or less, rTMS has inhibitory effects on cortical signal transmission. At higher frequencies of 5 Hz or more, rTMS has excitatory effects. The rationale in rTMS application in AVH is that hallucinations derive from overactivation of posterior temporal speech processing regions of (mainly) the left hemisphere. Hoffman et al. (2000) published the first report in this regard, finding a significant reduction in AVH after rTMS treatment, compared to sham stimulation, in a crossover design study in 12 patients with schizophrenia. Aleman, Sommer & Kahn (2007) recently conducted a meta-analysis of studies applying 1 Hz rTMS in the treatment of hallucinations in a randomized, placebo controlled design. The majority of studies employed very similar parameters: rTMS was focused mainly on the left temporo-parietal junction, with intensities of 80 to 100% of the resting motor threshold. Durations of the rTMS sessions and the total treatment varied somewhat, but were mostly confined to 15 to 20 minutes daily over a period of 4 to 10 days. The meta-analysis revealed a mean effect size of .76, providing rather compelling evidence of the efficacy of this treatment in reducing AVH severity. Another meta-analysis on the application of TMS in both negative and positive symptoms in schizophrenia confirmed the previous finding of a large and significant effect size in the treatment of AVH (Freitas, Fregni, & Pascual-Leone, 2009). Interestingly, the rTMS effect appears to be restricted to hallucinations and does not generalize to other positive symptoms or general psychopathology. Although rTMS is a promising technique, a number of unresolved issues need to be addressed. The mean effect sizes reported in both meta-analyses are impressive, but still not all studies report uniformly positive effects compared to sham stimulation (e.g. see Fitzgerald et al., 2005; Lee et al., 2005; McIntosh et al., 2004; Saba et al., 2006). Variations in treatment response could be due to significant interindividual variability in the neural substrate of AVH. Neuroimaging studies in fact point to the involvement of a network of speech, emotion and memory related processing regions in AVH. A potential solution to this issue is the application of individually tailored fMRI-guided rTMS. Areas of significant activation are first identified on individual fMRI scans, and neuronavigation may be employed to target specific brain regions showing hallucination-related activity.

However, Sommer et al. (2007) did not find that this particular strategy improved rTMS treatment efficiency when compared to the traditional method of coil positioning based on the 10/20 international EEG positions. Jardri, Pins, Delmaire, Goeb & Thomas (2007) report a case study of an 11-year old boy with treatment-resistant AVH. fMRI guided rTMS of the left temporo-parietal area resulted in a significant improvement of his symptoms. A problem with this approach is that it is only applicable in a limited number of patients, as the determination of fMRI activation patters associated with AVH requires discrete AVH epochs and non-AVH epochs during the approximately 1 hour scan session. A more general limitation of all rTMS studies is that neither the cognitive nor the neural basis of the rTMS effect is well understood.

In contrast to these more biologically oriented treatment strategies involving direct of indirect interventions at the level of neurotransmission, in recent years, it has become clear that psychological approaches may also be effective in the treatment of several symptom dimensions in patients with schizophrenia. For AVH in particular, three strategies have proven efficiency: (1) distraction or counter-stimulation, (2) focusing/concentrating on the AVH, and (3) cognitive behavior therapy.

