STUDYING THE BRAIN CORRELATES OF HALLUCINATIONS

-Perceptual abilities of patients with schizophrenia compared with first-degree relatives and controls - investigated with psychometric measurements and magnet resonance tomography (MRI)

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ABSTRACT

The present study consists of two parts: The first part is made up of questions concerning the cognitive underpinnings of auditory verbal hallucinations in schizophrenia. As this thesis framed schizophrenia as a multivariate problem, neural correlates to auditory verbal and visual hallucinations were investigated in the second part.

The main finding is that vividness of mental imagery was increased in all putative high-risk groups as well as the patients themselves, compared with low-schizotypy controls. Therefore, it seems that vivid imagery is a trait rather than a state marker, and may be related to the genetic liability to develop schizophrenia.

However, no evidence was found for a linear relationship between vividness of mental imagery and predisposition to hallucinate. Self-reported imagery vividness and predisposition to hallucinate did not depend on psychomotor speed or intelligence. In addition, individual psychopathology ratings did not correlate significantly with the mental imagery scores.

Furthermore, the analysis of the control orientation and the degree of dysfunctional psychopathological status across the schizophrenia spectrum, showed an independence of control orientation and dysfunctional status from each other, as well as from other markers of schizophrenia or schizophrenic-like individuals. As a conclusion, external control orientation seems to be a symptom or a trait marker of schizophrenia. The results lead to the assumption that, beside schizophrenic individuals, first-degree relatives and schizotypy controls have some impairments and visible signs without suffering from the illness directly. This would lead to the further assumption that the illness schizophrenia is not only genetic but also dependent on environmental factors.

In the second part of the study, we investigated anatomical and functional brain abnormalities in the schizophrenia patients compared with first-degree relatives and healthy controls. Here, the results followed the continuum of healthy controls, first-degree relatives and schizophrenic patients in the functional and anatomical data sets, and in the language lateralization. The decrease of lateralisation correlated with the severity of symptoms in the patient group.

The investigation of visual hallucinations showed activity in higher visual areas during the experience of visual hallucinations in a schizophrenia patient and in a blindfolded subject. The activity in higher visual areas followed the boundaries of category-selective areas in both subjects. In contrast to the memory-related areas found in the schizophrenic patient experiencing visual hallucinations, we did not observe memory-related areas during visual hallucinations induced by blindfolding. This suggests that the neural mechanisms underlying hallucinations in schizophrenia are at least partly distinct from those operational in cortical deafferentation.

It is proposed that individual differences in psychopathology, as well as neuropsychological and psychosocial functioning may provide further means to understand the

complex and highly dynamic aspects of hallucinations specifically and schizophrenia in general. The enlargement of the subject sample to high-schizotypy controls and first-degree relatives of patients allowed new insights into the mental imagery debate and the dysfunctional connectivity pattern known to be responsible for psychotic symptoms. Further topics of research are discussed.

ABSTRACT IN DEUTSCHER SPRACHE

Die hier präsentierte Arbeit untersucht die Erkrankung Schizophrenie, und speziell das Phänomen der Halluzinationen, unter multivariaten Gesichspunkten: es werden kognitive und neuronale Korrelate von Halluzinationen analysiert.

In der ersten Teiluntersuchung wurde geprüft, ob sich die mentale Vorstellungskraft bei den verschiedenen Versuchspersonengruppen, schizophrene Patienten, erstgradige Verwandte der Patienten, hoch-schizotype Kontrollpersonen und normale Kontrollpersonen, signifikant unterscheidet, und ob diese potentiellen Unterschiede eine Verbindung zu Halluzinationen, aufweisen. Das Hauptergebnis ist, dass die Lebhaftigkeit der mentalen Vorstellung in allen potentiellen Risikogruppen, also Verwandten, hoch-schizotypen Personen und schizophrenen Patienten selbst, erhöht ist, wenn man sie mit der Lebhaftigkeit der mentalen Vorstellungskraft bei normalen Kontrollprobanden vergleicht. Die Ergebnisse zeigen Hinweise auf eine genetische Disposition zu einer vermehrten Lebhaftigkeit visueller Vorstellungen im schizophrenen Spektrum. Jedoch zeigten die Ergebnisse nicht, wie von verschiedenen Autoren vermutet, einen direkten Zusammenhang zwischen der mentalen Vorstellungskraft und der Prädisposition zu halluzinieren. Beide Konstrukte scheinen darüber hinaus von psychomotorischer Verarbeitungsgeschwindigkeit und kristalliner Intelligenz unabhängig zu sein. Darüber hinaus besteht kein Zusammenhang zwischen der individuellen Ausprägung der psychopathologischen Symptome der schizophrenen Patienten und der subjektiven Einschätzung der mentalen Vorstellungskraft. Die Ergebnisse weisen darauf hin, dass die Lebhaftigkeit der Vorstellung eher etwas Überdauerndes (trait marker) als ein aktuell untersuchter Zustand (state marker) ist. Die Lebhaftigkeit der mentalen Vorstellungskraft scheint eine von Halluzinationen oder anderen psychopathologischen Symptomen unabhängige Auffälligkeit zu sein, die sich über das Schizophrenie-Spektrum erstreckt.

Weiterhin konnten bei der Untersuchung weiterer möglicher Korrelate zu Halluzinationen andere kognitive Konstrukte mit den gleichen Probandengruppen untersucht werden: das Ausmaß an externaler Kontrollüberzeugun sowie an dysfunktionalen psychopathologischen Zustandsbild. Hier zeigte sich, dass schizophrene Patienten eher zu einer externalen Kontrollorientierung neigen, während Kontrollprobanden eine internal orientierte Kontrollüberzeugung hatten. Hoch-schizotype Personen sowie Verwandte der Patienten bildeten die Mitte zwischen den beiden anderen Probandengruppen. Auch bezüglich des dysfunktionalen Status konnte das eben beschriebene Kontinuum gezeigt werden. Beide Konstrukte zeigten sich unabhängig voneinander, wie auch von Halluzinationen. Jedoch zeigte sich ein Zusammenhang zwischen der externalen Kontrollüberzeugung und einem anderen psychopathologischen Symptom der Schizophrenie, den Wahnvorstellungen.

Also scheint eine externale Kontrollüberzeugung ein Symptom oder ein Trait marker der des Schizophrenie-Spektrums zu sein. Diese Probandengruppen zeigen im Vergleich zu normalen

Kontrollprobanden Auffälligkeiten, ohne dass sie an der Erkrankung direkt leiden. Dies könnte zu dem Schluss führen, dass gewisse Auffälligkeiten genetisch veranlagt sind, die Grenze zur Erkrankung Schizophrenie aber nur überschritten wird, wenn Umgebungs- oder andere Faktoren ungünstig dazu kommen.

Im zweiten Teil der Studie untersuchten wir anatomische und funktionelle Auffälligkeiten des Gehirns. Die neurologischen Daten zeigen eine niedrigschwellige Aktivität im auditorischen Kortex außerdem eine reduzierte Sprachlateralisierung bei Schizophrenen und ihren Verwandten im Vergleich zu Normalpersonen. Sprache wird normalerweise stärker linksseitig im Gehirn verarbeitet, bei unseren Patienten scheint dieser Mechanismus jedoch gestört zu sein. Weitergehende Fragen zeigten, dass die Reduzierung der Sprach-Lateralisierung bei den Patienten in direkter Verbindung zu psychotischen Symptomen stehen. Je mehr psychotische Symptome die Patienten während des Zeitraums der Untersuchung aufwiesen, desto deutlicher gestaltete sich die Reduktion der Sprachlateralisierung. Diese Ergebnisse konnten auch für die Untersuchung des anatomischen Volumens des auditorischen Kortex gezeigt werden. Die hier vorliegenden Befunde sprechen für das schon zuvor beobachtete Kontinuum der Ergebnisse, von den Normalpersonen ohne Auffälligkeiten, zu den Verwandten mit leichten Auffälligkeiten, bis hin zu den Patienten mit deutlichen Auffälligkeiten in auditorischen und visuellen Verarbeitungsbereichen.

Im weiteren Verlauf untersuchten wir das Phänomen der visuellen Halluzinationen bei einem schizophrenen Patienten sowie bei einer Probandin, die visuelle Halluzinationen durch sensorische Deprivation bewusst herbeigeführt hat. Wir konnten zeigen, dass höhere visuelle Areale während des Erlebens von visuellen Halluzinationen aktiviert sind, die direkt mit den Grenzen Kategorie-spezifischer Areale einhergingen. Während es gelungen ist, bei dem schizophrenen Patienten Gedächtnis-Areale zu finden, die während visueller Halluzinationen aktiviert waren, konnte dieser Befund für die Probandin mit den durch sensorische Deprivation herbeigeführten Halluzinationen nicht bestätigt werden. Dieser Befund bestätigt die Vermutung, dass die neuronalen Mechanismen, die den visuellen Halluzinationen bei schizophrenen Patienten zugrunde liegen, teilweise anders als bei operationaler kortikaler Deafferentation sind.

Es wird vermutet, dass die Erkenntnis über individuelle Unterschiede in der Psychopathologie, sowie im neuropsychologischen und psychosozialen “funktionieren” helfen werden, die komplexen und hoch dynamischen Aspekte von Halluzinationen und, im weiteren Zusammenhang, von Schizophrenie generell, zu verstehen. Durch die Erweiterung der Stichprobe durch Hinzunahme von hoch-schizotypen Personen sowie von erstgradigen Verwandten schizophrener Patienten konnten wir neue Erkenntnisse bezüglich der Mental-Imagery Diskussion, aber auch bezüglich dysfunktionaler Konnektivitäts-Muster finden, die für psychotische Symptome verantwortlich sind. Weitere Möglichkeiten für die Forschung werden diskutiert.

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CHAPTER 1: GENERAL INTRODUCTION

This thesis deals with a patient group suffering from one of the most common and interesting psychiatric disorders: *Schizophrenia*. Eugen Bleuler (1911; cited in: Bleuler, 1950) established the term schizophrenia, a construct of *split* (schizo) and *mind* (phrenia), which means split consciousness. The term doesn't implement a split of personality, as understood in popular films and books, but a split between the person and the environment. The individual character and the personality of the patient remain constant.

Although the term schizophrenia describes a relatively new disease, which turned up in the psychiatric literature not before the end of the 19th century, the symptoms that belong to it were described as early as 460 BC by Hippocrates of Cos (in: Taylor and Fink, 1991) who named this illness *stupiditas*. Although there are some descriptions of individual symptoms of schizophrenia by some theorists and other authors, e.g. the figure of "poor Mad Tom" in *King Lear* (Shakespeare), none of these descriptions pointed to schizophrenia according to the present definition. Two researchers (Haslam [London] and Pinel [Paris]) in the early 19th century first described patients with classical symptoms of schizophrenia without having a clear name of this illness (in: Taylor and Fink, 1991).

The current literature provides different approaches to investigate schizophrenia. First of all, the psychiatric literature includes behavioural and phenomenological descriptions of schizophrenic trait markers. Then, cognitive models try to explain the illness with a deficiency in the information processing system. The neurophysiological approach includes, beside several brain anatomy studies, functional tasks as well in order to provide evidence for a deficient neuronal network in schizophrenic (SZ) patients. In addition, there have been biochemical findings, and high risk studies have identified schizophrenia as a heritable illness with a genetic vulnerability. Therefore, the study of several markers and their potential relation to hallucinations should not be confined to patients with a clinical diagnosis of schizophrenia, but should be enlarged to high-risk populations. Even though there are a large amount of studies regarding this patient group, some aspects still remain in the dark.

The aim of the present thesis is to get a better understanding of the presence and occurrence of the symptoms and the trait markers of schizophrenia, and above all, deals with hallucinations in SZ patients. It has to be stated that not all SZ patients necessarily suffer from hallucinations, but on the other hand, there are also people who experience hallucinations without having the illness schizophrenia. Nevertheless, the construct of hallucinations remain an interesting tool for psychiatric research. As they are seen as a type of "mental image", research has tried to decode the complex "mental imagery" in order to assign hallucinations a place in the complex. At present, this attempt hasn't brought clear results. Hallucinations are still, in the understanding of a SZ patient, a typical "mental image", which comes to the patient through a

voice to his senses. We know, however, that the hallucinating patient experiences no external stimuli during his hallucinations. The process of hallucinating thus seems an intricate matter, which several theories try to understand through different ways: on a cognitive basis, on a phenomenological basis and on a neurophysiological basis. The current thesis tries to determine phenomenological (vividness of mental imagery), cognitive (control orientation) and neuronal correlates (functional and anatomical) of hallucinations. Of main interest are: psychotic symptoms like hallucinations and the vividness of mental imagery and their potential relationship to each other, as well as their relationship with additional potential markers like control orientation during acting (Locus-of-control-construct; Rotter, 1966), the general ability of self-report of schizophrenic patients and other cognitive applications, compared to the individual's psychopathology ratings.

In this thesis, we examine the question of whether an increased vividness of mental imagery is related to an increased tendency towards hallucinations or if the two phenomena are totally independent from each other. The involvement of mental imagery in hallucinations has proven to be controversial. Some authors suggest that hallucinations and vivid imagery are somehow related (e.g. Mintz and Albert, 1972; Bentall and Slade, 1985), other investigations find no relationship between the two noticeable problems (Brett and Starker, 1977; Starker and Jolin, 1982; Sack et al, 2005). Our investigation has two major approaches: a huge test battery and a neuroimaging study. The goal was to combine different approaches of investigation into one model to explain hallucinations and mental imagery. Therefore, findings from subjective data sets, coming from psychometric tests and questionnaires, were combined with an objective measurement of potential neural deficits (functional MRI and structural MRI).

In order to take potential genetic vulnerability into account, the investigation was conducted with three subject groups: patients diagnosed with paranoid Schizophrenia according to DSM-IV criteria (295.30; American Psychiatric Association, 1994), first-degree relatives (parents and siblings) and normal controls. In addition, the control group was divided into low- and high-schizotypy controls. *Chapter one* gives a theoretical overview of the concept of schizophrenia, including multidimensional models. The chapter also includes a description of major symptoms and important diagnostic aspects. To gain neurophysiological knowledge in order to understand the later findings better, an overview of the anatomy of the brain, important areas and their main functions will be given, followed by a description of the principles of imaging methods. The research design will complete the chapter. *Chapter two* introduces and describes the psychometric investigation of mental imagery and its relationship to hallucinations in schizophrenia, and deals with a potential underlying personality structure which could contribute to the symptoms. *Chapter three* and *four* include functional and anatomical neurophysiological findings. Here, the main interest is on the underlying pathology of hallucinations in different sensory modalities (auditory, visual). The description of the individuals' results will be followed by

a correlation between the neurophysiological findings and the individuals' psychopathology. *Chapter five* provides a summary of all results and potential approaches for further research.

1.1 The concept of schizophrenia

1.1.1 Introduction

Schizophrenia is a chronic recurring psychotic illness that characteristically begins in younger adult years and lasts a lifetime. Typically, the persons get sick between the age of 15 and 30, sometimes one can find first episodes at the age of 40. The onset of the illness doesn't occur immediately, but bit by bit over several years ("*prodromal phase*"). *Prodromal symptoms* often precede acute psychosis, including cognitive dysfunctions like attention and vigilance deficits. Additionally, the patients seem nervous and stressed, they suffer from sleep disorder, uneasiness, loss of weight, loss of appetite, and changes in sleep-, eating- and drinking-behaviour. Furthermore, social retreat and depressive symptoms occur as well as aggressive behaviour, enragement, suspiciousness and a sensibility for sensory input, like loudness.

In the first episodes of the illness or in the prodromal phase, many patients remark physiological changes, e.g. pain in the heart, in shoulders and in the neck, or they experience affective physical movements (spasms etc.). These signs lead to a lack of self-assuredness. Other physiological signs are disturbances of drive (decrease or increase of physical drive). Usually these problems result in a loss of energy, a loss of motivation, a loss of spontaneity and social retardation. Most common in chronic SZ patients is a deficit in emotions. The listed signs are a small selection of many possible ones. In several cases, the most remarkable indication is a loss of power in their job, and lower performance at school or university.

The prevalence of schizophrenia in the general population is 1 %. The disease occurs in all cultures and peoples around the world (with rare exceptions) and with similar genetic risk estimates. Twin studies have been pivotal in verifying a genetic predisposition. The more closely one is related to an individual with schizophrenia, the greater the risk of contracting the illness.

The course of the illness can be different:

- 10 - 20 % of the patients suffer from only one psychotic episode and recover fully.
- 40-60 % of the patients experience more than one psychotic episode. Between these episodes, they function without any or few problems.
- 20 - 30 % of the patients are chronically ill. They suffer from medium to strong symptoms at all times, sometimes with small improvements in between.

The initial years of the illness are often the most symptomatic and include severe psychosocial deterioration. The years in-between are more benign, and later, frank symptom recovery has been described. Within this simplistic framework, episodes of psychosis regularly occur. One can say schizophrenia is a disease of childbearing years, even though elderly persons with the illness

may still retain symptoms. Various interactions between schizophrenia and aging have been reported. Some clinical samples show symptom improvement accompanied by psychosocial stability with aging, whereas other clinical samples show a precipitous age-related deterioration with losses of cognitive function and frank dementia.

There are two prominent diagnostic systems, which are used in clinical and research settings: first, the *Diagnostic and Statistic Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994), and the *International Classification of Disease* (ICD-10; World Health Organization, 1992; view appendix D for further details). In the present study, chronic SZ patients according to DSM IV (APA, 1994) are included. Those patients are characterized most of all by hallucinations and delusions. In addition inadequate affect and catatonic symptoms could be identified as compensatory symptoms, but are not necessary. For a differential diagnosis, it is important to exclude organically caused psychoses, drug abuse, schizotypy or schizotypal disorders, as well as delusion disorders or manic-depressive disorders.

1.1.2 Historical overview

The modern concept of schizophrenia and the systematic study of this disorder in the history of psychiatry are associated with the work of Kraepelin, (*dementia praecox* [Kraepelin, 1919]), Bleuler (1919), who divided the wide range of symptoms and signs of the illness into primary and secondary symptoms, and Schneider (1959), who primarily proposed first rank and second rank symptoms. The current approach is based on the concept of positive and negative symptoms (Crow, 1985; view table 1.1 for an overview).

Table 1.1: *Overview of all concepts of schizophrenia.*

	Author	**Construct**	
Historical view	Hippocrates (460 BC)	Stupiditas	
	Kraepelin (1899)	Dementia praecox	3 different subgroups: paranoia, hebephrenia, catatonia
	Bleuler (1911)	Schizophrenia	Primary symptoms Secondary symptoms
	Schneider (1959)		First rank symptoms Second rank symptoms
Current Perspectives	Crow (1985)		Positive symptoms Negative symptoms
	Lindenmayer et al. (1994)	5-factor model	Negative, positive, excitement, depression, cognitive/disorganisation

Kraepelin linked several psychotic symptoms to propose a new disease, *dementia praecox* (Kraepelin, 1919). *Dementia* means loss of intellectual functioning, *praecox* means early onset. The defining feature of dementia praecox was the early onset of the disorder and a general intellectual decline. The main issue of the concept lies in the distinction of the affective disorders. Kraepelin's nosology was the first comprehensive attempt to arrive at a fundamental classification of psychiatric disorders. Previously, only a multitude of loosely defined symptoms had existed. His emphasis on psychiatric disorders as distinct entities with a specific organic pathology prepared the way for modern psychiatric diagnostics.

The term dementia praecox by Kraepelin was served by three, previously independent syndromes: *catatonia* (Kahlbaum, 1868; in Kraepelin, 1919), *hebephrenia* (Hecker, 1871; in Kraepelin, 1919) and *paranoia* (Sander, 1868; in Kraepelin, 1919). The syndromes include the following characteristic symptoms:

1. *Catatonia* → motoric symptoms such as stupor, alogia, stereotypy, mutism, thought disorder, hallucinations and delusions in the early phase.
2. *Hebephrenia* → thought disorder, delusions, avolition, apathy, flattened affect, inappropriate affect, bizarre behaviour.
3. *Paranoia* → pronounced delusions, hallucinations.

In 1911, Bleuler (cited in 1950) elaborated significant corrections of the concept of dementia praecox. He adopted Kraepelin's subgroups, but rejected the notion of dementia and endorsed a more optimistic outlook regarding the course of the disease. He coined the term schizophrenia to capture the splitting or fragmentation of mental processes which was seen to constitute the *primary disturbance* in schizophrenia. The symptoms which dominated the clinical picture, such as delusions and hallucinations, were considered to be *secondary / accessory* symptoms. Both symptom groups represented distinct etiologies. Bleuler differentiated not only between the disease process and its symptoms, but also between an organic pathology (primary symptoms) and psychogenetic symptoms (secondary symptoms). The four primary symptoms were defined as: disturbances of association, affectivity, ambivalence (affective, of the will, intellectual) and autism.

Under the subgroup of *schizophrenia simplex*, Bleuler described a group of patients who exhibited, above all, the primary symptoms, without the secondary ones. His descriptions of relatives of patients and individuals with personality disorders as "latent" schizophrenic patients were the most frequent expression of the schizophrenias. However, the concept of schizophrenia as defined by Kraepelin and Bleuler left many questions unresolved, e.g. a potential somatic pathology, clarity of the diagnostic criteria and the boundaries of the diseases.

Schneider (1959) developed the concept of *first and second rank symptoms*. The first rank symptoms defined by Schneider (1965) included: Voices commenting on one's action, voices conversing, audible thoughts (symptom group: hallucinations), somatic passivity, thought

withdrawal, thought broadcasting, thought insertion (ego disturbances) and delusional perception (delusions). First rank symptoms were seen as most important in the diagnosis of schizophrenia. The second rank symptoms according to Schneider (1965) are: other auditory hallucinations, optical hallucinations, olfactory hallucinations, gustatory hallucinations, paranoia and delusions of grandeur. Schneider believed that second rank symptoms were non-specific to schizophrenia and did not entail a diagnosis of schizophrenia. A diagnosis of schizophrenia could be made in the absence of first rank symptoms only if second rank symptoms occurred frequently and included symptoms such as stilted and inappropriate affect (Schneider, 1965).

Schneider's contribution provided a reliable source of diagnostic criteria, but the status of first rank symptoms as pathognomic to schizophrenia has been questioned by empirical work. First rank symptoms can also occur in psychiatric disorders other than schizophrenia, such as manic-depressive disorder (Carpenter et al., 1973), and are not useful in differentiating schizophrenia from other psychotic disorders (Peralta and Cuesta, 1999).

1.1.3 Current perspectives: positive and negative symptoms

Another classification of the symptoms of schizophrenia came from Crow (1985), who suggested a distinction between *positive* and *negative* symptoms. Positive symptoms refer to phenomena that are normally not present, e.g., hallucinations (sensory experiences in the absence of external stimulation). Negative symptoms describe functions that are normally present, but are absent in schizophrenia. Crow subdivided the symptoms of SZ patients as follows:

- *Positive symptoms:* hallucinations (e.g. hearing voices), delusions (false beliefs that persist despite evidence against them), reality distortion, formal thought disorder, perception deficits, bizarre behaviour (e.g., repetitive and stereotyped behaviour), disorganized speech, disturbances of the ego (the person's psychical processes, created by his own soul, are seen as produced, directed, and influenced by the outside environment), persecution mania (the feeling of being the victim of dark machinations, of being in danger from poison, radiation or magnetism), theft or manipulation of thoughts by other people.
- *Negative symptoms:* anhedonia (inability to experience pleasure), asociality, alogia (impoverished thinking and cognition), blunted affect, affect withdrawal, psychomotoric retardation, avolition (lack of energy), social avoidance.

- *In addition cognitive deficits*: attention, working memory, executive functions

Crow (1985) suggested two major dimensions of schizophrenia: *Type I* is characterized by positive symptoms (hallucinations, delusions, thought disorder), which tend to occur mainly in the acute form of the disorder. *Type II* is characterized by negative symptoms, such as affective

flattening, poverty of speech, which are typical of chronic SZ patients who are not in an acute episode of the illness. From a clinical point of view, it remains doubtful if type I and type II are independent of each other. Most patients will exhibit both positive and negative symptoms during the course of the disease. Usually, the patients have an acute episode during which they have hallucinatory experiences and delusions (positive symptoms), which lasts a few months, and is followed by an episode of negative symptoms, where social avoidance and depression are the most common signs.

The distinction between positive and negative is, as McKenna proposed in 1994, more a symptom than a patient group classification. Andreasen et al. (1990) found that only 26 out of 110 patients with a diagnosis of schizophrenia could be assigned clearly to either the positive or negative category. The suggestion of Crow (1985) that negative symptoms are related to poor response to neuroleptic treatment could not be replicated (e.g. Feinberg et al., 1988). Different research studies (e.g. Wing, 1978) reported that some symptoms, such as thought disorder, did not fit into any of these categories. In addition, the concept of positive symptoms seems to have low internal consistency (r = .45; Andreasen and Olsen, 1982), whereas negative symptoms have demonstrated high internal consistency (r = .85; Andreasen and Olsen, 1982).

The lack of an underlying paradigm has been criticized (e.g. Maj, 1998) and raises questions concerning the validity of the concept as a whole (Bentall, 1990). For example, different diagnostic systems (view chapter 1.1.1) are poorly correlated with each other. The current concept of schizophrenia has poor construct validity, as manifested by the fact that the large majority of criteria are not specific to schizophrenia and can frequently be found in other psychiatric disorders (Peralta and Cuesta, 1999). Kraepelin`s hypothesis that schizophrenia has a chronically deteriorating course, has been disproved by a number of large longitudinal studies (Huber et al., 1980; McGlashan, 1988). These studies suggest that the outcome is enormously variable, ranging from a chronic course in one third of the patients to an almost complete recovery in 20-30 % of the patients.

The validity of the subtypes remains uncertain. In recent attempts to reduce the heterogeneity of schizophrenia at the level of signs and symptoms, the possibility has been examined that different symptoms occur together to form syndromes, an idea which allows a more useful approach. The boundaries of the concept also remain disputed. Crow (1990) argued that a continuum of psychosis exists that crosses diagnostic boundaries. In his view, schizophrenia, schizoaffective disorder and affective illnesses exist along one or more such continua.

Factorial models try to reduce a large number of independent variables to a smaller, conceptually more coherent set of variables. Although the large majority of studies have demonstrated that two factors are insufficient to capture the complex clinical picture of schizophrenia, there is inconsistency regarding the composition of the third factor which has been

labelled disorganisation (Liddle, 1987) or cognitive factor (Peralta et al., 1992). The majority of studies (see review by Buchanan and Carpenter, 1994) reported the presence of three factors: hallucinations and delusions (factor I), negative symptoms (factor II) and cognitive impairment (factor III). The only variation of the results lay in the composition of the individual factors, mainly in the cognitive factor.

Lindenmayer et al. (1994) proposed a 5-factor solution, which replicates the three factor models but names two additional factors, a depression and an excitement factor (view appendix for further details). Peralta and Cuesta (2001) suggested that the contradictory findings on the number of factors and the item-composition of individual syndromes in schizophrenia can be attributed to methodological issues (statistical methodology, instruments for assessing symptoms, levels of analysis, characteristics of the illness) influencing the delineation of symptom dimensions.

A number of theorists suggested alternative concepts based on the critical validity of the current concept of schizophrenia. For example, Bentall (1990) proposed to regard the symptoms of schizophrenia, such as delusions or hallucinations, from a cognitive and biological point of view as abnormal mental processes. This led to a number of theories looking at the etiology of hallucinations (Hoffman and Rappaport, 1994) and delusions (Bentall, 1990). Others (i.e. Tsuang et al., 2000) suggested that future diagnostic criteria should incorporate neuropsychological and biological abnormalities of the disorder instead of relying on psychotic symptoms. The focus on the psychotic symptoms could lead to the identification of the more specific expressions of schizophrenia (Meehl, 1962) as opposed to overt psychotic symptoms influencing treatment and approaches to research.

In sum, the definition of the illness, as we know it at present, contains many of the ideas and views proposed by Kraepelin, Bleuler and Schneider. Patients with a possible diagnosis of schizophrenia are evaluated on the basis of a set of constellations or symptoms. However, there is no single symptom that is unique for schizophrenia. Thus, a person can be diagnosed with schizophrenia, if, for example, there are only commenting auditory hallucinations. This also depends on other criteria or symptoms that occur. Similarly, a diagnosis of schizophrenia is made if a person exhibits a negative symptom, i.e., the flattening of affect, and disorganized speech, corresponding to two Bleulerian primary symptoms. However, in the present clinical work, the diagnostic approach of Crow (1985), who divided into positive and negative symptoms, is used as the standard.

1.2 Symptomatology

1.2.1 General overview

Patients diagnosed with schizophrenia are known to suffer from a deficit in perception, in processing and memorizing stimuli, followed by a loss of control over their sensations. Even in acute episodes of the illness, the patients view their thoughts as real and "normal", they try to find explanations for their behaviour and their thoughts. The main explanation of the illness deals with an overload of stimuli and perception, which leads to deficits in the input capacity. At the beginning, there is no deficit in intelligence, but capacity and attention problems. The capacity deficit causes problems at work and in the social relationships of these patients.

Likewise, SZ patients are known to be very sensitive, perhaps too sensitive, to stimuli. This sensitivity leads to emotional processing for all things that happen in their lives. The consequences are depressive symptoms, as well as anxiety and aggressive behaviour, in some cases ending in suicide.

Beside characteristic psychopathological symptoms of schizophrenia (e.g. hallucinations), cognitive deficits are the most common signs of the illness, mainly in the memory and language domains. It is to note that normal thought processing, like logical thinking, association, creativeness and processing of information is not impaired, even in an acute time span. As a result, the patients try to find explanations for their "perception experiences", which are not real. The belief that these experiences, such as hallucinations, are real, must result in conflicts, most of all in a conflict with their environment which shows in their behaviour. As other persons don't experience their hallucinations, the behaviour of the patients seems strange and without coherence.

Characteristically, patients with schizophrenia have a poorer performance on neuropsychological tasks than normal subjects. No cognitive domain is entirely spared and abnormalities are highly inter-correlated within a single individual. This performance defect is explained as a consequence of ongoing psychotic symptoms, early disease onset, and/ or chronic institutionalization, additional assets of specific deficits associated with the pathophysiology of schizophrenia, e.g. tasks associated with attention, memory and executive function. Schizophrenic persons consistently perform poorly on so-called *vigilance tests* (specific attendance ability). Another deficit was found in *working memory* tasks, where task-relevant information is kept active for only brief periods.

In the following section, the focus lies on mental imagery and hallucinations, two main aspects of the illness. As has already been mentioned above, the "perception and processing problems" of the schizophrenic patients are meant to be in the focus of this study which means that there ought to be a few words about hallucinations and – closely connected – mental imagery. The approach will begin with a phenomenological description, followed by an overview of cognitive theories (including cognitive dysfunctions). The approach will be closed by results of

neurophysiological investigations. The actual status of the research regarding mental imagery and hallucinations will first be described separately, followed by a discussion of the relationship of both phenomena. Finally, critical issues for research and theories will be discussed.

1.2.2 Hallucinations

Hallucinations are among the most severe and puzzling forms of psychopathology. The term hallucination (from the Latin *alucinari* = "to wander in mind") was introduced in the psychiatric literature by Esquirol (1832), who first distinguished it from other disorders of perception. The phenomenology of hallucinations covers elementary acoustic, optic, olfactory, gustatory or tactile perceptions as well as complex experiences based on different sensory information. Hallucinations are most common in SZ patients (appear mainly in the auditory modality), but also a substantial minority of otherwise normal individuals report hallucinatory experiences (Barrett and Etheridge, 1992). There are different kinds of conditions and pathological processes usually connected with hallucinations: schizophrenia and affective psychosis, disturbance of sensory systems (Charles-Bonnet syndrome), physiological disorders (sensory deprivation or fever) and migraine. They also occur during withdrawal from various drugs and alcohol and under the influence of hallucinogenic drugs such as LSD, mescaline and psilocybin. In addition, hallucinatory experiences in the normal population can occur under conditions of sensory deprivation, emotional stress, religious exaltation, or great fatigue (Ohayon et al., 1996). Some descriptions of acoustic hallucinations in dementia (Wilson et al., 2000) and epilepsy (Winawer et al., 2000) can also be found in the literature.

Of main interest is the question of which processes are underlying the phenomenon "hallucinations". Attempts to define the distinctive features of hallucinations have drawn attention to the variety of hallucinatory phenomena and the difficulty in distinguishing between these phenomena and other normal or abnormal mental states. There exist different ways to explain hallucinations, including phenomenological descriptions, cognitive models and neurophysiological evidence. Table 1.2 summarizes the theories of origin and occurrence of hallucinations.

Table 1.2: *Summarized theories of origin and occurrence of hallucinations.*

Phenomenological Descriptions	
	- **Appear in all sensory modality**; mainly in the auditory - Not only in SZ patients, but in normal and other conditions (e.g. migraine, Charles-Bonnet syndrome) (Barrett and Etheridge, 1992)
	"Perceptual error"
	Lack of control over the sensations
	Continuum hypothesis (Bentall, 1990) → Perception → Mental imagery → Hallucinations
	Relation between vivid mental images and prone to hallucinations (Mintz and Alpert, 1972; Slade, 1972; Barrett and Etheridge, 1992, Barrett, 1993)

Cognitive theories	
	Attribution bias (Bentall, 1990; David, 1999; Slade, 1994), **Reality monitoring bias** (Aleman et al., 2003; Böcker et al., 2000; Bentall and Slade, 1985, Slade and Bentall, 1998, Bentall, 1990, Brebion et al., 1997)
	Theory of mind, self-monitoring-bias, **disturbance of wilful movement** (Frith, 1992)
	Capacity problem of the information processing system
Dopamine-neurotransmitter-deficit	**Arousal overload**
Neuroimaging studies	
fMRI	→ **Similar processing** of auditory hallucinations / real auditory perception (Heschl' gyrus, Broca' s area, Wernicke' s area) (Dierks et al. 1999; Lennox et al., 2000; Linden et al., 2002)
fMRI	**"Cognitive Dissymetry"** → Disconnectivity between main brain areas (frontal, parietal, temporal) in SZ patients (Van de Ven et al., 2005), → Increased thalamo-cortical connectivity (Schlösser et al., 2005) → Abberant connectivity between limbic and sensory areas (Kubicki et al., 2003)
PET/fMRI	Visual / auditory modality → **visual association cortex** during visual hallucinations (Silbersweig et al., 1995) Visual → **specialized cortex** / contents of hallucinations (Kubicki et al., 2003)
fMRI	**Dopaminergic hyperactivity** → damage to cholinergic projections to visual cortex (ffytche, 2005)
DTI	**Reduced anisotropy changes in the white matter** (Hubl et al., 2004, Agartz et al., 2001; Kubicki et al., 2002); **Connection deficit** between Broca's and Wernicke' area (Hubl et al., 2004)

To begin with phenomenological descriptions: a number of authors have suggested that hallucinations exist on a continuum ranging from relatively benign forms to pathological manifestations as seen in schizophrenia (Bentall, 1990). In their opinion, there exists a continuum from normal perceptual experiences, mental imagery to abnormal mental experiences, like hallucinations. Bentall (1990) and Slade and Bentall (1998) concluded that hallucinations have a common origin in psychiatric patients and normal people. According to these authors, the phenomenon of hallucinations represents a failure in what they call *discrimination reality process*, which implies that internally generated experience would be mistakenly ascribed to an external source.

Specific cognitive deficits have recently been linked to psychotic phenomena, including hallucinations and disorganized speech. The difference between mental imagery and hallucinations is defined by the affected person itself, convinced that the phenomenon is occurring outside, in the real world. This lack of control contributes to the pathophysiology of the symptom. Hallucinations can be defined as perceptions without a sensory stimulation, e.g. in the DSM-IV (APA, 1984), hallucinations are defined as a "sensory perception that has the compelling

sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ".

Slade and Bentall (1998) agree with this definition by defining hallucinations as "any perception-like experience which occurs in the absence of an appropriate stimulus, has the full force or impact of the corresponding actual (real) perception and is not amenable to direct and voluntary control by the affected person". Hallucinations are seen as the result of a perceptual error based on internal processes, with no evident relationship between perception and any external stimulus.

In conclusion, hallucinations can be seen as experiences, differing from other perceptual experiences by a lack of control over the sensation and a perceptual error. The question is, which are the underlying processes of these deficits? Several authors suggest that the underlying problem is to be found in major cognitive deficits of SZ patients.

Several theories suggest that hallucinations are connected to a deficit in attribution, called *attribution bias*. This means individuals who suffer from hallucinations have a problem identifying internal thoughts as coming from inside. The *attribution bias* (or *reality monitoring* bias; Bentall, 1990; David, 1999; Slade, 1994) can be seen as a lack of control over the thoughts and the mind. The *theory of mind* (Frith, 1992) sees a disturbance of the attribution of mind phenomena to exterior sources, followed by a disturbance of the attribution of mind phenomena to interior sources (*self monitoring*) and by a disturbance of wilful movement (*agency*), which could be responsible for the pathophysiology.

Another theory deals with a potential capacity problem of the information processing system of SZ patients. The content of hallucinations is based on memory content. Overload or redundancy of sensory information leads to a lack of control over the memory-related information. Furthermore, SZ patients seem to suffer from connectivity damage. Some results lead to the assumption that they are not able to integrate incoming information into a whole entity (Uhlhaas et al., 2006).

The cognitive theories are related to the knowledge of a deficit in the neurotransmitter-system of SZ patients. There is the assumption that the dopamine system is responsible for distinguishing important from non-important information. If there is an arousal overload, the system fails and leads to non-sensible associations (hallucinations). As a conclusion, hallucinations in SZ patients seem to occur because of an overload of information (drugs, neurotransmitter disturbance, epilepsy).

Beside phenomenological and cognitive approaches to hallucinations, there are neuroimaging studies that focus on the neurological basis for hallucinatory experience. Important findings come from *functional magnet resonance imaging (*fMRI*;* view chapter 1.6) studies (Dierks et al., 1999; Lennox et al., 2000; Linden et al., 2002; Weiss and Heckers, 1999; Shergill et al., 2004; Van de Ven et al., 2005). These detected neurological evidence for a similar

processing of auditory verbal (AV) hallucinations and real auditory perception in the brain. During auditory hallucinations of SZ patients, they identified several brain areas involved in speech processing (Broca's area), for the encoding of speech (Wernicke's area), and for the processing of auditory stimuli (primary and higher level auditory areas) as active. The studies suggest that auditory hallucinations and the processing of auditory stimuli share similar brain mechanisms. Other studies (e.g. Van de Ven et al., 2005) found disconnectivity between main brain areas (frontal, parietal and temporal) during functional tasks in SZ patients. Schlösser et al. (2005) analysed a group of SZ patients and identified a disturbance of fronto-striato-thalamo-cortical circuits, especially an increased thalamo-cortical connectivity. The authors concluded that schizophrenia could be seen as a disconnectivity disorder ("cognitive dissymmetry"). Furthermore, Hoffmann et al. (1999) stimulated temporal brain regions of a small patient group in a repetitive magnetic-stimulation study and could influence the frequency and gravity of hallucinations.

Imaging studies that investigated auditory hallucinations with *diffusion tensor imaging* (DTI; view chapter 1.6), showed controversial issues. Several DTI studies (e.g. Agartz et al., 2001; Kubicki et al., 2002) showed a reduced *anisotropy* (anisotropy means the directionality of the water diffusion; the amount of anisotropy correlates with the directionality and the coherence of the fibre tracts in schizophrenic patients), whereas others (Lim and Helpern, 2002) could not find any difference in the anisotropy of patients compared with controls. Hubl et al. (2004) showed that there are changes in the white matter of the brain, in those parts which are known to be involved in auditory processing. These changes in the white matter could lead to abnormal activation of external stimuli. Hubl et al. (2004) suggested that these results contribute to the assumption that patients with schizophrenia are not able to distinguish between self-generated thoughts and external stimulation. Here it is possible to connect cognitive models of hallucinations with neurophysiological findings.

Studies regarding the visual modality of the hallucinations are rarely done. A functional imaging study of a SZ patient with both visual and auditory hallucinations that used positron emission tomography (Silbersweig et al, 1995) found activation in the visual association cortex, but not in the primary visual area. An association between the location of activity within specialized cortex and the contents of visual hallucinations has been observed for patients with Charles-Bonnet syndrome (Ffytche et al., 1998). Trojano et al. (2004) found - during the appearance of visual hallucinations - a prominent prefrontal activity, which reflects the active ideation. Possible pathophysiological mechanisms include dopaminergic hyperactivity in the mesolimbic pathway, which might also explain the common phenomenon of L-dopa-induced hallucinations in Parkinson's disease, damage to cholinergic projections to visual cortex (Ffytche, 2005) and aberrant connectivity between limbic and sensory areas (Kubicki et al., 2003).

1.2.3 Mental imagery

Hallucinations evidently being a type of "mental image", the research tried to decode the complex "mental imagery" in order to assign hallucinations a place in the complex. The difference between hallucinations and mental images lies primarily in the intensity and the degree of reality similarity of the perceptual experience. Mental imagery ("seeing with the mind's eye") is defined as a perceptual experience, which occurs in the absence of an appropriate stimulus for the relevant perception (Finke, 1989). A normal perception arises from an interaction between afferent signals and prior knowledge. Mental imagery, the generation and manipulation of mental representations in the absence of sensory stimulation, is a core element of numerous cognitive processes. Normal mental imagery may be an example of a percept that is entirely dependent on prior knowledge. Such images are not hallucinations since we are aware that their origin is in our heads and not in the outside world. Thus, mental imagery is often believed to play a role in memory (Paivio, 1986) and motivation (McMahon, 1973). It is also commonly believed to be centrally involved in visuo-spatial reasoning and inventive or creative thought. Several authors researched mental imagery processes in order to get a better understanding of the presence of hallucinations.

Kosslyn (1983) proposed that "imagery is a particular type of cognitive process or underlying representation that is involved in specific cognitive functions". These representations or processes are generally understood in the manner that their presence or activity can be consciously experienced as imagery in the original sense. Apart from that, it is supposed that the internal representation coincides with a certain brain state, which generates the conscious experience on the basis of stored information, not on the basis of actual sensory input. Therefore, there is an underlying brain state for imagery. If a person has the experience of *seeing with the mind's eye*, his brain state is attendant (Kosslyn, 1989).

Assuredly, imagery and perception are closely related. The purpose of imagery is to perceive optical characteristics of imaged objects. This provides access to memory where information is stored. In addition, people are able to use imagery abilities to forecast the consequences of movements (Shepard and Metzler, 1971) and to achieve abstract learning and thinking. Sometimes the models of images are utilized to support higher-level reasoning. Through the storage of images of objects, events and faces, the matter is better retained and can be retrieved more easily.

An interesting phenomenon is that imagery seems to use mechanisms specialized for processing in a specific sensory modality (Kosslyn, 1989). Some findings predicate, that imagery selectively interferes with like-modality perception (Kosslyn, 1989). According to Segal and Fusella (1971), visual perception is affected more when a visual image is received as compared to an auditory image. Investigating this interference, e.g. Goebel et al. (1998) and Formisano et al. (2002), stated that imagery uses central perceptual mechanisms.

The cognitive processes required to generate mental images and to analyze them are subserved by a distributed network of brain regions. Different authors examined the underlying neuronal processes of imagery and spatial analysis in several sensory modalities. The neurophysiological studies focused on a potential left hemispheric lateralisation during mental imagery tasks (Sato et al., 2004; Mazard et al., 2005), category-selective attention (Gardini et al., 2005; McGuire et al., 1996; Cohen et al., 1996; Mechelli et al., 2004; Silbersweig and Stern, 1998; Shergill et al., 2000), the potential involvement of primary / secondary brain regions (Bunzeck et al., 2005; Ducreux et al., 2002) and the question of whether perception and imagery share similar areas (Slotnick et al, 2005; Jeannerod, 1994; Klein et al., 2004).

Furthermore, results from brain-damaged patients support the hypothesis that visual mental imagery and visual perception share many mechanisms. Nevertheless, both functions are not performed through identical processes (Trojano and Grossi, 1994). Perception does not require activation of information in the memory when the stimulus is not present. In contrast to perception, imagery does not require low-level processing (Kosslyn et al., 2001).

In sum, the neurophysiological data provides controversial issues. Some steps involved in mental imagery seem to share the same brain areas as during perceptual processes, while others seem to be more related to hallucination experiences. These results would prove the continuum-hypothesis. However, the current status of knowledge is puzzling. Therefore, the present thesis aims to get a better understanding of the relationship between mental imagery and hallucinations. The next chapter gives a survey of the current status of psychiatric literature regarding potential correlates of hallucinations and mental imagery, on a phenomenological, on a cognitive and on a neurophysiological level. The literature is inconsistent with respect to the role of mental imagery in hallucinations.

1.2.4 Mental imagery and hallucinations: Discussion

The theories about mental imagery and a possible failure or increase in imagery abilities in hallucinating individuals are used as a way to find explanations for the rise of hallucinations. Studies regarding the relationship between mental imagery and hallucinations show controversial results. Several authors propose a high connectivity between the vividness of mental imagery and the predisposition towards hallucinations, while others could not find any connection between the two symptoms.

Some authors support the idea that hallucination and vivid imagery are somehow related. Hallucinations and mental imagery do not have a clear boundary between one another, but the difference lies in the intensity and degree of reality similarity. Mintz and Alpert (1972) and Slade (1972) claimed that individuals who hallucinate are characterized by having very vivid images and a weak ability for distinguishing real perception from imagery. They showed higher mental

imagery in schizophrenics and approved the theory of a capacity problem of the information processing and integrating system. An increase in mental imagery vividness would lead to an overload of information, which leads to an excessive demand on the information processing system. Here, a higher vividness of mental imagery is suggested to be responsible for the genesis of hallucinatory experiences. According to Mintz and Alpert (1972) and Slade (1972), the overload on information is responsible for the fact that hallucinating SZ patients are not able to distinguish between real perception and information close to reality.

Morrison et al. (2002) developed a semi-structured interview to regard the connection between mental images and psychotic symptoms. 74.3 % of the subjects stated their psychotic symptoms to be dependent on their imagery ability.

In contrast, Brett and Starker (1977) and Starker and Jolin (1982) concluded that imagery is not more vivid in hallucinating SZ patients than in normal controls. In accordance, Chandiramani and Varma (1987) also found no significant differences in the vividness of imagery between hallucinating SZ patients, non-hallucinating schizophrenics and normal controls. Brebion et al. (1997) investigated a number of schizophrenics and controls with a reality monitoring task and identified the following abilities impaired in the patient group: discrimination of old items from new items (with a higher bias toward reporting new items as if they were old (false alarms) compared to controls), discrimination of self-generated items from externally generated items and discrimination of the modality of the item. The authors replicated other findings that imagery is not more vivid in hallucinatory SZ patients.

Böcker et al. (2000) used the term *reality discrimination failure* to test the hypothesis that hallucinations result from confusing external and internal stimulus sources, i.e., perception and imagery, respectively. They tested 13 hallucinating, 19 non-hallucinating SZ patients and 14 controls with multiple tests of perception and vividness of mental imagery in the auditory and visual modalities. The hallucinating SZ patients showed a higher level of vividness of mental imagery, especially in the auditory modality. However, they found no group differences of perceptual acuity.

In contrast, Bentall and Slade (1985) found no difference in perceptual sensitivity between hallucinatory SZ patients and non-hallucinating schizophrenics. They used a signal detection task and suggested that, if hallucinatory experiences were related to vivid mental imagery, participants reporting such experiences would perform poorly on signal-detection tasks due to a decrease of sensitivity for their scores on an instrument measuring the predisposition towards hallucinating (Launay and Slade, 1981). They found no differences in performances.

Several studies relying on various experimental paradigms support the finding that vivid imagery per se does not account for reports of hallucinatory experiences (Aleman et al., 1999). Aleman et al. analysed the relationship between hallucinations and imagery ability. In 1999, they investigated the relation between subjective and objective indices of vividness of imagery and

disposition towards hallucination in 74 college students. After assigning subjects to a high and a low hallucination group on the basis of scores on the *Launay Slade Hallucination Scale* (LSHS; Launay and Slade, 1981), two measurements of the vividness of mental imagery were carried out. The subjective measure was based on two subscales (visual, auditory) of the *Betts Vividness Upon Imagery Scale* (QMI; Sheehan, 1967). The objective task concerned the difference between a perceptual and an imagery condition of judgement of visual similarity of named objects. Subjects reporting hallucinatory experiences tended to show higher imagery vividness rating on the QMI than non-hallucinating subjects. It is important to note, that this result could not be reported in an experimental imagery task.

However, in another study, Aleman et al. (2003) compared non-hallucinating and hallucinating SZ patients with a normal comparison group on multiple behavioural measures of auditory and visual mental imagery and could not find any difference in the imagery ability. They suggested that there is no stable disposition towards abnormal mental imagery associated with hallucinations. This finding is consistent with Sack et al. (2005), who showed an independence of vividness of mental imagery and the predisposition towards hallucinations. They concluded that hallucinations arise from a deficit in processing and integrating information, which is not per se related to imagery abilities. Hallucinations have been suggested to result from an increased influence of top-down sensory expectations on conscious perception. In contrast, they propose mental imagery vividness as a new and independent trait marker of schizophrenia. This would imply a new way of explaining hallucinations.

Van de Ven and Merckelbach (2003) examined a sample of undergraduate students with a task called *fantasy proneness task* and related it to measurements of vivid images and hallucinatory experiences. In the fantasy proneness task, subjects were asked to listen to "white noise" and instructed to press a button when they believed hearing a recording of *Bing Crosby´s White Christmas Song* without his record actually being presented. They found that participants who reported hallucinatory experiences during the *White Christmas task* scored higher on mental imagery and fantasy proneness compared with those who did not report such experiences. Furthermore, self-reported imagery ability and fantasy proneness were strongly related.

More recent studies on the incidence of hallucinations in non-clinical populations have been carried out by Barrett (1993), and Barrett and Etheridge (1992). They revealed that nearly 50 % of their subjects had hallucinatory experiences once a month. They concluded that people with hallucinations had a more vivid imagery, but no better control of images in comparison to people who did not experience hallucinations. However, it remains obscure as to how these individuals differ from those who say they have never had hallucination-like experiences.

In sum, the involvement of mental imagery in hallucinations has proven to be a controversial issue. The inconsistent results regarding the connectivity between mental imagery and hallucinations could be due to the fact that most of the authors used self-administered

questionnaires. In addition, some studies examined hallucinating vs. non-hallucinating-patients, while other studies compared hallucinating patients with normal controls etc. Thus, the selection of the participants is not sufficient. Furthermore, the theory of the underlying processes which cause hallucinations is not yet clear. Some evidence exists from phenomenological, cognitive and neurophysiological approaches, albeit without a clear connection between the different manners of data collection.

Therefore, the present thesis tries to include several methods to investigate hallucinations and their potential connection to mental imagery. Per se, it is not yet clear, which status vividness of mental imagery has in SZ patients. If vividness of mental imagery is not a cause of or connected with hallucinations, the question is to what kind of symptom is mental imagery related in such patients. Mental imagery may not be directly related to hallucinations, but may be a general characteristic of schizophrenia (Sack et al., 2005). It is thus important to determine whether vividness of mental imagery can be regarded as a marker of schizophrenia itself.

1.3 Theory of schizophrenia: a multi-factorial approach

The cause of the illness still remains unresolved, although there are different explanations and hypotheses. In the next section, a multi-factorial model of schizophrenia will be discussed, followed by a further description of the most common and important parts of the model. In discussion are cognitive impairments, biochemical changes in the brain, genetic influence, environmental and other factors which could increase the risk to develop a schizophrenia disorder.

To begin with, there is a clear indication for a defect in the information processing system. The result of several EEG investigations could be summarized as deficits in the attention and information processing system. Neurochemical research and treatment give clear evidence for disconnectivity in the dopamine-system. In PET-studies signs of depressed blood circulation in prefrontal regions could be shown. Neuroimaging studies (CT [computer tomography], MRT [view chapter 1.6]) showed, even in post-mortem studies, an increase of ventricle volumes and a decrease of the limbic system volume as well as disconnectivity mostly in frontal brain regions. Several authors proposed a gender difference in the symptomatology of the illness. Schizophrenic men seem to suffer from more and more severe symptoms and the onset of the illness is earlier (between 3 and 5 years) in men than in women. Several studies proved a biological basis for the gender effect (Turetsky et al., 1999; Slewa-Youman et al., 2004). At present, the search for a biological basis is in progress, although many genes have been identified as associated with the illness. Several risk factors are known to be multiplicative, although each risk factor confers a small risk, with the genetic factors being the most potent.

Environmental factors have also been suggested as risks for schizophrenia. These, most

prominently, include the use of marijuana (and other forms of drug abuse). Not only does cannabis constitute a risk factor for psychosis, but there is evidence showing concrete synergetic effects between cannabis and the pre-existing liability to psychosis. Certainly, stressful life-events could be responsible for relapses and first-episodes, if there are other factors like a genetic risk. Trauma is often mentioned as a proximal risk factor for the illness, although only few studies focusing this exist. An emotional and stressful environment is also often identified as a precipitant for schizophrenia. In this case, some theorists proposed influence of the communication network in the families, which is called *expressed emotion*. Vaughn and Leff (1976) focused on the network of family communication associated in schizophrenic patients. Expressed emotions refer to the degree of emotional communication in a family. The higher the expressed emotion the higher the vulnerability for relapses (Kavanagh, 1992). Other explanations focus on pre- or post-natal neuronal developments.

In contrast to pure biological or neuro-pathological models, the multi-factorial model or *vulnerability-stress-model* (Liberman et al., 1986) suggests schizophrenia as a nosological entity. Liberman et al. tried to integrate biological, neuro-pathological, genetic, family and environmental factors to form a larger model. Their approach is that stressful life-events and other psychosocial factors in combination with a high biological and genetic risk, sometimes also a special sensitivity, can cause schizophrenia. They proposed an increased sensibility and vulnerability in SZ patients. The vulnerability for developing schizophrenia originates in an interaction between several conditions. Adverse biological conditions, like a genetic risk for schizophrenia, can be compensated to a certain degree by a good psychosocial environment, whereas negative biological conditions could be reinforced in an adverse psychosocial environment. It is important to note, that an adverse environment does not necessarily lead to schizophrenia. In contrast, a high biological or genetic risk for developing schizophrenia will not automatically lead to the illness. Other risk factors are catastrophic pre- or postnatal events, like exposure or famine, radiation or a maternal viral illness, especially during the second trimester. These early events do not have as much predictive power as the genetic factors, but can nonetheless explain significant variances.

Evidence for the vulnerability-stress-model comes from several adoption studies (e.g. Tienari et al, 1987). Children with a high vulnerability are more sensitive to negative environmental factors and therefore more often develop a psychiatric disorder, particularly schizophrenia. According to the model, the first episode of illness occurs after a stressful life-event. A highly vulnerable person has no abilities to get over the stressful event. Cognitive deficits will occur, followed by an increase in social stress. At this point, they reach a hypothetic threshold and will enter the prodromal phase, which leads to the outburst of the disorder.

In the following parts of the chapter, a further description of the biological factors,

followed by genetic and neuropathological factors will be presented. Figure 1.1 shows the main factors which are known to be involved in the outburst of schizophrenia.

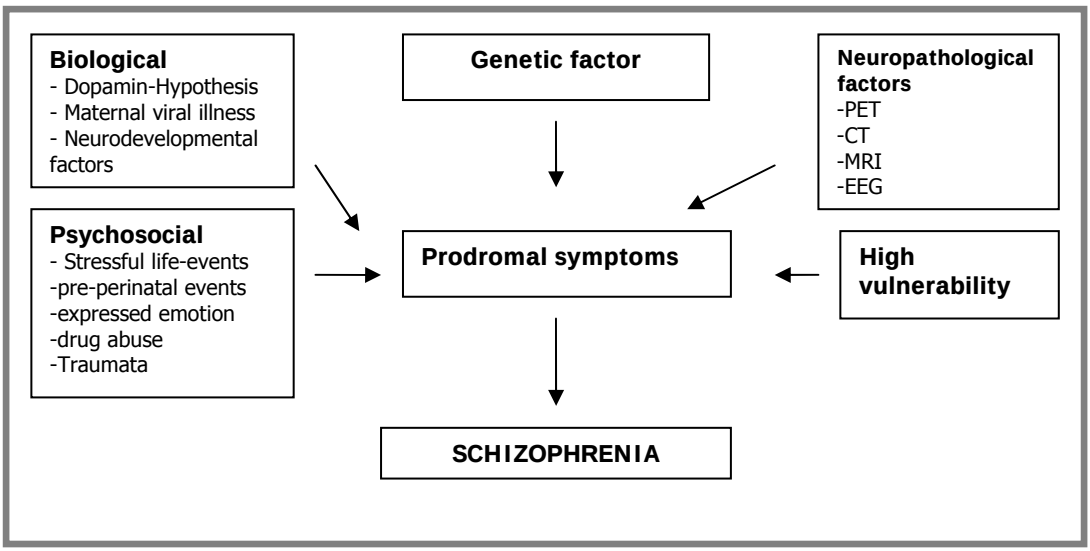


Figure 1.1: *Multi-factorial model of the illness schizophrenia.*

1.3.1 The dopamine-hypothesis

SZ patients suffer from an imbalance of information-processing neurotransmitters. This could lead to an overload of perception and problems with the processing of stimuli. Many models suggest that there is a distortion in the metabolic system, which influences the degree of risk to develop schizophrenia. Dopamine, Serotonin and Glutamate are known to be important neurotransmitters for information processing and cognitive function.

Two main types of dopamine receptors exist, namely D1 and D2. D1 has two subgroups, D1 and D5, whereas D2 consists of three subgroups D2, D3 and D4 (Hietala and Syvälahti, 1996). Possitrons Emissions Tomography (PET) scan analysis of dopamine usage in the brain and post-mortem molecular analysis of brain tissue have revealed different levels of dopamine receptors in patients with schizophrenia compared with non-schizophrenics. The quantitative analysis of dopamine receptors in the brain indicates that the striatum, limbic system and cortex have the highest density of dopamine receptors. Examination of the striatum does not show a difference in levels of any of the dopamine receptors in SZ patients. However, a multitude of research indicates that the prefrontal cortex of these patients has decreased levels of D1, D3 and D4 receptors (Hirsch and Weinberger, 1995).

While there is no doubt that dopamine is somehow involved in the production of the symptoms in schizophrenia, its exact role is difficult to determine. It seems that increased levels of dopamine in the striatum are responsible for some of the positive symptoms. However, it also seems that the prefrontal cortex (PFC) may be responsible for the activation of positive

symptoms. The prefrontal cortex controls and organizes the flow of information between different cortical and subcortical regions. Thus, a decrease in the activity of PFC would result in a lack of the organization of thoughts and perception, and later in hallucinations and disorganized thoughts. In addition, the correlation between D1 receptors and negative symptoms is explained by the fact that the prefrontal cortex puts out to the rest of the brain. D1 receptors may be involved in the production of movement from signals initiated in the cortex. A decrease in these receptors would result in an inhibiting effect on behaviour, which would be similar to the negative symptoms.

Both the positive and negative emotional symptoms can be explained by the activity of dopamine in the limbic system. The limbic system has a particularly high concentration of D3 and D4 receptors. The two receptors seem to be involved in the production of dopaminergic pathways in the striatum. Patients with schizophrenia have smaller frontal lobes and larger ventricles. They also have a higher incidence of head injury during childhood. Each of these factors could result in damage to the prefrontal cortex, which would then result in a decrease in activity. The inactivity would then result in a lack of inhibition of the striatal pathway. This would be particularly evident in adolescence, when the prefrontal cortex finishes its development (Hirsch and Weinberger, 1995).

1.3.2 The psychiatric treatment

Neuroleptics (= greek, "that seize the nerves system") are known to have a positive effect on psychotic symptoms. Since the introduction of the first antipsychotic medication of chlorpromazine by the French psychiatrists Delay and Deniker (1952; in: Seeman, 1995), neuroleptics have played an important role in the treatment of schizophrenia. The finding of a neuroleptic effect on the dopaminergic system by Carlsson and Lindqvist (1963) led to a higher acceptance of the dopamine hypothesis. Further support for the dopamine hypothesis was the observation that amphetamine psychosis is closely related to paranoid schizophrenia (Connell, 1958). Amphetamines exert their effect by enhancing dopamine release in the brain (Randrup and Munkrad, 1967).

On a nerve impulse the nerve cell produces transmitting substances that combine with protein molecules specifically answering to a certain transmitting substance, the so-called receptors, in the receiving cell. The dopamine receptors are subdivided into a number of groups. All the neuroleptics have a more or less strong affinity to one of these specific subgroups. In this way, dopamine is prevented from fulfilling its transmitting function at these receptors, thus the increased production of dopamine in SZ patients doesn't lead to an increased transmission of impulses any longer but is reduced to "normality".

With the use of neuroleptics, the treatment of schizophrenia has been changed significantly. Neuroleptics have proven to be a highly efficient medication in the acute treatment

phase and in relapse prevention (Lutejin and Moleman, 1998). Following the work of Deniker, neuroleptics based on chlorpromazine have been used over several decades until the present time. In 1963, Carlsson proved the hypothesis that the input of chlorpromazine and haloperidol leads to an increased activity of the dopaminergic system, which blocks the postsynaptic dopamine-receptors of acute illness.

After new developments, neuroleptics are now divided into the so-called *typical* and *atypical* neuroleptics. In classical neuroleptics the antipsychotic effect is accompanied by extrapyramidal side effects. Following the clinical definition, a neuroleptic drug can be called atypical, if it either has a good antipsychotic effect with no or only slight extrapyramidal side effects or if it is effective in treating negative symptoms, e.g., avolition, alogia, anhedonia and flat affect (Riederer et al., 1998). In comparison with classical antipsychotics, the atypical ones seem to be more effective in the treatment of negative symptoms. Yet, the pharmacological profile responsible for the improvement of the negative pathology is not clear. In any case, it seems to be unlikely that only one receptor subtype plays a role in all the atypical effects. Presumably, the different affinities for different dopamine receptors are responsible for the manner of the regulation of the dopamine metabolism.

Today, the influence of transmitter systems other than the dopaminergic is intensively discussed (Julien, 1998). The very intricate play of multiple connections among nerve cells and different transmitting substances suggests that besides dopamine other transmitting substances, like serotonin or glutamate, play an important role in schizophrenia. This is why anti-psychotics were developed to take effect not only on the dopamine system but also on the serotonin system.

Additionally, serotonin (5-HT2) receptor-agonism seems to play a role (Ziekenfondsraad, 1999). Compared with the conventional antipsychotics, the atypical medication clozapine (Leponex®) is featured by less pronounced extrapyramidal-motoric side effects (Safferman et al., 1991). Clozapine is a dibenzodiazepin-derivate with an antipsychotic and fast sedative effect. It has strong noradrenolytic, parasympathicolytic and antihistaminergic properties and a weak antidopaminergic effect. Clozapine selectively blocks the D4-receptor (a sub-D2-receptor), mainly found in cortico-limbic areas. In view of the good antipsychotic effects of clozapine, its blockade of dopamine receptors is rather slight. Clozapine has a high affinity for histaminergic (H1), serotonergic (5-HT2), α-adrenergic and anticholinergic receptors. The antipsychotic effect can be explained by the combined D2- and 5-HT2-blockade (Kerwin and Taylor, 1996). The first atypical agent after clozapine is risperidone. It has been shown that risperidone and the other atypical neuroleptics, which are serotonin-dopamine-antagonists, are as effective as the conventional antipsychotics, e.g. haloperidol (Haldol®), with regard to the favourable influence on positive symptoms. Moreover, they are superior with reference to negative symptoms (Kerwin and Taylor, 1996).

1.3.3 Genetic influence

Risk factors for schizophrenia are most prominently genetic, and scientists anticipate that contributions from the new genetic information in the human genome will help to progress towards discovering a disease mechanism. Crow (Crow et al., 1989; Crow, 1997) has propounded the view that schizophrenia results from a failure of the development of cerebral lateralization, and that this failure is genetically determined. According to this theory, lateralization and mixed-handedness, which is known to be present in schizophrenia, reflects a less complete lateralized pattern (Crow, 1997) and should be found in excess among the relatives of SZ patients.

There is significant statistical evidence for a familiar risk for schizophrenia. The disposition is genetic, not the illness itself. Association studies in schizophrenia suggest that schizophrenia is a complex multi-genetic disorder. The genetic risk for schizophrenia in terms of prevalence estimates (Holcomb et al., 2000) is the following: *General population*: 1%, *Second-degree relative*: 2.5 %, *Parent*: 3.8%, *Siblings*: 8.7%, *Child, 1 parent*: 12 %, *Child, 2 parents*: 30-40 %, *Twin, monozygotic*: 40-50 %. There is evidence that the urban environment as an important environmental risk factor interacts with genetic risk. It has been hypothesized that the mechanism involves the cumulative effects of social interactions at the individual level and possibly also at the level of the social environment, such as the neighbourhood.

Family, twin and adoption studies suggest an important genetic role in the etiology of schizophrenia (Cardno and Gottesman, 2000; McGuffin et al., 1995). The mode of transmission of the disorder is still unknown (Tsuang et al., 1999). One attempt to resolve this issue is to search for endophenotypic markers: characteristics that mark the presence of a genetic predisposition to schizophrenia. Endophenotypic markers may help to identify the genetic loci involved in schizophrenia. Endophenotypes are intermediate phenotypes that provide a more reliable index of liability than the illness itself (Snitz et al., 2005). Gottesman and Gould (2003) summarize five criteria for identifying useful endophenotypes in psychiatry:

- The endophenotype should be associated with illness in the population,
- The endophenotype should be heritable,
- The endophenotype should be primarily state independent,
- Within families, the endophenotype and the illness should co-segregate,
- The endophenotype should be found in non-affected family members at a higher rate than in the general population.

Faraone et al. (2005) analysed neuropsychological functioning in non-psychotic adult relatives of SZ patients compared with normal controls. They used a scale for neuropsychological functions, which included ten neuropsychological functions: abstraction / executive function, verbal ability, spatial ability, verbal memory, visual memory, learning, perceptual-motor speed,

mental control / encoding, motor function and auditory attention. Ming et al. (2000) found that relatives of SZ patients have deficits in abstraction / executive function, verbal memory and components of attention (auditory attention and vigilance). The two groups did not differ in terms of visual / spatial ability, visual memory or perceptual / motor function. The deficits observed were not accounted for by psychopathology, level of education or parental social class in the relatives. Ming et al. (2002) proposed that neuropsychological risk indicators in non-psychotic relatives of SZ patients lead to an underlying genotype not to be found in the controls, which cannot be detected with psychiatric assessments.

Some recent studies suggest that men with schizophrenia may have greater neuropsychological deficits than women. It is not known, however, whether similar gender differences may exist in biological relatives of patients with schizophrenia. A study by Ming et al. (2000) showed significant group-by-sex interactions for verbal memory and motor function, and statistical trends toward significant interactions for auditory attention and mental control/encoding. They concluded that perhaps women have a higher threshold than men for developing schizophrenia. As a conclusion, female relatives might be able to withstand greater impairments than male relatives before developing psychotic symptoms. These results are consistent with the idea that neuropsychological dysfunction among relatives of schizophrenic patients is a stable trait that assesses the predisposition to schizophrenia.

Data based on neuropsychological studies of non-psychotic relatives of schizophrenic patients revealed the relatively specific neuropsychological deficits in schizophrenic patients and their relatives and the stability of these deficits over time. In general, findings of studies including biological relatives of schizophrenia patients indicate that relatives are also impaired, albeit to a lesser degree than patients, on a variety of different cognitive tasks, sustained attention, perceptual-motor speed and concept formation and abstraction (Faraone et al, 1995; Appels et al., 2003; Cosway et al., 2000; Grove et al., 1991; Park et al., 1995; Cannon et al., 1994; Curtis et al., 2001). However, the findings are less consistent than those of patients, because findings of no impairment have also been reported (e.g. Stratta et al., 1997; Brownstein et al., 2003).

