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Treatment-refractory auditory verbal hallucinations in patients with schizophrenia – Neurofunctional correlates of attention and working memory

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I want to thank everybody who was involved in the process of writing this doctoral thesis.

I dedicate this doctoral thesis to my family.

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"Eugen Bleuler (who in 1911 coined the word 'schizophrenia') once said that in the end his patients were stranger to him than the birds in his garden. But if they're strangers to us, what are we to them?" (Greenberg, 2009)

1 Introduction

Evidence from the Global Burden of Disease Study in 2010 suggests that schizophrenia, especially in its acute form, is one of the top ten public health concerns and the mental illness with the highest disability weights world-wide (Salomon et al., 2012). The introduction of antipsychotics during the '50s of the last century contributed significantly to the reduction of acute symptoms as well as to the prevention of relapses (Leucht et al., 2012). About 70% of patients with schizophrenia in the acute phase of illness show remission of positive symptoms (Dixon, Lehman, & Levine, 1995). The WHO concludes that antipsychotic drug treatment is highly effective in reducing positive symptoms in schizophrenia, while negative symptoms commonly remain unchanged (Barbato, 1998), leaving behind patients that do not benefit from antipsychotic drug treatment. Those so-called 'non-responders' do not achieve recovery or remission and are left with residual symptoms of significant functional relevance. Looking closer at responders vs. non-responders, the extant evidence suggests limited therapeutic effects of antipsychotics to positive symptoms such as delusions, hallucinations, and thought disorder in a substantial proportion of patients (Crow, 1980; Falkai et al., 2015). However, although positive symptoms better respond to medication, in approximately 25-30% positive symptoms prevail and thus become treatment-resistant and persistent. Keefe et al. (1987) point to exactly those cases of chronic schizophrenia that create great social burden and economic cost. They report for 1983 that although only 5% of the psychiatric population were patients with schizophrenia, they accounted for almost one third of the total social expenditure of mental illness.

Among positive symptoms, auditory verbal hallucinations (AVH) are one of the most common and characteristic symptoms of schizophrenia as approximately 50% of patients diagnosed with schizophrenia experience life-time AVH (Vauth & Stieglitz, 2007). Again, a subgroup of 25-

30% experiences chronic AVH despite antipsychotic medication. Treatment-refractory AVH are associated with enormous distress and high risk of suicide (Falloon & Talbot, 1981). It may lead to severe functional impairment, feelings of hopelessness and powerlessness, self-harm and substance misuse (Mind in Camden, 2012).

Since the last decade research has focused on early manifestations and disease process despite the subgroup of chronic voice-hearers whose therapy refraction causes major distress and affects their lives substantially (Vauth & Stieglitz, 2007). It should, therefore, be clear that treatment-refractory AVH are highly in need of fundamental research. To date, the underlying mechanism and pathophysiology of the phenomenon are still largely unknown. So far, the neuroscientific state of evidence regarding AVH in schizophrenic patients points to morphological changes and abnormal network connectivity in the brain. Multiple neuronal systems seem to be involved, i.e., networks that essentially subserve language, attention, and executive control (see chapter 2.2.2 on neurobiological abnormalities). To achieve a comprehensive understanding a combination of detailed registration of clinical symptoms as well as multimodal structural and functional neuroimaging is mandatory. Therefore, the present thesis used a combined approach to record functional resting-state networks (RSN) as well as experimentally activated neuronal systems to investigate a potential association between functional neuroimaging data, clinical symptoms, and specific cognitive processes.

The aim of the present thesis is to link the field of neurobiology with (neuro-)psychology thereby closing knowledge gaps with respect to AVH in patients suffering from schizophrenia. As outlined above, there is a clear need for a better understanding of causal mechanisms to translate this knowledge into improved treatment interventions. I would like to share my work and findings with the interested reader outside the academic context as well. Therefore, I will consider the technical terms as demanded by scientific convention and discourse as well as the

requirements of a doctoral thesis. However, by doing so, I nevertheless want to balance appropriate use of technical terms with simple expression.

For clinical information and diagnostic criteria, the present study relies on the ICD-10 published by the WHO. The ICD-10 is used internationally and represents the most important guide for classification and diagnosis of (mental) illnesses in Germany. Furthermore, it must be noted that the following discussion regarding hearing voices refers to AVH in the course of a schizophrenic disorder. AVH are phenomena that can occur in up to 15% of the healthy population throughout lifetime according to the Continuum Model of Psychosis (Badcock & Hugdahl, 2012). However, research data suggests significant differences between AVH heard by healthy individuals compared to those experienced by patients with schizophrenia, e.g., frequency, valence, and sense of control (Honig et al., 1998; Powers, Kelley, & Corlett, 2017). Therefore, the discussion is limited to the latter.

If not mentioned otherwise explanations apply both to males and females.

2 Theoretical and empirical background

The intention of the present thesis is to elucidate the neuroscientific knowledge gap regarding AVH in patients suffering from schizophrenia. Therefore, the undertaken study is to be classified as fundamental research aiming to link functional neuroimaging data with clinical symptoms and specific cognitive processes. This chapter reviews the theoretical and empirical background and serves as a guide for the interested reader. First, schizophrenia as mental disorder is specified in detail including core symptoms, disease course and impact, followed by explanatory models to provide a common understanding. Subsequently, the focus shifts to AVH in schizophrenia describing known neurobiological deficits and related cognitive models. Thereafter, currently recognized and scientifically validated treatment options for hallucinations are presented. The theoretic framework concludes with the derived research questions to be answered and corresponding hypotheses.

2.1 Schizophrenia

The World Health Organization (WHO) defines schizophrenia as a heterogeneous and severe mental disorder that is characterized by a varying degree of dysfunction in cognition, perception, affect, motivation as well as the sense of self (2016). Most prominent are psychotic experiences, such as hearing voices or delusions, which may result in the inability to grasp the extent of reality and may thus lead to depressive and anxious symptoms and concurrent behavior such as social withdrawal and self-neglect. Associated malfunctions include concentration and attention, content and formal thought, perception, intentionality as well as emotions and psychomotility (Falkai, 2008).

In the acute stage of illness patients often lose touch with reality, the ability to reason, and the ability to cope with the requirements of everyday life (Bäuml, 1994). Acute illness severity is

associated with poor insight, i.e., schizophrenic patients often are entirely controlled by their abnormal and pathological perceptions (Klaas et al., 2016). By the time the psychotic experiences recede insight is most often regained (Jorgensen, 1995). Normally, consciousness is unaffected as well as the general intellectual ability despite potential cognitive deficits (World Health Organization, 2013). In accordance with that, the extant evidence does not clearly suggest progressive decline in neuropsychological abilities but rather certain deficits in cognitive functioning as trait-marker (Özgürdal & Juckel, 2008).

The following Table presents the diagnostic criteria formulated by the WHO. These are the criteria used in clinical practice internationally as well as in the process of study inclusion and validation of diagnosis. As a side note should be mentioned that the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association (APA) and the International Statistical Classification of Diseases and Related Health Problems (ICD) by the WHO hold comparable diagnostic criteria for the diagnosis of schizophrenia (Jansson, Handest, Nielsen, SÆbye, & Parnas, 2002). The difference in time criterion between ICD-10 (1 month) and DSM-IV (6 months) still results in high concordance between the two diagnostic systems (Jansson et al., 2002; Wciorka et al., 1998). With the development of DSM-5 came three changes whose impact on clinical practice seems to be negligible, too: (1) two Criterion A symptoms are required instead of one, (2) one of them having to be hallucinations, delusions or disorganized speech, and (3) the subtypes were eliminated (Tandon, 2014). The diagnostic criteria proposed by the WHO use the patient's self-reported symptoms as well as clinical evidence established by a mental health professional through detailed history taking, psychopathological assessment and clinical observation.

Table 1

General criteria for schizophrenia

F20.0- F20.3 General criteria for schizophrenia of the subtypes paranoid, hebephrenic, catatonic, and undifferentiated

G1. The normal requirement for a diagnosis of schizophrenia is that a minimum of one very clear symptom (and usually two or more if less clear-cut) belonging to any one of the groups listed under 1. or symptoms from at least two of the groups referred to as 2. should have been clearly present for most of the time during a period of 1 month or more.

1. At least one of the following characteristics:
    a. Thought echo, thought insertion or withdrawal or thought broadcasting
    b. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception
    c. hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body
    d. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);

2. *Or* at least two of the following characteristics:
    a. Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end.
    b. breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms
    c. catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
    d. "negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication;

G2. Exclusion criteria

1. If patients meet criteria for a manic episode (F30) or a depressive episode (F32), too, criteria listed under G1.1. and G1.2. need to be emerged previously.
2. The disorder cannot be attributed to an organic brain disorder (in the sense of F00-F09) or an alcohol- or substance intoxication (F1x.0), an addiction disorder (F1x.2) or a withdrawal syndrome (F1x.3, F1x.4).

Note. Derived from ICD-10 English version (World Health Organization, 1992), rearranged meeting the outline of the German version (World Health Organization, 2013)

Those unfamiliar with schizophrenia often use various related concepts synonymously that share similar symptoms or the same word stem providing the possibility of confusion. Therefore, to clearly distinguish related terms, those must be defined properly:

- **Psychosis.** Any severe mental illness characterized by impairment in reality testing, often featuring delusions and hallucinations. The term psychosis is often used synonymously with schizophrenia. However, psychosis is an umbrella term for all psychotic disorders of which schizophrenia is one (Bäuml, 1994).
- **Paranoia.** A mental illness that is characterized by delusions of persecution; another name for delusional disorder (Colman, 2006).
- **Schizophreniform disorder.** A mental illness with psychotic symptoms meeting the criteria for schizophrenia but not meeting the time criterion of symptoms being present at least 1 month (Colman, 2006; World Health Organization, 2013).
- **Schizoaffective disorder.** A mental illness with episodes of simultaneous affective and psychotic symptoms that are both clinically relevant (World Health Organization, 2013). Due to its high overlap with affective disorders as well as schizophrenia its reliability is subject to ongoing debate (Santelmann, Franklin, Busshoff, & Baethge, 2015).
- **Paranoid personality disorder.** A personality disorder characterized by an enduring mistrust, exaggerated sensitivity to insult, and the tendency to twist the seen and experienced into hostile and threatening constructions. The consequence is often quarrelsome behavior in order to carry their point and have their will (World Health Organization, 2013).
- **Schizotypal personality disorder.** A personality disorder characterized by an enduring pattern of eccentric behavior as well as thought disorders and perceptual distortions similar to those seen in schizophrenia, often accompanied by a tendency to social withdrawal with marked discomfort in close personal relationships. Criteria for schizophrenia must not have been fulfilled at any time (Colman, 2006; World Health Organization, 2013).
- **Schizoid personality disorder.** A personality disorder characterized by an enduring and unambiguous lack of need and desire for close personal relationships. Persons concerned

have a preference for fantasy and solitary behavior and show a restricted range of emotional expression and in experiencing happiness (Colman, 2006; World Health Organization, 2013).

2.1.1 Clinical core symptoms

As mentioned previously, schizophrenia is a very heterogeneous disorder with great variability in symptoms. That is, two patients suffering both from schizophrenia may vary substantially in symptom patterns.

Schizophrenia symptoms can be grouped into three categories: positive symptoms, negative symptoms, and cognitive symptoms.

Positive symptoms

Positive symptoms are thought to occur in addition to or as an exaggeration of normal thoughts and perceptions. Such symptoms predominate in the acute phase of the illness. In general, they respond effectively to antipsychotic medication. For a substantial proportion of patients, however, positive symptoms persist over time and thus become chronic. Positive symptoms include thought disorder, behavioral agitation, delusions, hallucinations, self-disturbance, passivity and alien control phenomena (Bäuml, 1994).

Negative symptoms

The term ’negative symptoms’ indicates that there is a kind of deficiency in behaviors that are normally present in the general population as well as in the affected individual in a healthy condition. They can be thought of as an impairment in ‘normal experiencing’ that was available prior to the illness. For the most part negative symptoms occur during prodrome or remission but may also be present simultaneously with positive symptoms. Negative symptoms include

emotional blunting, incongruity of emotional responses, paucity of speech, lack of motivation, and social withdrawal.

Cognitive deficits

In a recent article reviewing research findings regarding cognitive impairment in schizophrenia Keefe and Harvey (2012) outline that "although cognition is not a formal part of the current diagnostic criteria for schizophrenia [and therefore neither a positive nor a negative symptom][…][it] is a core feature of the illness and not simply the result of the symptoms or the current treatments of schizophrenia" (p. 12). Reports show that as many as 75-80% of schizophrenic patients have cognitive deficits that exceed clinical significance (Keefe et al., 2004). The individual cognitive profiles, however, seem to be very heterogeneous (Pfueller, Roesch-Ely, Mundt, & Weisbrod, 2010). They concern various cognitive domains with prominent deficits found in higher-order cognitive domains such as executive functioning, memory (short-term, long-term as well as working memory) and learning, as well as lower-order cognitive functions such as attention and speed of processing (Reichenberg et al., 2009). Cognitive deficits are "present at the beginning of the first psychotic episode, […] are stable over time, largely independent of positive symptomatology, and partly independent of medication treatment" (Frommann et al., 2011, p. 862). A reduction in cognitive capacity is even present in patients before the initial manifestation of psychotic symptoms (Pfueller et al., 2010).

2.1.2 Epidemiology and disease course

The WHO (2016) estimates a lifetime prevalence of schizophrenia of 1% and about 29 million affected individuals worldwide. Schizophrenia typically begins in late adolescence or early adulthood, first onset mostly developing between puberty and the age of 35 (Falkai et al., 2015). A second peak incidence affecting roughly 25% of patients is to be found at the age of 40-50

and called late onset (Eissa, Hassan, Hwedi, & Khalil, 2013). Schizophrenia affects both women and men equally (Hahlweg & Dose, 1998), however, men fall ill earlier in comparison to women (Bäuml, 1994). That is, men show the peak incidence in the early twenties while women have it in their late twenties (Barbato, 1998; Hahlweg & Dose, 1998).

Disease onset can be acute and very dramatic in which psychotic symptoms develop within days or weeks, but more often it is a much more subtle and longer-lasting, on average five years, gradual process of prodromal phase with unspecific symptoms that precede the overt psychotic illness (Gaebel & Wölwer, 2010). Those prodromal symptoms vary between individuals and may include reduced concentration and attention, social withdrawal, neglect of body hygiene, and inflated mistrust (Rodewald, 2010) as well as increased noise sensitivity, general restlessness and nervousness, sleeplessness, irritability, loss of interest, and depression (Bäuml, 1994). They cause high distress in early/acute stages of disease development already. However, these behavioral changes are not specific to schizophrenia and are therefore often not correctly recognized but rather misinterpreted as temporary crisis or symptoms of other psychological disorders (Gaebel & Wölwer, 2010). They are recognized as early symptoms of schizophrenia-spectrum disorders in retrospect only.

The acute stages of illness vary in length and number of episodes. In 1972 Bleuler formulated his famous ‘rule of thirds’ which states that about a third of patients with schizophrenia achieve complete remission after one or a few episodes, another third has repeated episodes with a mild degree of impairment and the last thirst develops a severe and chronic disability (Rodewald, 2010). This classification, however, appears to be oversimplified and outdated, since the course of disease exhibits great intra- and interindividual variability. The course of disease is reflected in the fifth character of the ICD-10 code and can be further classified as continuous, episodic with progressive deficit, episodic with stable deficit, episodic remittent, incomplete remission, complete remission, or other (World Health Organization, 1992). While a quarter of patients

concerned with schizophrenia experience only one episode of illness - the numbers vary between 10-25% (Bäuml, 1994; Gaebel & Wölwer, 2010) - most patients develop multiple episodes with different degrees of impairment. Of those approximately 20-30% exhibit an unfavorable clinical course with multiple recurrences and chronic residual symptoms with increasing disability (Barbato, 1998; Gaebel & Wölwer, 2010). This residual phase is accompanied by negative symptoms such as social withdrawal, affective blunting, lack of motivations and interest (Hahlweg & Dose, 1998).

2.1.3 Impairment and burden

More than a century after Bleuler coined the term schizophrenia approximately half of affected patients still have a poor outcome (Falkai, 2008; Falkai et al., 2015). Studies suggest that about 40% of male and 25% of female patients with schizophrenia actually experience chronic impairment of moderate to severe extent (Barbato, 1998). Not surprising, schizophrenia is among the most burdensome and cost-intensive illnesses worldwide although it has a relatively low prevalence rate. According to the Global Burden of Disease Study (World Health Organization, 2004), schizophrenia causes such a vast amount of disability that it accounts for 1.1% of the total disability-adjusted life years (DALYs) and 2.8% of years lived with disability (YLDs). In the World Health Report (World Health Organization, 2001), schizophrenia is even ranked as the 8th leading cause of DALYs and 3rd leading cause of YLDs for the group aged 15-44 years (Rossler, Salize, van Os, & Riecher-Rossler, 2005). Disability affects the essential domains of emotional experience and human behavior, particularly social functioning in various areas such as self-care and body hygiene, occupational performance, but also functioning in interpersonal relationships as well as in a broader social context (Barbato, 1998; Falkai, 2008) As a consequence, only one third of patients are employed in the primary labor market and are able to maintain a stable relationship (Falkai, 2008; Falkai et al., 2015). In

addition, life expectancy is reduced by approximately 10 years. Schizophrenia is no fatal disease per se, but death rates of affected patients are twice as high as those in the healthy population due to exorbitantly higher lifetime risk of suicide (times 12, Barbato, 1998; DeVylder & Hilimire, 2015).

Estimates of economic cost of schizophrenia range between 1,6-2,6% of total health care expenditures (Barbato, 1998). Germany‘s economic burden of schizophrenia ranged between €9.63 billion and €13.52 billion in 2008 (Frey, 2014).

Apart from the financial burden of a schizophrenic disorder to society, there is substantial strain on relatives (Rossler et al., 2005), e.g., financial burden and emotional distress due to unusual behavior and social/emotional withdrawal (Barbato, 1998).

2.1.4 Explanatory models

Stephan and colleagues (2009) point out that “schizophrenia has largely remained an enigma. Despite all research efforts, there is still no consensus about its exact pathophysiological mechanisms” (p. 509). Marcotte and colleagues (2001) go on to remark that “current research into schizophrenia has remained highly fragmented, much like the clinical presentation of the disease itself.” (p. 395). Accordingly, several hypotheses that were formulated in an attempt to explain the symptomatic cause and separate pathogenic mechanisms of schizophrenia are introduced in the following before presenting one of the more prominent theories, the integrated sociodevelopmental-cognitive model by Howes and Murray (2014).

Dopamine hypothesis

The dopamine (DA) hypothesis was formulated in the 1970s based on two findings: First, the clinical effectiveness of antipsychotics works by blocking DA receptors. Second, drugs that work on the DA system, e.g., amphetamine, have the potential to induce psychotic symptoms

(Creese, Burt, & Snyder, 1976; Seeman & Lee, 1975). The theory aims to explain the pathogenic mechanism of schizophrenia by suggesting DA dysfunction to be the underlying cause of positive symptoms. Initially, the emphasis was on increased presynaptic DA synthesis. More specific, greater DA release was thought to be associated with more severe psychotic symptoms (Howes & Murray, 2014). The mechanism is illustrated in Figure 1.

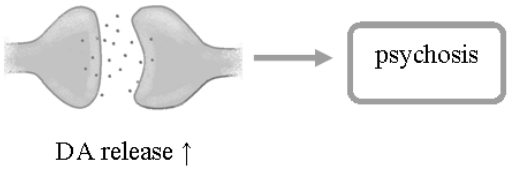

Figure 1. Dopamine hypothesis of schizophrenia.

According to the DA hypothesis of schizophrenia, an increased release of DA into the synaptic gap caused by a dysregulation of the dopaminergic system is thought to be underlying the development of psychotic symptoms. DA=dopamine.

Although the DA hypothesis provides a reliable model for positive symptoms it does not account sufficiently for negative or cognitive symptoms in schizophrenic patients (Steeds, Carhart-Harris, & Stone, 2015).

Neurodevelopmental hypothesis

The neurodevelopmental hypothesis tries to explain the origin of schizophrenia by recognizing prenatal and perinatal hazards as major influence, see Figure 2. Factors that have been shown to contribute to the development of schizophrenia are prenatal or perinatal risk factors such as birth complications, low birthweight, and in-utero infection, abnormal early childhood development, i.e., motor delay, social alterations, and cognitive impairments, as well as brain structural alterations, i.e., ventricular enlargement, grey matter reductions, and white matter disruption (Howes & Murray, 2014). Within the neurodevelopmental hypothesis DA dysregulation is regarded as a manifestation of the presynaptic dysfunction and is considered

as secondary to the interaction between primary neurobiological lesions and maturational processes (Howes & Murray, 2014).

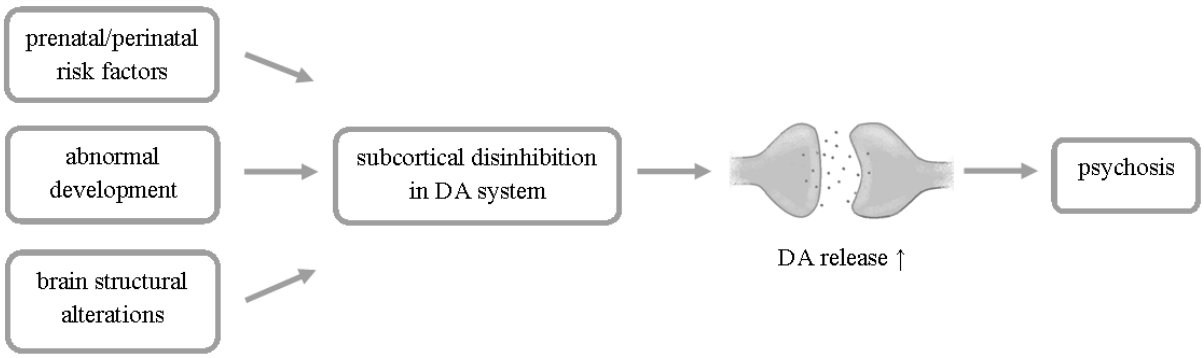

*Figure 2***.** Neurodevelopmental hypothesis of schizophrenia.

The figure illustrates the suggested pre- and perinatal factors that influence the dopaminergic system leading to an exaggerated release of DA into the synaptic gap resulting in psychotic symptoms. DA=dopamine.

Cognitive model

The biology of schizophrenic disorders is explained by the dopamine and developmental hypotheses. However, they do not help sufficiently to understand the individual symptoms. Cognitive models of schizophrenia focus on psychological mechanisms in an attempt to elucidate this knowledge gap (Frith, 2015). Cognitive models propose that schizophrenic patients are cognitively biased due to deviations in neurodevelopment and, therefore, are more likely to misperceive certain internal and external information. Those models draw a vicious circle in which stress intensifies existing cognitive disturbances such that the processed content is perceived as threatening to the self. The search for a plausible explanation for the deviant experiences is then, again, biased by cognitive appraisal processes resulting in the faulty judgement that these experiences are externally driven. In this way, paranoid delusions for example are presumed to be formed (Howes & Murray, 2014). For a flow chart diagram illustrating the mechanisms see Figure 3.

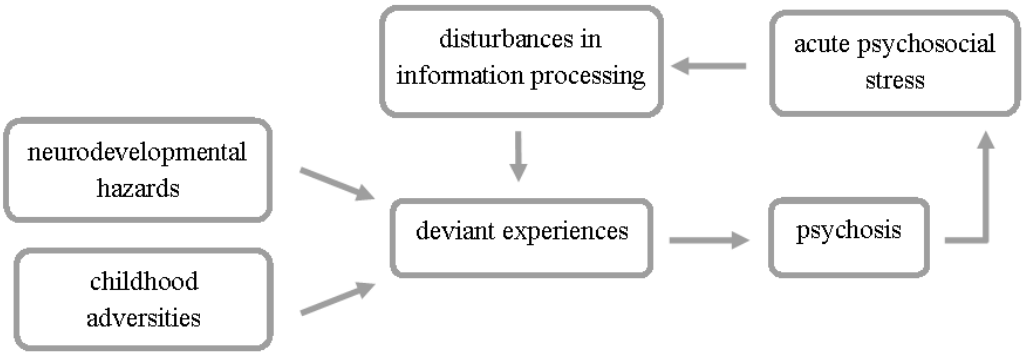

Figure 3. Cognitive model of schizophrenia.

Neurodevelopmental hazards and childhood adversities in combination with various psychological mechanisms and cognitive biases thought of as triggering and maintaining factors for psychotic symptoms.

Integrated sociodevelopmental-cognitive model

Although cognitive models represent a major advancement in understanding the development of schizophrenia and symptom occurrence in specific the dopamine hypothesis and neurodevelopmental hypothesis have not been integrated satisfactorily. It is for this reason that the integrated sociodevelopmental-cognitive model has been postulated by Howes and Murray (2014). The integrated sociodevelopmental-cognitive model takes into account the underlying biological determinants and combines those with childhood risk factors, biased cognitive schemas, and acute environmental stress (see Figure 4). In their model Howes and Murray suggest that a combination of developmental changes secondary to variant genes, early risk factors for neural development, and childhood adversities sensitize the dopamine neurotransmitter system. Consequently, this process leads to excessive presynaptic synthesis and release of dopamine. This results in a bias in individual's cognitive schema that is used to process stimuli towards paranoid interpretation. Thus, the amendment to previous cognitive models appears in the more detailed explanation of the development of cognitive biases by adding diverse social and biological abnormalities that subsequently lead to dopamine sensitization and thereby to an abnormal information processing. The integrated sociodevelopmental-cognitive model goes on to explain that subsequent stress triggers the

sensitized dopamine synapse resulting in dysregulated dopamine release. As a consequence, stimuli are misattributed and misinterpreted. As the resulting delusions and hallucinations in turn cause further stress, a vicious cycle is established, and eventually hardwired through repeated dopamine dysregulation (Howes & Murray, 2014).