Exemplifying the first strategy, reading out loud seems to (temporarily) suppress the experience of hallucinated voices. Many patients notice that watching TV may have the same effect, potentially because these activities occupy the same cognitive resources as those responsible for the genesis of AVH. Such coping strategies tend to develop naturally in the majority of patients (Nayani et al., 1996; Carter, Mackinnon, & Copolov, 1996). The second strategy encourages the patient to focus on the AVH, and at the same time label to "voices" as non-real. Slade & Bentall (1988) remarked that this focusing probably works because the patient learns to identify the sensory characteristics associated with internally generated events, compared to external ones. Additionally, the conscious labeling of the experience as non-real may serve alter perceptual expectations, such that ambiguous sensory experiences are less likely to be observed as having an external origin. From a number of meta-analysis it has become clear that cognitive behavior therapy (CBT) is effective in alleviating positive psychotic symptoms (e.g. see Dickerson, 2000; Garety, Fowler, & Kuipers, 2000) . The general aim of CBT is to reduce distress, disability and emotional disturbance caused by the symptoms, and to assist the patient in arriving at an understanding of psychosis, in order to promote active participation in the prevention of relapse. Cognitive behavioral techniques are employed to question the patients' beliefs with regard to malevolence, power and omnipotence of the hallucinated voices. When patients attain a more indifferent attitude toward their AVH, associated anxiety and feelings of depressions diminish, improving daily global functioning, even though the AVH itself do not necessarily disappear (Valmaggia, van der Gaag, Tarrier, Pijnenborg, & Slooff, 2005). Group therapy has the additional advantage that patients, who are often socially isolated and experience feelings of loneliness, are encouraged to share their experiences with others, observe that their symptoms are mirrored in others with the same condition and may share intuitive coping strategies (Wykes, 2004). A recent study employing a randomized controlled trail design showed that although no effect was seen on the general severity of hallucinations, this form of therapy led to significant improvement in social functioning 6 months post treatment (Wykes et al., 2005). Hallucination-focused-Integrative Treatment (HIT) deserves a particular mention in this regard. This approach uses multiple modalities to maximize control of persistent AVH, combining CBT with supportive counseling, psychoeducation, training in coping strategies, crisis intervention and pharmacotherapy (Jenner, 2002). The intervention covers 20 sessions, over the course of a 6 to 12 month period. Several studies provide evidence for the efficiency of this integral approach in chronic patients (Jenner, Nienhuis, van de, & Wiersma, 2006), as well as adolescents with psychotic symptoms (Jenner & van de Willige, 2001). Effects lasted for up to 18 months.

2. *Perspective of the current thesis*

Hallucinations are a relatively common and very variable phenomenon, occurring in a multitude of forms, modalities and situations, and may or may not be indicative of pathology. The current thesis will focus on one type of hallucinations, namely, auditory-verbal hallucinations (AVH) in the context of schizophrenia. AVH are a characteristic and particularly ubiquitous phenomenon in this disorder. The study samples in the reported experiments thus mostly consist of patients with a diagnosis of schizophrenia. As mentioned earlier, however, the study of otherwise healthy individuals with a proneness towards hallucinations can be particularly informative. Investigations in healthy subjects are not hampered by potential confounding variables related to the disease process, such as general cognitive deficits, effects of medication, effects of hospitalization, etc. The underlying mechanisms are nevertheless thought to be similar, implying that investigations in clinical and non-clinical groups are complementary and may give a more thoroughgoing explanation of the precursors of AVH.

As reviewed above, a body of research exists on the putative causes and processes involved in hallucinations. However, in the literature no general consensus exists with regard to the psychological, cognitive and (neuro-)physiological mechanisms of AVH. Although most researchers will agree that AVH represent internally generated events that are somehow misattributed to an external source, often acquiring particular attentional and affective salience, it is unclear just how this takes place, although a number of candidate processes have been put forward in the past, including defective self-monitoring, failing working memory, etc. (cf. supra). Findings from neuroimaging teach us that AVH are accompanied by activation in relevant sensory cortices, as well as brain regions involved in attention, memory, and emotion. Whether these aberrant neural processes are causative towards AVH is nevertheless unclear. Furthermore, AVH are complex cognitive-perceptual events and most likely not to be traced back to a single neurophysiological deficit in a particular brain region, but linked to dysfunction in a network of interrelated neural processes.

3. Overview and rationale of the experiments

In this thesis, auditory-verbal hallucinations were investigated on different levels of explanation. The first part of the empirical studies focuses on *cognitive* processes thought to contribute to the genesis of AVH. In particular, AVH are hypothesized to relate to an imbalance in the normal processes involved in (speech) perception. When top-down influences, such as perceptual expectations take precedence over bottom-up inputs, particularly in the case when the input is degraded or ambiguous, subjective perceptions may arise that are uncoupled from reality. In **Chapter 4.1.** this hypothesis was tested in a sample of university students with differing scores on a questionnaire polling the experience of hallucinatory phenomena. Semantic expectations were induced by manipulating sentence context, and the influence of these expectations on subsequent auditory perception of words in acoustic noise was tested. In **Chapter 4.2.** the influence of top-down processes on perception was again tested, this time in a sample of patients with schizophrenia, with and without auditory-verbal hallucinations, in comparison to healthy, matched controls. In this speech discrimination task, the top-down influence was established on the level of phonological, rather than semantic processing. Participants had to decide whether a particular spoken word was identical to a previously presented speech stimulus, embedded in noise. Signal Detection Theory was employed on the data to reveal the underlying cognitive processes, which makes it possible to distinguish between deficits in perception and biases in responding.