In this thesis, unaffected first-degree relatives of schizophrenic subjects are also examined to test whether there is a genetic basis for cognitive dysfunctions and a predisposition towards hallucinations, followed by default language processing in the brain. We hypothesize that there is a decrease of language lateralization and an aberrant language processing in these unaffected relatives. This abnormal processing compared with controls may index genetic liability for schizophrenia.

1.3.4 Environmental factors

More than 10 studies have consistently shown that around one third of all schizophrenia incidence may be related to unknown but probably incoherent environmental factors operating in the urban environment that have an impact on developing children and adolescents to increase, relatively specifically, the later expression of psychosis-like mental states and overt psychotic disorders. The available evidence suggests that causation (urban environment causes psychosis) is more important than selection (high-risk individuals more in urban areas) and that the effect of the environmental factors in the urban environment is conditional on genetic risk.

Early trauma is another aspect of the environment that has recently been linked prospectively to psychosis, and meta-analytic work demonstrates conclusively that a minority status is a risk factor, part of which may be mediated by chronic exposure to discrimination. Prenatal environmental effects may involve folate or vitamin D deficiency, viral infections or adverse effects associated with low or high birth weight. The mechanism by which the environment is likely to impact on the risk is through cognitive and emotional pathways on the one hand, and biological pathways, possibly involving dopamine sensitization, on the other. Weiser et al. (2005) suggested that the diagnostic boundaries of mental illness, including schizophrenia, have to be redefined. This idea is reinforced by recent findings indicating that on the one hand multiple genetic factors, each exerting a small effect, come together to manifest as schizophrenia, and on the other hand, depending on interaction with the environment, the same genetic variations can appear as diverse clinical phenotypes. Rather than attempting to find a unitary biological explanation for a DSM construct of schizophrenia, it would be reasonable to deconstruct it into the most basic manifestations, some of which are common with other DSM constructs, such as cognitive or social impairment, and then analysed the biological substrate of these manifestations.

1.3.5 Neuropathological factors

Schizophrenia is known to be a brain disorder characterized by a heterogeneous clinical symptomatology. However, many consider schizophrenia to have a neurodevelopmental basis (Murray et al., 1992; Weinberger, 1987). Current hypotheses focusing on schizophrenia as a neurodevelopment illness suggest that the pathology of the illness is already set at birth and only expresses itself as a psychosis later. In accordance with the idea of a neurodevelopmental basis of schizophrenia, schizophrenia appears in the proximity of pregnancy and birth complications (PBCs) (Murray et al., 1992; Verdoux et al., 1997a and b), of poor premorbid function (Jones et al., 1994; Cannon et al., 1997a, b) and of a low premorbid IQ (Aylward et al., 1984).

In detail, the neurodevelopmental approach sees schizophrenia as a disease of the brain development based on genetic or environmental factors (Weinberger, 1987). Anomalies of the

brain development affect the early processes of neuron, migration and synaptogenese, probably also extending to the processes myelinasation and synaptic priming (reduction of initially existing synaptic connections). The *cognitive "dissymmetry"* means the cognitive functional anomalies within prefronto-cerebello-thalamic operating entities. This defect of the cognitive coordination is seen as a dysfunction in processing information, in setting priorities and of mimicry, in analogy to the motor symmetry. However, the course of the illness does not conform to a traditional neurodevelopment illness like mental retardation, where the symptoms appear at birth.

Structural and functional imaging studies show abnormalities in the brain (for details view chapter 1.5.4). The functional approaches are based on advances in the understanding of normal cognition also derived from functional imaging data. Regional cerebral blood flow (rCBF) studies in schizophrenia have been used to identify CNS regions of abnormal function in the illness. Ingvar and Franzen (1974) first detected a reduced *prefrontal cortical blood flow*. Further studies also noted alterations in delimited cerebral areas, especially reductions in the metabolism of rCBF in the *anterior cingulate* and in the *middle frontal cortex* (frontal cortex). While no single region has been identified in all laboratories, several distinct abnormalities are prominent and suggest the possibility that an abnormality of several systems in the brain underlies the illness. For sure, most of the studies point to abnormal middle frontal cortex, anterior cingulate cortex (ACC) and the hippocampus.

Studies on primates have shown that there is a close functional interaction between parietal and frontal brain areas along cortico-cortical fibre connections. Far-reaching operating entities have also been described, which - with the participation of basal ganglia and the cerebellum - have their part in the maintenance and the modulation of higher cognitive performances.

DeLong and Dwyer (1988) proposed that, as many of the cognitive and functional abnormalities in schizophrenia involve the frontal cortex and its functions, an alteration in these feedback systems offers strong validity to explain certain symptoms in schizophrenia. Regions of the frontal cortex project to the caudate or putamen in segregated, parallel neuronal pathways. Within the basal ganglia, these projections are propagated to related downstream structures, including specific thalamic nuclei, and are then projected back to the discrete frontal cortex regions. Since the basal ganglia have a diversity of neurotransmitters and modulators, and are richly innervated by diverse brain structures, there is opportunity within these pathways to capture significant regional influence and to subsequently modulate frontal cortical function. Any abnormality in the dopaminergic dynamics, the balance of neurotransmitter function in the basal ganglia or the influence of the thalamus could alter frontal cortical function through these pathways.

However, it is on debate that schizophrenia is not associated with pathological changes in a circumscribed brain region, but with widely distributed morphological changes. The leading

hypothesis is a fronto-temporo-limbic network disturbance with cytoarchitectural changes in the heteromodal association cortex. The frontal lobes also showed impaired activity in SZ patients which proves the brain damage hypothesis. Possibly, due to a decrease of activity in the frontal lobes the memory-contents flow without any filtering into the consciousness which could be the reason for several of these patients' problems.

We know that schizophrenia is associated with a reduction of brain volume, an increase of ventricles space, a complex disturbance of the information processing system and a disconnection of the fronto-temporo-limbic network. Ventricular size is a crude and non-specific indication of cerebral dysfunction. This leads to the assumption that schizophrenia is based on a lesion of the brain areas, the ventricles, which are known to be involved in inhibitory functions. Additional volumetric differences have been identified in the schizophrenic brain. Several laboratories focusing on the superior temporal gyrus have reported volume decreases in schizophrenia and a correlation between the volume changes and clinical characteristics of the illness. Csernansky et al. (1998) identified hippocampal shape irregularities, and some other studies found the medial temporal cortex, including the parahippocampal, entorhinal and hippocampal cortex to be reduced in patients with the illness. Results from post-mortem studies on schizophrenic brains lead to the conclusion that the limbic system, the hippocampus and many chemical systems are affected in schizophrenia. However, many structural changes are not associated directly with clinical symptoms. Table 1.3 shows an overview of the neuropathological findings concerning schizophrenia.

Table 1.3: *Overview of neuropathological findings concerning schizophrenia.*

	Finding	**Author**
Neurodevelopmental	Excess of pregnancy and birth complications (PBCs)	Murray et al., 1992; O'Callaghan et al., 1992 Verdoux et al., 1997a and b
	Poor premorbid function	Jones et al., 1994; Cannon et al., 1997a, b
	A low premorbid IQ	Aylward et al., 1984
	Brain development → neuron, migration and synaptogenese, myelinasation and synaptic priming	Weinberger, 1987
Functional deficits	A reduced prefrontal cortical blood flow	Ingvar and Franzen (1974)
	Deficit in frontal-regions	e.g. DeLong and Dwyer (1988)
	Fronto-temporo-limbic network disturbance	Van de Ven et al. (2004)
Structural findings	Volume differences: ventricle, hippocampal shape irregularities, medial temporal cortex, frontal lobe differences	e.g. Csernansky et al. (1998)
	Reduction of brain volume, an increase of ventricles space, a complex disturbance of the information processing system	Tsuang et al. (2000)

Tsuang et al. (2000) proposed that neuropsychological deficits in relatives as well as structural brain abnormalities of patients with schizophrenia reflect their degree of genetic predisposition towards schizophrenia. First-degree relatives of SZ patients show abnormalities in both specific brain regions and patterns of brain activation. In a structural MRI study, Tsuang et al. (2000) showed (with only a small sample size) smaller grey matter volumes of subcortical structures as well as larger ventricular volumes in relatives compared with the control group. In addition, they identified significant volume reductions in the thalamus, the right amygdala, the right pallidum, the right putamen and the brain stem. In contrast, volume enlargement was found bilaterally in the inferior lateral ventricles in relatives. In a further study with a larger sample size (29 SZ patients, 28 non-psychotic first-degree relatives, 26 normal controls), the relative group had significant bilateral volume reductions in the amygdale-hippocampal region, the thalamus and the cerebellum, furthermore a significantly increased volume in the pallidum. Compared with relatives, patients had a significantly larger putamen and amygdale-hippocampal regions and smaller cerebral cortices.

In sum, Tsuang et al. (2000) see an abnormal brain structure of non-psychotic relatives of SZ patients, which overlaps with abnormalities in patients. This supports the hypothesis that the genetic liability to schizophrenia is expressed as brain abnormalities in key subcortical structures, including the thalamus and amygdale-hippocampal regions. These results are consistent with other studies of SZ patients, in which third and lateral ventricle enlargements are the most common findings. Tsuang et al. (2000) made an additional fMRI study, where the subjects (13 non-psychotic relatives, 12 matched controls) had to fulfil a working memory task. The most interesting finding of this study is the difference in the number of regions activated and the extent of regional activations (number of "voxels") in relatives compared with the controls. The authors showed more activation during the task performance, representing significantly more activated voxels than the controls. Tsuang et al. (2000) concluded, that relatives may have compensatory exertion of inefficient neural circuitry in attempting to perform an effortful task to produce accurate output and abnormal connectivity in the circuitry required to perform these tasks. For an overview of neuropathological findings concerning schizophrenia, see table 1.3.

1.4 Schizophrenia spectrum disorders

While some *schizophrenia spectrum disorders* are almost as severe as schizophrenia (e.g. schizoaffective disorder), others are milder and do not involve psychosis (e.g. schizotypal personality disorder). In the construct of schizophrenia spectrum disorders, the following disorders, beside schizophrenia itself, are included: schizotypy, schizoaffective disorder, schizotypal personality disorder. The spectrum concept has numerous implications for treatment. The fact that psychosis is not a major feature of all schizophrenia spectrum disorders suggests

that other symptoms might better reflect the underlying aetiology of schizophrenic illness, throughout the associated spectrum of disorders. If such deficits are identifiable, they may provide a foundation for treatment. Here, the discussion of spectrum disorders will focus on symptoms that may reflect the genetic predisposition for schizophrenia.

Schizotypy has been identified (Meehl, 1962) as the behavioural manifestation of an integrative neural deficit (schizotaxia) which represents the underlying genetic predisposition for schizophrenia. Meehl (1962) suggests that schizotypal symptom structure is characterized by a cognitive-perceptual, interpersonal and disorganisation factor which is similar to the three factor model of schizophrenia. In order to identify schizophrenia-like traits (often referred to as "schizotypy"; Claridge and Broks, 1984) in the normal population, some authors suggest schizotypal characteristics. These characteristics could be divided into several classes: positive schizotypy, negative schizotypy and cognitive disorganisation, which correspond to clinical subdivisions seen in schizophrenia (Bentall et al., 1989; Claridge and Broks, 1984; Loughland and Williams, 1997). Hallucinatory experiences are commonly assigned to positive schizotypy. Schizotypy has often been investigated as a trait which helps the insight into schizophrenia, but without the confounding effects of medication or institutionalization.

Meehl (1962) called a group of persons with a genetic predisposition to schizophrenia *schizotaxia* persons. In Meehl`s view, a *schizotaxia* person will develop either schizotypy or schizophrenia, depending on environmental circumstances. Later, Meehl noticed that some of the schizotaxia people developed neither schizotypy nor schizophrenia. In a current point of view, schizotaxia has clinical conditions, including abnormalities in affect, cognition, social functioning, and brain function among the non-schizotypal and non-psychotic relatives of SZ patients. Schizotaxia has neurobiological and psychiatric features that justify research on a more than theoretical point of view. Schizotaxia is used as a term where an underlying defect among people genetically predisposed to schizophrenia is remarkable, like Meehl proposed in his textbook. Tsuang et al. (2000) enlarged the theory of Meehl and suggested schizotaxia as the predisposition to schizophrenia, which includes both genetic and non-genetic biological consequences of early adverse environmental circumstances. In contrast to Meehl, Tsuang et al. (2000) suggested that schizotaxia does not necessarily progress into a more severe disorder, e.g. schizotypy, although they identified core symptoms of schizotaxia in 20 to 50 % of non-psychotic relatives of schizophrenic patients in their studies. Tsuang et al. (2000) proposed a change in the diagnostic criteria in the way that schizophrenia has to be broadened into two categories: schizotaxia and schizotaxia plus psychosis (= schizophrenia). Tsuang et al. (1999a and b) defined criteria for schizotaxia which requires: first-degree relative of patients with schizophrenia, speak English as first language, have estimated IQ scores of at least 70, be between 19 and 50 years of age, no lifetime history of psychosis.

1.5 Neurophysiological basics

The human brain is a compact mass with a certain number of structures. While the anatomy and structure of brainstem structures are reasonably well preserved across species, the structure of the neocortex is substantially different in primates. It even shows wide diversity across primate species. This makes it very difficult to infer relationships between responses found in animal studies and the expected functional properties in humans. A large amount of information has been gathered on cortical responses in cats, bats and owls. These studies provide important information, and often represent the cutting edge in electrophysiology.

Our neuroanatomical structures cannot be appreciated directly, but only indirectly by knowledge of their spatial relationship to other visible structures. The computertomography (CT) and magnetic resonance (MR) scanner have enlarged the possibilities of the localisation of different brain areas in a spectacular manner by making almost all components of the brain and its pathologic processes visible - if not always identifiable.

At present we know about the importance of brain deficits for schizophrenia. The study of psychiatric illness, especially schizophrenia and the symptoms involved like hallucinations, has received new and innovative impulses from the development of functional imaging techniques, where it is possible to measure brain activity in-vivo. In order to understand the neuroimaging results of the present thesis, the following section provides a basic knowledge of the human brain and its anatomical structures. The important parts of the brain will be explained, including the CNS, the hemispheres, the lobes and the division into cyto-architectonic areas. The introduction gives hints about the connection between the brain structures and their function in the information process. The focus of the next subpart lies on the visual and the auditory system, because of their importance in the current thesis.

1.5.1 The central nervous system

The *central nervous system* (CNS) consists of 7 main parts: the spinal cord, the medulla oblongata, the bridge (latin: pons), the cerebellum, the mesencephalon, the interbrain (diencephalon) and the cerebrum (telencephalon) including both hemispheres. The imaging techniques (view chapter 1.6), which were established in neurophysiology research in the 90s, allow us to view these structures on a live human brain. The brain imaging research of the last decades includes the knowledge of a specialized task for each brain region. Figure 1.2 shows the CNS.

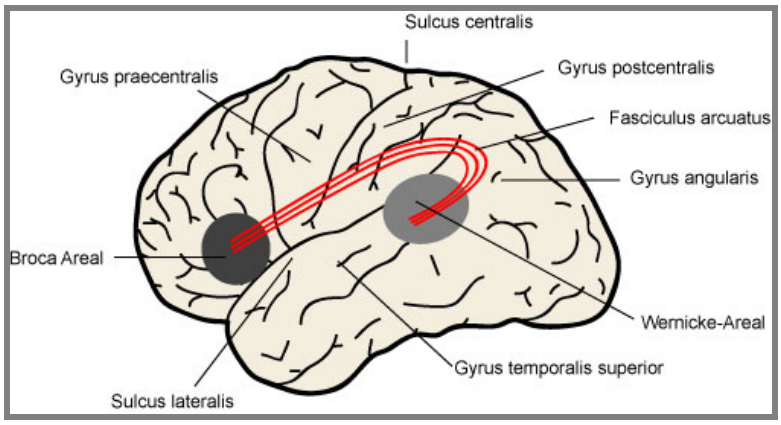


Figure 1.2: *The central nervous system (CNS; Kandel et al., 2000; revised version: Janson et al., 2007).*

In the current section, we will focus on the two hemispheres and their functions. Each hemisphere consists of the *cerebral cortex*, (=cortex), the *basal ganglia*, the *hippocampus* and the *amygdala*. The basal ganglia are responsible for the control of motor activities, the hippocampus plays an important role in the memory retrieval system and the amygdala is involved in emotion processing. The cortex can be divided into four lobes: the *frontal lobe* (lobus frontalis), the *parietal lobe* (lobus parietalis), the *occipital lobe* (lobus occipitalis) and the *temporal lobe* (lobus temporalis). The lobes listed above exist in each hemisphere. Each lobe has a special task in the human brain: the frontal lobe is responsible for the strategy of further activities and for the control of motor behaviour; the parietal lobe controls the sense of touch and physical perception. Hence, the occipital lobe, as the name tells us, is responsible for processing and controlling sight, whereas the temporal lobe controls hearing and additionally some aspects of learning, memory and emotion information processing.

Each lobe itself has many different subparts, called *gyri* (singular: gyrus) and *sulci* (singular: sulcus). The larger subparts are similar in individuals and have special names, for example the *gyrus praecentralis* (motor function) and the *gyrus postcentralis* (sensory function). The *limbic system* is not a separate region, but consists of the medial (middle) parts of the frontal-, the parietal- and the temporal lobe and controls learning, memory and emotion.

One important finding of the research is that each hemisphere is predominantly responsible for sensory and motor processing of the opposite body areas. Sensory and motor information from outside comes from the spinal cord into the cortex, then changing sides. After this step, the information is led to higher levels. Note that both hemispheres are not fully symmetrical and don't fulfil the same functions.

In 1861, Paul Broca wrote in his textbook the important sentence "nous parlons avec l`hémisphère gauche!" ("we speak with the left hemisphere"). The left frontal lobe is known to be responsible for speech, and is called, after the famous German scientist, the *Broca area*. In 1881, another German scientist, Carl Wernicke, detected the so-called *Wernicke´s area*, which processes speech information. The wernicke area is located near the *primary auditory cortex* and

has a strong connection (*fasciculus* arcuatus) to the broca area. In addition, Wernicke first suggested the hypothesis of a *distributed processing*. This concept is based on the opinion, that only elementary functions will be processed in one brain region, whereas all other functions will activate parallel processing in different brain regions.

In addition, Korbinian Brodmann (1909) identified 52 fields in the cortex, called area 1 to 52, which are divided into categories in their function for human information processing. The subdivision of the cerebral cortex into cyto-architectonic areas does not imply a parcellation of cerebral function, even if certain cortical areas appear to correspond to a univalent neural activity accessible in its totality or partially to techniques of exploration in vivo, e.g. sensory perceiving areas.

Most of the brain regions of the cortex are responsible for the processing of sensory and motor information coming from outside (see figure 1.3). They are subdivided into *primary*, *secondary* and *tertiary* motor and sensory areas, dependent on the level of information processing they are responsible for. The *primary visual cortex* is located in the occipital lobe, near the cerebellum, whereas the *primary auditory cortex* is located near the speech areas in the temporal lobe (in the left hemisphere). The *primary somatosensory cortex* lies over the gyrus postcentralis, the *primary motor cortex* is located near the primary somatosensory cortex, over the gyrus praecentralis. The secondary and tertiary areas bound the primary areas. Higher level sensory areas integrate information coming from the primary areas, whereas higher level motor areas transmit complex information for a motor act to the primary motor cortex.

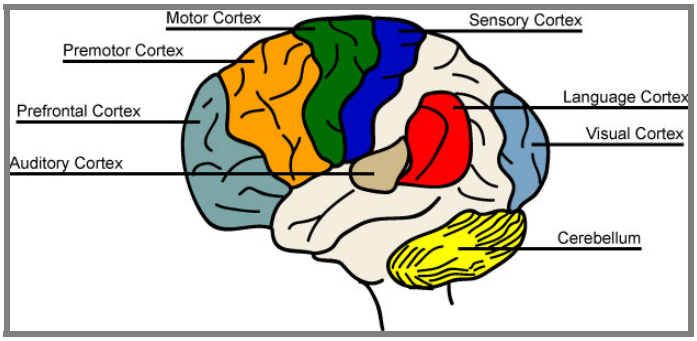


Figure 1.3: *The motor and sensory areas (Janson, 2007).*

Four principles are important to know about information processing in the brain. All main areas of the brain and the spinal cord are linked through so-called processing centres, which receive, send and process information. Furthermore, the main areas have several subsystems, which have different tasks and are linked together, the so-called *tracts*. The most important tracts in the human brain are the following: the *pyramidal tract* ([PT], motor system), the *optic pathway* (visual system), the *auditory fibres* (auditory system), the *olfactory tract* (sensory system) and the *large association bundles* (all systems). The tracts are topographically organized, so that we are able to create a neural map. Additionally, during most physical acts, the three

important systems, the sensory, the motor and the limbic, are involved together. Therefore, several *association cortices* exist. The following table lists the most important areas for this study (table 1.4).

Table 1.4: *The most important brain areas and their functions.*

Lobe	Functional name	Brodmann area
Frontal lobe	Primary somatomotor area Broca`s area Primary motor cortex Secondary motor cortex Prefrontal association cortex (cognitive behaviour and planning of motion)	4 44, 45 4 6,8 near 6
Parietal lobe	Primary and secondary somatosensory cortex Posterior-parietal cortex Parietal-temporal-occipital (higher sensory functions and speech)	1,2,3 5 = somato, 7 = visual 39,40
Occipital lobe	Primary visual sensory area, visual cortex V1, V2, V3, V3a, V4, V5	17, 18, 1
Temporal lobe	Primary auditory receptive cortex Auditory integration region Visual inferior-temporal area	41 42 21, 20
Parietal lobe, temporal lobe, occipital lobe	Parietal-temporal-occipital association cortex (higher sensory functions and speech)	39,40 (19,21, 22, 37)
Temporal lobe, parietal lobe, frontal lobe	Limbic association cortex (feelings and memory)	23, 24, 38, 28, 11

1.5.2 The auditory system

The human auditory system provides us with vast amounts of information about the world around us. Our auditory system allows us to make pitch and tone judgments, which are essential for e.g. the appreciation of music and understanding speech. In terms of physics, pitch tells us about the frequency of sound. Our ears also allow us to locate the source of a sound. To perform this localization function, the brain combines timing (or more specifically delay or phase) and amplitude information about the sound with information from other senses. The auditory system consists of the following structures: auditory nerve (CNV III), cochlear nuclei, superior olivary complex, lateral lemniscus and nuclei, inferior coliculus, thalamus, auditory cortex (for detailed description of these structures view Haines, 1991; Rubel and Dobie, 1989; Ehret and Romand, 1997).

The auditory cortex is located in the sylvian fissure of the temporal lobe. It can be divided into primary auditory cortex (AI) and secondary auditory cortex (AII). The *primary auditory cortex*, called *Heschl's gyrus* or anterior transverse temporal area (Brodmann [BA] 41 and 42), is the region of the brain that is responsible for the processing of auditory (sound) information. As with other primary sensory cortical areas, auditory sensations reach perception only if received and processed by a cortical area. Heschl's gyrus is located in the posterior half of the superior

temporal gyrus that has two major parts: the lateral sulcus and the transverse temporal gyri (= Heschl's gyri). It is a subdivision of the cytoarchitecturally-defined temporal region of the cerebral cortex, occupying the anterior transverse temporal gyrus (H) in the bank of the lateral sulcus on the dorsal surface of the temporal lobe. BA 41 is located on the border of the parainsular area 52 (H) and the posterior transverse temporal area 42 (H) (BA 42; Brodmann, 1909). BA 42 is located on the border of the anterior transverse temporal area 41 (H) and the superior temporal area 22 (Brodmann, 1909). Input for the *secondary auditory cortex* (AII) comes primarily from AI and AII; output goes to sensory association areas, to the parietal lobe, to the temporal lobe, as well as the speech areas (Broca's area and Wernicke's area).

Neurons in the auditory cortex are organized according to the frequencies of sound. Neurons at one end of the auditory cortex respond best to low frequencies; neurons at the other respond best to high frequencies. There are multiple auditory areas (much like the multiple areas in the visual cortex), which can be distinguished anatomically and on the basis that they contain a complete *frequency map*. The purpose of this frequency map (known as a tonotopic map) is unknown and likely to reflect the fact that the sensory epithelium of the auditory system, the cochlea, is arranged according to sound frequency. The auditory cortex is involved in tasks such as identifying and segregating auditory "objects" and identifying the location of a sound in space. Human brain scans have indicated that a peripheral bit of this brain region is active when trying to identify pitch. Individual cells consistently get aroused by sounds at specific frequencies, or multiples of that frequency.There also appears to be a spatiotopic map with sounds from the contralateral hemifield being more excitatory in a given hemisphere. Regions with specific temporally sensitive responses have also been found, which may play a role in several phenomena of perception including virtual pitch perception, timbre discrimination, spatial localization, or even noise filtering.

1.5.3 The visual system

The visual system is divided into five separated areas: V1, V2, V3, V4 and V5. The *primary visual cortex* (striate cortex, V1) is located in BA 17 (occipital cortex). V1 receives its information directly from the lateral geniculate nucleus (LGN). Following processing in this region, the visual neuronal impulses are directed to the secondary visual cortex (V2) which projects to V3, V4 and V5. Each of these areas can be subdivided into further regions, which send information to any other area of the brain that processes visual information. This general arrangement is subdivided into three parallel pathways. Although each pathway is somewhat distinct in function, there is strong intercommunication between them.

In the first and completely parvocellular pathway, neurons in the interblobs of V1 project to the pale stripes of V2. The pale stripes of V2 project to the inferior temporal cortex. Neurons found in the *inferior temporal cortex* respond to very complex stimulus features of a specific

nature regardless of size or position on the retina. Some neurons in the region respond selectively to faces of particular feature characteristics. In addition, this region is intimately involved in visual memory. Damage in this pathway will induce disorders of object recognition. Common examples of such disorders include visual agnosia, or the inability to identify objects in the visual areal, and prosopagnosia, a subtype of visual agnosia that especially affects the recognition of once familiar faces. In the second visual cortical pathway, the neurons of V1 project to the thick stripes of V2. Area V2 then projects to V3 and V5 (middle temporal cortex) and to the medial superior temporal cortex. This pathway continues the processing of visual detail leading to the perception of shape in area V3 and movement or motion in areas V4 and V5. Finally, the neurons in the blobs of V1 project to the thin stripes of V2, which build the third and mixed visual cortical pathway. The thin stripes of V2 project to V4, which is known to be involved in the perception and maintenance of colour perception regardless of lighting (colour constancy).

In humans and other primates, the visual information processing system is a domain-specific organisation. Visual processing involves two systems in the brain, the *dorsal* (="where") and the *ventral* (="what")-pathways. The dorsal stream runs from the occipital lobes to the posterior parietal lobes and involves the interaction of vision with the motor cortex. It permits spatial perception. Thus, the dorsal stream may be responsible for the hand-eye coordination required to perform such activities as picking something up. When the dorsal or "spatial properties processing" pathway is damaged, the person cannot register location. The other main visual pathway, the *ventral stream*, runs from the occipital lobes down to the inferior temporal lobes. The ventral stream is related to object recognition and categorization. When this "object properties processing" pathway is damaged, shape registration is not possible (Kohler et al., 1995; McInttosh et al., 1994). Parallel deficits appear in imagery. Damage to the dorsal pathways destroys the ability to visualize locations, and damage to the ventral pathway disrupts the ability to visualize shape (Kosslyn et al., 2001).

1.6 Magnetic resonance imaging (MRI)

Making accurate visual representations of the structure of the human brain has been one of the most challenging tasks of anatomical research for the past 50 years. Several technical methodological principles have been developed over the last 20 years. MRI has been developed in many settings and has proven to be a powerful tool for medical and scientific purposes. The study of psychiatric illness, especially schizophrenia and symptoms like hallucinations, has received new and innovative impulses from the development of functional imaging techniques, where it is possible to measure brain activity in-vivo. Brain-imaging techniques have opened up the human brain for direct inquiries in terms of structure, neurochemistry and function. New hypotheses of pathophysiology, e.g. for schizophrenia, do not overlook dopamine as playing a

major role, but do emphasize the participation of integrative neural systems in the expression of the illness and of the limbic system in generating symptoms (Holcomb et al., 2000).

In contrast to X-ray, magnet-resonance-imaging (MRI; see figure 1.4) is a diagnostic technique that represents organs and tissue with the help of magnetic fields and radio waves. The phenomenon of nuclear magnetic resonance has been known since the 1940s (LeBihan, 1995; LeBihan et al., 2001). Independently from each other, Bloch and Purchell (1946) first detected the technical basics of MRI. In 1952, the authors got the Nobel Prize for research for this important development. Lauterbur and Mansfield (in: Lauterbur (1973); Mansfield and Grannell, 1973) developed specific mechanisms to use the technical principle for medical use. They also got a Nobel Prize, in 2003, for medical research. Since 1984, the MRI-technique has been used in practical clinical settings.

The development of non-invasive techniques for the measurement of brain activity and for its stimulation in the 1980s and 1990s has led to considerable progress in functional brain mapping and stimulated the parallel development of advanced tools for the topographical anatomical visualization of these activation maps, including 3-dimensional reconstructions of the cortical sheet, inflation and cortical flattening. In the nineties, the technique became prominent and was used in several clinical and research settings for medical, psychological and neurophysiological implications.

MRI uses an intrinsic brain signal and can therefore be used repeatedly on a person. Furthermore, it uses a signal contrast that is merely based on biochemical tissue properties. MRI functions on a radio frequency energy band (RF). At this energy level, most biological tissue is transparent. Thus, it has a high spatial resolution in deep brain structures as well. The whole brain or parts of it are measured in an extremely large set of three-dimensional (3-D) spatial units (voxels) of a few millimetres in each dimension, constituting a very high spatial resolution or detailedness. A whole-brain measurement can be achieved within one or several seconds, constituting a moderate temporal resolution in comparison with the superior resolution of milliseconds in electroencephalography. Because the measurement can be repeated many times, brain activity can be sampled to a high degree, increasing the statistical power of the method. The consecutive measurements for each voxel constitute the voxel timecourse, representing the changes in brain activity over time for a spatial location. For a basic understanding of the underlying mechanism, a short course on the physical and chemical mechanism will follow.

Figure 1.4: *Picture of an "open" MRI-scanner (www.netdoktor.de).*

1.6.1 Principles of MRI

The human body consists of atom cells, most of all hydrogen atoms. Normally, the atoms are without any order. However, in the MRI there is a strong magnetic field, which lays out the atom cores in a specific direction. With the help of radio waves the atoms' position and direction can be changed. After a decrease of the air waves the atoms will fall into position, which is determined by the magnetic field. During this process the atoms send signals which can be measured and analyzed by the computer. The outputs of these analyses are the cut pictures from different perspectives.

Magnetic resonance imaging is based on the fact that a nuclear magnetic resonance signal is created by the interaction of a charged nucleus with a magnetic field. The most commonly used nucleus is that of the hydrogen atom, which contains a single proton (H+). A horizontally orientated fixed magnetic field (B0) is created, in clinical settings usually a 1.5 Tesla magnetic field. Charged nuclei (e.g. hydrogen protons) have a magnetic moment and spin around their axis. Placed in a fixed magnetic field, the spinning protons line up in the same orientation as the fixed magnetic field. This is called longitudinal magnetization (view figures 1.5 and 1.6).

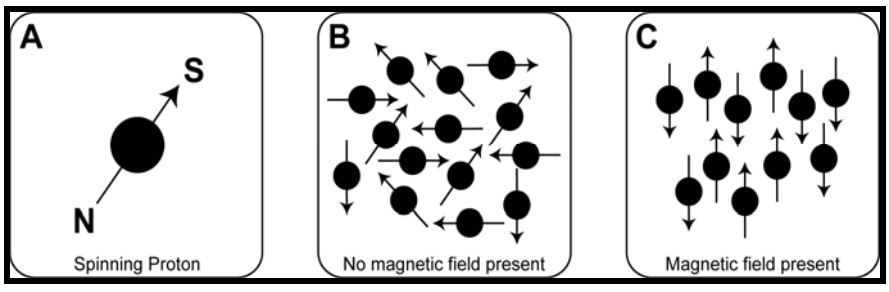


Figure 1.5 a) *the spinning hydrogen protons create a magnetic field, and thus act like a tiny magnet with a north and south pole* **b)** *when no magnetic field is present, the axis of the atoms point in different directions.* ***c)*** *when placed within a magnetic field, a torque will be exerted upon them, resulting in a slight energetic advantage of one orientation (parallel to the field) over another (the anti-parallel orientation).*

Then, a pulse of electromagnetic energy at a specific frequency, the RF-pulse, is generated. The frequency depends on the resonance frequency of the nucleus of interest (the *Larmor* frequency) and on the strength of the local magnetic field. Due to excitation of the protons, the longitudinal magnetization is rotated by the RF-pulse and a transverse magnetization component arises. The amount of rotation, called the *flip angle*, is a function of amplitude and duration of the radio frequency pulse. After termination of the RF-pulse, the protons return to the longitudinal magnetization. This generates the nuclear magnetic resonance signal (with the Larmor frequency), which can be detected by the receiving coils. This signal provides the basis of the MR image.

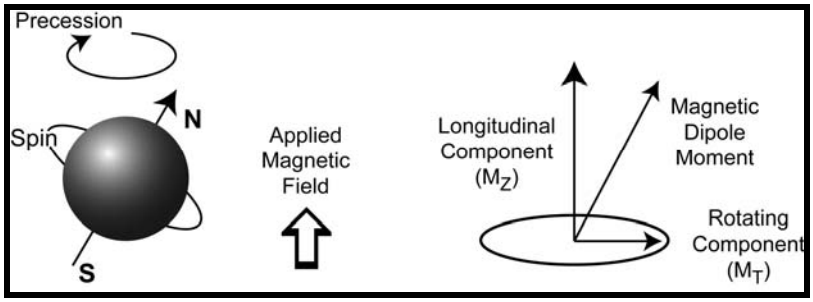


Figure 1.6 a) *Magnetic properties of the proton nucleus of the hydrogen atom* **b)** *Vector description of proton magnetization.*

A three-dimensional image is generated by applying a gradient of magnetic field to all three orientations. This makes the resonance frequency at all positions in the 3D-space slightly different. By means of a *Fourier* analysis, the frequency information can be transformed to spatial information, and signal intensity at all positions in the 3D-space can be determined.

There are different sources of image contrast: density of nuclei and temporal decay. The first contrast arises from the fact that the signal strength in a region is dependent on the density of the nuclei of interest in that region. Nucleus density varies between different kinds of tissues. This provides a source of image contrast. The nuclear magnetic resonance signal is transient, and the characteristic of the temporal decay is different for each kind of tissue. Two forms of temporal decay can be distinguished. One is the gradual recovery of the longitudinal magnetization, which is called the *longitudinal relaxation time* (T1) representing the time the spin system needs to recover its thermal equilibrium. The second is called the *transverse relaxation time* (T2), representing the time needed by the excited spins to develop a phase incoherence before relaxing back to the equilibrium state. The T2 is the gradual loss of transverse magnetization due to the dephasing of the individual protons. Because the dephasing is not only an effect of spin-spin interactions, it is also affected by inhomogeneities in the applied magnetic field, so it is not possible to measure T2 decay. To obtain data based on T2-decay, these inhomogeneities must be compensated for. The transverse relaxation time is then called the *effective transverse relaxation time* (T2*). Both forms of temporal decay are a source of image

contrast, provided that the signal is measured at the appropriate time (echo time, TE). T2 is always shorter than T1, and T2* is shorter than T2 (Sanders, 1995; Savoy, 1996).

1.6.2 Functional magnetic resonance imaging (fMRI)

The use of MRI to provide a map of areas of neuronal activation associated with a given mental operation is called *functional MRI (fMRI)*. The functional magnet resonance tomography is one of the most important methods used to gain the functional topography of the brain and for the mapping of cognitive performance under normal and pathological conditions. fMRI-data sets don't produce quantified data, but only relative information between different conditions under different cognitive tasks, which are used in parametric designs.

Activation refers to an increased rate of neuronal firing. The vast majority of fMRI studies use localized blood flow as an indirect measure of brain activity, relying on the coupling between changes in neuronal activity and blood flow. With increased neuronal firing more oxygen-enriched blood flows into the area of increased neuronal activity. The resulting change in magnetic properties of the blood flow in this brain area forms the basis of the measured signal, termed the blood-oxygen-level dependent (BOLD) contrast. Thus, in fMRI increased neuronal activity is represented by an increase in signal amplitude. Typically, the BOLD signal is sluggish and delayed by several seconds with respect to the neuronal activity.

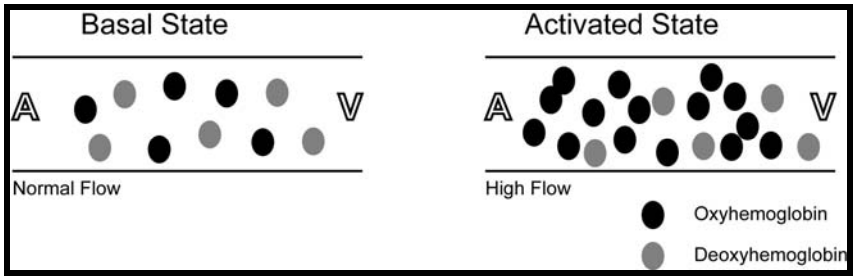


Figure 1.7: *Basal state – activated state. During periods of neuronal activity, local blood flow and volume increase with little or no change in oxygen consumption. As a consequence, the oxygen content of the venous blood is elevated, resulting in an increase in the MR signal.*

The hemodynamic changes can be studied with MRI by choosing the parameters to make the MR images sensitive to blood flow and composition. fMRI makes use of the difference in MR-signal intensity between oxygenated and deoxygenated blood (see figure 1.8). Because magnetic susceptibility is decreased in oxygenated blood, the dephasing of the protons after the radio frequency pulses takes more time. Hence, the T2* is longer in oxygenated blood. T2*-weighted images result in an increasing signal intensity of oxygenated blood compared with deoxygenated blood. The difference in T2* between oxygenated and deoxygenated blood is called the *blood oxygenation level dependent signal* (BOLD; Ogawa et al., 1990; Belliveau et al., 1990). The BOLD effect is the basis of the imaging of the brain activation.

When a brain region is active in the processing of certain information, e.g. during the performance of a specific task, neurons in this region will require more oxygen. Fresh oxygenated blood flow in activated regions exceeds the increase in oxygen consumption. This results in a net increment of the blood oxygenated level and therefore in increased signal intensity in active brain areas (Savoy, 1996; Ogawa et al., 1992). Brain areas with more blood flow have been shown to have better visibility on MRI images (Cohen and Bookheimer, 1994).

With the advent of fMRI in the study of hallucinations, new insights have been obtained, leading to a better understanding about the neural underpinnings of the aberrant perceptual experience. However, much controversy remains to be solved. One of the challenges has been the issue of the involvement of primary sensory areas in hallucinations. Many studies found evidence that activity in the primary visual and auditory cortex could be significantly increased during sensory-specific attention, but only the primary visual cortex has been found activated during mental imagery. In 1999, Dierks and colleagues published a report of increased activity in the primary auditory cortex during auditory hallucinations by using fMRI; and made the intriguing suggestion that this activity may reflect the increased vividness that is commonly associated with such hallucinations. The primary auditory cortex does not seem to be active during auditory mental imagery in healthy individuals, where the internally invoked auditory images are experienced as less vivid than sensory-driven, externally evoked percepts. For details of structural MRI, please read the thesis of Rotarska (2007).

1.7 Summary and conclusion (research design)

Schizophrenia is one of the most interesting psychiatric disorders. The vulnerability-stress-model by Liberman et al. (1986) includes several approaches to explain the outbreak and cause of the illness. As we know at present, Schizophrenia is a mental illness with multivariate factors. Some of them seem clear, while others are still unknown and need to be investigated. This thesis uses multivariate methods in the study of symptoms and trait markers of schizophrenia. The main motivation was to analyse subjective data sets of psychometric tests and questionnaires and combine them with an objective, neural measurement of potential neural deficits (fMRI and structural MRI). Of main interest are hallucinations, one of the most common symptoms in schizophrenia, and possibly related symptoms and markers, such as mental imagery. In sum, the present thesis deals with possible markers and explanations for schizophrenic symptoms, especially with psychotic symptoms like hallucinations. They were examined in different contexts (e.g. psychometric data sets and underlying processing mechanisms in the brain).

In detail, the present investigation includes two major approaches regarding hallucinations: a huge test battery and an MRI study that includes functional and anatomical aims. The whole study includes patients diagnosed with paranoid schizophrenia according to

DSM-IV criteria (295.30; American Psychiatric Association, 1994), a number of first-degree relatives (siblings or parents) as well as a group of matched controls (view figure 1.8 for the research design).

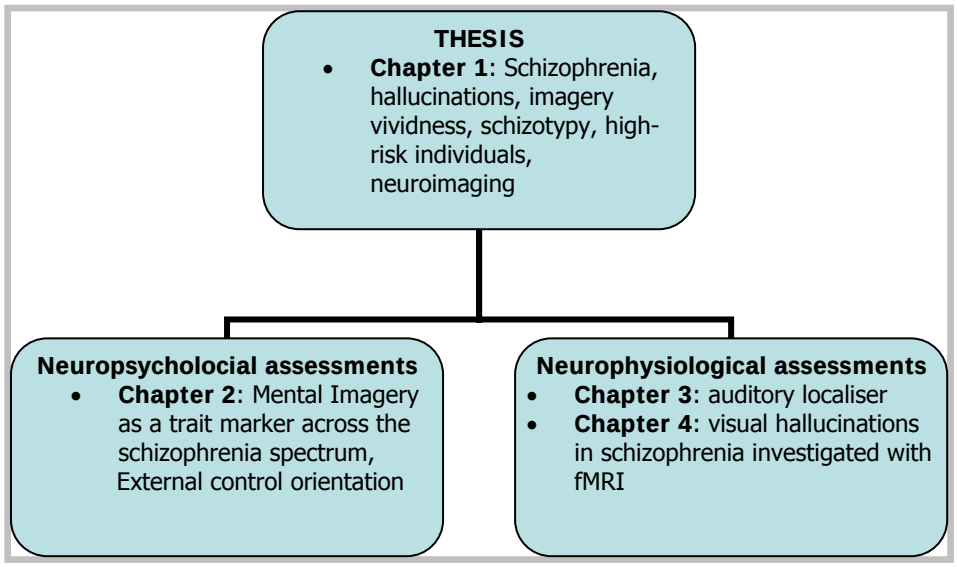


Figure 1.8: *Research Design*

1.7.1 Neuropsychological assessments

Neuropsychological assessments were connected to a multivariate set of analyses in order to characterize the relations between hallucinations, mental imagery, personality structure and a small set of cognitive and perceptual abilities. The whole test battery consists of a number of diagnostic interviews, five clinical and three psychometric tests and questionnaires. The large test battery was split into two parts based on the two main hypotheses made at the beginning: The first was the association between the presence and severity of auditory hallucinations and the vividness of mental imagery, the second deals with the underlying personality structure of the subjects and the association with the dysfunctional status and psychopathological symptoms including hallucinations and delusions.

In detail, we analysed the question of an increased vividness of mental imagery in relation to an increased tendency towards hallucinations or whether the two constructs are totally independent from each other (chapter 2). Predisposition towards hallucination (Revised Hallucination Scale [RHS]; Morrision, 2002) and the vividness of mental imagery (Betts Questionnaire upon mental imagery [QMI]; Sheehan, 1967) were obtained by self-report questionnaires in all subject groups. The research also included an investigation of the perceptual performance (Leistungsprüfsystem [LPS]; Horn, 1962). The first goal of this part of the study was to determine whether a tendency towards a vivid mental imagery is associated with a predisposition towards hallucinations.

We propose that schizophrenia is characterized by an increased vividness of mental imagery. In addition, one of the main aims of this research is to clarify the role of schizophrenia spectrum disorders (schizotypal personality disorder, schizotypy, high-risk individuals) as well. We suggest a continuum of the vividness of mental imagery: SZ patients will score lower on the QMI than the first-degree relatives (means higher vividness of mental imagery), followed by high-schizotypy controls and normal controls.

The second hypothesis deals with the predisposition towards hallucinations, where we also suggest a continuum with the patients as most predisposed towards hallucinations, followed by high-risk individuals (relatives) and both control groups (high- and low-schizotypy). Finally, the current thesis deals with the question of whether greater imagery vividness is related to increased reports of hallucinations or not. We suggest an independence of mental imagery and hallucinations in all three subject groups.

The second part of the test battery investigated the personality structure and the degree of dysfunctional status and its relation to schizophrenia (Chapter 2). Here we focused on personal traits which could be responsible for the differentiation between SZ patients and high-risk individuals or persons who suffer from abnormal perceptual experiences. The test battery that was used here comprised questionnaires for the control orientation of the subjects (German Version of the Competence and Belief Scale (CCBS; Krampen, 1981) and a measurement of dysfunctional symptoms which could lead to the illness (Eppendorfer Schizophrenie Inventar [ESI]; Maß, 2000). As an assumption the results should show a continuum of performance with patients more impaired than first-degree relatives, high-schizotypy individuals and normal controls in the control orientation and the dysfunctional status. We suggest further a correlation between the external control orientation in schizophrenics and pychopathological symptoms like hallucinations or delusions.

Additional control scales for the cognitive abilities (Mehrfachwahl-Wortschatztest [MWT-B]; Lehrl, 1989; Trail making-Test [TMT]; Reitan 1979) for both parts of the investigation were used. In addition several diagnostic instruments for the diagnosis of the patients (PANSS; Kay et al., 1987), a schizotypy-screening for the relatives and controls (Schizotypy Personality Questionnaire [SPQ]; Raine and Baker, 1991) and a screening for psychiatric disorders (SKID I and II; Wittchen et al., 1996) were used. We propose that the SZ patients show deficits in the cognitive abilities, but that those cognitive abilities are independent of predisposition towards hallucinations, vividness of mental imagery and the locus of control. Table 1.5 shows an overview of the assessments for the neuropsychological parts of the thesis. Furthermore, we suggest an independence of sociodemographic data of the subjects of the questionnaires.

Table 1.5: *Overview of the neuropsychological assessments.*

Construct	Questionnaires
Self-administered questionnaires	**QMI** Questionnaire upon mental imagery (Sheehan, 1967) **RHS** Revised Hallucination Scale (Morrison et al., 2002)
Objective psychometric measurement	**LPS** Leistungsprüfsystem (Horn, 1962)
Cognitive Measures	**MWT** Mehrfachwahl-Wortschatz-Test (Lehrl, 1989) **TMT** Trail making test (A and B) (Reitan, 1979)
Additional clinical scales	**CCBS** (German Version of the Control and Belief Scale; Krampen, 1981) **ESI** Eppendorfer Schizophrenie Inventar (Maaß, 2000)
Individual Psychopathology	**PANSS** The Positive and Negative Symptom Scale (Kay et al., 1987) **SPQ** Schizotypy Questionnaire (Stöber, 1999) **SKID** Strukt. Klin. Interview psych. Störungen (Wittchen, 1996)
Sociodemographic data	Age, years of education, gender, handedness, medication, years of illness, onset of illness, symptom description, socio-economic status, socio-economic-status of the parents **QAH** Questions about hallucinations

1.7.2 Neurophysiological assessments

In the second main part of the dissertation, several MRI sessions to examine brain deficits of the subjects were conducted. As a minimal amount, 15 subjects in each group described above were measured on the 3 TESLA Allegra magnetic resonance tomograph (Siemens, Erlangen) in the Frankfurt Brain Imaging Center (BIC), Germany. The MRI measurement could be divided into functional and structural data sets and analysis methods (Chapter 3 and 4). Chapter three includes functional data sets in the auditory modality, compared to structural imaging data. In addition, chapter four presents the investigation of two visual hallucinating individuals as well as a pilot study of a visual localizer. The activity pattern during visual stimulation and visual hallucination will be compared in order to identify identical and different brain areas involved in the processing of the brain. For the fMRI-sessions, several EPI-sequences (echo-planar-imaging) were used. The anatomical measures include a high-resolution T1-weighted 3D session with an MP-rage sequence (magnetization prepared rapid acquisition gradient echo) and a DTI measurement.

In the functional and anatomical data, as a main hypothesis, we suggest also a continuum. The schizophrenic patient group ought to show dysfunctions in the information processing system in the brain, all over the different tasks in the different modalities (visual, auditory). As well, we expect noticeable problems in the first-degree relatives group, although they don't suffer from psychopathological symptoms. In addition, we demand that the activation pattern of visual hallucinations will show abnormalities in the information processing in the brain, especially for the visual modality.

CHAPTER 2: PSYCHOMETRIC CORRELATES OF HALLUCINATIONS, MENTAL IMAGERY AND LOCUS OF CONTROL

Part I: MENTAL IMAGERY VIVIDNESS AS A TRAIT MARKER ACROSS THE SCHIZOPHRENIA SPECTRUM

The following part is based on the publication: Oertel, V., Rotarska-Jagiela, A., van de Ven, V., Haenschel, C., Grube, M., Stangier, U., Maurer, K., Linden, D.E.J.. Mental Imagery vividness as a trait marker across the schizophrenia spectrum (2008; Schizophrenia Research, in press).

Abstract

We investigated vividness of mental imagery and its possible relationship with the predisposition towards hallucinations in 52 schizophrenia (SZ) patients, 44 of their first-degree relatives (R) and two healthy control groups (high-schizotypy [CHS; n = 24]; low-schizotypy [CLS; n = 24]). We investigated phenomenological and cognitive trait markers of schizophrenia, including cognitive correlates of hallucinations and vividness of mental imagery, and the influence of individual psychopathology. Overall**,** scores on the mental imagery questionnaire (QMI [Sheehan, 1967]) suggested higher mental imagery vividness in first-degree relatives, high-schizotypy controls and patients, compared with low-schizotypy controls. However, vividness of mental imagery was independent of predisposition towards hallucinations and cognitive test performance scores. These results suggest that vividness of mental imagery may be am independent trait marker across the schizophrenia spectrum. In addition we propose that imagery proneness exists relatively independently from the individual psychopathology.

2.1 Introduction

Mental imagery is defined as a perceptual experience that occurs in the absence of an adequate physical stimulus (Finke, 1989). It is associated with core psychological mechanisms such as perception and memory and may facilitate cognitive performance (Kosslyn, 1994). It has been proposed that increased mental imagery vividness may be associated with hallucinations in schizophrenia. Vividness of imagery denotes the degree of perceptual detail that is experienced when there are mental images of sounds or speech, visual scenes or objects, touch, smells or tastes. Imagery vividness can be measured when we use a self-report questionnaire (e.g., Betts' Questionnaire of Mental Imagery; Sheehan, 1967) that probes the subjective vividness of imagery experience across different sensory dimensions.

Auditory verbal hallucinations (AVH), the perception of voices in the absence of sensory input, constitute an important clinical phenomenon, affecting about 60% of the patients with schizophrenia (Sartorius et al., 1978; Hahlweg, 1998). Hallucinations in other sensory modalities may also appear in schizophrenia, but are much less prevalent. AVH differ from mental imagery

by the lack of control over the sensations (David, 1994; Hahlweg, 1998). Studies investigating the distribution of hallucinations in the general population yielded consistent findings showing that a considerable proportion of individuals experience hallucinations at some time in their lives (Johns and van Os, 2001). Tien (1991) reported a lifetime prevalence of hallucinations (not related to drugs or medical problems) of 10% for men and 15% for women, and the overall rates were similar for visual, auditory, and tactile hallucinations.

Psychological and neurobiological data suggest that hallucinations in schizophrenia arise from a combination of both monitoring and perceptual abnormalities (Mintz and Alpert, 1972; Horowitz, 1975; Cahill and Frith, 1996; Brebion et al., 1997; Dierks et al., 1999; Behrendt, 2003). Mintz and Alpert (1972) suggested that hallucinations in schizophrenia are characterized by a tendency to perception-like internally generated experiences and a weak ability to distinguish real perception from imagery. Böcker et al. (2000) tested the hypothesis that hallucinations in schizophrenia result from confusing internal with external stimulus sources (perception and mental imagery, respectively). These authors found that the hallucinating patients showed a higher level of vividness of mental imagery, especially in the auditory modality, in comparison with healthy participants.

However, the literature is inconsistent with respect to the role of mental imagery in hallucinations. Occasional reports of increased imagery vividness in relation to hallucinations (Mintz and Alpert, 1972; Morrison et al., 2002a, b) were not supported by other studies (Brett and Starker, 1977; Starker and Jolin, 1982). Several studies have suggested that vivid imagery per se does not account for reports of hallucinatory experiences (Aleman et al., 1999). Evans et al. (2000) showed that inner speech and AVH are not connected in a direct way. The study of imagery and its potential relation to hallucinations has not been confined to patients with a clinical diagnosis of schizophrenia. A number of non-clinical populations report hallucinatory experiences as well (Barrett and Etheridge, 1992; Poulton et al., 2000). Van de Ven and Merckelbach (2003) investigated hallucination predisposition and mental imagery vividness in healthy individuals and found that increased reported hallucinatory experience was explained better by non-specific response bias than by increased imagery vividness (Merckelbach and van de Ven, 2001; Van de Ven and Merckelbach, 2003). This finding suggests that the role of mental imagery in non-clinical hallucinations is indirect, and may be associated with hallucinations via other traits or cognitive systems. A recent study showed increased vividness of mental imagery in schizophrenia patients independent from hallucinations or other symptoms (Sack et al., 2005), which suggested that a vivid mental imagery may be a trait of schizophrenia. It is thus important to determine whether higher vividness of mental imagery is a general feature of the schizophrenia spectrum.

In contrast to categorical models of schizophrenia that posit a qualitative difference between normal and psychotic experiences, some authors suggested that differences may be

quantitative rather than qualitative (Hahlweg, 1998; Van Os, 2003) and that hallucinatory experiences are found on a continuum of schizophrenia and non-clinical psychosis. The wider context for this hypothesis is provided by the identification of schizophrenia-like traits in the normal population, which are often referred to as "schizotypy" (Claridge and Broks, 1984; Raine, 1991). Schizotypy is thus defined and identified by personality features that correspond to attenuated forms of psychotic symptoms typical of schizophrenia (Meehl, 1962; 1990). They may include perceptual aberration, magical thinking, delusional beliefs, a disposition to experience hallucinations, cognitive impairments and attentional dysfunction, but also symptoms corresponding to the negative symptoms of schizophrenia (Meehl, 1990; Lenzenweger 1994; van Kampen, 2006). The role of mental imagery for hallucinations in schizotypy has not been widely studied, but it seems that the association between imagery vividness and hallucinations is obscure at best (van de Ven and Merckelbach, 2003).

The current study is the first study of mental imagery vividness across the putative psychosis continuum that includes high schizotypy participants and genetically vulnerable but unaffected participants (first-degree relatives). We expected higher vividness of imagery in both the relative and the high schizotypy group in the present study. In contrast, we did not expect an association between imagery and predisposition to hallucinations across our groups.

For further theoretical implications of hallucinations and mental imagery, please view chapter 1.2.

2.2 Methods

2.2.1 Participants

We included 52 patients (see table 2.1) diagnosed with paranoid schizophrenia according to DSM-IV criteria (295.30 [APA, 1994]). All patients were in-patients of the departments of psychiatry of Frankfurt University and Höchst hospitals (Germany). Current psychopathology was assessed through standardized scales and interviews (see below; table 2.2).

Additionally, 44 first-degree relatives (R) and 92 healthy controls (view table 2.1) participated in the study. Contact to the relatives was established through participating patients, from a support group for relatives of schizophrenia patients, through newspaper articles, flyers and advertisements in the hospitals. The relatives were requested to bring a letter from the psychiatrist treating the affected family members to determine the diagnosis. We conducted a diagnostic session (PANSS and the Structured Clinical Interview for DSM-IV-TR (Strukturiertes Klinisches Interview Psychischer Störungen [SKID I (psychiatric disorders) and SKID II (personality disorders)] [Wittchen et al., 1996]) with the relatives to exclude any psychiatric disorder. Only first-degree relatives of patients who had been suffering from paranoid or chronic schizophrenia for more than 5 years were included in the study. The relatives group included 21

parents, 19 siblings and 4 children of schizophrenia patients. The relatives were not necessarily related to the patient sample used in this study, and they were not related to each other.

The control groups were matched with the patient group for handedness (all right handed) (The Edinburgh Inventory; Oldfield, 1971) age, sex and parental education. We considered the possibility that patient's education was affected by the onset of the illness (mean [SD] age of onset: 26.17 [8.78] years). To take this into account we matched according to premorbid education levels and added the parental education as a covariate to the analysis. Exclusion criteria for control participants were any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV (see below), left-handedness, current drug-abuse, neurological pathology and inability to provide informed consent.

All participants were provided with a complete description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethics committee of the Medical School of the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.

Table 2.1: *Demographic variables of all four subject groups.*

	SZ Patients	**Relatives (R)**	**High-Schizotypy (CHS)**	**Low-Schizotypy (CLS)**	**Total**
Participants	52	44	24	24	192**
Sex*	18 w / 34 m	22 w / 22 m	16 w / 8 m	11 w / 13 m	98 w / 94 m
Years of Education***	13.64 (3.23)	15.25 (3.71)	14.80 (2.44)	16.28 (2.45)	15.16 (3.09)
Parental Education	Mother: 12.59 (2.96) Father: 12.47 (2.76)	Mother: 12.15 (3.77) Father: 13.38 (3.55)	Mother: 12.55 (3.05) Father: 13.09 (3.08)	Mother: 13.13 (3.31) Father: 13.14 (3.98)	Mother: 13.23 (3.17) Father: 13.23 (3.17)
Age	38.90 (9.93)	41.27 (14.92)	31.42 (11.64)	32.89 (8.46)	36.24 (11.71)
Handedness	right	right	right	right	all right handed

*w = women, m = men
** incl. 48 controls which were not included in the final analysis
*** p values < .01 between all groups

2.2.2 Assessment Procedures

First, a brief interview was conducted to collect information about age, gender, handedness, the years of education (years of school, university, „ years of education"), job, socioeconomic status of the parents (rated in years of education of mother and father), and history of psychiatric problems. Any psychiatric disorder in the family history was proved and written down. In addition, parts of the *Prämorbide Anpassungsskala* (PAS; Raine, 1997) were conducted to ask for problems in childhood and potential genetic and environmental influence of the illness. The relative group were also interviewed and rated based on items of the *Prämorbide Anpassungsskala* (PAS; Raine, 1997).

Prior to the assessment of psychopathology, written informed consent was obtained from all participants. At the beginning of the testing, the patients were asked about their experience with hallucinations. After that, they were rated and subdivided based on their status of history of hallucinations: 43 SZ patients had history of hallucinations, 8 had no history of hallucinations. The group of patients with a history of hallucinations were asked about the time span of the last hallucination. Then, they were subdivided into the following groups: a group of patients, who experienced hallucinations during the week of the testing (n = 20), a group of patients, who had hallucinations during the current episode of the illness (n = 8) and a group with patients, who had heard voices during past episodes of the illness (n = 8). After that, all patients with a history of hallucinations were interviewed, and then rated, about the content of their hallucinations (after Aggernea, 1972). The ratings were done following the work of Aggernea (1972) (for detailed item list view Appendix D). Additionally, all relatives and control subjects were asked about their hallucinatory experience. None of them reported any hallucinations during their lives. Further information concerning the medication, the diagnosis, the onset of the illness, the duration of the treatment during this episode was written down.

In a second step, the test battery and rating on individual psychopathology of the patients were put in use. The test sessions were done with each subject individually and were divided dependent on attention and memory function of the individuals. The first session normally lasted approximately between 1 and 1 ½ hours, including the individual interview and the test battery. In a second session (in the same week as the other session), we assessed the psychopathological measures, which lasted between one and two hours. Patients with problems in attention were assessed in three sessions. All subjects were informed that they could stop the investigation at each point without an explanation.

The investigation was done in the laboratory of the hospital of Psychiatry, Psychosomatic and Psychotherapy, Johann Wolfgang Goethe-University, Frankfurt, Germany. Testing sessions took place in a quiet, well-lit room, so that objective testing conditions were ensured. The test sessions were done by V. Oertel (with the help of A. Rotarska-Jagiela), who is engaged in clinical work and is used to the SKID and the PANSS rating.

2.2.3 Self-administered questionnaires

In order to assess the predisposition towards hallucinations, we included a self-administered questionnaire which asks about psychotic experiences. The predisposition towards hallucinations was measured with the RHS (Revised Hallucination Scale; Morrison et al., 2002), which consists of 20 descriptions of hallucinatory experience. In 1981, Launay and Slade designed a scale to measure predisposition towards hallucinations (Launay-Slade Hallucination Scale [LSHS]), which was modified several times. Launay and Slade proposed the tendency towards hallucinations to be not a stable state, but which exists in a continuum of items, which are related to daydreams

and items which are closely related to psychotic experiences. In our experiment, we used the version of Morrison (2002), which is called the revised hallucination scale [RHS].

The RHS is based on a widely used questionnaire to assess hallucination predisposition in non-clinical populations (Bentall and Slade, 1985). Some of the items are related to daydreams while others refer to psychotic experiences (for an example item view table 2.2). Items must be rated according to degree of occurrence of the experience on a 4-point Likert scale (1 = never; 2 = sometimes; 3 = often; 4 = almost always). A high score on the RHS indicates an increased predisposition towards hallucinations.

Vividness of mental imagery was assessed with the use of the QMI (Sheehan, 1967). The 35 items of the QMI are statements regarding the imagery ability in seven different sensory modalities (visual, auditory, olfactory, cutaneous, kinaesthetic, gustatory and organic; see table 2.1 for an exemplary item). The descriptions correspond to the seven different sensory modalities: visual ("the sun rising"), auditory ("the mewing of a cat"), olfactory ("the smell of leather"), cutaneous („the prick of a pin"), kinaesthetic ("running upstairs"), gustatory ("the taste of oranges") and organic ("the feeling of fatigue"). Participants are asked to rate their imagery vividness on a 7-point scale (ranging from 1 [I perceive it perfectly clearly, as if it were real] to 7 [I think about it, but I cannot imagine it]). A high score on the QMI indicates *less* vivid imagery. We used the German version of the test, which has been translated from Sack et al. (2005) by three independent translators.

The reliability of the short version of the questionnaire was tested in schizophrenic patients by Datts et al. (1997), who developed the longer version, too. High correlations obtained between scores on the QMI and the direct practice of imagery had been demonstrated repeatedly in different experimental settings, and the psychometric properties are well documented. For example, test criteria of the short version were tested in different experimental settings: the internal consistence (Sheehan, 1967; Westcott and Rosenstock, 1976), the stability over time (Sheehan, 1967; Sutherland et al., 1987; Westcott and Rosenstock, 1976), the predictivness of imagery-related criteria (Hatakeyama, 1984; Sheehan and McConkey, 1982; Sutherland et al., 1987), and the correlation with other scales measuring the imagery ability (Kihlstrom et al., 1991; Morris and Gale, 1974; Rehm, 1973; Rossi and Fingeret, 1977). As a conclusion, the QMI can be used as an instrument for imagery research.

2.2.4 Cognitive-perceptual tests

In order to assess if perceptual and cognitive skills influence the vividness of mental imagery and the predisposition towards hallucinations, we added several tests. As a measure of perceptual and cognitive skills we used three subscales of the LPS (Leistungsprüfsystem or "General Performance Test" [Horn, 1962]; view table 2.2). The LPS is a standardized, valid and highly reliable (total test-retest reliability = .69) test battery for fourteen different cognitive skills, which

are related to Thurstone's primary mental abilities (Thurstone, 1938). Thurstone developed an instrument to test the ability, which is called *perceptual speed of closure*. This ability is related to "quick thinking" and consists of the ability to a total picture from incomplete or ambiguous material. Furthermore, the test asks for the ability to grasp and unify a complex situation. We assessed subscales 10 (flexibility of closure), 11 (object-based speed of closure) and 12 (verbal-based speed of closure).

Subscale 10 consists of 40 complex geometrical forms. One of five predefined target figures is embedded and thus "hidden" within these forms. This target figure has to be detected. The test is limited to 3 minutes. The flexibility of closure is related to the construct of *field dependence* of Witkin (1954; r tt = .69).

Subscale 11 requires fast object recognition. Participants are asked to recognize 40 sketches of common objects (e.g. car, apple, house) with portions of them erased. The test is limited to 1 minute. Participants have to recognize and name the respective objects. The performance in this test depends on the extent of the speed of access to visual memory representations.

Subscale 12 demands fast recognition of 40 visually degraded words. Each word contains one false letter, which has to be identified and crossed out. All participants have 2 minutes to complete subscale 12. Figure 2.1 shows examples of the subscales.

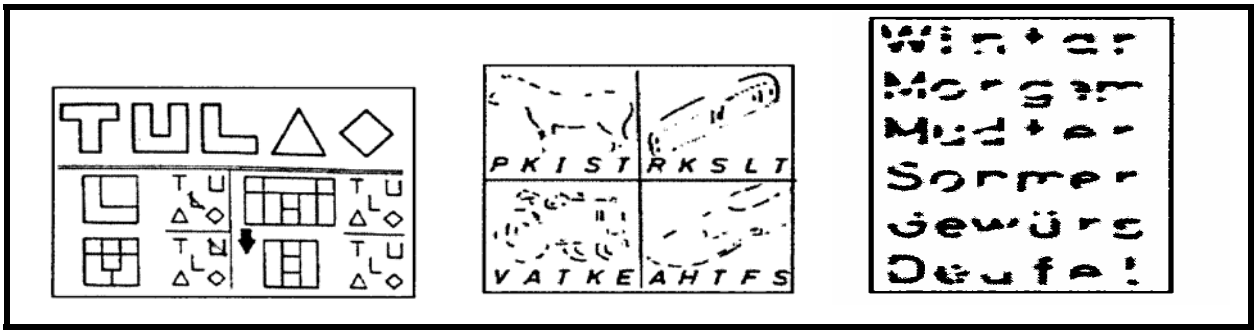


Figure 2.1: *Examples of subscale 10, 11 and 12 (from left to right).*

2.2.5 Psychometric assessments

Measurements of verbal intelligence (MWT [Mehrfachwortschatz-Test or "Multiple Choice Word Comprehension Test"]; Lehrl, 1989) and of psychomotor speed (TMT [Trail-making Test]; Reitan, 1979) were included in the test battery.

The MWT is a widely used German test that assesses crystallized intelligence, operationalized as semantic knowledge (Horn and Cattell, 1966). Horn and Cattell (1966) distinguish between two main parts of the intelligence, the *fluid* and the *crystalline intelligence*. The construct fluid intelligence means elementary/simple knowledge about new and unknown situations. This part of the human intelligence is known to be genetically determined and physiologically mediated. In contrast, crystalline intelligence is related to problem-solving abilities. Crystalline intelligence increases with age and experience, whereas fluid intelligence

decreases during the aging (Eysenck, 1985). The test is developed on a primitive plan: words known from colloquial speech, science and/or from literature are hidden under four not-known/nonsense-words (e.g. NOSE-VOSE-GLOST-NAIS-NUM). The test consists of 37 rows with 5 words in each row. The difficulty increases during the rows in the way, that the first row is the easiest; the last is the most difficult one. Subjects were asked to identify and to mark well-known words in each row. The subjects therefore have to recognize well-known words as well as differentiate unknown words from known words.

We used the MWT, form B, in our experiment. The average correlation coefficient between the MWT (median score from 32 investigations) and other global intelligence tests is relatively high at r = .72, which makes the MWT a good screening instrument for general intelligence and the premorbid intelligence level of the patients. The MWT can be considered as the German equivalent to the Spot-the-Word test (Baddeley et al., 1993). The MWT doesn't ask for fluid intelligence, therefore it can be used in the absence of psychiatric and mental illness. The test is stable over time and age. There exist norms for age group 20 to 64 years. The MWT-B cannot differentiate above an IQ of 125.