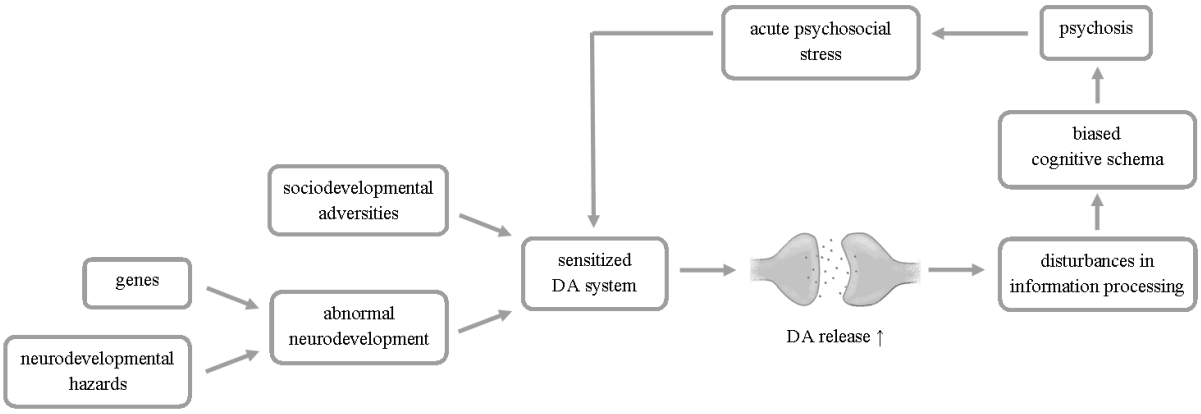

Figure 4. The integrated sociodevelopmental-cognitive model of schizophrenia.

Expanding upon the previous explanatory models, the sociodevelopmental-cognitive model combines biological, social and cognitive factors that are thought of to result in psychotic symptoms. The figure illustrates the mechanisms of action and interactions with regard to the underlying biological determinants, childhood risk factors, biased cognitive schemas, and acute psychosocial stress. DA=dopamine.

2.2 Auditory verbal hallucinations (AVH) in schizophrenia

In former times, AVH were sometimes considered as ‘message from god’. Today some 15% of the healthy population at times hear voices (Laroi et al., 2012). Still, hallucinations are now frequently regarded as abnormal and a sign of mental illness, especially when embedded in a multitude of other symptoms that accompany manifest psychosis (see also section 2.1.1). Hallucinations are a core symptom and therefore characteristic of schizophrenia and schizophrenia-spectrum disorders. They are defined as perceptual experience with the impression of a real perception in the absence of a provoking stimulus to the sensory organ (Colman, 2006). Hallucinations can occur in any modality of perception, i.e., optical, olfactory, gustatory, tactile, and auditory with about two-third of patients experiencing one or the other hallucination (Andreasen & Flaum, 1991; Gaser, Nenadic, Volz, Buchel, & Sauer, 2004). Prevalence data of hallucinations in schizophrenic patients found in literature indicate that auditory hallucinations are the most common with about 50-80% (Slade & Bentall, 1988), followed by visual hallucinations with 15%, and tactile hallucinations with 5% (Cutting, 2007). Most often auditory hallucinations are manifested in the form of auditory verbal hallucinations (AVH), i.e., ‘hearing voices’, but might include music, ringing, animal sounds, clicks, and humming as well (McCarthy-Jones, Trauer, et al., 2014). Basically, AVH can be distinguished between commenting, commanding, and conversing voices, and further differentiated in their number of voices, voice identity (male/female), perceived location (internal/external), frequency and duration, loudness (from whispering to shouting), clarity (from mumbling to clear sounds), complexity (from single words to phrases), and content (positive/negative, often insulting) (Laroi et al., 2012; McCarthy-Jones, Trauer, et al., 2014). Typically, AVH involve personal degradation, abusive terms and threats without the person concerned perceiving any control over onset or end of the experience making them feel as intrusions and thus leading to high levels of distress (Laroi et al., 2012). Although the symptoms respond to antipsychotic

medication in the majority of cases, 25-30% of AVH persist and become chronic (Shergill, Murray, & McGuire, 1998). Those chronic, persistent hallucinations are then called 'treatment-refractory'. Treatment-refractory persistent AVH not only cause great distress but are also associated with an unfavorable prognosis, reduced quality of life and economic costs *(*for more details go to www.gbe-bund.de).

2.2.1 Treatment concepts for AVH

Schizophrenia is a mental illness that is not curable but treatable. Therefore, treatment goals include symptom reduction, acquisition of coping skills, stability and according relapse prevention as well as reintegration (Rossler et al., 2005). According to the WHO, 50% of people coping with schizophrenia do not receive treatment although different treatment concepts are available that can be provided at community level (World Health Organization, n.d.). As the causes of the development of schizophrenia are still largely unknown, treatments are mostly symptomatic in that they focus on the reduction and/or elimination of symptoms. Available treatments include antipsychotic medication, psychoeducation, psychotherapy, various psychosocial support programs and in some instances both non-invasive and invasive brain stimulation techniques (Sommer et al., 2012).

Pharmacotherapy

The introduction of chlorpromazine in 1952 by Delay and Deniker and its potential use as antipsychotic medication provided a significant improvement in symptomatic treatment and relapse prevention (Ban, 2007; Leucht et al., 2012). Pharmacotherapy in patients with schizophrenia is directed at specific symptoms rather than at the disorder itself. Therefore, the main goals of psychopharmacological treatment are symptom reduction and control as well as relapse prevention. Antipsychotic medication is the treatment of choice for schizophrenia in

general and hallucinations in specific (Finzen, 2009; Sommer et al., 2012). Antipsychotic drugs are capable of inducing a rapid decrease in hallucination severity as well as a general improvement of acute symptoms (Sommer et al., 2012). However, as mentioned previously, pharmacotherapy can fail to improve AVH leaving them to remain in a clinically significant severity in approximately 25% of patients with schizophrenia (Davis, Schaffer, Killian, Kinard, & Chan, 1980; Shergill et al., 1998). In specific, treatment-resistance is a failure to demonstrate an adequate response with an adequate treatment which is defined as two antipsychotics of different classes with sufficient dosage and duration (Berman, Narasimhan, & Charney, 1997). In cases of treatment-refractory symptoms, clozapine poses another treatment option that renders the potential of symptom reduction (Kane, 1992). If clozapine also falls short of an effect, it is called clozapine-resistance.

Cognitive-Behavioral Therapy

The objective of psychotherapy, i.e., Cognitive-Behavioral Therapy (CBT), in medicated patients with residual AVH is much more multi-faceted than that of pharmacotherapy alone. It includes the development of a common understanding of the problem, destigmatization and normalization, challenging negative beliefs and developing coping strategies, as well as the acceptance of unchangeable conditions, thereby trying to reduce symptoms or at least making them feel more controllable. CBT for AVH, thus, does not aim to reduce severity and frequency of hallucinations in the first place. Rather, CBT is based on a cognitive approach as it assumes that AVH occur more often because of their emotional valence (Lincoln, 2014) consequently targeting the way hallucinations are appraised. Specifically, CBT aims at changing appraisals of AVH that makes them appear more powerful, e.g., omnipotence, omniscience, and malevolent. Furthermore, CBT involves the development of new coping strategies. As a consequence, targeting emotional appraisal may not only reduce the experienced severity and

related distress of AVH (Sommer et al., 2012) but symptom frequency as well. In addition, CBT involves behavioral changes in that it requests confrontation with the voice, spoken content and associated thoughts (Lincoln, 2014) as well as testing of alternative ways to deal with particular situations (Sommer et al., 2012) thereby reducing behavioral avoidance. Furthermore, relapse prevention presents a major treatment goal for CBT (Klingberg & Wittorf, 2012).

Research results indicate that CBT for AVH in schizophrenia is indeed helpful in changing patients' beliefs about their voices (Pinkham, Gloege, Flanagan, & Penn, 2004), reducing conviction in the power of and compliance to commanding voices (Penn et al., 2009; Trower et al., 2004), reducing symptom distress (Newton et al., 2005; Wykes, Parr, & Landau, 1999), increasing the number and effectiveness of coping strategies (Wykes et al., 1999), and in improving overall symptom severity over the treatment phase (Newton et al., 2005) as well as after a follow-up interval of 12-months (Penn et al., 2009). In addition, recurrence rate is reduced by 54% due to CBT (Wiedemann & Klingberg, 2003). This, however, is not specific for AVH but refers to the general recurrence of psychotic symptoms in schizophrenia. In contrast, Wykes et al. (2005) who compared group CBT to treatment as usual found no effect on AVH severity but on social functioning. Still, there were improvements in AVH in some of the therapy groups emphasizing the importance of therapist experienced and early treatment availability. To conclude, CBT may provide a significant improvement in the patients' quality of life (Shergill et al., 1998).

Avatar therapy

Expanding upon the CBT-idea of directly relating to the voice, a novel and innovative computer-based therapy program for persistent AVH was developed. Avatar therapy is based on the idea that a dialogue between affected patients and their voices may facilitate a regain in

feeling of control (Leff, Williams, Huckvale, Arbuthnot, & Leff, 2014). In the computer program, the patient is instructed to construct an avatar with a face and voice that approximates the entity he hears as AVH. With the therapist's encouragement the patient enters a dialogue with the digital representation of his hallucination. The avatar is under the control of the therapist who is speaking with the patient from an adjacent room with a control panel. Over the course of six 30min sessions the avatar progressively changes its character from formerly negative to appreciative, supportive, and, most importantly, more controllable. A copy of the dialogue is handed out to the patient afterwards (Leff et al., 2014).

A first study examining avatar therapy in comparison to treatment as usual found significant reductions of AVH frequency and intensity post-treatment (Leff, Williams, Huckvale, Arbuthnot, & Leff, 2013). The follow-up assessment at three month showed further reductions in AVH frequency and intensity as well as additional reductions in depressive symptoms. A first randomized controlled trial study investigating the effectiveness of avatar therapy for treatment-refractory AVH compared the former to supportive counselling in schizophrenia and affective disorders with psychotic symptoms (Craig et al., 2018). Their results support the evidence that avatar therapy is effective in reducing AVH severity and frequency. This is of clinical importance as patients often suffer for many years from persistent AVH and the procedure seems to be cost- and time-saving.

Brain stimulation techniques

Different brain stimulation techniques are available as a treatment for otherwise treatment-refractory auditory verbal hallucinations. The goal of such kind of treatment in schizophrenic patients with AVH is symptom reduction.

Transcranial Direct Current Stimulation (tDCS). Transcranial Direct Current Stimulation (tDCS) is a non-invasive neurostimulation technique inducing weak electric currents via two electrodes that are placed directly on the individual's scalp. The electric current flows from the anode (positive charge) to the cathode (negative charge) (Mondino et al., 2015) resulting in modulation of neuronal activity of the desired brain areas. tDCS is a rather new technique (Brunelin et al., 2012), hence recommendations regarding treatment frequency and duration are based on recent research studies. Brunelin and colleagues (2012) administered ten sessions over five days in 30 patients with schizophrenia. With inhibitory stimulation over the left temporo-parietal cortex and excitatory stimulation over the left dorsolateral prefrontal cortex they achieved a significant reduction in severity of treatment-refractory AVH that lasted up to three-month follow-up. First reviews on this subject suggest that improvement may not be limited to hallucinatory symptoms but may be effective for negative and cognitive symptoms as well (Agarwal et al., 2013). Additionally, tDCS has only few side effects (Brunelin et al., 2012) rendering it a promising treatment option for persistent AVH in schizophrenia.

Repetitive Transcranial Magnetic Stimulation (rTMS). Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive and painless brain stimulation technique that makes use of repetitive electromagnetic pulses send through a stimulator coil. The coil is placed just above the individual's scalp, directly above the desired stimulation area. The electromagnetic pulse then penetrates the underlying brain tissue up to a depth of 3cm resulting in an intracranial flow of current and neuronal activation (Aleman, Sommer, & Kahn, 2007; Barker, Freeston, Jalinous, & Jarratt, 1987; Sommer et al., 2012). rTMS treatment consists of daily sessions for several consecutive days up to weeks (Aleman et al., 2007) depending on the severity of symptoms. The side effects are generally mild (Slotema, Blom, Hoek, & Sommer, 2010) without neurocognitive impairment to be expected (Aleman et al., 2007; Sommer et al., 2012).

For treating AVH in schizophrenia the left temporo-parietal cortex seems to be a promising target area as meta-analyses provide support for moderate to good therapeutic effects (Kubera, Barth, Hirjak, Thomann, & Wolf, 2015; Slotema et al., 2010; Sommer et al., 2012). However, not all features of AVH seem to benefit equally (Freitas, Fregni, & Pascual-Leone, 2009). The study by Hoffman's group (2013) found an effect on frequency but not on severity of AVH, while the meta-analysis by Slotema and colleagues (2010) found rTMS to improve severity of AVH. Then again, Fitzgerald et al. (2005) found an effect on the loudness of AVH but not on severity. In addition, the beneficial effects do not seem to be of lasting nature (approx. one month, Kubera et al., 2015; Slotema, Aleman, Daskalakis, & Sommer, 2012) and rTMS does not seem to improve positive symptoms in general (Aleman et al., 2007).

Theta burst transcranial magnetic stimulation (TBS). Because treatment with rTMS is time-consuming and shows only moderate, non-durable effects (Plewnia, Zwissler, Wasserka, Fallgatter, & Klingberg, 2014), theta-burst stimulation (TBS) might be a promising alternative. TBS is a modified rTMS-protocol with repeated application of low-intensity rTMS (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Its advantage over standard rTMS is the shorter application time. In the continuous TBS paradigm (cTBS), 40s of continuous 50Hz stimulation is applied (Huang et al., 2005) to the left (and sometimes also the right) temporo-parietal cortex (Plewnia et al., 2014).

Kindler and colleagues (2013) found 10-day treatment of cTBS to be equally effective in reducing AVH scores than 1Hz rTMS stimulation. Koops et al. (2016) found an effect on AVH severity but failed to demonstrate the superiority of cTBS when compared to a placebo group. Plewnia and colleagues (2014) compared cTBS with a sham-control group and found both to be equally effective in reducing AVH severity, too. However, they report a trend towards cTBS (p=.077).

In sum, according to the studies available to date cTBS does not seem to be more effective than rTMS. Still, cTBS indeed seems to be a promising technique in reducing AVH and is potentially more attractive as treatment as its application time is much shorter.

Electroconvulsive Therapy (ECT). Electroconvulsive Therapy (ECT) is usually considered the 'last resort' treatment for severe treatment-resistant schizophrenia (Folkerts et al., 2003). During ECT, a high electrical current is administered via electrodes attached to the individual's scalp to induce a generalized seizure. To avoid negative effects of the convulsion the procedure is performed under general anesthesia and muscle relaxation to prevent body spasms (Sommer et al., 2012). Treatment is repeated at least two times a week with a total number of ECT treatments of 11 on average (Lally et al., 2016). Side effects include serious cognitive impairments in memory performance that seem to accumulate with repeated treatment on the one hand and on the other hand are mostly reversible lasting up to several months (Kolb & Whishaw, 1996). As to treatment effects in schizophrenia, several studies show improvement of clinical status in general, however, the effect of ECT on AVH has not yet been shown on group level (Kubera et al., 2015; Sommer et al., 2012).

2.2.2 Neurobiological abnormalities in AVH

Clinical and phenomenological studies are interested in schizophrenia and in particular chronic and treatment-refractory AVH since decades. But not until the advent of neuroimaging technologies, especially magnetic resonance imaging (MRI) and computer tomography (CT) in the 1970s their neurobiological underpinnings could be examined.

Structural deviations

Structural neuroimaging studies as well as reviews on the existing literature point to abnormal gray as well as white matter volume in frontal, temporal and parietal regions as potential neural correlates of AVH in patients prone to hallucinations (Allen, Larøi, McGuire, & Aleman, 2008; Gaser et al., 2004). However, the topography of volume changes varies considerably across studies (Allen, Larøi, et al., 2008), probably as a consequence of clinical, psychometric and/or methodological heterogeneity.

Compared to non-hallucinating individuals, the hallucinating brain is consistently shown to be associated with a reduction in grey matter tissue in the temporal lobe (Allen, Larøi, et al., 2008), especially the left superior temporal gyrus (STG) including the left transverse temporal gyrus of Heschl, i.e., the primary auditory cortex (Gaser et al., 2004).

Studies have repeatedly shown an inverse relationship between severity of AVH and the STG (Neckelmann et al., 2006). In addition, reduced grey matter volume was reported in the middle temporal gyrus (MTG) (Onitsuka et al., 2004), the left insula (Shapleske et al., 2002), the thalamus (Neckelmann et al., 2006), left and right cerebellum (Neckelmann et al., 2006), and posterior cingulate cortex (Upthegrove et al., 2016). Furthermore, a reduced volume is observed in the right dorsolateral prefrontal cortex and the left (inferior) supramarginal gyrus (Gaser et al., 2004). Kubera and colleagues (2014) identified an AVH-specific structural network of reduced gray matter volume in medial and inferior frontal, insular and bilateral temporal cortical regions. This network was further associated with physical characteristics of hallucinations such as symptom frequency, duration, and intensity. Finally, when talking about brain structural deviations, it is not solely about atrophy in gray matter volume but also about abnormal gyrification. Cortical gyrification is thought of as stable morphological feature thus representing early neurodevelopmental indices. Kubera et al. (2018) presented evidence for an

abnormal cortical gyrification in Broca's area specific to AVH, supporting the notion of cortical vulnerability in key regions associated with speech and language.

In sum, structural neuroimaging in patients with persistent, treatment-refractory AVH demonstrates selective changes in brain morphology. However, this kind of research neither allows investigating the neurofunctional dynamics of AVH nor the impact of persistent symptoms on cognition.

Functional deviations

Evidence from functional MRI studies stems from two distinct approaches: 'symptom capture' and 'symptom interference' studies. The two approaches differ in the underlying assumption of either measuring the hallucinatory state or trait. Symptom capture studies addressing AVH in schizophrenia aim to capture neuronal activity of 'spontaneous' hallucinations during the scanning process (state). This is often done when the brain is otherwise 'at rest', so-called resting-state conditions. Those studies point to an increase in the blood oxygen level–dependent (BOLD) signal suggesting an increase in neuronal activity during AVH in temporal to frontal language-related areas (Upthegrove et al., 2016). In specific, increased blood flow is observed in the superior and middle temporal gyrus (Lennox, Park, Medley, Morris, & Jones, 2000), including transverse gyrus of Heschl matching the primary auditory cortex (Dierks et al., 1999), and Wernicke's area/secondary auditory cortex (Zmigrod, Garrison, Carr, & Simons, 2016). Further activity is reported regularly in the inferior frontal gyrus, i.e., Broca's area (Aleman, 2014; McGuire, Shah, & Murray, 1993). Other cortical areas that have been shown consistently to activate during AVH include (para-) hippocampal regions, the thalamus, the basal ganglia, the anterior cingulate cortex, and the cerebellum (Shergill, Brammer, Williams, Murray, & McGuire, 2000; Zmigrod et al., 2016). Meta-analyses suggest a strong left lateralization (Jardri, Pouchet, Pins, & Thomas, 2011). In sum, evidence from symptom capture studies suggest AVH

in schizophrenic patients to be correlated with frontotemporal language-related perceptual, e.g. Heschl's gyrus and Wernicke's area involved in speech perception and interpretation, and motor areas, e.g. Broca's area involved in speech production, as well as with medial temporal areas associated with verbal memory (Jardri et al., 2011; McGuire et al., 1993). To a lesser extent, AVH are also associated with activity in the anterior cingulate cortex which is involved in attentional processes (Allen, Larøi, et al., 2008; McGuire et al., 1993).

In contrast, symptom interference studies assume that AVH bound neural resources which are, therefore, less available to other mental operations. These studies use task-based designs involving material that is thought to make use of similar neural correlates as AVH. It follows the hypothesis of a decrease in neural activation patterns in hallucinating individuals. Those activation decreases may, then, reflect processes attributable to AVH generation (trait). A recent review addressing findings from symptom interference studies point to decreases in anatomical and functional connectivity of language-related brain areas (Curcic-Blake et al., 2017). In specific, decreased neural activity in the left STG, left MTG, anterior cingulate cortex (ACC), and left premotor cortex activity seems to be associated with AVH (Curcic-Blake et al., 2017; Kuhn & Gallinat, 2012).

However, research evidence shows some inconsistencies regarding the specific brain areas of altered activation when incorporating both, symptom capture and symptom interference studies: The meta-analysis by Kompus, Westerhausen, and Hugdahl (2011), exemplary, assumes what they call a 'paradoxical' brain activation regarding AVH. They point to an increased activation in the left primary auditory cortex and in the right rostral prefrontal cortex while at rest, and decreased activation in the presence of an external auditory stimulus in the same brain areas. In contrast, Kühn & Gallinat observed a dissociation between an activation in bilateral inferior frontal gyrus, postcentral gyrus, and left parietal operculum and decreased activation in the left STG as well as MTG, ACC, and left premotor cortex activity.

Dysfunctional neuronal connectivity

In addition to pathophysiology associated with hearing voices in schizophrenia, emerging evidence points to disturbances in functional connectivity (Gaebel & Zielasek, 2008). Functional connectivity is defined as the temporally and statistically correlated pattern of activity of two or more anatomically distinct brain regions (Friston, 1994). It follows that functional 'dysconnectivity' is an abnormal interaction between multiple brain areas (Friston & Frith, 1995). Wolf et al. (2011) examined functional resting-state networks (RSN) in schizophrenic patients with chronic AVH in a preliminary work for the current project. The goal was the exploration of neural network connectivity in four networks previously identified to be associated with AVH: (1) speech processing, (2) attention, (3) executive control and (4) the so-called 'default mode network' (DMN) (Allen, Laroi, McGuire, & Aleman, 2008; Thomas, Rossell, & Waters, 2016).

The network comprising language processing covers left fronto-temporo-parietal areas (Hugdahl, Loberg, & Nygard, 2009). In specific, it consists of Broca's and Wernicke's areas (Smith et al., 2009) as well as anterior insula, posterior inferior frontal cortex, and anterior inferior frontal cortex (Gitelman, Nobre, Sonty, Parrish, & Mesulam, 2005). The attentional network is located in the right fronto-parietal lobe and comprises areas in the intraparietal sulcus and inferior parietal lobule including temporo-parietal junction, supplementary and pre-supplementary motor areas, anterior insula, ventral occipital cortex, and dorsolateral prefrontal cortex (Fox et al., 2005; Markett et al., 2014). The executive control network "covers several medial–frontal areas, including anterior cingulate and paracingulate" (Smith et al., 2009). The DMN is a network of brain areas that are active at rest and deactivated during attention-demanding tasks. It comprises posterior medial and lateral cortices including precuneus and

posterior cingulate, and bilateral inferior–lateral–parietal and ventromedial frontal cortex (Smith et al., 2009; Williamson, 2007).

Wolf and colleagues (2011) found an association between AVH and functional connectivity in the speech network as well as in networks associated with attentional and executive performance. Within the language-related RSN, increased connectivity in bilateral temporal regions including left STG and bilateral MTG and decreased connectivity in the cingulate cortex was associated with AVH. Within the attention and executive control RSNs patients with AVH exhibited abnormal connectivity in the precuneus and right lateral prefrontal areas, respectively. Regarding AVH symptom severity, correlations of the extent of hallucinatory symptoms and functional connectivity of the left ACC, left STG and right lateral prefrontal cortex were demonstrated. However, they did not confirm DMN dysconnectivity. In contrast, Alderson-Day et al. (2016) reported altered DMN connectivity in addition to altered functional connectivity involving executive control, salience and sensory networks. The above-mentioned neural networks associated with AVH in schizophrenia are illustrated in Figure 5.

A recent review focusing on functional connectivity in AVH summarizes the research evidence as primarily lacking consistent replication (Curcic-Blake et al., 2017). The strongest evidence involves the left temporal cortex including the primary auditory cortex, STG and the left temporo-parietal junction (TPJ). However, regarding STG both elevated and reduced functional connectivity was observed across different studies. Furthermore, research results implicate an involvement of the DMN in the development of AVH (Alderson-Day, McCarthy-Jones, & Fernyhough, 2015). This hypothesis is plausible given the relevance of the DMN for self-reference and self-attribution (Buckner, Andrews-Hanna, & Schacter, 2008).