In the second part of the empirical studies neuroimaging methods were employed to elucidate the neural underpinnings of cognitive processes involved in AVH. In **Chapter 5.1.** structural abnormalities in the inner speech processing network were assessed. The literature suggests that there are abnormalities in this network, both in terms of function and structure. Regional volumes and covariation between regional volumes in separate brain areas were investigated using Voxel-based morphometry (VBM), and were correlated with severity of AVH in a sample of patients with schizophrenia. **Chapter 5.2.** describes a functional magnetic resonance (fMRI) study utilizing a Region-of-Interest approach to assess the relationship between perceptual characteristics of AVH and activity in brain regions associated with (inner) speech processing. Patients with schizophrenia and AVH performed a metrical stress evaluation task during fMRI, which is a task requiring the production of a words' phonological code and the assessment of its sound characteristics, and filled out self-report questionnaires on the perceptual characteristics of their hallucinations. It was hypothesized that if inner speech is involved in the production of AVH, activity in know speech processing regions should correlate with the subjective characteristics that impart the perceptual quality of AVH , such as “loudness” and “sense of reality”.

Although cognitive and neuroimaging studies have the potential to reveal processes that are related to AVH, the direction of the relationship is unclear, and the question remains whether the link is really causal. It could be that aberrant processes such as increasing reliance on top-down processes, or deficits in inner speech processing, arise from continuous abnormal, or unreliable perceptual experiences. Transcranial magnetic stimulation (TMS) is a technique that employs magnetic stimuli to either interfere with or stimulate neural activity in the cortex of the wakeful subject. As it allows direct interference with ongoing neural processes, it becomes possible to make causal inferences with regard to the role of the targeted brain area. **Chapter 6.1.** reports on a randomized controlled trial, in which 1 Hz repetitive TMS was applied to the temporo-parietal cortex of patients with medication resistant AVH. This area has been identified in previous neuroimaging studies to be hyperactive during the experience of AVH. Repetitive TMS, at frequencies of 1 Hz or less, has inhibitory influences on the underlying cortex, suggesting a potential therapeutic effect against this pathological hyperactivity. This study extended the existing literature on the effects of rTMS by including a treatment condition, in which the bilateral posterior superior temporal cortices were targeted by rTMS in the same session. The accompanying hypothesis is based on the evidence of decreased cerebral lateralization in schizophrenia, and accumulating evidence that the right hemisphere might have an important role in the non-linguistic aspects of speech/language processing, such as prosody perception, non-literal meaning and emotional significance. Therefore, targeting this hemisphere along with the traditional language areas of the left hemisphere was thought to lead to a more complete management of the AVH symptom, by influencing non-linguistic and emotional aspects of the experience. Outcome of the treatment consists of both clinical ratings and self-reported changes in AVH severity on a number of scales, polling perceptual and emotional characteristics of the AVH, as well as (delusional) belief systems regarding the hallucinated voices. In the final empirical **Chapter 6.2.**, results are reported from a subset of patients participating in the rTMS trial, who completed fMRI measurements before and after the treatment. rTMS may have effects locally, on the site of stimulation, which in this case consists of the left or bilateral temporo-parietal junction. However, rTMS may also affect distal brain regions because they are functionally connected. The goal of this study was to first identify patterns of functional connectivity associated with AVH, and then to assess the potential of rTMS to induce changes in the connectivity of the stimulated brain area. Subjects underwent an fMRI scan during the resting state before and after rTMS treatment. Changes in functional connectivity have previously been established in schizophrenia during task performance. The resting state on the other hand is characterized by default mode neural activity that is not evoked by a particular task, and is hypothesized to relate to self-referenced processing. Functional connectivity in this state could be affected by ongoing AVH activity, and rTMS may interfere with these processes.

Finally, the third part of this thesis provides a summary and discussion of the empirical findings described in this thesis. Critical reflections on the methods and suggestions for future research are postulated.