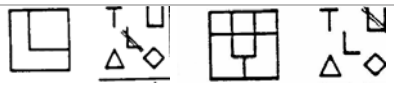
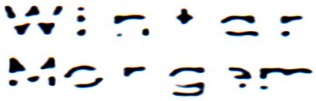
The TMT is a short, non-verbal test to examine cognitive speed (Reitan, 1979). The task material consists of two numerical matrices. The first (A) comprises numbers between 1 and 25 in a random order. Participants were asked to connect these numbers in ascending order by drawing lines between them as quickly as possible. The second (B) consists of numbers and letters. They were asked to connect numbers and letters in alternation (1-A-2-B-3-C….). The mean speed in seconds for each matrix is calculated as the score for psychomotor speed. We used only TMT trail A for the further analysis to assess cognitive speed as TMT B loads on frontal/ executive functioning (Reitan, 1979). The assessment is often used as a non-speech related instrument, which could be done quickly and with a huge age group. The test was administered individually, but could be done as well in a group of subjects. The connection between reaction time and intelligence were retested in several investigations. There are norms for each matrix including T, standard, C- and IQ-scores as well as percentile values for different age groups.

2.2.6 Clinical Scales

Controls and relatives completed the German version of the Schizotypy Personality Questionnaire (SPQ; Raine, 1991; Klein et al., 1997) in order to provide a measure of schizotypal personality traits. The SPQ is a 74 item self-report questionnaire that was designed to measure schizotypal traits in non-clinical populations. Items address unusual perceptual and cognitive experiences and participants are required to indicate (by marking true or false) whether an item is appropriate to their own situation. True-scores are summed to obtain a total score with a higher total score implying the presence of more schizotypal experiences.

The original SPQ factor structure comprised nine factors (Raine, 1991), which were referred to as RI (ideas of reference / paranoid ideation), MD (odd beliefs or magical thinking), UW (unusual perceptual experiences), EV (odd or excentric behaviour), US (odd speech), AW (suspiciousness), EA (constricted affect), KEF (no close friends) and SA (excessive social anxiety). Cronbach`s alpha for the total score is sufficient (.88). However, Klein et al. (1997) suggested a two-factor model of the SPQ, where the original factors were reconfigured into a cognitive-perceptual factor and an interpersonal factor. The current study used the two-factor SPQ model because a factor analysis of the data yielded two main factors in all groups, which conformed to the two-factor model of (Klein et al., 1997).

Table 2.2: *Overview of the behavioral tests and measurements.*

Questionnaire	Item example	Construct	Reliability
QMI	"Imaging the mewing of a cat".	Vividness of mental imagery	rα = .97
RHS	„In my daydreams I can hear the sound of a tune as clearly as if I were actually listening to it".	Tendency towards hallucinations	rα = .83
LPS 10*		Flexibility of closure	rtt = .69
LPS 11		Object-based speed of closure	rtt = .71
LPS 12		Verbal-based speed of closure	rtt = .88
MWT	NOSE-VOSE-GLOST-NAIS-NUM	Crystallized intelligence	rtt = .87
TMT	A: 1-2-3-4-5-.....25 B: 1-A-2-B-3.....13	Psychomotor speed	rtt = .95
SPQ	„Do normal objects appear sometimes exceptionally big or small? "	Schizotypy tendency	rα = .88
SKID I + II	"Have you ever experienced unusual occurrences ?"	psychiatric (I), personality (II) disorders	
PANSS	"Are you hearing voices ?"	Psychotic symptoms	
Edinburgh Inventory	"Which hand do you use to write your name ?"	Handedness	

Notes: QMI = Betts' questionnaire of mental imagery; RHS = Revised hallucination scale; LPS = General performance test; * : An example of the LPS 10: one of five predefined target figures on the right side is embedded and thus "hidden" in the left side forms, and has to be detected. The test is limited to 3 minutes. MWT = multiple choice word comprehension test; TMT = trail-making test; SPQ = Schizotypy Personality Questionnaire; SKID = Strukturiertes Klinisches Interview Psychischer Störungen; PANSS = Positive and Negative Syndrom Scale.

2.2.7 Individual psychopathology

An additional diagnostic session was conducted within one week after the first assessment. All patients` individual psychopathological profiles were assessed by means of a structured clinical interview (PANSS; Kay et al., 1987). The PANSS consists of a 30 to 40 minute formalized interview from which each of 30 symptoms are rated along a 7-point scale. The scale yields separate scores along nine clinical dimensions, including scales for a positive syndrome, a negative syndrome, depression, composite index and general psychopathology. Several studies have found the instrument to be highly reliable (e.g. Kay et al., 1994). The interview was conducted by V. Oertel and A. Rotarska-Jagiela. The inter-rater reliability of the PANSS interview, which was examined by comparing the ratings of V. Oertel and A. Rotarska-Jagiela, revealed a mean of .89.

In addition, we used a semi-structured interview based on the "Aggernea criteria" (Aggernea, 1972), called *"questions about hallucinations" (QAH),* to assess the psychopathology (contents, phenomenology, severity and occurrence) of hallucinations. This interview was done only with the patients who experienced hallucinations during their illness. Table 2.3 shows the sociodemographic and clinical variables of the patients (for further details about the QAH view chapter 2.4).

The assessment also included clinical ratings on the Structured Clinical Interview for DSM-IV-TR (Strukturiertes Klinisches Interview Psychischer Störungen [SKID I (psychiatric disorders) and SKID II (personality disorders); Wittchen et al., 1996]). First-degree relatives and controls were screened with the SKID I and SKID II in order to exclude axis I or II disorder, which resulted in the exclusion of 17 of the 61 relatives.

Each patient's medication status was monitored. All patients except two of them were on medication at the time of testing. 43 of the 52 patients were treated with atypical medication at the time of testing, three of them were medicated with typical medication, the rest with typical and atypical medication (n = 4) at the time of testing.

The clinical interviewers had at least 2 years expertise with conducting clinical interviews, received a training session for the assessments of individual psychopathology and were tested in a pilot project to ensure satisfactory inter-rater reliabilities (r = .79).

Table 2.3: *Sociodemographic and clinical variables of the schizophrenia patient group.*

Number of SZ patients	52
History of Hallucinations	• 8 no history of hallucinations • 43 history of hallucinations: • 20 acute auditory hallucinations during the week of testing, 8 during current episode, but not in week of testing, 15 hallucinations in an earlier episode • 1 not specified
Age of Onset	26.17 (8.78)
Years of Illness	12.65 (8.08)

SZ patients	number
Medication	43 atypical, 3 typical, 4 atypical and typical, 2 without any medication
Global symptomatology (PANSS [N=46]; points [SD])	Pos. 15.54 (5.79), neg. 16.35 (5.73), gen. 32.57 (10.25), sum 64.48 (18.61)

Notes: Pos = summary of positive symptom items; Neg = summary of negative symptom items; Gen = summary of general symptom items.

2.3 Statistical analysis

All data were analyzed with the S*tatistical Package for Social Sciences (SPSS)*, Version 11.5.
We divided the control group into two groups based on their total SPQ score (percentile values). The performances of patients, control groups and relatives on the different questionnaires and tests were compared, and group differences were tested for statistical significance using analyses of variance (ANOVAs; corrected for multiple comparisons). For all analyses Scheffé post-hoc analyses was computed to identify the sources of differences in performance: SZ patients vs. low-schizotypy group (CLS), SZ patients vs. high-schizotypy group (CHS), SZ patients vs. first-degree relatives (R), CLS vs. CHS, CLS group vs. R, CHS group vs. R group.

In addition, forty-six SZ patients were willing to participate in the individual psychopathology interview of the PANSS (view table 2.3 for individual's psychopathological profile). We correlated PANSS scores with those of the questionnaires.

2.4 Results

The control group (n = 92) was divided into two groups, based on the percentile values of their score on the SPQ (Raine, 1991; median = 8; mean score: 10.74 [9.88]; range = 0 - 45). The percentile values divided the observations into four groups of equal size. We took the extreme groups (top and bottom quarter) with the percentile values of the 25^{th} and 75^{th} percentile. The highest group (75^{th}) was defined as the "high-schizotypy" group (CHS: n= 24; mean age: 31.42 [11.64]; 16 women, 8 men; mean SPQ: 24.50 [7.25]), whereas the bottom quarter (percentile value: 25^{th}) was defined as the "low-schizotypy" group (CLS: n = 24; mean age: 32.89 [8.46]; 11 women, 13 men; mean SPQ: 1.57 [1.14]). The mean score of the high-schizotypy group is comparable to those found by normative studies (Raine et al., 1991). These control groups did not differ significantly in the demographic variables of parental education, age and in the cognitive abilities, except for years of education.

2.4.1 Reliability analysis

We computed internal consistency measures (Cronbach`s alpha: α) on the QMI, the RHS and the PANSS. The total alpha (α_t) coefficient of the QMI was .98 which conforms to the consistency score found in the literature (α = .97; view table 2.1). The internal consistency measures of the

RHS resulted in a higher score than found by the original authors (α_t = .88; compared to α = .83 in Morrison et al., 2002a). A high score was also obtained for the PANSS (α = .91 [only the patient group]).

2.4.2 Questions about Hallucinations (QAH)

In order to assess the experience and content of the hallucinations better, we developed a semi-structured interview based on Aggernea (1972). The patients were asked about potential history, duration, last onset of hallucinations and the sensory modality of their experienced hallucinations. After that, a list of questions regarding the content and the form of appearance of the hallucinations was given to the patients (for the list of questions view the appendix D). The encoding is the following: 0 = uncertain, 1 = no, 2 = yes. In the third category, 0 = uncertain, 1 = first word, 2 = second word. The scores of the three categories will then be summed up as a total score for hallucinations. The questions along the following categories:

- **1st Category (form of appearance):** clear as voices, gender, feed-back, recognizing of the voices, names, special knowledge, prognosing of the future, appearance in dreams, heard from other persons, seen as real.
- **2st Category (content):** voices express emotions, voices include doubts, self-protection, command voices, the appearance of hallucinations is typical/non-typical of the individual, physical manifestations, appearance in multiple sensory systems/modalities, extend in time/space, explanation of the voices regarding religion, voices are seen as real, because they appear repeatedly.
- **3st Category (Aggernea criteria [Aggernea, 1972]):** sensation vs. ideation, relevance for the behaviour, publicness, objectivity, existence, non-voluntary, independence.

20 out of the 52 patients participated in the interview of "questions about hallucinations" (mean age: 35.83 [8.78]; range: 21-48). The mean time span of the last hallucination (last day of the hallucination period) was 21.89 [30.61] days before the measurement (range: 0-90). The duration of the patients' illness had a range between 5-25 years. The current patient group scored in the first category with 14.95 (1.98) points (out of 20 points). That means, approximately 15 out of 20 of the patients know the form of appearance of their hallucinations. For example, 52.6 % of the patients believe that the voices appear as clear as spoken voices. In addition, the majority of the patients could detect a gender and think that the voices have special knowledge about them (73.7 %). The majority of our patient sample thought that their voices were real (57.9 %). In contrast, only 26.3 % believed that the voices can prognosticate the future, and only 15.8 % of the voices appeared in dreams.

The next category regarding the content of the voices, the patients reach a mean score of 14.78 (2.16) out of possible 20 points, which indicate that most of the individuals from the

sample have ideas about the content of the voices, e.g. 73.7 % think that the content of the voices is emotional, 57.9 % believe that the voices reach also in body symptoms and 63.2 % say that the voices appear on multi sensory systems at the same time. In contrast, only 36.8 % of the sample believes in religion themes which the voices are talking about and only 26.3 % of the voices appear as commanding voices. At least, in the Aggernea's criteria our sample reaches a mean score of 12.94 (7.08) and the total score of the QAH is 41.06 (4.56) (range: 34-50). In sum, the interview was developed in order to compare future samples with this investigation and to be more precise regarding the individual psychopathology of SZ patients. Probably it would be nice to conduct norms for the QAH, which could be a future project. Table 2.4 shows the results of the QAH in the SZ patient group.

Table 2.4: *Results of the QAH in our patient sample (n = 20).*

CATEGORY / ITEM	**MEAN SCORE / %**	**RANGE**
Duration (seconds)		5-25 (12)
Last hallucination (days)	21.90 (30.61%)	0-90 (5)
1. CATEGORY (form of appearance)	14.95 (1.98%)	12-18 (15)
1a. Clear as spoken voices	1 = 9 (47.4%), 2 = 10 (52.6%)	
1b. Gender	1 = 6 (31.6%), 2 = 13 (68.4%)	
1c. Feedback	1 = 9 (47.4 %), 2 = 10 (52.6%)	
1d. Recognition	1 = 5 (26.3 %), 2 = 14 (73.7 %)	
1e. Given names	1 = 8 (42.1%), 2 = 11 (57.9%)	
1f. Knowledge	1 = 5 (26.3%), 2 = 14 (73.7 %)	
1g. Future	1 = 14 (73.7%), 2 = 5 (26.3 %)	
1h. Dreams	1 = 16 (84.4%), 2 = 3 (15.8%)	
1i. Others	1 = 15 (78.9%), 2 = 4 (21.1%)	
1j. Real	1 = 8 (42.1%), 2 = 11 (57.9%)	
2. CATEGORY (content)	14.78 (2.16%)	12-20 (14.5)
2a. Emotions	1 = 5 (26.3%), 2 = 14 (73.7 %)	
2b. Doubts	1 = 8 (42.1%), 2 = 11 (57.9%)	
2c. Selfs	1 = 12 (63.2 %), 2 = 7 (36.8%)	
2d. Commands	1 =12 (63.2 %), 2 = 7 (36.8 %)	

2e. Others	1 = 14 (73.7 %), 2 = 5 (26.3 %)	
2f. Body symptoms	1 = 8 (42.1%), 2 = 11 (57.9%)	
2g. Multi-symptoms	1= 7 (36.8%), 2 = 12 (63.2 %)	
2h. Extends	1 = 14 (73.7 %), 2 = 4 (21.1%)	
2i. Religion	1 = 11 (57.9%), 2 = 7 (36.8%)	
3. CATEGORY (Aggernea's criteria)	12.94 (7.07)	7-40 (Median: 11.5)
TOTAL SCORE QAH	41.059 (4.56)	34-50 (Median: 41)

When we used the data for a multiple-correlation analysis (see table 2.5) the results revealed a significant correlation between the time point of the last appearance of hallucinations and the predisposition towards hallucinations (RHS; r = -.47, p = .04) which indicates that a small time period between the last hallucination and the measurement indicates a higher predisposition towards hallucinations.

Table 2.5: *Correlation analysis between the last appearance of hallucinations and the RHS.*

	QMI	RHS	Last hallu-cination (in days)	Form of appea-rance	Content	Aggerneas criteria	Total score
QMI	1	-.37 (.25)	.31 (.23)	.11 (.68)	-.19 (.47)	-.09 (.72)	-.02 (.93)
RHS	-.37 (.25)	1	-.47 (.04*)	.34 (.15)	-.09 (.73)	.02 (.95)	.21 (.41)
Last hallu-cination (in days)	.31 (.23)	-.47 (.42*)	1	-.20 (.40)	-.31 (.21)	-.24 (.34)	-.34 (.19)
Form of appearance	.11 (.68)	.34 (.15)	-.21 (.40)	1	.28 (.26)	.04 (.87)	.66 (.01**)
Content	-.19 (.47)	-.09 (.73)	-.31 (.21)	.28 (.26)	1	.23 (.37)	.76 (.00**)
Aggernea's criteria	-.09 (.72)	.01 (.95)	-.24 (.34)	.04 (.87)	.23 (.37)	1	.69 (.00**)
Total score	-.02 (.93)	.21 (.41)	-.34 (.18)	.66 (.01**)	.76 (.00**)	.69 (.00**)	1

2.4.3 Interview of the first-degree relatives

All relatives were asked in detail about the history of illness of the SZ patients to ensure the diagnosis and to know more about the prodromal phase and the premorbid adaptation. Some of the questions were created by our research team, others are taken from the Prämorbide Anpassungsskala (Raine, 1997). The questions in detail are listed in appendix D. All relatives (n= 44) who participated in our experiment were interviewed and rated about these questions

regarding their schizophrenic relatives. Each positive answer got one point. The relatives were asked to remember the childhood and youth of their affected relatives. The following categories were asked:

- Problems with speech, sight and hearing
- Hyperactivity, distractability
- Unconfident, anxious, temperamental
- Any other problems (psychopathological)
- Confirm an appointment by a psychiatrist, neurologist or psychologist or stay in a hospital
- Any stressful events (divorce of the parents, movement, financial problems, unemployment of the parents, illness of the parents or the siblings)

Table 2.6 *Interview about the premorbid adaptation of the patients (n = 44).*

Speech, sight, hearing	8
Hyperactivity, distractibility	24
Unconfident, anxious, temperamental	31
Any other problems	Social withdrawal: 29 Capacity problems (school, university): 34
Appointment by a psychiatrist, hospital....	19
Stressful live events	Divorce: 7, movement: 2 Financial problems: 5 Unemployment: 9 Illness: 24

2.4.4 Statistical group comparisons

In order to assess group differences in the vividness of mental imagery, tendency towards hallucinations and the performance on perceptual tasks across the schizophrenia spectrum, we computed five ANOVAs with group as independent factor and QMI, RHS, LPS 10, LPS 11 and LPS 12 as dependent variables.

The calculated mean of the QMI differed significantly between the groups ($F(3,137) = 19.13$, $p < .01$). The same analysis done with the different sensory modalities separately yielded comparable results. The scores of the RHS ($F(3, 137) = 21.72$, $p < .01$) and the LPS subscales (LPS 10: $F(3, 137) = 18.31$, $p < .01$; LPS 11: $F(3, 137) = 8.91$, $p < .01$; LPS 12: $F(3, 137) = 12.98$, $p < .01$) showed significant group differences. Including sex as a covariate did not affect the significant group differences for QMI and RHS.

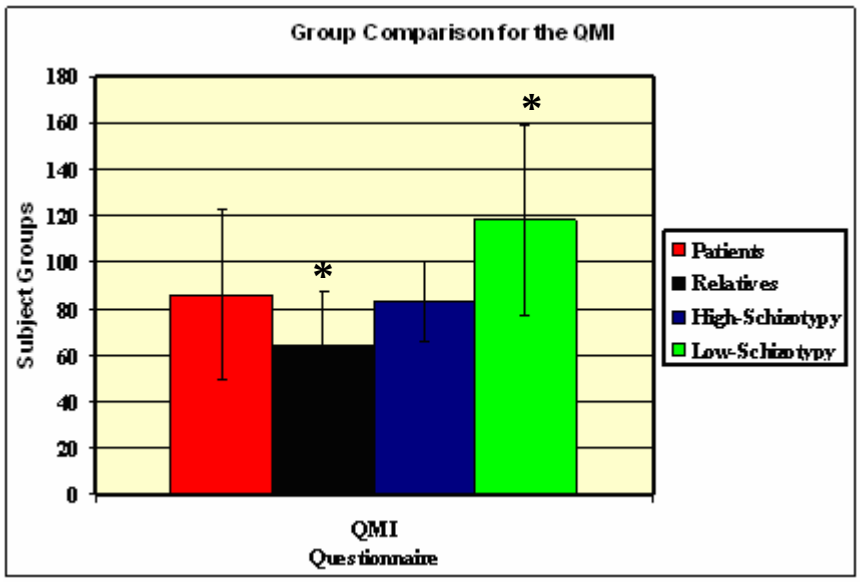
2.4.5 Post-hoc analyses

Post-hoc contrast analyses for the QMI showed that the mean value was lowest (i.e., imagery was most vivid) for the relatives and highest for the low-schizotypy group, with patients and

high-schizotypy group in between (mean scores [SD]: SZ patients: 86.81 [37.95], R: 64.48 [23.45], CHS: 73.85 [17.54], CLS: 125.79 [46.06], $p < .01$). No significant differences of QMI scores were found between the patients and high schizotypy controls (see Figure 2.2). Conversely, the differences between patients and relatives ($p = .03$) and between patients and low-schizotypy controls ($p < .01$) were significant (see table 2.7).

Scheffé post-hoc analyses for the RHS showed significant differences only between the patients and all the other groups (SZ patients: 34.81 [10.11], R: 26.48 [4.99], CHS: 29.95 [3.52], CLS: 24.61 [2.57], $p < .01$) indicating that patients scored significantly higher on the hallucination questionnaire (see table 2.7).

The group means for the cognitive-perceptual test battery (LPS) followed a linear increase across the schizophrenia spectrum, in the order of patients, relatives, high-schizotypy and low-schizotypy controls (see figure 2.2). Overall, patients performed worse than the control groups on all three subscales of the LPS, including flexibility of closure (LPS 10) (SZ patients: 20.19 [8.27], CHS: 26.65 [5.30], CLS: 28.86 [5.30], $p < .01$; R: 23.95 [5.48], n.s.), object-based speed of closure (LPS 11) (SZ patients: 17.46 [4.50], CHS: 20.30 [3.34], CLS: 20.50 [1.95], $p < .04$; R: 18.62 [2.99], n.s.), and verbal-based speed of closure (LPS 12) (SZ patients: 19.65 [7.44], R: 24.11 [4.07], CHS: 23.75 [4.23], CLS: 25.46 [2.38], $p < .05$). The performance of the patients and the first-degree relatives differed only in the subscale 12, verbal-based speed of closure ($p < .01$).



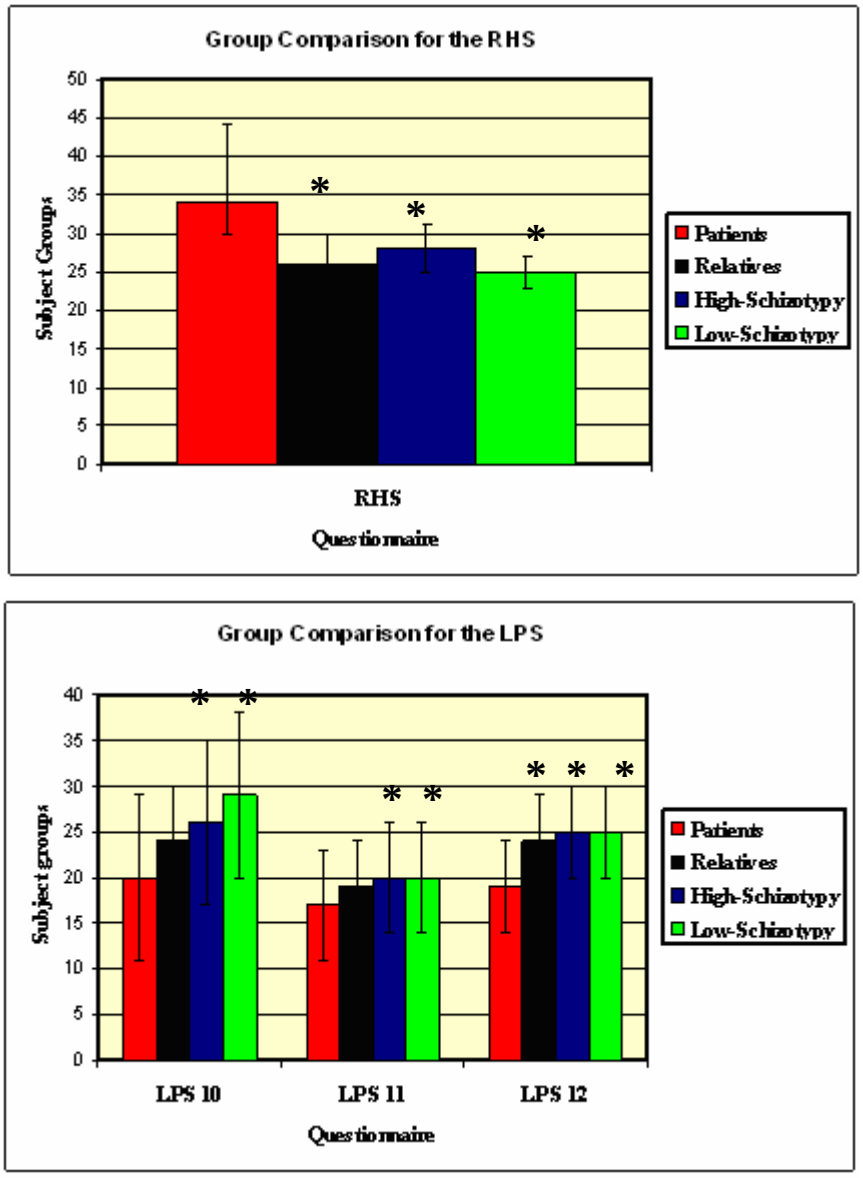


Figure 2.2: *Group comparison for the QMI, the RHS and the LPS subscales for all groups. The graph is divided into three separate segments: Figure 2.2a shows the group comparison for the QMI, Figure 2.2b shows the group comparison for the RHS, figure 2.2c shows the group comparison for the LPS. The x-axis represents the questionnaires, the y-axis represents the subject groups. The asterisks mark significant results ($p \leq .05$) for the patient group in comparison with other groups.*

Table 2.7: *Post-hoc contrast analysis of main tests.*

Test	Main effect	Post-hoc contrast analysis
QMI	F (3,137) = 19.48, p < .01	SZ Patients / R: .03 SZ Patients / CHS: n.s. SZ Patients / CLS : < .01
RHS	F (3, 137) = 17.57, p < .01	SZ P / all other groups: < .01
LPS 10	F (3, 137) = 10.04, p < .01	SZ Patients / R : n.s. SZ Patients / CHS : < .01 SZ P / CLS : < .01
LPS 11	F (3, 137) = 5.55, p = .01	SZ Patients / R : n.s. SZ Patients / CHS : < .04 SZ P / CLS : < .04

LPS 12	F (3, 137) = 8.21, p = .01	SZ Patients / R : < .01 SZ Patients / CHS: < .05 SZ Patients / CLS : < .05

2.4.6 Group comparisons of schizotypy

To assess group differences on the schizotypy measures, we computed three ANOVAs with the groups (without the patient group) as independent factor and the total score of the SPQ, the cognitive-perceptual and the interpersonal SPQ factors as dependent variables. The results showed significant differences across all included groups in the total score of the SPQ (F (2, 74) = 69.18, p < .01), in the cognitive-perceptual factor (F (2, 74) = 85.60, p < .01) and in the interpersonal factor (F (2, 74) = 17.11, p < .01).

Scheffé post-hoc analysis resulted in significant differences between all subject groups in the SPQ score as well as in the two sub-factors (respective p-values: < .01). Only the comparison between the relatives and the high-schizotypy group in the interpersonal factor had in a non-significant result (p = .26). As expected, the low-schizotypy group scored significantly lower on the SPQ than the high-schizotypy group and the relatives (CLS: 1.57 [1.14], R: 12.07 [6.38], CHS: 24.50 [7.25]). Interestingly, the high-schizotypy control group scored significantly higher on the SPQ than the relatives. On the cognitive-perceptual factor, the high-schizotypy group scored much higher than the relatives (CLS: 1.95 [1.58], R: 6.45 [4.03], CHS: 19.05 [5.52]. Conversely, the difference between relatives and high-schizotypy controls on the interpersonal factor was not significant (CLS: 0.42 [0.61], CHS: 4.11 [1.97], R: 5.10 [3.76]; see figure 2.3).

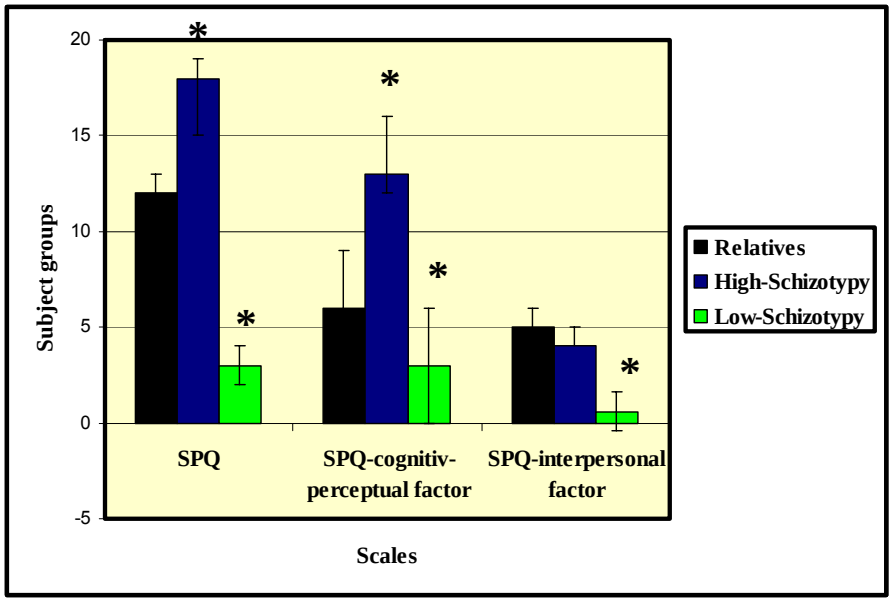


Figure 2.3: *Group comparison of the SPQ scores for the schizotypy groups and the relative group (without the patient group). The x-axis represents the questionnaires data, the y-axis represents the subject groups. The asterisks mark significant results (p ≤ .05) for the relative group in comparison with other groups. Note: SPQ = schizotypal personality scale.*

2.4.7 Correlation analyses

No significant correlation was found between the QMI and the RHS in any subject group (Bonferroni corrected $p > .2$). The correlation between the RHS and the seven subscales of the QMI representing the different sensory modalities of mental imagery was not significant either (Bonferroni corrected $p > .1$).

The correlation analysis between the QMI, the RHS and the psychometric tests measured with three subscales of the LPS, the MWT-B and the TMT revealed no significant results, which suggests that the performance on cognitive tests is independent from the vividness of mental imagery and the predisposition towards hallucinations in patients, first-degree relatives and controls with a low schizotypy score.

No significant correlation was found between the TMT (trail A) and the MWT-B in any subject group. Crystallized intelligence (MWT-B) and psychomotor speed (TMT trail A) thus seem to be independent factors.

The correlation analyses between the subscales of the LPS and the MWT-B, and the subscales of the LPS and the TMT (trail A) revealed several significant correlations, which could be due to the speed factor of the tests. Specifically, the correlation analysis between the MWT-B and the subscales of the LPS revealed significant results only between the MWT-B and the LPS 10 in the low-schizotypy group ($r = 0\ .47$, $p = .02$), and between the MWT-B and the LPS 11 ($r = .39$; $p = .01$) and the LPS 12 in SZ patients ($r = .48$; $p < .01$). We also observed significant correlations between subscales of the LPS and the trail-making test (TMT-LPS 10: SZ patients, R: $p < .01$; TMT-LPS 11: SZ patients, R: $p < .04$; TMT- LPS 12: SZ patients, CLS: $p < .04$; all other correlations: n.s.). All other correlations were non-significant. Poor patient performance on cognitive speed type-tests may be related to medication effects.

A correlation analysis across the whole control group yielded a significant correlation between the MWT-B and the predisposition towards hallucinations ($r = .29$, $p < .01$). In addition, the correlation analysis between the MWT-B and the LPS revealed a significant correlation between the MWT-B and the subscale 12 of the LPS ($r = .29$, $p < .01$). However, all other results showed no significant correlation between the QMI, the RHS and the psychometric tests. In sum, the correlation analysis computed across the whole control group and separately for the split control group revealed largely comparable results.

2.4.8 Analysis of individual psychopathology

The correlation analysis of the QMI and the PANSS ratings (n=46) revealed no significant results. This finding applies, beside overall QMI, to the subscales of auditory and other sensory modalities. The vividness of mental imagery thus seems to be independent of psychopathological variables. Likewise, no correlation was found between the predisposition towards hallucinations

(RHS), the imagery vividness in the auditory modality (QMI, subscale: auditory) and the degree of positive symptoms.

2.5 Young SZ patients: a pilot study

In addition to the experiment described above, a group of young SZ patients, inpatients of the Department of child and young adolescent Psychiatry, Psychosomatic and Psychotherapy, Johann Wolfgang Goethe-University, Frankfurt/Main, Germany or the Department of Psychiatry, Städtische Kliniken Höchst, Germany, were investigated with the test battery. This analysis was done in addition to the original planned experiment.

2.5.1 Participants

The young SZ patients were diagnosed with paranoid schizophrenia according to DSM-IV criteria (295.30; American Psychiatric Association, 1994). Current psychopathology was assessed with the Positive and Negative Syndrome Scale ([PANSS], Kay et al., 1987).

The group of young and adolescent patients included 12 participants (7 boys, 5 girls; mean age: 16.42 [1.83]). 6 of the participants are high-school students, 2 of them are working and 3 of them are unemployed (for socio-demographic data, see table 2.8). All SZ patients have their diagnosis since one year or more years. The control group was matched for handedness (all right handed), age, gender and parental education with the young SZ patient group.

Exclusion criteria for control subjects were any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV, left-handedness, current drug-abuse, neurological pathology and inability to provide informed consent. All subjects were provided with a complete description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethical board of the Medical School of the Johann Wolfgang Goethe University, Frankfurt/Main, Germany.

Table 2.8 *Socio-demographic data of the young SZ patient group.*

	Young SZ patients	**Healthy control group**
Number	12	12
Age	16.42 (1.83)	16.33 (2.01)
Gender	7 men, 5 women	6 men, 6 women
Education level	6 =students 2 = workers 3 = unemployed	8 = students 3 = workers 1 = unemployed
Parental Education	father: 16.42 (3.40) mother: 14.42 (3.28)	father: 15.33 (2.60) mother: 13.00 (3.07)
Age of onset	15.58 (1.44)	
PANSS	pos.: 13.53 (3.54), neg.: 08.54 (4.53), gen.: 31.51 (2.52), sum.: 65.54 (10.81)	
Medication	5 = atypical neuroleptics, 7 = atypical and typical neuroleptics	
Handedness	right	right

2.5.2 Assessment Procedures

The pilot study of the young SZ patients included two major parts: First, a brief interview was conducted to collect information about age, gender, handedness, education level, socioeconomic status of the parents (rated in years of education of mother and father) and history of psychiatric problems. Any psychiatric disorder in the family history was proved and written down. In addition, parts of the *Prämorbide Anpassungsskala* (PAS; Raine, 1997) were used to ask for problems and potential genetic and environmental influence of the illness.

Prior to the assessment of psychopathology, written informed consent was obtained from all participants. The interview included questions to the young SZ patients about their experience with hallucinations. All patients with a history of hallucinations (10 of 12 patients) were interviewed and rated about the content of their hallucinations (after Aggernea, 1972). Further information concerning the medication, the diagnosis, the onset of the illness, the duration of the inpatient status during this episode was written down.

Further, a test battery was put in use 2 questionnaires and 3 cognitive tests. The individual psychopathology was assessed by the PANSS (Kay et al., 1987). The test sessions were done with each subject individually and were divided dependent on attention and memory function of the individuals. The first session normally lasted approximately 1 hour, including the individual interview and the tests and questionnaires. In a second session (in the same week as the other session), we assessed the psychopathological questionnaires, which lasted between one and two hours.

The investigation was done in the laboratory of the hospital of Psychiatry, Psychosomatic and Psychotherapy, Johann Wolfgang Goethe-University, Frankfurt, Germany. Testing sessions took place in a quiet, well-lit room, so that objective testing conditions were ensured. The test sessions were done by Viola Oertel and Dr. Martin Holtmann (with the help of Anna Rotarska-Jagiela).

2.5.3 Materials and Methods

The test battery consisted of a measurement of the predisposition towards hallucinations (RHS; Revised Hallucination Scale; Morrison et al., 2002a and b) and a measurement of the vividness of mental imagery (QMI; Betts' Questionnaire of Mental Imagery; Sheehan, 1967). The cognitive ability of the participants was assessed using an objective measurement of perceptual and cognitive skills (three subscales of the LPS; Leistungsprüfsystem or "General Performance Test"; Horn, 1962). In addition, measures of verbal intelligence (MWT [Mehrfachwortschatz test or "Multiple Choice Word Comprehension Test"]; rtt = .87; Lehrl, 1989) and of psychomotor speed (TMT [Trail-making Test]; Reitan, 1979) were included as covariates in the test battery. For a further description of the tests and questionnaires view chapter 2.2..

Individual psychopathological profiles of the young patient group were set up by means of a structured clinical interview (PANSS; Kay et al., 1987) and the *"questions about hallucinations" (QAH)* to assess the psychopathology (contents, phenomenology, severity and occurrence) of hallucinations. This interview was done only with the patients who experienced hallucinations during their illness. All patients were on medication at the time of testing (8 = atypical, 4 = atypical and typical).

The control group was assessed with the German version of the Schizotypy Personality Questionnaire (SPQ; Klein et al., 1997; Raine, 1991) in order to provide a measure of schizotypal personality traits. Controls were screened with the SKID I and SKID II in order to exclude axis I or II disorder.

2.5.4 Statistical analysis

All data were analyzed with the S*tatistical Package for Social Sciences (SPSS)*, Version 11.5. The performances of patients and controls on the different questionnaires and tests were compared, and group differences were tested for statistical significance using analyses of variance (ANOVAs; corrected for multiple comparisons). For all analyses Scheffé post-hoc analysis were computed to identify where the potential differences in the performance lie: Patients vs. controls. To statistically control for potential differences in crystallized intelligence and psychomotor speed between young schizophrenia patients and normal controls, analyses of covariance (ANCOVA) were computed using the TMT and the MWT-B as covariates.

All hypotheses were examined with two-tailed tests. The significance level for rejecting the null hypothesis was .05 (marked *) respectively .01 (marked **).

We computed bivariate correlation analyses between our main questionnaires, the QMI and the RHS, in order to assess a possible influence of the degree of hallucinatory tendency towards increased mental imagery. We computed bivariate correlation analysis between the QMI, the RHS, the LPS subscales and the cognitive tests including the TMT and the MWT-B in order to assess a possible influence of cognitive abilities on vividness of mental imagery and tendency towards hallucinations. We used Bonferroni-correction for p-values because of the large number of correlation tests. In all cases, differences were deemed significant at a (corrected) p-value of 0.05, unless stated otherwise.

All young SZ patients were willing to participate in the individual psychopathology interview of the PANSS. Scores were correlated with those of the questionnaires.

2.5.5 Results of the young SZ patient group

2.5.5.1 Statistical group comparisons and analysis of variance

In order to assess group differences in the vividness of mental imagery, tendency towards hallucinations and the performance on perceptual tasks across the schizophrenia spectrum, we computed univariate ANOVAs with the groups as independent factor and QMI, RHS, LPS 10, LPS

11, LPS 12 as dependent variables (see table 2.9). The calculated means of the QMI differed significantly between the groups ($F (1, 23) = 28.68$, $p < .01$). Post-hoc contrast analyses (Scheffé) for the vividness of mental imagery (QMI) showed that the mean value was significantly lower for the SZ patients than for the control group (mean scores [SD]: patients: 74.58 (13.02), controls: 112.42 (20.72)). The results of the control group were comparable to those found in the other experiment (controls: 118.53 [43.65] and lower than the adult SZ patients (86.81 [37.95]).

Likewise, the scores for the tendency towards hallucinations (RHS) ($F (1, 23) = 18.03$, $p < .01$) also showed significant group differences. Scheffé post-hoc analyses showed significant differences between the patients and the controls (patients: 33.75 (8.18); controls: 23.08 (2.97). Likewise, the scores are comparable to those found in the adult study (adult patients: 34.15 [10.11], low-schizotypy: 25.29 [4.19], $p < .01$) indicating that patients scored significantly higher on the hallucination questionnaire.

Table 2.9: *Results of the ANOVAs for the young SZ patient group.*

	Young SZ patients	**Controls**	**Statistical values**
QMI	74.58 (13.02)	112.42 (20.72)	$F (1, 23) = 28.68$, $p < .01$
RHS	33.75 (8.18)	23.08 (2.97)	$F (1, 23) = 18.03$, $p < .01$
LPS 10	19.67 (3.31)	26.83 (4.47)	$F (1, 23) = 19.92$, $p < .01$
LPS 11	20.08 (3.68)	25.83 (5.29)	$F (1, 23) = 9.56$, $p < .01$
LPS 12	19.00 (3.57)	27.67 (6.14)	$F (1, 23) = 17.87$, $p < .01$

Overall, patients performed significantly worse compared with the control groups on all three subscales of the LPS (LPS 10: $F (1, 23) = 19.92$, $p < .01$; LPS 11: $F (1, 23) = 9.56$, $p < .01$; LPS 12: $F (1, 23) = 17.87$, $p < .01$), including flexibility of closure (LPS 10) (young patients: 19.67 [3.31], controls: 26.83 [4.47]), object-based speed of closure (LPS 11) (young patients: 20.08 [3.68], controls: 25.83 [5.29] and verbal-based speed of closure (LPS 12) (young patients: 19.00 [3.57], controls: 27.67 [6.14]). Likewise, the results were similar to those found in the adult group (LPS 10: adult patients: 20.19 [8.27], low-schizotypy controls: 29.32 [5.30]; LPS 11: adult patients: 17.46 [4.50], low-schizotypy: 20.45 [1.95]; LPS 12: adult patients: 19.65 [7.44], low-schizotypy: 25.32 [2.31]).

In order to check for possible confounding effects of group differences in general crystallized intelligence, psychomotor speed and social desirability behaviour on QMI, RHS and the LPS subscales, two independent ANCOVAs with MWT-B and TMT as covariates were computed (see table 2.10). These analyses revealed that the differences between groups in QMI, RHS and LPS remained significant after statistically controlling for variance explained by the group differences in general crystallized intelligence (MWT-B) and psychomotor speed (TMT).

Table 2.10: *ANCOVA with QMI, RHS; LPS 10, LPS 11, LPS 12 as dependent variables and MWT-B, TMT as covariates.*

Test	MWT-B			TMT		
	F	df	p	F	df	P
QMI	13.83	1, 23	<.01	14.07	1, 23	<.01
RHS	10.27	1, 23	<.01	8.74	1, 23	<.01
LPS 10	9.55	1,23	<.01	10.61	1,23	<.01
LPS 11	8.15	1,23	<.01	4.64	1,23	.02
LPS 12	8.56	1,23	<.01	10.57	1,23	<.01

Notes: ANCOVA = analysis of covariance; df = degrees of freedom
**Footnote: Lower values on QMI denote more vivid imagery, e.g. a negative correlation between the QMI and the MWT-B means that the vividness of imagery is higher if the MWT-B is higher.*

2.5.5.2 Correlation analyses

No significant correlation (Pearson correlation) was found between the QMI* and the RHS in any subject group (patients: r = -.01, p = .99; controls: -.06, p = .59). The correlation between the RHS and the seven subscales of the QMI representing the different sensory modalities of mental imagery was not significant either (all p values > .05).

The correlation analysis between the QMI, the RHS and the psychometric tests measured with three subscales of the LPS, the MWT-B and the TMT revealed no significant results, which leads to the assumption that the performance on cognitive tests is independent from the vividness of mental imagery (QMI) and the predisposition towards hallucinations (RHS) in young SZ patient and controls.

No significant correlation was found between the TMT and the MWT-B in any subject group. Crystallized intelligence (MWT-B) and psychomotor speed (TMT) thus seem to be independent factors. The correlation analysis between the MWT-B and the subscales of the LPS revealed no significant results between the MWT-B and the LPS subscales in any group. We also observed no significant result in the correlation analyses between subscales of the LPS and the trail-making test.

2.5.5.3 Analysis of individual psychopathology

In order to assess the influence of individual psychopathology on the main results, we computed additional bivariate correlation analyses including the PANSS ratings (n=12), the QMI and the RHS. The correlation analysis of the QMI and the PANSS revealed no significant results (r > .06). The vividness of mental imagery thus seems to be independent of psychopathological variables. Likewise, the results showed no significant correlation between the RHS and the PANSS ratings (r > .42). Only the correlation analysis between the total score of the PANSS and the positive subscale (r = .64, p = .03), the hallucination score (r = .74, p < .01) and the general psychopathology (r = .62, p = .03) revealed significant results.

2.6 Discussion

The present study investigated perceptual and cognitive abilities along the schizophrenia continuum and their relationship with predisposition towards hallucinations measured with a battery of tests and questionnaires. We compared questionnaire and test scores among groups that spanned the theoretically proposed schizophrenia continuum (Bentall, 1990): SZ patients, first-degree relatives of patients, healthy controls with high schizotypy and low schizotypy. The study extends a previous report (Sack et al., 2005) about enhanced vividness of mental imagery in schizophrenia with additional subject groups and measures.

Our main finding was a clear enhancement in the vividness of mental imagery in both the SZ patients and the first-degree relatives, but also in high-schizotypy compared with low-schizotypy controls. The results of the vividness of mental imagery measurement were comparable across sensory modalities. This result implies that mental imagery vividness is not modality-specific.

The vividness of mental imagery and the tendency towards hallucinations were independent of each other, and independent of cognitive abilities in all of the subject groups. Moreover, for the patient group imagery vividness was also independent of the current psychopathology. These results replicate our previous study (Sack et al., 2005), and further support our hypothesis of an independence of the vividness of mental imagery and hallucination experiences. Our data thus suggest that, in contrast to previous studies (Barrett, 1993; Morrison et al., 2002a), hallucination frequency and severity are not directly related to imagery vividness (Brett and Starker, 1977; Starker and Jolin, 1982; Sack et al., 2005), but that schizophrenia patients as a group are characterized by increased imagery vividness. Moreover, high-schizotypy controls scored equal to the patients, and relatives showed even higher vividness of mental imagery than the other groups. It therefore seems that vivid imagery is a trait rather than a state marker, and may be related to the genetic liability to develop schizophrenia. The finding that the unaffected relatives reported high imagery ability could indicate that imagery ability may be an endophenotype of schizophrenia in the sense proposed by Gottesman (1991), who suggested that genetic factors appear to be important in the development of schizophrenia, but are not sufficient to explain the entire pattern of occurrence. Somewhat unexpectedly, unaffected family-members reported the highest vividness of mental imagery. This finding will need to be confirmed before firm conclusions can be drawn. One possible explanation could be that the trait of high imagery vividness may be attenuated in patients compared to relatives as a consequence of neuroleptic treatment or cognitive impairment. Schizophrenia patients also had a poorer performance in the speed related tests (e.g. TMT) which could be due to medication effects.

As expected, the schizotypy measure of the non-clinical population in our sample resulted in a continuum of high-schizotypy participants, relatives and low-schizotypy controls, which is in accord with the concept of a "continuum" of schizophrenia symptoms (Bentall, 1990; Raine,

1991; Van Os, 2003). Higher schizotypy levels in first degree relatives of patients with schizophrenia, compared with levels in the general population have been described before (Appels et al., 2004). In contrast, Claridge et al. (1983) found that relatives of schizophrenia patients showed defensive responding in specific contexts. However, it is interesting to note that the two factor model of the SPQ (Klein et al., 1997) yielded a much higher cognitive-perceptual deficit in the high-schizotypy group, whereas the deficits in the relative group lay more in the interpersonal range. This notion is in line with a previous study (Calkins, 2004) that investigated first-degree relatives and controls with the SPQ and found that social-interpersonal deficits best differentiated relatives from controls. However, Kremen et al. (1998) found that relatives of schizophrenia patients had higher scores on the cognitive-perceptual factor of the SPQ than controls.

Our study shows that the SZ patients, the relatives and the high-schizotypy controls judge their vividness of imagery higher than the low-schizotypy controls. At the same time, mental imagery does not seem to be associated with experience of or predisposition to hallucinations along the schizophrenia spectrum. Therefore, imagery vividness may be a factor that characterizes both schizophrenia and the non-clinical manifestation of its traits, schizotaxia (Meehl, 1962; Tsuang et al., 2000). Family studies revealed that first-degree relatives of schizophrenia patients have neurocognitive dysfunctions (Kendler et al., 1995) comparable to those found in studies on schizotypy (Meehl, 1990). The substantial impact of the subgrouping of controls according to their SPQ scores in the present study highlights the importance of testing control groups in schizophrenia studies for the confounding effect of schizotypy. The conflicting results in the literature regarding more vivid imagery in patients than in controls may be due to the selection of participants. Possibly, the studies that did not find any difference between patients and controls selected a more schizotypal control group whereas the studies that did find a higher vividness of mental imagery in schizophrenia selected a group comparable to our low-schizotypy group (Brett and Starker, 1977; Starker and Jolin, 1982; Morrison et al., 2002a,b; Sack et al., 2005). Furthermore, high-risk studies are of great importance because they lead to a better understanding of the mechanisms involved in the inherited vulnerability for the disorder. Further studies on markers of schizophrenia should involve high-risk individuals and a schizotypy measurement for the control group, possibly in combination with investigations of brain structural and functional changes along the schizophrenia spectrum.

Some authors proposed higher vividness of mental imagery as a "risk-factor". However, Claridge (1984) and Goulding (2005) stated that some aspects of schizotypy might be well-adapted personality traits. In addition, Weinstein and Graves (2002) have linked psychotic-like thinking and creativity, and others (Siever and Davis, 2004; Mohr et al., 2005) consider positive schizotypal features as not necessarily related to psychopathology. It is possible that the vividness of mental imagery represents a positive aspect of the cognitive and perceptual traits

associated with the schizophrenia spectrum but further longitudinal studies of the relation between imagery vividness and cognitive and clinical outcome, ideally including prodromal patients, will be necessary to confirm this.

In our study we used a self-report instrument to measure individual mental imagery vividness. It has been suggested that self-report measures of mental imagery may not tap into the cognitive processes that underlie imagery manipulation (Richardson et al., 1999; Lequerica et al., 2002). Nevertheless, the QMI shows a high reliability in both patient and control groups, in this study as well as others (e.g., Merckelbach and van de Ven, 2001; Sack et al., 2005). In addition, the pilot study of young SZ patients showed the same pattern of results as indicated for adult patient groups.

In conclusion, vividness of mental imagery may be an independent symptom and a trait marker for the schizophrenia spectrum. The independence of vividness of mental imagery and hallucinations seems to be stable across the investigated subject groups. We propose that imagery proneness exists independently of the actual presence of hallucinations. This result is confirmed by the other findings of our study, in that relatives and high-schizotypy individuals had relatively high imagery ability without experiencing clinical hallucinations. This finding of a potential perceptual trait of schizophrenia in the relative groups complements previous findings of subtle cognitive and neurobiological changes in high-risk groups.

Part II: EXTERNAL CONTROL ORIENTATION IN THE SCHIZOPHRENIA SPECTRUM

Parts of this chapter are based on a manuscript, which is in preparation for publishing: Oertel, V., Rotarska-Jagiela, A., Van de Ven, V., Haenschel, C., Grube, M., Knöchel, C., Stangier, U., Maurer, K., Linden, D.E.J. (for further details view list of contributing authors). External control orientation in the schizophrenia spectrum.

Abstract

Patients with schizophrenia have been suggested to exhibit an external control orientation. However, the relationship between the locus of control to perceptual and paranoid symptoms has not been conclusively investigated. Information is also missing on the control orientation in high-risk groups.

The present study investigated the control orientation (Rotter, 1966), using the Competence and Control Beliefs Scale (CCBS; Krampen, 1991) and the psychopathological status (Eppendorf Schizophrenia Inventory [ESI]) in four different subject groups: 52 patients with schizophrenia (SZ patients), 44 unaffected first-degree relatives (R) and two healthy control groups, divided into high-schizotypy (CHS; n = 24) and low-schizotypy (CLS; n = 24) participants. The differentiation of the control groups was based on their values on the Schizotypal Personality Questionnaire (SPQ; Raine, 1991).

Overall**,** the performance on the Competence and Controls Beliefs Scale (Krampen, 1991) and the measurement of the dysfunctional status suggested a continuum between low-schizotypy controls, followed by first-degree relatives, high-schizotypy controls and SZ patients. Patients showed the most external control orientation.

In conclusion, high-risk groups suffer from dysfunctional signs without developing the illness. The external control orientation may be a trait marker, which is independent of other psychopathological symptoms, like predisposition towards hallucinations. In contrast, the dysfunctional status seems to be directly connected to the severity of psychopathological symptoms.

2.7 Introduction

Why do people have vivid sensory experience coupled with the firm believe in their outer reality in the absence of external stimulation? This question can be approached from a neurobiological and a psychological point of view, and ultimately these two approaches will have to be unified. Neurophysiological and neuroimaging studies have suggested that hallucinations may represent misattributed and vividly perceived inner speech, based on the coactivation of language production and reception areas (Dierks et al., 1999; Hubl et al. 2004). Long before functional imaging of hallucinations became available, theoretical models had suggested that hallucinations are misinterpreted mental images derived from internal sources of information (Horowitz, 1975;

Cahill and Frith, 1996). Images would be incorrectly evaluated as arising from external sources and appear as intrusions in the perceptual process. Some authors have suggested that hallucinations and vivid imagery are related (Mintz and Alpert, 1972). Others could not find a link between the appearance of hallucinations and mental imagery (Brett and Starker, 1977; Starker and Jolin, 1982). Sack et al. (2005) further promoted the vividness of mental imagery as an independent marker of schizophrenia.

Altered evaluation of mental images is by no means the only psychological mechanism that has been adduced to explain hallucinations. Baker and Morrison (1998) suggest that auditory hallucinations are experienced when mental events are misattributed to an external source. They examined attributional bias in patients experiencing auditory hallucinations and the role of metacognitive beliefs. Their study indicated that patients with hallucinations exhibited the predicted bias towards misattributing internal events to an external source, as measured by ratings of internality of responses in a word association task. These results offer considerable support to cognitive bias models of auditory hallucinations, particularly those that implicate metacognition or response bias (Bentall and Slade, 1985a).

Blakemore et al. (2000) tested the hypothesis that certain psychotic symptoms are due to a defect in self-monitoring. They investigated the ability of groups of psychiatric patients (SZ, bipolar) to differentiate perceptually between self-produced and externally produced tactile stimuli. The results showed that normal control subjects and psychiatric patients with neither auditory hallucinations nor passivity phenomena experienced self-produced stimuli as less intense, tickly and pleasant than identical, externally produced tactile stimuli. In contrast, psychiatric patients who experienced hallucinations or passivity did not show these differences between touch by self and others. Blakemore et al. (2000) concluded that auditory hallucinations and passivity experience are associated with an abnormality in the self-monitoring mechanism that normally allows us to distinguish self-produced from externally produced sensations. Stirling et al. (1998) examined Frith's (Frith and Dolan, 1998) hypothesis that schizophrenia is related to patients' failure to monitor effectively their own willed intentions, actions and thoughts. They examined a group of SZ patients with a battery of neuropsychological and cognitive tests, which included four putative measures of self-monitoring. Patients had greater difficulty than a control group with each of the self-monitoring tests, which were relatively independent of neuropsychological or general cognitive function.

All these suggested changes in source monitoring and response bias may be related to one unitary function, termed locus of control (Rotter, 1966). Loci of control are expressions of subjective intellectual evaluations about the outcome of action. Locus of Control refers to an individual's perception about the underlying main causes of events in his/her life or the belief that the person's destiny is caused by himself or by external forces. A locus of control orientation is a belief about whether the outcomes of our actions are contingent on what we do (internal control

orientation) or on events outside our personal control (external control orientation) (Zimbardo, 1985). Links between locus of control and mental health have been proposed by Frenkel et al. (1995), for example. Kaney and Bentall (1989) found that psychotic patients, compared to healthy controls, made excessively external attributions for negative events and internal attributions for positive events. Lasar (1997) found a constant external control orientation in SZ patients, which was correlated to the individual psychopathology.

Bandura (1982) suggested that judgements of personal efficacy and outcome expectancies affect behaviour. Rosenbaum et al. (1985) proposed that these two sets of beliefs characterize the thought structures of subjects, in that paranoid patients expected outcomes to be under the control of powerful others. Bandura (1982) further suggested that the perception of the effect of behavior on the environment is relevant to the locus of control construct. If a person is convinced that she cannot successfully produce the desired behaviour, while others can do this, she may be prone to developing paranoid ideas. The locus of control is seen as a general personal disposition (Lefcourt, 1980), although some authors propose a dependence of the construct of situational factors (Bandura, 1982). A related concept is Seligman's (1975) model of learned helplessness, which has mainly been linked to depression. .

One aim of this study was to examine whether locus of control abnormalities can explain positive symptoms in schizophrenia. Because of the increasing evidence that symptoms of schizophrenia are quantitative rather than qualitative phenomena (Van Os, 2003), we also assessed participants from the schizophrenia spectrum (relatives and high schizotypy controls) for abnormal locus of control. We hypothesised that patients would be characterised by an external control orientation, and controls by an internal control orientation. We further assumed the relatives and high-schizotypy participants to score between the extreme ends of SZ patients and controls. Furthermore, we suggest that the dysfunctional status (measured with the Eppendorf Schizophrenia Inventory [ESI]) and the predisposition to hallucinations connect with each other across the schizophrenia spectrum. This would reflect the cognitive deficit model of hallucinations.

We specifically investigated the relationship between locus of control and hallucinations, delusions and thought disorder. A link between locus of control and delusions may be motivated with Mahler's (1974) observation that delusions are often rational interpretations of the abnormal perceptions of psychotic patients. However, delusions may be independent of sensory abnormality (e.g. Williams, 1964) and such an abnormality would not be sufficient to generate delusional beliefs (Kaney and Bentall, 1989). Further metacognitive dispositions, such as locus of control, would therefore have to be present for paranoia to develop. We expected a correlation particularly between paranoid symptoms and the control by powerful others.

2.8 Methods

For details regarding the subject groups, see chapter 2.2.1 and table 2.1.

2.8.1 Procedure

Three clinical self-report scales (the German Version of the Competence and Control Beliefs Scale (CCBS), Krampen, 1991]; Eppendorf Schizophrenia Inventory [ESI], Maß et al., 2000; Schizotypy Personal Questionnaire [SPQ], Raine, 1991; Revised Hallucination Scale [RHS], Morrison et al., 2002) were assessed in all groups, except for the SPQ, which was examined in all but the patient group. The whole assessment lasted approximately 1 ½ hour.

An additional diagnostic session including SKID I (psychiatric disorders) and SKID II (personality disorders) ("Strukturiertes Klinisches Interview Psychischer Störungen für DSM IV"; Wittchen et al. 1996) and psychopathology ratings (Positive and Negative Syndrome Scale [PANSS]; Kay et al., 1987) was conducted separately from the first assessment and lasted approximately 2 hours. The time span between the first and the second measurement was not more than 1 week.

2.8.2 Clinical scales

The Competence and Control Beliefs Scale (CCBS; Krampen, 1991) is a 32-item self-report measure that was designed to evaluate the behaviour regarding the control and power orientation (locus of control; Rotter, 1966). The subjects are asked to rate their control orientation on a 6-point Likert Scale (ranging from 1 [very false] to 6 [very true]). It consists of seven scales including primary, secondary and tertiary scales. The four primary scales include the following: internality (I), powerful others external control orientation (P), chance control orientation (C), self-concept of own abilities (SK), whereas the two secondary scales (sum of the primary scales) included: self-efficacy (SKI) and general externality in control orientation (PC). The tertiary scale is called the "general internality vs. externality in control orientation" (SKI PC) and is the subtraction of the secondary scales. Each primary scale consists of 8 items. The scales of the CCBS can be divided (after the concept of Krampen, 1991) in external (P, C, PC) and internal control orientation scales (SK, I, SKI, SKI PC) on their extreme ends. In the further analysis we will follow the concept of Krampen (1991) and present the results of the scales based on a split of internal and external control orientation by simply adding the scores of the internal and external control orientation scales. A high score in the external control orientation means a more external control orientated way of acting, whereas a high score on an internal control orientation scale means a more internal-orientated way of acting.

A high score on the P scale indicates an increased tendency towards a loss of control over one's life. The person has a tendency to be socially dependent on powerful others. The interpersonal, social aspect is important here. In addition, a person with a high score on the C-

scale has a tendency to a chance control orientation, that means, the person thinks, only fate is responsible for all events in his life. A person who scores high on the PC scale believes in external causes outside of his own control when something happens to him.

A high score on the SK scale indicates a self-confidence way of acting. In contrast, a low score on these scale leads to a tendency to have fewer possibilities to act and a bad self-confidence. A person, who scores high on the I scale, will behave in an internal-oriented way, which means, the person thinks, that events which happen in his personal environment and his life, are controlled by him. In contrast, a low score on this subscale implies a feeling of low control over one's life. A high score on the SKI scale indicates a high self-confidence and an confident way of acting, whereas a person who scores low on this scale would probably behave in a passive and non-acting manner. A high score on the SKI PC scale indicates an increased predisposition towards an external control versus an internal control orientation. The CCBS scales have been found to be reliable measures with a reasonably stable trait (Cronbach`s alpha: 0.65-0.90; Krampen, 1991).

The German Version of the Eppendorf Schizophrenia Inventory (ESI; Maß, 2000) was used for self-assessment of disturbances in several cognitive and perceptual areas. The ESI is an instrument which is used also in non-psychiatric subgroups to assess psychopathology. The instrument accounts for possible psychosis or psychosis-related symptoms, for a dysfunctional status, e.g. for the subjective cognitive dysfunction, which lead to the illness of schizophrenia. The ESI consists of 40 items, based on 4 subscales: attention and speed impairment (AS ["I am not able to perceive exactly and clearly what happens around me"]), ideas of reference (IR ["I think that my thoughts are controlled"]), auditory uncertainty (AU ["sometimes my hearing is very fine, then I can hear normal noises exceptionally loud and clear"]), deviant perception (DP ["sometimes parts of my body seem to be smaller as in reality"]) and an additional control scale (frankness [FR]). The questions ask for the time period of the last 4 weeks. The ESI is seen as a sufficiently reliable and valid instrument (Cronbach's alpha: 0.60-0.90; Maß, 2000) which is widely used in research, diagnostic procedures, first-episode and high-risk population.

Controls and relatives completed the German version of the Schizotypy Personality Questionnaire (Klein et al., 1997; Raine, 1991) in order to provide a measurement of schizotypal personality traits. The SPQ is a 74 item self-report measure that was designed to measure schizotypal traits in non-clinical populations. Items address unusual perceptual and cognitive experiences and subjects are required to indicate whether an item is appropriate to their own situation, by marking true or false. True-scores are summed to obtain a total score. A high total score implies the presence of more schizotypal experiences. The original factor structure of the SPQ comprised nine subscales, which were referred to as RI (ideas of reference / paranoid ideation), MD (odd beliefs or magical thinking), UW (unusual perceptual experiences), EV (odd or excentric behaviour), US (odd speech), AW (suspiciousness), EA (constricted affect), KEF (no

close friends) and SA (excessive social anxiety). Cronbach`s alpha for the total score is sufficient (0.88). However, Klein et al. (1997) suggested a two-factor model of the SPQ, where the original factors were reconfigured into a cognitive-perceptual factor (comprising RI, MD, UW, EV, US and AW) and an interpersonal factor (comprising EA, KEF and SA). The two-factor model is used in the current study because a factor analysis computed on the present data yielded two main factors in all groups, which conforms to the two-factor model of Klein, Andresen and Jahn (1997).

The predisposition towards hallucinations was measured with the RHS (Morrison et al., 2002), which consists of twenty descriptions of hallucinatory experience. Some of the items are related to daydreams while others refer to psychotic experience (see table 2.11 for sample items), and they are rated on a 4-point Likert scale (1 = never; 2 = sometimes; 3 = often; 4 = almost always). A high score on the RHS indicates an increased predisposition towards hallucinations. The RHS does not ask for actual hallucinations but for the lifetime experience with unusual perceptual and psychotic-like experiences.

Table 2.11 *Overview of the behavioral tests and measurements.*

Questionnaire	ITEM EXAMPLE	CONSTRUCT	Reliability
CCBS	"It depends on fate, if I have a lot of friends or not".	Locus of control	rα = .65 - .90
ESI	ESI AS; "I am not able to perceive exactly and clearly what happens around me"	Dysfunctional status	rα = .60 - .90
SPQ	"Do normal objects appear sometimes exceptionally big or small? "	Schizotypy tendency	rα = .88
RHS	"In my daydreams I can hear the sound of a tune as clearly as if I was actually listening to it".	Tendency towards hallucinations	rα = .83

Notes: CCBS = Competence and Control Beliefs Scale; ESI = Eppendorf Schizophrenia Inventory; RHS = Revised Hallucination Scale; SPQ = Personal Schizotypy Questionnaire;

2.8.3 Statistical analysis

We divided the control group into two groups, based on their SPQ score (median split). The performances of SZ patients, control groups and first-degree relatives on the different questionnaires and tests (CCBS, ESI) were compared, and group differences were tested for statistical significance through multi-subject analyses of variance (ANOVA). These analyses were accompanied by Scheffé post-hoc analyses.

In addition, we computed bivariate correlations between the CCBS and the ESI for all subject groups. In all cases, differences were deemed significant at a (corrected) p-value of 0.05, unless stated otherwise.

Forty-six patients were willing to participate in the individual psychopathology interview of the PANSS. There scores were then correlated with the questionnaires. The individual psychopathology of the patients is listed in table 2.3.

2.9 Results

The control group was splitted in the same manner as described in chapter 2.4.

2.9.1 Statistical group comparisons

In the following section we computed ANOVAs with the groups as independent factor and CCBS scales and ESI scales as dependent variables in order to assess group differences in the control orientation and the dysfunctional status, followed by Scheffé post-hoc analysis in order to show where the potential differences were located. We also included ANCOVAs with age, gender and years of education as covariates.

2.9.1.1 ANOVA and post-hoc analysis of the CCBS

The following results follow the split of the CCBS scales into internal (SK, I, SKI, SKI PC) and external (P, C, PC) control orientation scales. To support the grouping of the subscales into internal vs. external control orientation scales, we computed a factor analysis for the different scales, separate for the four different subject groups. The results conform to the model suggested by Krampen (1991). Furthermore, we report only the sum of the internal scales (SKI), the sum of the external scales (PC) and the division of internal minus external scales (SKI PC). The external control orientation (PC: $F [3, 137] = 5.45$, $p < .01$) and the internal control orientation (SKI: $F [3, 137] = 19.94$, $p < .01$) were significantly different. The internal vs. external control orientation scale was significant, either (SKI PC: $F [3, 137] = 13.07$, $p < .01$). The results are listed in table 2.12.

Table 2.12: *Main task effect and post-hoc contrast analysis of the subscales of the CCBS.*

CCBS Subscale	Control orientation	Main effect	Post-hoc contrast analysis
SK	Internal ; primary scale	$F (3, 137) = 49.98$, $p < .01$	SZ patients / all other groups : $p < .01$, R / CLS: .03 all other groups: n.s.
I	Internal ; primary scale	$F (3, 137) = 2.50$, $p = .06$	All p's > .05
SKI	Internal ; secondary scale	$F (3, 137) = 19.94$, $p < .01$	SZ patients / all other groups: $p < .01$ All other groups: n.s.
SKIPC	Internal; tertiary scale	$F (3, 137) = 13.07$, $p < .01$	SZ patients / CLS: $p < .01$ SZ patients / CHS: $p = .04$ SZ patients / R : $p < .01$
P	external; primary scale	$F (3, 137) = 2.85$, $p = .04$	R / CHS: $p = .04$ All other groups: n.s.

CCBS Subscale	Control orientation	Main effect	Post-hoc contrast analysis
C	external ; primary scale	F (3, 137) = 8.24, p < .01	SZ Patients / R : n.s. SZ patients / CHS: n.s. SZ patients / CLS : p < .01 CLS / CHS: p = .02 CLS / R : p = = .01
PC	External ; secondary scale	F (3, 137) = 5.45, p = .01	SZ patients / CLS: p = .03 CLS / CHS: p < .01 All other groups : n.s.

Post-hoc analysis for the internal control orientation scale (SKI) showed that the mean value was lowest for the SZ patients (26.54 [3.48]), followed by the first-degree relatives (32.61 [5.78], the high-schizotypy controls (34.17 [3.05]) and the low-schizotypy controls (35.68 [3.26]). Differences between the SZ patients and all other subject groups were significant (all ps < .01). Likewise, the difference between the first-degree relatives and the low-schizotypy controls was significant (p = .03). The differences between the control groups, first-degree relatives and high-schizotypy controls were all non-significant (p > .05).

As expected, Scheffé post-hoc analysis showed significance between the SZ patients and all other subject groups in the general internality vs. general externality scale (SKI PC) (SZ patients: 5.90 [9.13]; R: 26.84 [17.56]; CHS: 13.10 [11.85]; CLS: 21.02 [9.52]; p < .04).