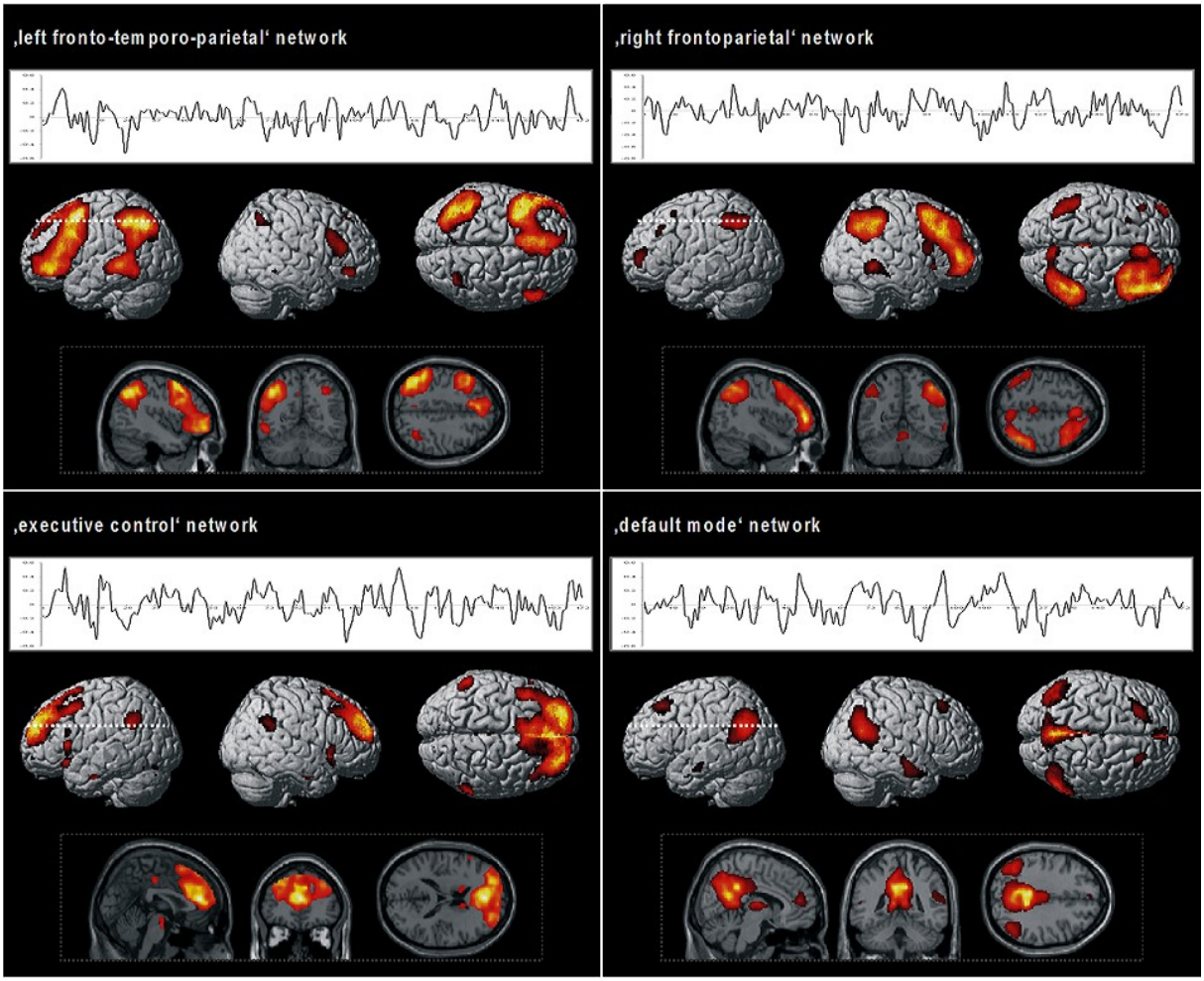

Figure 5. AVH-related resting-state networks (RSN).

This figure provides a pictorial overview of four neural networks that are thought to be associated with AVH in schizophrenia: language, attention, executive control, and DMN (from upper left to bottom right). With kind permission, illustration taken from Wolf et al. (2011)[1], p. 369.

In sum, research on functional connectivity in schizophrenic patients with chronic AVH has highlighted various regions and functional networks including areas associated with language and DMN. Gaser et al. (2004) suggest that AVH "are not associated with a single regional

[1] Reprinted from Wolf, N. D., Sambataro, F., Vasic, N. … Wolf, R.C.: Dysconnectivity of multiple resting-state networks in patients with schizophrenia who have persistent auditory verbal hallucinations, Fig. 1. Canadian Medical Association Journal 2011;36(6):366-74. © Canadian Medical Association (2011). This work is protected by copyright and the making of this copy was with the permission of the Canadian Medical Association Journal (www.cmaj.ca) and Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law.

deficit. Rather, several nodes of a more complex circuitry might be involved. Changes in primary auditory cortex and temporo-parietal areas might be at the core of this abnormality, and together with prefrontal deficits this could result in deficient frontotemporal interaction" (p. 95).

2.2.3 Linking cognitive models of AVH with neural deviations

To account for the heterogeneous phenomenology of auditory verbal hallucinations several neurocognitive models have been proposed. They are based on findings with regard to common features of AVH, e.g., internally generated but attributed externally, clear perceptual quality with sense of reality, experienced loss of control, and often accompanied by emotional valence. Four major theoretical models have been proven useful to some extent in understanding the nature of AVH in patients with schizophrenia: aberrant auditory imagery, intrusive memories, misattribution of inner speech, and the predictive processing framework.

Auditory imagery

One of the earliest explanations for AVH can best be described as far-fetched 'chance discovery'. In 1883, Galton started an inquiry among members of the Fellows of the Royal Society in order to investigate their "hereditary faculties" (Galton, 1883, p. 1). Galton's objective had been to identify those characteristics that render those individuals 'superior' to the rest of humankind to promote the evolution of men. In his inquiry, he found a relationship between the experience of particularly vivid mental imagery and hallucinations in 'great man in history' whom he calls "visionairies" (Galton, 1883, pp. 112-128). Consequently, the vivid imagery account of AVH was born. Studies trying to scientifically examine an association between vividness of auditory imagery and proneness to AVH in patients with schizophrenia usually failed except for one (Seal, Aleman, & McGuire, 2004). Mintz and Alpert (1972) found

a positive correlation between the presence of hallucinations and vividness of auditory imagery whereas the majority of studies found no such relationship or even reduced mental imagery in hallucinating patients (Seitz & Molholm, 1947). Summarizing the current state of evidence, there seems to be no robust association between auditory imagery and auditory hallucinations in schizophrenia.

Aberrant memory processing

The presence of AVH in schizophrenia has also been linked to intrusive memories in general (Badcock & Hugdahl, 2012). In specific, it is argued that AVH result from a process of an inability to inhibit the intrusive activation of memories on the one hand (Curcic-Blake et al., 2017) and an impairment in monitoring the source of memories on the other hand (Seal et al., 2004). It is thought of as unintended memory activation out of context. Indeed, research results indicate that hallucinating individuals have poor inhibitory control and suffer from frequent intrusive memories (Badcock & Hugdahl, 2012) providing evidence for the first part of the aberrant memory account. The defective inhibitory system offers a way to explain the experienced involuntariness and loss of control that comes with AVH (Badcock & Hugdahl, 2012). Furthermore, the often negative and derogative content of AVH could be explained in terms of memories of childhood traumatic events that are frequent among schizophrenic patients, and particularly in those with hallucinations. Verbal hallucinatory content that can be linked to the experience of traumatic events often involve, for example, the voice of the former abuser that commands self-harm. This phenomenon has been also referred to as ‘voices as traumatic experiences’ (Upthegrove et al., 2016). In the context of trauma, it is important to point out whether these are true hallucinations or so-called ‘pseudohallucinations’, defined as hallucination-like sensory experience that are recognized as not being caused by any sensory source and that occur in posttraumatic stress disorder, for example (Wearne & Genetti, 2015).

On a neurobiological level, if inhibition as well as memory processes are implicated in AVH, areas involved include the prefrontal cortex (PFC) for inhibition, the hippocampus for memory, the amygdala for emotional processing, the putamen for translation of memory into conscious language experience as well as auditory networks (Curcic-Blake et al., 2017). In support, immediately prior to AVH a hippocampal deactivation has been observed (Curcic-Blake et al., 2017) while a hyperactivation is apparent during hallucinations (Upthegrove et al., 2016) suggesting an involvement of the hippocampus and amygdala. In addition, PFC dysfunction has been constantly associated with AVH in schizophrenia (Badcock & Hugdahl, 2012) supporting the theory of intrusive memories.

However, despite the appeal of the aberrant memory model of AVH conclusive evidence of a source memory deficit in schizophrenia that is specific for self-generated material is lacking. In contrast, a current review summarized the existing literature as suggesting "that the nature of memory deficit observed amongst those with prominent positive symptoms is not a problem with identifying the *source* of memories but with remembering what they said or imagined in the first place" (Seal et al., 2004, p. 55, italics from original). Additionally, the model does not account for the more severe and complex auditory hallucinations (Upthegrove et al., 2016).

Self-monitoring of inner speech model

A phenomenological key aspect of AVH is the experience's origin outside the self, which holds true for 'thought echo' as well (Hugdahl et al., 2007). This property has inspired a series of research and theories regarding a neurocognitive model of AVH as misattribution of inner speech to an external source due to defective self-monitoring (Frith, 2015). I will subsume the different accounts regarding source- and self-monitoring and their extensions under this subtitle. Frith and Done (1988) suggested that internally generated stimuli, e.g., inner speech, are connected to planned or willed action. Subsequently, Frith (2015) argues that inner speech

will be misinterpreted as externally generated if the sense of one's own intention is not experienced properly. Thus, central to the theory of impaired self-monitoring in AVH is not the inner speech per sé but that patients fail to recognize that it is self-generated. In sum, a dysfunction in the source- or self-monitoring system of intentional processes leading to a mismatch between the predicted and actual sensory consequences is suggested to cause the external attribution bias observed in AVH (Allen, Larøi, et al., 2008).

Research results in cognitive psychology do indeed find that schizophrenic patients in general exhibit a bias in that they tend to attribute their inner experiences to external sources (Shiraishi et al., 2014). Furthermore, hallucinating subjects in particular demonstrate higher error rates in identifying their own voice and erroneously misattribute their own speech to an external agent more often compared to non-hallucinating patients (Seal et al., 2004). Moreover, recent meta-analyses provide strong evidence for an impaired self-recognition (Waters, Woodward, Allen, Aleman, & Sommer, 2012) as well as externalizing bias (Brookwell, Bentall, & Varese, 2013) in patients with schizophrenia and particularly those with AVH.

At a neuronal level, according to the model, areas of interest include the temporal cortex involved in inner speech perception, medial prefrontal cortex, posterior cingulate cortex, and precuneus for processing information about self (Heatherton, 2011) as well as the PFC that facilitates monitoring processes. The PFC dysfunction was already mentioned earlier relating to the aberrant memory model of AVH and may explain why hallucinations are experienced as involuntary. The dysfunction of the right dorsolateral PFC in combination with a volume reduction in the left hemisphere auditory and speech perception areas may underlie the inability to inhibit and correctly attribute inner speech (Gaser et al., 2004). In addition, a series of studies using a task that requires subjects to monitor their own speech found an atypical pattern of temporal, parahippocampal, and cerebellar cortical activation in hallucinating patients (Seal et

al., 2004). A very recent review article on the subject matter summarizes the evidence as follows:

> Auditory cortex responses are suppressed during vocalization. Connectivity between frontal (perhaps Broca's area) and temporal areas (auditory cortex) has been suggested to be responsible for the auditory cortical suppression, as the degree of connectivity between these areas during talking is related to the degree of suppression. This communication could signal the arrival of self-generated sensations (Curcic-Blake et al., 2017, pp. 3-4).

Taken together, these findings support the theory that AVH reflect abnormal activation of auditory pathways (Lennox et al., 2000). However, several researchers in the field agree that the model is insufficient in that it falls short of accounting for the complexity and severity of AVH as well as certain aspects of their phenomenology, e.g., multiple voices, third-person talk (Curcic-Blake et al., 2017; Fovet et al., 2016; Upthegrove et al., 2016).

Predictive processing framework

Following on from the above-mentioned shortcomings of the self-monitoring account, Wilkinson (2014) expressed a need for explanation on the emerging challenges of auditory phenomenology and varieties of AVH. The first challenge entails the transformation into hallucinations that often have the acoustical properties of someone else speaking, e.g., pitch and timbre. Yet, inner speech is generally lacking these characteristics (Cho & Wu, 2013). The second one emphasizes the heterogeneity of AVH, e.g., first-person vs. second- or third-person, and single or multiple voices, which, too, cannot be accounted for by self-monitoring processes exclusively. Wilkinson realized that these AVH-specific phenomena can be accounted for within a predictive processing framework (PPF, Fletcher & Frith, 2009). According to the PPF, to explain input the brain generates hypotheses about its cause and based on these determines

subsequent predictions about expected input. It settles for one hypothesis rather than another if "it better *minimises prediction error*" (Wilkinson, 2014, p. 146, italics from original). This can be done either by altering predictions to fit the incoming input or by altering the 'world' (oneself, including bodily posture and attention) to fit the predictions. Thus, within the framework of PPF, AVH are seen as 'abnormalities in predictive processing' due to defective precision weighting. More specific, heightened attention on, for example, ongoing thoughts or memories causes erroneous amounts of prediction error that needs to be accounted for by adopting the (faulty) hypothesis of perception (Wilkinson, 2014).

Evidence for this account stems from studies examining perceptual illusions (in which expectancies play a crucial role) that usually find those not working for schizophrenic patients, e.g., the Hollow Mask Illusion (Schneider et al., 2002) or the McGurk Effect (Pearl et al., 2009) suggesting a breakdown in perceptual and predictive processing. Furthermore, the prediction error signal is thought to be modulated by the neurotransmitter dopamine which is of particular importance in schizophrenia (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010). Neuroimaging studies of prediction error dysfunction suggest involvement of the midbrain, i.e., the basal ganglia, the prefrontal cortex, especially the anterior cingulate cortex and the orbitofrontal cortex, and the hippocampus (Corlett et al., 2010). And indeed, hallucinations in schizophrenia seem to be associated with dysfunction in these and other brain regions: "[…] a reasonably robust pattern of implicated regions has emerged including the […] inferior frontal gyrus […]; […] the parahippocampal gyrus and hippocampus […]; the middle and superior temporal gyri […]; and the thalamus" (Tracy & Shergill, 2006, p. 651). Moreover, limbic and paralimibic regions, including the cingulate gyrus, as well as orbitofrontal cortex have been demonstrated to show abnormal activation in hallucinating individuals (Silbersweig et al., 1995) supporting the notion that prediction error dysfunction may underlie AVH. Figure 6 presents a pictorial overview of the involved brain areas.

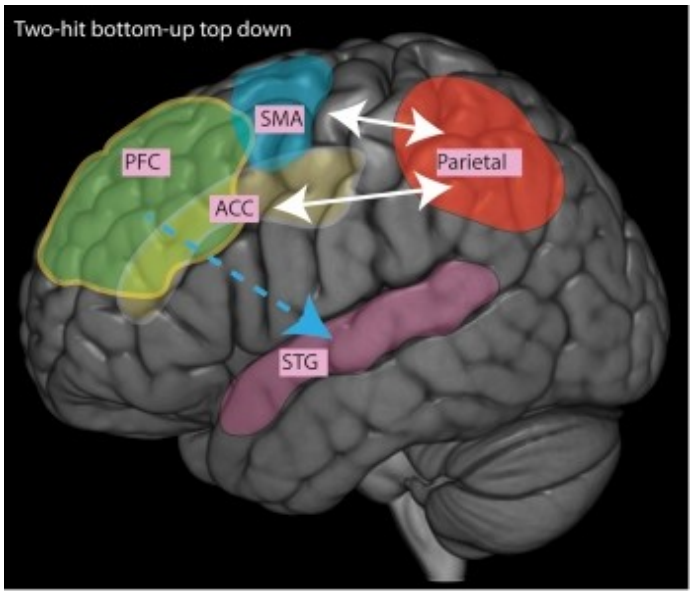

Figure 6. Predictive processing framework.

Arrows illustrate the direction of influence; the dashed blue line illustrates an increase in excitation. With kind permission, illustration taken from Curcic-Blake et al. (2017), p. 4; detail.

Summarizing the above explanations, each presented cognitive model of AVH in schizophrenia builds upon flaws and serious challenges faced by the aforementioned account. At present, the predictive processing framework is best able to explain a vast amount of research findings, whether neurocognitive or phenomenological. However, as Powers, Kelley, and Corlett (2016) put it: "precision weighting awaits more extensive empirical investigation in humans" (p. 4). It should be further noted that the neuroimaging evidence presented for each model, in fact, overlaps in large parts and thus, for itself, does not favor any of the presented theories.

2.3 Summary

AVH are defined as a sensory experience of hearing voices in the absence of a corresponding external stimulus with a compelling sense of reality. They are one of the core symptoms of schizophrenia. About 50-80% of patients with schizophrenia experience AVH (Andreasen & Flaum, 1991; Cutting, 2007; Shergill et al., 1998), such as commenting, commanding, and conversing voices. Although in a majority of cases 'hearing voices' can be sufficiently treated

by antipsychotic medication, 25-30% do not respond to pharmacological treatment and thus persist and become chronic (Davis et al., 1980; Shergill et al., 1998). Other treatment options include CBT and various brain stimulation techniques. Treatment-refractory AVH, obviously, cause significant psychosocial impairment and a reduction in quality of life. Therefore, AVH have attracted extensive clinical and phenomenological research for several decades. With the introduction of neuroimaging techniques such as the MRI and CT in the 1960s and '70s the focus has shifted to investigate the neurobiological underpinnings of AVH. Consequently, this development has led to a better understanding of this subjective phenomenon. In the last few years, however, research has focused on early manifestations and disease process despite the subgroup of chronic voice-hearers whose therapy refraction causes major distress and affects their lives substantially (Vauth & Stieglitz, 2007). It should, therefore, be emphasized that treatment-refractory AVH are highly in need of fundamental research. To date, the precise neurocognitive and neurobiological mechanisms contributing to AVH occurrence are still largely unknown with partly divergent models and different studies providing inconsistent results. So far, the neuroscientific state of evidence regarding AVH in schizophrenic patients points to morphological and functional changes in frontal, temporal and parietal regions as well as abnormal network connectivity in the brain. Multiple neuronal systems seem to be involved, i.e., language, attention, and executive control. In addition, research results accumulate indicating that AVH on a neurocognitive level are associated with "impaired verbal self-monitoring and impaired memory for own speech; an abnormal influence of top-down processing on perception; and an externalizing response bias" (Seal et al., 2004, p. 60). However, the overall trend in schizophrenic research is a failure to find a positive correlation of cognitive deficits with positive symptoms (Keefe & Harvey, 2012). These inconsistencies suggest that the extent of cognitive deficit associated with AVH in schizophrenic patients, especially in comparison with non-AVH patients is still largely a matter of debate.

To conclude, persistent treatment-refractory AVH are associated with circumscribed neuronal deficits and potentially with cognitive deficits. However, the patients' heterogeneity as well as unsuccessful attempts to reproduce some of the published findings leave questions on the exact relationships between functional and structural aberrancy as well as psychopathology at the symptom level. Therefore, Thönnessen and Mathiak (2008) advocate an integrated neuroimaging method that combines dynamic and connectivity dimensions with anatomical information to achieve a functional understanding of these dysfunctions.

2.4 The present study

As the present thesis is part of a larger DFG-funded project (WO 1883/2-1) the derived research questions and associated hypotheses present only a part of the full spectrum of potential research focus. This doctoral thesis focuses on the potential association between functional neuroimaging data, clinical symptoms, and specific cognitive processes regarding treatment-refractory and persistent AVH in schizophrenia. To achieve a comprehensive understanding a combination of a detailed registration of clinical symptoms as well as multimodal structural and functional neuroimaging is advantageous. Therefore, the present thesis used a combined approach to record functional RSN and experimentally activated neuronal systems as well as psychometric data and neuropsychological test results. The majority of studies so far are limited to a comparison between a patient group of schizophrenic patients with persistent AVH (pAVH) and a healthy control group (HC). Few compare with a clinical control group comprising schizophrenic patients without AVH additionally (nAVH). For example, to date, not a single study has been conducted to compare the cognitive profile of hallucinating individuals to that of non-hallucinating patients and healthy control participants. The aim of this thesis is to complement the existing literature in that regard by comparing two patient groups (with and without AVH) with a healthy comparison group. Thus, the present cross-sectional study used a

between-subjects factor design with group (hallucinating, non-hallucinating, and healthy individuals) as naturally occurring condition that could not be randomized.

A symptom interference approach was chosen, in which AVH are thought to compete with auditory stimuli and verbal processing for neuronal resources (Plaze et al., 2006). The alertness task and n-back task were chosen as functional MRI (fMRI) activation paradigms; the alertness task measuring intrinsic and phasic alertness and the n-back task measuring verbal working memory (WM). Both paradigms were chosen, inter alia, because of their auditory/verbal nature: The alertness task possesses an auditory component by using an auditory stimulus as preceding warning tone while the n-back task makes use of verbal processing by using letters as visual stimuli. Furthermore, both paradigms were successfully used in the past (Wolf et al., 2012), the underlying cognitive domains (Kathmann & Reuter, 2008; Wolf & Walter, 2008) as well as neural correlates and involved networks are well described (Muller & Knight, 2006; Sturm & Willmes, 2001) and show a well-documented association with schizophrenia (Wolf et al., 2011; Wolf, Vasic, Höse, Spitzer, & Walter, 2007; Wolf, Vasic, & Walter, 2006), rendering them attractive for study in relation with AVH. In addition, deficits in WM are thought to underlie the genesis of AVH (Jenkins, Bodapati, Sharma, & Rosen, 2018). Not only that, the n-back has been extensively studied internationally in the context of schizophrenia (Glahn et al., 2005).

The present study tries to answer the question whether AVH are associated with common or distinct neural activation patterns in frontal, parietal and temporal areas compared to two control groups, i.e. one clinical population and a healthy control sample. Furthermore, it tries to elucidate the question of spatial correspondence between these functional activation patterns and performance on the task, neuropsychological measures of cognitive functioning, as well as psychopathology as defined by symptom-specific psychometric measures.

Considering the extant functional neuroimaging data on AVH in schizophrenia and expanding on previous findings as described above, based on the presented research questions the following hypotheses will be examined:

1. Both fMRI activation paradigms lead to different functional neural activation patterns in pAVH compared to nAVH as well as HC.
   a. Specifically, for the alertness task, it is predicted that pAVH will show a specific attenuated activation in brain areas where attentional processes are required, i.e. the right fronto-parietal attention network comprising the intraparietal sulcus, the inferior parietal lobe, and the dorsal premotor cortex as well as in the auditory cortex and supplementary motor area (Fox et al., 2005). According to the aforementioned symptom interference studies the alertness task is hypothesized to exert reduced neural activation in the attention network of pAVH when compared with both control groups.
   b. For the n-back task, it is predicted that patients with AVH in relation to both comparison groups show attenuated activation in a network commonly associated with WM tasks, comprising the DLPFC, the VLPFC, and the inferior parietal lobule (Wolf et al., 2009). Again, in accordance with assumptions of symptom interference studies the n-back task is thought to lead to reduced neural activation in the WM network in pAVH when compared with both control groups.

2. In patients with AVH, the extent and location of neural dysfunction related to hallucinating will interfere with neural function, i.e. attention and WM elicited by specific cognitive tasks, i.e. alertness and n-back task.
   a. For the alertness task, it is predicted that for hallucinating individuals there is a negative correlation between brain activation and behavioral performance as operationalized in

terms of reaction times and false negative rates. That is, the lower the neural activation in the attention network due to it being 'bound' by AVH, the higher the reaction times and the false negative rates; thus, the poorer the performance.

b. For the n-back task, in patients with AVH, it is predicted that there is a negative correlation between brain activation and behavioral performance as operationalized in terms of reaction times and error rates (false negatives and false positives). In accordance with the identical hypothesis for the alertness task, reduced neural activation in the corresponding networks is thought to be associated with higher reaction times and error rates.

3. AVH-related neural activation on both paradigms is associated with neuropsychological performance off-line, i.e. outside the MRI scanner. That is, hallucinations interfere with other ongoing cognitive processes, beyond alertness and verbal WM. The rationale of this prediction is best described in terms an 'extended symptom interference' assumption, i.e. that neural substrates associated with symptom occurrence will interfere with several cognitive functions apart from what can be investigated with fMRI. Therefore, it is predicted that hallucinating subjects exhibit worse performance in tasks demanding attention, spatial and verbal WM and executive function compared to controls and non-hallucinating patients.

4. AVH-related brain regions exhibiting task-related neural dysfunction are predicted to be negatively correlated with psychopathology. Following and expanding upon the findings by Kubera et al. (2014), it is predicted that physical characteristics, such as loudness, intensity and spatial location are associated with a dysfunction of temporo-parietal regions whereas affective and cognitive dimensions are associated with cingulate and dorsolateral prefrontal cortex function, respectively. Reduced neural activation in pAVH is predicted to

be associated with higher scores in physical characteristics, in accordance with the basic concept of the symptom interference approach.

Since the statistical null hypothesis does not postulate any difference between the groups, the representative null hypothesis for all alternative hypotheses is mentioned at this point: The groups do not differ on any of the postulated comparisons and, furthermore, the group has no effect on any measurement variable.

3 Methods

The current chapter comprises a detailed description of the research questions and according hypotheses as well as the methodology used for the purpose of scientific investigation. First, the process of study enrollment, including inclusion and exclusion criteria of participants is described followed by a description of the studied sample. Subsequently, the procedure each individual has undergone is outlined. Thereafter, the used measurements, divided in subchapters comprising fMRI, applied neuropsychological assessment, and psychiatric interview, are presented in detail. Finally, the statistical procedures for the data analysis are depicted.

The illustrations were created using Paint Version 6.1 (Microsoft Windows 7), Microsoft Publisher and Excel (v14.0.7015.1000, Microsoft Office Professional Plus 2010) as well as MRIcron version 6 6 2013.

3.1 Participants

3.1.1 Inclusion/exclusion criteria

Inpatients and outpatients aged 18-65 years were considered if the attending psychiatrist had established a clinical ICD-10 F20 schizophrenia diagnosis that was confirmed by the research psychiatrist based on clinical impression and semi-structured interviews. All patients were assessed using the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Furthermore, study inclusion was bound to the absence of an organic and/or mental disorder, neurological disease or head injury as well as any signs of mental retardation, substance abuse within the last six weeks and substance dependence (except nicotine) in the past year, and the absence of any type of suicidal ideation.

The patient group was divided into individuals experiencing AVH and individuals who did not experience such symptoms for at least 12 months prior to neuropsychological assessment and MRI scanning, based on detailed information regarding clinical history, current symptoms as well as test scores (PANSS-P item 3, BPRS item 12). In particular, patients were assigned to the pAVH group if they reported hearing voices daily and scored equal to or higher than 4 on item 3 (hallucinations) of the PANSS Positive Symptom Scale and 5 or higher on item 12 (hallucinations) of the BPRS. The inclusion criteria are summarized in Table 2.