Post-hoc analyses for the external control orientation scales showed - first of all - in the powerful others control orientation scale (P) a significant group difference between the first-degree relatives and the high-schizotypy controls (p = .04), caused by a higher score in the high-schizotypy controls than in the other groups (SZ patients: 25.27 [5.27]; R (23.77 [5.75]; CHS: 27.04 [6.55]; CLS: 24.50 [4.93], p = .04). All other group differences were non-significant.

Further post-hoc analyses for the general externality scale (PC) resulted in a continuum from the low-schizotypy controls with the lowest score (44.59 [6.69]), to the first-degree relatives (47.84 [11.65]), the SZ patients (49.79 [6.90]) and the high-schizotypy controls with the highest score on this scale (51.69 [9.25]). The difference in the results was significant between the SZ patients and the low-schizotypy group (p = .03) and between the two schizotypy groups (p < .01). Overall, the results showed a continuum with the patients in front for most external / minimal internal control orientation, to the relatives, the high-schizotypy controls and the low-schizotypy controls.

In order to control for possible confounding effects of group differences in gender, age and years of education on the CCBS scales, three independent ANCOVAs with age, gender and years of education as covariates were computed. These analyses revealed after statistically controlling for the variance, which can be explained by the group differences in age, gender and years of education, that the observed differences between the groups in the CCBS scales

remained significant. ANCOVAs showed no influence of the social demographic variables on the group differences in the CCBS scales.

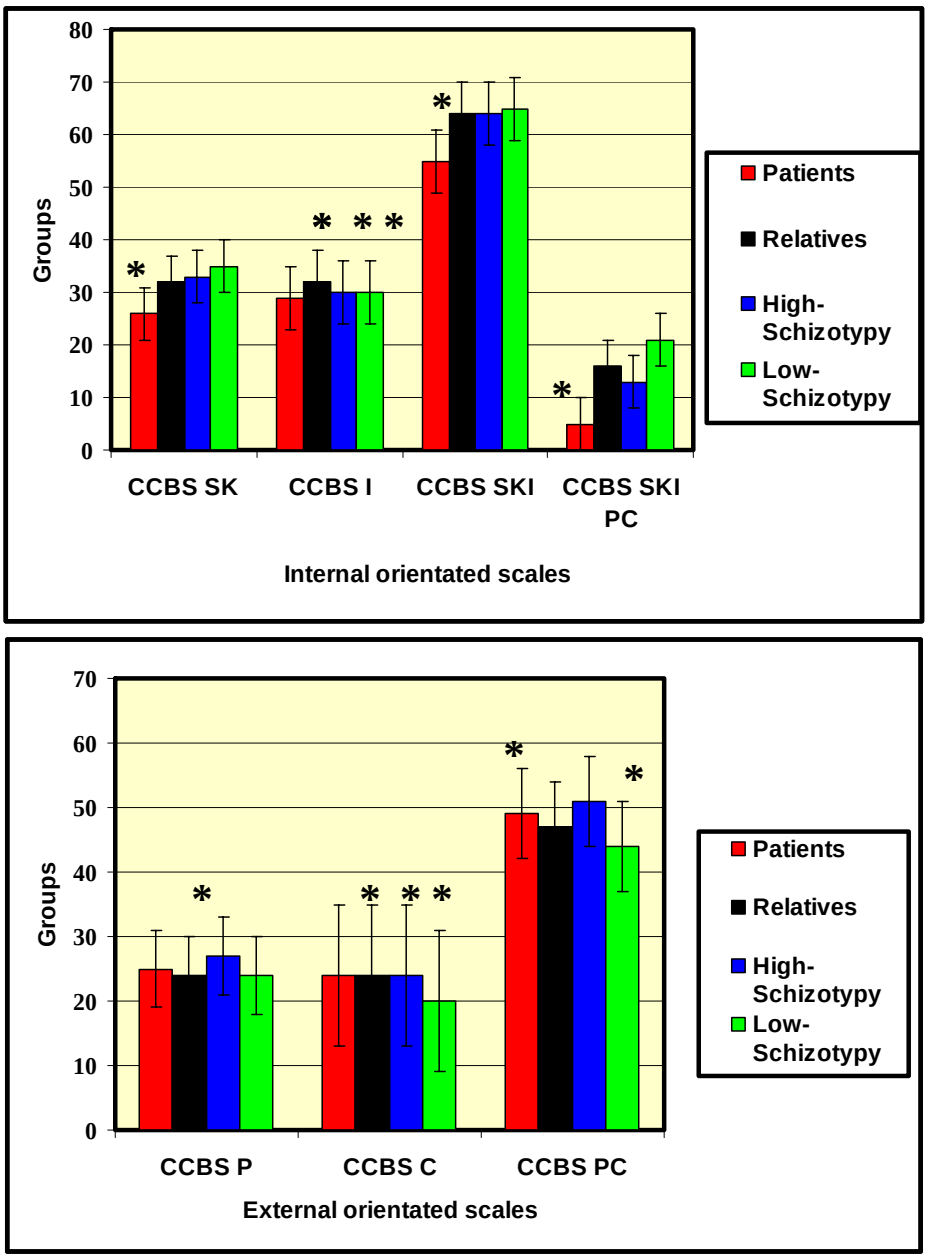


Figure 2.4: *Group comparison for the internal and external orientation scales. The figure shows the scores in all subject groups for the CCBS scales. The graph is divided into two separate segments: Figure 2.4a shows the group comparison for the internal control orientation scales: self-concept of own abilities (CCBS SK), internality (CCBS I), self- confidence (CCBS SKI) general internality vs. externality in control orientation (CCBS SKI-PC). Figure 2.4b shows the group comparison for the external control orientation scales: powerful others control orientation (CCBS P), chance control orientation (CCBS C) and general externality in control orientation (CCBS PC). The x-axis represents the questionnaires, the y-axis represents the subject groups. The asterisks mark significant results ($p \leq .05$) for the patient group in comparison with other groups. Colour code (RGB-system): SZ patients: red, first-degree relatives: black, high-schizotypy controls: blue, low-schizotypy controls: green.*

2.9.2.2 ANOVA and post-hoc analysis of the ESI

As expected, the computed ANOVA for the ESI score revealed a significant group effect ($F [3,137] = 64.39$, $p < .01$; view figure 2.5). Post-hoc analysis showed the SZ patients scoring significantly higher on the ESI (23.81 [12.74]) than the other subject groups ($p < .01$), followed by the high-schizotypy group (8.87 [9.68]), the first-degree relatives group (4.55 [4.20]) and the low-schizotypy group (1.43 [1.55] with the lowest score. The differences between the other groups in the ESI scores were not significant.

The ANOVAs for the subscales showed the same pattern of results with significant group effects (ESI AS: $F [3, 137] = 58.05$; ESI AU: $F [3, 137] = 55.26$; ESI IR: $F [3, 137] = 71.54$; ESI DP: $F [3, 137] = 39.81$; all p's $< .01$). The Scheffé post-hoc contrast analyses showed a continuum with the low-schizotypy group with the lowest scores, followed by the first-degree relatives group, the high-schizotypy controls, and the SZ patients with higher scores on the scales than the others (all p's $< .01$).

ANCOVAs done for the social demographic variables age, gender and years of education showed no confounding effects of group differences in these covariates. The differences between the groups in the ESI scores remained significant after statistically controlling for the variance, which can be explained by the group differences in age, gender and education level.

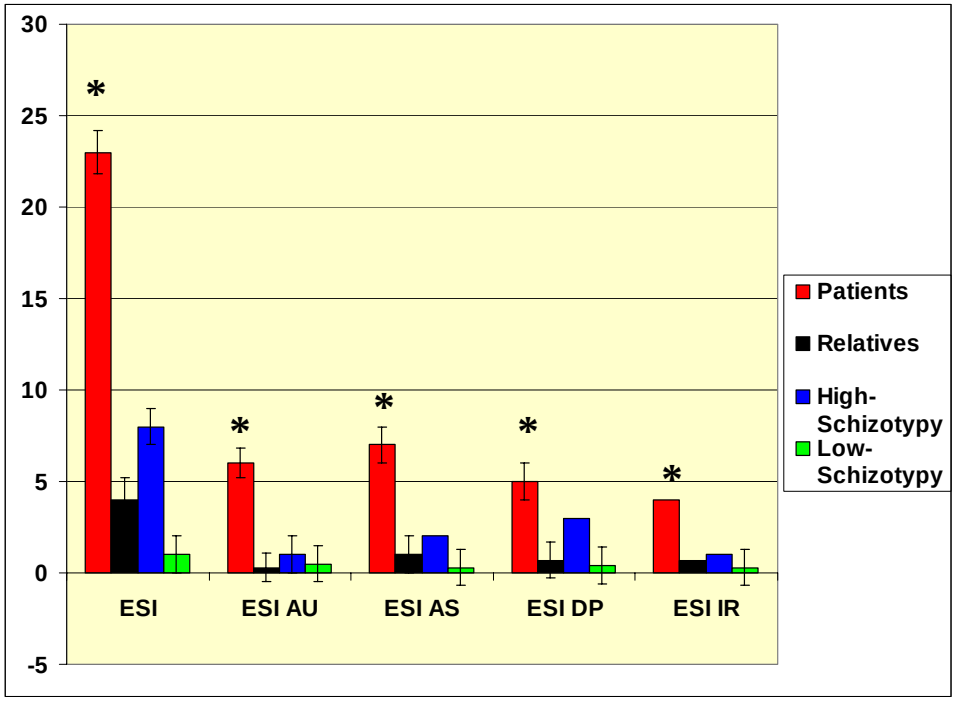


Figure 2.5: *Group comparison of the ESI scales. Task performance in all subject groups for the ESI total score (ESI) and the subscales auditory uncertainty (ESI AU), attention and speed impairment (ESI AS), deviant perception (ESI DP) and ideas of reference (ESI IR). The x-axis represents the scores of the subscales of the questionnaire, the y-axis represents the subject groups. The asterisks mark significant results ($p \leq .05$) for the patient group in comparison with other groups. Colour code (RGB-system): SZ patients: red, first-degree relatives: black, high-schizotypy controls: blue, low-schizotypy controls: green.*

2.9.2 Correlation analyses

We computed bivariate correlation analyses (Pearson Product-Moment correlation; 2-tailed) to test if the control orientation and the dysfunctional status have any connection with each other. In addition we calculated bivariate correlation analyses between the tendency towards hallucinations and the ESI and the CCBS to test whether hallucination tendency has any influence on these scales.

The computed multiple correlation analysis between the scales of the CCBS and the ESI and its subscales revealed no significant results in the different subgroups ($p > .05$) except in the first-degree relatives group (ESI – CCBS SK; ESI – CCBS SKI; ESI – CCBS SKI PC; ESI AS – CCBS C; ESI - ESI IR, all p's $< .04$). No significant correlation was found between the RHS and the CCBS. Correlation analysis between the RHS and the ESI revealed significant results in the SZ patients and in the high-schizotypy control group (SZ patients: $r = .68$, $p = .02$: CHS: $r = .57$, $p = .03$; all other correlations: n.s.; view figure 2.6). The results of the correlation analysis between the ESI subscales and the RHS revealed comparable results. The highest correlation was found between the auditory uncertainty subscale of the ESI and the RHS (SZ patients: $r = .73$, $p < .01$; CHS: $r = .63$, $p < .01$).

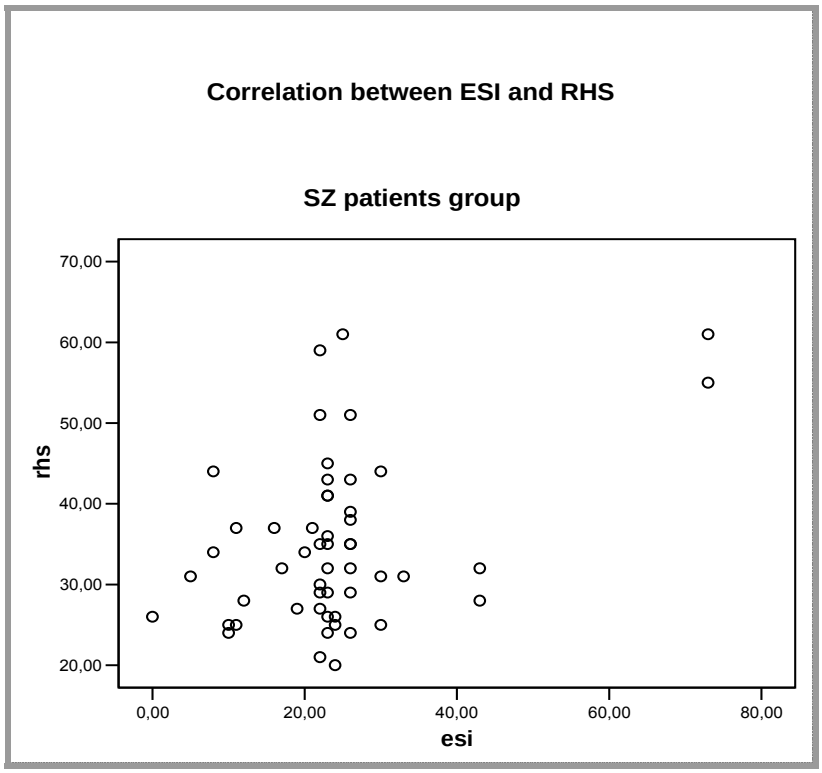


Figure 2.6: *Scatterplot of the correlation analysis between the RHS and the ESI in the a) SZ patients group b) in the high-schizotypy group. The x-axis represents the scores of the ESI, the y-axis represents the scores of the RHS.*

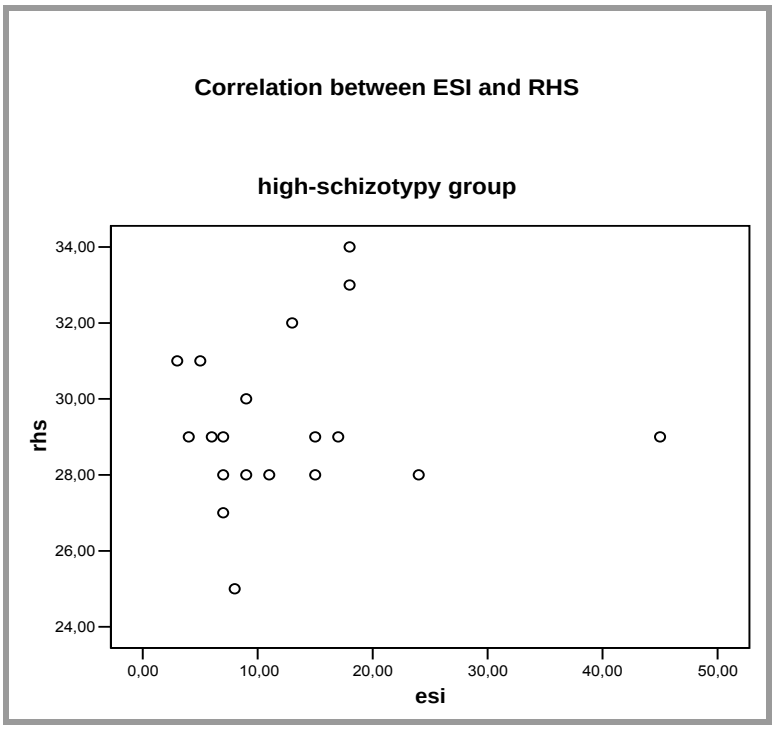


Figure 2.6 continued: *Scatterplot of the correlation analysis between the RHS and the ESI in the a) SZ patients group b) in the high-schizotypy group. The x-axis represents the scores of the ESI, the y-axis represents the scores of the RHS.*

2.9.3 Analysis of individual psychopathology

The correlation analysis for the 46 SZ patients who were rated with the PANSS revealed significant positive correlations between the global symptomatology (PANSS) and the subscales of general psychopathology, global level of positive symptoms, global level of negative symptoms and the hallucination score (all p' s < .03).

However, no significant correlation could be found between the PANSS scales, including all subscales and the items for hallucinations, delusions and thought disorder, and the measurement of the dysfunctional status (ESI). We only observed weak correlations between the ideas of reference subscale (ESI IR) and the hallucination item of the PANSS, and between the deviant perception subscale (ESI DP) and the negative subscale of the PANSS (ESI IR – gen PANSS: r =.36; ESI DP – neg. PANSS: r = -.32; p < .04).

Similarly, we computed correlations between the PANSS scores and the CCBS and its subscales. The correlation between the PANSS general score and the powerful others control orientation (P) (r = .30, p < .05) was significant. With regard to specific symptoms, the delusions item of the PANSS correlated significantly with the powerful others control orientation (P) scale of the CCBS (p = .03) and the general externality in control orientation (PC) scale (p = .04).

2.10 Discussion

We investigated loci of control as cognitive attitudes in patients suffering from chronic schizophrenia and the relationship between loci of control, perceptual and cognitive trait markers of schizophrenia and the predisposition towards hallucinations and delusions. The administered questionnaires were compared between groups that spanned the proposed schizophrenia continuum (Bentall, 1990; van Os, 2003): SZ patients, first-degree relatives of patients, high-schizotypy, and low-schizotypy controls.

Our main finding was a clear difference in the locus of control across the subject groups. The SZ patients had the most external control orientation. They rated their way of acting in a more external, chance orientated way (SKI PC) than all other groups. In addition, the SZ patients were characterised by weaker self-efficacy (SKI) and a tendency towards a higher belief in fate than in own abilities (PC) than the other groups. In contrast, the control subjects showed a more internal control orientation. Overall, the subject groups spanned a continuum of results with the low-schizotypy controls showing the lowest scores on the external control orientation, followed by the first-degree relatives, the high-schizotypy controls and the SZ patients. The results correspond to results in the literature (Frenkel et al., 1995; Kaney and Bentall, 1989) which show an external control orientation of SZ patients. Furthermore, our results confirm those of Nieznanski (2004), who linked self-structure deficits (defined as problems identifying the own person or to perceive the own person as it is in reality), to a source-monitoring task. He found that the basic features of self-structure were significantly related to problems in discriminating self-generated stimuli in the source monitoring task. He concluded that their self-representation tended to falsely attribute items to themselves. Our results are also in line with those of Hooley (1998), who investigated high- and low-critical relatives and found differences in the locus of control. Hooley (1998) defined high-critical relatives as relatives with a low score of expressed emotions. He linked the degree of high expressed emotions and the person's belief to have the ability to control their behaviors. Furthermore, he suggested that high levels of expressed emotions in relatives might be linked to attributions and beliefs about the patient's ability to control his or her symptoms or problem behaviors.

The control orientation seemed to be independent of the predisposition towards hallucinations, but to correlate with delusions. Moreover, the locus of control was independent of subjective cognitive-perceptual deficits, which were found across the schizophrenia spectrum. Beyond this, delusions can possibly be connected to an external locus of control. Delusions can be connected to an external control orientation in the case that during delusion the person projects his or her sensations into the external world.

In addition, the results of the subjective cognitive dysfunction measurement (ESI) confirm the continuum-hypothesis of the SZ patients as scoring highest, followed by the high-schizotypy controls, the first-degree relatives, and the low-schizotypy controls. As expected, the patients

suffering from chronic schizophrenia had a higher dysfunctional status than the other subject groups. Interestingly, first-degree relatives of SZ patients scored lower than the high-schizotypy control group. This could lead to the assumption, that the environment, together with genetic vulnerability, plays an important role in the development of those symptoms. Analyses of the subscales showed the same pattern of results with the low-schizotypy group with the lowest dysfunctional status followed by the first-degree relatives group, the high-schizotypy group and the SZ patients. The findings of the ESI, comparable in all subscales, suggest a general dysfunctional status rather impairments in specific domains in schizophrenia/ schizotypy. The results imply that the dysfunctional status is not domain specific. Nevertheless, the results support the hypothesis of a more general dysfunction of patients, a state, which is comparable to prodromal phase, suffering from chronic schizophrenia as opposed to an individual pool of symptoms.

Nevertheless, these two constructs seem to be totally independent of each other in all groups. The control orientation and the dysfunctional status seemed to be independent markers of schizophrenia or schizophrenia-related symptoms. This lead to the assumption that both groups have a vulnerability, which lead to the development of specific symptoms, like external control orientation and the dysfunctional status independently. The only commonalty lies in the continuum of results in the different subject groups.

In contrast, complete independence was found between the predisposition towards hallucinations (RHS) and the locus of control construct (CCBS). The results give further evidence for the independence of the individual psychopathology (PANSS) and clinical measurements regarding the control orientation (CCBS). Only a higher external control orientation was correlated to a more general psychopathology. This indicates that the external control orientation of the patients is related to a general psychopathological manner, but not to specific symptoms.

As opposed to the control orientation, the dysfunctional status correlated with the individual predisposition towards hallucinations. The dysfunctional status may be directly connected to psychopathological symptoms, especially in the patient and in the high-risk groups. The dysfunctional status should be a clear marker for the development of psychotic symptoms. Nevertheless, high-risk groups suffer from dysfunctional signs without developing the illness. Accordingly, the locus of control may be an independent trait marker of schizophrenia, which is not connected directly to hallucinations, but to general psychopathological symptoms. A direct possible influence of the control orientation on the reality monitoring system, as supposed by Horowitz (1975), Cahill and Frith (1996) and others, which is seen to be connected to hallucination experiences, remained still unresolved. One possible model to explain the lack of correlation between LOC and hallucinations is that external locus of control is a trait marker of the schizophrenia spectrum but that other factors – measured by the ESI like auditory uncertainty, deviant perception – have to be present in addition for hallucinations to arise. Here,

neurobiological studies showed direct connectivity of psychotic symptoms with neurobiological deficits. Dierks et al. (1999) and Hubl et al. (2004) found evidence for the direct influence of psychotic symptoms like hallucinations on the neurophysiological functions.

The observation that the first-degree relatives and the high-schizotypy group showed a deviant pattern of results, compared to healthy controls, lead to the assumption that, beside individuals who suffer from the illness directly, some others like relatives and controls that score high on schizotypy-related symptoms have some impairments and visible signs without suffering from the illness directly. This would lead to the further assumption that the illness schizophrenia is not only genetic but also dependent on environmental factors. The finding that the unaffected relatives reported high external control orientation and dysfunctional status could indicate that those signs may be specific for an endophenotype of schizophrenia in the sense proposed by Gottesman (1991). The continuum of the results confirmed the findings by Oertel et al. (2008), and is in accord with the concept of a "continuum" of schizophrenia symptoms (Bentall, 1990; Raine, 1991; Van Os, 2003). Higher schizotypy levels in first degree relatives of patients with schizophrenia, compared to levels in the general population have been described before (Appels et al., 2004). In addition, Claridge et al. (1983) found that relatives of schizophrenia patients showed defensive responding in specific contexts. Further studies may focus on a catalyst which disrupts the border between mental health and psychiatric illness.

We suggest that an external control orientation is a "risk-factor" for schizophrenia. This risk factor may be seen a personality trait. Claridge (1984) and Goulding (2005) stated that some aspects of schizotypy might be well-adapted personality traits. Weinstein and Graves (2002) (Siever and Davis, 2004; Mohr et al., 2005) stated that positive schizotypal features are not necessarily related to psychopathology. It is possible that the locus of control represents a negative aspect of the traits associated with the schizophrenia spectrum. Further longitudinal studies, including the schizophrenia spectrum and prodromal patients, will be necessary to confirm this.

The results of the study are limited by the fact, that we did not examine the relationship between the dysfunctional status scores and objective cognitive deficits. We were not able to test a possible medication effect on the scores of the questionnaires because nearly all patients had the same medication, and we had only one patient without any medication.

. The finding of a potential external control orientation as a trait of schizophrenia in the relative groups complements previous findings of subtle cognitive and neurobiological changes in high-risk groups. Furthermore, high-risk studies are of great importance because they lead to a better understanding of the mechanisms involved in the inherited vulnerability for the disorder. Further studies on markers of schizophrenia should involve high-risk individuals and a schizotypy measurement for the control group, possibly in combination with investigations of brain structural and functional changes along the schizophrenia spectrum.

The knowledge of these cognitions can support long term out-patient care of patients with chronic schizophrenia. The consideration of cognitive attitudes is part of a concept of therapeutic interventions, which improve personal skills by finding a model of the illness.

CHAPTER 3: FUNCTIONAL AND ANATOMICAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA

PART I: TEMPORAL LOBE ABNORMALITIES AND REDUCED HEMISPHERIC LATERALIZATION IN SCHIZOPHRENIA PATIENTS AND UNAFFECTED RELATIVES

The following part is based on the manuscript: Oertel, V., Knöchel, C., Rotarska-Jagiela, A., Schönmeyer, R., Lindner, M., Van de Ven, V., C., Haenschel, C., Uhlhaas, P., Maurer, K., Linden, D.E.J. Temporal lobe abnormalities and reduced hemispheric lateralization in schizophrenia patients and unaffected relatives. The manuscript is in preparation for publishing.

Abstract

The aim of this study was to identify neural functional and anatomical correlates of dysfunctional auditory and language processing, which may contribute to the development of hallucinations in schizophrenia. Several studies have shown a different activation pattern during the presentation of auditory stimuli of schizophrenia patients and healthy control subjects. However, none of the previous experiments examined first-degree relatives, and thus a possible genetic contribution to abnormal auditory and language processing is not clear. In addition we included a gray matter volume analysis of the planum temporale.

The present study included three age-matched subject groups: 15 schizophrenic patients, 11 first-degree relatives and 15 healthy controls. High-resolution 3D-anatomical MRI and functional MRI with auditory stimulation were performed. The auditory stimulation consisted of 13 non-prosodic text fragments presented for 15, 20 or 30 seconds, alternating with a rest-condition (inter-stimulus-interval: 15 s). The subjects had to listen passively to the texts and press a button at the onset and offset of the stimulation.

Cortical activation to auditory stimuli was lower for patients than controls and intermediate for relatives. In addition, patients showed a lower lateralisation of language areas towards the left hemisphere compared to the control group. This decrease of lateralisation correlated with the severity of symptoms. Patients with more severe positive symptoms also showed lower lateralization. Relatives again had intermediate values between patients and controls. The gray matter volume analysis mirrored the results from functional imaging, with a pronounced loss of temporal lobe volume in patients, and less severe reductions in relatives.

Temporal lobe abnormalities (volume loss, reduced functional activation and lateralisation) were not confined to patients with schizophrenia but present, albeit to a lesser degree, in unaffected relatives. This suggests that they may represent a biological genetic marker of schizophrenia. The extent of temporal lobe abnormalities correlated with the severity of symptoms in patients. Loss of normal hemispheric asymmetry may thus be a factor in the development of schizophrenia and a key determinant of disease severity.

3.1 Introduction

SZ patients can show numerous abnormalities in language function, including disorganized speech, neologisms, auditory verbal hallucinations and verbal memory impairments. Auditory verbal hallucinations (AVH) occur in about 70% of patients at least during one clinical episode (Bentall, 1990). They are commonly perceived as being located in external auditory space ("outside the head"), similar to real auditory perceptions, but in the absence of a speaker or other external stimulus (Bentall, 1990; David, 1999; Slade, 1994). Studies of speech samples of SZ patients yielded anomalies at multiple levels of language processing (Chaika, 1974; Shedlack, 1997; Hoffman, 1986).

Previous neuroimaging studies have suggested certain patterns of brain activity to be associated with sub-syndromes (Liddle et al., 1992; Schröder et al., 1996) or single symptoms of schizophrenia. The functional network of auditory hallucinations comprises superior temporal areas (Lennox et al., 2000), including the primary auditory cortex at least in some patients (Dierks et al., 1999, van de Ven et al., 2005), Broca's area (McGuire et al., 1993), limbic areas (Dierks et al., 1999), and the basal ganglia (Silbersweig et al., 1995). Electrophysiological studies have also linked the superior temporal gyrus (Ishii et al., 2000) and temporo-parietal cortex (Line et al., 1998) to auditory hallucinations in schizophrenia. Accordingly, Kircher et al. (2004) found that altered interaction of regions within the superior temporal plane and across hemispheres could be in part responsible for language-mediated cognitive and psychopathological symptoms in schizophrenia.

In most healthy right-handers, the planum temporale, which comprises Wernicke's area in the dominant hemisphere, is larger and the Sylvian fissure longer on the left. This L>R asymmetry is also present in schizophrenia, but was found to be reduced in the majority of imaging and post-mortem studies (Crow 1997). This reduced lateralisation may result in deficient interhemispheric inhibition (Artiges et al. 2000; Crow, 2000) and has been proposed to underlie abnormal language and auditory processing in schizophrenia. Crow (Crow et al., 1989; Crow, 1997) even proposed that schizophrenia results form a failure of the development of cerebral lateralization, and that this failure is genetically determined. According to this theory, reduced lateralization and mixed-handedness, which is known to be present in schizophrenia, reflects a less complete lateralized pattern (Crow, 1997) and should also be found among the relatives of schizophrenia patients. In general, studies including biological relatives of SZ patients indicate that relatives are also impaired, albeit to a lesser degree than patients, on a variety of different cognitive tasks, including sustained attention, perceptual-motor speed and concept formation and abstraction (e.g. Grove et al., 1991; Cannon et al., 1994; Faraone, et al, 1995; Park et al., 1995; Cosway et al., 2000; Curtis et al., 2001; Appels et al., 2003). Family, twin and adoption studies suggest an important genetic role in the etiology of schizophrenia (McGuffin et al., 1995; Cardno et al., 1999; Bediou, 2007; Crow, 2007; Whalley, 2007). We therefore included unaffected first-

degree relatives of SZ patients in order to investigate whether there is a genetic basis for the predicted decreased lateralisation of auditory processing.

The planum temporale (PT) is located on the superior temporal gyrus (STG). The anterior portion of the PT is part of the unimodal auditory association cortex (part of BA 22) that surrounds Heschl's gyrus, and the posterior portion adjacent to the temporoparietal junction is partially coextensive with Wernicke's area. Geschwind and Levitsky (1968) proposed that the PT is the area of the human brain that shows most left-right asymmetry, which would conform to its critical role in language processing (Galaburda et al., 1978). About two thirds of structural imaging studies of schizophrenia patients report reductions in superior temporal gray or white matter. Some studies on PT gray matter volume, surface area, and length also reported reduced left gray matter volumes or loss of normal asymmetry in SZ patients (e.g. Kwon et al. 1999; Petty et al., 1995), whereas others did not find such differences (Barta et al., 1997; Frangou et al., 1997; Shapleske et al., 2001; Kulynych et al., 1995). One reason for these discrepancies may be that temporal lobe changes are progressive rather than static (Kasai et al., 2003). Moreover, it is not clear how the anatomical changes affecting the temporal lobes of schizophrenia patients relate to functional abnormalities, the duration of illness and clinical symptoms. This question is important for an understanding of the contribution of the temporal cortex to the pathophysiology, etiology and the progression of the disease (Crow, 1998; Downhill et al., 2000).

In the present study, we applied a combination of manual and automatic segmentation methods (Schönmeyer et al., 2007; Rotarska-Jagiela et al., 2008) to examine anatomical differences in the PT of SZ patients, their first-degree relatives and control participants who were matched for age, gender, handedness and parental years of education. In order to provide the link to temporal lobe function, we identified regionally specific alterations of auditory information processing in the same subject groups.

3.2 Methods

3.2.1 Participants

We included 15 patients (SZ patients) (mean age: 37.57 [SD: 7.84]; range: 26-56; 6 women, 9 men) diagnosed with paranoid schizophrenia according to DSM-IV criteria (295.30; American Psychiatric Association, 1994). All patients were in-patients of the Department of Psychiatry of Frankfurt University, Germany. Current psychopathology was assessed using the PANSS (Positive and Negative Symptom Scale; Kay et al. [1987]; positive: 15.67 [3.31], hallucinations: 3.07 [1.39], negative: 15.07 [1.83]; general: 32.07 [4.22]; total score: 62.80 [5.48]). All patients were treated with atypical antipsychotics, and four patients additionally with typical neuroleptic medication at the time of testing. In addition, the duration of illness of the patients had to be more than 5 years (13.71 [6.87]; range 5-31; view table 3.1 for further details of the patients' psychopathology.

Table 3.1: *Sociodemographic and clinical variables of the schizophrenia patient group.*

Number	15 SZ Patients
Diagnosis	Paranoid Schizophrenia (DSM-IV criteria 295.30 [APA, 1994])
History of hallucinations	All (n = 15) history of hallucinations → 9 in this episode, but not in this week → 6 in an earlier episode
Age of onset	24.43 (6.63)
Medication	11 atypical 4 atypical and typical
Years of illness	13.71 (6.87)
Global symptomatology (PANSS (N=15)	Positive: 15.67 points [3.31], negative: 15.07 points (1.83), general: 32.07 points (4.22), sum: 62.80 points (5.48), hallucination score: 3.07 points (1.39)

Eleven first-degree relatives (REL) (41.87 [8.55]; range: 26-59; 11 women, 4 men) and 15 healthy controls (CON) (mean age: 39.31 [10.98], range: 26-56; 7 women, 8 men) also participated in the experiment (table 3.2). Contact to the relatives was established through participating patients, from a support group for relatives of schizophrenia patients, through newspaper articles, flyers and advertisements in the hospital. The relatives were requested to bring a letter from the psychiatrist treating the patient of the affected family members to confirm the diagnosis. The relative group included parents (n = 2) and siblings (n = 9) of SZ patients. They were not necessarily related to the patient sample in this study, and they were not related to each other.

The control group was matched with the patient and relatives groups for handedness (all right handed; The Edinburgh Inventory; Oldfield, 1971), age, sex and parental education. We considered the possibility that patients' education was affected by the onset of the illness (mean age of onset: 24.43 years [6.63], range: 13-36 years). To account for this we matched according to pre-illness onset education and added the parental education as a covariate to the analysis. Statistical tests (ANOVA, Scheffé post-hoc contrast analyses) for differences between the groups regarding age, years of education and parental education revealed no significant differences. Exclusion criteria for control participants were any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV, left-handedness, current drug-abuse, neurological pathology and inability to provide informed consent.

All subjects had normal hearing, were native German speakers and were provided with a complete description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethical board of the medical department of the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.

Table 3.2: *Demographic variables of all three subject groups.*

	Patients	**Controls**	**Relatives**	**Total**
Subjects	15	15	11	41
Gender	6 women, 9 men	7 women, 8 men	8 women, 3 men	21 women, 20 men
Years of education	13.00 (2.53)	14.75 (2.24)	13.81 (2.81)	14.83 (2.08)
Parental Education (years, SD)	Mother: 15.11 (2.35) Father: 15.89 (3.12)	Mother: 14.24 (1.31) Father: 15.31 (2.45)	Mother: 13.89 (1.43) Father: 14.95 (1.89)	Mother: 14.41 (1.85) Father: 15.38 (2.13)
Age (years, SD)	37.57 (7.84)	39.31 (10.98)	41.87 (8.55)	41.06 (10.75)
Handedness				All right handed

3.2.2 Assessment of individual and underlying psychopathology

An additional diagnostic session was conducted within one week after the scanning session. The assessment included clinical ratings on the Structured Clinical Interview for DSM-IV (Strukturiertes Klinisches Interview Psychischer Störungen [SKID I (psychiatric disorders) and SKID II (personality disorders)]; Wittchen, 1996) to determine the diagnosis of the patients and to exclude any psychiatric diagnoses in controls and first-degree relatives. Several initially recruited relatives had to be excluded on this basis because of evidence for psychiatric or neurological disorders. The final sample (n = 11) included only first-degree relatives without any psychiatric, neurological or personality disorders.

In addition all participants were screened for predisposition towards hallucinations with the Revised Hallucination Scale (RHS; Morrison et al., 2002). The SZ patients differed by 1.5 SD from the control group, conforming to data obtained from a larger sample (Oertel et al., 2008; in press). The first-degree relatives had significantly higher scores than the control group.

All patients` individual psychopathological profiles were assessed by means of the PANSS (Kay et al., 1986). The score on item 3 (hallucinations) was used to express the severity of hallucinations. In this item, presence and degree of hallucinations are rated on a scale ranging from 1 ("absent") to 7 ("extremely severe"). All patients had a history of auditory hallucinations as assessed by the PANSS interview and a semi- structured interview based on the criteria proposed by Aggernaes (Aggernaes, 1972) to assess the contents, phenomenology, severity and occurrence of hallucinations in more detail. The last period of auditory hallucinations ranged from 13 days to 8 months before the scanning. None of the patients reported any hallucinations while they were scanned.

We performed a number of tests in order to ensure that the functional activation results were not owed to impairment of hearing, speech disorders or pathologies other than

schizophrenia. Auditory analysis by an otologist revealed normal hearing. The anatomical MRI scans were reviewed by a neuroradiologist who did not find underlying pathology in the auditory cortex or surrounding areas.

3.2.3 Stimulus material

The auditory stimulation consisted of three scenarios with similar stimuli presented in a random order across the subjects. Each scenario consisted of 13 fragments of spoken texts of three categories, e.g. "weather", "flowers", "garden". Periods of acoustic stimulation varied between 15, 20 or 30 seconds, each alternated with an inter-stimulus interval (rest condition) of 15 s (view figure 3.1 for experimental paradigm).

The goal was to create material closely related to auditory hallucinations in length, duration and time-span. Secondly, the material was not to include bias coming from emotional contents or further thinking processes. The final choice aimed at texts spoken by neutral voices, without any deep emotional content for the individuals.

The texts were recorded digitally and edited on a personal computer with standard computer software (real player®, RealNetworks, Inc., www.real.com; Presentation, Neurobehavioral Systems, www.neurobs.com). During the fMRI examination, the stimuli were delivered at constant sound pressure level through a custom-made pneumatic sound transmission device with headphones that accurately preserve tone frequencies and attenuate scanner noise.

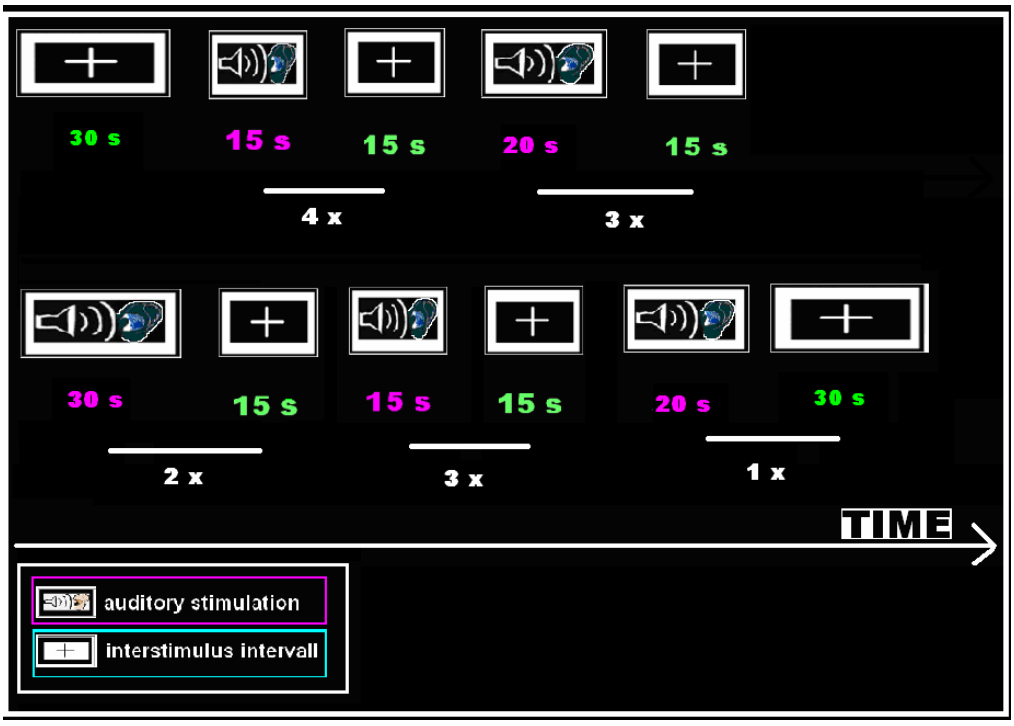


Figure 3.1: *Experimental paradigm of the auditory stimulation.*

3.2.4 Data acquisition and image processing

All subjects underwent a functional scan and an anatomical scan, which were measured on a SIEMENS Allegra 3.0 Tesla system (Brain Imaging Center, Frankfurt/ Main, Germany). Each session began with a functional scan (auditory stimulation; EPI-sequence, 480 volumes, voxel size: 3.3*3.3*5.0 mm, TR = 1000 ms, TE = 30 ms, 16 slices, slice thickness = 5mm, dist. factor: 10%, inter slice time 62, Gap thickness = 0.5, flip angle: 60 degrees). For anatomical measurement, we acquired a high-resolution T1-weighted MDEFT sequence (Deichmann et al., 2004; 176 slices, $1x1x1mm^3$) covering the whole brain. We synchronized stimulus presentation with the fMRI sequence at the beginning of each trial. The subjects' heads were fixed by placing foam pads on each side of the head within the head coil in order to prevent large head movements.

During the functional scan, participants were scanned while 13 blocks of auditory stimulation alternated with a rest condition. The baseline condition comprises a fixation cross, back-projected on the centre of the screen play. The participants were instructed to look at the fixation cross during the baseline condition.

Participants were instructed to listen attentively to each stimulus. During the stimulus periods, the patients were not engaged in overt speech. The participants were asked to press a button with their left index finger at the onset of a spoken voice and to press the button again when it stopped. For each subject a stimulation protocol was recorded showing the button press time points. The loudness of the voices was well above that of the ambient noise of the MRI scanner. In a short pre-experiment with 15 volunteers, we delivered a series of fragments of the texts to adjust the sound loudness, allowing a comfortable hearing level and a clear sound perception in the session. Afterwards, the stimulus intensity was delivered similar for all participants. Preliminary to the main session, a short empirical test session, which lasted approximately one minute, was done to make sure that the stimulus intensity was comfortable for each subject.

The whole session lasted approximately 25 minutes, a duration all participants were able to manage. The sessions were done in complete darkness. Subjects were told to keep their eyes open, to prevent them from falling asleep during the measurements, and to move as little as possible.

3.3 Statistical analysis

We pre-processed and analyzed the fMRI data using the BrainVoyager software, versions 2000 and QX (Brain Innovation, Maastricht, The Netherlands; www.brainvoyager.com). Further analysis was done with the Matlab (MathWorks, Natick, MA) software. We applied the following pre-processing steps: slice-time correction, motion correction, spatial smoothing using a Gaussian kernel of 4mm full-width at half-maximum, linear trend removal and highpass temporal filtering

with 3 cycles in time course. We manually coregistered the fMRI data with the anatomical scans. We transformed the 3D anatomical scans into Talairach space (Talairach and Tournoux, 1988) and subsequently used the parameters for this transformation to transform the coregistered functional data. We then resampled the 3D functional data set to a voxel size of 1x1x1 mm^3.

To include only those brain areas which are relevant for the present question, we preselected volumes of interest (VOIs) based on standardized anatomical information. The preselected VOIs were used to create an anatomical auditory cortex mask. The auditory VOI comprised auditory regions that are often the regions of interest for functional connectivity analysis during resting state and auditory hallucinations (Van de Ven et al., 2004; Van de Ven et al., 2005). We used a probabilistic map of Heschl's gyrus, the putative site of primary auditory cortex (Rademacher et al., 2001). Such maps depict the probability for any anatomical voxel to belong to left or right Heschl's gyrus with respect to an anatomically averaged template. In our study, the probability level of the maps was thresholded at a minimum of 20% to capture the high anatomical and functional variability of the auditory cortices (Talairach coordinates for Center of Mass [CoM] of left auditory cortex: x = -40, y = -20, z = 8, Number of Voxels [NoV = 1021; right CoM: x = 45, y = -13, z = 10, NoV = 9199. Figure 3.2. shows the auditory cortex mask on a MNI template.

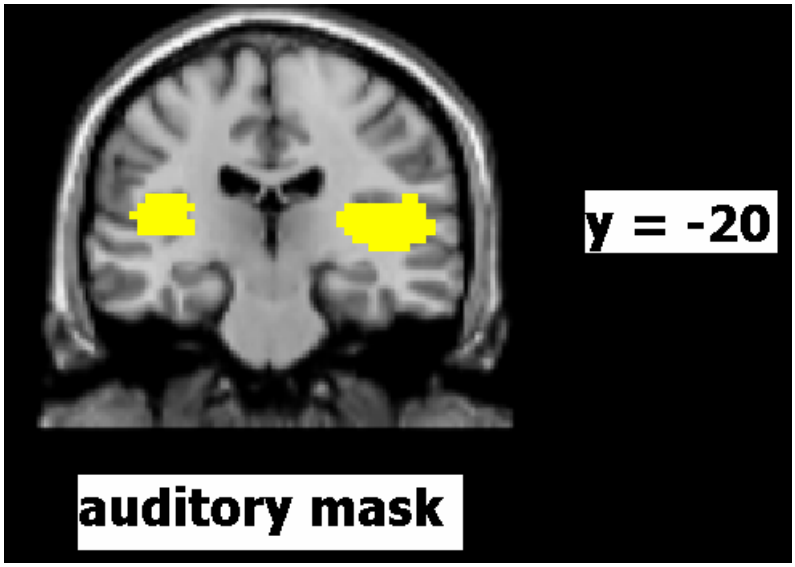


Figure 3.2: *Auditory cortex mask on a MNI template. The image shows the auditory mask (y = -20; colour code [RGB-system] = yellow).*

The periods of stimulation were used as the reference function for a general linear model of the BOLD signal time course (Goebel et al., 1998a, 1998b). We defined group as a between factor to compute a 1-way ANOVA. We convolved the predictors with a hemodynamic response function (Boynton et al., 1996). We used the false discovery rate (Benjamini and Yelutieli, 2001). An F-statistic was calculated for each voxel to create the activation maps to find cortical regions

sensitive to phonological stimulation. Activation maps were created for all participants to identify regions significantly activated during speech perception (thresholded at p = .05, corrected) followed by activation maps for each group (SZ patients, first-degree relatives, controls) separately. For the region-of-interest (ROI = all supra-threshold voxels in the functional map for a VOI) analysis, the beta values of all individuals were extracted, followed by a MANOVA including Scheffé-post-hoc contrast analyses (see table 3) using the SPSS-software (SPSS 12.0; www.spss.com).

Furthermore, we provided lateralisation indices and correlated those indices with the severity of symptoms of the SZ patients. The lateralisation index was defined by Sommer et al. (2001) as the difference in the number of active voxels in the left versus the right hemisphere (within the VOIs) divided by the total sum of activated voxels in both hemispheres *(nr. of voxels left – Nr. of voxels right) / total sum of active voxels*.

A negative lateralisation index thus implies more right hemispheric activation during the task, whereas a positive lateralisation index implies more left hemispheric activation. For each participant separately, lateralisation indices were computed using the ROIs of the preceding analyses. First, the analysis includes the ROIs of the auditory cortex map. Second we computed lateralization indices for a whole-brain analysis. After that, the mean lateralisation indices for each group were summarized as the total lateralisation index (TLI).

Furthermore, we conducted a morphometric analysis of the PT. The high-resolution T1-weighted MDEFT sequence (Deichmann, 2004; 176 slices, 1x1x1mm^3) was used for delineating and measuring the PT. Preprocessing of the data included AC-PC (anterior commissure – posterior commissure)-alignment. The PT gray matter regions of interest (ROIs) were manually outlined without knowledge of diagnosis using a software package for cortical segmentation (vmr-segmenter, Schönemeyer et al., 2007). The landmarks for delineating PT gray matter have been described by Hirayasu et al., (2000). For initial identification of PT, PT gray matter was traced on coronal images to the end of the Sylvian fissure, and the gray matter of the ascending ramus of the sylvian fissure was also included. Our definition of the PT followed the work of Kasai et al. (2003), who included PT proper and its parietal extension. Finally, sagittal MRIs were used to check and confirm PT boundaries. After drawing, the PT ROIs could be viewed in any plane and as a 3-dimensional object for further editing.

Intracranial volume was measured using a region-growing intensity-based thresholding segmentation implemented in the BrainVoyager software, versions 2000 and QX (Brain Innovation, Maastricht, The Netherlands; www.brainvoyager.com) with a segmentation limit set at the brain stem. The sum of all marked voxels was used as the intracranial volume score. In addition, the total brain volume (BV) was measured with the same semi-automated segmentation method using BrainVoyager (for details see Rotarska-Jagiela et al., 2008).

For interrater reliability, raters (V.O., C.K., A.R.-J.) blinded to group membership, independently drew ROIs. The intraclass correlation coefficient was .96 / .94 for left / right PT gray matter. Furthermore, interrater reliability (computed by using all of the slices from 1 randomly selected brain and measured by each of the 3 raters) was .96 to .98 for all structures.

One-way analysis of variance (ANOVAs) with group as fixed factor (patients, relatives, controls) was used to test for group differences in the left and right PT gray matter volume and the lateralisation index. The relative gray matter volume of left and right PT (number of voxels, quotient of PT volume and intracranial or brain volume, respectively [% values]) was the dependent variable for statistical measures. Afterwards we defined the lateralisation index (see above) for the relative PT gray matter volume. In addition, we performed correlation analyses in order to assess influences of age, gender, years of education and individual psychopathology on PT volume.

3.4 Results

3.4.1 Main effect auditory stimulation

Group data were superimposed on an anatomical brain template (courtesy of the Montreal Neurological Institute [MNI]). Significant activation (thresholded at p = 0.05, Bonferroni-corrected for multiple tests; minimum cluster size = 200 voxels) during passive listening to auditory stimulation was found in primary and higher auditory areas (Fig. 4.3). Across all subjects, the highest activation was found bilaterally in the transverse temporal gyrus (Heschl's gyrus; BA 41) and the planum temporale (BA 42). The activated areas are known in the literature as being involved in auditory processing (Sommer et al., 2001). Figure 3.3 shows the results of the main effect of auditory stimulation.

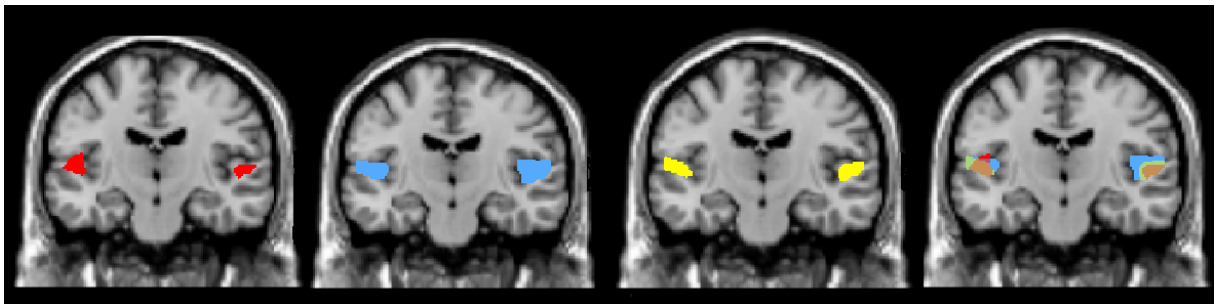


Figure 3.3: *Main effect auditory stimulation. From left to right: SZ patients, first-degree relatives, controls; overly map. Colour code (RGB-system): red = SZ patients, blue = first-degree relatives, yellow = controls, green = overlay first-degree relatives / controls, purple = overlay SZ patients, first-degree relatives, orange = overlay controls / SZ patients, grey = overlay SZ patients, first-degree relatives, controls.*

The analysis of the main task effect was followed by a ROI-analysis on the individual mean beta values for the auditory cortex ROI. We calculated a 2-way ANOVA on the beta-values with group (three levels: controls, first-degree relatives, SZ patients) and hemisphere (two levels:

left hemisphere, right hemisphere) as fixed factors. The ANOVA was followed by a Scheffé post-hoc contrast analysis in order to compare the individual groups. The results (table 3) showed a significant effect of group in both hemispheres (beta values left hemisphere, controls: .72 [.20]; first-degree relatives: .63 [.37], SZ patients: .55 [.20]; F (41) = (8.72), p = .01; right hemisphere: controls: .87 [.37], first-degree relatives: .81 [.31], SZ patients: .55 [.23]; F (41) = 4.98, p = .01). Furthermore, the Scheffé post-hoc contrast analysis showed for the left hemisphere significant contrasts between all groups (all $p < .05$) and for the right hemisphere significant contrasts between the controls and the SZ patients (p = .03) and the first-degree relatives and the SZ patients (p = .05). The contrast between the controls and the first-degree relatives in the right hemisphere was non-significant. Accordingly the results showed a significant interaction effect hemisphere * group (F (41) = 13.94, $p < .01$).

Table 3.3: *Location of activation in brain regions during acoustic stimulation (neutral voices) (p (Bonf) = .01, voxel size > 200).*

	SZ patients **Talairach coordinates (Nr. of voxels)**	**First-degree relatives** **Talairach coordinates (Nr. of voxels)**	**Controls** **Talairach coordinates (Nr. of voxels)**	**Significance**
Left auditory cortex	-50, -16, 5 (1146)	-46, -21, 8 (4721)	-46, -18, 8 (5758)	F (41) = 8.72, p = 0.001 SZ P / REL: p = .01 CON / REL: p = .05 SZ P / CON: p = .04
Right auditory cortex	49, -13, 6 (889)	51, -13, 8 (2104)	50, -10, 7 (3021)	F (41) = 4.98, p = .01 SZ P / REL: p = .04 SZ P / CON: p = .03 REL / CON: n.s.

3.4.2 Lateralisation

The lateralisation indices for the auditory cortex map (TLI^a) showed less left lateralized auditory processing for the schizophrenia patients (TLI^a: .11), followed by the first-degree relatives (TLI^a: .31) and the controls with the most left lateralized activation (TLI^a: .38). The ANOVA computed with LI as dependent variable and group as fixed factor showed a significant main effect for the lateralisation indices (F [3.38] = 4.68, p = .03). Scheffé post-hoc contrast analysis showed significant differences for the contrast SZ patients vs. controls (p = .04), but the other contrasts were non-significant (view figure 3.4).

The lateralisation indices for the whole-brain analysis (TLI^w) showed less left lateralized processing of speech for the patients (TLI^w: - .07 [.19], followed by the first-degree relatives (TLI^w: .05 [.12]) and the controls with the most left lateralized activation (TLI^w: .15 [.19]). The

ANOVA (SPSS-software) computed with the TLI^w as a dependent variable and group as fixed factor showed a significant main effect for the lateralisation indices ($F [3, 38] = 4.44$, $p = .02$). Scheffé post-hoc contrast analysis showed significant differences for the contrast SZ patients vs. controls ($p = .02$), with the other contrasts remaining non-significant.

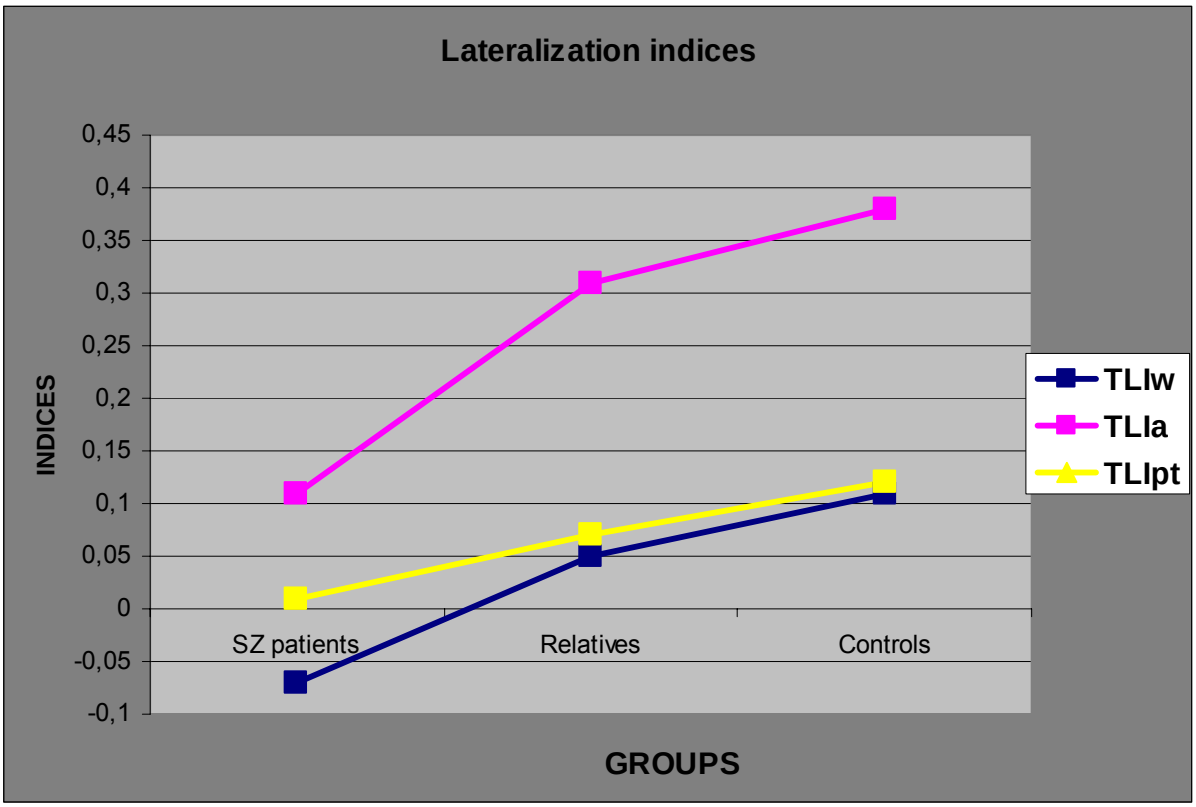


Figure 3.4: *Lateralization indices (TLI) of the different subject groups.*

3.4.3 Correlation to symptoms

The mean total score of the PANSS at the time of scanning was 51.67 (19.81). The mean total score on the positive subscale was 13.80 (7.80), and the mean total score on the negative subscale was 23.13 (12.61). The mean score on item 3 (hallucinations) was 2.87 (1.60). The score of the positive symptoms was calculated without the hallucination score in order to enable subsequent separate correlations. All SZ patients had a history of hallucinations, 9 had experienced auditory hallucinations in the current episode, but not in the week of measuring, 6 patients had experienced auditory hallucinations only in a previous episode of illness.

A significant negative correlation was found between the TLI^a and the TLI^w of the SZ patients and the total score of the PANSS (TLI^a – PANSS: r [Pearson] = -.48, $p = .04$; TLI^w – PANSS: r [Pearson] = - .57, $p = .03$). No correlation was found between the lateralisation indices and the severity of negative symptoms ($p > .05$). In contrast, a significant negative correlation was found between the lateralisation indices of the whole-brain (TLI^w) and the auditory cortex

(TLI[a]) and the severity of positive symptoms (TLI[a] – positive symptoms: r = -.37, p = .03; TLI[w]-PANSS: r = -.58, p = .02). Similarly, a significant negative correlation between the severity of auditory hallucinations and the lateralization was found in the auditory cortex and in the whole brain (TLI[a] – hallucination score: r = -.67, p = .02; TLI[w] – hallucination score: r = -.73, p < .01). In sum, lower relative activation in the left hemisphere was associated with more severe positive symptoms and auditory hallucinations (view fig. 3.5).

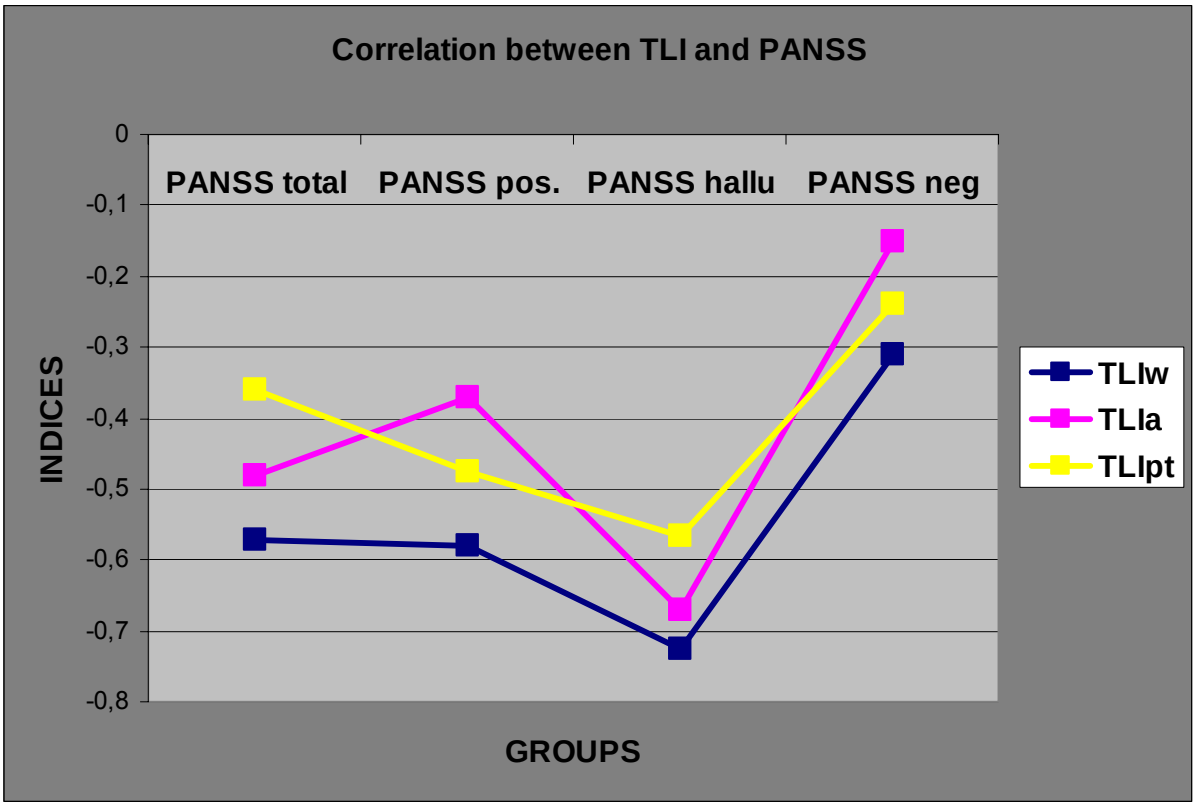


Figure 3.5: *Correlation indices of the TLI and the PANSS scores.*

3.4 Morphometric analysis of the planum temporale

The ANOVA with the mean values for BV (all absolute volume measures are shown in mm^3) and ICV as dependent variable and group (SZ patients, relatives, controls) as fixed factor showed no significant differences (BV, ICV; p > .05; for further details view table 3.4). In addition, post-hoc contrast analysis showed no significant group differences (p > .05).

In contrast, the ANOVA of the mean gray matter volumes in the left and right PT showed significant group differences for the left side (left: SZ patients: 944 [190], relatives: 1290 [311], controls: 1605 [268]; F (38) = 24.27, p < .01). The post-hoc Scheffé single contrast analysis showed significant differences between all groups (p = < .01). Similar, the mean gray matter volume of the right PT showed the same continuum with SZ patients having a smaller volume (934 [197]), followed by the relative group (1125 [368] and the control group (1260 [191]; F

[38] = 6.32, p < .01). Post-hoc Scheffé contrast analyses revealed a significant difference between patients and controls only (p < .01).

These analyses were followed by a percent value analysis. We calculated percent values

for the left and right PT, compared to the whole intracranial volume (% left /% right ICV) and

the brain volume (% left / right BV). The following results are based on the percent values based

on the intracranial volume (for the percent values based on the brain volume, view table 3.4).

Here, the ANOVA showed the same pattern of results with a significant main effect for the gray matter volume of the PT (left: F [38] = 15.57, p < .01, right: F [38] = 4.44, p = .02), with the SZ patients having the lowest percent value for the left and the right PT (0.04 %, 0.05 %), followed by the relatives (0.06 %, 0.06 %) and the controls (0.08 %, 0.07 %). The post-hoc contrast analysis showed significant differences for the contrast SZ patients / controls in the left and the right PT (p = .02). In addition, the contrast SZ patients / first-degree relatives in the left PT was significant (p < .01).

Table 3.4: *Anatomical analysis of Brain volume (BV), intracranial volume (ICV), Nr. of volumes of the planum temporale (PT) and the lateralisation indices across the subject groups. In addition, the percent values of the PT compared to the BV and ICV are listed above. The table includes mean scores, ANOVAs, followed by post-hoc Scheffé contrast analysis.*

Group	Patients (PAT)	Relatives (REL)	Controls (CON)	Significance
Brain Volume mean (SD)	1396171 (138022)	1347747 (251430)	1414199 (137276)	F (38) = .47, p = .63
Post-hoc	PAT / CON: p = .96	PAT / REL: p = .78	CON / REL: p = .64	
Intracranial Volume (SD)	2039035 (200150)	1952364 (180099)	2054205 (234738)	F (38) = .84, p = .44
Post-hoc	PAT / CON: p = .98	PAT / REL: p = .58	CON / REL: p = .48	
Volume of left PT	955 (190)	1290 (311)	1605 (268)	F (38) =24.27, p < .01**
Post-hoc	PAT / CON: p = .00**	PAT / REL: p = .01**	CON / REL: p = .01**	
Volume of right PT	934 (197)	1125 (368)	1260 (191)	F (38) = 6.32, p < .01**
Post-hoc	PAT / CON: p = .00**	PAT / REL : p = .18	CON / REL: p = .41	
% left ICV	0.04 % (.01)	0.06 % (.01)	0.08 % (.02)	F (38) =15.57, p < .01**
Post-hoc	PAT / CON: p = .00**	PAT / REL : p = .01**	CON / REL: p = .10	
% left BV	0.06 % (.01)	0.09 % (.02)	0.11 % (.01)	F (38) =15.94, p < .01**
Post-hoc	PAT / CON: p = .00**	PAT / REL: p = .01**	CON / REL: p = .15	

% right ICV	0.05 % (.01)	0.06 % (.01)	0.07 % (.02)	F (38) = 4.44, p = .02*
Post-hoc	PAT / CON: p = .02*	PAT / REL: p = .18	CON / REL: p = .75	
Group	**SZ Patients (PAT)**	**Relatives (REL)**	**Controls (CON)**	**Significance**
% right BV	0.06 % (.02)	0.08 % (.03)	0.09 % (.01)	F (38) = 4.46, p = .02*
Post-hoc	PAT / CON: p = .02**	PAT / REL: p = .05*	CON / REL: p = .79	
Lateralisation	0.01 (.08)	0.07 (.16)	0.12 (.08)	F (38) = 3.69, p = .03*
Post-hoc	PAT / CON: p = .03*	PAT / REL: p = .34	CON / REL: p = . 61	

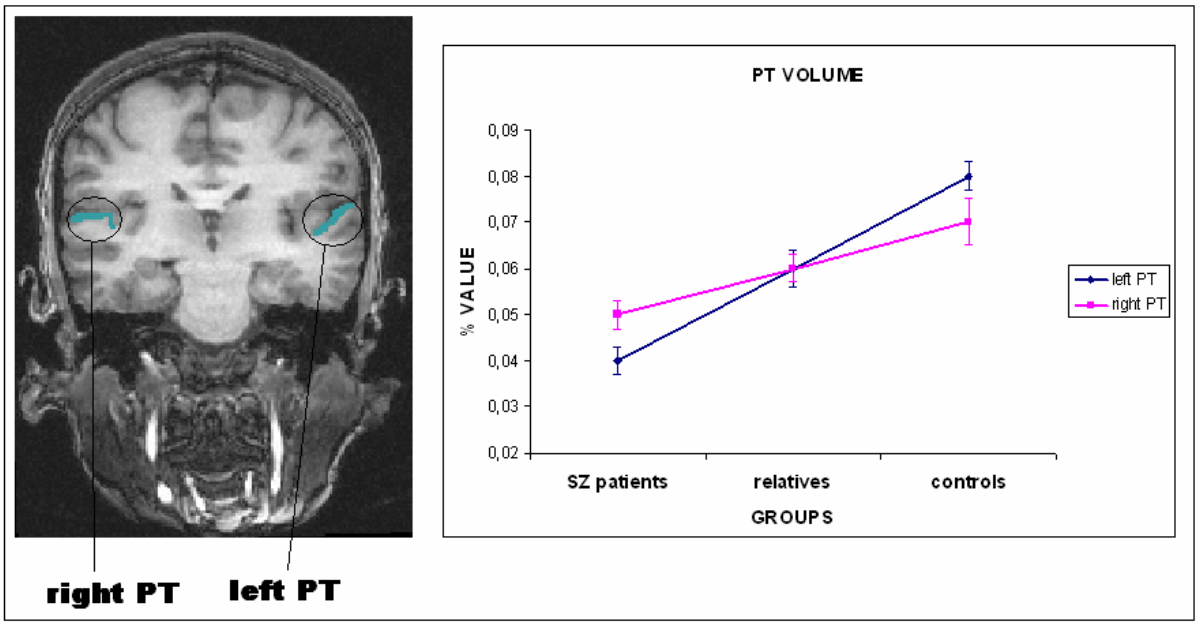


Figure 3.6: *Left and right PT volume (% value) in the different subject groups.*

In addition, we calculated lateralisation indices (TLI^{PT}) for the PT gray matter volume. The lateralisation index was calculated in analogy to the functional LI as the volume of left PT - volume of right PT divided by the sum of left and right PT volume. We then calculated an ANOVA with group as fixed factor and lateralisation index as dependent variable, followed by Scheffé post-hoc single contrast analyses. The results showed a significant main effect (F [38] = 3.69, p = .03). The control group showed a clear lateralisation towards the left (lateralisation index: .12 [.08], as described before for the functional data. The following groups showed the same continuum as described for the functional data with the relatives showing less lateralization (.07 [.16]) and the patients almost none (.01 [.08]). Post-hoc contrast analyses revealed a significant difference between patients and controls (p = .03; view figure 3.4).