Table 2

Inclusion criteria

	inclusion criteria
general	(1) Subjects are between 18 and 65 years of age. (2) Subjects have no neurological disorder. (3) Subjects have no history of unconsciousness or coma related to head trauma. (4) Subjects do not fulfill the criteria for substance abuse or -dependence during the last 12 months. (5) Subjects have no contraindication for MRI-scanning[2].
schizophrenic patients with AVH	(1) Subjects are diagnosed with schizophrenia according to ICD-10 criteria. (2) Subjects have sufficient insight into the illness. (3) Subjects have persistent auditory verbal hallucinations daily. (4) AVH remain persistent despite unsuccessful medication with at least two antipsychotics.
schizophrenic patients without AVH	(1) Subjects are diagnosed with schizophrenia according to ICD-10 criteria. (2) Subjects have sufficient insight into the illness. (3) Subjects did not have any AVH during the last 12 months.
healthy controls	(1) Subjects do not have any psychological or neurological disorder. (2) Subjects have a negative family history of neurological or mental disorders.

[2] General MRI contraindications include for example metal parts in or on the body such as piercings or tattoos with magnetic color particles, implants, coronary stents, insulin pumps, pacemakers, and pregnancy.

Healthy control subjects were matched on age, gender, and education on a group-wise level. They were excluded from participation when self-reports revealed a neurological and/or mental disorder, a positive family history of neurological and/or mental disorder or past and/or present substance abuse or dependence excluding nicotine.

3.1.2 Subject enrollment

During the term of the present research study 135 inpatients with a diagnosis of schizophrenia were identified. In addition, nine outpatients volunteered for participation coming to a total of 144 potential study participants regarding the patient group. Of those, 15 patients presented with acute symptoms, had no insight into their illness or had restricted cognitive abilities, 13 had physical or mental conditions that were incompatible with the study design (epileptic seizures, stroke, other brain injuries, claustrophobia or non-removable metal parts in or on the body), in seven patients the diagnosis of schizophrenia could not be confirmed, nine had a recent history of substance abuse or dependency, two patients had communication/ language comprehension problems, one did not meet inclusion criteria for one of the two groups, i.e., the patient did not experience AVH at the moment but did experience AVH during the last 12 months, and one out-patient lived outside of the recruitment area leaving 96 potential study participants. Of those ten were lost due to discharge or relocation and 29 refused to take part in the study so that 57 of the initial 144 patients could be included. With drop-outs during the study due to discomfort in the MRI scanner (n=3), and again, disconfirmed diagnosis (n=2) and unfulfilled inclusion criteria for the two groups (n=2) 50 individuals remained. This gives a response rate of 34.72% among patients. Of these 50 patients, 3 had to be excluded due to left-handedness, 13 because of missing data, 7 because of ghosting artifacts (5 for the alertness task), and another 4 (3) because of movement artifacts, leaving 23 (26) patients for analyses.

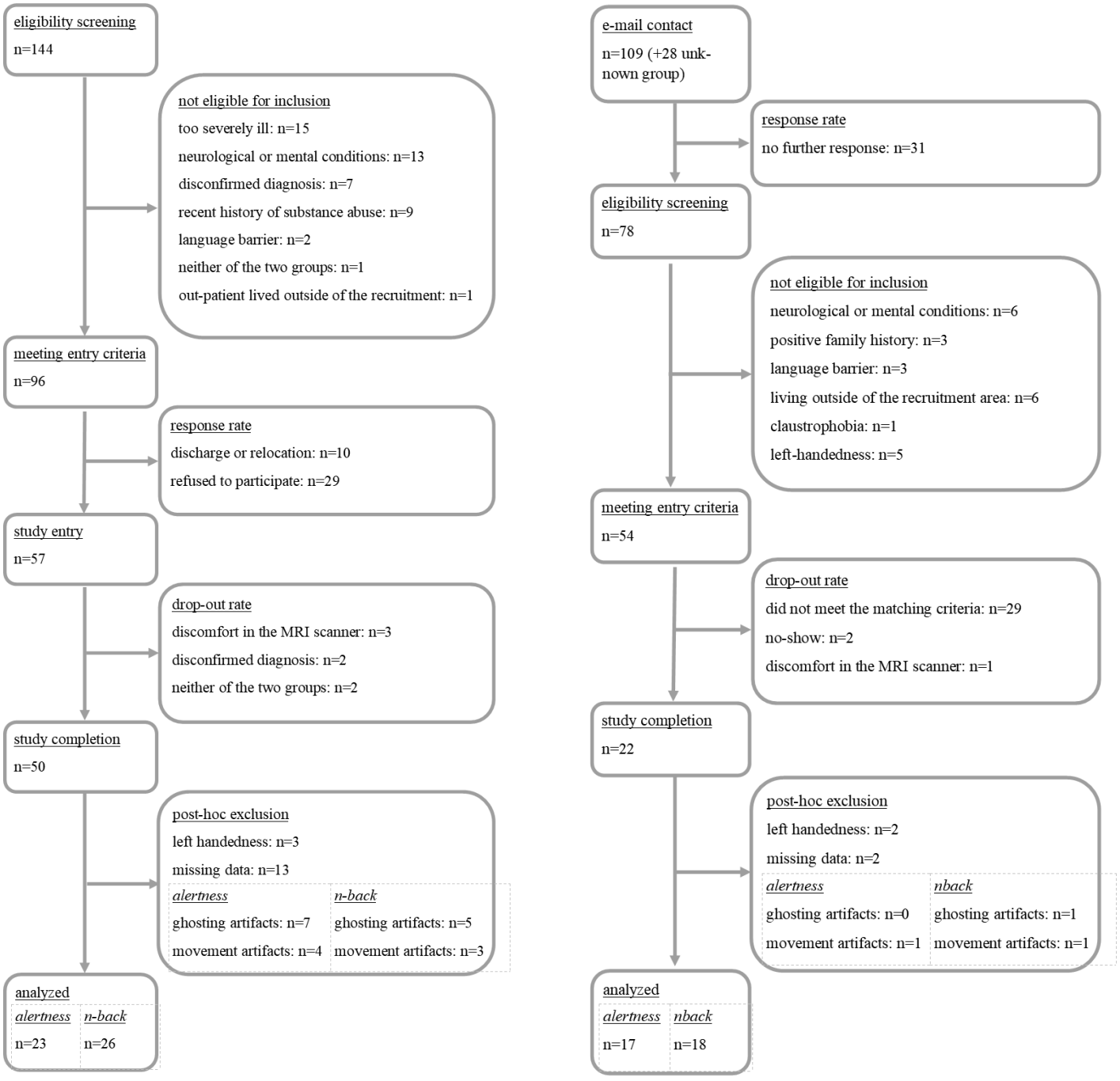

Figure 7. The enrollment process for patients with schizophrenia and control participants.

Enrollment process for both, patients with schizophrenia (including hallucinating as well as non-hallucinating individuals) and healthy control subjects, is presented in Figure 7.

3.1.3 Sample description

A total of 44 participants participated in the current study, schizophrenic patients: n=26 and healthy controls: n=18. Participant's mean age was *M*=34.57 years (*SD*=12.31; range 18-57) and 59.09% (male to female ratio 26:18) were male. Group comparisons were performed using analyses of variance (ANOVA) for three groups as well as independent-samples t-tests for numerical data for two groups and the Chi-square test for continuous data. Chlorpromazine equivalents (CPZ) were calculated for both patient groups according to Woods and supplemented by Leucht (Leucht, Samara, Heres, & Davis, 2016; Leucht et al., 2015; Woods, 2003). Table 3 provides an overview of participants' characteristics.

The three groups - pAVH, nAVH, and HC - did not differ significantly in age ($F(2,41)=.276$, $p>.05$), gender ($\chi^2(2)=2.764$, $p>.05$), years of education ($F(2,40)=1.915$, $p>.05$), and fluid intelligence as measured with the 'Leistungsprüfsystem' (Horn, 1983) ($F(2,41)=.290$, $p>.05$). The two patient groups did not differ on duration of illness ($t(24)=-.023$, $p>.05$), antipsychotic treatment dosages measured in CPZ ($t(24)=1.460$, $p>.05$), negative symptoms as measured with the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS) ($t(24)=1.340$, $p>.05$), and global symptom severity as measured with the PANSS global severity index ($t(24)=1.405$, $p>.05$). However, patients with and without AVH did differ in positive symptoms as measured with the PANSS positive symptom subscale (pAVH: *M*=17.43, *SD*=4.36; nAVH: *M*=12.0, *SD*=4.51), $t(24)=3.105$, $p=.005$ and overall symptomatology as measured with the BPRS total score (pAVH: *M*=44.64, *SD*=6.77; nAVH: *M*=34.75, *SD*=9.43), $t(24)=3.027$, $p=.007$. When factoring out the AVH-item, thus subtracting it from the respective total score, the group differences were no longer significant (PANSS-P: $t(24)=1.112$, $p>.05$; BPRS: $t(24)=1.857$, $p>.05$).

Table 3

Demographic and clinical characteristics of the study sample

	Group; mean (SD)			
Characteristic	**pAVH, n=14**	**nAVH, n=12**	**HC, n=18**	***p* value**
age, a	32.93 (11.63)	34.08 (11.91)	36.17 (13.53)	*ns*
sex, male:female	10:4	8:4	8:10	*ns*
education, a	13.64 (2.82)	15.5 (2.57)	15.24 (2.68)	*ns*
fluid intelligence, raw	29.71 (4.39)	30.92 (5.05)	29.22 (7.49)	*ns*
duration of illness, a	10.91 (10.98)	11.0 (8.55)	-	*ns*
CPZ equivalents	549.71 (305.87)	380.82 (280.39)	-	*ns*
PANSS-P	17.43 (4.36)	12.0 (4.51)	-	*.005*
PANSS-P min AVH item	12.93 (4.29)	11.0 (4.51)	-	*ns*
PANSS-N	17.71 (5.58)	14.25 (7.31)	-	*ns*
PANSS-G	33.86 (6.35)	29.92 (7.74)	-	*ns*
BPRS	44.64 (6.77)	34.75 (9.43)	-	*.007*
BPRS min AVH item	39.79 (6.65)	33.75 (9.43)	-	*ns*
PSYRATS emotional index	11.36 (2.341)	-	-	-
PSYRATS physical index	6.00 (1.569)	-	-	-
PSYRATS cognitive index	9.50 (2.245)	-	-	-
PSYRATS total	26.86 (4.312)	-	-	-

Note. a=years, CPZ=chlorpromazine, PANSS=Positive and Negative Syndrome Scale, PANSS-P=PANSS Positive symptoms subscale, PANSS-N=PANSS negative symptoms subscale, PANSS-G=PANSS global severity index, BPRS=Brief Psychiatric Rating Scale; fluid intelligence as measured with subtest 3 from the Leistungsprüfsystem; regarding the PSYRATS only the auditory hallucination subscale was used.

All patients were receiving standard antipsychotic medication with a stable drug treatment regime for at least two weeks prior to study enrollment.

3.2 Measures

The measures used in the current project can be divided as belonging to three domains: fMRI, neuropsychology, and psychopathology (including psychometric data). Figure 8 gives a pictorial overview over the used measures that will be introduced and explained in the course of this chapter.

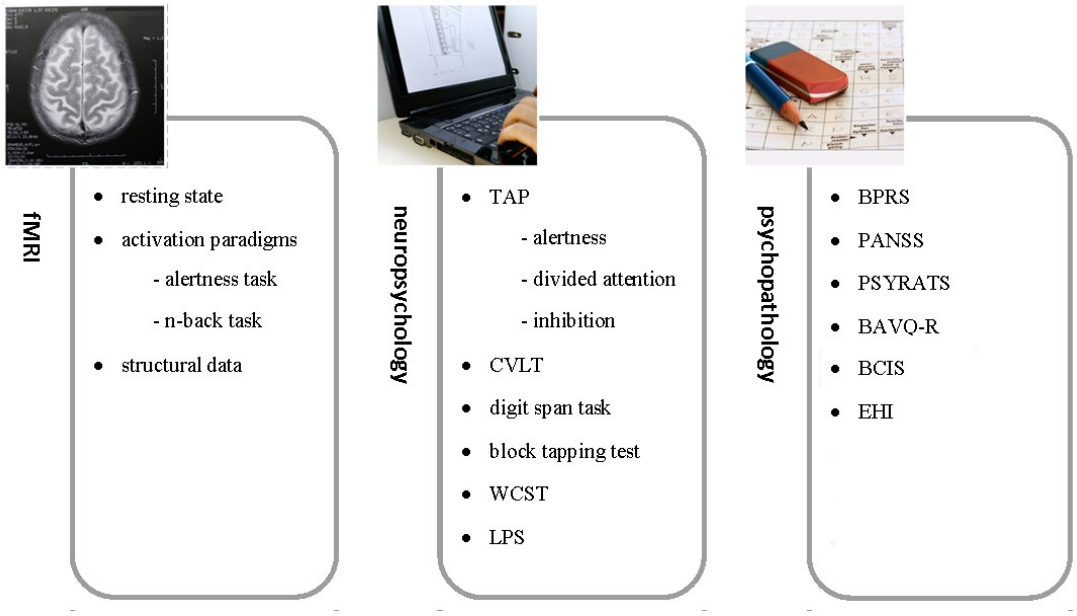

Figure 8. Overview over the used measures.

TAP=Test for Attentional Performance, CVLT=California Verbal Learning Test, WCST=Wisconsin Card Sorting Test, LPS=Leistungsprüfsystem, BPRS=Brief Psychiatric Rating Scale, PANSS=Positive and Negative Syndrome Scale, PSYRATS=Psychotic Symptom Rating Scale, BAVQ=Beliefs About Voices Questionnaire, BCIS=Beck Cognitive Insight Scale, EHI=Edinburgh Handedness Inventory. A detailed description of all procedures and measures follows throughout the chapter. With kind permission for free usage, illustrations taken from www.pixelio.de from Dieter Schütz, I-vista, and birgitH.

3.2.1 Functional magnetic resonance imaging – fMRI

Magnetic resonance imaging (MRI) is a neuroimaging procedure. It is based on the physical principle that protons have an intrinsic 'spin' and are therefore magnetic. The MRI procedure makes use of a combination of static and high-frequency magnetic fields that selectively excite protons in the examined tissue. While the static magnet field results in a parallel alignment of the protons, the high-frequency pulse provokes a transverse magnetization. After switching off the high-frequency pulse, the transverse magnetization decreases so that the protons return to a parallel alignment to the static magnetic field. This process can be measured. FMRI is based on the different magnetic properties of oxygenated and non-oxygenated hemoglobin (Blood Oxygen Level Dependent, BOLD effect). Neural activity increases the local metabolism. This results in increased blood flow leading to regional changes in the oxygen content of the blood. The measurement of these changes accordingly allows conclusions about the neural activity (Schneider & Fink, 2013).

Neuroimaging data were acquired in cooperation with the Department of Neuroradiology at the University Hospital Heidelberg, Germany. Prior to fMRI scanning, subjects received training in the experimental paradigms that were to be carried out in the scanner. In addition, the equipment was tested for appropriate functioning. Furthermore, participants received further MRI specific instructions by the staff and were informed about the bell to alert the technician in case of emergency.

A 3 Tesla Siemens MRI Scanner equipped with a 32-channel head coil was used to collect whole-brain structural and functional scans. Where applicable, stimuli were presented on a screen behind the MRI-scanner that was visible to participants via a mirror placed above the coil. Scans were performed in darkness. The scanner protocol included four measurements in the following order: a resting-state scan, two experimental paradigms, and a structural scan. Participants were instructed to not fall asleep and move as little as possible during the scanning

process. Task-related performance measures such as reaction times were recorded using MRI-compatible devices.

Resting-state

In the absence of external task demands, the inherent pattern of brain activity becomes observable. These so-called 'resting-state fMRI' approaches offer the potential of identifying brain activity at 'rest'. Resting-state fMRI is based on the assumption that the resting brain always exerts a certain amount of neural background activity that can be measured by fluctuations in the local BOLD signal (Grodd & Beckmann, 2014). Participants were instructed to keep their eyes closed and to not think about anything in particular during resting-state MRI. The resting-state protocol lasted 6min and 44s. In this time, 200 whole brain volumes were recorded in a transverse (axial) orientation with a repetition time (TR) of 2000ms; echo time (TE)=30ms, field of view (FoV)=192mm, flip angle=90°, voxel size=3×3×3mm, 33 slices, slice thickness=3mm, distance factor between slices (slice 'gap')=33%.

Activation paradigms for fMRI

The used experimental activation paradigms (one examining alertness and one examining verbal WM) fall within the category of symptom interference studies. Both paradigms were successfully used in the past (Wolf et al., 2012), show a well-documented association with schizophrenia (Wolf et al., 2011; Wolf et al., 2007; Wolf et al., 2006), rendering them attractive for study in relation with AVH, and the underlying neural correlates are well described (Muller & Knight, 2006; Sturm & Willmes, 2001).

Alertness task. Intrinsic and phasic alertness were assessed using a non-verbal alertness task. The task was programmed with Presentation® (Neurobehavioral Systems, Inc.) to match the

corresponding task from the 'Test for Attentional Performance' (TAP; Zimmermann & Fimm, 1995) according to a description found in Wolf et al. (2012). The programming was accomplished with the help of Dr. Ruth Schmitt, Dr. Ruth Adam, and Dr. Stephan Walther, employees of the Department of General Psychiatry in 2014.

The task is to press a button immediately after the appearance of an oblique cross on the otherwise black computer screen. It comprises two conditions: The first condition is meant to measure intrinsic alertness (IA). In the IA condition, the task is simply to press the button on the appearance of the visual stimulus. The stimulus is, however, presented at quasi random time intervals with a jittered intertrial interval (595-1495ms) and a second jitter prior to the appearance of the stimulus (160-1060ms) to create nonrhythmic appearance. The second condition is meant to measure phasic alertness (PA). In the PA condition, the oblique cross is preceded by a short auditory warning tone, a 'beep', of approximately 460hz and a fixed duration of 500ms. Participants were instructed to not respond with the button press until the oblique cross appears thereafter. Again, there was a programmed intertrial interval jitter (755-955ms) and a pre-target jitter (200-400ms). Figure 9 outlines the procedure in visual form.

Presentation of the visual stimulus had a fixed duration of 500ms, with a response dependent abortion. The conditions were presented in a block design with each block consisting of 10 trials with duration of each trial of approximately 2,2ms and each block lasting 22s. Each condition was presented 4 times in a pseudo-randomized order: IA(1) – PA(1) – PA(2) – IA(2) – IA(3) – PA(3) – PA(4) – IA(4). Between two blocks, an interblock interval acting as baseline consisting of a white dot in the center of the black screen was presented for another 22s. Before scanning, all participants were trained offline. Task performance is recorded in terms of reaction times (RT) as well as hits and stimulus omissions.

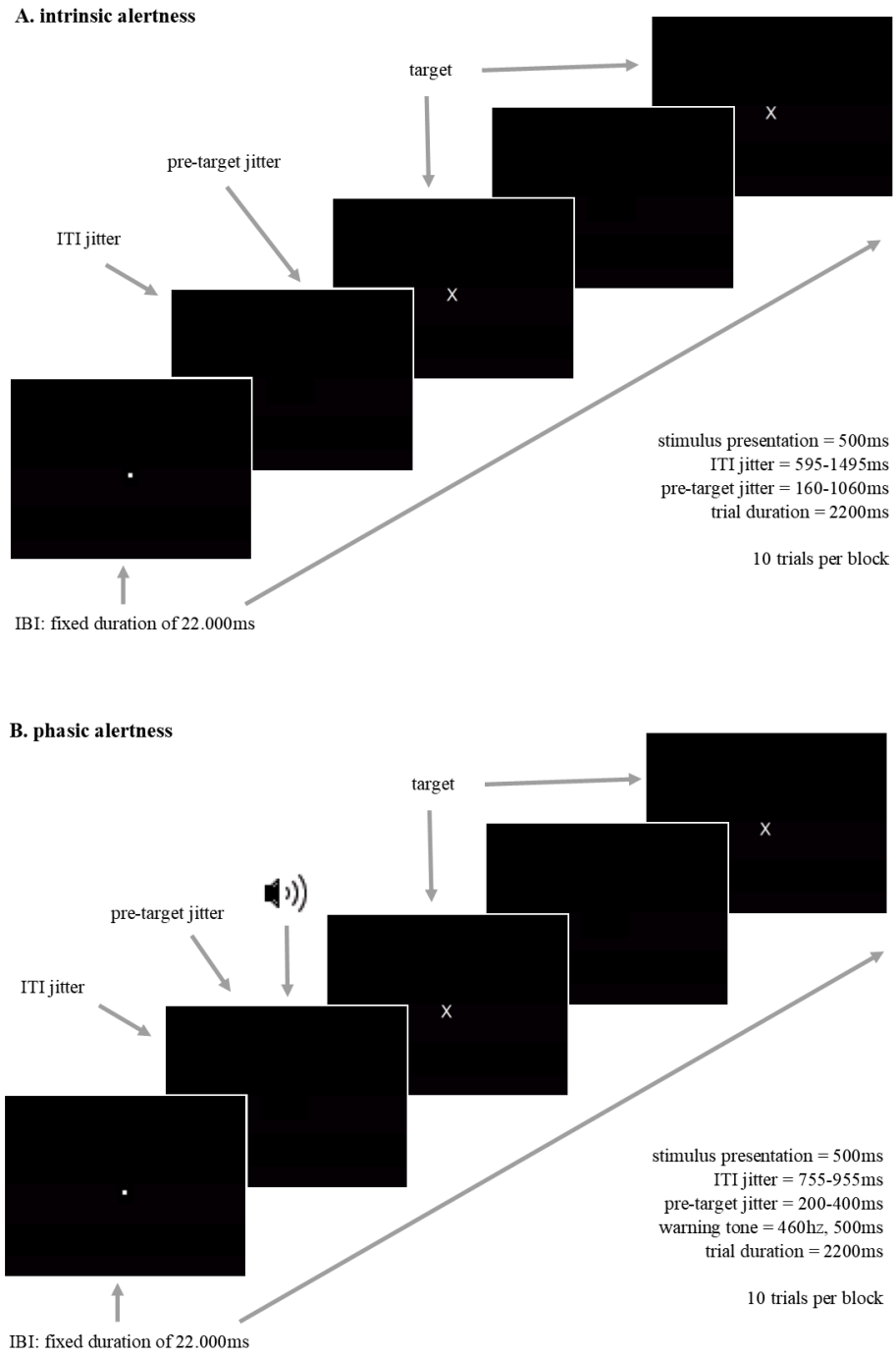

Figure 9. Outline of the alertness task.

A. Condition without preceding warning tone measuring intrinsic alertness, **B**. Condition with preceding warning tone measuring phasic alertness. In both conditions, the participant is instructed to reply with a button press to the target, 'X'. ITI=inter trial interval, IBI=inter block interval.

In total, the alertness task protocol lasted 5min 56s. 160 T2*-weighted whole brain EPI images were acquired in an axial orientation; TR=2200ms, TE=29ms, FoV=192mm, flip angle=85°, voxel size=3×3×3mm, 36 slices, slice thickness=3mm, slice 'gap'=33%.

N-Back task. The n-back task (Kirchner, 1958) was used to assess verbal WM. The task was programmed by Dr. Jacob Lahr and provided by Dr. Elisa Scheller, both from the University Hospital in Freiburg, Germany. The task was adopted by Dr. Stephan Walthers to fit the requirements of the current project.

During the task, participants are presented a sequence of visual stimuli, in this case letters. The presentation takes place one by one. White letters are presented on a black screen. The task demands to indicate for each individual letter if the current stimulus is the same as the one n trials ago. The n indicates the number of trials, e.g., 1-back asks participants to remember the letter one trial back. The higher the number, i.e., the more trials you must remember, the more difficult the task. Participants need to press the response button only for those trials where the stimulus matches the one n trials ago and are instructed not to respond on all other trials. Figure 10 shows an exemplary representation of the 2-back condition.

The task used in this project comprises a 0-back, i.e., an attention task of low-complexity, as well as 1-back and 2-back condition. The letters 'A', 'B', 'H', 'K', 'T', 'U', and 'V' were used as visual stimuli as they are easy distinguishable in visual appearance. The specific sequence of letters was presented in a pseudo randomized order.

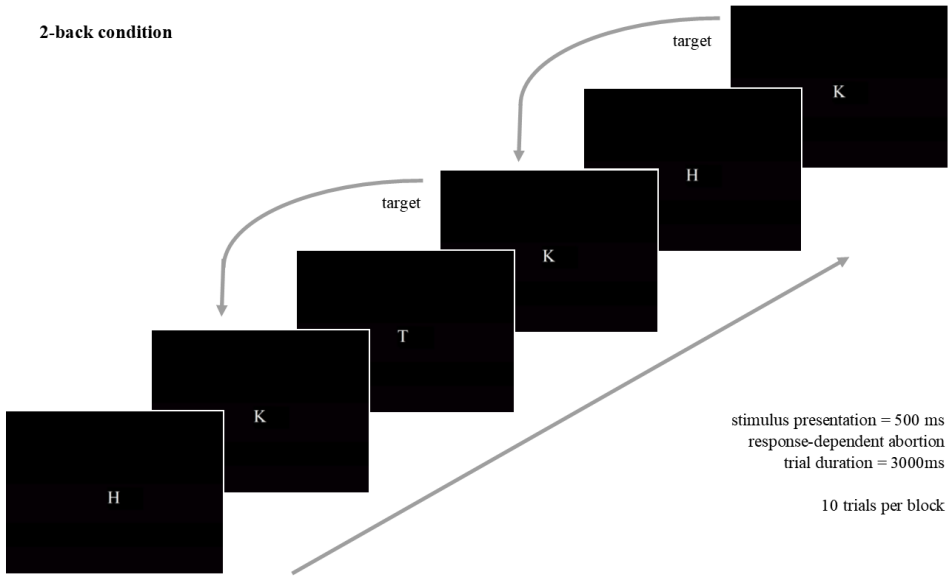

Figure 10. Outline of the n-back task.

The 2-back condition asks the participant to remember the penultimate letter and respond with a button press whenever the current stimulus matches the second last.

Presentation of the visual stimulus had a fixed duration of 500ms, with a response-dependent abortion. Total trial duration including response time was fixed at 3s. No jitter was added before or after the stimulus presentation. The conditions were presented in a block design with each block consisting of 10 trials. Each condition was presented 4 times in a predefined order: 1-back(1) – 2-back(1) – 0-back(1) – 2-back(2) – 0-back(2) – 1-back(2) – 1-back(3) – 2-back(3) – 0-back(3) – 0-back(4) – 1-back(4) – 2-back(4). Before scanning, all participants were trained offline.