Furthermore, we calculated bivariate correlation analyses for all groups separately between the PT gray matter volume and age, gender and years of education, and for years of

illness and years of onset for the SZ patient group separately. These correlation analyses yielded no significant results. Additionally, we calculated bivariate correlations between the PT gray matter volume and the scores of the PANSS for the SZ patient group. Here, the results showed a significant negative correlation between the left PT gray matter volume and the hallucination score of the PANSS ($r = -.60$, $p = .02$) and the general psychopathology subscale ($r = -.52$, $p = .04$).

In addition, no correlation was found between the TLIPT and the total score, the negative score and the hallucination score of the PANSS ($p < .05$). Instead of, a significant negative correlation was found between the TLI^{pt} and the severity of positive symptoms (TLI^{pt} – positive symptoms: $r = -.49$, $p = .03$). Similarly, a significant negative correlation between the severity of auditory hallucinations and the lateralization index of the anatomical volume was found (TLI^{pt} – hallucination score: $r = -.55$, $p = .04$). In sum, lower relative volume in the left hemisphere was associated with more severe positive symptoms and auditory hallucinations (fig. 3.5).

3.5 Discussion

We assessed temporal lobe abnormality and lateralization changes in schizophrenia for the first time with a combined functional and structural imaging approach that also incorporated a control group of unaffected first-degree relatives. Overall, auditory stimulation with speech led to a robust activation in each participant in the superior temporal lobes bilaterally when contrasted with a low-level baseline (scanner noise), consistent with much previous work (Hickock, 2000; Hickock, 2004). The results showed several differences between patients, relatives and controls, most of them along a continuum with relatives showing intermediate values.

First, controls showed significantly higher activation in the auditory areas, followed by the first-degree relatives and the patients. This effect was particularly pronounced in the left hemisphere, statistically supported by an interaction effect between group and hemisphere. The STG of the non-dominant hemisphere has been implicated in the processing of differences in melody, pitch, and sound intensity (Jäncke et al., 1998; Samson et al., 2001), whereas the dominant STG is more involved in the generation and understanding of individual words (Warren et al., 2005). Both of these functions seem to be impaired in SZ, but disruption of semantic processing is more consistently reported (Sommer et al., 2001). Our findings of more marked changes in the left STG would be in keeping with such distribution of neuropsychological deficits in SZ.

Second, we show remarkable gray matter volume reduction in the PT in SZ patients and unaffected family members. These volume reductions were independent of age, gender and years of education. Our results conform to the work of Kasai et al. (2003) and Hirayasu et al. (2000) who also found volume reduction in PT for SZ patients using similar methods. The present

study was novel in that it investigated also a relative group and documented intermediate levels of absolute and relative PT volumes, suggesting that PT volume may be a biological genetic marker of SZ.

Third, the lateralisation indices of the functional and anatomical measures showed a continuum with controls being most left lateralized, followed by the first-degree relatives and the SZ patients. The SZ patients showed no dominant left lateralisation in the auditory cortex. This finding conforms to the finding of Sommer et al. (2001), who found a decrease of left hemispheric lateralisation vs. an increase of right hemispheric lateralisation in SZ patients. Here again, our study extends previous work by showing that unaffected relatives have intermediate levels of anatomical and functional lateralization between patients and controls.

Sommer et al. (2001) suggested a relationship between language-related brain activation patterns and the severity of symptoms. As in the study of Artiges et al. (2000) and Sommer et al. (2001), our results revealed a correlation between lack of lateralisation and the severity of symptoms. Sommer et al. (2001) also found that decreased lateralisation of language processing was associated with more severe hallucinations. Artiges et al. (2000) found - in a PET-study - an increased activity of the right-sided frontal areas. Our patient sample is comparable to those of Artiges et al. (2000) and Sommer et al. (2001) in the severity of positive symptoms. We postulate that decreased language lateralisation in schizophrenia, may result from failure to inhibit the right hemisphere, and that this process may contribute to the generation of positive symptoms. Disinhibition of the auditory cortex in both hemispheres indeed seems to be a contributing factor to auditory verbal hallucinations (Dierks et al., 1999; van de Ven et al., 2005).

The precise neurobiological mechanism that underlies the volume loss in the PT is still unknown. As always in psychiatric research, a combination of factors preceding the disease, for example a neurodevelopmental abnormality, and factors following the disease, such as medication, has been suggested. Our finding of a significant volume loss in the relative group in the left PT indicates a genetically determined mechanism leading to loss of neurons in schizophrenia. This hypothesis is supported by the findings of genetic examinations of families affected with schizophrenia. Many genes implicated in schizophrenia have a direct influence on brain development regulating such processes as neuronal migration, axonal guidance, myelination, neurotransmission and synaptic plasticity (Owen et al., 2004, Harrison and Weinberger, 2005). Some of these genes have been associated with anatomical brain abnormalities in schizophrenia patients and their first-degree unaffected relatives (Addington et al.; Gruber, O, et al., 2008; Winterer G, et al., 2008; Van Heren et al., 2008; Zinkstok et al., 2008). Many researchers now agree that genetic abnormalities observed in schizophrenia further predispose and sensitize the brain to environmental insults resulting in a life-long dysregulation of brain development and plasticity (Bartzokis, 2000; Pantelis et al., 2005).

Annett (1992) suggested that normal lateralisation, right-handedness and normal cerebral asymmetry are coupled to a dominant allele, called the "right shift factor". Proneness to psychosis could then be related to an abnormality of the right shift factor (Annett, 1999; Crow, 1999). This factor is thought to accomplish cerebral lateralisation by disrupting the growth of right-sided language-related cortex, rather than through enhancement of these areas in the left hemisphere. In keeping with this, Shapleske et al. (1999) observed, in a structural MRI-study, a normal-sized left planum temporale (BA 42) compared with a shift in the right planum temporale. Our study partly confirms this theory in that we show that the abnormality of cerebral asymmetry is not confined to SZ patients, but affects also first-degree relatives. However, our finding of markedly smaller PT volume in the left hemisphere in patients suggests that additional factors may be in place that either promote left hemisphere PT growth in healthy individuals or inhibit it in SZ.

One important limitation of the present study is the fact that all patients were treated with antipsychotic medication during the time of measurement. It is not clear, to what extent such medication has an effect on auditory cortex activation. Reduction of motor cortex activity after antipsychotic medication has been demonstrated (Braus et al.). However, a dichotic listening study by Gruzelier and Hammond (1980) reported that withdrawal and reinstatement of neuroleptic medication did not affect the results. The confounding effect of medication is a frequent problem in studies of SZ. Because it is not realistic for all research questions to be addressed in medication-naïve samples, the investigation of high-risk groups, who share biological features with SZ patients but are not affected by the many disease specific factors that may affect the brain over the lifetime, provides a unique opportunity to study SZ traits.

In sum, we found temporal lobe dysfunction in SZ patients, which correlated with positive symptoms. Our results support the hypothesis that anatomical changes lead directly to impaired activation in the temporal lobe. Furthermore, a reduced hemispheric lateralization was found for both functional and anatomical parameters. This abnormal lateralization could be a new biological genetic marker, because also it was also shown by unaffected first-degree relatives.

Part II: ANATOMICAL CONNECTIVITY AND SYMPTOMS OF SCHIZOPHRENIA

The following part is based on the manuscript: Rotarska-Jagiela, A., Oertel, V., DeMartino, F., van de Ven, V., Formisano, E., Roebroeck, A., Rami, A., Schoenmeyer, R., Haenschel, C., Hendler, T., Maurer, K., Linden, D.E.J. Anatomical Brain Connectivity and Positive Symptoms of Schizophrenia: a Diffusion Tensor Imaging Study. (submitted in Molecular Psychiatry).

V. Oertel contribution to this part lies in the measurement and analysis of the psychometric tests, and in helping with analyzing the DTI data. For further details view thesis of Rotarska-Jagiela, 2008).

Abstract

Anatomical brain abnormalities in schizophrenia are well documented in the neuroimaging literature. The classical approach of volumetric analysis of MRI data has recently been supplemented by Diffusion Tensor Imaging (DTI), which mainly assesses changes in white matter (WM). Although DTI studies increasingly provide evidence for abnormal anatomical connectivity in schizophrenia, most often using fractional anisotropy (FA) as an indicator of the integrity of WM tracts, the clinical significance of such anatomical changes is still not well understood. We performed a whole-brain group comparison of FA values of patients with paranoid schizophrenia and a history of auditory hallucinations and matched healthy controls using DTI data acquired with a 3T magnetic resonance scanner. The relationship of WM changes to psychopathology was assessed by correlation of FA values with PANSS scores measuring positive symptoms and the severity of auditory hallucinations. Schizophrenia patients showed overall disturbance of WM tracts in prefrontal lobe, external capsule, pyramidal tract, occipitofrontal fasciculus, superior and inferior longitudinal fasciculi, and corpus callosum. The arcuate fasciculus was the only WM tract which showed increased FA values in patients. Increased FA values in this region correlated positively with increased severity of auditory hallucinations. Our results suggest that local changes in anatomical integrity of WM tracts in schizophrenia may be related to clinical presentation. The aim of future DTI research in schizophrenia should be to further enhance our understanding of the relationship between anatomical connectivity, psychopathology and cognitive deficits.

3.6 Introduction

Numerous volumetric neuroimaging studies have shown differences between groups of schizophrenia patients and controls (for a recent review see Honea et al., 2005). The integrity of fiber bundle tracts has recently become a focus of research as well, aided by the advances of Diffusion Tensor Imaging (DTI) (Basser et al., 1994), which mainly assesses changes in white matter (WM). The value most often used to characterize the integrity of fibers is fractional

anisotropy (FA), which describes the degree to which displacement of water molecules varies in space. FA values allow an estimate of the presence and coherence of oriented structures, e.g. myelinated axons, which provide an obstacle to free diffusion (Cergignani et al., 2001).

Most studies have reported decreased FA values in schizophrenia in WM regions including the frontal (Kumra et al., 2004, Wolkin et al., 2003) and occipital lobes (Kumra et al., 2004, Agartz et al., 2001), and fiber tracts of the uncinate fasciculus (Burns et al., 2003, Kubicki et al., 2002), cingulum (Kubicki et al., 2003) and corpus callosum (Foong et al., 2000). These findings are commonly interpreted as evidence for anatomical dis- or hypoconnectivity (Burns et al., 2003, Hubl et al., 2004). So far, only one study has reported increased FA values in a subgroup of schizophrenia. Patients with a history of hearing voices had higher FA values in the arcuate fasciculus than healthy controls and patients who never experienced auditory hallucinations (Hubl et al., 2004). A similar difference between patients with and without a history of auditory hallucinations was confirmed in a second study (Shergill et al., 2007). Higher FA values in the arcuate fasciculus suggest that increased anatomical connectivity between speech and auditory areas may be related to occurrence of auditory hallucinations (Hubl et al., 2004).

The association of DTI findings with clinical symptoms has not been studied comprehensively. Although two studies did not find a significant association between symptoms and FA values (Foong et al., 2000, Minami et al., 2003), one (Wolkin et al., 2003) found an inverse relationship between negative symptoms and FA of frontal WM. Additional evidence for a relationship between anatomical changes in WM and clinical symptoms comes from volumetric examinations which showed that patients with prominent auditory hallucinations had an increased volume of the temporal lobe WM (Shapleske et al., 2002).

In the current study, we examine whether increased integrity of WM tracts in schizophrenia patients with a history of auditory hallucinations would be reflected in the severity of positive symptoms and the severity of the hallucinations in particular. Such correlation would corroborate that increased FA values previously observed in the arcuate fasciculus (Hubl et al., 2004, Shergill et al., 2007) are indeed related to occurrence of auditory hallucinations and not to other factors, which hallucinating paranoid schizophrenia patients may have in common. As this is the first study of this type, a whole brain exploratory analysis was performed to avoid limiting the analyses by a priori hypotheses and potentially missing important findings. FA values were correlated with positive symptom and hallucination scores as measured by the Positive and Negative Syndrome Scale (PANSS) in a group of 24 patients with paranoid schizophrenia and a history of auditory hallucinations. We also performed a whole-brain group comparison of the FA values.

Based on the previous literature, we hypothesized that patients would have overall decreased anatomical connectivity, as indexed by decreased FA values, compared with controls.

However, because all our patients had a history of hearing voices, increased FA in the arcuate

fasciculus was expected in line with the finding of earlier studies (Hubl et al., 2004, Shergill et al., 2007). In addition, we predicted a positive correlation with hallucination scores in this region, which would suggest a relationship between increased anatomical integrity of WM tracts between speech and auditory areas and predisposition to auditory hallucinations and thus establish the first DTI correlate of a specific psychiatric symptom.

3.7 Methods

3.7.1 Participants

24 paranoid SZ patients diagnosed according to the DSM IV and 24 matched controls participated in the study. Patients were recruited from the wards and clinics of the Department of Psychiatry of the Frankfurt University Hospital. Only patients who met diagnostic criteria for paranoid schizophrenia and had a history of auditory hallucinations were included in the study. The patient and control groups were matched for age, gender, and parental years of education. In addition, for patients whose university education was interrupted by the illness, we recruited university graduate controls, assuming that the education level prior to the disease onset was a more valid matching criterion than years in higher education. Participants with a history of other psychiatric or neurological disorders or drug abuse were excluded. All subjects were right-handed. The study was approved by the local ethics committee and written informed consent was obtained from all participants after the goals of the project had been explained to them.

3.7.2 Clinical Tests

Diagnosis of paranoid schizophrenia was confirmed with a Structured Clinical Interview (SKID I). Current psychopathology was assessed with Positive and Negative Syndrome Scale (PANSS). Control participants were also interviewed with the SKID I and II to ensure that they did not suffer from any psychiatric or personality disorder. Both patients and controls were examined with the ESI (Eppendorfer Schizophrenie Inventar), which measures characteristic subjective signs and symptoms of schizophrenia. Detailed demographic and clinical data of study participants are included in Table 3.5.

Table 3.5: *Demographic and clinical data of study participants.*

	Schizophrenia Patients	**Controls**
Gender (M/F)	12/12	12/12
Age (Mean ± SD)	39.00 ± 9.35	39.21 ± 8.95
Handedness (Left/Right)	0/24	0/24
Years of Education (Mean ± SD)*	13.64 ± 3.02	15.96 ± 2.66
Parental Years of Education (Mean ± SD)		
Mother	12.12 ± 2.67	12.68 ± 3.06
Father	12.57 ± 2.84	12.86 ± 2.87
DSM IV Diagnosis (295.30)	24	n/a
Age at Onset (Mean ± SD)	26.21 ± 9.16	n/a
Years of Illness (Mean ± SD)	12.58 ± 7.36	n/a
Medication (atypical / typical / atypical + others / no medication)	16/1/6/1	n/a
PANSS (Mean ± SD)		
Total	58.94 ± 14.59	n/a
Positive	13.95 ± 5.12	
Negative	14.31 ± 5.02	
General	28.26 ± 9.91	
ESI (Mean ± SD)*	22.54 ± 13.18	4.38 ± 1.02

*Notes: * Difference significant at p < .01. n/a: not measured.*

3.7.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed on a 3 Tesla Allegra system (Siemens, Erlangen, Germany). T1-weighted 3D anatomical data were acquired using an MDEFT sequence with 176 slices and 1x1x1mm^3 voxel size. For a DTI measurement, we used a spin-echo EPI sequence (TR/TE = 5400/80ms, 40 slices, 1.8x1.8x2mm^3 voxel size) covering the whole brain except for the temporal pole and the inferior cerebellum. Six diffusion-weighted volumes were measured in the axial plane parallel to the AC-PC line in 6 directions with a *b*-value = 1000s/mm^2 and one T2 weighted image without diffusion weighting. The DTI measurement was performed five times and averaged for further processing. The total scan time, which included additional measurements for resting state functional MRI (not reported), lasted 25 minutes.

3.7.4 Image Pre-processing and analysis

To correct for eddy current distortion and motion, all diffusion images were aligned to the reference volume (first B0 image) using the FSL FDT Diffusion toolbox (www.fmrib.ox.ac.uk/fsl). Co-registration to a common MNI reference image (www.mni.mcgill.ca) and re-sampling of the data into 1x1x1 mm^3 was performed with the FSL FLIRT toolbox using an affine twelve parameter registration with correlation ratio cost function and tri-linear interpolation (Jenkinson et al., 2002). The resulting datasets were spatially smoothed with a Gaussian kernel (full-width-at-half-maximum [FWHM] = 7mm). In-house software was used to estimate and diagonalize the

diffusion tensor in each voxel. Subsequently, FA maps were calculated for all participants from the eigenvalues of the diagonalized tensor (Pierpaoli and Basser, 1996). In order to identify WM tracts, the results of the analyses were transformed into Talairach space.

3.7.5 Whole-Brain Group Comparison

In order to decrease the number of statistical tests performed and to ensure that only WM voxels were included in the analysis, a WM mask was created for each participant based on a T2 image acquired during DTI measurement using BrainVoyager (www.brainvoyager.com) and the VMR Segmenter software (www.bic.uni-frankfurt.de/bv-tools). For an initial WM masking, a region-growing intensity-based thresholding segmentation implemented in BrainVoyager was used. The resulting masks were grouped to obtain an overall WM map that included only voxels classified as WM in all participants (see Figure 4.7 for illustration of WM masking steps). A voxel-based t-test was performed only on voxels included in the final grouped WM mask. This very conservative masking method allowed us to examine only large white matter tracts. Note that the whole basal ganglia region was included because of inability to reliably segment WM in this area, owing to poor tissue contrast.

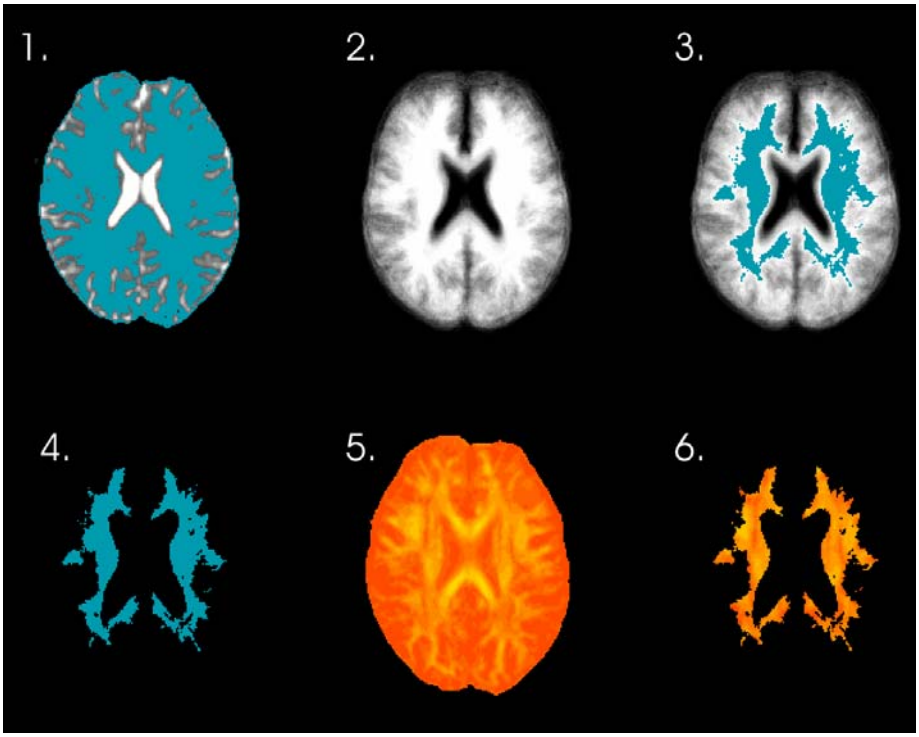


Figure 3.7: *Steps of WM masking. 1. WM of an individual participant is masked using region-growing intensity-based thresholding segmentation. 2. WM masks of all 48 participants overlaid on top of each other (brighter color indicates more overlay between individual masks). 3. Voxels marked in green are those indicated as WM in all our participants. 4. Average WM mask. 5. Individual FA map. 6. Masked individual FA map, which was included in the group analysis.*

3.7.6 Correlation of FA values with symptoms

For the patient group, voxel-by-voxel Pearson correlation coefficients were calculated between individual FA values and PANSS positive subscale and hallucination scores. As in group comparison, the average patient WM mask was applied.

3.8 Results

3.8.1 Behavioral and clinical data

The control group had significantly higher mean years of education (mean = 15.96, SD = 2.66) compared with patients (mean = 13.64, SD = 3.02). This result was expected since, as mentioned above, we matched the participants on the level of education rather than on the exact number of years in higher education. As an additional matching criterion, we used parental years of education, which indeed was not significantly different between the two groups (mother: controls mean = 12.12, SD = 2.67 vs. patients mean = 12.68, SD = 3.06; father: controls mean = 12.57, SD = 2.84 vs. patients mean = 12.86, SD = 2.87). On the ESI, the controls scored significantly lower compared with patients (mean = 4.38, SD = 1.02 vs. mean = 22.54, SD = 13.18), which was expected in view of our selection criteria for controls (no psychiatric history and no pathology on the SKID). Detailed demographic and clinical data of study participants are included in Table 3.5.

3.8.2 Whole-brain group comparison

All reported results of group comparison were corrected for multiple comparisons using cluster-size thresholding (Forman et al., 1995), as implemented in BrainVoyager, at $t > 2.01$, $df = 46$, $p < .05$ two-tailed with a cluster size of at least 150 anatomical voxels. The results of the whole-brain group comparison are illustrated in Figure 4.8 and summarized in Table 4.7 with Talairach coordinates for the most significant voxel.

Schizophrenia patients had significantly lower FA values in the right external capsule and pyramidal tract (bilaterally). Also, the FA values of the corpus callosum were lower in the patient group. In addition, association fibers including left superior and bilateral inferior longitudinal fasciculi and occipitofrontal fasciculus (bilaterally) also showed lower anisotropy values in patients. The only region with increased FA compared with controls was arcuate fasciculus (bilaterally).

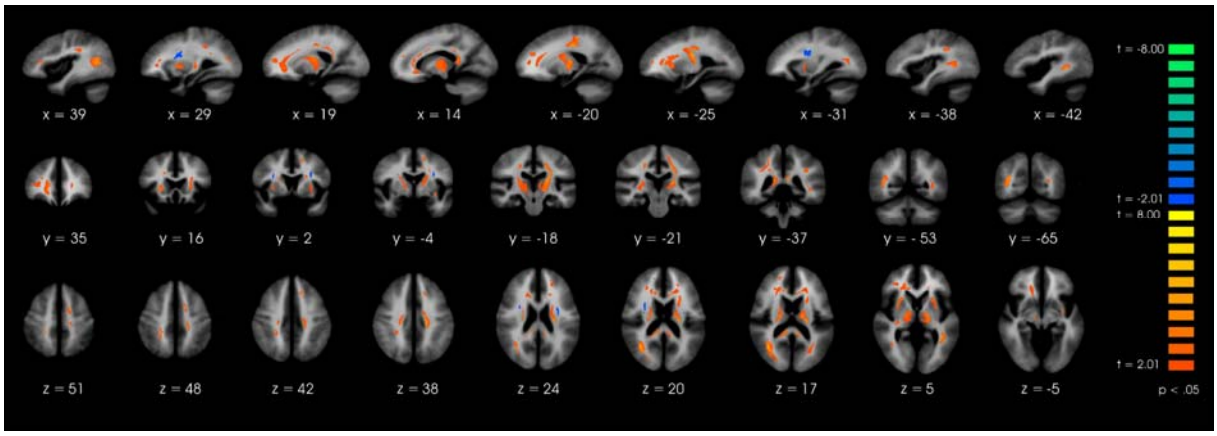


Figure 3.8: *Results of a group comparison of FA values (blue – areas of higher FA values in patients, red – areas of higher FA values in controls) significant at t > 2.01, df = 46, p < .05 two-tailed, corrected, with a cluster size of at least 150 anatomical voxels. The Talairach coordinates for the respective planes are indicated.*

Table 3.7: *Results of the whole-brain group comparison (t > 2.01, df = 46, p < .05, two-tailed, corrected).*

Type of Fibers Region / Fiber Tract	Talairach coordinates (x, y, z)	Number of voxels in the cluster	Group with higher FA value
Projection Fibers		3662	controls
Pyramidal tract		7855	controls
	12, -14, -6	572	controls
External capsule			
	-25, -19, 25	1564	controls
		337	controls
	23, 17, 4		
Commissural fibers			
Corpus callosum		305	controls
		187	patients
	7, -33, 16	364	patients
		2571	controls
Association Fibers	-8, -37, 16	1108	controls
Superior longitudinal fasciculus		3539	controls
		171	controls
Arcuate fasciculus			
Inferior longitudinal fasciculus			
		228	controls
Occipitofrontal fasciculus	-38, -38, 32	199	controls
		411	controls
	30, 6, 19	1173	controls
Other regions	-32, -7, 28		
Superior frontal gyrus			
	38, -60, 16		
Postcentral gyrus	-40, -44, 4		
	16, 33, 2		
	-22, 46, 11		
	-20, 40, 26		
	-16, 23, 41		
	-16, -3, 54		
	21, -36, 53		

3.8.2.1 Correlation of FA values with symptoms

The correlation map of FA values and symptom ratings was corrected for multiple comparisons using the above method at $r > .42$, $df = 22$, $p < .05$ two-tailed, and a cluster size of at least 150 voxels. The results are summarized in Table 4.8 with Talairach coordinates for the most significant voxel, and illustrated in figures 3.9 and 3.10. Figure 3.11 presents, for illustration purposes only, arcuate fasciculus with the region of statistically significant increased connectivity and positive correlation with symptoms highlighted.

The score of the positive subscale of the PANSS correlated positively with FA values in left arcuate fasciculus, prefrontal lobe (Brodmann area 9/10), corpus callosum, occipitofrontal

fasciculus (bilateral), left postcentral gyrus and bilateral superior parietal lobe (Brodmann area 7). FA values in the cingulum (bilateral, Brodmann area 31), right inferior parietal lobe and right optic radiation were negatively correlated with that scale. The hallucination subscore of the PANSS correlated positively with FA values in arcuate fasciculus (bilateral), left thalamus and prefrontal lobe (Brodmann area 9/10) and negatively with left cingulum and right pyramidal tract. Table 3.7 shows the correlation of FA values with symptoms measured with the PANSS.

Table 3.7: *Correlation of FA values with symptoms as assessed with PANSS (r > .42, df = 22, p < .05 two-tailed, corrected).*

Scale	Type of fibers region / fiber tract	Talairach coordinates (x, y, z)	Cluster size	Mean r value of the cluster (maximum r value)
Positive (PANSS)	**Commissural fibers**			
	Corpus callosum	-10, 22, -1	157	.46 (.53)
	Association fibers			
	Arcuate fasciculus	-40, 27, 16	414	.47 (.54)
		-47, -34, 12	325	.50 (.65)
	Cingulum	11, -38, 32	189	-.46 (-.55)
		-9, -42, 27	155	-.45 (-.50)
	Occipitofrontal fasciculus	22, 39, 19	546	.46 (.55)
		-24, -28, 32	168	.47 (.68)
	Other Regions			
	Inferior parietal lobe	32, -58, 20	488	-.49 (-.63)
	Middle frontal gyrus	25, 19, 38	199	.47 (.58)
		-24, 35, 17	455	.45 (.52)
	Optic Radiation	29, -77, 14	152	-.47 (-.55)
	Postcentral gyrus	-19, -44, 49	225	.44 (.53)
	Superior frontal gyrus	21, 56, 6	217	.45 (.54)
		-18, 29, 34	152	.46 (.53)
	Superior parietal lobe	29, -44, 40	395	.47 (.56)
		-23, -52, 33	220	.48 (.60)
Hallucination (PANSS)	**Projection fibers**			
	Pyramidal tract	25, -5, 32	532	-.50 (-.65)
	Association fibers		342	.45 (.55)
	Arcuate fasciculus	54, -7, 25	611	.48 (.63)
		-47, -8, 26	208	-.47(-.60)
	Cingulum	-10, -44, 28		
	Other Regions			
	Middle frontal gyrus	24, 42, 17	424	.46 (.52)
		-23, 37, 18	285	.47(.58)
	Superior frontal gyrus	-18, 29, 36	356	.50 (.64)
	Thalamus	-13, -19, 13	252	.49 (.65)

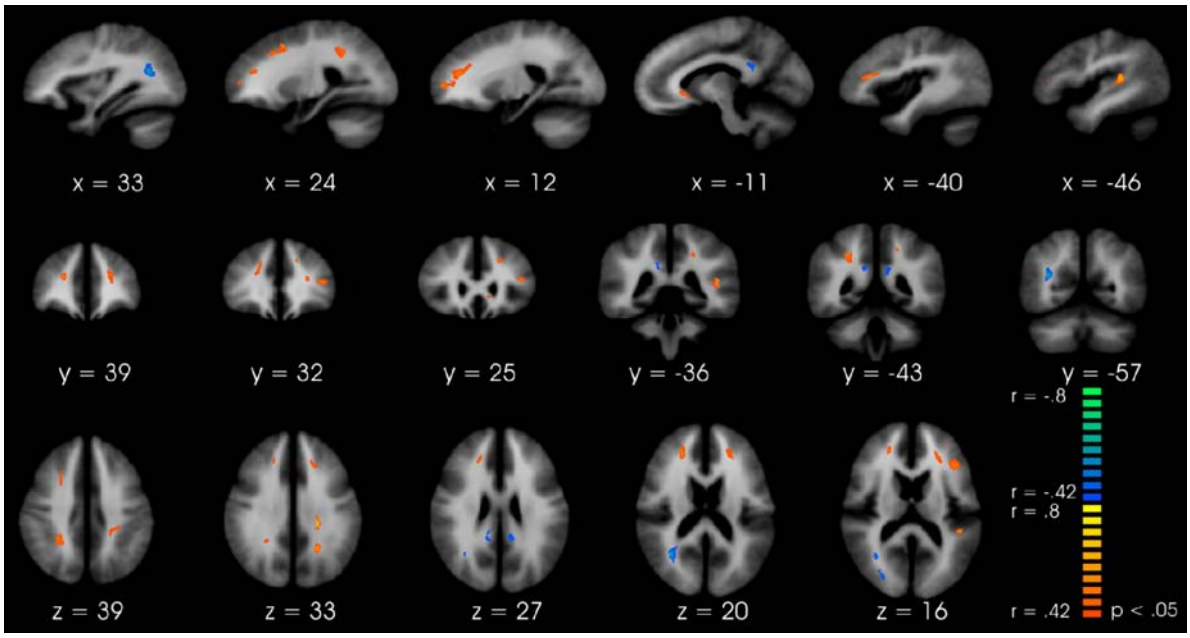


Figure 3.9: *Correlation of FA values with positive PANSS score (r > .42, df = 22, p < .05 two-tailed, corrected, with a cluster size of at least 150 voxels). The Talairach coordinates for the respective planes are indicated.*

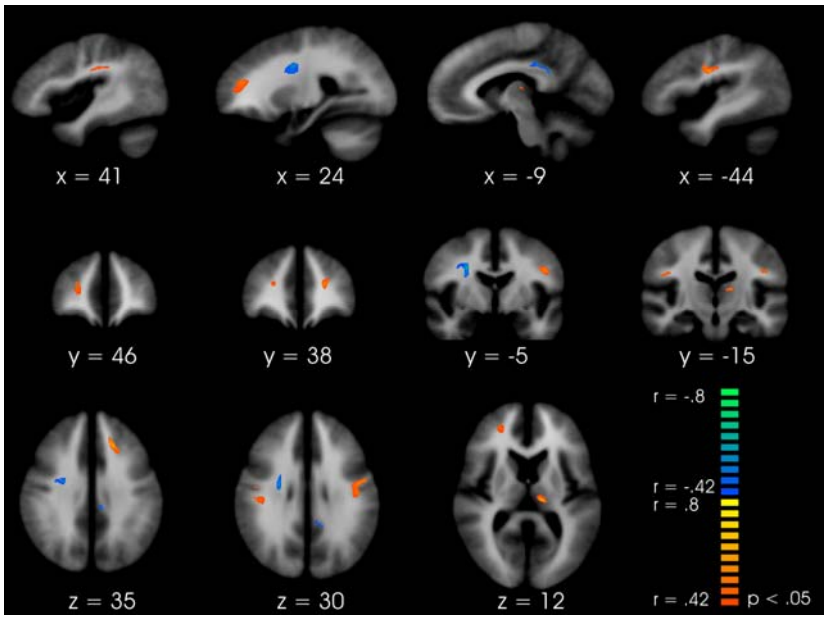


Figure 3.10: *Correlation of FA values with hallucination PANSS score (r > .42, df = 22, p < .05 two-tailed, corrected, with a cluster size of at least 150 voxels). The Talairach coordinates for the respective planes are indicated.*

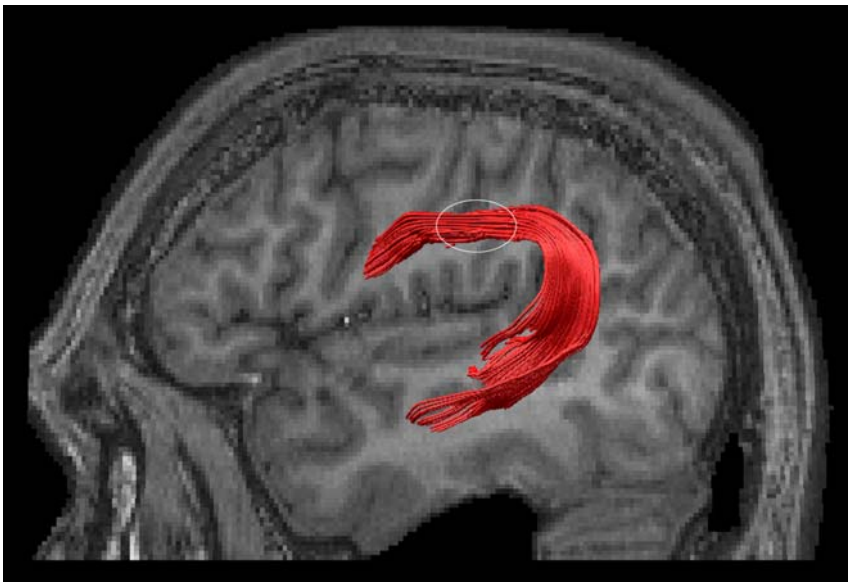


Figure 3.11: *The arcuate fasciculus with the region of statistically significant increased connectivity and positive correlation with symptoms highlighted.*

3.9 Discussion

The results of the current study, here a whole-brain group comparison, show overall disturbance of anatomical connectivity in schizophrenia patients. We present the first evidence of reduced FA of projection fibres in the external capsule. Only one other study examined FA values in this tract (Sun et al., 2003), but did not find statistically significant differences. However, the researchers placed regions of interest on only two slices, which did not overlap with clusters in our study. We also found changed FA in association fibres, with the occipitofrontal fasciculus showing lower FA values in patients, as reported previously (Hubl et al., 2004). In addition, in keeping with previous studies, patients had significantly decreased FA in the corpus callosum and pyramidal tract (6, 10), as well as the superior and inferior longitudinal fasciculi . We also found decreased FA in prefrontal regions of our patient group replicating findings of previous literature (Kumra et al., 2004; Wolkin et al., 2003).

As hypothesized, our sample of patients with a history of hallucinations had bilaterally increased FA values in the arcuate fasciculus, which is in line with previous DTI findings (Hubl et al., 2004) and results of volumetric studies of WM (Shapleske et al., 2002, Shin et al., 2005). The main finding of the present study, correlation between FA values and positive symptoms in general and specifically hallucinations in the arcuate fasciculus bilaterally, conforms to previous group comparisons between patients with and without a history of hallucinations (Hubl et al., 2004, Shapleske et al., 2002) but extends it in an important way. Evidence for aberrant connectivity in patients with a history of hallucinations compared with those without one can be interpreted in two ways. The altered connectivity may result in a predisposition for hallucinations generally, e.g. by providing a possible pathway of aberrant fronto-temporal communication, but severity and frequency of hallucinations then depend on other biological or environmental

factors. Alternatively, the degree of altered connectivity may determine not just whether but also how often and intensely patients hear voices. The correlation between symptom ratings and FA values with coefficients around .5, amounting to about a quarter of explained variance, points clearly to the latter model.

FA values are commonly interpreted as an index of anatomical connectivity with lower values indicating hypoconnectivity (Burns et al., 2003) and higher values corresponding to hyperconnectivity (Hubl et al., 2004, Shapleske et al., 2002). Such interpretation of FA has to be considered with care as there are multiple other factors, which can influence the values, as already shown by DTI examinations of other diseases (Englund et al., 2004, Larsson et al., 2004). Increased anisotropic diffusion may also be due to the loss of crossing fibers in the voxels in question, which may result in the same net effect of increased FA. Independent validation, e.g. through post-mortem tracer studies (Galuske et al., 2000), would therefore be needed to confirm that higher FA values indeed indicate higher numbers of fibers in the arcuate fasciculus. However, in the following discussion we will introduce findings of fMRI and EEG studies, which provide evidence supporting the interpretation of increased FA as increased anatomical connectivity.

4.9.1 Hyperconnectivity and pathophysiology of schizophrenia

The localization of the areas in arcuate fasciculus and prefrontal WM, whose FA values were consistently correlated with the clinical scores is compatible with the current pathophysiological models of hallucinations. Functional imaging studies showed increased co-activity during auditory hallucinations in multiple brain regions including speech production and perception areas and auditory cortex (Dierks et al., 1999; van de Ven et al., 2005), which are anatomically connected through the arcuate fasciculus. Aberrant connections along this fiber tract, as indicated by our study, may facilitate such abnormal co-activation of language and auditory areas. Our data would thus be compatible with neuropsychological models of schizophrenia that emphasize the imbalance of activation between language production and perception areas as a possible mechanism of hallucinations (David, 2004; Woodruff, 2004).

The view that hyperconnectivity, as indexed by higher FA values, may contribute to symptom-generating neural activity is further supported by results of an electrophysiological study where long-range synchrony of the EEG was positively correlated with the PANSS hallucination score (Uhlhaas et al., 2006). Patients with auditory hallucinations were also shown to have increased beta frequency oscillations in speech-related areas (Lee et al., 2006). Increased anatomical connectivity may facilitate spreading of oscillations between sensory areas and therefore lead to generation of neural activity resembling that produced in response to auditory stimulation (Uhlhaas and Singer, 2006).

In addition to this prominent finding of increased integrity of the temporal part of the arcuate fasciculus and the correlation of local increased FA values with positive symptoms, we also found consistent changes in prefrontal WM. FA values of WM underlying the middle frontal gyrus in dorsolateral prefrontal cortex (DLPFC) correlated with positive symptoms. This region crucially supports working memory, particularly at higher load (Linden et al., 2003). Thus, aberrant connectivity within the DLPFC may contribute to the well-documented working memory deficit in schizophrenia . The link with positive symptoms may arise because a reduced working memory capacity might lead to impaired context updating and source monitoring. This in turn may result in erroneous attribution of internally generated speech or thoughts to external sources, as in auditory verbal hallucinations or first-rank symptoms (Frith, 2005).

4.9.2 Hyperconnectivity and brain development

The seemingly counterintuitive findings of hyperconnectivity in schizophrenia may be explained in a neurodevelopmental context. Brain development is a complex process of establishing and pruning of axonal connections. This process is regulated by multiple factors, including sensory input, availability of neurotrophic substances, molecular markers and hormones, many of which have been found to be dysregulated in schizophrenia (Lewis and Levitt, 2002; Rapoport et al., 2005). Pruning, or elimination of transient axons, and the establishment of functional axonal contacts occur simultaneously to ensure that transient connections, which compete with functional contacts for neurotrophic factors, are eliminated (Hua and Smith, 2004). As a result, excessive pruning, which has been shown to occur in schizophrenia (Garey et al., 1998), may lead to the preservation of exuberant connections (Webster et al., 1991). This could account for the possible increased anatomical connectivity in the arcuate fasciculus observed in the present study.

4.9.3 Future research

The aim of future DTI research in schizophrenia should be to enhance our understanding of the relationship between anatomical connectivity, psychopathology and cognitive deficits. DTI presently only provides information about traits rather than states. Therefore, for a deeper understanding of the pathophysiological processes that yield the phenomenology of schizophrenia, it should be combined with measures that directly assess neural correlates of symptoms, such as EEG (Uhlhaas and Singer, 2006) or functional imaging (Linden, 2006). The findings of the current study contribute to the previous literature on auditory hallucinations in schizophrenia by providing a possible anatomical substrate for abnormal co-activation of speech

and auditory areas. In analogy to the present study's focus on hallucinations, future studies might examine whether changes in specific fiber tracts are associated with symptom dimensions and underlie the distinctive EEG patterns observed for different syndromes of schizophrenia (Lee et al., 2003). Our finding of quantitative association between altered connectivity and symptoms should also encourage research into white matter changes in individuals with attenuated psychotic symptoms, e.g. as part of a schizophrenia prodrome, or those with varying degrees of hallucination proneness, reflecting their position along the schizotypy continuum. Markers like the ones investigated here may then be helpful in deciding between more categorical and more dimensional approaches to psychiatric disease classification and inform about the neural basis of the putative psychosis continuum.

CHAPTER 4:
INVESTIGATION OF VISUAL HALLUCINATIONS WITH fMRI

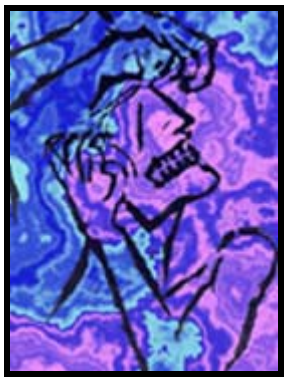


Figure 4.1: *Illustration of a patient suffering from visual hallucinations: "Ich sehe etwas, was Du nicht siehst!" (www.maodes.de/erikasten/Neue Dateien/halluzination.html).*

Abstract

Brain correlates of hallucinations in other modalities than the auditory have rarely been investigated with functional neuroimaging. As a precedent study, a visual localizer was created in order to map the visual areas of the human brain. We did a pilot study with a sample of control subjects in order to test the usability and quality of the localizer.

We investigated a 27-year old patient with chronic schizophrenia with fMRI while he was experiencing visual hallucinations. We have recently succeeded in obtaining the first (to our knowledge) fMRI measurements of a schizophrenia patient during visual hallucinations, for which we also have localizer data of higher visual areas. As an assumption, the investigation of brain activity during this important clinical phenomenon might be of interest to a general psychiatric audience. A description of activation of higher visual areas and the limbic system (hippocampus and posterior cingulate), conforming to the intensity of the visual and emotional experience normally described by patients experiencing hallucinations is included. Interestingly, activity in higher visual areas followed the boundaries of category-selective areas corresponding to the patient's experience of bodies, faces and landscapes.

Brain activity related to hallucinations was found in higher visual areas and the hippocampus. The specialisation of the higher visual areas corresponded to the content of the hallucinations (faces, bodies, scenes). We assume that the hippocampal activity is related to the retrieval of visual images from memory. The pattern of brain activity may explain both the lack of subjective control over hallucinations and their vividness.

Next, a functional MRI study was conducted with a 37-year-old healthy female subject with visual hallucinations after several weeks of visual deprivation. We compared the visual hallucination-induced brain-activity with a mental imagery task. FMRI data of hallucinations were acquired and, after recovery from blindfolding, an additional measurement was conducted, where

the subject had to generate the hallucinated phenomena deliberately by mental imagery. The subject reported the occurrence of moving amorphous patterns, flashes and changing colours during the scan. Neural activity correlated to hallucinations was found in occipital visual, bilateral posterior parietal and prefrontal regions. In contrast, mental imagery of the phenomena did not lead to activations in occipital regions. This result suggests that alterations in visual and attentional regions are related to the experience of visual hallucinations. Furthermore visual hallucinations seem to be more vivid and more strongly related to activations in visual areas than mental imagery.

Part I: Localisation of the visual areas

4.1 Introduction

Hallucinations are a core symptom of schizophrenia, affecting more than 60% of patients and often causing considerable distress. They can be defined as perceptual experience in the absence of sensory input and occur in all sensory modalities (APA, 1994). Importantly, hallucinations differ from mental imagery by the lack of control over the sensations. Previous functional magnetic resonance imaging (fMRI) studies of hallucinations in schizophrenia focused on the auditory modality and yielded activity of auditory cortex, language and limbic areas during auditory verbal hallucinations (AVH) (e.g. Dierks et al., 1999; Weiss and Heckers, 1999; Shergill et al., 2004; Van de Ven et al., 2005).

Brain correlates of hallucinations of SZ patients in other modalities than the auditory have rarely been investigated with functional imaging. Visual hallucinations, as in the auditory modality, not only occur in psychiatric disorders, but as well in several other disorders. Possibly, normal individuals sometimes experience visual hallucinations. If somebody asks someone "don't think of a crocodile" (in german: „Denken Sie jetzt auf gar keinen Fall an ein Krokodil!") all people will think and imagine –if only for some seconds- a picture of a crocodile. This suggests to the ability of the human brain to imagine objects, faces, animals etc, even if they are not there at the moment. And, as the example shows us, sometimes it is hard to suppress the image. This expresses the thin border between the fantasy proneness of individuals and hallucinations of persons who suffer from a psychiatric illness.

After drug abuses, several individuals suffer from illusions and visual hallucinations. A. Hofmann, the developer of LSD, described *„phantastic coloured pictures of extraordinary vividness"* or *„I saw landscapes, gold mountains covered with jewels, geometrical figures, flowers, birds and other coloured things, even beside scenes of animals, objects and persons acting which I memorized from my childhood or my past*". Also during epilepsy or migraine or during sensory deprivation visual hallucinations appear. The effect of hallucinogens like LSD is based on the similarity of these substances with transmitters of the human brain, e.g. mescaline is similar to noradrenalin and dopamine, psilocybin and LSD are similar to serotonin. If there is an

overload of there substances, there will be a change in the perception of the sensory systems up to hallucinations.

Some patients with late developed blindsight - intact visual cortex but a lesion of the eyes or the optic nerve - describe complex visual hallucinations (= Charles-Bonnet-syndrome). A comparable description is known from patients with late acoustic damage. A previous functional neuroimaging study of visual hallucinations concerned patients with Charles-Bonnet-Syndrome and reported activity mainly in higher visual areas corresponding to the categories of the visual experience (Ffytche et al., 1998).

Figure 4.2: *Picture shows the painting of one subject experiencing hallucinations (by ffytche et al., 1998)*

The following study is divided into two parts. First, a pilot study will be presented where we investigated several control subjects in order to localize specific visual areas. Secondly, we investigated a SZ patient with visual hallucinations. The present case report is the first fMRI study that reveals the direct neural correlates of visual hallucinations in schizophrenia and investigates them in relation to functionally defined category-selective visual areas. Visual hallucinations are much less common than AVH in schizophrenic patients but have been described in several other disorders, including Parkinson's disease (e.g. Oishi et al., 2005), Lewy body dementia (e.g. Imamura et al., 1999) and Charles-Bonnet-syndrome (ffytche et al., 1998). In these disorders, patients are commonly able (unless they are in the later stages of dementia) to question the reality of the hallucinated perceptual experience, which is not normally the case in the psychotic hallucinations reported in schizophrenia.

4.2 Methods

4.2.1 Subjects

To localize the specific visual areas, a visual localizer was created and tested in a pilot study on seven control subjects from the laboratory (3 men, 4 women; mean age: 32.5 [5.43], range: 21-39). The participants were all native German speakers, without any neurological or psychiatric disorder (tested with SKID – screening). An assessment of underlying pathology and visual acuity was done with all of them (for further details view chapter 4.4) to ensure that none of them suffered from any impairment of vision or other pathologies of the eyes. The subjects of the pilot study had normal vision.

4.2.2 Stimuli material – Face-house-object localizer

Functional magnetic resonance imaging (fMRI) research on visual perception has revealed several distinct bilateral occipitotemporal brain areas that respond selectively to certain categories of visual stimuli (Peelen and Downing, 2005). These include the extrastriate body area (EBA), which responds selectively to human bodies and body parts (Downing et al, 2001a), the fusiform face area (FFA) and the occipital face area (OFA), which respond selectively to faces (Halgren et al., 1999; Kanwisher et al., 1997; Puce et al., 1996)., and the parahippocampal place area (PPA), which responds selectively to places and scenes (Epstein and Kanwisher, 1998).

We created a face-house-object localizer to map the visual areas of the human brain. It consisted of three scenarios with similar stimuli presented in a random order. Each scenario consisted of 40 full colour pictures of four categories (faces, scenes, bodies, chairs; see Figure 4.3 for examples) presented in blocks of 20 stimuli. We performed three runs with 32 blocks (four for each condition) each. The stimuli material was selected from several sources: stimuli of the categories chair, scene and body originated from a database of the laboratory, the "face"-stimuli originated from the database of the University of Stirling, Scotland; www.psychology.stir.ac.uk). The order of the blocks was symmetrically counterbalanced within each run. Each stimulus was presented for 300 ms, with an inter-stimulus interval of 450 ms. Each block thus lasted 15s. The experimental paradigm is shown in figure 4.4.

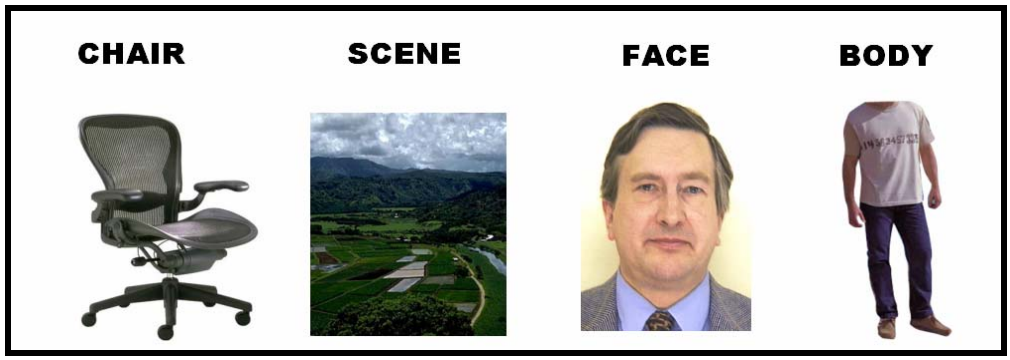


Figure 4.3: *Examples of the four categories of the face-house-object localizer.*

Stimuli were back-projected on the centre of a screen, which was in view of the subjects through an angled mirror positioned on top of the head coil. Within-session reproducibility was assessed by comparing the sessions. (In this way, each between-session comparison had an equal amount of runs, identical stimuli, and the same stimulus orders on both sides of the comparison). The same assessment procedure as during the auditory stimulation was done: the subjects were asked to press a button when a stimulus (picture) occurred and to press a button when the picture disappeared.

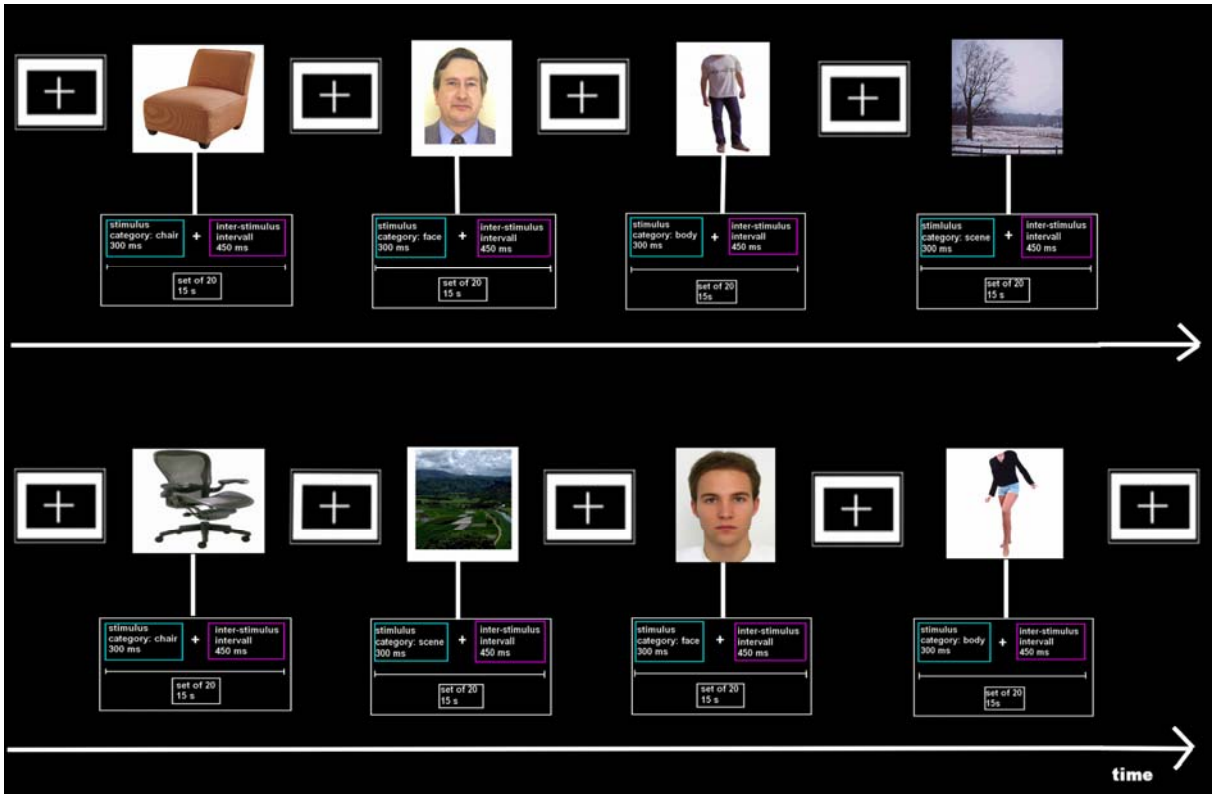


Figure 4.4: *Experimental paradigm.*

Predictors for fMRI analysis were obtained by convolving the epochs of stimulus presentation for each visual category with a hemodynamic reference function. These were entered into the general linear model of the experiment. In order to localize the higher visual areas, we computed contrasts (t-maps) between the respective predictor of interest and the remaining predictors. Thus, activation to images of bodies was contrasted with the average activation of the remaining three stimulus categories in order to identify EBA. Similarly, faces were contrasted with the other categories to localize the FFA and OFA, and scenes were contrasted with the other categories to localize the PPA.

4.2.3 Experimental procedure

We conducted two steps: First, we presented all subjects the stimulation program on a standard PC in order to check the usability and quality of the experimental material. Afterwards an MRI session on a 3T Allegra MR tomography (Siemens, Erlangen, Germany) was done. The session

included a functional scan with stimulation (face-house-object localizer) with the following scanning parameters: EPI-sequence, 480 volumes, 16 slices, inter slice time 62 ms, TR = 1000, TE = 30ms, flip angle = 60°, slice thickness 5mm, voxel size: 3.3*3.3*3.3, distance factor = 10. An anatomical MR data set with the following parameters (T1-weighted, MDEFT sequence [Deichmann, 2004]): 176 slices, $1*1*1mm^3$ voxel size was collected in addition. The pre-processing steps (using the Brainvoyager software) included 3D motion correction, slice scan time correction, linear trend removal, temporal highpass filtering (3 Hz), Gaussian filtering (2.8 sec.), and spatial smoothing (8mm). After the pre-processing analysis steps, we did a multi-subject study analysis (general linear model [GLM]). None of the subjects of the pilot study showed head movement larger than 1mm, therefore, no motion predictor was conducted.

4.2.4 Results of the pilot study

The results of the activation during localizer condition are listed below (table 4.1; figures 4.5 and 4.6). As you can see, our localizer conforms to the EBA, the PPA, the FFA and the OFA known in the literature (Peelen and Downing, 2005; view right column of table 4.1). The contrast analysis of the object stimuli contrasted with the other stimuli categories reflects (precuneus, middle occipital gyrus) a more general visual activation than a specific known area.

Table 4.1: *Talairach coordinates of brain areas active during visual localizer conditions in the pilot control group compared with published coordinates of higher visual areas* (max. cluster spread range: 30; max. cluster size: 300 voxels).

Localizer	Anatomical name (Brodmann area [BR])	Talairach coordinates	Cluster size	Localizer Literature (Peelen and Downing; 2005)
Body	Inferior temporal gyrus/middle temporal gyrus (37)	-46, -71, -1 45, -61, -3	2388 4219	EBA: -43, -72, -2 46, -70, -1
Scene	Lingual gyrus (18/ 19)	-17, -67, -6 15, -71, -4	4516 8392	
Scene	Posterior cingulate (30)	-18, -55, 6 21, -57, 14	3576 2450	PPA: -23, -44, -9 27, -40, -7
Face	Precuneus (31)	-10, -56, -33	870	FFA: -38, -46,-16 41, -47, -17
Face	Superior/middle temporal gyrus	-46, -72, 29 58, -59, 26	1449 1963	OFA: -36, -73, -17 37, -74, -17
Face	Superior frontal gyrus (8/9)	-14, -42, 42 24, 39, 33	915 994	
Object	Middle occipital gyrus (19)	-38, -72, 4 38, -77, 8	372 324	
Object	Precuneus (31)	-4, 68, 27	779	

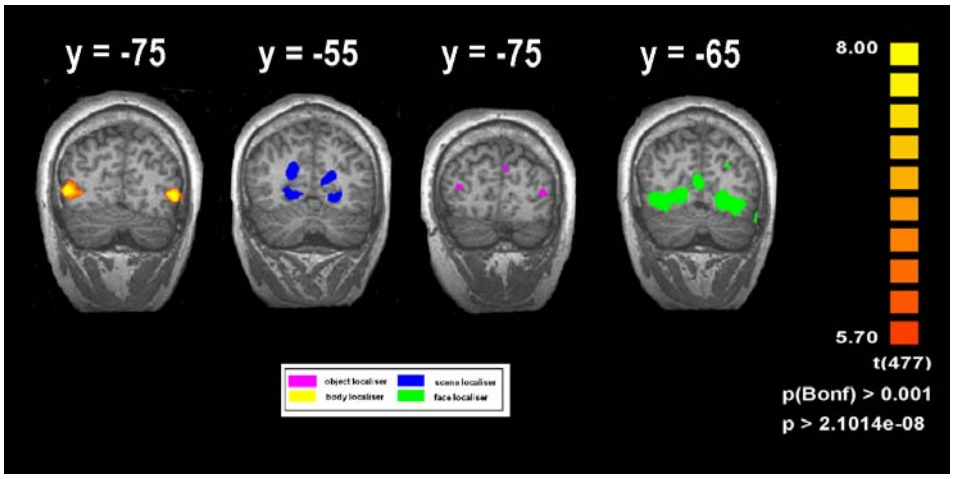


Figure 4.5: *Coronal slices showing activity during localizer scans at the level of the EBA (bilateral inferior temporal and middle occipital gyrus: y = -75), PPA (parahippocampal gyrus: y =-55), object localizer (middle occipital gyrus (y = -75) and OFA (superior / middle temporal gyrus: y = -65). The left side of the images shows the right side of the brain. Colour code (RGB-system): purple object localizer, yellow = body localizer condition, blue = scene localizer condition, green = face localizer condition. OFA = occipital face area, FFA = fusiform face area, PPA = parahippocampal place area, EBA = extrastriate body area.*

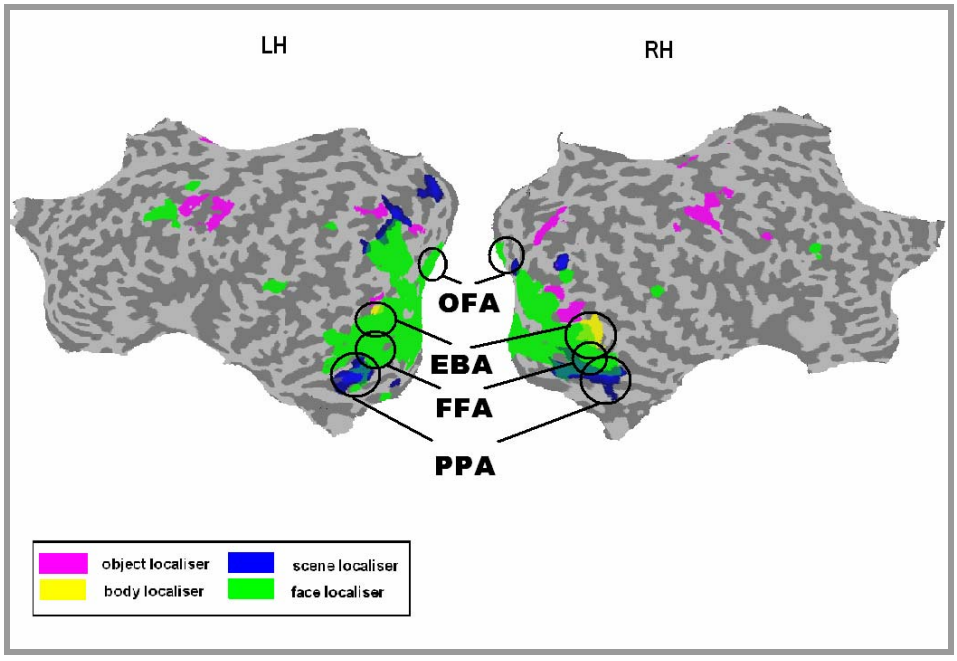


Figure 4.6: *Cortical activation maps (displayed on the MNI template brain) of the control group during localizer condition. Form left to right: a) flatmap of the controls' left hemisphere b) flatmap of the controls' right hemisphere. Colour code (RGB-system): purple object localizer, yellow = body localizer condition, blue = scene localizer condition, green = face localizer condition. OFA = occipital face area, FFA = fusiform face area, PPA = parahippocampal place area, EBA = extrastriate body area*

Part II: Visual hallucinations in schizophrenia investigated with fMRI

This part of the thesis is based on the publication: Oertel, V., Rotarska-Jagiela, A., van de Ven, V., Haenschel, C., Maurer, K., Linden, D.E.J. (2008). Visual Hallucinations in Schizophrenia investigated with fMRI. Psychiatry Research Neuroimaging 156; 269-273..

Abstract

We investigated a 27-year old patient with paranoid schizophrenia. Brain activity related to visual hallucinations was found in higher visual areas corresponding to the content of the hallucinations (faces, bodies, scenes), and the hippocampus. We assume that the hippocampal activity is related to the retrieval of visual images from memory.

4.3 Introduction

Hallucinations are a core symptom of schizophrenia, often causing considerable distress. They can be defined as a perceptual experience in the absence of sensory input and can occur in all sensory modalities. They are most common in the auditory modality (70 %; Stephane et al., 2001; Verdoux and van Os, 2002), followed by the olfactory and visual (up to 32 %; Bracha et al., 1989) and tactile (4%; Bracha et al., 1989) domain. Previous functional magnetic resonance imaging (fMRI) studies of hallucinations in schizophrenia focused on the auditory modality and yielded activity of auditory cortex, language and limbic areas (e.g., Dierks et al., 1999; Van de Ven et al., 2005). The present case report is the first fMRI study that reveals the direct neural correlates of visual hallucinations in schizophrenia.

4.4 Material and methods

4.4.1 Assessment of psychopathology

We examined a 27-year old, right-handed male out-patient with paranoid schizophrenia (295.30 according to DSM-IV criteria [American Psychiatric Association, 1994]), with a 12-year duration of the illness, currently treated with clozapine (150mg/d). Psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS [Kay et al., 1987]; total score: 53; positive: 16; negative: 11; general: 26). A measure of predisposition towards hallucinations (Revised Hallucination Scale; Morrison et al., 2002) differed by over 2 SD from those in a comparable healthy cohort (Sack et al., 2005). The last period of auditory hallucinations had occurred four weeks before the scanning, whereas he was experiencing visual hallucinations on a daily basis when we scanned him.

In addition, the visually hallucinating patient showed significantly lower values in the cognitive abilities like verbal intelligence, psychomotor speed and perceptual abilities compared with 12 non-hallucinating and 8 hallucinating patients with SZ (view chapter 2). Additionally, the patient had a high feeling of social dependency, a higher chance control orientation and a

powerful others external control orientation (as assessed in the questionnaire CCBS [Krampen, 1991]).

The quality and content of the hallucination episodes was recorded directly after the measurement by verbal report and a brief interview based on Aggernea's criteria (1972). Additionally, the patient was instructed to draw his hallucination images on paper after the measurements. The patient reported visual hallucinations of common objects, faces and bodies of people in his surroundings, sitting or standing in a landscape. The hallucinations varied in size and colour but not in the content, and the images seemed well-defined. The eight hallucination episodes recorded during scanning (average duration: 28.38s (SD = 20.80 s, range: 6-74 s) always included one or several family members who had objects in their hands or were sitting on a table or in a known room. On all occasions the patient reported seeing both the actual objects and people, and their shadows, and that the perceptions were always as clear as those evoked by visual stimuli. He was convinced that the people he perceived were actually in the room but that no other person could perceive them.

The anatomical MRI scans were reviewed by a neuroradiologist who did not find underlying pathology in the visual cortex or surrounding areas. Optometric analysis revealed normal visual acuity (monocular and binocular) and normal stereoscopic vision, and no abnormal eye movements. Monocular and binocular visual acuity were tested independently (critical value > 1.0 decimal) through the aperture angle of the eyes by means of the subject's ability to discriminate between maximum black and white colour levels at fixed luminance.

Unequal scores of monocular vision below the critical value may be manifestations of unbalanced binocular input such as found in strabismus or amblyopia. There optical impairments have been related to binocular rivalry and attentional splits of the visual field (Sireteanu et al., 1993). Consequently, cortical processes underlying visual integration, such as neural synchronisation, may have been impaired due to the visual deprivation of one eye (Sireteanu, 2000). To ensure that the participant had normal or near to normal binocular vision, i.e. the ability to merge binocular visual input into a stable visual representation, the patient was additionally examined with a stereoscopic vision test of the apparatus. The critical score for binocular vision was 4 (on a scale from 1 to 9) and participants whose scores were below this value were excluded from further participation. Finally, the SZ patient was screened for eventual height and side aberrations of the optical musculature, a condition that may also impair visual integration. The assessment of underlying pathology and visual acuity was done also for the control subjects of the pilot study.

The patient experienced hallucinations despite neuroleptic treatment (clozapine, 150mg/d). The patient gave informed consent, and the experimental procedures were approved by the ethics board of the Johann Wolfgang Goethe University Medical School, Frankfurt am Main, Germany.

4.4.2 Image acquisition and analysis

We collected whole-brain functional (EPI sequence, 480 volumes, 16 slices, TR 1000 ms, TE = 30 ms, flip angle = 60°, voxel size: 3.3x3.3x5 mm3, distance factor 10 %,) and anatomical MRI data sets (T1-weighted, MDEFT sequence [Deichmann, 2004]: 176 slices, 1x1x1mm3 voxel size) on a 3 T Allegra MR tomograph (Siemens, Erlangen, Germany). The functional data set was aligned to anatomical images and transformed into Talairach space (Talairach and Tournoux, 1988). Pre-processing steps included slice scan time correction, 3D motion correction, linear trend removal, temporal highpass filtering (3 cycles/run), temporal Gaussian filtering (2.8 s full-width-at-half-maximum [FWHM]), and spatial smoothing (8mm FWHM).

We conducted two fMRI scans, one with button press for the hallucination measure, one for the localizer condition. During the first fMRI scan session, the patient was asked to press a button with his left index finger at the onset of a hallucination and to press the button again, when it stopped. The patient was instructed to keep his eyes open during scanning, which is a standard procedure to ensure that the participants stay awake during long scanning sessions. The scanner room was completely dark during scanning. The first hallucination episode began 28 seconds after the start of the scanning, and the interval between the eight hallucination episodes lasted between 15 and 48 seconds (see table 4.2).

Table 4.2: *Report of the patient's visual hallucinations during the scan.*

	Number of hallucinations per 8-minute-scan	**Duration of the hallucinations (in seconds)**	**Mean duration of hallucinations (s)**	**Phenomenology**	**Motion corrected**
	8	11, 18, 6, 34, 74, 27, 30, 27	28,375	See description in the text	3 (13, 11, 18)

The sequence of hallucination periods was convolved with a hemodynamic response function and used as a hallucination predictor for the general linear model analysis. An additional "motion" predictor accounting for head movement was included in the design matrix. Data preprocessing and analysis were performed with the BrainVoyager QX software (BrainInnovation, Maastricht, The Netherlands).

We performed an additional fMRI session with a face-house-object-body localizer (Peelen and Downing, 2005) in order to map the higher visual areas FFA (fusiform face area), OFA (occipital face area), EBA (extrastriate body area) and PPA (parahippocampal place area) of the patient (for further detail view supplementary material). Both the hallucination epochs and the localizer conditions can be conceptualised as a block design, with blocks lasting on average 28.38s for hallucinations, and 15s for the localizer stimuli. Eight blocks of stimuli were presented in each condition of the localizer scan.

For the analysis of the functional data, we first computed a general linear model (Friston et al., 1995; Wicker and Fonlupt, 2003). The procedure provided maps of contrasts of interest for the subject. The averaged contrasts across the hallucination condition and the rest condition of the subject were then compared with a t-test.

The hallucinations button press protocol served as the basis of appropriate reference functions specifying experimental (hallucination) and control conditions (rest) (experimental condition = 1, control condition = 0). The resulting correlation map was thresholded at p (Bonf) < 0.001 (corrected) and the coefficients for the correlation between the main time course of each cluster of activated voxels and the reference function were calculated. For the activation clusters in the presumend primary auditory cortex (PAC) probability values were in addition corrected for multiple comparisons, using the estimates for left and right PAC that were derived by probabilistic mapping and MR volume measurements (Penhune et al., 1996). Activation of PAC was then thresholded again at p < .01 (corrected) to confirm its activation.

The results of the localizer session were then directly compared with the hallucination condition. The results of the regions of interests (ROI) of the localizer condition (EBA, PPA, FFA; LOC) counted as a basis and the hallucination activity in these specific regions was overlayed over the localizer activity to view the shared activation points.

4.5 Results

Significant activation (p = .01, corrected for multiple comparisons; cluster size threshold = 800 voxels) for the hallucination predictor was found in several higher visual areas (Fig. 4.7, Table 4.3), posterior cingulate, right hippocampus, superior parietal lobule, precuneus and the right middle temporal gyrus.

The results of our localizer scan conform to those of Peelen and Downing (2005) (Table 4.1). The higher visual areas activated during hallucinations corresponded well to the PPA bilaterally and to the left EBA, whereas the activation cluster in right fusiform gyrus was located posterior to the FFA and closer to the OFA (Peelen and Downing, 2005) (Fig. 4.8). Additional activation during hallucinations was found in left inferior temporal-/ middle occipital gyrus, corresponding to the lateral occipital complex (LOC), which is known to be engaged in object recognition.

Table 4.3: *Talairach coordinates and estimates of extent and amplitude of activation during visual hallucinations and localizer and comparison with published coordinates of higher visual areas.*

Area[a]	**Talairach coordinates**[b,c]		
	Hallucinations	**Visual localizer**	**Reference**[d]
Left lingual gyrus (19) **Right lingual gyrus (19)**	-15, -54, -2 (4592, 0.326) 14, -58, -1 (4148, 0.301)		
Right fusiform gyrus (19/37/20)	48, -65, -16 (3156,0.507)	**Faces:** 39, -45, -15 (5847, 0.178)	 41, -47, -17 37, -74, -17
Cuneus (18)	-5, -96, 16 (1960, 0.572)		
Parahippocampal gyrus left (19/35), right (19)	-17, -53, -8 (4211, 0.321) 19, -51, -5 (4639, 0.311)	**Scenes:** -31 -44 -3 (4939, 0.263) 24, -47, -5 (5065, 0.396)	 -23, -44, -9 27, -40, -7
Middle/inferior occipital gyrus left, right (19/20)	-44, -68, -5 (1705, 0.189) 46, -77, 11 (930, 0.284)	**Bodies:** -52, -75, 10 (2225, 0.122) 46, -71, 2 (2319, 0.083)	 -43, -72, -2 46, -70, -1
Right middle temporal gyrus (20/21)	58, -43, -14 (956, 0.290)	**Faces:** 58, -22, -13 (1978, 0.519)	
Right middle occipital gyrus (19)	44, -82, 11 (860, 0.284)	**Scenes:** 36, -81, 24 (1735, 0.452)	
Left and right superior parietal lobule (7)	-21, -59, 59 (829, 0.317) 12, -63, 54 (947, 0.295)		
Left intraparietal sulcus (7/19)	-28, -69, 34 (3034,0.244)	**Scenes:** -35, -74, 34 (1435)	
Left posterior cingulate/ parahippocampal gyrus (26/29/30)	-3, -50, 2 (1708, 0.305)		
Right posterior cingulate (30)	9, -54, 5 (1904, 0.320)	**Scenes:** 6, -55, 10 (1746)	
Right hippocampus	26, -13, -15 (875, 0.222)		
Right lateral occipital complex	48, -65, -16 (3156, 0.508)		43, -73, -18[e]

Notes: [a] Brodmann area (BA) where applicable, [b] in parentheses cluster size in number of voxels and [c] beta estimate for specific region and predictor; [d]source: Peelen and Downing, 2005; [e] source: Malach et al., 1995

Activation of sensory areas was not confined to the occipitotemporal stream of visual processing but included parietal areas involved in attention (superior parietal lobule and precuneus) and the right middle temporal gyrus. The limbic areas active during visual hallucinations were the posterior cingulate, and the right hippocampus.

Table 4.4: *Results of the region of interest analysis for EBA, PPA and FFA (corrected for serial correlations, contrast-analysis, degress of freedom = 1).*

Anatomical name (Brodmann area)	**Centre of mass of localizer cluster**	**t- (and p)-values for contrast hallucination vs. baseline**
EBA [16]: Right middle/inferior occipital gyrus (19/20)	46, -71, 2	4.224 (0.000029)
PPA [17]: Parahippocampal gyrus (19/35)	-31 -44 -3 24, -47, -5	3.388 (0.000763) 3.568 (0.000396)
FFA [18,19]: Right fusiform gyrus (19/38/20)	39, -45, -15	4.181 (0.000035)

The spatial correspondence of localizer and hallucination-related activity in higher visual areas (fig. 4.7, right column) was confirmed by a region of interest analysis, which yielded significant contrasts for hallucination vs. baseline in all higher visual areas identified by the localizer scan of the patient (table 4.4). Additional activation during hallucinations was found in the left inferior temporal-/middle occipital gyrus, corresponding to the lateral occipital complex (LOC), which is known to be engaged in object recognition (Malach et al., 1995).

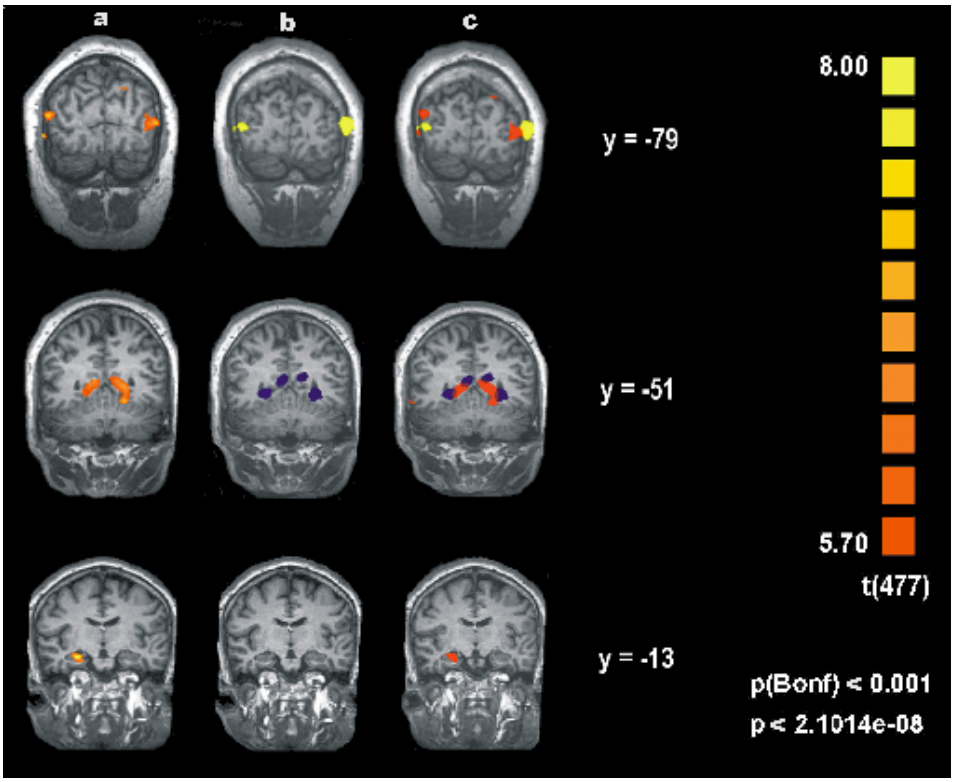


Figure 4.7: *Coronal slices showing activity, thresholded at p< .001, corrected for multiple comparisons (Bonferroni), during hallucinations (left column), localizer scans (middle column) and the overlay maps (right column) at the level of the EBA (bilateral inferior temporal and middle occipital gyrus: y = -79), PPA (parahippocampal gyrus: y =-51) and hippocampus (y = -13). The left side of the images shows the right side of the brain. Colour code for middle and right columns: red = hallucinations, yellow = body localizer, overlap hallucinations – body localizer = orange, blue = scene localizer, violet = overlap hallucinations – scene localizer.*

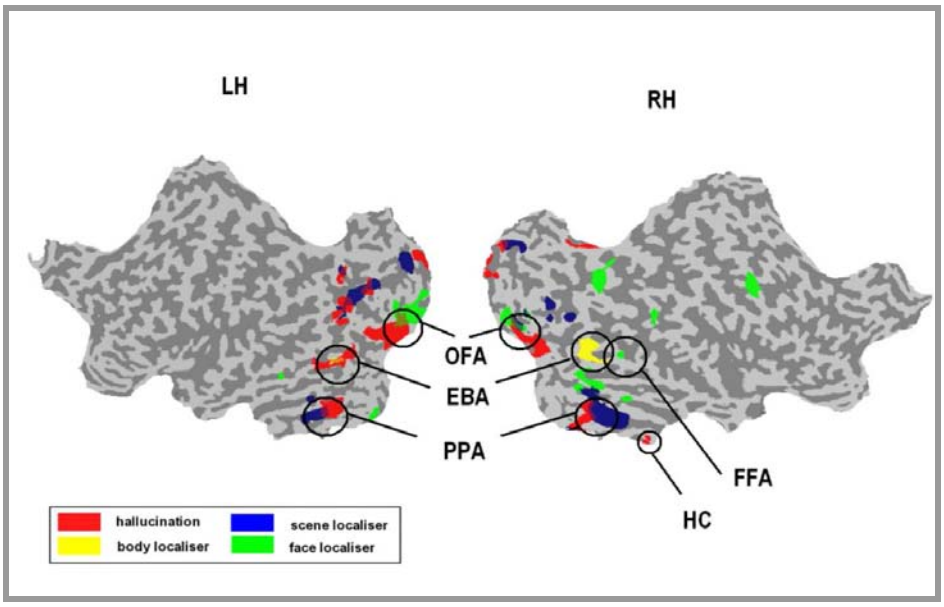


Figure 4.8: *Cortical activation maps (displayed on a flatmap of the patient's anatomy) of the patient during hallucination button press condition and localizer condition, thresholded at p< .001, corrected for multiple comparisons (Bonferroni). Form left to right: LH) flatmap of the patient's left hemisphere with the frontal pole pointing to the left RH) flatmap of the patient's right hemisphere with the frontal pole pointing to the right. Colour code (RGBsystem): red = hallucination button press, yellow = body localizer condition, blue = scene localizer condition, green = face localizer condition. OFA = occipital face area, FFA = fusiform face area, PPA = parahippocampal place area, EBA = extrastriate body area, HC = hippocampus.*

4.6 Discussion

The current study provides evidence for the involvement of visual, attention (superior parietal lobule, precuneus) and memory-related (posterior cingulate, hippocampus) areas in the generation or experience of visual hallucinations in schizophrenia. Sensory cortex activity might underlie the vividness and subjective reality of hallucinations (Dierks et al., 1999). However, in contrast to the primary auditory cortex activation found by Dierks et al. (1999) for auditory hallucinations, we did not observe activation in primary visual areas. Higher visual areas were activated in both hemispheres. Although we cannot infer patterns of lateralisation of hallucination-related activity from a single case, our finding of bilateral activation of sensory cortex conforms to the recent finding that sensory cortex activity related to auditory hallucinations is bilateral at least in some patients (van de Ven et al., 2005). The activation of higher visual areas during the patient's hallucinations of objects, faces and bodies corresponded to those commonly reported for visual stimulation with comparable material. A previous functional imaging study of a schizophrenia patient with both visual and auditory hallucinations that used positron emission tomography (Silbersweig et al, 1995) also found activation in visual association cortex. However, this study predates the discovery of category-selective higher visual areas and thus did not address the issue of content-specificity. Our findings also conform to studies of visual hallucinations in Parkinson's disease (Oishi et al., 2005) and Charles-Bonnet-

syndrome (ffytche et al., 1998). Oishi et al. (2005) used single photon emission tomography (SPECT) and found a hyperperfusion in the right superior and middle temporal gyri and associated this with the role of these regions in visual object recognition.

A similar association between the location of activity within specialized cortex and the contents of visual hallucinations has been observed for patients with Charles-Bonnet-syndrome (ffytche et al., 1998). However, that study had not reported activity of memory-related areas, which suggests that the neural mechanisms underlying hallucinations in schizophrenia are at least partly distinct from those operational in cortical deafferentation. The activation pattern during hallucinations was different from that commonly found in studies of visual imagery, where a prominent prefrontal activity reflects the active ideation (Trojano et al., 2004). In contrast to imagery, hallucinations are not under the subject's control, which might explain the absence of prefrontal activity in our study.

In sum, our data suggest that both limbic areas involved in retrieval from long-term memory and category-specific visual areas contribute to the generation of visual hallucinations in schizophrenia. Possible pathophysiological mechanisms include dopaminergic hyperactivity in the mesolimbic pathway, which might also explain the common phenomenon of L-dopa-induced hallucinations in Parkinson's disease, damage to cholinergic projections to visual cortex (Ffytche, 2005) and aberrant connectivity between limbic and sensory areas (Kubicki et al., 2003).

Part III: Functional neuroimaging of visual hallucinations during prolonged blindfolding

The part III of the present chapter is based on the manuscript: Sireteanu, R., Oertel, V., Mohr, H., Linden, D.E.J., Singer, W. (submitted). Graphical illustration and functional neuroimaging of visual hallucinations during prolonged blindfolding: A comparison to visual imagery. V. Oertel's contribution to the manuscript lies in the fMRI investigation and analysis, as well as the assessment of psychopathology.

Abstract

Visual hallucinations can occur in healthy subjects during prolonged visual deprivation. In this study, we investigated the visual percepts and the associated brain activity in a 37-year-old healthy female subject who developed visual hallucinations during three weeks of blindfolding, and then compared this activity with the cortical activity associated with mental imagery of the same patterns. We acquired fMRI data with a Siemens 3T Magnetom Allegra towards the end of the deprivation period, to assess hallucination-related activity, and again after recovery from blindfolding, to measure imagery-related activity. Detailed subjective descriptions and graphical illustrations were provided by the subject after blindfolding was completed. The subject reported the occurrence of simple and elementary hallucinations, consisting of flashes and coloured and moving patterns during the period of blindfolding. Neural activity related to hallucinations was found in extrastriate occipital, posterior parietal and several prefrontal regions. In contrast, mental imagery of the same percepts led to activation in prefrontal, but not in posterior parietal and occipital regions. These results suggest that deprivation-induced hallucinations result from increased excitability of extrastriate visual areas, while mentally-induced imagery involves active read-out under the volitional control of prefrontal structures. This agrees with the subject's report that visual hallucinations were more vivid than mental imagery.

4.7 Introduction

Vision can occur without adequate visual stimulation. Flashes of light, called *phosphenes*, can be induced by mechanical, electrical or magnetic stimulation of the retina or the brain. Phosphenes are well localized in the visual field and might appear in different colours, they are usually amorphous, but can develop into geometric patterns; their appearance depends on the stimulated location (Marg, Rudiak 1994; Kammer 1999).

Visual hallucinations occur in a wide range of diseases like schizophrenia, dementia with Lewy bodies (Parkinson desease), narcolepsy, Charles-Bonnet-syndrome and can be induced by hallucinogenic drugs or pharmacological treatment (Linden and Dierks, 2002). They have also

been reported during prolonged blindfolding in healthy subjects. Merabet et al. (2004) reported the occurrence of visual hallucinations after 1-2 days of blindfolding in ten of thirteen subjects.

Visual hallucinations can be defined as an involuntary image in the absence of sensory input. They can be classified into simple and complex hallucinations. Simple hallucinations mostly consist of dots, lines, shapes and moving patterns. Complex hallucinations often include the occurrence of other people, animals and more rarely objects like cars or tables (Collerton et al., 2005). Merabet et al. (2004) reported both simple and complex visual hallucinations after visual deprivation.

The underlying cognitive and neuronal mechanisms of visual hallucinations are still obscure. Schultz and Melzack (1991) proposed that lack of sensory input causes the release of stored images by disinhibition. Burke (2002) claimed that sensory deprivation leads to an increase in excitability of deafferented neurons in the visual cortex and is associated with an increase in spontaneous activity. Collerton et al. (2005) suggest in their Perception and Attention Deficit model (PAD) that impaired attentional binding and deficits in visual object perception cause the occurrence of complex visual hallucinations, reflected by disturbances in a lateral frontal cortex–ventral visual stream system.

The voluntary generation of mental visual images should be distinguished from involuntary visual hallucinations. Many authors suggest that visual imagery and perception share similar resources (Farah, 1988; Kosslyn et al., 1997), and activations in the visual cortex are often reported during mental imagery (Kosslyn et al., 1997; Cui et al., 2007).

In the current case we conducted a functional MRI scan with a female subject (MS) with simple visual hallucinations after three weeks of visual deprivation. In contrast to patients with Charles-Bonnet-syndrome, neurophysiologic changes by blindfolding are reversible, enabling us to compare directly the activation for visual hallucinations with the mental imagery of the hallucinated content. MS is a professional artist who covered her eyes as part of her art project *Blindversuch*. She initiated the study by contacting the Max-Planck-Institute and asking if we were interested in a scientific investigation. Since she experienced vivid visual hallucinations and at the same time was exquisitely able to verbalize and visualize her subjective experience, we decided to investigate the pattern of cortical activity related to deprivation-induced hallucinations. In addition, we performed a direct comparison of the brain activation related to hallucinations to that evoked by the mental imagery of the hallucinated images.

4.8 Material and Methods

4.8.1 Nomenclature

The visual percept experienced during blindfolding differs in several respects from the clinically experienced visual hallucinations. Patients with schizophrenia or under pharmacological influence usually do not distinguish between real images and those experienced during a hallucinatory episode; this was not the case with our subject. Therefore, terms like 'pseudohallucinations' or 'entoptic phenomena' (Tyler, 1978) might be more appropriate to describe her perceptual experience. However, since the subjective percepts occurring during prolonged blindfolding were already referred to as 'hallucinations' in the literature (Merabet et al. 2004), we opted to use this term throughout this study.

4.8.2 Assessment of psychopathology

The participant was a 37-year-old, university educated right-handed female subject without any psychiatric disorders according to DSM-IV criteria (American Psychiatric Association, 1994). She lived with a blindfold for a period of 22 days. To prevent binocular dissociation due to the unusually long period of visual deprivation, the blindfold was removed for 5 minutes each morning and evening, during which she performed vergence exercises in a darkened room. Care was taken to keep the visual input at a minimum during this time. Throughout the blindfolding period, she kept a diary on a dictaphone, in which she described her impressions. We screened her for psychiatric disorders (Structured Clinical Interview for DSM-IV-TR (SKID I [psychiatric disorders] and SKID II [personality disorders]; Wittchen, 1996; Positive and Negative Symptome Scale [PANSS]; Kay et al., 1987; German Version of the Schizotypy Personality Questionnaire [SPQ]; Raine, 1991; Klein et al.1997) or neurological pathology (optometric analysis).

Furthermore measures of predisposition towards hallucinations (Revised Hallucination Scale [RHS]; Morrison et al., 2002) and vividness of mental imagery (visual and auditory modality of the Betts Questionnaire upon mental imagery [QMI]; Sheehan, 1967) were both comparable to a healthy cohort (Sack et al., 2005). There were no psychiatric or neurology disorders in the family biography.

The subject was provided with a complete description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethical board of the Medical School of the Johann Wolfgang Goethe University, Frankfurt/Main, Germany.

The participant experienced simple and complex visual hallucinations during the state of sensory deprivation. The first appearance of hallucinations was two days after covering her eyes. She was experiencing visual hallucinations on a daily basis, until the first scanning session, which was conducted after three weeks of visual sensory deprivation.

During the fMRI measurement, the subject reported seeing mostly simple visual hallucinations. The quality, frequency and content of the visual hallucinations were assessed with a semi-structured interview in the week of the measurement and directly preceding the scan, and immediately after scanning. Additionally the subject drew her hallucination images on a paper after scanning. The visual hallucinations varied in size and colour but not in the content, and the images seemed well-defined. Specifically, on ten occasions she reported seeing coloured and non-coloured dots, lines, shapes and moving patterns. She was convinced that no other person could perceive the hallucinations she experienced.

A complete orthoptic examination, including visual acuity, colour vision, stereopsis, pattern of fixation, vergence, and eye motility, was administered by a professional orthoptist after collecting the fMRI data. The results of this examination did not reveal any abnormalities.

4.8.3 Image acquisition and analysis

We collected functional (EPI sequence, 16 slices, TR 1000 ms, TE = 30 ms, voxel size: 3.3x3.3x5 mm^3) and anatomical MRI data sets (T1-weighted, MDEFT sequence [Deichmann, 2004]: 176 slices, 1x1x1mm^3 voxel size) on a 3 T Allegra MR tomograph (Siemens, Erlangen, Germany). The fMRI acquisition volume covered all of neocortex except the most dorsal part of the medial frontal cortex, and the limbic system. The functional data sets were aligned to anatomical images and transformed into Talairach space (Talairach and Tournoux, 1988). Pre-processing steps included slice scan time correction, 3D motion correction, linear trend removal, temporal highpass filtering (3 cycles/run) and temporal Gaussian filtering (2.8 s full-width-at-half-maximum [FWHM]).

In sum, we computed six fMRI scans, consisting of two hallucination scans, three localizer scans (category localizer, MT-mapping, retinotopy-mapping) and one imagery scan. We computed all functional measurements and one anatomical data set with the same parameters. Only the number of volumes varied between the functional data sets (visual hallucinations and mental imagery: 480 volumes, retinotopy-mapping: 256 volumes, MT-mapping: 560 volumes).

The hallucination scans were conducted during a first measurement. After the first two fMRI and one anatomical measurement, the subject went out of the scanner. She had several hours to get off the tissue covering her eyes, open her eyes and habituate them in the surrounding. The time span between the first and the second measurement was three hours.

At the second scan session (on the same day), several localizer scans (retinotopic polar mapping, category localizer) were conducted in order to identify primary and higher visual areas. A third fMRI scan session was done after a 4-week break, including a MT-mapping and a mental imagery scan.

4.8.3.1 Hallucination scans

During the first and second fMRI scans (480 volumes), the subject was asked to press a button with her left index finger at the onset of a hallucination and to press the button again, when it stopped. The scanner room was completely dark during scanning. The subject had covered her eyes with a black tissue and dark sunglasses.

Altogether, the subject reported 10 periods of visual hallucinations, eight in the first session, and two in the second session. The duration of the hallucinations varied between 1 and 16 seconds (mean = 4, 5 sec.).

The sequence of hallucination periods was convolved with a hemodynamic response function and used as a hallucination predictor for the general linear model analysis. The head movement was under 1mm. Data preprocessing and analysis were performed with the BrainVoyager QX software (BrainInnovation, Maastricht, The Netherlands).

4.8.3.2 Localizer scans

We used retinotopic polar mapping, MT-mapping and a category localizer in order to identify primary and higher visual areas. Human MT localization was done by a GLM-contrast between presentation of static and a flow field of dots. The face-house-object-body localizer (Peelen and Downing, 2005) was conducted in order to map the higher visual areas FFA (fusiform face area), OFA (occipital face area), EBA (extrastriate body area) and PPA (parahippocampal place area) of the subject. The stimuli consisted of 40 full colour pictures of four categories (faces, scenes, bodies, chairs). Stimuli were back-projected on the centre of a screen, which was in view of the subject through an angled mirror positioned on top of the head coil.

4.8.3.3 Mental imagery scan

During the four weeks break between the hallucination scan and the mental imagery scan, the subject drew her experiences during the visual deprivation in several paintings. These paintings were used as a guideline for the imagery task. Previous to the scan, the subject was instructed to imagine the paintings and the images experienced during her visual hallucinations. Afterwards, during the fMRI scan, the subject was instructed to imagine the images for ten second periods, alternating with 15 second rest periods. In addition, she was asked to press a button with her left index finger at the onset of a mental image and to press the button again, when it stopped. The subject did not report hallucinations during the mental imagery and localizer sessions.

4.9 Results

4.9.1. Cortical activation during deprivation-induced hallucinations

Significant activation (p = .01, Bonferroni corrected for multiple tests; cluster size = 100 voxels) for the hallucination predictor was found in higher visual areas of the temporal lobe, parietal cortex, sensorimotor cortex and prefrontal cortex (PFC) (view fig. 4.9).

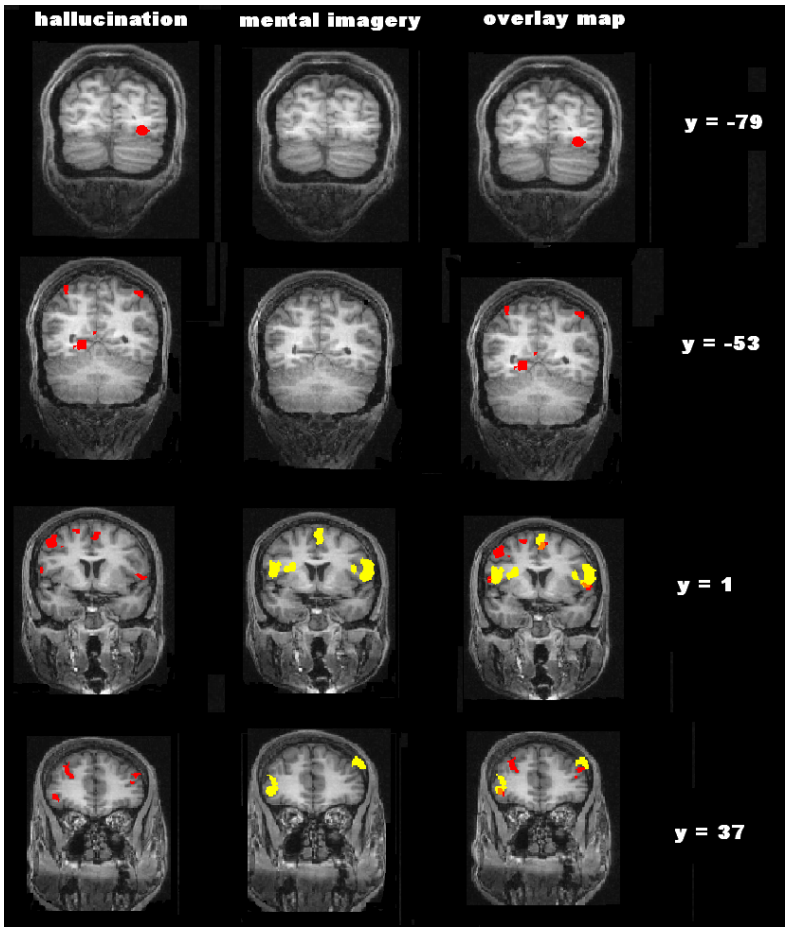


Figure 4.9: *Coronal slices showing activity during hallucinations (left column), mental imagery (middle column) and the overlay maps (right column: hallucinations – red, mental imagery – yellow) at the level of the lingual gyrus (y = -79), parahippocampal gyrus (y =-53), middle / superior frontal gyrus (y = 1) and inferior frontal gyrus (y = 37). The left side of the images shows the right side of the brain. Colour code RGB-system): red = hallucinations, yellow = mental imagery, overlay hallucinations – mental imagery = orange.*

Visual areas active during hallucinations included the left lingual gyrus and the right parahippocampal gyrus (Table 4.5, left column). In PFC, left medial frontal gyrus, bilateral inferior frontal gyrus and bilateral middle frontal gyrus were activated.

4.9.2. Cortical activation during mental imagery of the same patterns

The results of our mental imagery scan conform to those found in the hallucination scan regarding the location of the activation cluster of frontal areas (Table 4.1, right column). However, the cluster size of frontal areas during mental imagery was considerably stronger than observed during hallucinations. Furthermore, a non-parametric statistical comparison (Wilcoxon-

test) ranking size of frontal clusters revealed significant larger cluster size of imagery condition versus hallucinations ($z = 2.07$, $p < .05$).

In contrast, none of the visual areas activated during visual hallucinations were found during the mental imagery process.

Table 4.5: *Talairach coordinates of brain areas active during visual hallucinations and localizer conditions in subject (p[bonf] = .01, range = 30, 100 voxel).*

Anatomical name (Brodmann area [BA])	**Hallucination button press condition** Talairach coordinates (cluster size)	**Mental imagery** Talairach coordinates (cluster size)
Left Lingual gyrus (18)	-23, -78, -6 (735)	
Parahippocampal gyrus (19)	22, -50, -1 (750)	
Insula (13)		-40, 8, 18 (2030) 30, 11, 23 (2727)
Superior parietal lobule (7)	-12, -70, 57 (140) 10, -67, 55 (368)	
Inferior parietal lobule (40)	-37, -50, 60 (508) -51, -47, 39 (177) -46, -34, 51 (119) 56, -37, 24 (839) 53, -34, 45 (640) 37, -44, 79 (2268)	-46, -54, 59 (101) -49, -42, 60 (102) -64, -35, 43 (735) 42, -40, 51 (239)
Postcentral gyrus (3, 2, 5)	-38, -31, 60 (350) 41, -40, 58 (2589)	
Precentral gyrus (6)	-30, -12, 58 (168)	40, -8, 59 (2743)
Precentral gyrus (4)	-48, -7, 51 (214)	-53, -9, 57 (1790)
/Inferior frontal/ Precentral gyrus (44)	-45, 5, 8 (741) 43, -15, 10 (2752)	-52, 6, 16 (4480) 48, 4, 21 (2868)
Inferior frontal gyrus (46)	42, 37, 3 (278)	
Medial frontal gyrus (6)	-8, -11, 57 (256)	-3, 3, 58 (1649)
Middle / superior frontal gyrus (6)	25, -1, 62 (679)	
Middle frontal gyrus (9)	-42, -38, 34 (125) 29, 41, 37 (657)	41, 32, 15 (1989) -46, 36 37 (1946)

The results of our category localizer scan conform to those of Peelen and Downing (2005) (Table 4.1 and 4.6). The higher visual areas activated during hallucinations corresponded well to the parahippocampal place area PPA bilaterally. Activation in lingual gyrus overlapped with V2, ventral posterior area (VP) and ventral V4, generated by retinotopic polar mapping (see figure 4.10).

Table 4.6: *Results of the category localizer.*

Category	Cluster
Face	Fusiform Face area: 39, -45, -13 (127)
Body	Middle occipital gyrus (37): -50, -58, 3 (170) 45, -65, 4 (2742)
Scene	Parahippocampal gyrus (36): -27, -41, -10 (648) 28, -38, -8 (432)
Object	Precuneus (19): -40, -74, 40 (596) 47, -69, 39
Flow Field	MT: -49, -59, 3 (320) 40, -64, 0 (527)

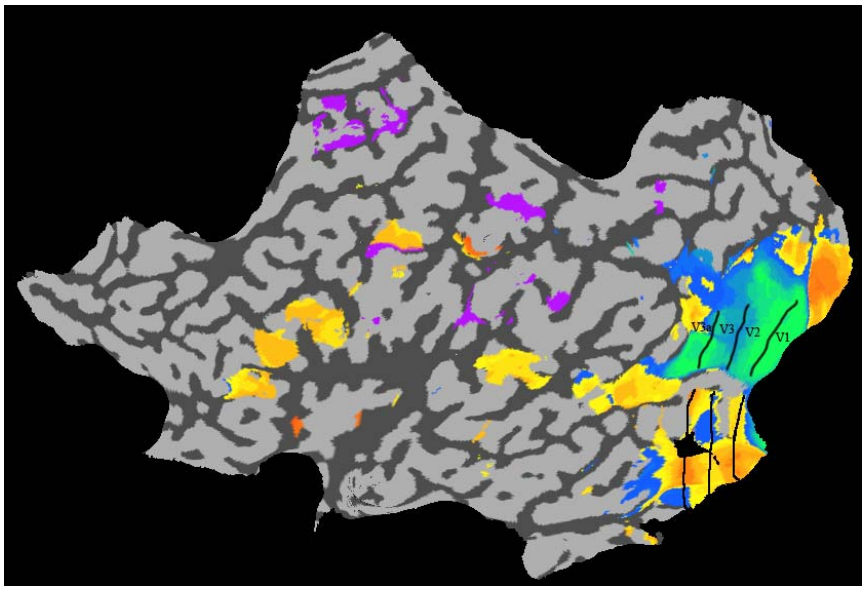


Figure 4.10: *Cortical map showing the activation map during hallucination including a V1-V4 map. Colour code (RGB-system): black = hallucination, all other colours: retinotopy. The black stripes show the borders between V1-V4.*

4.9.3 Comparison of hallucination-related with imagery-related activation patterns

There are clear distinctions between the two activation patterns. Visual areas in the occipital region (V2 and VP) and on the ventral visual pathway (V4, PPA) were involved in the generation of visual hallucinations, but not of imagery; visual hallucinations, but not mental imagery, activated areas in the superior parietal lobule (Brodmann area 7). The inferior parietal lobule (Brodmann area 40) showed stronger activity in the hallucination than in the mental imagery condition. The premotor (BA 6) and motor cortices (BA 4) were activated in both hallucination and mental imagery conditions; in both cases, activity was stronger in the mental imagery than

in the hallucination condition. Activity in several regions of the prefrontal cortex (Brodmann areas 9, 44 and 46) was seen with both hallucinations and imagery, but was more focused and significantly stronger for the mental imagery than for the hallucination condition. Cluster sizes in frontal areas were significantly larger during mental imagery than those observed during hallucinations, as revealed by a non-parametric statistical comparison (Wilcoxon-test) based on ranking size of frontal clusters ($z = 2.073$, $p < .05$).

Fig. 4.9 shows examples of the activation patterns during perception of visual hallucinations induced by blindfolding (left column) and during wilfully generated images of the same patterns (middle columns), as well as the overlay regions between the two patterns (right columns).

4.10 Discussion

Our results suggest that blindfolding-induced visual hallucinations are based on the spontaneous activation of a string of cortical regions, including visual areas in the occipital cortex and the extrastriate ventral pathway. Activity in the posterior parietal and frontal cortex might emerge secondary to the hallucination percept. This activation pattern differs from that evoked by mental imagery. These findings support the assumption that blindfolding enhances the excitability of the deafferented, unimodal visual areas on the ventral visual pathway, and of regions in the parietal and frontal cortex involved in the control of visual attention.

The current study provides evidence for the involvement of visual areas (V2, V3, V4), upon the ventral pathway, in the generation of vivid simple visual hallucinations, but not for mental imagery. The mental imagery condition, which was reported to be less vivid, did not elicit activations in visual and ventral pathway regions. Sensory cortex activity might underlie the vividness and subjective reality of hallucinations (Dierks et al., 1999).

Our finding is compatible with Burke's (2002) suggestion that sensory deprivation leads to an increase in excitability of deafferented neurons in the visual cortex and is associated with an increase in spontaneous activity.

However, in contrast to Dierks et al. (1999), who found primary cortex activation for auditory hallucinations, we did not observe activation in the primary visual area V1. We found activation of secondary and higher visual areas of ventral pathway during the subject's simple hallucinations. This corresponds to those reported for visual hallucination in a SZ patient used positron emission tomography (Silbersweig et al, 1995). There, activation in visual association cortex was found, either. However, ffytche (1998) found cerebral activity in ventral extrastriate visual cortex during complex visual hallucinations of patients with Charles-Bonnet-syndrome.

In contrast to the memory-related areas found by Oertel et al. (2007) for visual hallucinations in a schizophrenic patient, we did not observe activity in memory-related areas.

The study of ffytche (2005) had not reported activity of memory-related areas, which suggests that the neural mechanisms underlying hallucinations in schizophrenia are at least partly distinct from those operational in cortical deafferentation.

The finding of superior parietal lobule activation during blindfolding-induced hallucinations could be due to spatial attention during hallucination. During mental imagery, no evidence for superior parietal activation was found.

Conversely, a larger amount of activated voxels in prefrontal areas occurred during imagery condition in comparison with hallucinations. The activation pattern in frontal areas for mental imagery may reflect a stronger top-down control in voluntary generation of mental images (Trojano et al., 2004). In contrast, during hallucinations, visual images emerge spontaneously without voluntary top-down control of prefrontal areas.

The results suggest that blindfolding-induced visual hallucinations are based on the activation of visual ventral and posterior parietal areas. This finding contributes to the assumption that blindfolding changes the activation of sensory areas, which are, together with attention processes, involved in hallucination experiences. Collerton et al. (2005) propose that complex visual hallucinations are due to pathological processing in visual areas and to a deficit in attentional binding. Possibly, the hypothesis could be extended to simple visual hallucinations as experienced during this study. This theory might contribute to explain our finding of the involvement of visual areas during hallucinations.

In sum, our data suggest that visual and ventral areas both contribute to the generation of blindfolding-induced visual hallucinations. Visual hallucinations are more vivid and seem to be more strongly related to activations in visual areas than mental imagery. Conversely, prefrontal activation was higher during imagery. Differences in prefrontal activation, reflecting effortful generation and control over the experience, may be a main difference in the brain activation patterns of imagery and hallucinations.

CHAPTER 5: GENERAL DISCUSSION

Overview

In this thesis the investigation of the neural and cognitive underpinnings of auditory verbal (AV) and visual hallucinations in schizophrenia was framed as a multivariate problem. Beside the individual's psychopathology and its correlation to several cognitive parameters, neural substrates and underlying processing mechanisms of the brain are known to be responsible for the outcome of schizophrenia.

The experience of hallucinations is known to be one of the most important symptoms of schizophrenia. Hallucinations are sensory experiences which occur in the absence of external stimuli. However, their form of appearance and content are comparable to perception. The main factor is the lack of control over their sensations. Hallucinations can occur in all sensory modalities and under several conditions and pathological processes, e.g. during sensory deprivation, drug abuse, disturbances of the sensory systems (Charles-Bonnet-syndrome), epilepsy or affective disorders (Manford and Andermann, 1998). Hallucinations can even occur in normal individuals in non-psychiatric environments. Of special interest are AV hallucinations, the perception of voices in the absence of corresponding agents in the external world. In many cases the voices cause considerable distress and anxiety because they produce derogatory comments and / or command the patients to engage in shameful, dangerous or otherwise undesirable behaviours. Hallucinations in general have a lifetime prevalence of over 65 % (Bentall and Slade, 1988).

The most common opinion is that hallucinations are caused by damage that makes patients view internally generated information as coming from an external source. This deficit can be described as a loss of control by the mind which is known as *reality monitoring bias* (Bentall, 1990; David, 1999; Slade, 1994). The ability to distinguish between internal and external phenomena may be affected (Bentall et al., 1991). Overall, SZ patients may suffer from a cognitive deficit that prevents several memory-contents to be formed into a whole entity.

Mental images are also perceptual experiences which can occur in the absence of external stimuli, but, in contrast to hallucinations, mental images can be controlled and even stopped by the affected person (Kosslyn, 1994).

The present study begins with an investigation of a potential association between hallucinations and mental imagery. The involvement of mental imagery in hallucinations has proven to be a controversial issue. Some authors suggested that hallucinations and vivid imagery are somehow related (e.g. Mintz and Albert, 1972; Slade, 1972). In contrast, other investigations found no relationship between the two symptoms (Brett and Starker, 1977; Starker and Jolin, 1982; Sack et al, 2005). Furthermore, we explored the question of whether an increased

vividness of mental imagery is related to an increased tendency towards hallucinations or if the two constructs are totally independent from each other.

Another cognitive theory which could explain some aspects of the misinterpreted source of information is the locus of control concept which is based on the work of Rotter (1966). Loci of control are expressions of subjective intellectual evaluations to give an opinion of individual results of action. Levenson (1972) and Krampen (1981) extended the concept in a theory of three main control orientation personality traits. The relationship between the self-structure of a person (internal vs. external control orientation) and a source monitoring bias leading to hallucinations still remains unsolved. In sum, the consideration of cognitive attitudes, scanned in this thesis in a number of approaches, is part of a concept of therapeutic interventions, which improve personal skills by finding a model of illness.

Two main paper-pencil-studies were conducted. First, several psychometric instruments were used to identify cognitive and clinical correlates of hallucinations. Here, we investigated phenomenological and cognitive trait markers of schizophrenia, including cognitive correlates of hallucinations and the vividness of mental imagery. Then, clinical scales which assess susceptibility, attribution bias, personality structure, self concept and their relation to schizophrenia were examined. Here we focused on personal traits which could be responsible for the differentiation between SZ patients and high-risk individuals or persons who suffer from abnormal perceptual experiences. The test battery comprised questionnaires for the control orientation of the subjects and a measurement of cognitive dysfunction which could lead to the illness. Different cognitive correlates, a deficit in attribution systems ("attribution bias") and dysfunctional processing and integration of information could be responsible for the genesis of hallucinations. In addition, the individual psychopathology could also be an important fact in the genesis.

Many studies have focused on the perceptual aspects of hallucinations. This thesis follows a new line by collecting and comparing anatomical and functional brain imaging data with behavioural data sets. In the second main part of the work, several MRI sessions to investigate brain deficits of the subjects were implemented.

The main multivariate approach for the analysis of functional imaging data sets is the localisation of deficits in the auditory perception and processing brain areas. The auditory modality is the sensory modality where most SZ patients suffer from hallucinatory experiences. These results were compared with connectivity patterns in hallucinating patients (structural MRI data sets) and with behavioural data sets. Combining analysis tools with methods for measuring functional and anatomical connectivity (e.g. diffusion tensor imaging) was realised in order to better understand the role functional and anatomical connections between sensory cortex and higher-order areas play in hallucinations. A small number of structural imaging studies revealed decreased amounts of gray matter in schizophrenia in the left primary auditory cortex and

superior temporal gyrus, important for complex analyses of auditory signals (e.g., language, object identity). These structural changes are correlated with the presence and severity of auditory hallucinations. Other brain areas are known to be involved in hallucination processing as well. However, the exact relation between structure and hallucinations remains to be elucidated.

Moreover, the thesis included functional data sets of individuals experiencing visual hallucinations, which have rarely been investigated so far. The activity pattern during visual stimulation and visual hallucination was compared in order to identify identical and different brain areas involved in the processing of the brain.

The study of several markers and their potential relation to hallucinations should not be confined to patients with a clinical diagnosis of schizophrenia. A substantial minority of non-clinical population report hallucinatory experiences as well (Poulton, 2000; Laroy, 2006). While traditional models of schizophrenia posit a qualitative difference between normal and psychotic experience, van Os (2003) suggested that the differences may be quantitative rather than qualitative. Such a concept of a "continuum" of schizophrenia symptoms, such as hallucinations and delusions, would challenge a view of schizophrenia as a homogeneous disease entity. However, the attempt to find attenuated positive symptoms, akin to those described in the prodromal phase of schizophrenia (McGorry, 2003), in first-degree relatives of patients has so far been futile. The situation is different for certain brain abnormalities and cognitive deficits associated with schizophrenia, where similar but less pronounced deficits have been described in those with increased genetic vulnerability to the disorder (Whalley, 2005). Therefore we enlarged the study sample to include first-degree relatives and high-schizotypy individuals beside SZ patients and normal controls.

In sum, the present thesis deals with possible markers and an explanation for schizophrenia symptoms, especially for psychotic symptoms like hallucinations and their neural substrates and underlying processing mechanisms in the brain. The thesis includes phenomenological, cognitive and neuronal correlates of hallucinations, which were correlated with the individual's psychopathology.

Summary of results

Hallucinations and the mental imagery debate (chapter 2)

The scientific literature does not show an agreement on whether or not hallucinations are related to an increased vividness of imagined percepts. In 2005, members of our group published the finding of increased vividness of mental imagery in SZ patients (Sack et al., 2005). We have since continued on this line of research with a new sample, expanding the range of psychometric tests and questionnaires and including a group of first-degree relatives and high-schizotypy individuals.

Chapter two ("Mental imagery across the schizophrenia spectrum") presents the analyses of a set of cognitive and perceptual tasks, and mental imagery and hallucination questionnaires

that were answered by paranoid SZ patients, first-degree relatives and high- and low-schizotypy individuals. The cognitive tasks tapped into psychomotor speed and crystallized intelligence. The perceptual tasks measured aspects of perceptual closure, where subjects had to visually complete objects or written words, and had to extract geometric targets from a complex constellation of figures. Subjects were also given self-report questionnaires on the vividness of their mental imagery and the predisposition to hallucinate.

The main finding is that vividness of mental imagery was increased in all putative high-risk groups, relatives, high-schizotypy individuals and the patients themselves, compared with low-schizotypy controls. Therefore, it seems that vivid imagery is a trait rather than a state marker, and may be related to the genetic liability to develop schizophrenia. We would suggest that these findings constitute an important extension of the present reports on mental imagery.

However, no evidence was found for a linear relationship between vividness of mental imagery and predisposition to hallucinate. Self-reported imagery vividness and predisposition to hallucinate did not depend on psychomotor speed or crystallized intelligence. In addition, individual psychopathology ratings did not correlate significantly with the mental imagery scores. These findings suggest that increased (self-reported) vividness of imagery is strongly related to schizophrenia, regardless of the degree and severity of hallucinations. Thus, our data suggest that, in contrast to previous studies, hallucination frequency and severity do not directly correspond to imagery vividness, but that schizophrenia patients as a group are characterized by increased imagery vividness.

The substantial impact of the subgrouping of controls according to their SPQ scores in the present study highlights the importance of testing control groups in schizophrenia studies for the confounding effect of schizotypy. The conflicting results in the literature regarding more vivid imagery in patients than in controls may be due to the selection of participants. The finding of a potential perceptual trait of schizophrenia in the relative groups complements previous findings of subtle cognitive and neurobiological changes in high-risk groups.

External control orientation of SZ patients (chapter 2)

Chapter two also presents the analysis of the underlying personality structure and the degree of dysfunctional psychopathological status across the schizophrenia spectrum is presented. We focused on personal traits which could be responsible for the difference in the psychopathological status across unaffected SZ patients and high-risk individuals and subjects who suffer from abnormal perceptual experience, but don't suffer from acute symptoms of the illness schizophrenia directly.

In detail, we conducted two main paper-pencil tests: the German Version of the Competence and Control Beliefs Scale (CCBS; Krampen, 1991; based on the "locus of control"-construct [Rotter, 1966]) which was connected with measurements of dysfunctional symptoms of

schizophrenia (ESI, Maß et al., 2000). The questionnaires were then correlated to the predisposition towards hallucinations and the influence of individual psychopathology.

Overall, the results suggested that low-schizotypy controls as most internal-control-orientated contrasted to the SZ patients as most external-control-orientated. The first-degree relatives and the high-schizotypy controls form the centre of the continuum. In almost the same manner, the low-schizotypy controls had no visible signs of a dysfunctional status, whereas the SZ patients showed variable dysfunctional cognitive traits. As before, the first-degree relatives and the high-schizotypy controls scored higher than the low-schizotypy controls, but lower than the "sick" patients.

However, results showed an independence of control orientation and dysfunctional status from each other, as well as from other markers of schizophrenia or schizophrenia-like individuals, like the degree of predisposition towards hallucinations and individual psychopathology. Instead, the external locus of control correlated to delusions. Possibly, an attribution towards external power can lead to the appearance of delusions.

As a conclusion, a more external control orientation seems to be a symptom or a trait marker of schizophrenia. The results lead to the assumption that, beside individuals who suffer from the illness directly, first-degree relatives and schizotypy controls have some impairments and visible signs without suffering from the illness directly. This would lead to the further assumption that the illness schizophrenia is not only genetic but also dependent on environmental factors. Or, as the case may be, the characteristic of the genetic defect seems to be variable, e.g. in family members not as strong as in affected schizophrenia patients.

Functional and anatomical brain abnormalities of SZ patients (chapter 3)

The aim of this study was to identify neural correlates of dysfunctional auditory and language processing, which may contribute to the development of hallucinations in schizophrenia. Several studies have shown a different activation pattern during the presentation of auditory stimuli to SZ patients and healthy control subjects. However, none of the previous experiments examined first-degree relatives, and thus a possible genetic contribution to abnormal auditory and language processing is not clear.

Chapter three presents the results of an auditory stimulation task, measured with fMRI. During auditory stimulation (speech), SZ patients and their first-degree relatives had significantly lower activity in Wernicke's area bilaterally in comparison with controls. However, the activity in planum temporale was highest in patients, followed by first-degree relatives and the controls. In addition, the SZ patients showed a lower lateralisation of language areas towards the left, followed by the first-degree relatives and the controls. The decrease of lateralisation correlated with the severity of symptoms. The gray matter volume analysis mirrored the results from

functional imaging, with a pronounced loss of temporal lobe volume in patients, and less severe reductions in relatives.

Temporal lobe abnormalities (volume loss, reduced functional activation and lateralisation) were not confined to patients with schizophrenia but present, albeit to a lesser degree, in unaffected relatives. This suggests that they may represent a biological genetic marker of schizophrenia. The extent of temporal lobe abnormalities correlated with the severity of symptoms in patients. Loss of normal hemispheric asymmetry may thus be a factor in the development of schizophrenia and a key determinant of disease severity.

FMRI findings on visual hallucinations (chapter 4)

Brain correlates of hallucinations in other modalities than the auditory have rarely been investigated with functional neuroimaging. In chapter five, two individuals experiencing visual hallucinations were investigated with functional magnetic resonance imaging. We investigated a 27-year old male patient with chronic schizophrenia and a 37-year old healthy female subject with visual hallucinations after three weeks of visual deprivation. The activity patterns during visual stimulation and visual hallucination were compared in order to identify identical and different brain areas involved in the processing of the brain.

First, we have recently succeeded in obtaining the first fMRI measurements of a SZ patient during visual hallucinations, for whom we also have localizer data of higher visual areas ("Visual hallucinations in schizophrenia investigated with fMRI"). We describe activation of higher visual areas and the limbic system (hippocampus and posterior cingulate), corresponding to the intensity of the visual and emotional experience normally described by patients experiencing hallucinations. Interestingly, activity in higher visual areas followed the boundaries of category-selective areas corresponding to the patient's experience of bodies, faces and scenes. We assume that the hippocampal activity is related to the retrieval of visual images from memory. The pattern of brain activity may explain both the lack of subjective control over hallucinations and their vividness.

Second, we compared the visual hallucination-induced brain-activity during prolonged blindfolding with a mental imagery task ("Functional neuroimaging of visual hallucinations during prolonged blindfolding"). The healthy subject reported the occurrence of moving amorphous patterns, flashes and changing colours during the scan. Neural activity correlated to hallucinations was found in occipital visual, bilateral posterior parietal and prefrontal regions. In contrast, mental imagery of the phenomena did not lead to activations in occipital regions. Sensory cortex activity might underlie the vividness and subjective reality of hallucinations (Dierks et al., 1999). This result suggests that alterations in visual and attentional regions are related to the experience of visual hallucinations. Furthermore, visual hallucinations seem to be more vivid and more strongly related to activations in visual areas than mental imagery.

In contrast to the memory-related areas found in the SZ patient experiencing visual hallucinations, we did not observe activated memory-related areas during visual hallucinations induced by blindfolding. This suggests that the neural mechanisms underlying hallucinations in schizophrenia are at least partly distinct from those operational in cortical deafferentation. In sum, the data suggest that visual and ventral areas both contribute to the generation of blindfolding-induced visual hallucinations.

We believe that these case reports are of general interest in a field where studies in larger samples cannot be easily performed. We have been screening patients with hallucinations for fMRI for years now, and this is the first schizophrenia patient with visual hallucinations who could be scanned. This seems to be of interest to a general medical audience because hallucinations are not confined to neuropsychiatric disorders but also occur in a number of medical conditions, i.e. sensory deprivation (toxic or metabolic, for example). We would suggest that it is of crucial conceptual importance to study hallucinations in schizophrenia with functional imaging in order to determine their relationship with non-psychotic hallucinations, and with hallucinations in other sensory modalities. This method also demonstrates the power of functional imaging as a "window into the patient's mind".

Direct answers to the expressed hypotheses

The assumption, that schizophrenia is characterized by an increased vividness of mental imagery was approved in this thesis. Furthermore, the suggestion of a continuum of SZ patients, first-degree relatives, high-schizotypy and low-schizotypy controls in the vividness of mental imagery and the predisposition towards hallucinations was approved, too. However, the hypothesis, that an increased vividness of mental imagery is related to an increased tendency towards hallucinations, could be refused. In the additional performed analyses of young SZ patients, the results reflected the same pattern as shown for the normal SZ patient group.

Furthermore, our results confirmed to the hypothesis, that schizophrenia is characterized by an external control orientation and a more dysfunctional status than the other subjects. The results showed here, as we suggested, also a continuum of SZ patients, first-degree relatives, high-schizotypy and low-schizotypy controls. In addition, the results of the correlation analysis between the external control orientation and psychopathological symptoms are consistent with the assumption, that the external control orientation is related to delusions.

The assumption that the constructs predisposition towards hallucinations, vividness of mental imagery, external control orientation and dysfunctional status are independent of sociodemographic data could be approved.

The suggested continuum of SZ patients, first-degree relatives and healthy controls in the neurophysiological processing in the brain, was confirmed to the results. The cortical activation to

auditory stimuli was lower for patients than controls and intermediate for relatives. In addition, patients showed a lower lateralisation of language areas towards the left hemisphere compared to the control group. This decrease of lateralisation correlated with the severity of symptoms. Relatives again had intermediate values between patients and controls. The gray matter volume analysis mirrored the results from functional imaging, as we suggested at the beginning, with a pronounced loss of temporal lobe volume in patients, and less severe reductions in relatives.

At the beginning, we demand an abnormal activation pattern of visual hallucinations in the brain. This hypothesis could be approved, too. We did an additional analysis with a subject without suffering from schizophrenia. Here, we suggested that the cortical mechanisms underlying visual hallucinations differed in several parts to the mechanisms reported for visual hallucinations in SZ patients. This suggestion could be approved, too.

Conclusions and future directions

In summary, the findings of the present research allow a number of conclusions regarding dysfunctional processes in schizophrenia spectrum disorders. The results of the study could be seen as stable, because the sample size is sufficient. The group of patients could be seen as representative in the factors of gender, educational status, psychotic experience and acute symptoms. A qualification of the interpretation comes from a possible medication effect, because all patients were on medication during the measurement. As this medication did not, however, present identification of the patients as affected by schizophrenia, nor identification of their symptoms or dysfunctions, its effect may be seen as quantitative rather than qualitative, and so does not fundamentally impair the findings of this thesis which can be summarized as follows.

The results of the first study show that increased vividness of mental imagery is not a unique characteristic of hallucinations, but extends to the (paranoid) schizophrenia group as a whole. The associated cognitive impairments may be the expression of a single pathological factor, which is phenotypically expressed largely via negative symptoms. It would be interesting to investigate whether schizophrenics and their relatives could positively use their enhanced imagery ability for cognitive performance. This can be tested with the mental clock task (Trojano et al., 2000). Indeed, what can be problematic are the deficits in working memory and in executive functions that are extant in schizophrenia. It must be assumed that these deficits may overbalance the possible advantages of enhanced imagery ability. But the question of whether enhanced imagery ability is a trait marker of the schizophrenia spectrum ought to be closed. They are independent. So, an increased vividness of mental imagery seems to be a more accurate marker of schizophrenia than hallucinations: there are schizophrenics without hallucinations, but it seems, none without an increased imagery vividness.

The controversial results regarding the connectivity between mental imagery and hallucinations could be due to the fact that most of the authors used self-administered questionnaires. For this reason, additional control scales were used in the present thesis. There are currently no available means to study hallucinations separately from the subjectivity of the patients that experience them. An interesting point is the question of the existence of good and bad imagers, independent of individual psychopathology but dependent perhaps on age, handedness, social behaviour or attribution bias.

Functional magnetic resonance imaging (fMRI) is now being used routinely to measure variations in the level of brain activity, with a spatial resolution of several millimetres and a temporal resolution of several seconds. This technological advance is enabling a new area of research, namely of the relationship between brain and behaviour in humans. By combining introspective reports with this technique, new insights to the functioning of the mind would be possible.

The results of the imaging parts of this thesis suggest several lines of future directions in research. Why do not all hallucinating patients show primary (sensory) cortex activity? Is it possible that such activity is associated with the phenomenological content of the hallucinations? Several studies have shown that higher-order, but not primary cortices are active during auditory mental imagery in healthy controls and non-hallucinating patients. On a different level, it is not well understood in what sense functional and anatomical connections between sensory cortex and higher-order areas play a role in hallucinations in schizophrenia. Combining analysis tools with methods for measuring functional and anatomical connectivity (e.g. DTI) will likely be the path to answering these questions.

Individual differences in psychopathology as well as neuropsychological and psychosocial functioning may provide further means to understand the complex and highly dynamic aspects of hallucinations specifically and schizophrenia in general. At the same time, many of these questions require the recruitment of SZ patients, especially in the context of cognitive or neural disease-related changes. Other questions can be studied in healthy and non-clinical, schizophrenia-related subjects, for example non-clinical subjects that show a high loading of schizotypal traits, or close relatives of SZ patients. The enlargement of the subject sample to high-schizotypy controls and first-degree relatives of patients allowed new insights into the mental imagery debate and the dysfunctional connectivity pattern known to be responsible for psychotic symptoms. The question is, where is the border between cognitive and noticeable brain problems which are present in the schizophrenia spectrum and in relatives, and the illness schizophrenia itself ? This is maybe the most interesting question.

And something else: we have found at least four markers of schizophrenia following a continuum from the healthy individual to the schizophrenic patients: vividness of mental imagery, predisposition towards hallucinations, external control orientation and functional and anatomical

markers. This suggests, of course, a genetic origin of the illness. And, as we cannot assume that a malicious fate hit our schizophrenic patient in four places simultaneously, and with four different stages of development, we can only infer that the continua once had a beginning, that this beginning was triggered by something, that the present state is one moment in a development, and that a "culprit", presumably only one, may be detected, if we collect as many continua as possible and follow them back to where they perhaps converge, their source. Even if this might sound too simplistic and optimistic to many, it is maybe worth its while.

Zusammenfassung in deutscher Sprache

Das Ziel dieser Studie war, ein besseres Verständnis des Auftretens und der Ursache von Halluzinationen bei Patienten mit Schizophrenie zu bekommen. Da Schizophrenie und dessen klinische Symptome als ein multivariates Problem angesehen werden, wurde in dieser Arbeit das Phänomen der Halluzinationen von verschiedenen Ansatzpunkten aus betrachtet. Von besonderem Interesse war dabei, mögliche Zusammenhänge zwischen verschiedenen kognitiven Konstrukten, wie der Lebhaftigkeit der mentalen Vorstellungskraft und der Kontrollüberzeugung, eventuell in Verbindung zur individuellen Psychopathologie, und Halluzinationen zu bekommen. Darüber hinaus interessierten jedoch auch biologische Marker der Schizophrenie, die direkt mit Halluzinationen in Verbindung stehen könnten. Zusammenfassend suchten wir nach phänomenologischen, kognitiven und biologischen Markern der Schizophrenie. Von einem besseren Verständnis der den Halluzinationen zugrunde liegenden zerebralen und kognitiven Prozesse verspricht man sich bessere Möglichkeiten für die frühe Diagnose und Therapie von Schizophrenie. Die gesamte Studie wurde an drei Versuchspersonengruppen durchgeführt: schizophrene Patienten, ihren erstgradigen Verwandten und gesunden Kontrollprobanden. Bei den psychometrischen Testverfahren wurde die Gruppe der Kontrollprobanden zusätzlich noch in hoch- und niedrig- schizotype Personen unterteilt.

1896 wurde von Emil Kraeplin (1919) erstmals die Erkrankung, die wir heute als Schizophrenie kennen, als *dementia praecox* (premature dementia) benannt. Er ging davon aus, dass vor allem Jüngere von dieser Krankheit betroffen seien und dass sie dadurch vorzeitig altern würden. Die Bezeichnung der Erkrankung als Dementia sagte Eugen Bleuler, einem Schweizer Zeitgenossen von Emil Kraeplin, nicht zu, da er bemerkte, dass einige der Patienten Perioden hatten, in denen es ihnen besser ging. Bei einer Dementia jedoch geht man von einer nicht-reversiblen Erkrankung aus. Er etablierte 1911 daher den Namen *split* (schizo) *minds* (phrenia). Er ging klar von einer Gehirnabnormalität, nicht einer Hirndegeneration aus. Er ging primär von folgenden Symptomen aus, die die Erkrankung ausmachen: Halluzinationen, Wahnvorstellungen und Denkstörungen. Die aktuelle vertretene Auffassung der Erkrankung Schizophrenie stammt von Corw (1985), der eine Unterteilung zwischen positiven und negativen Symptomen postulierte. Positive Symptome z.B. beinhalten Halluzinationen und Wahnvorstellungen, negative beinhalten z.B. Denkstörungen, Affektstörungen und sozialer Rückzug. In dieser Arbeit interessierte vor allem das Symptome der Halluzinationen.

Halluzinationen sind sensorische Erfahrungen, die in der Abwesenheit von externen Reizen auftreten, aber den gleichen Inhalt wie eine „richtige Wahrnehmung" aufweisen können und von der erlebenden Person nicht direkt kontrolliert werden können. Das Erleben von Halluzinationen gilt als eines der häufigsten Symptome bei schizophrenen Patienten. Sie können alle sensorischen Modalitäten betreffen und unter verschiedenen Bedingungen und pathologischen Prozessen auftreten, z.B. bei einer Störung des sensorischen Systems (Charlet-

Bonnet Syndrom), physiologischen Störungen (sensorische Deprivation oder Fieber), unter der Einnahme von Medikamenten, bei Störungen des zentralen Nervensystems (Hirnunfälle), durch Halluzinogene verursachte Zustände, Epilepsie oder affektive Störungen (Manford and Andermann, 1998). Außerdem können Halluzinationen unter dem Einfluss verschiedener Drogen oder unter sensorischen oder Schlaf-Deprivationen auftreten (Ohayon et al., 1996). Von besonderer klinischer Bedeutung ist das Erleben von akustischen Halluzinationen, deren Prävalenz bei schizophrenen Patienten auf circa 60 % geschätzt wird (Bentall and Slade, 1988), da sie mit ihrem oft bedrohlichen und herabsetzenden Inhalt die Patienten sehr beeinträchtigen und einen großen Leidensdruck verursachen. Halluzinationen treten aber nicht ausschließlich bei an Schizophrenie erkrankten Menschen, sondern auch bei verschiedenen anderen psychiatrischen und neurologischen Krankheitsbildern und gelegentlich auch bei Normalpersonen auf.

Die meisten Forscher stimmen darin überein, dass Halluzinationen durch eine fehlerhafte Attribuierung (Zuschreibung) intern generierter Information an eine äußere Quelle zustande kommen. Diese fehlerhafte Attribuierung kann als ein Verlust der Kontrolle der Gedanken gesehen werden und wird dann auch als *reality monitoring bias* bezeichnet (Bentall, 1990; David, 1999; Slade, 1994).

Weiterhin scheinen Schizophrene unter einem kognitiven Defizit zu leiden, die eingehenden Informationen mit Gedächtnisinhalten zu einem kongruenten Ganzen zu verbinden. Dieses Defizit könnte spezifisch für diejenigen Bereiche sein, die starke Beachtung im Denken und Handeln der Patienten finden (z.B. halluzinatorische Erfahrungen).

Mentale Vorstellungen haben ebenfalls Wahrnehmungsqualitäten und treten auch in der Abwesenheit von erkennbaren Reizen aus. Der Unterschied zwischen Halluzinationen und mentalen Vorstellungen liegt darin, dass letztere normalerweise unter der Kontrolle der Personen liegen und durch den eigenen Willen generiert werden können (Kosslyn, 1994), während das bei Halluzinationen nicht möglich ist (Bentall, 1990). Bei Patienten mit Schizophrenie scheint die Fähigkeit, zwischen Halluzinationen und externe Reizen zu unterscheiden, gestört zu sein. Patienten scheinen häufig interne Ereignisse als von außen kommend zu beurteilen (Bentall et al., 1991).

Bisher sind die Befunde über den Zusammenhang der Lebhaftigkeit der mentalen Vorstellung und der Prädisposition hinsichtlich Halluzinationen widersprüchlich. Unklar ist bisher, ob diese beiden Symptome miteinander zusammenhängen oder als voneinander unabhängige Symptome der Schizophrenie zu betrachten sind. Mentale Vorstellungen sind ebenfalls Wahrnehmungserfahrungen ohne Anwesenheit eines Reizes, sie können aber von der erlebenden Person selbst - bis zu einem gewissen Maße - kontrolliert werden.

In einigen Studien wird ein enger Zusammenhang zwischen beiden Symptomen postuliert (Mintz and Albert, 1972; Slade, 1972). In diesen Studien konnte gezeigt werden, dass Schizophrene eine lebhaftere mentale Vorstellung haben, die über mehr perzeptuelle

Informationen verfügt, als das kognitive System aufnehmen und verarbeiten kann. Mintz and Albert (1972) gehen davon aus, dass Menschen, die Halluzinationen erfahren, nicht zwischen realen Wahrnehmungen und realitätsnahen mentalen Vorstellungen differenzieren können. Die lebhaftere Vorstellungskraft wird hier als wichtiger Faktor für die Genese von Halluzinationen angesehen.