Neuroimaging data acquisition for the n-back task included 205 T2*-weighted whole brain EPI images in an axial orientation; TR=2230ms, TE=30ms, FoV=192mm, flip angle=85°, voxel size=3×3×3mm, 36 slices, slice thickness=3mm, slice gap=20%. Task performance is recorded in terms of reaction times (RT) as well as hits and misses. In total, the n-back task protocol lasted 7min 42s.

Structural data

At the end of the functional protocol, structural MRI images needed for data preprocessing were acquired. In specific, 192 T1-weighted images were acquired in an axial orientation; TR=1900ms, TE=2.52ms, FoV=256mm, flip angle=9°, voxel size=1.0×1.0×1.0mm, 192 slices, slice thickness=1mm, slice gap=50%. The protocol lasted 4min 26s.

3.2.2 Neuropsychological assessment

For the assessment of cognitive functioning we composed a battery of tests supposed to measure those cognitive functions that were found to be impaired in schizophrenic patients, and are presumably affected in patients with persistent AVH as well (Nuechterlein et al., 2004; Nuechterlein et al., 2008). These are attention (Reichenberg, 2010; van Erp et al., 2015), executive control processes including problem solving skills and flexibility (Neill & Rossell, 2013), inhibition (Laurenson et al., 2015; Neill & Rossell, 2013), WM (Kern et al., 2011), verbal learning (Holmen, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010; Nehra, Grover, Sharma, Sharma, & Kate, 2016), visual learning (Holmen et al., 2010), as well as processing speed (Kern et al., 2011; Reichenberg, 2010; van Erp et al., 2015).

Thus, the cognitive domains assessed in this study included 1. attention, 2. inhibition, 3. learning and memory, 4. verbal and spatial WM, 5. executive function, and 6. processing speed being assessed indirectly via reaction times.

The neuropsychological test battery included the following standardized tests: computerized tests for alertness, divided attention, and inhibition from the ‘Test for Attentional Performance’ (TAP), ‘California Verbal Learning Test’ (CVLT), digit span and Corsi block forward and backward, and a computerized version of the ‘Wisconsin Card Sorting Test’ (WCST). In addition, fluid intelligence and thereby premorbid intelligence was estimated using the ‘subtest 3’ of the ‘Leistungsprüfsystem’.

The computer-based tests from the test battery were run on a computer using Windows 7 Professional as operating system. They were presented on a 15-inch computer screen and 4:3 screen format. Screen resolution was 1280x1024. Participants were seated approximately 50-60cm in front of the screen which was placed on eye-level.

Leistungsprüfsystem

The Leistungsprüfsystem (LPS; English translation: performance test system) is an intelligence test and was developed by Wolfgang Horn (Horn, 1983). The subtest 3: Recognition of (ir-)regularities in geometric figures, version A1, was used as estimation of premorbid intelligence. It is a paper-and-pencil test and based on Raven's 'Progressive Matrices' (Raven, 1938). The test consists of 40 lines and thus 40 trials with each eight symbols in a row. Participants are instructed to find the one symbol that does not fit to the rest of the symbols in the row. Trials are of increasing difficulty level. The time limit is set to 10min. The evaluation is carried out by means of a template with number of correctly identified stimuli as chosen measurement.
According to the manual, standard scores and percentiles are available for the age groups 9 – '50 and older'. They are based on 100 male and 100 female participants each for the groups up to the age of 18; thereafter there were not enough female participants available (Horn, 1983). Test-retest reliability for the overall score is found to be excellent (r=0.95), however, subtest 3 in itself is not that reliable (r=0.66), indicating considerable learning success with repeated tests. In contrast, split-half reliability is found to be 0.90. Regarding validity, subtest 3 is mainly correlated with mathematics and not necessarily with general school performance.

Test for Attentional Performance (TAP)

To measure attention two tests from the 'Test for Attentional Performance' (TAP; Zimmermann & Fimm, 1995) were selected: 'Alertness' and 'Divided Attention'. Inhibition was measured with the 'Go/NoGo' task from the same test battery.

Alertness. Alertness means the ability to maintain in a vigilant state over time that allows responding quickly and adequately to a given challenge and thus represents a basic function of attention. The alertness task used during the neuropsychological assessment resembles the one used during fMRI scanning and is thus already described in the according chapter. In short, alertness is measured with reactions times during two conditions: As a start, the reaction time is simply assessed as button press after the presentation of an oblique cross that is presented at randomly varying intervals (i.e., intrinsic alertness, IA). In the second condition, an audio warning tone is preceding the cross (i.e., phasic arousal, PA). Here, the test consists of four blocks with 20 trials each and is performed according to an experimental ABBA design: IA(1) – PA(1) – PA(2) – IA(2). Before each block, two exercise trials are presented that are not included in the final evaluation. The time required for the test is approximately 4min 30s. The difference between the two reaction times (the auditory warning condition was subtracted from the condition without sound stimulus) is used as measure for alertness.

Divided Attention. Divided attention refers to the ability to attend to multiple requirements at the same time. For the current study, implementation form I (German: 'Durchführungsform I') was chosen from the TAP (Zimmermann & Fimm, 1995) test battery in order to measure divided attention. It is measured with a dual task that demands the simultaneous handling of two tasks, one visual and one auditory. The visual task asks participants to monitor a screen showing a square field of 4x4 positions. At these 16 positions, 6-8 small crosses appear on each

trial. The visual stimuli switch positions at a fixed rhythm of 2s. A button press is required if four adjacent crosses form a square. Simultaneously and synchronously to the change of position of the crosses, participants are presented with two different sounds – a high-pitched tone and a low tone. Presentation of auditory stimuli is 1s and 433ms. For the auditory modality, a button press is required when two consecutive tones are similar. For the visual modality, 100 stimuli are presented of which 17 require a response and thus are critical. The number of auditory stimuli is 200, including 16 targets. Total execution time is 3min and 25s. Hits and misses are recorded. D'prime as sensitivity index for the false-alarm and hit rate over both conditions, calculated using the log-linear correction (Hautus, 1995) was used as measure for divided attention.

Inhibition. In order to assess inhibition the subtest 'Go/NoGo' implementation form '1 out of 2' was selected from the TAP (Zimmermann & Fimm, 1995). The task asks participants to focus attention on the predictable appearance of a stimulus that then requires a selective response. More specific, the Go/NoGo task requires participants to only respond to one critical stimulus in a task with two stimuli. Two stimuli, a plus ('+') and an oblique cross ('x'), are presented in white on the middle of a black screen in an alternating sequence. Participants are instructed to only respond to the oblique cross with a button press as soon as possible. The presentation of stimuli is short (200ms) to provoke a quick response. In total, 20 critical and 20 non-critical stimuli are presented. The task takes approximately 2min. Corresponding hits and misses are recorded. Again, log-linear corrected d'prime was used as measurement of inhibition.

Digit span task

In order to measure verbal WM the digit span task adapted from the Wechsler Memory Scale (WMS-R, Wechsler, 2000) was used. The digits used are not the same as in the original version. However, since the test results were used as raw values to compare them with those of the current sample and not with those from the standard sample of the manual there should be no consideration regarding their use.

Participants are presented with a sequence of numbers increasing in length, and thus in difficulty level, every two trials. The experimenter reads the sequence at a speed of approximately one digit per second. First, participants are instructed to repeat the numbers in the same order as read by the experimenter (forward-condition). Subsequently, the task is to repeat the numbers in reversed order (backward-condition). In the beginning, the sequence entails three digits, both, in the forward and the backward condition. There are two trials per difficulty level. At least one proper response is required to continue with the next longer sequence adding one digit at a time. The task is aborted as soon as the participant fails to repeat at least one of the two trials during the presentation of the same string length correctly. There is no time constriction. The number of correct trials before discontinuation (range: 0-12) for both, forward and backward condition, were used as measurement for verbal WM. The forward condition is thought to test maintenance of information, whereas the backward condition requires both maintenance and further manipulation (Wolf & Walter, 2008) and thus is considered to measure a slightly different aspect of WM.

Block tapping test

Visuo-spatial WM was assessed using an adaptation from the Corsi block, also known as block tapping test or spatial span task (Corsi, 1972), found in the WMS-R (Wechsler, 2000). The test material consists of a wooden board (approx. 22 x 27cm) with spatially similar separated nine

wooden blocks. Participants watch the experimenter tap a sequence of blocks and are asked – analogous to the digit span – to first, mimic the shown pattern (forward-condition) and then to repeat the pattern in reversed order (backward-condition). The blocks are numbered on the experimenter's side of the board, invisible to the participant, to ease the tapping of fixed sequences as well as the recording of the participant's performance. During any particular tapping sequence each block is tapped only once with a speed one block per second. The task starts with a small number of blocks, i.e., three, gradually increasing in length, adding one block every two trials, until the participant's performance suffers. This is the case when two consecutive errors occur within a sequence of the same block length. There is no time restriction on the test. Parallel to the digit span task, the number of correct responses (range: 0-12) is used for analysis.

Standardization for the WMS-R including both tasks, digit span and block span, was performed in 1996-97 with 210 participants between the ages 15-74 years (Wechsler, 2000). Demographic variables were based on the statistical yearbook for Germany in 1995. Test-retest reliability for the digit span task scores r=0.83 and r=0.60 for block span. A review on WM span tasks in general comes to the conclusion that these " show considerable construct validity insofar as they predict performance on a wide array of tasks for which control of attention and thought are important" (Conway et al., 2005).

California Verbal Learning Test (CVLT)

The California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) version 1 was used as an off-line measurement of verbal learning and memory. Participants are presented orally with 16 words from four categories (fish, vegetables, kitchenware, and clothing) that are read to them by the experimenter one by one every second. Participants are unaware of the number of stimuli and their categories. After presentation, participants are asked to repeat the

words they recall. The same procedure is applied five times, every time presenting the same 16 words in the same order. This is followed by a memory test after an interfering word sequence and, again, after a delay of about 20 minutes. Total duration including the 20min waiting period equals approximately 30-40min without time restrictions for the individual rounds. The sum of words recalled after five consecutively repeated presentations of the same 16 words was used as measure of verbal learning (range 0-80).

The odd-even reliability of the CVLT was calculated to be 0.96 while the test-retest reliability after 9 months gave a value of 0.60. Regarding validity, the correlation between the sum score of the CVLT and the subtest logical memory from the Wechsler-Memory-Scale-Revised was calculated to be 0.53. Standardization was achieved with 303 participants without neurological disorder for the age range 20-60 years. Corrections for age, gender, and education were made where needed (Testzentrale, n.d.).

Wisconsin Card Sorting Test (WCST)

The Wisconsin Card Sorting Test (WCST) in its computerized form (Loong, 1989) was chosen as a measurement of executive functioning as it is a well-known instrument and most frequently used in schizophrenia research. It was run with the help of DOSBox Version 0.74 (www.dosbox.com), a free DOS emulator, in full screen mode.

The WCST is composed of response cards that are presented one by one and four stimulus cards that are placed side by side. These stimulus cards show one red triangle, two green stars, three yellow crosses, and four blue circles, respectively. The WCST requires the participant to match the response cards displaying various figures to the stimulus cards by a certain sorting principle, i.e., color, form, or number. This is done by striking the corresponding number on the keyboard (1-4). The participant is, however, not told how to match though he receives feedback on the correctness of his matches on every single trial. The feedback is given in the form of an auditory

response (high tone for correct and low tone for incorrect) as well a visual response ('right' or 'wrong' flashes on the screen). The matching rule is switched after 10 correct responses in a row. Every sorting principle is repeated two times in a predefined order that looks as follows: color(1) – form(1) – number(1) – color(2) – form(2) – number(2). The test has a maximum of 128 trials and ends when six sequences of 10 correct responses have been achieved or when the maximum of trials has been reached. It lasts approx. 20-30mins.

Normative data is available for the manual version of the WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) which is based on 899 subjects. According to the manual, the (manual) WCST has excellent interrater reliability (r=.83-1.00) and research support for its construct validity as a measurement of executive functioning. However, a few findings should be taken into consideration when using the WCST: First, a study conducted to compare the manual and computerized version found significantly different variances from the manual version. This means there is a need for validation and normative (Feldstein et al., 1999). Therefore, interpretation of the computerized version should be done with caution. Second, it should be noted that performance on the WCST does not purely measure executive functioning but reflects a variety of cognitive functions (Keefe & Harvey, 2012). Classically, performance on the WCST is seen as measure of abstract thinking and problem-solving as well as the ability to effectively change problem-solving strategies within the specific context and thus as a measure of cognitive flexibility (Wolf & Walter, 2008). It has been shown to be sensitive to generalized brain damage, i.e., frontal-lobe damage, as well as schizophrenia specific aberrant performance (Feldstein et al., 1999). Nevertheless, the percentage of conceptual level of responses was used as a measurement of executive functioning as it is thought to best assess insight into task principles. It is defined as 'consecutive correct responses occurring in runs of three or more' (Heaton et al., 1993). Note, however, that all performance scores of the computerized version must be treated with caution as is explained above.

3.2.3 Psychiatric interview

Whereas fMRI scan and neuropsychological assessment was realized by the author herself the psychiatric interview was conducted by an experienced psychiatrist (Dr. Katharina M. Kubera, Dr. Dusan Hirjak, or Dr. Falk Mancke). It consisted of both, self-rating questionnaires to be filled out by the participant as well as interview assessment tools that were filled out by the psychiatrist after a thorough interview and clinical observation. The measurement tools are presented thematically sorted.

Brief Psychiatric Rating Scale (BPRS)

The BPRS (Overall & Gorham, 1962) is an observer-rating assessment tool that is based on a clinical interview and is thought to be filled out afterwards. It was developed mainly for the use of efficiently evaluating symptom change in psychiatric patients for the previous week (Overall & Gorham, 1962). It takes approximately 20 minutes and consists of 18 items that are rated on a 7-point scale ranging from 'non-existent' to 'extremely strong': 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderately strong, 6=severe, and 7=extremely severe. Each item was developed based on previous research to assess patients' symptomatology in a relatively discrete symptom complex and is accompanied by a detailed description to facilitate administration. In addition to the total value which can be regarded as the global extent of pathology (total score range 18-126), a five factor structure was suggested for subjects with diagnosis of schizophrenia (Guy, Cleary, & Bonato, 1975): Four items each form the scales of anxiety/depression (4-28), anergy (4-28), and thought disturbance (4-28), respectively, and three items each are necessary for the scales of activation (3-21), and hostility/suspiciousness (3-21). However, recent research findings imply that these subscales might not be quite valid (Lachar et al., 2001; Shafer, Dazzi, & Ventura, 2017) and suggest different factors, e.g., resistance, positive symptoms, negative symptoms, and psychological discomfort. According

to Overall and Gorham, the administration of the BPRS demands a certain level of training. Then, inter-rater reliabilities between 0.56 (for item 6: tension) and 0.87 (for item 12: hallucinations, and item 5: guilt feelings) for the individual items may be achieved.

Positive and Negative Syndrome Scale (PANSS)

The PANSS was developed by Kay, Fiszbein, and Opler (1987) as a standardized measurement for multiple psychotic symptoms. It is a 30-item, 7-point rating psychiatric instrument for the use of clinical interview which can also be answered by reports of primary care staff or relatives. Diagnostic information concern symptoms present during the previous week. Direct questions may be complemented by observation of affective, cognitive, interactive, psychomotor, and perceptual functions. Each item includes detailed operational definitions for each of the seven rating points which represent an increase in severity: 1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderately strong, 6=severe, and 7=extreme. Four scales can be derived from the 30 items measuring positive (score range 7-49) and negative symptoms (7-49), a composite score indicating the magnitude of difference and predominance of one of the syndromes (0-42), and general psychopathology (16-112). Of the 30 items, seven were chosen to represent the positive symptom scale, further seven for the negative symptom scale, and the remaining 16 form the general psychopathology scale. Administration takes approximately 40-50min,

Normal distribution of the four scales of the PANSS was demonstrated by a research study of 101 schizophrenic patients of ages 20-68 ages (Kay et al., 1987). Internal consistency, split-half and test-retest reliability were supported as well as its construct and criterion-related validity.

Psychotic Symptom Rating Scale (PSYRATS)

The PSYRATS (Haddock, McCarron, Tarrier, & Faragher, 1999) is another interview assessment tool based on psychotic symptoms experienced during the previous week. It is

designed to quantify the severity of delusions and hallucinations in patients with schizophrenia. We used the auditory hallucinations subscale, since the major focus was to characterize AVH. The item pool of the hallucination subscale taps various symptom indices as frequency, duration, loudness, sense of controllability, severity and intensity of distress and disruption by hearing voices. A 5-point rating scale is used to rate symptom scores: 0=absent … 4=constant voices/very loud/content is very negative and distressing. In addition to a total score (range 0-44) which represents the general severity of AVH, three subscores based on Haddock et al. (1999) and Woodward et al. (2014) were computed. Factor analyses revealed three factors constituting of an emotional characteristics factor (0-16) encompassing distressing and negative content, a physical characteristics factor (0-12) including descriptions of the voice(s) as well as a cognitive factor (0-16) containing assumptions regarding the origin of voices and attributions of control.

A study with six raters each rating the same six patient interviews found the inter-rater reliability for the hallucinations subscale to be very high; between r=.79 (item disruption) and r=1.0 (loudness and distress) (Haddock et al., 1999). This finding was validated and expanded by Drake, Haddock, Tarrier, Bentall, and Lewis (2007). For the hallucinations subscale, they found internal consistency values between 0.63 and 0.76 for each item with the total excluding that item. Regarding concurrent validity, they found a significant correlation with the PANSS hallucination item ($r_{Sp=}$0.81).

Beliefs About Voices Questionnaire (BAVQ-R)

The revised BAVQ (Chadwick, Lees, & Birchwood, 2000) is a 35-item, 4-point self-rating questionnaire measuring patients' beliefs concerning AVH as well as their emotional and behavioral reactions. The revision was launched to better assess individual differences. That is, in contrast to the previous version where participants answered 'yes' or 'no', all responses are

now rated on a 4-point scale: 0=disagree, 1=unsure, 2=agree slightly, and 3=agree strongly. Participants are instructed to answer the questionnaire with regard to their experience during the previous week. In addition, individuals having AVH who hear more than one voice are instructed to complete the questionnaire for their most dominant voice. Evaluation is performed for five subscales: malevolence (six items, total score range 0-18), benevolence (six items, 0-18), omnipotence (six items, 0-18), resistance (nine items, 0-27), and engagement (eight items, 0-24).

Overall, the BAVQ-R seems to be a reliable and valid instrument to assess "people's relationships with their auditory hallucinations" (Chadwick & Birchwood, 1995; Chadwick et al., 2000).

Beck Cognitive Insight Scale (BCIS)

The BCIS is a self-report instrument to evaluate patients' self-reflectiveness in their interpretations of their experiences (Beck, Baruch, Balter, Steer, & Warman, 2004). The questionnaire was constructed to contain two sets of items converging into two subscales: self-reflectiveness and self-certainty. Subjects are asked to indicate how much they agree with each of the 16 items on a 4-point rating scale (0=completely disagree, 1=mildly agree, 2=agree, 3=completely agree). Besides scores on the two subscales a composite index is calculated by subtracting the score for self-certainty from that of the self-reflectiveness scale. The questionnaire was used to make sure that patients have enough cognitive insight into their illness to participate. As a score of 10 points or higher signifies good cognitive insight an appropriate cut-off for that purpose was chosen.

The BCIS composite index correlates significantly with other scales assessing awareness and successfully differentiated between inpatients with psychotic diagnoses from inpatients without demonstrating good convergent, discriminant, and construct validity (Beck et al., 2004).

Edinburgh Handedness Inventory (EHI)

The EHI is a brief method of assessing handedness for screening purposes. It is a 10-item self-report measurement where respondents indicate whether they rather perform an act with the right or left hand. R is the number of acts performed with the right hand and L is the number of acts performed with the left hand. A laterality index is calculated by the difference between R and L divided by the total cumulative. A score of 40 or higher indicates right-handedness (Oldfield, 1971).

Table 4 represents an overview of the utilized measures and the measured construct.

Table 4

Overview of utilized measures

	Measured construct
fMRI	
resting-state	neural activation during rest
alertness task	neurofunctional correlates of attention
n-back task	neurofunctional correlates of WM
Neuropsychological assessment	
LPS – subtest 3	premorbid intelligence
TAP – alertness	retention of an alert state
TAP – divided attention	division of attention upon multiple tasks
TAP – inhibition	inhibition a reflexive response
digit span task	verbal WM (backward: manipulation of information)
block tapping task	visuospatial WM (backward: manipulation of information)
California Verbal Learning Task (CVLT)	verbal memory
Wisconsin Card Sorting Test (WCST)	executive functioning, cognitive flexibility
Psychiatric interview	
Brief Psychiatric Rating Scale (BPRS)	psychotic symptom severity
Positive and Negative Syndrome Scale (PANSS)	psychotic symptom severity, divided in negative, positive, and a general symptom severity index
Psychotic Symptom Rating Scale (PSYRATS)	AVH severity
Belief About Voices Questionnaire (BAVQ-R)	emotional and behavioral reactions to AVH
Beck Cognitive Insight Scale (BCIS)	cognitive insight
Edinburgh Handedness Inventory (EHI)	handedness

3.3 Procedure

Data was collected from April 2014 to February 2017 mainly at the Department of General Psychiatry, University Hospital Heidelberg, Germany. Inpatients and patients of a day-care hospital were recruited at the above-named clinic as well ‘Klinik für Spezielle Psychiatrie, Sozialpsychiatrie und Psychotherapie, Bürgerhospital Stuttgart’. Healthy control subjects were recruited via advertisement in a local newspaper and social media as well as recruitment flyers. In addition, outpatients were recruited via assigning psychiatrists and psychotherapists as well as a speech at the local self-help group.

After providing informed consent participants underwent a cross-sectional assessment of cognition, psychopathology, and neuroimaging. Consequently, the study consisted of three parts that took place on two or three dates within one week up to a maximum of 8 weeks to patient's stress levels at a minimum. Structural and functional neuroimaging data were obtained. Furthermore, participants completed a comprehensive cognitive test battery. In addition, participants were asked to answer various questions regarding their symptoms, in the form of a semi-structured psychiatric interview as well as self-report questionnaires. Each of the three parts took approximately one hour for completion. Independent thereof, all participants being inpatients received treatment as usual, which consisted of pharmacotherapy in combination with cognitive-behavioral treatment, including both individual and group sessions.

This study was approved by the Ethics Review Committee and was conducted in accordance with the Declaration of Helsinki.

3.4 Data Analysis

As the current thesis was part of a larger project, not all measures and variables were taken into account in the statistical analyses. They were chosen thoroughly based on their purpose in helping to answer the postulated research questions of interest. As a reminder, the current thesis focuses on (1) potential group differences in neural activation patterns. Furthermore, it wants to correlate AVH-specific neural correlates with (2) test performance on-line, i.e., in the MRI scanner, with (3) neuropsychological test performance as well as with (4) specific psychopathology.

Before data analysis, data cleaning and preprocessing of the MRI data was performed. As described in the sample description, data cleaning involved the exclusion of participants for whom the diagnosis of schizophrenia could not be confirmed during hospital stay, for whom

the inclusion criteria for one of the two patient groups could not be confirmed, with known difficulties during the completion of the tests and thus insufficient complete test results.

3.4.1 Psychometric and behavioral data

IBM SPSS Statistics 24 (IBM Corp., 2013) was used for statistical analyses. Raw test scores were used for most variables, except for the divided attention as well as the inhibition task, where the false-alarm and hit rate were first calculated and then transformed into d'prime as sensitivity index using the log-linear correction (Hautus, 1995). Furthermore, for the alertness task, a composite score was calculated by subtracting the reaction time on the condition with preceding warning tone from the no-warning tone condition. An analogous procedure was carried out to calculate an average reaction time for the n-back task (0-back subtracted from 2-back).

Testing the assumptions

Prior to actual statistical analyses of the specific hypotheses, data was screened regarding the fulfillment of the assumptions given by the chosen statistical method.

According to the central limit theorem in big samples, usually defined as greater 30, the sample distribution will take the shape of a normal distribution regardless of the underlying distribution in the population from which the sample was drawn (Field, 2009). However, the present sample is smaller than the advised n=30. Therefore, normal distribution cannot be assumed and needs to be tested. For testing the assumptions I followed the guideline on exploring assumptions described in Field's 'Discovering Statistics using SPSS' (2009).

Testing for normal distribution. As the planned analysis involved comparing groups, the distribution in each group, i.e. pAVH, nAVH, and HC was tested regarding normality. The

Kolmogorov-Smirnov test was used for that purpose with the suggested critical p-value of $p<.05$ (Field, 2009). The results are presented in Table 5. Note, several variables were significant which means that the distribution deviates from a normal distribution.

Table 5

Test of normal distribution

	Group; D (*p* value)		
Variable	**pAVH**	**nAVH**	**HC**
Test performance on-line			
alertness, RT composite	.146 (*ns*)	.165 (*ns*)	.116 (*ns*)
alertness, FN rate	.417 (.000)	.240 (*ns*)	.263 (.002)
n-back, RT composite	.173 (*ns*)	.234 (*ns*)	.212 (.031)
n-back, FN	.190 (*ns*)	.262 (.023)	.281 (.001)
n-back, FP	.195 (*ns*)	.308 (.003)	.203 (.049)
Test performance off-line			
CVLT, sum	.217 (*ns*)	.135 (*ns*)	.192 (*ns*)
digit span forward	.295 (.002)	.206 (*ns*)	.222 (.019)
digit span backward	.148 (*ns*)	.214 (*ns*)	.109 (*ns*)
block span forward	.156 (*ns*)	.195 (*ns*)	.142 (*ns*)
block span backward	.191 (*ns*)	.317 (.002)	.159 (*ns*)
WCST, conceptual lvl	.207 (*ns*)	.118 (.023)	.253 (.003)
alertness, composite	.199 (*ns*)	.244 (.046)	.167 (*ns*)
divided attention, d‘prime	.138 (*ns*)	.248 (.039)	.127 (*ns*)
Inhibition, d‘prime	.252 (.016)	.165 (*ns*)	.256 (.003)
Psychopathological scores			
PSYRATS, total	.207 (*ns*)	-	-
PSYRATS, emotional	.180 (*ns*)	-	-
PSYRATS, cognitive	.214 (*ns*)	-	-
PSYRATS, physical	.177 (*ns*)	-	-

Note. D= Kolmogorov-Smirnov test statistic, RT=reaction time, FN=false negative, CVLT=California Vernal Learning Test, WCST=Wisconsin Card Sorting Test, conceptual lvl=conceptual level of response score, PSYRATS=Psychotic Symptom Rating Scale, ns=non-significant.

Testing for homogeneity of variance. In order to test for homogeneity of variance the untransformed Levene’s test was used with a threshold of $p<.05$. The documented test results

in Table 6 are based on the mean as suggested by Field (2009). Significance indicates different variances. In sum, the assumption of homogeneity of variances has been violated for some variables.

Table 6

Test of homogeneity of variance

Variable	F	df1	df2	*p* value
Test performance on-line				
alertness, RT composite	.633	2	41	*ns*
alertness, FN rate	2.166	2	41	*ns*
n-back, RT composite	1.589	2	41	*ns*
n-back, FN	1.686	2	41	*ns*
n-back, FP	2.778	2	41	*ns*
Test performance off-line				
CVLT, sum	5.104	2	41	.010
digit span forward	.463	2	41	*ns*
digit span backward	2.328	2	41	*ns*
block span forward	2.258	2	41	*ns*
block span backward	5.295	2	41	.009
WCST, conceptual lvl	3.810	2	41	.030
alertness, composite	.533	2	41	*ns*
divided attention, d‘prime	2.946	2	41	.000
Inhibition, d‘prime	.516	2	41	*ns*
Psychopathological scores				
PSYRATS, total	*			
PSYRATS, emotional	*			
PSYRATS, cognitive	*			
PSYRATS, physical	*			

Note. The asterisk indicates an error message by SPSS that there are not enough unique spread/level pairs to compute the Levene statistic.

Outliers

Potential outliers, i.e., extreme or unusual values that deviate from the rest of the data, were identified for by visual inspection using boxplot graphs. Potential outliers were suspected for the variables digit span forward, WCST, alertness, divided attention, and inhibition. The

observed suspected outlier values were inspected regarding correctness and meaningfulness as they may indicate bad data, e.g., incorrect data. Outlying values were not found to be erroneous; however, one participant from the healthy control group stood out as he/she produced outlying test results on multiple variables, suggesting exceptional poor performance or little motivation. As the chosen non-parametric test is insensitive to outliers because it works on the principle of ranking the data (Field, 2009) it was not removed. The remaining outliers were considered 'real observations' and random variation from the given sample.

Hypothesis testing

The data was screened for violation of assumptions prior to analysis. As mentioned above, the assumptions for parametric tests were partially violated. This concerns the analyses of two of the four hypotheses. Transformation of data was taken into consideration but was decided against as "the payoff of normalizing transformations in terms of more valid probability statements is low, and they are seldom considered to be worth the effort" (Glass, Peckham, & Sanders, 1972). Instead, non-parametric tests, the Kruskal-Wallis test, the Mann-Whitney U test as well as Spearman's correlation, were conducted where necessary. Non-parametric tests are based on ranks or medians instead of means. Both, ranks and medians are not affected by extreme values and as such are more robust to outlier values in comparison to means (Scibilia, 2015). For the normal-distributed data, parametric tests were chosen, i.e. Pearson's correlation and analysis of variance: ANOVA. Where applicable, the significance level was corrected for multiple comparisons according to the Benjamini-Hochberg approach (Benjamini & Hochberg, 1995) for false discovery rate (FDR). The Excel-spreadsheet provided by McDonald (2014) was used for this purpose with a FDR of .05.

A group comparison revealed that the two patient groups differed on global symptom severity, in specific on positive symptomatology. However, this difference was considered intrinsic to

the grouping process as patients with AVH are considered to be more affected than patients without AVH, experiencing higher levels of distress and functional disability (Hubl et al., 2008). Therefore, no analysis of covariance was carried out.

3.4.2 Neuroimaging data

Data Analysis of neuroimaging data was carried out under supervision of Dr. Dipl.-Biol. Mike Michael Schmitgen, 75% estimated own contribution. The analysis of neuroimaging data was performed using the Statistical Parametric Mapping 8 (SPM8, r6313; Wellcome Trust Centre for Neuroimaging) software package implemented in MATLAB R2015a (MathWorks). Neuronal structures were identified and masks created using the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) from the WFU PickAtlas Tool (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) for SPM. Furthermore, the MarsBaR (version 0.44, MARSeille Boîte À Région d'Intérêt; Brett, Anton, Valabregue, & Poline, 2002) toolbox for SPM was used to extract mean activation of anatomical regions of interest (ROI) identified by the second level analyses.

Preprocessing

Prior to data preprocessing, for the alertness task the first eight and for the n-back task the first five images were discarded as 'dummy scans' to account for MRI equilibration effects. Furthermore, to improve reliability of normalization, the origin of all images was reoriented to the anterior commissure.

As visual inspection demonstrated significant motion and ghosting artifacts in 13 subjects, it was decided to use the ArtRepair Version 5b toolbox (Mazaika, Hoeft, Glover, & Reiss, 2009; Mazaika, Whitfield-Gabrieli, & Reiss, 2007; Mazaika, Whitfield, & Cooper, 2005) along with standard SPM routines. The ArtRepair software is a motion adjustment algorithm that is

supposedly able to correct for rapid motion and bad volumes (Artifact Repair), bad slices (Slice Repair), residual errors that occur after realignment (Motion Regress) and voxel-wise noisy time series (Despike and Filter). Its functions can be recognized by the prefix "art_".

In specific, the function art_slice was applied with a threshold modifier of 10 to repair bad slices and voxel spike noise. After performing a slice time correction, data was corrected for head movement over the time course of the images using realignment, i.e., an approximation to an average image, and art_motionregress, i.e., reduction of the realignment residuals. Participants should not have more than 3mm maximum displacement in x, y or z and 3° of angular motion. Moreover, art_global was applied to the realigned scans to detect and repair large scan-to-scan motion. Then, to enable group analysis, functional images were coregistered to the subject's structural image and spatially normalized to the SPM 8 standard EPI template (voxel size: 2x2x2mm). Finally, the normalized images were smoothed with a 9mm full width at half maximum Gaussian kernel.

After preprocessing, 7 data sets had to be discarded for the alertness paradigm due to uncorrectable MRI ghosting artifacts (6 for the n-back paradigm) and 5 (4) due to movement artifacts. Another 5 participants had to be excluded due to left-handedness. Thus, 40 data sets were included in the further data analysis for the alertness task and 44 for the n-back task.

First level analysis

A first level analysis was conducted using SPM8. This was done without the realignment parameter as Art Repair routines were used for preprocessing. Thereafter, Art Redo was run with the existing SPM.mat files, i.e., the first level was repeated with the repaired data. In order to perform a 'sanity check' on the individual level (referring to the plausibility of the effect with respect to the expected activations, see hypotheses in chapter 2.4), the statistical thresholds for these analyses were set at $p<0.05$, FWE-corrected.

For the alertness task, the contrast condition with preceding warning tone ('Xsound') vs. without warning tone ('X') was chosen as contrast of interest. Five participants were chosen at random for visual inspection. Statistical analysis and visual inspection of the contrast Xsound>X in healthy control subjects revealed a significant activation in the left as well as right STG. That is, healthy individuals show more activation in the STG when confronted with an auditory signal in comparison to the absence of that beep tone. The STG comprises the primary auditory cortex as well as Wernicke's area and thus necessarily plays an important role in the sensation of sound, speech perception and comprehension (Saffran, 2002; Zevin, 2009).

For the n-back task, the contrast 2-back>0-back was analyzed. Visual inspection in healthy individuals revealed a much broader and more diverse neural activation than that of the alertness paradigm. The largest and most prominent clusters were identified using the Anatomy toolbox (Eickhoff et al., 2005). Activation was found in the left as well as right middle frontal gyrus, the left angular gyrus, and left as well as right cerebellum, but also in the left precuneus, the left inferior parietal lobule, the right inferior and superior parietal lobule, and the left as well as right superior frontal gyrus. The n-back activation pattern includes several brain regions that are well described in the literature as associated with language (Motelow & Blumenfeld, 2014), attention (Vossel, Geng, & Fink, 2014), and visual as well as verbal WM (Na et al., 2000; Tomlinson, Davis, Morgan, & Bracewell, 2014).

Second level and region of interest analysis

On the second level, neural activation patterns between the three groups, pAVH, nAVH, and HC were compared using an ANOVA. Four covariates were entered into the analysis as these variables have been shown to influence functional brain activation, i.e., age and gender (Takahashi, Ishii, Kakigi, & Yokoyama, 2011), education (Posner & Rothbart, 2005), and chlorpromazine equivalents (CPZ, Nejad, Ebdrup, Glenthoj, & Siebner, 2012). Analyses of

covariance (ANCOVA) were carried out on the repaired first level data following up on the previously defined contrasts: Xsound>X (alertness task) and 2-back>0-back (n-back task).

The ROI analysis was performed following the online-guideline ‘MarsBar: step-by-step instructions to extracting region of interest data’ (Grahn, n.d.) using the masks previously identified and created by the AAL atlas (Tzourio-Mazoyer et al., 2002) for SPM. The obtained activation parameter estimates were entered into the SPSS data table to perform correlational analyses between mean local activation in the ROIs and psychometric as well as psychopathological measures.

4 Results

The following chapter presents the results of the present cross-sectional study according to the aforementioned research questions. Where applicable, the findings are additionally depicted in graphical as well as tabular form. The structure resembles the initially formulated research questions and associated hypotheses postulated in chapter 2.4. As a reminder, group, i.e. pAVH, nAVH, and HC, is the independent variable in all run analyses. For some analyses, pAVH and nAVH were grouped together to form the group of schizophrenic patients (Sz) in general. The results are reported at the peak-level with cluster extent (*k*) and Z-scores. Note that only significant cortical and subcortical regions are reported; clusters indicative of cerebrospinal fluid (CSF) are considered as artifacts and are not reported.

4.1 Hypothesis 1

pAVH will show an AVH-related functional neural activation patterns

For the alertness task, a second-level analysis, an ANCOVA, was run for the contrast Xsound>X and the covariates gender, age, education, and CPZ to examine if group has an effect on neuronal activation patterns when a preceding warn tone is presented compared to no warn tone. It was predicted that pAVH will show a reduced activation in the right fronto-parietal attention network comprising the intraparietal sulcus, the inferior parietal lobe, and the dorsal premotor cortex as well as in the auditory cortex and SMA. The threshold was set at $p<.005$ and cluster size>34.088 (expected number of voxels per cluster, *k*) following the recommended procedure by Lieberman and Cunningham (2009) in order to balance Type I (α) and II (β) errors in fMRI research.

There was no significant effect between the groups. Nevertheless, post-hoc t-contrasts for HC>pAVH and nAVH>pAVH as well as the respective inverse were calculated to examine the

directed hypothesis of reduced activation in pAVH. The threshold was set at p<.005, uncorrected, and k>54.920. The results are summarized in Table 7.

Table 7

Post-hoc contrasts for neural activation during the alertness paradigm

Anatomic region	**Cluster size *k* (voxel)**	**equivZ**	**Maximum Voxel Localization (MNI)**		
			x	**y**	**z**
pAVH > HC					
l middle occipital gyrus	138	3.47	-48	-80	10
		3.47	-38	-92	6
		2.91	-30	-98	8
l superior temporal pole	71	3.04	-42	8	-24
l superior frontal gyrus	71	3.22	-26	60	14
pAVH > nAVH					
r angular gyrus	208	3.03	44	-70	44
		3.00	44	-58	54
		2.94	38	-64	48

For the contrast pAVH>HC, significant activation at the peak-level (p<.005) was found in the left middle occipital gyrus (MOG; MNI coordinates: x -48, y -80, z 10), the left superior temporal pole (STP; x -42, y 8, z -24) as well as the left superior frontal gyrus (SFG; x -26, y 60, z 14). The contrast pAVH>nAVH yielded significant activation in the right angular gyrus (AG; x 44, y -70, z 44). All other contrasts yielded no significant effects, p>.005.

In summary, for the alertness task, pAVH demonstrated significantly increased neural activation at p<.005 and k>34.088 in the left MOG, the left STP, and the left SFG when compared to HC as well as in the right AG when compared to nAVH (see Figure 11). Note, these results do not match the predicted right fronto-parietal hypoactivation in pAVH.

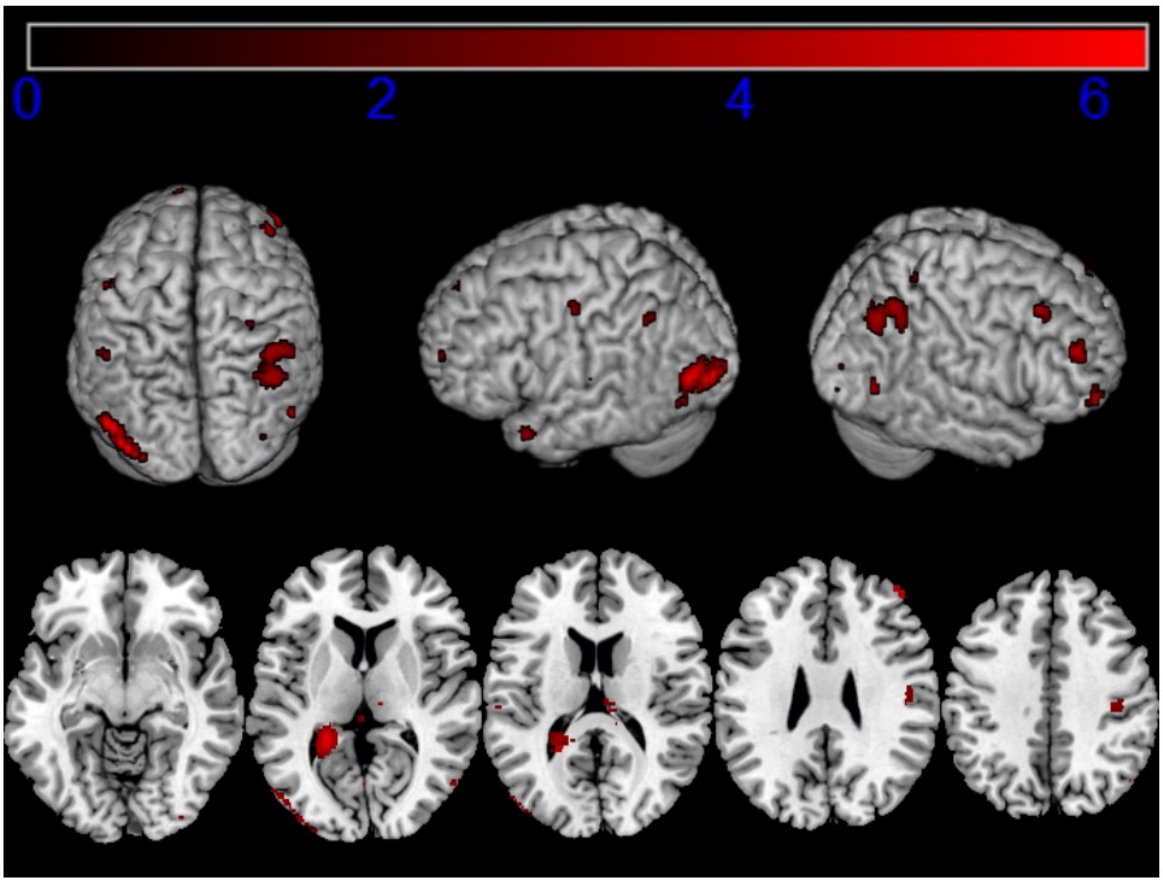

Figure 11. AVH-related neural activation pattern during the alertness task.

AVH-related results from the post-hoc contrasts pAVH>HC and pAVH>nAVH for the contrast Xsound>X and the covariates gender, age, education, and CPZ (p<.005, uncorrected, spatial extent threshold > 0 voxels for illustration purposes). The color bar on the top indicates the intensity of local neural activation measured in Z scores from 0=lowest to 6=highest.

For the n-back task, an ANCOVA for the contrast 2-back>0-back was performed with the same covariates and thresholds as described above (k>40.142). It was predicted that pAVH show a reduced activation compared to both comparison groups in a network commonly associated with WM tasks, comprising the DLPFC, the VLPFC, and the inferior parietal lobule. The results are summarized in Table 8.

Table 8

Main effect and post-hoc contrasts for neural activation during the n-back paradigm

Anatomic region	Cluster size *k* (voxel)	equivZ	Maximum Voxel Localization (MNI)		
			x	y	z
Effect of group					
l Rolandic operculum	867	4.37	-46	-14	16
		3.97	-40	-8	12
		3.85	-56	-2	10
r superior temporal pole	128	3.31	46	-22	-2
		2.99	46	-12	-6
		2.84	56	-20	-2
r middle occipital gyrus	124	3.20	26	-92	10
		3.12	36	-86	4
l postcentral gyrus	121	3.26	-42	-22	48
		3.26	-38	-22	40
r Rolandic operculum	116	3.08	56	2	12
		2.87	50	-12	14
		2.69	52	-24	10
r cuneus	67	3.54	20	-84	40
r superior temporal pole	60	3.34	68	-36	18
pAVH > HC					
r middle cingulate cortex	665	3.47	10	2	38
		3.20	-2	-2	40
		3.19	-2	22	38
r superior temporal pole	354	3.76	46	-22	-2
		2.87	34	-20	0
		2.80	52	-24	8
l superior temporal pole	246	3.60	-56	-18	6
		2.75	-52	-8	0
l Rolandic operculum	144	3.21	-46	0	12
		3.13	-36	-6	10
r superior temporal pole	131	3.84	68	-36	18
l postcentral gyrus	104	3.23	-44	-22	50
		2.92	-38	-22	40
r supplementary motor area	100	3.26	12	10	64
r Rolandic operculum	87	3.28	64	8	12
r postcentral gyrus	79	3.10	56	-8	28
pAVH > nAVH					
r angular gyrus	190	3.08	46	-62	34
		2.78	34	-54	26
l angular gyrus	84	3.09	-44	-52	32

The between-group effect was significant at the peak-level (p<.005) in the left Rolandic operculum (ROL; x -46, y -14, z 16), the right STP (x 46, y -22, z -2), the right MOG (x 26, y -92, z 10), the left postcentral gyrus (PoCG; x -42, y -22, z 48), the right ROL (x 56, y 2, z 12), the right cuneus (CUN; x 20, y -84, z 40), and the right STP (x 68, y -36, z 18). It is shown in Figure 12.

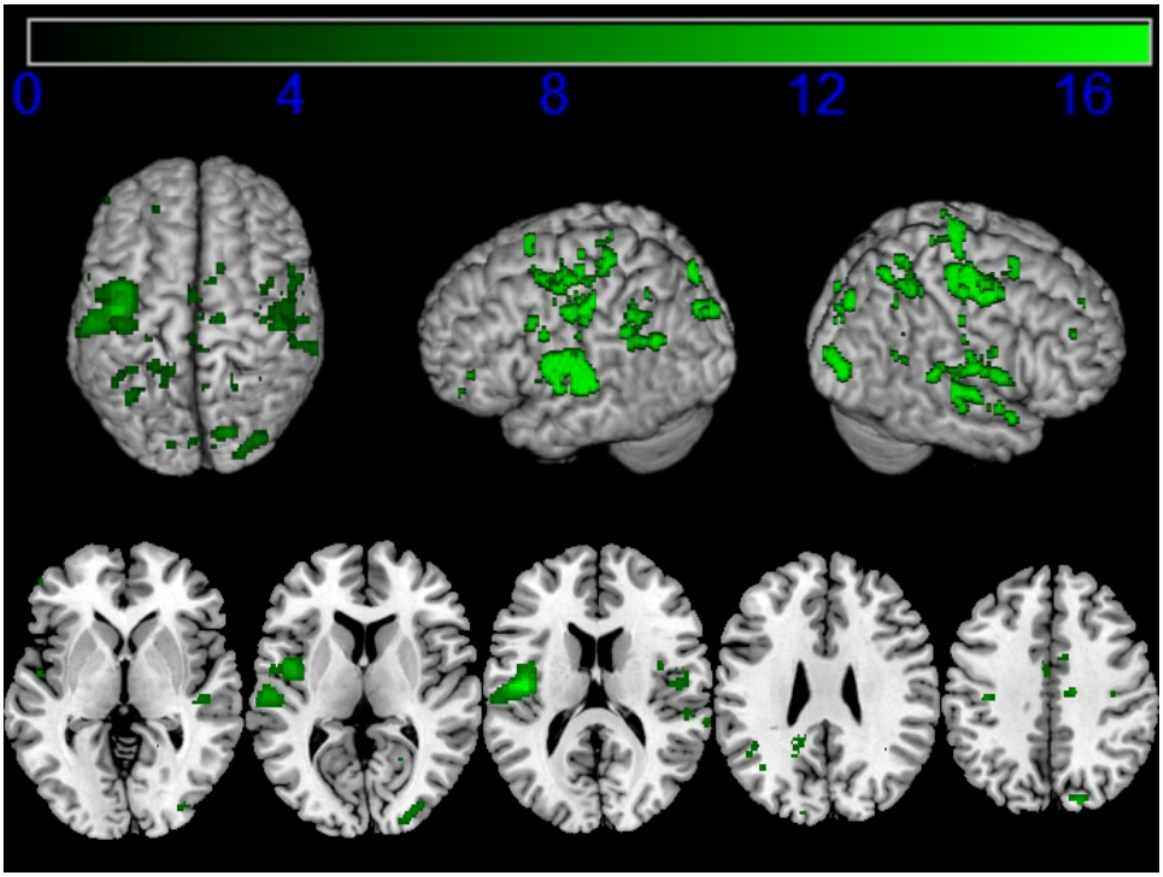

Figure 12. Spatial pattern of the group effect during the n-back task.

Results from the second-level analysis for the contrast 2-back>0-back. F-contrast with the covariates gender, age, education, and CPZ describing the differences between pAVH, nAVH, and HC (p<.005, uncorrected, spatial extent threshold > 0 voxels for illustration purposes). The color bar on the top indicates the intensity of local neural activation measured in Z scores from 0=lowest to 16=highest.

Post-hoc t-tests were calculated for the contrasts HC>pAVH, and nAVH>pAVH as well as their respective inverse. The threshold was set at p<.005, uncorrected, and cluster size>64.267. The results are graphically depicted in Figure 13. For the contrast pAVH>HC, significant neural activation was found in the right middle cingulate cortex (mCGC; x 10, y 2, z 38), the right STP (x 46, y -22, z -2 & x 68, y -36, z 18), the left STP (x -56, y -18, z 6), the left ROL (x -46, y 0, z 12), the left PoCG (x -44, y -22, z 50), the right SMA (x 12, y 10, z 64), the right ROL (x 64,

y 8, z 12), and the right PoCG (x 56, y -8, z 28). The contrast pAVH>nAVH yielded a significant neural activation in the right and left AG (x 46, y -62, z 34 and x -44, y -52, z 32, respectively).

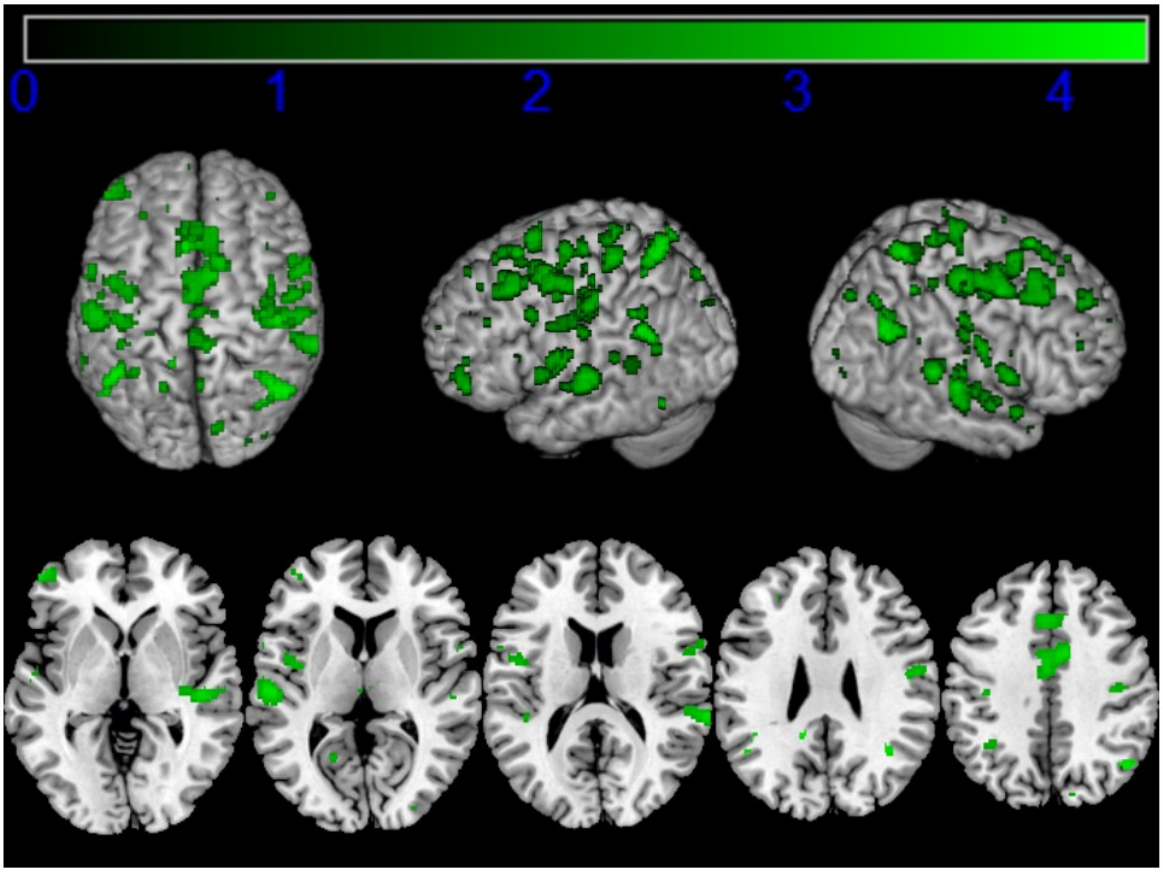

Figure 13. AVH-related neural activation pattern during the n-back task.