In anderen Studien konnte kein Zusammenhang zwischen dem Auftreten von Halluzinationen und der Lebhaftigkeit der mentalen Vorstellung gefunden werden. Brett and Starker (1977) und Starker and Jolin (1982) konnten in ihren Studien keinen Unterschied in der Lebhaftigkeit der mentalen Vorstellung zwischen halluzinierenden schizophrenen Patienten und nicht - halluzinierenden Patienten finden.

Sack et al. (2004; eingereicht) konnten in ihrer Studie zeigen, dass zwischen der Prädisposition zu Halluzinationen und lebhafterer mentaler Vorstellung kein statistischer Zusammenhang besteht. Es wird angenommen, dass Halluzinationen relativ unabhängig von der Lebhaftigkeit der Vorstellung eines Menschen auftreten und ferner vor allem durch die oben genannten Defizite in der Verarbeitung und Zuordnung von Informationen bedingt sein können.

Die widersprüchlichen Befunde können zum Teil dadurch bedingt sein, dass in den meisten Studien, die bisher zu dem Zusammenhang zwischen Halluzinationen und lebhafter Vorstellungskraft veröffentlicht wurden, die Daten durch subjektive Skalen erfragt wurden.

In dieser Studie soll zunächst ein möglicher Zusammenhang zwischen Halluzinationen und mentaler Vorstellungskraft untersucht werden. Das Ziel ist es herauszufinden, ob die Personen, die Halluzinationen erfahren, eine stärkere Vorstellungskraft aufweisen im Vergleich zu Normalpersonen.

Weiterhin werden noch andere kognitive Theorien, die verschiedene Aspekte einer fehlinterpretierten Quelle an Informationen beinhalten, diskutiert. Eine dieser Theorien basiert auf der Arbeit von Rotter (1966), der das Konzept der Kontrollüberzeugung etablierte. Levenson (1972) und Krampen (1981) erweiterten das Konzept hinsichtlich internaler und externaler Kontrollüberzeugung. Eine Person, die eine externale Kontrollüberzeugung aufweist, geht davon aus, dass ihr Leben vom Schicksal, von anderen Personen oder anderen Handlungen beeinflusst wird, dass sie selber jedoch wenig Einfluss nehmen kann. Es stellt sich die Frage, ob eine solche Überzeugung möglicherweise dazu führt, dass man einige Prozesse des Gehirns als von außen eingegeben betrachtet, ein Vorgang, der mit Halluzinationen und Wahnvorstellungen in Verbindung stehen könnte.

Zusammenfassend ergaben sich folgende Ziele in dieser Arbeit: es sollten phänomenologische, kognitive und neuronale Korrelate von Halluzinationen bestimmt werden. Dabei wird angenommen, dass die Lebhaftigkeit der mentalen Vorstellung möglicherweise ein Marker der Schizophrenie ist, der unabhängig von dem Auftreten von Halluzinationen ist. Verschiedene kognitive Korrelate wie ein fehlerhaftes Attribuierungssystem und ein Defizit in der

Verarbeitung und dem Zusammenschluss von Informationen könnten sich als wichtige kognitive Symptome für die Genese von Halluzinationen herausstellen. Die individuelle Psychopathologie sowie andere kognitive Parameter wurden als Kovariaten in die Analyse aufgenommen.

Zur Einschätzung der Lebhaftigkeit der mentalen Vorstellungskraft wurde der *Betts Questionnaire upon mental imagery (QMI;* Sheehan, 1967) eingesetzt. Zur Bestimmung der Prädisposition zu Halluzinationen wurde die revidierte Fassung der *Launay-Slade Hallucination Scale (RHS;* Launay & Slade, 1981) verwendet. Um ein mögliches Defizit im Attributionsstil der Probanden zu überprüfen (*attribution bias)*, wurden die Probanden mit dem *Fragebogen für Kompetenz- und Kontrollüberzeugungen (CCBS;* Krampen, 1981) untersucht.

Des weiteren wurden verschiedene Testverfahren zur Beurteilung der perzeptuellen und kognitiven Leistungsfähigkeit eingesetzt: *Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B; Lehrl, 1989)* zur Überprüfung der verbalen Intelligenz, 3 Untertests des *Leistungsprüfsystems (LPS;* Horn, 1962*)* zur Beurteilung des perzeptuellen Leistungsvermögens und der *Trail making*-Test (Reitan and Wolfson, 1988) zur Beurteilung der psychomotorischen Geschwindigkeit.

Zusätzlich wurde allen Probanden zur Bestimmung des psychopathologischen Bildes das SKID (Strukturelles Klinische Interview Psychischer Störungen), den Patienten zusätzlich die deutsche Version der „p*ositive and negative Symptom Scale*" *(PANSS)* sowie den Verwandten der Patienten die prämorbide Anpassungsskala (PAS; Raine, 1997) und die deutsche Version des „Schizotypie-Questionnaire" (STQ) vorgelegt.

Einige Studien haben bereits kognitive und perzeptuelle Aspekte von Halluzinationen untersucht. Diese Arbeit verfolgt einen multivariaten Ansatz, in dem die in dieser Studie durch Fragebogenverfahren gewonnenen Daten mit hirnanatomischen und hirnphysiologischen Daten verglichen werden. Dabei interessiert besonders ein möglicher Zusammenhang zwischen anatomischen und funktionellen Verbindungsmustern des Gehirns und der Prädisposition zu Halluzinationen. Man weiß, dass schizophrene Patienten verschiedene Defizite bei der Verarbeitung von Informationen im Gehirn aufweisen. Dazu gehört z.B. eine verminderte Sprachlateralisierung, und verminderte Aktivierung in relevanten Gehirnbereichen. Darüber hinaus geht man von Volumenminderung verschiedenen anatomischer Bereiche im Gehirn bei Schizophrenie aus. In dieser Arbeit wurden Gehirnbereiche, die direkt mit Halluzinationen in Verbindung stehen könnten, wie auditorische und visuelle Bereiche, bezüglich Defizite in der Informationsverarbeitung und möglicher Volumenänderung untersucht.

Dazu wurden mit einem 3 Tesla Kernspintomographen funktionelle und anatomische Messungen aufgenommen und anschließend hinsichtlich möglicher Korrelate der Prädisposition zu Halluzinationen hin ausgewertet. Die funktionellen und anatomischen Bilder wurden dann mit den individuellen psychopathologischen Parametern verglichen. Die fMRT-Untersuchungen wurden mit so genannten *EPI*-Sequenzen (echo-planar-imaging) durchgeführt. Bei jeder Messung wurden 16 Schichten, die das gesamte Großhirn abdecken, in einem Abstand von 1 Sekunde

aufgenommen. Außerdem wurden eine hochauflösende T1-gewichtete dreidimensionale anatomische Messung mit einer *MP-RAGE*-Sequenz (magnetization prepared rapid acquisition gradient echo) und eine DTI-Messung, die den Fasciculus arcuatus und angrenzende Hirnregionen abdeckte, mit einer Dauer von je ca. 10 Minuten durchgeführt.

Direkte Beantwortung der Hypothesen

Die Hypothese, dass Schizophrenie durch eine vermehrte Lebhaftigkeit mentaler Vorstellungskraft charakterisiert sind, konnte in dieser Arbeit bestätigt werden. Weiterhin konnte die Vermutung eines Kontinuum in den Ergebnissen aus schizophrenen Patienten, erstgradigen Verwandten und hoch- und niedrig-schizotypen Kontrollprobanden bestätigt werden. Jedoch konnte die Hypothese, dass die Lebhaftigkeit der Vorstellungskraft einen Zusammenhang zu Halluzinationen aufweist, nicht bestätigt werden. Diese beiden Konstrukte scheinen unabhängig voneinander zu sein. Eine zusätzlich durchgeführt Studie mit jungen schizophrenen Patienten konnte die Befunde replizieren.

Darüber hinaus bestätigten die Ergebnisse die Vermutung, dass schizophrene Patienten eine mehr externale Kontrollüberzeugung aufweisen. Auch hier konnte die Kontinuum-Hypothese bestätigt werden. Die Hypothese, dass die externale Kontrollüberzeugung mit Halluzinationen in Zusammenhang steht, konnte nicht bestätigt werden. Jedoch konnte ein Zusammenhang zwischen der externalen Kontrollüberzeugung und Wahnvorstellungen gefunden werden.

Die Hypothese, dass die Konstrukte der Prädisposition zu halluzinieren, der Lebhaftigkeit mentaler Vorstellungskraft, der externalen Kontrollüberzeugung sowie des dysfunktionalen Status unabhängig von soziodemographischen Daten sind, konnte ebenfalls bestätigt werden.

Weiterhin zeigten die Ergebnissse der neurophysiologischen Untersuchung, wie vorher vermutet, ebenfalls das KOntinuum aus schizophrenen Patienten, erstgradigen Verwandnte sowie gesunden Kontrollprobanden, sowohl für die funktionellen als auch für die anatomischen Datensätze. Die zu Beginn der Studie aufgestellt Hypothese, dass visuelle Halluzinationen durch eine abnormale Verarbeitsmechanismus im Gehirn entstehen, konnte bestätigt werden. Die zusätzlich durchgeführte Analyse mit einer Probandin, die nicht unter Schizophrenie leidet, bestätigte unsere Vermutung eines teilweise unterschiedlichen Verarbeitungsmechanismus, der visuellen Halluzinationen zugrundeliegt.

Zusammenfassung der Ergebnisse

In der ersten Teiluntersuchung wurde geprüft, ob sich die mentale Vorstellungskraft bei den verschiedenen Versuchspersonengruppen, schizophrene Patienten, erstgradige Verwandte der Patienten, hoch-schizotype Kontrollpersonen und normale Kontrollpersonen, signifikant unterscheidet, und ob diese potentiellen Unterschiede eine Verbindung zu Halluzinationen, aufweisen. Das Hauptergebnis ist, dass die Lebhaftigkeit der mentalen Vorstellung in allen

potentiellen Risikogruppen, also Verwandten, hoch-schizotypen Personen und schizophrenen Patienten selbst, erhöht ist, wenn man sie mit der Lebhaftigkeit der mentalen Vorstellungskraft bei normalen Kontrollprobanden vergleicht. Die Ergebnisse zeigen Hinweise auf eine genetische Disposition zu einer vermehrten Lebhaftigkeit visueller Vorstellungen im schizophrene Spektrum. Jedoch zeigten die Ergebnisse nicht, wie von verschiedenen Autoren vermutet, einen direkten Zusammenhang zwischen der mentalen Vorstellungskraft und der Prädisposition zu halluzinieren. Beide Konstrukte scheinen darüber hinaus von psychomotorischer Verarbeitungsgeschwindigkeit und kristalliner Intelligenz unabhängig zu sein. Darüber hinaus besteht kein Zusammenhang zwischen der individuellen Ausprägung der psychopathologischen Symptome der schizophrenen Patienten und der subjektiven Einschätzung der mentalen Vorstellungskraft. Die Ergebnisse weisen darauf hin, dass die Lebhaftigkeit der Vorstellung eher etwas Überdauerndes (trait marker) als ein aktuell untersuchter Zustand (state marker) ist. Die Lebhaftigkeit der mentalen Vorstellungskraft scheint eine von Halluzinationen oder anderen psychopathologischen Symptomen unabhängige Auffälligkeit zu sein, die sich über das Schizophrenie-Spektrum erstreckt.

Weiterhin konnten bei der Untersuchung weiterer möglicher Korrelate zu Halluzinationen andere kognitive Konstrukte mit den gleichen Probandengruppen untersucht werden: das Ausmaß an externaler Kontrollüberzeugun sowie an dysfunktionalen psychopathologischen Zustandsbild. Hier zeigte sich, dass schizophrene Patienten eher zu einer externalen Kontrollorientierung neigen, während Kontrollprobanden eine internal orientierte Kontrollüberzeugung hatten. Hoch-schizotype Personen sowie Verwandte der Patienten bildeten die Mitte zwischen den beiden anderen Probandengruppen. Auch bezüglich des dysfunktionalen Status konnte das eben beschriebene Kontinuum gezeigt werden. Beide Konstrukte zeigten sich unabhängig voneinander, wie auch von Halluzinationen. Jedoch zeigte sich ein Zusammenhang zwischen der externalen Kontrollüberzeugung und einem anderen psychopathologischen Symptom der Schizophrenie, den Wahnvorstellungen.

Also scheint eine externale Kontrollüberzeugung ein Symptom oder ein Trait marker der des Schizophrenie-Spektrums zu sein. Diese Probandengruppen zeigen im Vergleich zu normalen Kontrollprobanden Auffälligkeiten, ohne dass sie an der Erkrankung direkt leiden. Dies könnte zu dem Schluss führen, dass gewisse Auffälligkeiten genetisch veranlagt sind, die Grenze zur Erkrankung Schizophrenie aber nur überschritten wird, wenn Umgebungs- oder andere Faktoren ungünstig dazu kommen.

Im zweiten Teil der Studie untersuchten wir anatomische und funktionelle Auffälligkeiten des Gehirns. Die neurologischen Daten zeigen eine niedrigschwellige Aktivität im auditorischen Kortex außerdem eine reduzierte Sprachlateralisierung bei Schizophrenen und ihren Verwandten im Vergleich zu Normalpersonen. Sprache wird normalerweise stärker linksseitig im Gehirn verarbeitet, bei unseren Patienten scheint dieser Mechanismus jedoch gestört zu sein.

Weitergehende Fragen zeigten, dass die Reduzierung der Sprach-Lateralisierung bei den Patienten in direkter Verbindung zu psychotischen Symptomen stehen. Je mehr psychotische Symptome die Patienten während des Zeitraums der Untersuchung aufwiesen, desto deutlicher gestaltete sich die Reduktion der Sprachlateralisierung. Diese Ergebnisse konnten auch für die Untersuchung des anatomischen Volumens des auditorischen Kortex gezeigt werden. Die hier vorliegenden Befunde sprechen für das schon zuvor beobachtete Kontinuum der Ergebnisse, von den Normalpersonen ohne Auffälligkeiten, zu den Verwandten mit leichten Auffälligkeiten, bis hin zu den Patienten mit deutlichen Auffälligkeiten in auditorischen und visuellen Verarbeitungsbereichen.

Im weiteren Verlauf untersuchten wir das Phänomen der visuellen Halluzinationen bei einem schizophrenen Patienten sowie bei einer Probandin, die visuelle Halluzinationen durch sensorische Deprivation bewusst herbeigeführt hat. Wir konnten zeigen, dass höhere visuelle Areale während des Erlebens von visuellen Halluzinationen aktiviert sind, die direkt mit den Grenzen Kategorie-spezifischer Areale einhergingen. Während es gelungen ist, bei dem schizophrenen Patienten Gedächtnis-Areale zu finden, die während visueller Halluzinationen aktiviert waren, konnte dieser Befund für die Probandin mit den durch sensorische Deprivation herbeigeführten Halluzinationen nicht bestätigt werden. Dieser Befund bestätigt die Vermutung, dass die neuronalen Mechanismen, die den visuellen Halluzinationen bei schizophrenen Patienten zugrunde liegen, teilweise anders als bei operationaler kortikaler Deafferentation sind.

Es wird vermutet, dass die Erkenntnis über individuelle Unterschiede in der Psychopathologie, sowie im neuropsychologischen und psychosozialen "funktionieren" helfen werden, die komplexen und hoch dynamischen Aspekte von Halluzinationen und, im weiteren Zusammenhang, von Schizophrenie generell, zu verstehen. Durch die Erweiterung der Stichprobe durch Hinzunahme von hoch-schizotypen Personen sowie von erstgradigen Verwandten schizophrener Patienten konnten wir neue Erkenntnisse bezüglich der Mental-Imagery Diskussion, aber auch bezüglich dysfunktionaler Konnektivitäts-Muster finden, die für psychotische Symptome verantwortlich sind. Weitere Möglichkeiten für die Forschung werden diskutiert.

CHAPTER 6: REFERENCES

Chapter 1

Aleman, A., Böcker, K.B.E., and de Haan, E.H.F. (1999). Disposition towards hallucinations and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual differences*, *27,* 707-714.

Aleman, A., Böcker, K.B.E., Hijman, R., de Haan, E.H.F., and Hahn, R.S. (2003). Cognitive basis of hallucinations in schizophrenia: role of top-down information processing. *Schizophrenia Research*, *15,* 64(2-3), 175-85.

Agartz, I., Andersson, J.L., and Skare, S. (2001). Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. *Neuroreport*, *12*, 2251-2254.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders* (4th edition). Washington, D.C.: APA.

Andreasen, N.C., and Olsen, S. (1982). Negative vs. positive schizophrenia: Definition and validation. *Archives of General Psychiatry*, *39*, 789-794.

Andreasen, N.C., Flaum, M., and Swayze, V.W. (1990). Positive and negative symptoms in schizophrenia. *Archives of General Psychiatry*, *47*, 615-621.

Appels, M.C.M., Sitskoorn, M.M., Westers, P., Lems, E., and Kahn, R.S. (2003). Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. *Schizophrenia Research, 63 (3),* 285-293.

Aylward, E., Walker, E., and Bettes, B. (1984). Intelligence in schizophrenia: meta-analysis of the research. *Schizophrenia Bulletin, 10 (3)*, 430-59.

Barrett, T.R., and Etheridge, J.B. (1992). Verbal hallucinations in normals I. People who hear "voices". *Applied Cognitive Psychology, 6*, 379-387.

Barrett, T.R. (1993). Verbal hallucinatiosn in normals, II: Self-reported imagery vividness. *Personality and Individual Differences, 15,* 61-67.

Belliveau, J.W., Rosen, B.R., Kantor, H.L., Rzedzian, R.R., Kennedy, D.N., McKinstry, R.G., Vevea, J.M., Cohen, M.S., Pykett, I.L., and Brady, T.J. (1990). Functional cerebral imaging by susceptibility-contrast NMR. *Magn. Reson. Med. 14 (3)*, 538-46.

Bentall, R.P. and Slade, P.D. (1985). Reality testing and auditory hallucinations: a signal detection analysis. *British Journal of Clinical Psychology, 24*, 159-169.

Bentall, R. and Slade, P. D. (1988). Towards an integrative model. In Sensory Deception (pp. 208-228).

Bentall, R.P., Claridge, G.S., and Slade, P.D. (1989). The multidimensional nature of schizotypal traits: a factor analytic study with normal subjects. *British Journal of Clinical Psychology, 28*, 363-375.

Bentall, R.P. (1990). The illusion of reality: A review and integration of psychological research on hallucinations. *Psychological Bulletin, 17*, 82-95.

Bentall, R.P., Baker, G.A., Havers, S. (1991). Reality monitoring and psychotic hallucinations: a brief report. *British Journal of Clinical Psychology, 30*, 213-222.

Berrios, G.E. (1996). *The History of Mental Symptoms*. Cambridge: Cambridge University Press.

Bleuler, E. (1950). *Dementia Praecox or the Group of Schizophrenias*. New York: International University Press (original work published in 1911).

Bloch, F., and Purchell, E. (1946). In: Rinck, P., Bjørnerud, A., de Francisco, P., Hennig, J., Jones, R.A., Kværnes, J., Muller, R.N., Southon, T.E., and Torheim, G. (2003). *Magnetic Resonance in Medicine.* The Basic Textbook of the European Magnetic Resonance Forum 5th edition.

Böcker, K.B.E., Hijman, R., Kahn, R.S., and de Haan, E.H.F. (2000). Perception, mental imagery and reality discrimination in hallucinating and non-hallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39*, 397-406.

Brebion, G., Smith, M.J., Gorman, J.M., and Amador, X. (1997). Discrimination Accuracy and Decision Biases in Different Types of Reality Monitoring in Schizophrenia. *Journal of Nervous and Mental Disease. 185(4),* 247-253.

Brett, E.A., and Starker, S. (1977). Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease, 163*, 394-400.

Broca, P. (1861). Sur le principe des localisations cérébrales. *Bulletin de la Société d' Anthropologie, tome II*, 190-204.

Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Johann Ambrosius Barth Verlag: Leipzig.

Brownstein, J. Krastoshevsky, O., McCollum, C., Kundamel, S., Matthysse, S., Mendell, N.R. and Levy, D.L. (2003). Antisaccade performance is abnormal in schizophrenia patients but not in their biological relatives. *Schizophr. Res.* 63, 13–25.

Buchanan, R.W., and Carpenter, W.T. (1994). Domains of psychopathology. *Journal of Nervous and Mental Disease, 182*, 193-202.

Bunzeck, N., Wuestenbergb, T., Lutzc, K., Heinzea, H-J., and Janckez, L. (2005). Scanning silence: Mental imagery of complex sounds. *Neuroimage 9.*

Cannon, T.D., Huttunen, M.O., Lonnqvist, J., Tuulio-Henriksson, A., Pirkola, T., Glahn, D., Finkelstein, J., Hietanen, M., Kaprio, J. and Koskenvuo, M. (1994). The Inheritance of Neuropsychological Dysfunction in Twins Discordant for Schizophrenia. *The American Journal of Human Genetics*, 67, 369–382.

Cannon, M., Jones, P., Murray, R.M. and Wadsworth, M.E.J., (1997a). Childhood laterality and later risk of schizophrenia in the 1946 British birth cohort. *Schizophr. Res.* 26, 117–120.

Cannon, M., Jones, P., Gilvarry, C., Rifkin, L., McKenzie, K., Foerster, A. and Murray, R.M. (1997b). Premorbid social functioning in schizophrenia and bipolar disorder: similarities and differences. *Am. J. Psychiatry* 154**,** 1544–1550.

Cardno, A.G., Gottesman, I.I. (2000). Twin-studies of schizophrenia: From bow-and-arrow concordances to Star Wars Max and functional genomics. *American Journal of Medical Genetics 97,* 12–17.

Carlsson, A., and Lindqvist, M. (1963). Effect of chlorpromazine or haloperidol on formation of 3-methoxytryamine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol., 20,* 140-144.

Carpenter, W.T., Strauss, J.S., and Muleh, S. (1973). Are there pathognomic symptoms in schikzophrenia? An empirical investigation of Schneider`s first-rank symptoms. *Archives of General Psychiatry, 28*, 847-852.

Carpenter, W.T., Heinrichs, D.W., and Alphs, L.D. (1988). Deficit and nondeficit forms of schizophrenia: The concept. *American Journal of Psychiatry, 145*, 578-583.

Chandiramani, K., and Varma, V.K. (1987). Imagery in schizophrenic patients compared with normal controls. *British Journal of Medical Psychology, 60*, 335-341.

Claridge, G. and Broks, P. (1984). Schizotypy and hemispheric function: I. Theoretical consideration and the measurement of schizotypy. Personality and Individual Differences, 5, 633-648.

Cohen, M.S., and Bookheimer, S.Y. (1994). Localisation of brain function using magnetic resonance imaging. *Techniques in Neuroscience, 17,* 268-277.

Cohen, M.S., Kosslyn, M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K., Bookheimer, S.Y., Rosen, B.R., and Belliveau, J.W. (1996). Changes in cortical activity during mental rotation. A mapping study using functional MRI. *Brain*, *119*, 89-100.

Cosway, R., Byrne, M., Clafferty, R., Hodges, A., Grant, E., Abukmeil, S.S., Lawrie, S.M., Miller, P. and Johnstone, E.C. (2000). Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychological Medicine, 30*, 1111-1121.

Crow, T.J. (1985). The two-syndrome concept: origins and current status. Schizophrenia Bulletin, 11, 471-486.

Crow, T.J., Ball, J., Bloom, S.R., Brown, R., Bruton, C.J., Colter, N., Frith, C.D., Johnstone, E.C., Owens, D.G., and Roberts, G.W. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Arch. Gen. Psychiatry,* 46 (12).

Crow, T.J. (1990). The continuum of psychosis and its genetic origins: The sixty-fifth Maudsley lecture. *British Journal of Psychiatry, 156,* 788-797.

Crow, T.J. (1997). Is schizophrenia the prize that Homo sapiens pays for language? *Schizophrenia Research, 28*, 127-141.

Csernansky, J.G., Joshi, S., Wang, L., Haller, J.W., Gado, M, Miller, J.P., Grenander, U., and Miller, M.I. (1998). Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Neurobiology, 95*, 19, 11406-11411.

Curtis, C.E., Calkins, M.E., and Iacono, W.G. (2001). Saccadic disinhibition in schizophrenia patients and their first-degree biological relatives. *Experimental Brain Research, 137 (2)*, 228-236.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatr. Scand.* 99, 95–104.

Datts, M.R., Bovbjerg, D.H., and Redd, W.H. (1997). Imagery in human classical conditioning. *Psychological Bulletin, 122*, 89-103.

Delay, S., and Deniker, D. (1952). In: Seeman, P. (1995). Dopamine receptors and psychosis. *Science and Medicine, 2(5),* 28.

DeLong, R., and Dwyer, J.T. (1988). Correlation of Familiy History with Specific Autistic Subgroups: Asperger'S syndrome and Bipolar Affective Disease. *Journal for Autism and Developmental Disorders, 18*, 4.

Dierks, T., Linden, D.E.J., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., and Singer, W. (1999). Activation of Heschl`s gyrus during auditory hallucinations. *Neuron, 22* , 615-621.

Ducreux, D., Petit-Lacour, M.C., Benoudiba, F., Castelain, V., and Marsot-Dupuch, K. (2002). Diffusion-weighted imaging in a case of Wernicke encephalopathy. *J. Neuroradiol.* 29, 39–42.

Ehret, G., and Romand, R. (1997). *The Central Auditory System*. Oxford University Press: New York.

Esquirol, J.E.D. (1832). Sur les illusions des sens chez alienes [On the sensory illusions of the insane].*Archives Generales de Medicine*, *2*, 5–23.

Faraone, S.V. Kremen, W.S., Lyons, M.J., Pepple, J.R., Seidman, L.J. and Tsuang, M.T. (1995). Diagnostic accuracy and linkage analysis: how useful are schizophrenia spectrum phenotypes? *Am J Psychiatry, 152*, 1286-1290.

Faraone, S.V., Seidman, L.J., Kremen, W.S., Toomey, R., Pepple, J.R., and Tsuang, M.T. (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. *Journal of Abnormal Psychology, 108* ,176-181.

Faraone, S.V., Skol, A.D., Tsuang, D.W., Young, K.A., Haverstock, S.L., Prabhudesaoi, S., Mena, F., Menon, A.S., Leong, L., Sautter, F., Baldwin, C., Bingham, S., Weiss, D., Collins, J., Keith, T., van den Eng, J.L., Boehnke, M., Tsuang, M.T. and Schellenberg, G.D. (2005). Genome scan of schizophrenia families in a large Veterans Affairs Cooperative Study sample: evidence for linkage to 18p11.32 and for racial heterogeneity on chromosomes 6 and 14. *Am J Med Genet B Neuropsychiatr Genet. 5, 139(1)*, 91-100.

Feinberg, I. (1988). Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophrenia Bulletin, 4*, 636–640.

Fenton, W.S. and McGlashan, T.H. (1991). Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Archives of General Psychiatry 48* (11).

Finke, R.A. (1989). *Principles of Mental Imagery*. Cambridge: MIT Press.

Formisano, E., Esposito, F., Kriegeskorte, N., Tedeschi, G., Di Salle, F., and Goebel, R. (2002). Spatial independent component analysis of functional magnetic resonance imaging time-series: characterization of the cortical components. *Neurocomputing, 49*, 241-254.

Frith, C.D. (1992*). The cognitive neuropsychology of schizophrenia*. Hillsdale: LEA publishers.

Ffytche, D.H., Howard, R.J., Brammer, M.J., David, A., Woodruff, P., Williams, S. (1998). The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nature Neuroscience, 1*, 738 – 742.

Ffytche, D.H. (2005). Visual Hallucinations and the Charles Bonnet Syndrome. Current *Psychiatry Reports, 7*,168-179

Gardini, S., De Beni, R., Cornoldi, C., Bromiley, A., and Venneri, A. (2005). Different neuronal pathways support the generation of general and specific mental images. *Neuroimage 27(3)*, 544-52.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., and Singer, W. (1998). The contstructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *European Journal of Neuroscience 10,* 1563-1573.

Gottesman, I.I. and Gould, T.G. (2003). The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry, 160,* 636-645.

Grossi, D., Modafferi, A., Pelosi, L., and Trojano, L. (1989). The "o'Clock Test" in two clinical cases. On the different roles of the cerebral hemispheres in mental imagery. *Brain cognition, 10(1)*, 18-27.

Grove, W.M., Lebow, B.S., Clementz, B.A., Cerri, A., Medus, C., and Iacono, W.G. (1991). Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. *J Abnorm Psychol., 100(2)*, 115-21.

Haines, D.H. (1991). Neuroanatomy: *An Atlas of Structures, Sections and Systems*. Williams and Wilkins: Baltimore.

Haslam, N. In : Hieke, J. (2003). *Schizophrenie-Erkennen und Verstehen.* Arbeiten aus dem Fachbereich Pädagogik-Pädagogische Psychologie.

Hietala, J., and Syvälahti, E. (1996). Dopamine in schizophrenia. *Annals of Medicine 28,* 557-561.

Hirsch, S.R. and Weinberger, D.R. (1995). *Schizophrenia.* London: Blackwell Science Ltd..

Hoffmann, R.E. and Rappaport, J. (1994). A psycholinguistic study of auditory/verbal hallucinations: Preliminary findings. In A.S. David and J.C. Cutting (Eds.), *The Neuropsychology of Schizophrenia,* 99-116. Hove: Lawrence and Erlbaum.

Hoffmann, R.E. Boutros, N.N., Berman, R.M., Roessler, E., Belger, A., Krystal, J.H., and Charney, D.S. (1999). Transcranial magnetic stimulation of left temporo-parietal cortex in three patients reporting hallucinated voices. *Biological psychiatry, 46*, 130-132.

Holcomb, H.H., Lahti, A.C., Medoff, D.R., Weiler, M., Dannals, R.F., and Tamminga, C.A. (2000). Brain activation patterns in schizophrenic and comparison volunteers during a matched-performance auditory recognition task. *Am J Psychiatry. 157(10*), 1634-45.

Horn, W. (1962). *Leistungsprüfsystem (LPS)*. Göttingen: Verlag für Psychologie.

Huber, G., Gross, G., Shuttler, R. and Linz, M. (1980). Longitudinal studies of schizophrenia patients. *Schizophrenia Bulletin, 6,* 592-605.

Hubl, D., Koenig, T., Strik, W, Federspiel, A., Kreis, R., Boesch, C., Maier, S.E., Schroth, G., Lovblad, K., and Dierks, T. (2004). Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatriy, 61*, 658-668.

Ingvar, G., and Franzen, G. (1974). Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr. Scand*, *4*, 203-218.

Jeannerod, M. (1994). The representing brain: neuronal correlates of motor intention and imagery. *Behavioral and Brain Sciences, 3*, 320-328*.*

Jones, P., Guth, Ch., Lewis, S., and Murray, R. (1994). Low intelligence and poor educational achievement precede early onset schizophrenic episodes. In A.S. David and J.C. Cutting (Eds.), *The Neuropsychology of Schizophrenia,* 99-116. Hove: Lawrence and Erlbaum.

Julien, R.M. (1998). *A primer of drug action: A concise nontechnical guide to the actions uses and side effects of psychoactive drugs.* New York: Freeman.

Kandel, E.R., Schwartz, J.H., and Jessell, T.M. (editor) (1996). *Neurowissenschaften: Eine Einführung. Spetrum Akademischer Verlag*: Heidelberg, Berlin, Oxford.

Kay, S.R., Fiszbein, A., Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*, 261-76.

Kerwin, R. and Taylor, D. (1996). New Antipsychotics. A Review of their Current Status and Clinical Potential. *CNS Drugs, 6 (1),* 71-82.

Klein, I., Duboisa, J., Mangina, J.-F., Kherifa, F., Flandina, G., Polinea, J.-B., Denisb, M., Kosslyn, S.M., and Le Bihana, D. (2004). Retinotopic organization of visual mental images as revealed by functional magnetic resonance imaging. *Cognitive Brain Research, 22,* 26–31.

Kohler, S., Kapur, S., Moscovitch, M., Winocur, G. and Houle, S. (1995). Dissociation of pathways for object and spatial vision: a PET study in humans. *Neuroreport, 6,* 1865-1868.

Kosslyn, S.M. (1978). Measuring the visual angle of the mind`s eye. *Cognitive psychology, 10,* 356-389.

Kosslyn, S.M. (1983). *Ghosts in the Mind`s Machine: Creating and Using Images in the Brain.* NY: Norton.

Kosslyn, S.M. (1989). *Readings from the Encyclopedia of Neuroscience: Learning and Memory.* Boston.

Kosslyn, S.M. (1994). *Image and brain: the resolution of the imagery debate*. Cambridge, MA: MIT Press.

Kosslyn, S.M., Ganis, G., and Thomson, W.L. (2001). Neural foundations of Imagery. *Nature, 2,* 635-642.

Kraepelin, E. (1899). *Ein Lehrbuch für Studierende und Ärzte 6th Edition*. Leipzig: J.A. Barth.

Kraepelin, E. (1919). *Dementia Praecox and Paraphrenia*. Edinburgh: Livingstone.

Krampen, G. (1981). *Fragebogen zu Kompetenz- und Kontrollüberzeugungen (FKK)*. *Handanweisung*. Hogrefe: Göttingen.

Kubicki, M., Westin, C.F., Maier, S.E., Frumin, M., Nestor, P.G., Salisbury, D.F., Kinins, R., Jolesz, F.A., McCarley, R.W., and Shenton, M.E. (2002). Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Am J Psychiatry, 159*, 813-820.

Kubicki, M., Westin, C.F., Nestorm, P.G., Wible, C.G., Frumin, M., Maier, S.E., Kikinis, R., Jolesz, F.A., McCarley, R.W., and Shenton, M.E. (2003). Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Biol. Psychiatry, 54*, 1171-80.

Launay, G., and Slade, P.D. (1981). The measurement of hallucinatory predisposition in male and female prisoners. *Personality and Individual Differences, 2*, 221-234.

Lauterbur, P.C. (1973). Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature, 242*, 190–191.

Le Bihan, D. (1995). NIH conference : Functional magentic resonance imaging of the brain. *Annals of Internal Medicine, 122,* 296-303.

Le Bihan, D. Mangin, J.-F., Poupon, C., Clark, C.A., Pappata, S:, Molko, N., and Chabriat, H., (2001). Diffusion Tensor Imaging: Concepts and Applications. *Journal of magnetic resonance imaging, 13*, 534-546.

Lehrl, S. (1989). *Mehrfachwahl-Wortschatz-Intelligenztest MWT-B*. Erlangen: Perimed.

Lennox, B.R., Park, S.B., Medley, I., Morris, P.G., and Jones, P.B. (2000). The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Research Neuroimaging, 100*, 13-20.

Liberman, R.P., Mueser, K.T., and Wallace, C.J. (1986). Social skills training for schizophrenic individuals at risk for relapse. *Am J Psychiatry,* 143, 523-526.

Liddle, P.F. (1987). The symptoms of schizophrenia: A re-examination of the positive-negative dichotomy. *British Journal of Psychiatry, 151,* 145-151.

Lim, K.O., and Helpern, J.A. (2002). Neuropsychiatric applications of DTI-a review. *NMR Biomed, 15*, 587-593.

Linden, D.E.J., and Dierks, T. (2002). Funktionelle Bildgebung akustischer Halluzinationen bei der Schizophrenie. *Nervenheilkunde, 7,* 331-335.

Lindenmayer, J.P., Bernstein-Hyman, R., and Grochowski, B.A. (1994). Preatttentive information processing in schizophrenia. *Schizophrenia Research, 14,* 47-56.

Loughland, C.M., Williams, L.M. (1997). A cluster analytic study of schizotypal trait dimensions. *Personality and Individual Differences, 23 (5)*, 877-883.

Lutejin, L.B., and Moleman, P., 1998. Antipsychotica. In P. Moleman (red.), *Praktische Pharmafarmacologie.* Houten:Bohn Stafleu Van Loghum.

Maj, M. (1998). Critique of the DSM-IV operational diagnostic criteria for schizophrenia. *British Journal of Psychiatry, 172,* 458-460.

Mansfield, P, and Grannell, P.K. (1973). NMR "diffraction" in solids? *J Phys C Solid State Phys*, 6, 422.

Mazard, A., Laou, L., Joliot, M., Mellet, E. (2005). Neural impact of the semantic content of visual mental images and visual percepts. *Brain Res Cogn Brain Res.* 24(3):423-35.

McGlashan, T.H. (1988). A selective review of recent North American long-term follow up studies of schizophrenia. *Schizophrenia Bulletin, 14,* 515-542.

McGuffin, P., Owen, M.J., and Farmer, A.E. (1995). Genetic basis of schizophrenia. *Lancet, 346 (8976),* 678-82.

McGuire, P.K., Silbersweig, D.A., Murray, R.M., David, A.S., Frackowiak, R.S. and Frith, C.D. (1996). Functional anatomy of inner speech and auditory verbal imagery. *Psychological medicine, 26*, 29-38.

McMahon, C.E. (1973). Images and Motives as Motivators: A Historical Perspective. *American Journal of Psychology, 86,* 465-490.

McInttosh, A.R, Grady, C.L., Ungerleider, L.G:, Haxby, J.V., Rapoport, S.I., and Horwitz, B. (1994). Network analysis of cortical visual pathways mapped with PET. *J Neurosci. 14(2)*, 655-66.

McKenna, P.J. (1994). *Schizophrenia and related symptoms.* Oxford: Oxford University Press.

Mechelli, A., Price, C.J., Friston, K.J., and Ishai, A. (2004). Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cereb Cortex, 14(11)*, 1256-65.

Meehl, P.E. (1962). Schizotaxia, Schizotypy, Schizophrenia. *American Psychology, 17,* 827-838.

Ming, X., Stein, T.P., Brimacombe, M., Johnson, W.G., Lambert, G.H., and Wagner, G.C. (2000). Increased excretion of a lipid peroxidation biomarker in autism. *Prostaglandins, Leukotrienes and Essential Fatty Acids, 73*, 379-384.

Mintz, S. and Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79*, 310-316.

Morrison, A.P. Wells A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychology, 41(3)*, 259-270.

Murray, R.M., O`Callaghan, E., Castele, D.J., and Lewis, S.W. (1992). A neurodevelopmental approach towards the classification of schizophrenia. *Schizophrenia Bulletin, 18,* 319-332.

Ogawa, S., Lee, T.M., Kay, A.R., and Tank, D.W. (1990). Brain magnetic resonance imaging with contrast dependant on blood oxygenation. *Proceedings of the National Academy of Sciences USA, 87,* 9868-9872.

Ogawa, S., Tank, D., Menon, R., Ellerman, J., Kim, S., Merkle, H., and Ugurbil, K. (1992). Intrinsic Signal Changes Accompanying sensory Stimulation: Functional Brain Mapping With Magnetic Resonance Imaging. *Proceedings of National Academic Sciences, 89,* 5851-5955.

Ohayon, M.M., Priest, R.G., Caulet, M., and Guilleminault, C. (1996). Hypnagogic and hypnapompic hallucinations: pathological phenomena? *British Journal of Psychiatry, 169*, 459-467.

Paivio, A. (1978). A dual coding approach to perception and cognition. In H.L. Pick and E. Saltzman (Eds.). *Modes of perceiving and processing information, 39-52.* Hillsdale, NJ: Erlbaum.

Paivio, A. (1986). *Mental Representations: a Dual Coding Approach.* NY: Oxford University Press.

Park, S., Holzman, P.S., and Goldman-Rakic, P.S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry, 52(10)*, 821-8.

Peralta, V., de Leon, J., and Cuesta, M.J. (1992). Are there more than two syndromes in schizophrenia ? *British Journal of Psychiatry, 161,* 343.

Peralta, V. and Cuesta, M.J. (1999). Diagnostic significance of Schneider's first-rank symptoms in schizophrenia. *British Journal of Psychiatry, 174,* 243-248.

Peralta, V. and Cuesta, M.J. (2001). How many and which are the psychopathological dimensions in schizophrenia ? Issues influencing their ascertainment. *Schizophrenia Research, 49,* 269-285.

Pinel, P. In : *Genèse de la psychiatrie : les premiers écrits psychiatriques de Philippe Pinel* (1981). Le Sycomore : Paris.

Raine, A., Benishay, D., Lencz, T., Scarpa, A., 1997. Abnormal orienting in schizotypal personality disorder. *Schizophrenia Bulletin 23(1)*, 75-82.

Reitan, R.M. (1979). *The Trail Making Test (TMT)*. Hogrefe: Erlangen.

Riederer, P, Laux, G., Pöldinger, W. (1998). *Neuropsychopharmaka.* Wien: Springer.

Rotarska-Jagiela, A. (2007). Dissertation zur Erlangung des Doktorgrades Dr. rer. Nat. Johann Wolfgang Goehte-Universität, Frankfurt / Main,´.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs, 80*, 609.

Rubel, E.W., and Dobie, R.A. (1989). The Auditory System: Central Auditory Pathways. In: *textbook of Physiology: Excitabel Cells and Neurophysiology*, 1, edited by Patton et. al. (1989). WB Saunders: Philladelphia.

Safferman, A., Lieberman, J.A., Kane, J.M., Szymanski, S. and Kinon, A. (1991). Update on the clinical efficacy and side effects of clozapine. *Schizophrenia Bulletin, 17(2),* 247-261.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D. and Linden, D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-8.

Sanders, J.A. (1995). Magnetic Resoance Imaging. In: Orrision, W.W., Levine, J.D., Sanders, J.A., and Hartshorne, M.R. (Eds.). *Functional Brain Imaging*. St.Louis: Msbay.

Sato, M., Baciu, M., Loevenbruck, H., Schwartz, J.L., Cathiard, M.A., Segebarth, C., and Abry, C. (2004). Multistable representation of speech forms: a functional MRI study of verbal transformations. *Neuroimage, 23(3)*, 1143-51.

Savoy, R.L. (1996). Magnetic Resonance Imaging (MRI). *FMRI2 Day ‚A Two Day Workshop on functional MRI.* Boston: Massachusetts.

Schlösser, R., Wagner, G., Köhler, S. und Sauer, H. (2000). Funktionelle Bildgebung in der Psychiatrie-Schizophrenie als Diskonnektionssyndro. Studien mit funktioneller Magnetresonanztomographie und Strukturgleichungsmodellen. *Der Radiologie Zeitschrift für diagnostische und interventionelle Radiologie, Radioonkologie, Nuklearmedizin*. Springer Medizin Verlag.

Schlösser, R., Wagner, G., Kohler, S., and Sauer, H. (2005). Schizophrenia as a disconnection syndrome. Studies with functional magnetic resonance imaging and structural equation modelling. Radiologe 45(2):137-40.

Schneider, K. (1959). *Clinical Psychopathology*. New York: Grune and Stratton.

Schneider, K. (1965). *Klinische Psychopathologie (6th Ed)*. Stuttgart: Thieme.

Segal, S.J., and Fusella, V. (1971). Effects of Images in Six Sense Modalities on Detection of Visual signal from Noise. *Psychognomic Science, 24,* 55-56.

Sheehan, P.W. (1967). A shortened form of Bett`s questionnaire upon mental imagery. *Journal of Clinical Psychology, 23*, 386-389.

Shepard, R.N., and Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science, 171,* 701-703.

Shergill, S.S., Brammer, M.J., Williams, S.C. Murray, R.M., and McGuire, P.K. (2004). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of Genetic Psychiatry, 57*, 1033-1038.

Shergill, S.S., Bullmore, E., Simmons, A., Murry, R., and McGuire, P. (2000). Functional anatomy of auditory verbal imagery in schizophrenic patients with auditory hallucinations. *American Journal of Psychiatry, 157 (10)*, 1691-1693.

Silbersweig, D.A., Stern, E., Frith, C., Cahill, C., Holmes, A., and Grootoonk, S. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-9.

Silbersweig, D.A., and Stern, E. (1998). Towards a functional neuroanatomy of conscious perception and its modulation by volution: implications of human auditory neuroimaging studies. *Phil. Trans. R. Soc. London. B., 353*, 1883-1888.

Slade, P.D. (1972). The effects of systematic desensitisation on auditory hallucinations. *Behav Res Ther., 10(1)*, 85-91.

Slade, P.D. (1994) Models of hallucination: from theory to practice. In: A.S. David and J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Slade, P.D., and Bentall, R.P. (1998). *Sensory deception: A scientific analysis of hallucination.* Baltimore: John Hopkins University Press.

Slotnick, S.D., Thompson, W.L., Kosslyn, S.M. (2005). Visual mental imagery induces retinotopically organized activation of early visual areas. *Cerebral Cortex, 15(10)*, 1570-83.

Slewa-Younan, S., Gordan, E., Harris, A.W., Haig, A.R., Brown, K.J., Flor-Henry, P., and Williams, L.M. (2004). Sex Differences in Functional Connectivity in First-Episode and Chronic Schizophrenia Patients. *American Journal of Psychiatry, 161(9)*, 1595-1602.

Snitz, B.E., MacDonald, A 3rd, Cohen, J.D., Cho, R.Y., Becker, T., and Carter, C.S. (2005). Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *Am J Psychiatry, 162(12)*, 2322-9.

Starker, S. and Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Diseases, 170, 448-451.*

Stratta, P., Mancini, F., Mattei, P., Daneluzzo, E., Casacchia, M., Rossi, A. (1997). Association between striatal reduction and poor Wisconsin card sorting test performance in patients with schizophrenia. *Biol Psychiatry 1, 42(9),* 816-20.

Taylor, A., Fink, M. (1991). *Melancholia. The Diagnosis, Pathophysiology and Treatment of Depressive Illness*. Stony Brook: New York.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Moring, J., Pohjola, J., and Wynne, L.C. (1987). Genetic and psychosocial factors in schizophrenia: the Finnish Adoptive Family Study. *Schizophrenia Bulletin, 13(3)*, 477-84.

Trojano, L., and Grossi, D. (1994). A Critical Review of Mental Imagery defects. *Brain and Cognition, 24, 213-243.*

Trojano, L., Linden, D.E.J., Formisano, E., Goebel, R., Sack, A.T., and Di Salle, F. (2004). What clocks tell us about the neural correlates of spatial imagery. *European Journal of Cognitive Psychology, 16,* 653-672.

Tsuang, M.T., Stone, W.S., and Faraone, S.V. (1999a). The genetics of schizophrenia. *Current Psychiatry Report, 1(1)*, 20-4.

Tsuang, M.T., Stone, W.S., Seidman, L.J., Faraone, S.V., Zimmet, S., Wojcik, J., Kelleher, J.P., and Green, A.I. (1999). Treatment of nonpsychotic relatives of patients with schizophrenia: four case studies. *Biological Psychiatry, 41,* 1412-1418.

Tsuang, M.T., Stone, W.S., and Faraone, S.V. (2000). Schizophrenia: family studies and treatment of spectrum disorders. *Dialogues in Clinical Neuroscience, 2, (4)*, 384-391.

Turetsky, B.I., Colbath, E.A., and Gur, R.E. (1999). P300 subcomponent abnormalities in schizophrenia, I: physiological evidence for gender and subtype specific differences in regional pathology. *Biological Psychiatry, 43*, 84-96.

Uhlhaas, P.J., Phillips, W.A., Mitchell, G., and Silverstein, S.M. (2006). Perceptual grouping in disorganized schizophrenia. *Psychiatry Res. 7, 145(2-3),* 105-17.

Van de Ven, V., and Merckelbach, H. (2003). The role of schizotypy, mental imagery and fantasy proneness in hallucinatory in undergraduate students. *Personality and Individual Differences, 35*, 889-896.

Van de Ven, V.G., Formisano, E., Röder, C.H., Prvulovic, D., Bittner, R.A., and Dietz, M.G. (2005). The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage, 27(3),* 644-55.

Vaughn, C.E., and Leff, J.P. (1976). The influence of family and social factors on the course of psychiatric illness. A comparison of schizophrenic and depressed neurotic patients. *British Journal of Psychiatry, 129*, 125-37.

Verdoux, H., Geddes, J.R., Takei, N., Lawrie, S.M., Bovet, P., Eagles, J.M., Heun, R., McCreadie, R.G., McNeil, T.F., O'Callaoghan, R., Stober, G., Willinger, M.U., Wright, P., and Murray, R.M. (1997a). Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *Am J Psychiatry, 154(9)*, 1220-7.

Verdoux, H., Takei, N., Cassou de Saint-Mathurin, R., Murray, R.M., Bourgeois, M.L. (1997b).
Seasonality of birth in schizophrenia: the effect of regional population density. *Schizophr Res, 7, 23(2)*, 175-80.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry, 44*, 660-669.

Weiss, A.P., and Heckers, S. (1999). Neuroimaging of hallucinations: a review of the literature. *Psychiatry Research, 20, 92(2-3),* 61-74.

Weiser, M., van Os, J., and Davidson, M. (2005). Time for a shift in focus in schizophrenia: from narrow phenotypes to broad endophenotypes. *Br J Psychiatry. 187*, 203-5.

Wernicke, C. (1881). *Lehrbuch der Gehirnkrankheiten für Ärzte und Studierende*. Kassel: Fischer.

Wilson, R.S., Gilley, D.W., Bennett, D.A., Beckett, L.A., and Evans, D.A. (2000). Hallucinations, delusions and cognitive decline in Alzheimer`s Disease. *Journal Neurol Neursurg Psychiatry, 69,* 172-177.

Winawer, M.R., Ottman, R., Hauser, W.A., and Pedley, T.A. (2000). Autosomal dominant parietal epilepsy with auditory features: defining the phenotype. *Neurology, 54*, 2173-2176.

Wing, J.K. (1978). Clinical concepts of schizophrenia. In J.K. Wing (eds.), *Schizophrenia: Toward a New Synthesis (pp. 1-30).* London: Academic Press.

World Health Organisation (WHO) (1992). *The ICD-10 Classification of Mental and Behavioural Disorders.* Geneva.

Ziekenfondsraad, (1999). *Farmacotherapeutische Kompass.* Amstelveen: Ziekenfondsraad.

www.netdoktor.de/ratschlaege/untersuchungen/magnetresonanztomographie.htm

www.maodes.de/erikasten/Neue_Dateien/halluzinationen.html (PD. Dr. Erich Kasten, Universitätsklinikum Magdeburg)

Chapter 2

Aggernea, A. (1972). The experienced reality of hallucinations and other psychological phenomena. An empirical analysis. *Acta Psychiatrica Scandinavica, 48*, 220-238.

Aleman, A., Böcker, K.B.E., and de Haan, E.H.F. (1999). Disposition towards hallucinations and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual differences, 27*, 707-714.

Aleman, A., Böcker, K.B.E., Hijman, R., and de Haan, E.H.F. (2003). Cognitive basis of hallucinations in schizophrenia: role of top-down information processing. *Schizophrenia Research, 64*, 175-85.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders (4th edition)*. APA, Washington, D.C.

Appels, M.C., Sitskoorn, M.M., Vollema, M.G., and Kahn, R.S. (2004). Elevated levels of schizotypal features in parents of patients with a family history of schizophrenia spectrum disorders. *Schizophrenia Bulletin, 30(4)*, 781-90.

Baddeley, A., Emslie, H., and Nimmo-Smith, I. (1993). The Spot-the-word test: a robust estimate of verbal intelligence based on lexical decision. *British Journal of Clinical Psychology, 32*, 55-65.

Bandura A (1982). Self-efficacy mechanism in human agency. *American Psychologist*, *37*, 122-147.

Barrett T.R., and Etheridge J.B. (1992). Verbal hallucinations in normals I. People who hear "voices". *Applied Cognitive Psychology, 6*, 379-387.

Barrett, T.R. (1993). Verbal hallucinations in normals: II. Self-reported imagery vividness. *Personality and individual differences, 15*, 61-67.

Beck, A.T., Brown, G., Eidelson, J.I., Steer, R.A., Riskind, J.H. (1987). Differentiating anxiety and depression: A test of the cognitive content – specificity hypothesis. *Journal of Abnormal Psychology, 96*, 179-183.

Behrendt, R.P. (2003). Hallucinations: Synchronisation of thalamocortical gamma oscillations underconstrained by sensory input. *Consciousness and Cognition, 12*, 413-451.

Bentall, R.P., and Slade, P.D. (1985). Reliability of a scale measuring disposition towards hallucinations: a brief report. *Personality and Individual Differences, 6*, 527–529.

Bentall, R.P. (1990). The illusion of reality: A review and integration of psychological research on hallucinations. *Psychological Bulletin, 17*, 82-95.

Blakemore, S.J., Smith, J., Steel, R., Johnstone, C.E., and Frith, C.D. (2000). The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychol Med., 30(5),* 1131-9.

Böcker, K.B.E., Hijman, R., Kahn, R.S., and de Haan, E.H.F. (2000). Perception, mental imagery and reality discrimination in hallucinating and non-hallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39*, 397-406.

Brebion, G., Smith, M.J., Gorman, J.M., and Amador, X. (1997). Discrimination Accuracy and Decision Biases in Different Types of Reality Monitoring in Schizophrenia. *Journal of Nervous and Mental Disease, 185(4)*, 247-253.

Brett E.A., and Starker, S. (1977). Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease, 164*, 394-400.

Cahill, C., and Frith, C.D. (1996). A cognitive basis for the signs and symptoms of schizophrenia. In: Pantelis, C., Nelson, H.E., Barnes T.R.E. (Eds.). *Schizophrenia: A neuropsychological perspective*. Wiley: London, U.K, 373-396.

Calkins, M.E., Curtis, C.E., Grove, W.M., and Iacono, W.G. (2004). Multiple dimensions of schizotypy in first degree biological relatives of schizophrenia patients. *Schizophrenia Bulletin, 30(2)*, 317-25.

Claridge, G. (1983). Schizophrenia and lateralization of galvanic skin response. *British Journal of Psychiatry, 142*, 425-426.

Claridge, G., and Broks, P. (1984). Schizotypy and hemisphere function: I. Theoretical consideration and the measurement of schizotypy. *Personality and Individual Differences, 5*, 633–648.

David, A.S. (1994). The neuropsychological origins of auditory hallucinations. In: David A.S., Cutting, J.C. (Eds.). *The Neuropsychology of Schizophrenia*. LEA, 269-313.

David, A.S. Intelligence and schizophrenia. *Acta Psychiatr Scan* 100(1):1-2, 1999.

Dierks, T., Linden, D.E., Jandl, M. Formisano, E., and Goebel, R. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22(3)*, 414-5.

Eysenck, H.J. (1985). *Personality and individual differences: A natural science approach*. NY: Plenum Press.

Evans, C.L., McGuire, P.K., and David, A.S. (2000). Is auditory imagery defective in patients with auditory hallucinations? *Psychological Medicine, 30(1)*, 137-48.

Finke, R.A. (1989). *Principles of Mental Imagery*. Cambridge: MIT Press.

Frenkel, E., Kugelmass, S., Natham, M., Ingraham, L.J. (1995). Locus of control and mental health in adolescence and adulthood : Israeli high-risk study. *Schizophrenia bulletin, 21*, 2, 219-226.

Frith, C., and Dolan, R.J. (1998). Images of psychopathology. *Current Opinion Neurobiology, 8(2)*, 259-62.

Gottesman, I.I. (1991). *Schizophrenia Genesis: The Origins of Madness*. W.H. Freeman, New York, 96.

Goulding, A. (2005). Healthy schizotypy in a population of paranormal believers and experiments. *Personality and Invidividual differences, 38(5)*, 1069-1083.

Hahlweg, K. (1998). Störungstheorien und –modelle. In: Hahlweg, K., Dose, M. (Eds.). *Schizophrenie*. Hogrefe: Göttingen, 25-35.

Hatakeyama, T. (1984). Individual differences in imagery ability and mental size comparison. *Tohoku Psychologica Folia, 43*, 112-116.

Hooley, J. (1998). Expressed Emotion and Locus of Control. Journal of Nervous & Mental Disease, *186(6)*, 374-378.

Horn, W. (1962). *Leistungsprüfsystem (LPS)*. Verlag für Psychologie: Göttingen.

Horn, J.L., and Cattell, R.B. (1966). Refinement and test of the theory of fluid and crystallized intelligence. *Journal of Educational Psychology 57*, 253-270.

Horowitz, M. (1975). Hallucinations: An information processing approach. In: Siegel, R.K., West, L.J. (Eds.). *Hallucinations: Behaviour, Experience and Theory*. NY Wiley: New York,

163–196.

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., et al. (2004). Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry, 61*, 658-668.

Johns, L.C., van Os, J. (2001). The continuity of psychotic experiences in the general population. *Clinical Psychological Review, 21(8)*, 1125-41.

Kaney, S., Bentall, R.P**.** (1989). Persecutory delusions and attributional style. *Br J Med, 62(Pt 2)*,191-8.

Kay, S.R., Fiszbein, A., and Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*, 261-76.

Kay, S.R., Opler, L.A., and Fiszbein, A. (1994). Reliability and validity of the Positive and Negative Syndrom Scale (PANSS) in schizophrenia. *Psychiatry Research, 53*, 31-40.

Kendler, K.S., McGuire, M., Gruenberg, A.M., and Walsh, D. (1995). Schizotypal symptoms and signs in the Roscommon Family Study. Their factor structure and familial relationship with psychotic and affective disorders. *Archives General Psychiatry, 52(4)*, 296-303.

Kihlstrom, J.F., Glisky, M.L., Peterson, M.A., Harvey, E.M., and Rose, P.M. (1991). Vividness and control of mental imagery: A psychometric analysis. *Journal of Mental Imagery, 15*, 133-142.

Klein, C., Andreasen, B., Jahn, T. (1997). Erfassung der schizotypen Persönlichkeit nach DSM-III-R: Psychometrische Eigenschaften einer autorisierten deutschsprachigen Übersetzung des „Schizotypy Personality Questionnaire" (SPQ) von Raine. *Diagnostica, 43*, 347-369.

Kosslyn, S.M. (1994). *Image and brain: the resolution of the imagery debate*. Cambridge, MA: MIT Press.

Krampen, G. (1991). *Fragebogen zu Kompetenz- und Kontrollüberzeugung (FKK)*. Göttingen: Hogrefe.

Kremen, W. S., Faraone, S.V., Toomey, R., Seidman, L.J., and Tsuang, M.T. (1998). Sex differences in self-reported schizotypal traits in relatives of schizophrenic probands. *Schizophrenia Research, 34*, 27-37.

Lasar, M. (1997). Kognitive Handlungsbewertung bei akut erkrankten chronisch schizophrenen Patienten. *Psychologische Beiträge*, *39,* 297-311.

Lefcourt, H.M. (1980). Personality and locus of control. In Garber J. and Seligman MEP (Eds.), *Human helplessness* (pp. 245-260). New York: Academic Press.

Lehrl, S. (1989). *Mehrfach-Wortschatz-Intelligenztest (MWT-B)*. Perimed: Erlangen.

Lenzenweger, M.F. (1994). Psychometric high-risk paradigm, perceptual aberrations, and schizotypy: an update. *Schizophrenia Bulletin, 20(1)*, 121-35.

Lequerica, A., Rapport, L., Axelrod, B.N., Telmet, K., and Whitman, R.D. (2002). Subjective and objective assessment methods of mental imagery control: construct validation of self-report measures. *Journal Clinical Exp Neuropsychology, 24(8)*, 1103-16.

Maß, R., Haasen, C., and Wolf, K. (2000). Das Eppendorfer Schizophrenie-Inventar (ESI). Entwicklung und Evaluation eines Fragebogens zur Erfassung charakteristischer Selbstwahrnehmungen kognitiver Dysfunktionen schizophren Erkrankter. *Der Nervenarzt, 71* (11), 885-892.

Maher BA (1974). Delusional thinking and perceptual disorder. *Journal of Individual Psychology, 30*, 98-103.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist, 17*, 827-838.

Meehl, P.E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders, 4*, 1-99.

Mintz, S., Alpert, M. (1972). Imagery vividness, reality testing and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79*, 310-316.

Merckelbach, H., and van de Ven, V. (2001). Another White Christmas: fantasy proneness and reports of 'hallucinatory experiences' in undergraduate students. *Journal of Behavioral Therapy Exp Psychiatry, 32(3)*, 137-44.

Mohr, C., Sándor, P.S., Landis, T., Fathi, M., and Brugger, P. (2005). Blinking and schizotypal thinking. *Journal of Psychopharmacology, 19(5)*, 513-520.

Morrison, A.P., Wells, A., and Nothard, S. (2002a). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychology, 41(3*), 259-270.

Morrison, A.P., Beck, A.T., Glentworth, D., Dunn, H., and Reid, G. (2002b). Imagery and psychotic symptoms: A preliminary investigation. *Behaviour Research and Therapy, 40*, 1053-1062.

Nienznanski, M. (2004). Features of the self-structure and source monitoring disorders in people with schizophrenia. *Psychiatr. Pol., 38(5)*, 819-32.

Oertel V, Rotarska-Jagiela A, Van de Ven V, Haenschel C, Grube M, Stangier U, Maurer K, Linden DEJ (2008). Mental imagery vividness as a trait marker across the schizophrenia spectrum. *Psychiatry Research, in press.*

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologica, 9*, 97-113.

Poulton, R., Caspi, A., Mofitt T.E., Cannon, M., Murray, R., and Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder. *Archives of General Psychiatry, 57*, 1053-1058.

Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin, 17*, 556-564.

Rehm, L.P. (1973). Relationship amoung measures of visual imagery. *Behavior, Research and Therapy, 11*, 265-270.

Reitan, R.M. (1979). *The Trail Making Test (TMT)*. Hogrefe, Erlangen.

Richardson, A.J., Easton, T., Gruzelier, J.H., and Puri, B.K. (1999). Laterality changes accompanying symptom remission in schizophrenia following treatment with eicosapentaenoic acid. *Int J Psychophysiol., 34(3)*, 333-9.

Rosenbaum M, Hadari D (1985). Personal Efficacy, External Locus of Control, and Perveived Contingency of Parental Reinforcement Among Depressed, Paranoid and Normal ubjects. *Journal of Personality and Social Psychology,* 49(2), 539-547.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs, 80(609*), 203-218.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D., and Linden D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-8.

Sartorius, N., Jablensky, A., and Shapiro, R. (1978). Cross-cultural differences in the short-term prognosis of schizophrenic psychoses. *Schizophrenia Bulletin, 4(1)*, 102-13.

Seligman, MEP (1975). *Helplessness: On depression, development, and death*. San Francisco: W.H. Freeman.

Sheehan, P.W., 1967. Reliability of a short test of imagery. *Perceptual and Motor Skills, 25*, 744.

Siever, L.J., and Davis, K.L. (2004). The Pathophysiology of Schizophrenia Disorders: Perspectives from the Spectrum. *American Journal of Psychiatry, 161*, 398-413.

Starker S., and Jolin, A., 1982. Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Diseases, 170*, 448-451.

Stirling, J.D., Hellewell, J.S., and Quraishi. N. (1998). Monitoring dysfunction and the schizophrenic symptoms of alien control. *Psychological Medicine, 28(3)*, 675-83.

Sutherland, M.E., Harrell, J.P., and Issacs, C. (1987). The stability of individual differences in imagery ability. *Journal of Mental Imagery, 11*, 97-104.

Thurstone, L.L. (1938). *Primary Mental Abilities*. University of Chicago Press, Chicago.

Tien, A.Y. (1991). Distributions of hallucinations in the population. *Social Psychiatry and Psychiatric Epidemiology, 26*, 287–292.

Tsuang, M.T., Stone, W.S., and Faraone, S.V. (2000). Schizophrenia: family studies and treatment of spectrum disorders. *Dialogues in Clinical Neuroscience, 2(4)*, 384-391.

Van de Ven, V., and Merckelbach, H. (2003). The role of schizotypy, mental imagery, and fantasy proneness in hallucinatory reports of undergraduate students. *Personality and Individual Differences, 35*, 889–896.

Van Kampen, D. (2006). The Schizotypic Syndrome Questionnaire (SSQ): Psychometrics, validation and norms. *Schizophrenia Research, 84(2-3)*, 305-22.

Van Os, J. (2003). Is there a continuum of psychotic experiences in the general population? *Epidemiol Psychiatr Soc., 12(4)*, 242-52.

Weinstein, S., and Graves, R.E. (2002). Are creativity and schizotypy products of a right hemisphere bias? *Brain and Cognition, 49(1)*,138-51.

Williams EB (1964). Deductive reasoning in schizophrenia. *Journal of Abnormal and Social Psychology, 69*, 47-61.

Wittchen, H.U., Wunderlich, U., Gruschwitz, S., and Zaudig, M. (1996). Strukturiertes Klinisches Interview für DSM-IV (SKID). Beltz-Test, Göttingen.

World Health Organisation (WHO) (1992). *The ICD-10 Classification of Mental and Behavioural Disorders.* Geneva.

Zimbardo, P.G. (1985). *Psychology and life 11th edition*. Glenview, III: Scott, Foresman.

Chapter 3

Part I

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders (4th edition)*. APA, Washington, D.C.

Addington et al. (2007). Neuregulin 1 and childhood-onset schizophrenia. *Mol Psychiatry, 12(2),* 195-205.

Aggernea, A. (1972). The experienced reality of hallucinations and other psychological phenomena. An empirical analysis. *Acta Psychiatrica Scandinavica, 48*, 220-238.

Annett, M. (1992). Spatial ability in subgroups of left- and right-handers. *British Journal of Psychology, 83(4)*, 493-515.

Annett, M. (1999). The theory of an agnosic right shift gene in schizophrenia and autism. *Schizophrenia Research, 19, 39(3)*, 177-82.

Appels, M.C.M., Sitskoorn, M.M., Westers, P., Lems, E., and Kahn, R.S. (2003). Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. *Schizophrenia Research, 63*, 285–293.

Artiges, E., Martinot, J.L., Verdys, M., Attar-Levy, D., Mazoyer, B., Tzourio, N., Giraud, M.J., and Paillere-Martinot, M.L. (2000). Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophrenia Bulletin, 26(3)*, 709-21.

Barta, P.E., Pearlson, G.D., Brill, L.B. 2nd, Royall, R., McGilchrist, I.K., Pulver, A.E., Powers, R.E., Casanova, M.F., Tien, A.Y., Frangou, S., Petty, R.G. (1997). Planum temporale asymmetry reversal in schizophrenia: replication and relationship to gray matter abnormalities. *Am J Psychiatry, 154(5),* 661-7.

Bartzokis, C. (2000). Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology, 27(4)*, 672-83.

Bediou, B., Asri, F., Brunelin, J., Krolak-Salmon, P., D'Amato, T., Saoud, M., and Tazi, I. (2007). Emotion recognition and genetic vulnerability to schizophrenia. *British Journal of Psychiatry, 191*, 126-30.

Belin, P. (2006). Voice processing in human and non-human primates. *Philos Trans R Soc Lond B Biol Sci 29, 361(1476)*, 2091-107.

Benjamini Y, Yekutieli D. (2001). The control of the false discovery rate in multiple testing under dependency. *Ann. Statist. 2001, 29(4),* 1165-1188.

Bentall R.P. (1990). The illusion of reality: A review and integration of psychological research on hallucinations. Psychological Bulletin, 17, 82-95.

Braus, D., Ende, G., Weber-Fahr, W., Sartorius, A., Krier, A., Hubrich-Ungureanu, P., et al. (1999). Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. *Schizophr Res, 39*(1), 19-29.

Brownstein, J., Krastoshevsky, O., McCollum, C., et al. (2003). Antisaccade performance is abnormal in schizophrenia patients but not in their biological relatives. *Schizophr Res., 3*, 63, 13–25.

Cannon, T.D., Zorrilla, L.E., and Shtasel, D. (1994). Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Arch Gen Psychiatry, 51*, 651–661.

Cardno, A.G., Jones, L.A., Murphy, K.C., Sanders, R.D., Asherson, P., Owen, M.J., and McGuffin, P. (1999). Dimensions of psychosis in affected sibling pairs. *Schizophrenia Bulletin, 25(4)*, 841-50.

Chaika E. (1974). A linguist looks at schizophrenic language. *Brain Language, 1,* 257-76.