AVH-results from the post-hoc contrasts pAVH>HC and pAVH>nAVH for the contrast 2-back>0-back and the covariates gender, age, education, and CPZ (p<.005, uncorrected, spatial extent threshold > 0 voxels for illustration purposes). The color bar on the top indicates the intensity of local neural activation measured in Z scores from 0=lowest to 4=highest.

In summary, for the n-back task, pAVH show increased neural activation at p<.005 and k>40.142 for the group effect and k>64.267 for post-hoc contrasts in the right mCGC, bilateral STP, bilateral ROL, bilateral PoCG, the right SMA, and bilateral AG. However, in contrast to the predicted hypoactivation in pAVH neural activation patterns during the n-back task show a hyperactivation. Also, the localization does not fully match the predictions. With regard to the

predicted activation patterns the inferior parietal areas including PoCG and AG seem to be most involved.

Summarizing the above-mentioned findings for both activation paradigms, the alternative hypothesis of an AVH-related hypoactivation in neural networks, i.e., the fronto-parietal attention network for the alertness task and the WM network for the n-back task, was neither supported for the alertness nor for the n-back task. Instead, significantly increased task-dependent neural activation was found for pAVH when compared with both, nAVH and HC. When comparing the results for both paradigms and looking for overlapping brain activation areas, it is interesting that there seems to be AVH-related activity in the right AG and left STP. The AG has been related to certain aspects of auditory hallucinations before (Alderson-Day et al., 2015; Allen et al., 2012) as has the left STP (Jardri et al., 2011).

Although the found neural activity during the two tasks did not match the predicted activation, it was used for further correlational analyses of mean brain activity and test performance in neuropsychological tests as well as symptom-specific psychopathology.

4.2 Hypothesis 2

AVH-related neural activation will be negatively correlated with task performance

Brain activation coefficients were extracted for both paradigms for the significant neural activation in the corresponding brain regions by means of the MarsBaR toolbox and then inserted into the SPSS data file for further analysis.

First, it was tested whether the three groups differed on performance data in the two fMRI paradigms, e.g. average reaction time as well as errors (false negatives and false positives). For this purpose, a non-parametric Kruskal-Wallis-Test was carried out, one for each paradigm. Test performance in the alertness task was not significantly affected by the group; $H(2)=1.692$,

p>.05 for the average reaction time and $H(2)$=.812, p>.05 for the false negative rate. In accordance, group had no effect on n-back task performance; average response time, $H(2)$=2.966, false negative count, $H(2)$=1.508, and number of false alarms, $H(2)$=.548, all ps>.05. That is, all groups performed equally well.

To examine the hypothesis of AVH-related neural activation interfering with task performance a correlation between brain activation coefficients and on-line task performance was run for the pAVH group. As the performance data was partially non-normal for both tasks, i.e., alertness and n-back task, a non-parametric Spearman bivariate correlation was performed.

There was no significant correlation between AVH-related brain activity in the left SFG, the left MOG, the left STP as well as the right AG and performance in the alertness task as measured with average response time and FN rate, r_s between -.192 and .385, all ps(one-tailed)>.05.

For the n-back task, significant correlations were found between total number of FN and activation in the right PoCG (r_s=.532, p=.025), between the total number of FP and the left PoCG (r_s=.458, p=.05), the left ROL (r_s=.570, p=.017) as well as the right AG (r_s=-.594, p=.012), and between the average RT and mean activation in the right SMA (r_s=-.530, p=.026). All other correlations were found to be non-significant, all ps(one-tailed)>.05. However, when FDR-correcting for multiple comparisons none of the correlations previously found to be significant retained its significance. Hence, the alternative hypothesis of a relation between neural dysfunction on task performance was neither supported for the alertness nor for the n-back task and has to be declined.

4.3 Hypothesis 3

AVH-related neural activation will be correlated with neuropsychological performance off-line[3]

Analogous to the approach for the previous hypothesis, it was first determined if there is a group effect on cognitive performance. Therefore, a non-parametric Kruskal-Wallis Test was performed. The performance on the California Verbal Learning Task (CVLT) was significantly affected by grouping, $H(2)=12.157$, $p=.002$. For the remaining tests, all groups performed equally well, $ps>.05$. Mann-Whitney U tests (two-tailed) on the comparisons HC>Sz, HC>pAVH, and pAVH>nAVH were used to follow up the previous finding. For the contrast HC versus Sz, HC performed significantly better on the CVLT (*Mdn*=65.5), when compared to Sz (*Mdn*=51.5), $U=374.0$, $z=2.301$, $p=.001$, $r=.27$. To follow-up these findings, the contrast HC versus pAVH was analyzed. HC performed significantly better on the CVLT (*Mdn*=65.5) when compared to pAVH (*Mdn*=51.5), $U=473.5$, $z=2.015$, $p<.001$, $r=.30$, see Figure 14.

[3] The predicted direction of effect depends on the operationalization of the exact variable measuring neuropsychological performance. In accordance with hypothesis 2, correlations between AVH-related mean local brain activation and FN rates as well as RT are predicted to be negative, i.e. the lower the neural activation in the corresponding network due to it being 'bound' by AVH, the higher the FN rates and RT; thus, the poorer the performance. In contrast, when test performance is defined in total sum scores the correlation is predicted to be positive, i.e., the lower the neural activation, the lower the total score; thus, the poorer the performance.

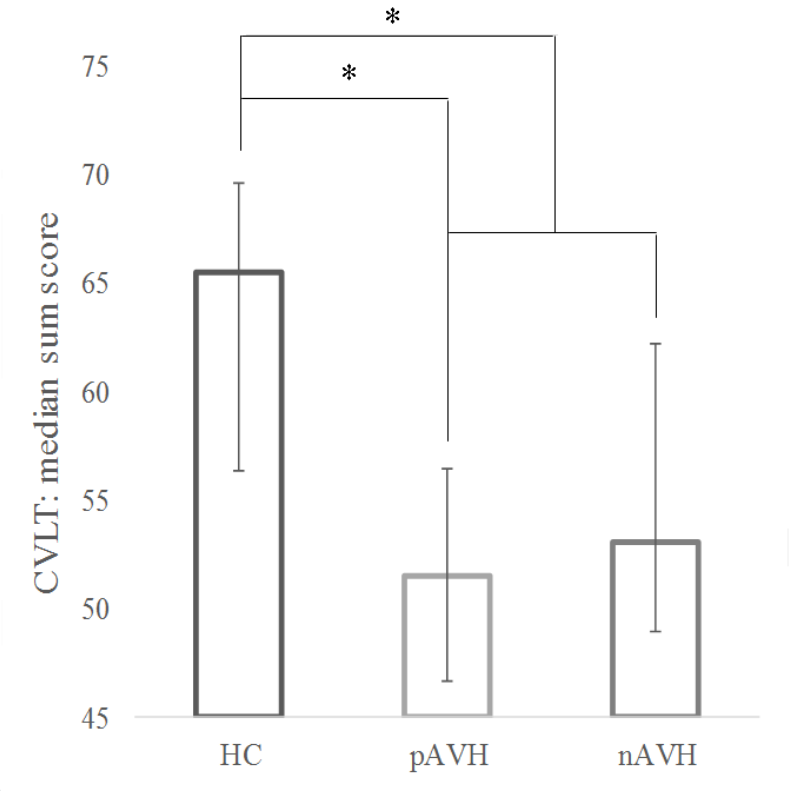

Figure 14. Group differences on verbal learning.

Schizophrenic patients in general, as indicated by the bracket spanning nAVH and pAVH, as well as pAVH in specific scored significantly lower on the sum score of the California Verbal Learning Task (CVLT) when compared to HC. With nAVH, there was no significant effect. Group medians are depicted with their corresponding 95% confidence interval, calculated from the standard error and critical t-value (Persike, 2012). The asterisk indicates significance at the .05 level.

For the remaining contrasts the tests failed to reject the null hypothesis, $p>.05$ each. When applying a FDR-correction, HC still performed significantly better on the CVLT when compared to Sz as well as pAVH. To conclude, healthy control subjects not only perform significantly better on verbal learning tasks compared to schizophrenic patients in general but compared to pAVH patients in specific.

In order to investigate the hypothesis of a correlation between AVH-related neural activation and neuropsychological performance off-line, a non-parametric Spearman correlation was performed for the pAVH-group on CVLT performance and mean neural activation during the

alertness as well as the n-back task. There was no significant correlation for the pAVH-group for the activation in the left SFG, the left MOG, the left STP, and the right AG during the alertness task and performance in the CVLT, r_S=.320, r_S=-.116, r_S=-.271, and r_S=-.193, respectively, all *ps*(one-tailed)>.05. In contrast, CVLT performance was significantly correlated with mean neural activation in the right AG (r_s=-.601, *p*=.011) and the right MOG (r_s=-.482, *p*=.041) during the n-back task. All other correlations fell short of significance, p>.05. However, after FDR-correction none of the previously significant results retained its significance.

In summary, the alternative hypothesis of a correlation between neural dysfunction and task performance during neuropsychological testing must be declined for the alertness as well as for the n-back task. The null hypothesis must be retained.

4.4 Hypothesis 4

AVH-related neural activation will be negatively correlated with symptom-specific psychopathology

As the last hypothesis was operationalized in terms of AVH-specific multidimensional psychometric measures, i.e., the auditory hallucinations subscale of the PSYRATS and scores on the emotional, physical, and cognitive domains as well as the total score regarding AVH, the groups (pAVH versus nAVH) differed per definition on these variables, *F*(3,22)=141.540, *p*(one-tailed)<.001. As the concerning variable was normally distributed Pearson's r was calculated for the correlation between mean local neural activation and symptom-specific psychopathology scores.

For the alertness task, significant correlations were found between the emotional index score and the left MOG (*r*=.666, *p*=.006) as well as the right AG (*r*=.558, *p*=.024), and between the physical index and the left SFG (*r*=-.559, *p*=.024). For the n-back task, significant correlations

were found between the emotional score and the right AG (r=.475, p=.043), the right mCGC (r=.522, p=.028), and the right STP (r=.655, p=.005); between the physical index score and the right PoCG (r=.555, p=.02) as well as the right STP (r=.474, p=.043); between the cognitive index score and the right CUN (r=-.663, p=.005), and between the total score and the right STP (r=.527, p=.026). That is, the right STP correlates with three aspects of the PSYRATS scale, the total score, emotional as well as physical index score. However, after FDR-correction none of the results remained significant.

In summary, the alternative hypothesis of a correlation between neural dysfunction and symptom-specific psychopathology must be declined for the alertness as well as for the n-back task. The null hypothesis must be retained. To sum up, all null hypotheses were retained.

5 Discussion

This doctoral thesis was interested in the neural correlates underlying treatment-refractory AVH in schizophrenia and its hypothesized relationship with clinical symptom severity and specific cognitive processes, i.e., attention and WM. I had set myself the task to answer the question whether AVH are associated with different neural activation in known brain areas of interest compared to two control groups: one clinical, i.e., non-hallucinating schizophrenic patients, and one comprising participants of the healthy population. Furthermore, I tried to elucidate the relationship between these functional neural activation patterns and performance on the on-line activation paradigms, neuropsychological measures of cognitive functioning, as well as psychopathology.

As a reminder, three groups of participants were enrolled in the study to enable a differentiation between the effects of schizophrenia in general and AVH in specific. These groups included schizophrenic patients with persistent treatment-refractory auditory verbal hallucinations (pAVH), schizophrenic patients without AVH (nAVH), and healthy controls (HC). For some analyses, pAVH and nAVH were grouped together to form the group of schizophrenic patients (Sz) in general. Four hypotheses were stated and then evaluated regarding confirmatory indicators of evidence:

- **Hypothesis 1**. Groups will differ in functional neural activation patterns. In specific and in accordance with the symptom interference idea, reduced neural activation in hallucinating patients when compared with both control groups was hypothesized.
- **Hypothesis 2**. AVH-related neural activation will interfere with task performance on-line. The direction of correlation was predicted to be negative.

- **Hypothesis 3**. AVH-related neural activation will be correlated with neuropsychological performance off-line. Here, the direction of effect depends on the operationalization of the exact variable measuring neuropsychological performance off-line.
- **Hypothesis 4**. AVH-related neural activation will be negatively correlated with symptom-specific psychopathology.

5.1 Summary of results

Regarding the first hypothesis, both fMRI activation paradigms, the alertness task and the n-back task, lead to significant AVH-related neural activation at $p<.005$ and cluster size>k (expected number of voxels per cluster). During the alertness task, pAVH demonstrated significantly increased neural activation at k>34.088 in the left MOG, the left STP, the left SFG as well as in the right AG when compared to both, nAVH and HC. These results however do not match the predicted reduced activation in the right fronto-parietal network in comparison to both control groups. During the n-back task, pAVH showed increased neural activation at k>40.142 and k>64.267 in the right mCGC, bilateral STP, bilateral ROL, bilateral PoCG, the right SMA, and bilateral AG. However, in contrast to the predicted hypoactivation in pAVH when compared to the control groups neural activation patterns during the n-back task show a hyperactivation. Also, the localization does not fully match the predictions, except for DLPFC and inferior parietal areas.

Although not matching the previous stated hypotheses with regard to the direction and localization of the effect, mean local brain activation was used for further analysis.

With regard to the second hypothesis, the three groups neither differed in task performance in the MRI scanner nor did the neural activation correlate with that performance after FDR-correction. This held true for both paradigms, the alertness task as well as the n-back task.

Regarding the third hypothesis, there was no FDR-correctable correlation between AVH-related neural dysfunction and task performance during neuropsychological tests for the alertness as well as for the n-back task. However, an additionally performed group comparison revealed that schizophrenic patients in general and hallucinating individuals in specific performed significantly worse on verbal learning when compared to healthy controls.

Regarding the last hypothesis, hypothesis 4, the correlation between the AVH-related mean local activation and symptom-specific psychopathology scores yielded no FDR-correctable effects.

The results are summarized in tabular form in Table 9.

Table 9

Summary of results

		result	**in addition**
Hypothesis 1	AVH-related neural activation patterns		
H_0:	pAVH=nAVH=HC		
H_a:	pAVH<nAVH, HC	pAVH>nAVH, HC	
Hypothesis 2	corr(AVH-related neural function,task)		
H_0:	$r \approx 0$	retained	
H_a:	$r < 0$	rejected	
Hypothesis 3	corr(AVH-related neural function,neuropsychology)		
H_0:	$r \approx 0$	retained	
H_a:	$r < 0$	rejected	CVLT:HC>pAVH
Hypothesis 4	corr(AVH-related neural function,psychopathology)		
H_0:	$r \approx 0$	retained	
H_a:	$r < 0$	rejected	

Note. H_0=null hypothesis, H_a=alternative hypothesis, r=correlation coefficient; ≈ 0 indicating no correlation and < 0 suggesting a negative correlation.

5.2 Discussion of results

Looking at Table 9, it becomes obvious that none of the initially formulated hypotheses could be confirmed with regard to the predicted direction of the effect. The initially formulated

hypotheses relied on the symptom interference approach. That is, AVH-related neural resources, primarily those who show activation during resting-state, are bound by these hallucinations and therefore less available to other mental operations, i.e. task performance. Therefore, a decreased neural activation pattern in patients suffering from treatment-refractory AVH compared to non-hallucinating schizophrenic patients and healthy control participants was predicted. Put differently, the increased resting-state activity is suggested to explain the difference to the predicted hypoactivation during task performance. However, significant task-induced hyperactivation with uniform $p<0.005$ and $k>$cluster size, an appropriate approach considering the hypotheses and the number of cases, in pAVH when compared to nAVH and HC was found for the alertness task as well as the n-back task. In light of the equal performance accuracy across all three groups this may point to neural compensation. That is, the neural correlates that were formerly thought of as bound by AVH (and therefore not available for task demands) might have been available to pAVH after all and thus exhibiting hyperactivation in order to match specific task demands. This matches the existing literature on a neural compensation hypothesis in schizophrenia showing that patients' normal performance is often associated with a larger neural response during task performance (Swerdlow, 2010). Indeed, the current study showed that task-related neural hyperactivation in multiple brain areas correlated with normal task performance during the n-back task, although significance did not withstand the correction for multiple testing. Quintana et al. (2003) point out that compensatory responses can be altered by manipulating specific task demands. Depending on whether these can be met by alternate, efficacious and available resources this may result in neural hypo- or hyperactivaton. These findings support the notion of successful neural compensation for inefficient brain functioning in schizophrenic patients (Swerdlow, 2010). Specifically, an extensive literature points to compensatory processes during WM tasks such as the n-back task (Callicott et al., 1999; Wolf et al., 2009). In this context, the Yerkes-Dodson curve is often

mentioned (Yerkes & Dodson, 1908). It illustrates the U-shaped relation between neural activity increasing with task load and difficulty and decreased accuracy and slower reaction times. That is, in difficult tasks task performance is best with intermediate neural activity. At both, high and low activation, i.a. WM performance is impaired. What at first glance might seem as contradictory to the symptom interference hypothesis and its predicted hypoactivation can be explained as follows: The compensatory response to task-specific hypo- or underactivation is a hyper- or overactivation in potentially higher, less functionally specialized network nodes (Crossley et al., 2016). In other words, symptom-interfered hypoactivation in task-relevant neural correlates might be observed as long as it cannot be compensated sufficiently by hyperactivation in available compensatory networks.

With respect to the found AVH-related neural hyperactivation (as a reminder: the MOG, the left STP, the left SFG, and the right AG for the alertness task as well as the right mCGC, bilateral STP, bilateral ROL, bilateral PoCG, the right SMA, and bilateral AG for the n-back task) the following can be concluded: most of the brain regions showing AVH-related hyperactivation in the current study have been associated with AVH in schizophrenia before, thus the results match previous findings. For example, the comprehensive meta-analysis by Jardri et al. (2011) noted that AVH are associated with increased activity in fronto-temporal areas that are involved in language function including the frontal opcerulum and the STG. Furthermore, attenuated activation associated with AVH has been observed in the PoCG (Kuhn & Gallinat, 2012), the STG (Kuhn & Gallinat, 2012; Lennox et al., 2000), the STP (Diederen et al., 2012), parts of the inferior parietal pole (Diederen et al., 2012), the SMA (Clos, Rottschy, Laird, Fox, & Eickhoff, 2014; McGuire et al., 1996) as well as visual areas in the occipital lobe (Zhuo et al., 2017). Furthermore, limbic and paralimibic regions, including the cingulate gyrus have been demonstrated to show abnormal activation in hallucinating individuals (Silbersweig et al., 1995). In addition, the anterior part of the STG has been bilaterally correlated with AVH

severity, as has been the left PoCG (Nenadic, Smesny, Schlosser, Sauer, & Gaser, 2010). Evidence also suggests a negative correlation between the white matter integrity in the cingulate cortex and the severity of hallucinations (Curcic-Blake et al., 2017; Curcic-Blake et al., 2015). Moreover, the AG has been related to certain aspects of auditory hallucinations (Alderson-Day et al., 2015; Allen et al., 2012). For example, Allen et al. (2012) and Vercammen, Knegtering, Bruggeman, and Aleman (2011) correlated loudness of voices with neural activity in bilateral AG. In addition, Nenadic et al. (2010) found the left AG to correlate with AVH severity. The AG is an interesting finding for two reasons: First, it has been found to show significantly increased activity in both tasks. Second, it has not been mentioned in the AVH literature that often compared to the other brain regions, thus presenting a so far overlooked but potentially promising result.

The AG lies in the posterior part of the inferior parietal lobule and is commonly considered part of the association cortex (Seghier, 2013). In general, the AG is associated with multiple functions, e.g., semantic processing, reading and comprehension, memory retrieval, attention, and social cognition. Furthermore, it has been related to the DMN as well (Seghier, 2013). Accounting for its multiple functions and neural connections, the AG is thought of as cross-modal integrative hub or, as Walker (1990) put it: the "association area of the association areas" (p. 335). According to the Wernicke-Geschwind model for language processing, the AG is involved in the connection of visual stimuli with and conversion into its auditory equivalent (Wickens, 2009). In other words, it translates visual information to a form accessible by Wernicke's area. This suggestion is supported by its anatomy and structural connections with the visual as well as the hearing association cortex (Walker, 1990). Not only that, because of its rich connectivity, the AG gives meaning to events, connecting them, based on prior expectations and conceptual knowledge (Seghier, 2013). Therefore, the association cortex in

general (Hoffman, 2007) and the AG in specific (Seghier, 2013) have been associated with AVH within the predictive processing framework (PPF) that we encountered in chapter 2.2.3. Figure 15 illustrates the AG as connecting hub between bottom-up multisensory inputs and top-down predictions based on prior knowledge and experiences as well as the sense of agency. It works by recurrently exchanging predictions and corresponding prediction errors to minimize the prediction error. By integrating this information, the AG improves the probabilistic representation of the cause of the received sensory input (Seghier, 2013). The purpose is to better understand events in the external world as well as internal mental processes, thereby contributing to cognitive processes as diverse as semantic access, retrieval of facts, categorization of events, and attention shifting (Figure 15A). Note, the exact role of the AG depends on the set of regions it interacts with, as illustrated in Figure 15B.

The PPF may explain the implication of the AG and its functions in the occurrence and physical characteristics of AVH. For instance, semantic processing is a key process in language comprehension and reading. Language processing is known to be impaired in schizophrenic patients with AVH, i.e. AVH are consistently associated with aberrant functioning of speech production (e.g., inferior frontal gyrus including Broca's area) and language perception areas (e.g., STG including Wernicke's area) (McGuire et al., 1996; Strik, Dierks, Hubl, & Horn, 2008; Zmigrod et al., 2016). Furthermore, AVH correlate with lower verbal IQ (Seal, Crowe, & Cheung, 1997). Likewise, fact retrieval as part of memory function is known to be impaired in AVH as is the case for verbal memory (Jardri et al., 2011; Seal et al., 1997), context and source memory (Brookwell et al., 2013; Waters, Badcock, Michie, & Maybery, 2006) and WM (Aleman, Böcker, Hijman, de Haan, & Kahn, 2003). This has led to the aberrant memory processing model of AVH that proposes AVH to be caused by intrusive

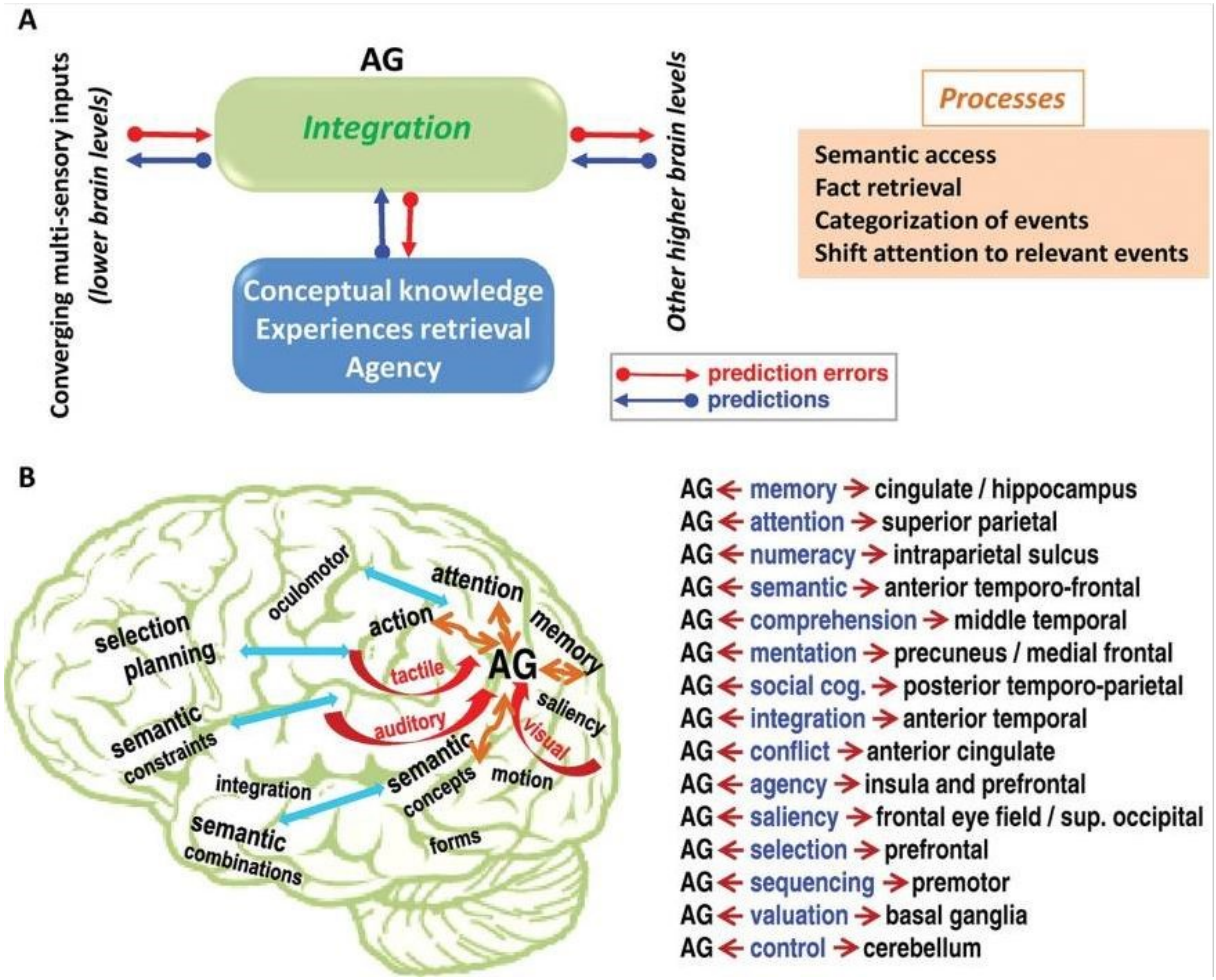

Figure 15. The function of the AG within the PPF.

A. The AG as connecting hub between multisensory inputs and predictions based on prior knowledge, learned experiences, and the sense of agency. The integration in the AG takes place via the recurrent exchange of predictions (blue arrows) and corresponding prediction errors (red arrows) in order to minimize prediction errors and to enable cognitive processes such as semantic access, fact retrieval, event categorization, and shifting attention. **B.** The AG in its function as connecting hub receives inputs from different modalities (red arrows) and interacts with different subsystems (orange arrows) including action, attention, saliency, and semantics. Blue arrows indicate potential other interactions. With kind permission, illustration taken from Seghier (2013), p. 53.

memories (Rossell, 2013). Various authors even hypothesize WM deficits as underlying cognitive dysfunction in schizophrenia (Goldman-Rakic, 1994; Keefe & Harvey, 2012). However, this is not specific for AVH. The categorization of events, relevant for example for understanding the external world (Baillargeon & Wang, 2002), language acquisition (Gentner

& Boroditsky, 2009) as well as social cognition and memory (Dominey, 2007), have been associated with schizophrenic patients experiencing AVH as well (Alderson-Day & Fernyhough, 2016; Brown & Kuperberg, 2015). In addition, attentional processes on psychological level (Hugdahl et al., 2007) as well as the attentional network on neural level have been associated with AVH (Vercammen, de Haan, & Aleman, 2008; Wolf et al., 2011). Moreover, bilateral AG is consistently associated with the DMN (Seghier, 2013) that itself has been correlated with the experience of AVH (Williamson, 2007). "In the case of the default network, the manipulation of conceptual knowledge, the sense of agency, and the retrieval of previous experiences (as predictions in Figure 15A) can modulate AG activity even in the absence of external sensory inputs", resulting in the experience of hallucinations without actual external sensation (Seghier, 2013, p. 52).

Following this trail of reasoning and comparing the current neuroimaging results with brain regions associated with the PPF, there is substantial overlap (see Figure 16). For instance, neural activation was found in part of the cingulate cortex, the anterior part of the STG, the SMA and parts of the parietal lobe including the AG and PoCG. However, the specific neural correlates do not match fully, i.e. the current study could not demonstrate neural activation in the PFC and ACC but in the SFG, MOG, ROL, and CUN. Furthermore, the comparison suggests and supports the idea of malfunctioning neural networks instead of isolated brain regions and/or structural deviations.

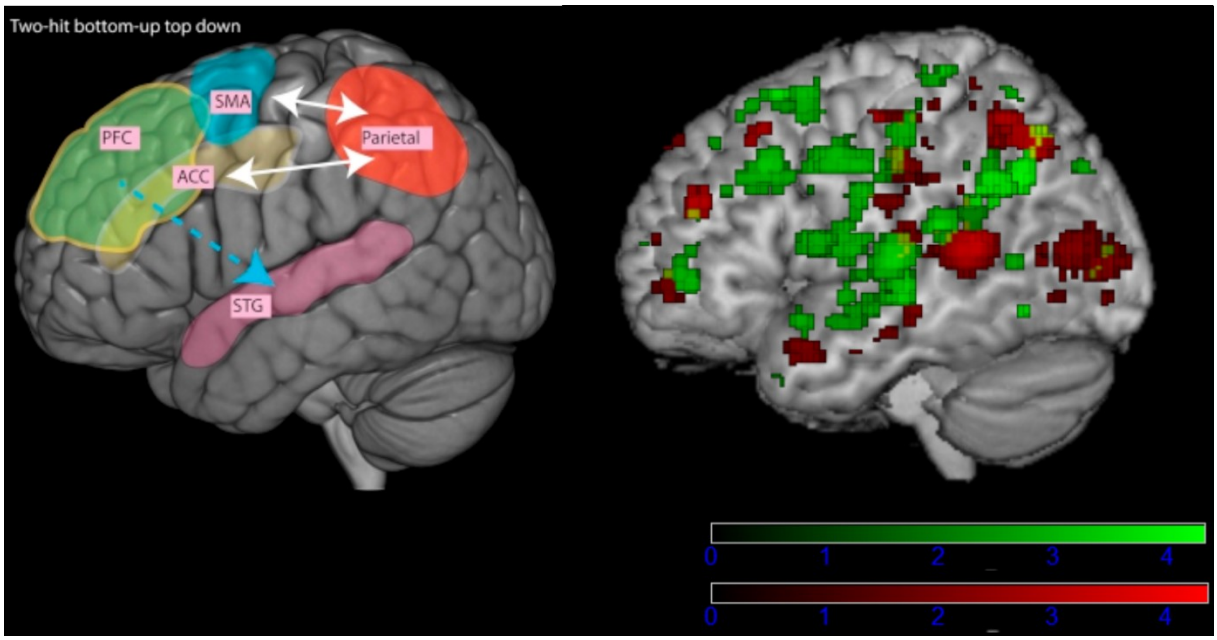

Figure 16. Juxtaposition of the found neural activation and the brain areas associated with the PPF

Comparison between neural correlates associated with the PPF and the current findings. **Left.** Interacting brain regions (arrows illustrate the direction of influence) associated with the PPF thought to be underlying AVH in schizophrenia. The dashed blue line illustrates an increase in excitation. With kind permission, illustration taken from Curcic-Blake et al. (2017), p. 4; detail. **Right.** Neural activation of post-hoc t-contrasts for both activation paradigms in the pAVH group, the alertness task (red) and n-back task (green). The color bars indicate the intensity of local neural activation measured in Z scores from 0=lowest to 4=highest

In summary, there is support for the hypothesis that deviant functioning of the AG may be at the core of AVH. That is, AVH in schizophrenia may be seen as resulting from a deficient integration of information or aberrant neural connectivity leading to erroneous prediction processing. Critically, these issues warrant further investigations. Potential implications and recommendations for further research are discussed below in chapter 5.4: Prospect.

For the remaining hypotheses, none of the results remained significant after FDR-correction and thus, the hypotheses had to be declined. These rather unexpected results or non-findings may indicate two underlying assumptions: First, opposing the current project's aim, there is no AVH-specific neural activation pattern in patients with schizophrenia and treatment-refractory

auditory verbal hallucinations that significantly correlates with neuropsychological performance and psychometric test scores. Second, there is a correlation between AVH-related functional activity and performance in neuropsychological test performance and psychopathology scores but the current project could not demonstrate it fully. That may have different reasons that will be discussed in chapter 5.3: Study strengths and limitations.

A growing body of research literature on AVH points to the second explanation as associations between neuroimaging and AVH characteristics as well as neuropsychological test performance have been demonstrated repeatedly. For example, Wolf et al. (2011) presented correlations between AVH severity and functional connectivity of the left ACC, left STG and right lateral prefrontal cortex. Furthermore, Kubera et al. (2014) found an association between AVH frequency, duration, and intensity and reduced gray matter volume in medial and inferior frontal, insular and bilateral temporal cortical regions. Moreover, Nenadic et al. (2010) pointed out that AVH severity seems to be associated with activity in the STP and PoCG.

In addition to non-confirmed hypotheses, there is a finding that needs to be acknowledged: Schizophrenic patients in general and hallucinating individuals in specific performed significantly worse on verbal memory when compared to healthy controls. This schizophrenia- and AVH-related deficit in verbal memory matches previous research results. Deficits in verbal learning and memory have consistently been associated with schizophrenia in general (Holmen et al., 2010; Nehra et al., 2016) and auditory hallucinations in specific (Allen et al., 2012). It has even been hypothesized that a malfunction of the verbal memory system may be (in part) responsible for the involuntary occurrence of AVH (Allen et al., 2012; Jardri et al., 2011) which was summarized in the previously mentioned AVH-model of aberrant memory processing. Expanding thereupon and bridging to the previous discussion on the PPF perspective, we now know that fact retrieval and language processing involve activation of the AG. Remember that AG is thought of as connecting hub integrating information. Verbal memory deficits in the

CVLT thus may suggest that new stimuli in the form of the presented words are not properly integrated, potentially leading to false prediction errors regarding the words to come (Fletcher & Frith, 2008). The correlation between CVLT performance and AG activity for both activation paradigms supports the notion, although significance did not withstand correction for multiple testing. The current study, thus, replicates and confirms earlier findings, thereby supporting the importance of verbal memory deficits in the symptom occurrence of hallucinating schizophrenic patients. Note, however, although verbal memory deficits were found in an off-line verbal memory task there was no indication of altered neural function in the hippocampus as should be expected if memory function was truly at the core of AVH.

5.3 Study strengths and limitations

There are strengths and limitations to the present project that need to be acknowledged.

The most apparent strength of the current project concerns the comparison of three groups instead of just two: one group of interest (pAVH) with two comparison groups – one clinical (non-hallucinating patients: nAVH) and one composed of individuals of the healthy population (HC). This is remarkable since the vast majority of AVH-related research so far has been limited to comparisons between pAVH and nAVH or pAVH and healthy controls (Curcic-Blake et al., 2017). This study design offers the opportunity to distinguish between effects of schizophrenia per se and hallucinations in specific.

Still, there are several limitations to be considered. First, the enrollment process turned out more difficult and lengthy than planned. Despite prolongation of the recruitment phase, the desired goal of n=25 per group was not reached. Patients suffering from schizophrenia are, per definition, suspicious and very often not eager to take part in research. Furthermore, a large percentage of affected individuals met exclusion criteria, most often substance abuse or dependence as well as lefthandedness (see Figure 7 on page 55). In addition, due to realistic

study conditions in a clinical setting, there was an unexpectedly high percentage of drop-outs and incomplete data sets due to early discharge. Of 96 patients found eligible for study entry, for the n-back task only 26 (23 for the alertness task) were included in the final analysis – 27.08% (23.96%). The included sample might, thus, be highly selective with the more severely affected individuals having refused to participate or dropping out. The fact that patients' performance during the alertness and n-back task did not significantly differ from healthy controls further supports the notion of a potential selection bias. Also, the modest sample size of the present study may have limited the significance of some of the statistical comparisons conducted. Second, although the two patient groups did not differ significantly in antipsychotic medication as measured in chlorpromazine equivalents, most of them did receive antipsychotic drug treatment during study participation. A potential effect of antipsychotic medication on neural activity and/or task performance cannot be fully ruled out. Third, schizophrenic patients with and without hallucinations did differ in global symptom severity with hallucinating individuals being more severely affected. Baethge, Janner, Gaebel, and Malevani (2017) state that "hallucinations are a sign, if not a cause, of greater illness severity. When compared with non-hallucinating individuals in either diagnostic group, hallucinators were more affected by delusions and by anxiety" (p. 299). This, however, leaves unanswered the question of whether the found effects reflect the difference between hallucinating and non-hallucinating patients with schizophrenia or whether they might also be accounted for by symptom severity in general. Fourth, there was no direct assessment of whether patients hallucinated during the MRI scan or not. Instead, AVH were assessed globally before scanning and were treated, as defined by inclusion criteria, as treatment-resistant and thus persistent. Fifth, the activation paradigms during MRI scanning relied on the button press method which means that it might have confounded the associated mean local activation to include the patients preparing and carrying out a motor response. However, this was the same for all three groups and, therefore, it should

balance out in the further analyses. Sixth, because of the large number of analyses performed, the reliability of individual results and specific coefficients must be interpreted with due caution due to multiplicity. However, it has been tried to cope therewith by correcting for multiple testing using FDR-correction. Note, that the fMRI analyses were exempted from the FDR-correction following the recommended procedure by Lieberman and Cunningham (2009) to balance Type I (false positives) and II (false negatives) errors. It is important to mention that (1) recommendations vary (e.g., Benjamini & Hochberg, 1995; Lohmann, Neumann, Mueller, & Lepsien, 2008) and that (2) fMRI research and the according results are being critically evaluated in an ongoing debate (e.g., Eklund, Nichols, & Knutsson, 2016; Kessler, Angstadt, & Sripada, 2017). Additionally, block designs, i.e. the block subtraction methodology has been criticized as overlapping brain regions subserving different functions could cancel each other out leading to an increase in false negatives (Logothetis, 2008). Furthermore, in his extensive overview Logothetis (2008) reminds that neural activity is way more complex than networks of neurons lighting up in the fMRI scanner meaning involvement in the task at hand. He goes on to explain that the earlier concept of the brain as information processing entity with input-elaboration-output is oversimplified and does not account for excitation–inhibition networks: „The fMRI signal cannot easily differentiate between function-specific processing and neuromodulation, between bottom-up and top-down signals, and it may potentially confuse excitation and inhibition“ (p. 877, for further information consult the article in question). That is, any given neurofunctional correlate resulting from fMRI research may represent a cause, a consequence, or neural compensation (Lewis & Gonzalez Burgos, 2008). These results indeed may call into question the validity of countless published and current fMRI studies. The extent and implication has yet to be fully evaluated. Note, however, that the technology as well as the statistical analyses in question are being developed and improved constantly relativizing the above-mentioned criqitue.

5.4 Prospect

Based on the current study, its results, strengths, and limitations, there are several recommendations that should be addressed in further research.

First, it is highly questionable whether an externally elicited, task-induced hypo- or hyperactivation in any one brain structure may reveal the full complexity of functional dynamics associated with symptom occurrence. Furthermore, at this stage of research where the intrinsic neuronal baseline of the hallucinating brain prior to extrinsic stimulation is not yet fully known, it remains open how results derived from symptom interference studies can be appreciated. In order to draw valid conclusions about neuronal interference processes it is essential to know which brain areas or -networks are associated with the occurrence of AVH prior to stimulation. Therefore, I suggest supplementing the performed analyses with results from resting-state as well as functional connectivity analyses based on the data from the current project. These additional analyses are beyond the scope of this doctoral thesis and are, therefore, planned as follow-up. As the AG and its function as connecting hub appears to be a promising site associated with AVH it should be considered as region of interest in the planned resting-state and task-based functional connectivity analyses.

Second, with regard to the discussed neural compensatory mechanisms it might be worthwhile to consider the effects of task performance in a more differentiated manner. For example, I suggest follow-up research to compare subgroups within the pAVH group that differ in their task performance. I predict that for the successful, neural compensation plays a more important role than for hallucinating patients with poor cognitive performance. In the existing literature, subtypes of AVH have been proposed based on different variables such as causal factors, phenomenological characteristics, associated cognitive processes, neural correlates, treatment response as well as diagnosis (McCarthy-Jones, Thomas, et al., 2014). Especially the last item,

i.e. the trandiagnostic character of AVH might be interesting for further research, too. The current study focused on hallucinating patients with schizophrenia, but AVH are a transnosological phenomenon. AVH might occur in borderline personality disorder, affective disorders such as bipolar disorder and posttraumatic stress disorder as well. Therefore, I suggest follow-up research to compare phenomenology, neural correlates and task performance for AVH between different disorders to better understand common and divergent mechanisms.

Third, the fact that hallucinating and non-hallucinating schizophrenic patients differ in their symptom severity poses another problem that needs to be addressed in further research. On the one hand, a greater overall symptom severity associated with hallucinations seems obvious and logically understandable and, therefore, disorder immanent. On the other hand, it may cause difficulties in the interpretation of results even if statistically controlling for its effect. In order to circumvent the aforementioned difficulties and facilitate the interpretation of results there are two possible changes to make for further research: One option is to match the patient groups on symptom severity. However, if greater illness severity is indeed disease immanent, then the sample presented will be biased. Therefore, for a follow-up project, I would like to propose adding one more comparison group: healthy participants with a history of AVH that do not meet the criteria for schizophrenia-spectrum diagnosis. The comparison between hallucinating schizophrenic patients, non-hallucinating patients, non-hallucinating healthy participants, and hallucinating healthy individuals would allow dividing the effects of schizophrenia, the intensity of their symptom severity, and that of pure hallucinations apart. Furthermore, this matches two current developments in the field of schizophrenia and AVH: First, there is an ongoing debate about the enormous heterogeneity within schizophrenia suggesting that a unitary disorder called schizophrenia does not exist but only a collection of psychological and cognitive symptoms (Berrios, Luque, & Villagrán, 2003). Of course, this is in part due the nature of descriptive psychopathology and categorial diagnostics. In addition, recent

developments are in line with the concept of dimensionality regarding schizophrenia, e.g., the elimination of schizophrenia subtypes and introducing schizophrenia-spectrum disorder in DSM-5 (American Psychiatric Association, 2013). Second, current research evidence suggests that AVH in healthy individuals and schizophrenic patients do not differ significantly in functional activity patterns pointing to the aspect of dimensionality (Diederen et al., 2012). However, of course, this is also a matter of practicability and the questions remains whether it would be manageable, with slight changes in the recruitment process, to enroll a fourth group. The same holds true for the aforementioned recommendation of comparing different AVH-related diagnoses.

Last but not least, considering potential clinical implications, if it turns out that the AG is indeed important in the symptom occurrence of AVH, it may prove to be a promising target site for non-invasive brain stimulation techniques, such as tDCS, rTMS, or TBS. At present, tDCS mainly focuses on inhibitory stimulation over the left temporo-parietal cortex and excitatory stimulation over the left dorsolateral prefrontal cortex (Brunelin et al., 2012) whereas rTMS targets the left temporo-parietal cortex (Kubera et al., 2015). However, it needs to be acknowledged that any proposed implication, may it be scientific or clinical, is pure speculation. That is, the role of the AG in AVH in schizophrenia might be a novel insight, if at all, but needs further scientific underpinning to ensure its veracity. At this stage of research it is too early to draw any definitive conclusions.

5.5 Overall appraisal

Summarizing the overall study including its results and their value, this doctoral thesis was interested in the neural correlates underlying treatment-refractory AVH in schizophrenia and potential associations with clinical symptoms and cognitive processes. AVH are defined as a sensory experience of hearing voices in the absence of a corresponding external stimulus with

a compelling sense of reality. They are one of the core symptoms of schizophrenia with 50-80% of patients experiencing AVH (Andreasen & Flaum, 1991). Treatment-refractory AVH, i.e., persisting hallucinations despite an adequate treatment which should be sufficient in intensity and duration (Berman et al., 1997), cause major distress and affect the lives of patients substantially (Vauth & Stieglitz, 2007). To date, the precise neurocognitive and neurobiological mechanisms contributing to AVH occurrence are still largely unknown with different studies providing inconsistent results. So far, the neuroscientific state of evidence regarding AVH in schizophrenic patients points to morphological and functional changes in frontal, temporal and parietal regions as well as abnormal network connectivity in the brain. Multiple neuronal systems seem to be involved, i.e., language, attention, and executive control. The current study was designed as a 'piece of the puzzle' to add to the existing literature and answer the question whether AVH in schizophrenia are associated with different neural activation in known brain areas of interest. In addition, the relationship between these functional neural activation patterns and performance on the on-line activation paradigms, neuropsychological measures of cognitive functioning, as well as psychopathology was assessed. Therefore, three groups of participants were enrolled in the study to enable a differentiation between the effects of schizophrenia in general and AVH in specific. The groups consisted of schizophrenic patients with treatment-refractory auditory verbal hallucinations, schizophrenic patients without AVH, and participants from the healthy population. For some analyses, hallucinating and non-hallucinating patients were grouped together to form the group of schizophrenic patients. Participants underwent one-time assessment of cognition, psychopathology, and neuroimaging on two or three dates each lasting approximately 1-1.5 hours. Structural and functional neuroimaging data was acquired. Furthermore, participants completed a cognitive test battery. In addition, participants were asked to answer various questions regarding their symptoms, in the form of a semi-structured psychiatric interview as well as self-report questionnaires.

Independent thereof, all participants being inpatients received treatment as usual, which consisted of pharmacotherapy in combination with cognitive-behavioral treatment, including both individual and group sessions.

Four hypotheses were evaluated regarding confirmatory indicators of evidence: (1) Groups will differ in functional neural activation patterns. In specific and in accordance with the symptom interference idea, reduced neural activation in hallucinating patients when compared with both control groups was hypothesized. (2) AVH-related neural activation will interfere with task performance on-line. The direction of correlation was predicted to be negative. (3) AVH-related neural activation will be correlated with neuropsychological performance off-line. And (4) AVH-related neural dysfunction will be negatively correlated with general psychopathology. The statistical analyses revealed that none of the initially formulated hypotheses could be confirmed with regard to the hypothesized direction of effect. However, both fMRI activation paradigms, the alertness task and the n-back task, lead to significant AVH-related neural activation at $p<.005$ and cluster size$>k$ (expected voxels per cluster) in contrast to the predicted hypoactivation. Neural activation was mainly demonstrated in fronto-temporo-parietal areas: The alertness task demonstrated increased activation in the left MOG, the left STP, the left SFG as well as in the right AG; the n-back task in the right mCGC, bilateral STP, bilateral ROL, bilateral PoCG, the right SMA, and bilateral AG when compared to both, nAVH and HC. The observed hyperactivation was put in the context of existing literature and discussed in the light of neural compensation. That is, the neural correlates that were formerly thought of as bound by AVH (and therefore not available for task demands) might have been available to pAVH after all and thus exhibiting hyperactivation in order to match specific task demands. To conclude, symptom interference not only needs to consider neuronal resting state activity but also potentially compensatory processes. With regard to the remaining hypotheses on the suspected correlation between AVH-related neural dysfunction and task performance during

neuropsychological tests as well as specific psychopathology, none of them revealed FDR-correctable results. However, there was a finding that needs to be acknowledged: An additionally performed group comparison revealed that schizophrenic patients in general and hallucinating individuals in specific performed significantly worse on verbal learning when compared to healthy controls. This fits perfectly in the already existing literature confirming that hallucinating patients show a clear deficit in verbal memory and learning. It should be mentioned that there was no difference in alertness and WM task.

The aforementioned results were discussed regarding their potential meaning and implications in the light of the predictive processing framework as model for the occurrence of AVH as well the clinical implications for the AG as potential target site for brain stimulation. In specific, the discussion of results focused on bilateral AG activity as it had been found to be significant in both activation paradigms and has not been mentioned in the AVH literature that often compared to the other brain regions that are already well established. Thus, the AG might present a so far overlooked but potentially promising result. The AG as part of the association cortex and in its function as connecting hub is associated with multiple functions, e.g., semantic processing, reading and comprehension, memory retrieval, attention, and social cognition. It is an important component in the predictive processing framework as presented by Seghier (2013). The PPF may explain the implication of the AG and its functions in the occurrence and physical characteristics of AVH. Summarizing the discussion, there is support for the hypothesis that aberrant functioning of the AG is at the core of AVH. That is, AVH in schizophrenia may be seen as resulting from deviant neural connectivity leading to erroneous prediction processing.

However, it needs to be acknowledged that this conclusion as well as any proposed implication, may it be scientific or clinical, is rather speculative and needs to be critically reflected and examined in the light of further research evidence. It was suggested to make use of additional

resting-state and connectivity analyses using the AG and its function as connecting hub as region of interest.

In addition, all speculation aside, please note that the hyperactivation in bilateral AG (and in other brain regions) in hallucinating individuals when compared to non-hallucinating patients was not corrected for multiple testing but merely a (promising) convention to use in further analyses. That is, the role of the AG in auditory verbal hallucinations in schizophrenia might be a rather novel insight, but needs further scientific underpinning to ensure its veracity.

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7 List of Tables

8 List of Figures

9 List of Abbreviations

AAL…….. Automated Anatomical Labeling

ACC…….. anterior cingulate cortex

AG……. angular gyrus

APA…….. American Psychological Association

AVH…….. auditory verbal hallucinations

BAVQ-R… Beliefs About Voices Questionnaire - Revised

BCIS…….. Beck's Cognitive Insight Scale

BPRS……. Brief Psychiatric Rating Scale

CDSS……. Calgary Depression Rating Scale for Schizophrenia

CVLT……. California Verbal Learning Test

CSF…… cerebrospinal fluid

CUN…….. cuneus

DA……. dopamine

df……..... degrees of freedom

DLPFC…... dorsolateral prefrontal cortex

DMN…….. default mode network

DSM…….. Diagnostic and Statistical Manual of Mental Disorders

EHI…… Edinburgh Handedness Inventory

EPI……. Echo-planar imaging

ERQ…….. Emotional Response Questionnaire

fMRI….. functional magnetic resonance imaging

FoV…… field of view

HDRS…… Hamilton Depression Rating Scale

HC……. healthy control subjects

ICD…..... International Statistical Classification of Diseases and Related Health Problems

LPS…..... Leistungsprüfsystem

LTM…….. long-term memory

mCGC…… middle cingulate cortex

MTG…….. middle temporal gyrus

MOG…….. middle occipital gyrus

nAVH…… non-hallucinating patients

N…… sample size

NEO-FFI… NEO Five-Factor Inventory

PANSS…... Positive and Negative Syndrome Scale

pAVH…... (patients with) persistent auditory verbal hallucinations

PFC…… prefrontal cortex

PoCG……. postcentral gyrus

PPF…… predictive processing framework

PSYRATS. Psychotic Symptom Rating Scale

ROL…….. Rolandic operculum

RSN…….. resting-state network

SD…….. standard deviation

SFG…… superior frontal gyrus

SPM…….. Statistical Parametric Mapping

STAI…….. State-Trait Anxiety Inventory

STG…….. superior temporal gyrus

STM…….. short-term memory

STP…… superior temporal pole

SPSS…….. IBM SPSS Statistics

Sz…….. group of schizophrenic patients composed of pAVH and nAVH for statistical analyses

TAP…….. Test for Attentional Performance

TE……. echo time

TPJ……. degrees of freedom

TR……. repetition time

VLPFC…... ventrolateral prefrontal cortex

WCST..... Wisconsin Card Sorting Test

WM……..... working memory

WHO……. World Health Organization

WMS-R…. Wechsler Memory Scale - Revised

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