Corbetta, M. and Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neuroscience 3(3),* 201-15.

Cosway, R., Byrne, M., and Clafferty, R. (2000). Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychological Medicine, 30(5)*, 1111–1121.

Crow, T.J., Ball, J., Bloom, S.R., Brown, R., Bruton, C.J., Colter, N., Frith, C.D., Johnstone, E.C., Owens, D.G., and Roberts, G.W. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Archives General Psychiatry, 46*, 1145-1150.

Crow, T.J. (1997). Is schizophrenia the price that *homo sapiens* pays for language ? *Schizophrenia Research, 28*, 127-141.

Crow, T.J. (1999). Cerebral asymmetry, language and psychosis--the case for a Homo sapiens-specific sex-linked gene for brain growth. *Schizophrenia Research, 19, 39(3)*, 219-31.

Crow, T. J. (2000). Schizophrenia as the price that Homo sapiens pays for language: A resolution of the central paradox in the origin of the species. *Brain Research Reviews, 31*, 118–129.

Crow, T.J. (2007). Genetic hypotheses for schizophrenia. *British Journal of Psychiatry 191*, 180.

Curtis, C.E., Calkins, M.E., Grove, W.M., Feil, K.J., and Iacono, W.G. (2001). Saccadic disinhibition in patients with acute and remitted schizophrenia and their first-degree biological relatives. *American Journal of Psychiatry, 158(1),*100–106.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatr. Scand., 99*, 95–104.

Deichmann, R., Schwarzbauer, C., and Turner, R. (2004). Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3T. *Neuroimage, 21*, 757-767.

Dierks, T., Linden, D. E. J., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., and Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22(3)*, 615-21.

Downhill, J.E. Jr., Buchsbaum, M.S., Wei, T., Spiegel-Cohen, J., Hazlett, E.A., Haznedar, M.M., Silverman, J., Siever, L.J. (200). Shape and size of the corpus callosum in schizophrenia and schizotypal personality disorder. *Schizophr Res., 5, 42(3)*, 193-208.

Faraone, S.V., Seidman, L.J., Kremen WS, Pepple JR, Lyons MJ, and Tsuang M.T. (1995). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a diagnosis efficacy analysis. *Journal Abnormal Psychology, 104*, 286-304.

Folstein, M.F., Folstein, S.E., and McHugh, P.R. (1975). Mini-Mental State: A practical method for grading the state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Frangou, S., Sharma, T., Sigmudsson, T., Barta, P., Pearlson, G., Murray, R.M. (1997). The Maudsley Family Study. 4. Normal planum temporale asymmetry in familial schizophrenia. A volumetric MRI study. *Br J Psychiatry, 170*, 328-33.

Friston, K.J. (1995). Commentary and opinion: II. Statistical parametric mapping: ontology and current issues. *J Cereb Blood Flow Metab., 15(3)*, 361-70.

Galaburda, A.M., and Geschwind, N. (1981). Anatomical asymmetries in the adult and developing brain and their implications for function. *Adv Pediatr., 28*, 271-92.

Geschwind, N., Levitsky, W. (1968). Human brain: left-right asymmetries in temporal speech region. *Science, 12, 161(837),* 186-7.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., and Singer, W. (1998a). The contstructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *European Journal of Neuroscience, 10*, 1563-1573.

Goebel, R., Linden, D.E., Lanfermann, H., Zanella, F.E., and Singer, W., (1998b). Functional imaging of mirror and inverse reading reveals separate coactivated networks for oculomotion and spatial transformations. *Neuroreport, 9, 9(4)*, 713-9.

Grove, W.M., Lebow, B.S., Clementz, B.A., Cerri, A., Medus, C., and Iacono, W.G. (1991). Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. *Journal of Abnormal Psychology, 100*, 115–121.

Gruber, O., Falkai, P., Schneider-Axmann, T., Schwab, S.G., Wagner, M., Maier, W. (2008). Neuregulin-1 haplotype HAP(ICE) is associated with lower hippocampal volumes in schizophrenic patients and in non-affected family members. *J Psych Res, 19*.

Harrison, P.J., and Weinberger, D.R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry. 10(1),* 40-68.

Hasson, H., Nusbaum, H.C., and Small, S. (2007). Brain Networks Subserving the Extraction of Sentence Information and Its Encoding to Memory. *Cerebral Cortex Advance Access*.

Hoffman, R.E., Stopek, S., and Andreasen, N.C. (1986). A comparative study of manic vs. schizophrenic speech disorganization. *Arch Gen Psychiatry, 43*, 831-8.

Hirayasu, Y., McCarley, R.W., Salisbury, D.F., Tanaka, S., Kwon, J.S., Frumin, M., Snyderman, D., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., Shenton, M.E. (2000). Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. *Arch Gen Psychiatry, 57(7),* 692-9.

Hickok, G., and Poeppel D. (2000). Towards a functional neuroanatomy of speech perception. *Trends Cogn Science, 4*, 131–138.

Hickok, G., and Poeppel, D. (2004). Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition, 92*, 67–99.

Hickok, G., and Poeppel, D. (2007). The cortical organization of speech processing. *Nat Rev Neuroscience, 8(5)*, 393-402.

Hunter, M. (2004). Locating voices in space: A perceptual model for auditory hallucinations?. *Psychology Press, 9 (1-2)*, 93 – 105.

Ishii, R., Shinosaki, K., Ikejiri, Y., Ukai, S., Yamashita, K., Iwase, M., Mizuno-Matsumoto, Y., Inouye, T., Yoshimine, T., Hirabuki, N., Robinson, S.E., and Takeda, M. (2000). Theta rhythm increases in left superior temporal cortex during auditory hallucinations in schizophrenia: a case report. *Neuroreport, 28, 11(14)*, 3283-7.

Jäncke, L., Shah, N.J., Posse, S., Grosse-Ryuken, M., Müller-Gärtner, H.W. (1998). Intensity coding of auditory stimuli: an fMRI study. *Neuropsychologia,. 36(9),* 875-83.

Kanwisher, N., and Wojciulik, E. (2000). Visual attention: insights from brain imaging. *Nat Rev Neuroscience, 1(2)*, 91-100.

Kasai K, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Spencer MH, Yurgelun-Todd DA, Kikinis R, Loesz FA, McCarley RW. Progressive Decrease of left Heschl gyrus and Planum temporale gray matter volume in first-episode schizophrenia. *Archives General Psychiatry*. 2003. 60: 766-775.

Kay, S.R., Fiszbein, A., Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin 13*, 261-76.

Kircher, T.T., Rapp, A., Grodd, W., Buchkremer, G., Weiskopf, N., Lutzenberger, W., Ackermann, H., Mathiak, K. (2004). Mismatch negativity responses in schizophrenia: a combined fMRI and whole-head MEG study. *Am J Psychiatry, 161(2),* 294-304.

Kulynych, J.J., Vladar, K., Fantie, B.D., Jones, D.W., Weinberger, D.R. (1995). Normal asymmetry of the planum temporale in patients with schizophrenia. Three-dimensional cortical morphometry with MRI. *Br J Psychiatry, 166(6)*, 742-9.

Kwon, J.S., McCarley, R.W., Hirayasu, Y., Anderson, J.E., Fischer, I.A., Kikinis, R., Jolesz, F.A., Shenton, M.E. (1999). Left planum temporale volume reduction in schizophrenia. *Arch Gen Psychiatry, 56(2)*, 142-8.

Lennox, B.R., Park, S.B., Medley, I., Morris, P.G., and Jones, P.B. (2000). The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Research Neuroimaging, 100*, 13-20.

Liddle, P.F., Friston, K.J., Frith, C.D., and Frackowiak, R.S. (1992). Cerebral blood flow and mental processes in schizophrenia. *J R Soc Med., 85(4)*, 224-7.

Line, P., Silberstein, R.B., Wrhight, J.J., and Copolov, D.L. (1998). Steady state visually evoked potential correlates of auditory hallucinations in schizophrenia. *Neuroimage, 8(4)*, 370-6.

Loberg, E.M., Hugdahl, K., and Green, M.F. (1999). Hemispheric asymmetry in schizophrenia: a "dual deficits" model. Biological Psychiatry, 1, 45(1), 76-81.

Mathiak, K., Menning, H., Hertrich, I., Mathiak, K.A., Zvyagintsev, M., and Ackermann, H. (2007). Who is telling what from where? A functional magnetic resonance imaging study. *Neuroreport, 26, 18(5)*, 405-9.

Massoud, S., Giuseppe, P., Charles, R., and McClannahan, K. (2007). Empirical evaluation of language disorder in schizophrenia. *BA J Psychiatry Neurosci., 32(4)*, 250–258.

McGuffin, P., Owen, M.J., and Farmer, A.E. (1995). Genetic basis of schizophrenia. *Lancet 346(8976)*, 678-82.

McGuire, P.K., Shah, G.M., and Murray, R.M. (1993). Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet, 18, 342(8873)*, 703-6.

Morrison, A.P., Wells, A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychology, 41(3)*, 259-270.

Oertel, V., Rotarska-Jagiela, A., Van de Ven, V., Haenschel, C., Grube, M., Stangier, U., Maurer, K., Linden D. (2008). Mental imagery vividness as a trait marker across the schizophrenia spectrum. *Psychiatry Research*, in press.

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9*, 97-113.

Owen, M.J., Williams, N.M., O'Donovan, M.C. (2004). The molecular genetics of schizophrenia: new findings promise new insights. *Mol Psychiatry 9(1),* 14-27.

Pantelis, C., Yücel, M., Wood, S.J., Velakoulis, D., Sun, D., Berger, G., Stuart, G.W., Yung, A., Phillips, L., McGorry, P.D. (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull., 31(3),* 672-96.

Park, S., Holzman, P.S., and Goldman-Rakic, P.S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Arch Gen Psychiatry, 52*, 821–828.

Petty, R.G., Barta, P.E., Pearlson, G.D., McGilchrist, I.K., Lewis, R.W., Tien, A.Y., Pulver, A., Vaughn, D.D., Casanova, M.F., Powers, R.E. (1995). Reversal of asymmetry of the planum temporale in schizophrenia. *Am J Psychiatry, 52(5)*, 715-21.

Rademacher, J., Bürgel, U., Geyer, S., Schormann, T., Schleicher, A., Freund, H.J., Zilles, K. (2001). Variability and asymmetry in the human precentral motor system. A cytoarchitectonic and myeloarchitectonic brain mapping study. *Brain, 124*, 2232-58.

Ragland, J.D., Goldberg, T.E., Wexler, B.E., Gold, J.M., Torrey, E.F., and Weinberger, D.R. (1992). Dichotic listening in monozygotic twins discordant and concordant for schizophrenia. *Schizophrenia Research, 7(2)*, 177-83.

Rotarska, A. (2007). Dissertation zur Erlangung des Doktorgrades Dr. rer. nat. Johann Wolfgang Goethe-Universität, Frankfurt / Main.

Samson, Y., Belin, P., Thivard, L., Boddaert, N., Crozier, S., Zilbovicius, M. (2001). Auditory perception and language: functional imaging of speech sensitive auditory cortex. *Rev Neurol (Paris), 157,* 837-46.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D., Linden D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-10.

Schack, B., Weiss, S., and Rappelsberger, P., 2003. Cerebral information transfer during word processing: where and when does it occur and how fast is it? *Hum Brain Mapping,19(1)*, 18-36.

Schönmeyer R. (2007). *Vollautomatische Segmentierung ausgesuchter Strukturen des menschlichen Gehirns aus kernspintomographischen Datensätzen*: der andere Verlag.

Schröder, J., Tittel, A., Stockert, A., Karr, M. (1996). Memory deficits in subsyndromes of chronic schizophrenia. *Schizophrenia Research, 21(1)*, 19-26.

Scott, S.K. (2005). Auditory processing: speech, space and auditory objects. *Current Opinion Neurobiology, 15*, 197–201.

Shapleske, J., Rossell, S.L., Woodruff, P.W., and David, A.S. (1999). The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Res Rev., 29(1)*, 26-49.

Shedlack, K., Leem G., and Sakuma, M. (1997). Language processing and memory in Ill and well siblings from multiple families affected with schizophrenia. *Schizophrenia Research,* 25, 43-52.

Shapleske, J., Rossell, S.L., Simmons, A., David, A.S., Woodruff, P.W. (2001). Are auditory hallucinations the consequence of abnormal cerebral lateralization? A morphometric MRI study of the sylvian fissure and planum temporale. *Biol Psychiatry, 15, 49(8)*, 685-93.

Shenton, M., Dickey, C., Frumin, M., and McCarley, R. (2001). A review of MRI findings in schizophrenia. *Schizophr Res, 49*(1-2), 1-52.

Silbersweig, D.A., Stern, E., Frith, C., Cahill, C., Holmes, A., and Grootoonk, S. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-9.

Slade P.D. (1994). Models of hallucination: from theory to practice. In: A.S. David and J.C. Cutting (Eds), *The neuropsychology of schizophrenia.* Hove: Psychology Press.

Sommer, I.E., Ramsey, N.F., and Kahn, R.S. (2001). Language lateralisation in schizophrenia, an fMRI study. *Schizophrenia Research, 1, 52(1-2)*, 57-67.

Sommer, I.E., Ramsey, N.F., Mandl, R.C., Kahn, R.S. (2003). Language lateralisation in female patients with schizophrenia: an fMRI study. *Schizophrenia Research 60(2-3)*, 183-90.

Stratta, P., Daneluzzo, E., Mattei, P., Bustini, M., Casacchia, M., Rossi, A. (1997). No deficit in Wisconsin Card Sorting Test performance of schizophrenic patients' first-degree relatives. *Schizophrenia Research, 26*, 147–151.

Talairach, J., and Tournoux, P. (1988). *Co-planar stereotexic atlas of the human brain*. New York: Thieme Medical.

Van de Ven, V., Formisano, E., Prvulovic, D., Roeder, C., and Linden, D. (2004). Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. *Hum Brain Mapp, 22*(3), 165-178.

Van de Ven, V.G., Formisano, E., Roder, C.H., Prvulovic, D., Bittner, R.A., Dietz, M.G., Hubl, D., Dierks, T., Federspiel, A., Esposito, F., Di Salle, F., Jansma, B., Goebel, R., and Linden, D.E. (2005). The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage, 27(3)*, 644-55.

Van Haren, N.E., Bakker, S.C., Kahn, R.S. (2008). Genes and structural brain imaging in schizophrenia. *Curr Opin Psychiatry, 21(2),* 161-7.

Warren, J.D., Jennings, A.R., Griffiths, T.D. (2005). Analysis of the spectral envelope of sounds by the human brain. *Neuroimage*. 15, 24(4), 1052-7.

Weiss, E.M., Hofer, A., Golaszewski, S., Siedentopf, C., Felber, S., Fleischhacker, W.W. (2003). Language lateralisation in unmedicated patients during an acute episode of schizophrenia: a functional MRI study**.** *Psychiatry Research, 31, 146(2),* 185-90.

Weiss, A.P., Zalesak, M., DeWitt, I., Goff, D., Kunkel, L., Heckers, S. (2004). Impaired hippocampal function during the detection of novel words in schizophrenia. *Biol Psychiatry, 1, 55(7)*, 668-75.

Whalley, H.C., Harris, J.C., and Lawrie, S.M. (2007). The neurobiological underpinnings of risk and conversion in relatives of patients with schizophrenia. *Int Rev Psychiatry, 19(4)*, 383-97.

Wicker, B., and Fonlupt, P. (2003). Generalized least-squares method applied to fMRI time series with empirically determined correlation matrix. *Neuroimage, 18(3),* 588-94.

Winterer, G., Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N. (2008). Association of 5' end neuregulin-1 (NRG1) gene variation with subcortical medial frontal microstructure in humans. *Neuroimage, 1, 40(2),* 712-8.

Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., and Zaudig, M. (1996). *Strukturiertes Klinisches Interview für DSM-IV (SKID)*. Göttingen: Beltz-Test.

Woldorff, M.G, Gallen, C.C., Hampson, S.A., Hillyard, S.A., Pantey, C., Sobel, D., Bloom, F.E. (1993). Modulation of early sensory processing in human auditory cortex during auditory selective attention. *Proc Natl Acad Science 15, 90(18)*, 8722-6.

Zinkstok, J., Schmitz, N., Van Amelsvoort, T., Moeton, M., Baas, F., Linszen, D. (2008). Genetic variation in COMT and PRODH is associated with brain anatomy in patients with schizophrenia. *Genes Brain Behav, 7(1),* 61-9.

www.brainvoyager.com

www.neurobs.com

www.spss.com

Part II

Agartz, I., Andersson, J.L., and Skare, S. (2001). Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. *Neuroreport, 12*, 2251-2254.

Basser, P.J., Mattiello, J., and LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophys Journal, 66,* 259-267.

Burns, J., Job, D., Bastin, M.E., Whalley, H., Macgillivray, T., Johnstone, E.C., et al. (2003). Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. *Br J Psychiatry, 182*, 439-443.

Cercignani, M., Horsfield, M.A. (2001). The physical basis of diffusion-weighted MRI. *J Neurol Science, 186(1)*, S11-14.

David, A.S. (2004). The cognitive neuropsychiatry of auditory verbal hallucinations: an overview. *Cognit Neuropsychiatry, 9*, 107-123.

Dierks, T., Linden, D.E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., et al. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22*, 615-621.

Englund, E., Sjobeck, M., Brockstedt, S., Latt, J., and Larsson, E.M. (2004). Diffusion tensor MRI post mortem demonstrated cerebral white matter pathology. J Neuron, *251(3)*, 350-2.

Foong, J., Maier, M., Clark, C.A., Barker, G.J., Miller, D.H., and Ron, M.A. (2000a). Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. *J Neurol Neurosurg Psychiatry, 68*, 242-244.

Foong, J., Maier, M., Barker, G.J., Brocklehurst, S., Miller, D.H., and Ron, M.A. (2000b). In vivo investigation of white matter pathology in schizophrenia with magnetisation transfer imaging. *J Neurol Neurosurg Psychiatry, 68*, 70-74.

Forman, S.D., Cohen, J.D., Fitzgerald, M., Eddy, W.F., Mintun, M.A., and Noll, D.C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med., 33*, 636-647.

Frith, C. (2005). The neural basis of hallucinations and delusions. *C R Biology, 328*, 169 175.

Galuske, R.A., Schlote, W., Bratzke, H., and Singer, W. (2000). Interhemispheric asymmetries of the modular structure in human temporal cortex. *Science, 289*, 1946-1949.

Garey, L.J., Ong, W.Y., Patel, T.S., Kanani, M., Davis, A., Mortimer, A.M., et al. (1998). Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry, 65*, 446-453.

Honea, R., Crow, T.J., Passingham, D., and Mackay, C.E. (2005). Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry, 162*, 2233-2245.

Hua, J.Y., and Smith, S.J. (2004). Neural activity and the dynamics of central nervous system development. *Nat Neuroscience, 7*, 327-332.

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., et al. (2004). Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry, 61*, 658-668.

Jenkinson, M., Bannister, P., Brady, M., and Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*, 825-841.

Kubicki, M., Westin, C.F., Maier, S.E., Frumin, M., Nestor, P.G., Salisbury, D.F., et al. (2002). Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Am J Psychiatry, 159*, 813-820.

Kubicki, M., Westin, C.F., Nestor, P.G., Wible, C.G., Frumin, M., Maier, S.E., et al. (2003). Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Biol Psychiatry, 54*, 1171-1180.

Kumra, S., Ashtari, M., McMeniman, M., Vogel, J., Augustin, R., Becker, D.E., et al. (2004). Reduced frontal white matter integrity in early-onset schizophrenia: a preliminary study. *Biol* Psychiatry, 55, 1138-1145.

Larsson, E.M., Englund, E., Sjobeck, M., Latt, J., and Brockstedt, S. (2004). MRI with diffusion tensor imaging post-mortem at 3.0 T in a patient with frontotemporal dementia. *Dement Geriatr Cogn Disorders, 17*, 316-319.

Lee, K.H., Williams, L.M., Haig, A., and Gordon, E. (2003). "Gamma (40 Hz) phase synchronicity" and symptom dimensions in schizophrenia. *Cognit Neuropsychiatry,* 8, 57-71.

Lee, S.H., Wynn, J.K., Green, M.F., Kim, H., Lee, K.J., Nam, M., et al. (2006). Quantitative EEG and low resolution electromagnetic tomography (LORETA) imaging of patients with persistent auditory hallucinations. *Schizophr Research, 83*, 111-119.

Lewis, D.A., and Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neuroscience, 25*, 409-432.

Linden, D.E. (2006). How psychotherapy changes the brain-the contribution of functional neuroimaging. *Mol Psychiatry, 11*, 528-538.

Linden, D.E., Bittner, R.A., Muckli, L., Waltz, J.A., Kriegeskorte, N., Goebel, R., et al.

(2003). Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. *Neuroimage,* 20, 1518-1530.

Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., et al. (2003). Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. *Neuropsychobiology,* 47, 141-145.

Pierpaoli, C., and Basser, P.J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magn Reson Med., 36*, 893-906.

Rapoport, J.L., Addington, A.M., Frangou, S., and Psych, M.R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry, 10*, 434-449.

Shapleske, J., Rossell, S.L., Chitnis, X.A., Suckling, J., Simmons, A., Bullmore, E.T., et al. (2002). A computational morphometric MRI study of schizophrenia: effects of hallucinations. *Cereb Cortex*, *12*, 1331-1341.

Shergill, S.S., Kanaan, R.A., Chitnis, X.A., O'Daly, O., Jones, D.K., Frangou, S., et al. (2007). A diffusion tensor imaging study of fasciculi in schizophrenia. *Am J Psychiatry, 164*, 467-473.

Shin, S.E., Lee, J.S., Kang, M.H., Ki, C,E,, Bae, J.N., and Jung, G. (2005). Segmented volumes of cerebrum and cerebellum in first episode schizophrenia with auditory hallucinations. *Psychiatry Research, 138,* 33-42.

Sun, Z., Wang, F., Cui, L., Breeze, J., Du, X., Wang, X., et al. (2003). Abnormal anterior cingulum in patients with schizophrenia: a diffusion tensor imaging study. *Neuroreport, 14*, 1833-1836.

Uhlhaas, P.J., Linden, D.E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., et al. (2006a). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci*ence, *26*, 8168-8175.

Uhlhaas, P.J., and Singer, W. (2006b). Neural Synchrony in Brain Disorders: Relevance for
Cognitive Dysfunctions and Pathophysiology. *Neuron, 52*, 155-168.

Van de Ven, V.G., Formisano, E., Roder, C.H., Prvulovic, D., Bittner, R.A., Dietz, M.G., et al. (2005). The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage,* 27, 644-655.

Webster, M.J., Ungerleider, L.G., and Bachevalier, J. (1991). Lesions of inferior temporal area TE in infant monkeys alter cortico-amygdalar projections. *Neuroreport* , *2*, 769-772.

Wolkin, A., Choi, S.J., Szilagyi, S., Sanfilipo, M., Rotrosen, J.P., and Lim, K.O. (2003). Inferior frontal white matter anisotropy and negative symptoms of schizophrenia: a diffusion tensor imaging study. *Am J Psychiatry, 160*, 572-574.

Woodruff, P.W. (2004). Auditory hallucinations: Insights and questions from neuroimaging. *Cognit Neuropsychiatry, 9*, 73-91.

www.bic.uni-frankfurt.de/bv-tools

www.brainvoyager.com

www.fmrib.ox.ac.uk/fsl

www.mni.mcgill.ca

Chapter 4

Part I

American Psychiatric Association (APA) (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. (DSM-IV). Washington, DC: APA.

Deichmann, R., Schwarzbauer, C., and Turner, R. (2004). Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3T. *Neuroimage, 21*, 757-767.

Dierks, T., Linden, D.E., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., et al. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22*, 615-621.

Epstein, R., and Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 9, 392(6676)*, 598-601.

ffytche, D.H., Howard, R. J., Brammer, M. J., David, A., Woodruff, P., Williams, S.,1998. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nature Neuroscience 1, 738 - 742.

Halgren, E., Dale, A.M., Sereno, M.I., Tootell, R.B., Marinkovic, K., and Rosen, B.R. (1999). Location of human face-selective cortex with respect to retinotopic areas. *Human Brain Mapping, 7(1)*, 29-37.

Kanwisher, N., McDermott, J., and Chun, M.M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neuroscience, 1, 17(11)*, 4302-11.

Peelen, M.V., and Downing, P.E. (2005). Within-subject reproducibility of category-specific visual activation with functional MRI. Human Brain Mapping 25, 402-408.

Puce, A., Allison, T., Asgari, M., Gore, J.C., and McCarthy, G. (1996). Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study. *Journal of Neuroscience, 15, 16(16)*, 5205-15.

Shergill, S.S., Brammer, M.J., Williams, S.C. Murray, R.M., and McGuire, P.K. (2004). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of Genetic Psychiatry, 57*, 1033-1038.

Van de Ven, V.G., Formisano, E., Roder, C.H., Prvulovic, D., Bittner, R.A., Dietz, M.G., et al. (2005). The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage,* 27, 644-655.

Weiss, A.P., and Heckers, S. (1999). Neuroimaging of hallucinations: a review of the literature. *Psychiatry Research, 20, 92(2-3),* 61-74.

www.maodes.de

www.psychology.stir.ac.uk

Part II:

Aggernea, A. (1972). The experienced reality of hallucinations and other psychological phenomena. An empirical analysis. *Acta Psychiatrica Scandinavica. 48*, 220-238.

American Psychiatric Association (APA) (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)*. Washington, DC: APA.

Bracha, H.S., Wolkowitz, O.M., Lohr, J.B., Karson, C.N., and Bigelow, L.B. (1989). High prevalence of visual hallucinations in research subjects with chronic schizophrenia. *American Journal of Psychiatry, 146*, 526-528

Deichmann, R., Schwarzbauer, C., and Turner, R. (2004). Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3T. *Neuroimage, 21*, 757-767.

Dierks, T., Linden, D. E. J., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., and Singer,W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22(3)*, 615-21.

ffytche, D.H., Howard, R. J., Brammer, M. J., David, A., Woodruff, P., and Williams, S. (1998). The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nature Neuroscience, 1*, 738 - 742.

ffytche, D.H. (2005). Visual Hallucinations and the Charles Bonnet Syndrome. *Current Psychiatry Reports, 7*, 168-179.

Friston, K.J. (1995). Commentary and opinion: II. Statistical parametric mapping: ontology and current issues. *J Cereb Blood Flow Metab., 15(3)*, 361-70.

Kay, S.R., Fiszbein, A., and Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*, 261-76.

Krampen, G. (1991). *Fragebogen zu Kompentenz- und Kontrollüberzeugung (FKK)*. Göttingen: Hogrefe.

Kubicki, M., Westin, C.F., Nestorm P.G., Wible, C.G., Frumin, M., Maier, S.E., Kikinis, R., Jolesz, F.A., McCarley, R.W., and Shenton, M.E. (2003). Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Biol. Psychiatry, 54*, 1171-80.

Malach, R., Reppas, J.B., Benson, R.R., Kwong, K.K., Jiang, H., Kennedy, W.A., Ledden, P.J., Brady, T.J., Rosen, B.R., and Tootell, R.B. (1995). Object-related activity revealed by functional magnet resonance imaging in human occipital cortex. *Proc. Nat. Ac. Science, 92*, 8135-8139.

Morrison, A. P., Wells, A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychiatry, 41*, 259-270.

Oishi, N., Udaka, F., Kameyama, M., Sawamoto, N., Hashikawa, K., and Fukuyama, H. (2005). Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. *Neurology, 65*, 1708-1715.

Peelen, M.V., and Downing, P.E. (2005). Within-subject reproducibility of category-specific visual activation with functional MRI. *Human Brain Mapping, 25*, 402-408.

Penhune, V.B., Zatorre, R.J., MacDonald, J.D., and Evans, A.C. (1996). Interhemispheric Anatomical Differences in Human Primary Auditory Cortex: Probabilistic Mapping and Volume Measurement from Magnetic Resonance Scans. *Cerebral Cortex, 6*, 661-672.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D., and Linden, D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia? *Schizophrenia Bulletin, 31*, 1-8.

Silbersweig, D.A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., Seaward, J., McKenna, P., Chua, S.E., Schnorr, L., Jones, T., and Frackowiak, R.S.J. (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-9.

Sireteanu, R., Singer, W., Fronius, M., Greuel, J.M., Best, J., Fiorentini, A., Bisti, S., Schiavi, C., and Campos E. (1993). Eye alignment and cortical binocularity in strabismic kittens: a comparison between tenotomy and recession. *Vis. Neuroscience, 10 (3)*, 541-9.

Sireteanu, R., and Rettenbach, R. (2000). Perceptual learning in visual search generalizes over tasks, locations, and eyes. *Vision Research, 40(21)*, 2925-49.

Stephane, M., Barton, S., and Boutros, N.N. (2001). Auditory verbal hallucinations and dysfunction of the neural substrates of speech. *Schizophrenia Research, 50*, 61-78.

Talairach, J., and Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. Thieme Medical: New York.

Trojano, L., Linden, D.E.J., Formisano, E., Goebel, R., Sack, A.T., and Di Salle, F. (2004). What clocks tell us about the neural correlates of spatial imagery. *European Journal of Cognitive Psychology, 16*, 653-672.

Van de Ven, V.G., Formisano, E., Röder, C.H., Prvulovic, D., Bittner R.A., Dietz, M.G., Hubl, D., Dierks, T., Federspiel, A., Esposito, F., Di Salle, F., Jansma, B., Goebel, R., and Linden, D.E. (2005).The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage, 27*, 644-55.

Verdoux, H., and van Os, J. (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia Research, 54(1-2)*, 59-65.

Wicker, B., and Fonlupt, P. (2003). Generalized least-squares method applied to fMRI time series with empirically determined correlation matrix. *Neuroimage, 18(3)*, 588-94.

www.psychology-stir.ac.uk.

Part III

American Psychiatric Association (APA) (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV).* Washington, DC: APA.

Burke, W. (2002). The neural basis of Charles Bonnet–hallucinations: a hypothesis. *Journal of Neurological Neurosurgery*, *Psychiatry, 73,* 535–541.

Collerton, D., Perry, E. and McKeith, I. (2005). Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. *Behav Brain Science, 28(6),* 737-57.

Cui , J.G., Hill, J.M., Zhao, Y., and Likiw, W.J. (2007). Expression of inflammatory genes in the primary visual cortex of late-stage Alzheimer's disease. *Neuroreport, 22*, 18(2), 115-9.

Deichmann, R., Schwarzbauer, C., and Turner, R. (2004). Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3T. *Neuroimage, 21*, 757-767.

Dierks, T., Linden, D. E. J., Jandl, M., Formisano, E., Goebel, R., Lanfermann, H., and Singer, W. (1999). Activation of Heschl's gyrus during auditory hallucinations. *Neuron, 22(3),* 615-21.

Farah, M.J. (1988). Is visual imagery really visual? Overlooked evidence from neurophysiology. *Psychological Review, 95*, 307-317.

ffytche, D.H., Howard, R.J., Brammer, M.J., David, A., Woodruff, P., and Williams, S. (1998). The anatomy of conscious vision: an fMRI study of visual hallucinations. *Nat Neuroscience, 1(8)*, 738-42.

ffytche, D.H. (2005). Visual hallucinations and the Charles Bonnet Syndrome. *Current Psychiatry Reports, 7*, 168-179.

Kammer, T. (1999). „Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: their topographic relationship". *Neuropsychologia, 37,* 191 – 198.

Kay, S.R., Fiszbein, A., and Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*, 261-76.

Klein, C., Andresen, B., and Jahn, T. (1997). Erfassung der schizotypen Persönlichkeit nach DSM-III-R: Psychometrische Eigenschaften einer autorisierten deutschsprachigen Übersetzung des „Schizotypy Personality Questionnaire" (SPQ) von Raine. *Diagnostica, 43*, 347-369.

Kosslyn SM, Thompson WL, and Alpert NM. (1997). Neural systems shared by visual imagery and visual perception: a positron emission tomography study. *Neuroimage, 6*, 320-34.

Linden, D. E. J., and Dierks, T. (2002). Functional imaging of auditory hallucinations in schizophrenia. *Nervenheilkunde, 21*, 331-335.

Merabet, L.B., Maguire, D., Warde, A., Alterescu, K., Stickgold, R., Pascual-Leone, A. (2004). Visual hallucinations during prolonged blindfolding in sighted subjects. *Journal of Neuroophthalmology, 24(2)*, 109-13.

Morrison, A. P., Wells, A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychiatry, 41*, 259-270.

Peelen, M.V., and Downing, P.E. (2005). Within-subject reproducibility of category-specific visual activation with functional MRI. *Human Brain Mapping, 25*, 402-408.

Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin, 17*, 556-564.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D., and Linden D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-8.

Schott, G. D. (2007). „Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration". *Brain, 130,* 1690 – 1703.

Schultz, G., and Melzack, R. (1991). The Charles Bonnet syndrome: 'phantom visual images'. *Perception, 20(6)*, 809-25.

Silbersweig, D.A., Stern, E., Frith, C., Cahill, C., Holmes, A., Grootoonk, S., et al., (1995). A functional neuroanatomy of hallucinations in schizophrenia. *Nature, 378*, 176-9.

Sheehan, P.W. (1967). A shortened form of Bett`s questionnaire upon mental imagery. *Journal of Clinical Psychology, 23*, 386-389.

Talairach, J., and Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain.* New York: Thieme Medical.

Trojano, L., Linden, D.E.J., Formisano, E., Goebel, R., Sack, A.T., and Di Salle, F. (2004). What clocks tell us about the neural correlates of spatial imagery. *European Journal of Cognitive Psychology, 16*, 653-672.

Tyler, C. W. (1978). "Some new entoptic phenomena" *Vision Research, 18,* 1633 – 1639.

Wilkinson F, 2004 "Migraine auras and other hallucinations: windows on the visual system" In *Roots of Visual Awareness* D Milner & C Haywood (Eds) Progress in Brain Research **144** 305 - 320

Wittchen, H.U., Wunderlich, U., Gruschwitz, S., and Zaudig, M. (1996). *Strukturiertes Klinisches Interview für DSM-IV (SKID)*. Beltz-Test, Göttingen.

Chapter 5 and Zusammenfassung

Bentall, R.P. (1990). The illusion of reality: A review and integration of psychological research on hallucinations. *Psychological Bulletin, 17*, 82-95.

Brett, E.A., and Starker, S. (1977). Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease, 163*, 394-400.

David, A.S. (1999). Auditory hallucinations: phenomenology, neuropsychology and neuroimaging update. *Acta Psychiatr. Scand.* 99, 95–104.

Bentall, R. and Slade, P. D. (1988). Towards an integrative model. *In: Sensory Deception*, 208-228.

Kosslyn, S.M. (1994). *Image and brain: the resolution of the imagery debate*. Cambridge, MA: MIT Press.

Krampen, G. (1981). *Fragebogen zu Kompetenz- und Kontrollüberzeugungen (FKK)*. *Handanweisung*. Hogrefe: Göttingen.

Levenson, H. (1972). Distinctions within the concept of internal-external control: Development of a new scale. Proceedings of the 80th Annual Convention of the American *Psychological Association, 7*, 261-26.

Manford, M., and Andermann, F. (1998). Complex visual hallucinations. Clinical and neurobiological insights. *Brain, 121 (10)*, 1819-40.

McGorry, P.D., Yung, A.R., and Philips, L.J. (2003). The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophrenia Bulletin, 29(4)*, 771-90.

Mintz, S. and Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79*, 310-316.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D. and Linden, D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-8.

Poulton, R., Caspi, A., Mofitt T.E., Cannon, M., Murray, R., and Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder. *Archives of General Psychiatry, 57*, 1053-1058.

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs, 80*, 609.

Slade, P.D. (1972). The effects of systematic desensitisation on auditory hallucinations. *Behav Res Ther., 10(1)*, 85-91.

Starker, S. and Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Diseases, 170, 448-451.*

Trojano, L., Grossi, D., Linden, D.E., Formisaon, E., Hacker, H., Zanella, F.E., Goebel, R., and Di Salle, F. (2000). Matching two imagined clocks: the functional anatomy of spatial analysis in the absence of visual stimulation. *Cerebral Cortex, 10(5)*, 473-81.

Van Os, J. (2003). Is there a continuum of psychotic experiences in the general population? *Epidemiol Psychiatr Soc., 12(4)*, 242-52*.*

Whalley, H.C., Simonotto, E., Marshall, I., Owens, D.G.C., Goddard, N.H., Johnstone, E.C., and Lawrie, S.M. (2005). Functional disconnectivity in subjects at high genetic risk of schizophrenia. *Brain, 128(9)*, 2097-2108.

Appendix

Aleman, A., Böcker, K.B.E., and de Haan, E.H.F. (1999). Disposition towards hallucinations and subjective versus objective vividness of imagery in normal subjects. *Personality and Individual differences*, *27,* 707-714.

Aleman, A., Böcker, K.B.E., Hijman, R., de Haan, E.H.F., and Hahn, R.S. (2003). Cognitive basis of hallucinations in schizophrenia: role of top-down information processing. *Schizophrenia Research*, *15,* 64(2-3), 175-85.

Barrett, T.R., and Etheridge, J.B. (1992). Verbal hallucinations in normals I. People who hear "voices". *Applied Cognitive Psychology, 6*, 379-387.

Barrett, T.R. (1993). Verbal hallucinatiosn in normals, II: Self-reported imagery vividness. *Personality and Individual Differences, 15,* 61-67.

Bentall, R.P. and Slade, P.D. (1985). Reality testing and auditory hallucinations: a signal detection analysis. *British Journal of Clinical Psychology, 24*, 159-169.

Bentall, R.P. (1990). The illusion of reality: A review and integration of psychological research on hallucinations. *Psychological Bulletin, 17*, 82-95.

Böcker, K.B.E., Hijman, R., Kahn, R.S., and de Haan, E.H.F. (2000). Perception, mental imagery and reality discrimination in hallucinating and non-hallucinating schizophrenic patients. *British Journal of Clinical Psychology, 39*, 397-406.

Brebion, G., Smith, M.J., Gorman, J.M., and Amador, X. (1997). Discrimination Accuracy and Decision Biases in Different Types of Reality Monitoring in Schizophrenia. *Journal of Nervous and Mental Disease. 185(4),* 247-253.

Brett, E.A., and Starker, S. (1977). Auditory imagery and hallucinations. *Journal of Nervous and Mental Disease, 163*, 394-400.

Bunzeck, N., Wuestenbergb, T., Lutzc, K., Heinzea, H-J., and Janckez, L. (2005). Scanning silence: Mental imagery of complex sounds. *Neuroimage 9.*

Chandiramani, K., and Varma, V.K. (1987). Imagery in schizophrenic patients compared with normal controls. *British Journal of Medical Psychology, 60*, 335-341.

Cuesta, M.J., and Peralta, V. (1995). Psychopathological dimensions in schizophrenia. *Schizophrenia Bulletin, 21,* 473-482.

Ducreux, D., Petit-Lacour, M.C., Benoudiba, F., Castelain, V., and Marsot-Dupuch, K. (2002). Diffusion-weighted imaging in a case of Wernicke encephalopathy. *J. Neuroradiol.* 29, 39–42.

Formisano, E., Esposito, F., Kriegeskorte, N., Tedeschi, G., Di Salle, F., and Goebel, R. (2002). Spatial independent component analysis of functional magnetic resonance imaging time-series: characterization of the cortical components. *Neurocomputing, 49*, 241-254.

Gardini, S., De Beni, R., Cornoldi, C., Bromiley, A., and Venneri, A. (2005). Different neuronal pathways support the generation of general and specific mental images. *Neuroimage 27(3)*, 544-52.

Jeannerod, M. (1994). The representing brain: neuronal correlates of motor intention and imagery. *Behavioral and Brain Sciences, 3*, 320-328.

Kay, S.R., Fiszbein, A., Opler, L.A. (1987). The Positive and Negative Symptom Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin, 13*, 261-76.

Klein, I., Duboisa, J., Mangina, J.-F., Kherifa, F., Flandina, G., Polinea, J.-B., Denisb, M., Kosslyn, S.M., and Le Bihana, D. (2004). Retinotopic organization of visual mental images as revealed by functional magnetic resonance imaging. *Cognitive Brain Research, 22,* 26–31.

Kosslyn, S.M. (1994). *Image and brain: the resolution of the imagery debate*. Cambridge, MA: MIT Press.

Lindenmayer, J.P., Bernstein-Hymaan, R., and Grochowski, B.A. (1994). A new five-factor model of schizophrenia. *PSychiaric Quaterly, 65,* 299-322.

Mazard, A., Laou, L., Joliot, M., Mellet, E. (2005). Neural impact of the semantic content of visual mental images and visual percepts. *Brain Res Cogn Brain Res.* 24(3):423-35.

McGuire, P.K., Silbersweig, D.A., Murray, R.M., David, A.S., Frackowiak, R.S. and Frith, C.D. (1996). Functional anatomy of inner speech and auditory verbal imagery. *Psychological medicine, 26*, 29-38.

Mechelli, A., Price, C.J., Friston, K.J., and Ishai, A. (2004). Where bottom-up meets top-down: neuronal interactions during perception and imagery. *Cereb Cortex, 14(11)*, 1256-65.

Mintz, S. and Alpert, M. (1972). Imagery vividness, reality testing, and schizophrenic hallucinations. *Journal of Abnormal Psychology, 79*, 310-316.

Morrison, A.P. Wells A., and Nothard, S. (2002). Cognitive and emotional predictors of predisposition to hallucinations in non-patients. *British Journal of Clinical Psychology, 41(3)*, 259-270.

Sack, A.T., Van de Ven, V., Etschenberg, S., Schatz, D. and Linden, D.E.J. (2005). Enhanced vividness of mental imagery as a trait marker of schizophrenia ? *Schizophrenia Bulletin, 31*, 1-8.

Sato, M., Baciu, M., Loevenbruck, H., Schwartz, J.L., Cathiard, M.A., Segebarth, C., and Abry, C. (2004). Multistable representation of speech forms: a functional MRI study of verbal transformations. *Neuroimage, 23(3)*, 1143-51.

Silbersweig, D.A., and Stern, E. (1992). Towards a functional neuroanatomy of conscious perception and its modulation by volition: implications of human auditory. *Philos Trans R Soc Lond B Biol Sci., 29, 353(1377)*, 1883-8.

Shergill, S.S., Bullmore, E., Simmons, A., Murry, R., and McGuire, P. (2000). Functional anatomy of auditory verbal imagery in schizophrenic patients with auditory hallucinations. *American Journal of Psychiatry, 157 (10)*, 1691-1693.

Slotnick, S.D., Thompson, W.L., Kosslyn, S.M. (2005). Visual mental imagery induces retinotopically organized activation of early visual areas. *Cerebral Cortex, 15(10)*, 1570-83.

Starker, S. and Jolin, A. (1982). Imagery and hallucinations in schizophrenic patients. *Journal of Nervous and Mental Diseases, 170, 448-451.*

Van de Ven, V., and Merckelbach, H. (2003). The role of schizotypy, mental imagery and fantasy proneness in hallucinatory in undergraduate students. *Personality and Individual Differences, 35*, 889-896.

APPENDIX

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APPENDIX A

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Location:

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- Brain Imaging Center, Johann Wolfgang Goethe-University, Frankfurt/Main, Germany.

APPENDIX B

Abbreviations

Chapter 1

SZ = schizophrenic

DSM-IV = Diagnostic and Statistic Manual of Mental Disorders

ICD-10 = International Classification of Diseases

APA = American Psychiatric Association

fMRI = functional magnetic resonance imaging

AV = auditory verbal

LSHS = Launay Slade Hallucination Scale

QMI = Betts' Questionnaire Upon Mental Imagery

EEG = Electroencephalography

PET = Positrons Emissions Tomography

CT = Computer Tomography

PFC = Prefrontal cortex

PBC = pregnancy and birth complications

CNS = central nervous system

rCBF = regional cerebral blood flow

ACC = anterior cingulate cortex

D1, d2, d3, d4, d5 = dopamine receptors

MR = magnet resonance

DTI = diffusion tensor imaging

PT = pyramidal tract

PAC = primary auditory cortex

AII = secondary auditory cortex

RF = radio frequency band

T1 = longitudinal relaxation time

T2 = transverse relaxation time

T2* = effective transverse relaxation time

BOLD = blood oxygenation level dependent signal

RHS = Revised Hallucination scale

LPS = Leistungsprüfsystem

CCBS = Competence and Control Beliefs Scale

MWT = Mehrfachwahl-Wortschatztest

TMT = Trail-making test

PANSS = Positive and Negative Symptom Scale

SPQ = Schizotypy Personality Questionnaire

ESI = Eppendorfer Schizophrenie Inventar

SKID I and SKID II = Strukturiertes Klinisches Interview Psychischer Störungen

QAH = Questions about hallucinations

Chapter 2

R = first-degree relatives

CHS = high-schizotypy controls

CLS = low-schizotypy controls

PAS = Prämorbide Anpassungsskala

SPSS = Statistical Package for Social Sciences

ANOVA = analysis of variance

Chapter 3

AVH = auditory verbal hallucinations

EPI = echo planar imaging

TR = transgressive-regressive

TE = transversely excited

MDEFT = 3D modified driven equilibrium Fourier transform imaging

RFX = random effects analysis

TLI = total lateralization index

FDR = false discovery range

ROI = region-of-interest

VOI = volume of interest.

Chapter 4

FFA **=** fusiform face area

EBA = extrastriate body area

OFA = occipital face area

PPA = parahippocampal place area

APPENDIX C

1. Diagnosis criteria for schizophrenia

a. International classification of diseases (ICD.10) criteria for schizophrenia:

Either at least one of the syndromes, symptoms and signs listed below under (1) or at least two of the symptoms and signs listed under (2) would have been present for most of the time during an episode of psychotic illness lasting for at least 1 month.

1. At least one of the following:

-Thought echo, thought insertion or withdrawal and thought broadcasting.

-Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations, and delusional perception.

-Hallucinatory voices giving a running commentary on the patients`behaviour or discussing him/ her between themselves or other types of hallucinatory voices coming from some part of the body.

-Persistent delusions of other kinds that are culturally inappropriate or implausible, such as religious or political identity, superhuman powers and ability etc.

2. At least two of the following:

-Persistent hallucinations in any modality, when accompanied by either fleeting or half-formed delusions without clear affective content or by persistent over-valued ideas or when accouting every day for weeks or months on end.

-Breaks of interpolations in the train of thought, resulting in incoherence or irrelevant speech or neologisms.

-Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.

-Negative symptoms such as marked apathy, paucity of speech and blunting or incongruity or emotional responses (these usually result in social withdrawal and lowering of social performance). It must be clear that these are not due to depression or neuroleptic medication.

-A significant and consistent change in the overall quality of some aspects of personal behaviour manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

Exclusion Criteria: The ICD-10 criteria specify that schizophrenia should not be diagnosed if the symptoms are better accounted for by a mood disorders, overt brain disease or drug intoxication or withdrawal.

b. Diagnostic & statistical manual of mental disorders (DSM IV) criteria for schizophrenia

A. Characteristics of Symptoms: two or more of the following, each present for a significant portion of time during a one month period (or less if successfully treated):

- Delusion
- Hallucinations
- Disorganised speech (e.g. frequent derailment or incoherence)
- Grossly disorganised or catatonic behaviour
- Negative symptoms, i.e. affective flattening, alogia or avolition

(Note: Only one "A" symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person`s behaviour or thoughts, or two more voices conversing with each other).

B. Social/Occupational Dysfunction: for a significant portion of time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations or self-care is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).

C. Duration: continuous signs of the disturbance persist for at least six months. This six month period must include at least one month of symptoms that meet criterion A (i.e. active phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form, e.g. odd beliefs, unusual perceptual experiences).

Exclusion Criteria: the remainder of the criteria (D-F in the DSM-IV text) specify that the signs and symptoms above are not better accounted for by another disorder, either psychiatric (i.e. mood disorder, schizoaffective disorder or pervasive developmental disorder), substance abuse (e.g. amphetamine intoxication or withdrawal) or general medical condition (e.g. hyperthyroidism).

Factor model of schizophrenia

Table A1: Five Factor Model of Schizophrenic Symptoms According to Lindemayer et al. (1994) and Cuesta and Peralta (1995). The numbers in the () replicate the item number of the PANSS (Positive and Negative Symptom Scale; Kay, 1987).

Factor			***Symptom***			
1. Negative	Emotional Withdrawal (N2)	Passive/ Apathetic Withdrawal (N4)	Lack of Spontaneity (N6)	Poor Rapport (N3)	Active Social Avoi-dance (G16)	Blunted Affect (N1)
2.Excitement	Excitement (P4)	Poor Impulse Control (G14)	Hostility (P7)	Tension (G4)		
3. Cognitive	Conceptual Disorgani-sation (P2)	Disorientation (G10)	Man-nerisms and Posturing (G5)	Poor Atten-tion (G11)	Difficulty in Abstract Thinking (N5)	
4. Positive	Suspiciousness Persecution (P6)	Delusions (P1)	Grandiosity (P5)	Unusual Thought Content (G9)		
5. Depression	Preoccupation (G15)	Guilt Feelings (G3)	Depression (G6)	Somatic Concern (G1)	Anxiety (G2)	
Disorganisation	Conceptual Disorgani-sation (P2)	Inappropriate Affect	Poor Attention (G11)			
Other PANSS Items	Uncooperative-ness (G8)	Motor Retardation (M7)	Stereotyped Thinking (N7)	Lack of Judge-ment and Insight (G12)	Distur-bances of Volition (G13)	Halluci-nations (P3)

Mental imagery and its neuronal representations

Table A2: *Studies regarding mental imagery and its neuronal representation.*

Construct	**Study**	**Region**	**Sensory modality**	**Task**
Hemispheric lateralization (left)	**Sato et al. (2004)**	Left-lateralized network: inferior frontal gyrus, supramarginal gyrus, superior temporal gyrus -additionally: anterior part of the right cingulate cortex, bilateral cerebellar cortex	Auditory	Verbal transformation task
	Mazard et al. (2005)	Left occipito-temporal-frontal network: left inferior frontal gyrus, left inferior temporal gyrus	Visual	-mental imagery -visual perception of 2 conditions: object drawings, non-object

				drawings
General	**Formisano et al. (2002)**	Left and right posterior parietal cortex	Visual	Mental clock task
	Silbersweig and Stern (1992)	Broca`s area (left inferior frontal gyrus), bilateral rostral supplementary motor cortex, adjacent bilateral anterior cingulate gyrus, bilateral lateral premotor cortex, right dorsolateral prefrontal cortex, left posterior-superior temporal gyrus	Auditory	Auditory-verbal imagery task
	Shergill et al. (2000)	left inferior and middle frontal gyri, pre- and postcentral gyri, inferior parietal lobule, lingual gyrus, supplementary motor area, right precentral and lingual gyri, posterior cerebellar cortex	Auditory	-listen words -inner speech -auditory verbal imagery in SZ hallucinating patients
Imagery and perception activate similar areas	**Slotnick et al. (2005)**	superior parietal lobule (r), intraparietal sulcus (R), postcentral gyrus (l), middle temporal gyrus (r), inferior temporal sulcus (r), bilateral fusiform gyrus, lateral occipital gyrus (r).	visual	-imagery -attention -perception
	Jeannerod et al. (1994)	Occipitotemporal pathway, posterior parietal cortex.	Motor	Motor imagery = motor preparation
	Klein et al. (2004)	Primary occipital cortex (V1), horizontal and vertical visual field meridians	Visual	Visualize horizontally or vertically oriented flashing bow-tie shaped stimuli
Modality specific brain regions	**Gardini et al. (2005)**	Left frontal areas +general images:right frontal areas +specific images: posterior cingulate, right thalamus, left superior frontal region	Visual	Specific and non-specific images (fMRI)
	McGuire et al. (1996)	Superior temporal cortex (auditory association cortex) + frontal regions (Broca)	Auditory	Imaging a sound of someone's voice
	Kosslyn (1996)	Occipital cortex (primary visual cortex)	Visual	Task of visual imagery
category-selective activation	**Mechelli et al. (2004)**	-category-selective activation: connections from prefrontal cortex, connectivity between parietal cortex and category-selective regions -superior parietal areas	Visual	-visual mental images -5 normal subjects
Primary / secondary cortices	**Bunzeck et al. (2005)**	-secondary auditory cortex (including planum temporale)	Auditory	-perception -imagery of complex sounds

				-normal subjects
	Ducreux et al. (2003)	Primary and secondary auditory cortices (Heschl gyrus and planum temporale) -temporal and insular regions involved in language processing	Auditory	-musical and lyrical sounds mental imagery 27 normal subjects

Table A3: *Studies regarding the connection between mental imagery and hallucinations in Schizophrenia. SP means schizophrenic patients (in alphabetical order). Notes: SP = schizophrenic patient, C = control.*

STUDY	PARTICIPANTS	TASK/ MEASURES	CONSTRUCT	SUMMARY OF FINDINGS
Aleman et al. (1999)	74 college students	-subjective (QMI, LSHS) -objective (judgement of visual similarity of objects)		-high LSHS subjects → higher mental images (QMI) -no replication in the objective task
Aleman et al. (2003)	-22 hallucinating SZ patients -35 non-hallucinating SZ patients -20 controls	Multiple behavioural measures of auditory and verbal mental imagery and perception	Reality monitoring	No differences between any of the mental imagery measures.
Barrett and Etheridge (1992), Barrett (1993)	- Controls, who hear voices each month (50% of the participants)		Schizophrenia-like traits	higher vividness of mental imagery → higher predisposition towards hallucinations
Bentall and Slade (1985), Bentall (1990)	- SZ patients - controls	Signal detection task	Failure in "reality discrimination process "	No difference in signal detection performance between both groups
Böcker (2000)	-19 non-hallucinating SZ patients -13 hallucinating SZ patients -14 controls	-mental imagery task in auditory and visual modality -perception task	Confused reality discrimination	No differences in the imagery ability between patient and control group, but the psychotic SP had higher imagery in the auditory modality
Brebion et al. (1997)	-31 SZ patients -31 controls	-reality monitoring task	Reality monitoring bias	SP were impaired in discriminating: - old items from new (reporting new items as if they were old [[false alarms]). - self-generated / externally generated items. - the modality (auditory vs. visual) in which the item was presented.

Study	Participants	Task/ Measures	Construct	Summary of findings
Brett and Starker (1977), Starker and Jolin (1982)	-SZ patients - controls			Imagery is not more vivid in hallucinatory schizophrenic patients
Chandiramani and Varma (1987)	-20 hallucinatory SZ patients, -20 non-hallucinatory SZ patients -20 controls	-QMI -Gordon`s test of the control of visual imagery		No differences in the vividness of mental imagery between the subjects groups
Mintz and Alpert (1972)	-Hallucinatory SP -non-hallucinatory SP -controls	-test of vividness of auditory imagery -listening task -test to assess the accurance of auditory perceptions	Poor "reality testing"	Individuals who hallucinate have very vivid images
Morrison et al. (2002)	-SZ patients -schizoaffective patients -schizophrenia spectrum disorder	Semi-structured interview		Mental images and psychotic symptoms are seen to be relative from the subjects
Sack et al. (2005)	-50 SZ patients -50 controls	-QMI -RHS	Mental imagery	Independence of imagery abilities and hallucination prone individuals
Van de Ven and Merckelbach (2003)	Undergraduate students (mean age: 20 years)	White christmas task	Schizotypy	Self-reported imagery ability and fantasy proneness were strongly related

4. Questionnaires

Kodierung
P

a. Allgemeine Daten

Datum_____Name des Patienten_____

Geburtsdatum_____Alter_____Geschlecht_____

Bildungsgrad/Ausbildungsgrad_____

Beruf/ sozioökonomischer Status _____

Beruf der Eltern_____

Medikation_____

Dauer des Aufenthaltes in der Klinik_____Anzahl Klinik-aufenhalte_____Zeitpunkt 1. Klinikaufenthalt/ Ersterkrankung ?_____

Anzahl Jahre der Erkrankung_____

Diagnose_____Station_____

Bestehen bei Familienmitgliedern psychiatrische Erkrankungen ?

Wenn ja, welche?_____

Ausschlusskriterien

Drogen/Alkoholmissbrauch/abhängigkeit?_____

Diagnose auf Achse II ?_____

Neurologische Erkrankung ? _____

Prämorbide Anpassung:

Gab es während Ihrer Kindheit irgendwelche Probleme mit Ihrer Sprache, dem Sehvermögen oder dem Hörvermögen ? Ja Nein

Wenn ja: Welche Art von Problemen ?_____

_____

Waren Sie hyperaktiv oder leicht ablenkbar, als Sie heranwuchsen ?

_____

Neigten Sie dazu, launisch, reizbar, unsicher oder ängstlich zu sein ?

_____

Hatten Sie irgendwelche seelischen Probleme, als Sie heranwuchsen ?

_____

Wurden Sie jemals einem Psychiater, Psychologen oder Berater wegen seelischer Probleme vorgestellt ? _____

_____

Gab es während ihrer Kindheit familiäre Stressoren (Wohnungswechsel, finanzielle Probleme, Arbeitslosigkeit, Eheprobleme) ?

_____

Psychopathologische Symptome:

Bestehen Halluzinationen zum Zeitpunkt der Untersuchung ?

Wenn ja,

Häufigkeit_____

Dauer_____

Art (akustisch, visuell) _____

Wenn nein, bestanden in früheren Krankheitsepisoden Halluzinationen ?

_____

Information und Einverständniserklärung zum Datenschutz

Wahrnehmungstörungen bei Patienten mit Psychosen im Vergleich zu Angehörigen und Kontrollprobanden – untersucht mit psychometrischen Verfahren und Kernspintomographie

Lieber Patient, liebe Patientin,

Bei der oben genannten Studie handelt es sich um eine wissenschaftliche Untersuchung, bei der persönliche Daten und medizinische Befunde über Sie erhoben, statistsisch ausgewertet und in anonymer Form in eine Datenbank aufgenommen werden. Die erhobenenen Daten werden mit einem Code aus den letzten beiden Buchstaben ihres Nachnamens und ihres Vornamens sowie ihrem Geburtsdatum versehen und so auf Studienprotokollen und elektronischen Datenträgern gespeichert.Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie folgende freiwillige Einwilligung voraus:

Ich bin mit der Aufzeichnung der im Rahmen der Studie an mir persönlichen Daten/ erhobenen Krankheitsdaten und ihrer anonymisierten Verwendung, z.B. für Veröffentlichungen, einverstanden.

Eine Kopie der Information und Einverständniserklärung zum Datenschutz habe ich erhalten.

Vollständiger Name

des/ der Probanden/in_____

(Druckbuchstaben)

Ort und Datum, Unterschrift des/ der Probanden/ in

Questionnaire about Hallucinations (QAH; according to Aggernea, 1972)

Nummer des Probanden/Kodierung

Datum:

Geschlecht: Alter:

Fragen an die Patienten bezüglich Halluzinationen

1) Hören Sie die Stimmen so klar wie sie jetzt das Geräusch meiner Stimme hören ?

2) Wenn Sie die Stimmen hören, was hören Sie dann ?

3) Haben Sie eine Art Rückmeldung und Konversation mit den Stimmen, so daß die Stimmen irgend etwas sagen, sie antworten, und die Stimmen dann Ihnen antworten ?

4) Erkennen Sie die Stimmen ?

5) Haben die Stimmen richtige Namen ?

6) Wissen die Stimmen Dinge über Sie ?
   Wenn ja, was ?

7) Können die Stimmen die Zukunft vorhersagen ?

8) Erscheinen die Stimmen in Ihren Träumen ?

9) Können andere Personen die Stimmen hören ?
   Wenn ja, wer ?

10) Denken Sie, daß die Stimmen real sind, oder denken Sie, daß sie Teil ihres eigenen Geistes
(mind) oder ihrer Vorstellung /Fantasie (imagination) sind ? oder : Sind die Stimmen real oder Vorstellung / Fantasie ?

Fragen	**Name des Items**	**Kodierung 0= unklar; 1=ja; 2=nein;**	**Bemerkungen**
1	Klar wie gesprochen		
2	Mit einem Geschlecht eingestuft		
3	Rückmeldung		
4	Bemerken der Stimmen		
5	Namen geben		
6	Stimmen haben spezielles Wissen		
7	Zukunft voraus sagen		
8	Erscheinen in Träumen		
9	Werden von anderen gehört		
10	Werden als real empfunden		
Punktzahl 1-10			
11	Stimmen drücken Emotionen aus.		
12	Stimmen haben die Zweifel der Patienten zum Inhalt		
13	Stimmen zeigen selbst-schützende Reaktionen		
14	Befehlende Stimmen		
15	Stimmen muß jemand anders sein Weil die Form der Halluzination nicht typisch für die erfahrende Person ist		
16	Stimme produziert Körperempfindungen Physische Manifestationen		
17	Stimmen werden in multipen Sinnessystemen erfahren		
18	Ausdehnungen in Zeit/Raum		
19	Stimmen werden durch Religion oder völkische Mystik erklärt.		
20	Wird dadurch als real empfunden, weil es immer wieder kehrt		
Punktzahl 11-20			

Aggerneas Kriterien			
1	Empfindung vs. Idee		
2	Relevanz für das Verhalten		
3	Öffentlichkeit		
4	Objektivität		
5	Existenz		
6	Unfreiwilligkeit		
7	Unabhängigkeit		

Gesamtpunktzahl:_____
Punktzahl 1-10:_____
Punktzahl 11-20:_____
Aggerneas Kriterien:_____
Keine Punkte:

QMI

Mit diesem Test soll die Stärke Ihrer bildlichen Vorstellungskraft gemessen werden. Sie werden gefragt, sich bestimmte Dinge vorzustellen, und dann zu bewerten, wie klar und deutlich Sie diese Dinge vor Augen haben. Ein Beispiel: denken Sie an eine rote Ampel. Wenn das Bild, dass Sie dann vor Augen haben, beschrieben werden kann als

so klar und deutlich wie in der Realität	entscheiden Sie sich für (1)
sehr klar und beinahe so deutlich wie in der Realität	entscheiden Sie sich für (2)
mittelmäßig klar und deutlich	entscheiden Sie sich für (3)
nicht so klar und deutlich, aber doch erkennbar	entscheiden Sie sich für (4)
wage und unscharf	entscheiden Sie sich für (5)
sehr wage und kaum zu erkennen	entscheiden Sie sich für (6)
ich denke daran, aber ich habe kein Bild vor Augen	entscheiden Sie sich für (7)

Machen Sie bitte dasselbe mit den nun folgenden Dingen. Suche Sie die Bewertung, die mit der obigen Beschreibung übereinkommt, um auszudrücken, in welchem Ausmaß Ihre bildliche Vorstellung
von jedem der folgenden Dinge klar und deutlich ist. Tragen Sie ihre Bewertung dann zwischen die Klammern hinter jedem Thema ein.

Denken Sie an einen Freund, eine Freundin oder einen Bekannten, den Sie regelmäßig sehen. Betrachten Sie das Bild, das Sie vor Augen haben, sorgfältig. Bewerten Sie dann, wie klar und deutlich Sie jedes der folgenden Dinge sehen:

1.die genauen Linien des Gesichtes, Kopfes, der Schultern und des Oberkörpers ( )
2. die Haltung von Kopf und Gesicht ( )
3. das genaue Verhalten beim Gehen (z.B. Schrittlänge) ( )
4. die verschiedenen Farben von zuletzt getragener Kleidung ( )

Wie klar und deutlich ist das Bild, das Sir vor Augen haben, wenn Sie denken an

5. eine untergehende Sonne ( )

Wie klar und deutlich können Sie sich das Geräusch vorstellen, wenn Sie denken an

6. das Pfeifen einer Dampflok ( )
7. die Hupe eines Autos ( )
8. das Miauen einer Katze ( )
9. das Geräusch von austretendem Dampf ( )
10. das Händeklatschen bei Applaus ( )

Denken Sie an das Gefühl, das beim Anfassen der folgenden Dinge entsteht. Wie klar und deutlich könne Sie sich das Gefühl vorstellen von

11. Sand ( )
12. Leinen ( )
13. Pelz ( )
14. einem Nadelstich ( )
15. der Wärme eines lauwarmen Bades ( )

Denken Sie daran, was Sie mit Armen, Beinen, Händen, Lippen etc. tun, wenn Sie die folgenden Aktivitäten ausführen. Wie klar und deutlich können Sie sich vorstellen, was Sie tun bei

16. eine Treppe hochlaufen ( )
17. über einen Balken springen ( )
18. einen Kreis auf Papier zeichnen ( )
19. sich nach einem Gegenstand auf einem hohen Regal recken ( )
20. etwas von den Füßen wegtreten ( )

Denken Sie an die folgenden Geschmackssorten. Wie klar und deutlich können Sie sich jeden Geschmack vorstellen ?

21. Salz ( )
22. weißer Kristallzucker ( )
23. Apfelsine ( )
24. Konfitüre ( )
25. Ihr Lieblingsgericht ( )

Denken Sie an jeden der folgenden Gerüche. Wie klar und deutlich können Sie sich den Geruch der folgenden Objekte vorstellen ?

26. ein muffiges Zimmer ( )
27. das Kochen von Rosenkohl ( )
28. das Braten von Fleisch ( )
29. frische Farbe ( )
30 Leder ( )

Denken Sie an jeder der folgenden Gefühle. Wie klar und deutlich können Sie sich jedes Gefühl vorstellen ?

31. Müdigkeit ( )
32. Hunger ( )

33. Halsschmerzen ( )
34. Schläfrigkeit ( )
35. satt sein nach einem ausgedehnten Essen ( )

SPQ-G

Sie werden auf diesen Seiten eine Reihe von Aussagen und Fragen zu persönlichen Meinungen, Erlebnissen und Verhaltensweisen finden. Bitte geben Sie zu jeder Aussage oder Frage an, ob Sie ihr zustimmen oder nicht zustimmen. Antworten Sie dabei bitte so, wie es für Sie in den letzten Jahren im Allgemeinen zutrifft.

	Ja	**Nein**
1.	Haben Sie manchmal das Gefühl, daß Dinge, die Sie im Fernsehen sehen oder in der Zeitung lesen, für Sie eine ganz besondere Bedeutung haben?	RI
2.	Ich vermeide es manchmal, an Orte zu gehen, wo sich viele Menschen aufhalten, weil ich dort Angst bekomme.	SA
3.	Haben Sie Erfahrungen mit dem Übersinnlichen gemacht?	MD
4.	Haben Sie oftmals Gegenstände oder Schatten für Menschen gehalten, oder Geräusche für Stimmen?	UW
5.	Andere Menschen halten mich für ein wenig seltsam.	EV
6.	Ich bin wenig daran interessiert, andere Menschen kennen zu lernen.	KEF
7.	Andere Leute finden es manchmal schwierig, zu verstehen, was ich sage.	US
8.	Die Leute finden mich manchmal unnahbar und distanziert.	EA
9.	Ich bin sicher, daß man hinter meinem Rücken über mich redet.	AW
10.	Wenn ich zum Essen oder ins Kino ausgehe, merke ich, daß mich die Leute beobachten.	RI
11.	Ich werde sehr nervös, wenn ich höfliche Konversation machen muß.	SA
12.	Glauben Sie an Gedankenübertragung ?	MD
13.	Haben Sie jemals gespürt, daß irgendeine Person oder Kraft um Sie herum ist, auch wenn niemand zu sehen ist ?	UW
14.	Die Leute machen manchmal Bemerkungen über mein ungewöhnliches Gehabe und meine eigentümlichen Gewohnheiten.	EV
15.	Ich ziehe es vor, für mich allein zu bleiben.	KEF
16.	Wenn ich spreche, springe ich manchmal schnell von einem Thema zum anderen.	US
17.	Ich kann meine wahren Gefühle nicht gut durch meine Sprechweise und Mimik ausdrücken.	EA

18.	Haben Sie oft das Gefühl, daß andere Leute es auf Sie abgesehen haben ?	AW
19.	Lassen manche Menschen Bemerkungen über Sie fallen, oder sagen sie Dinge mit einer doppelten Bedeutung ?	RI
20.	Werden Sie jemals nervös, wenn jemand hinter Ihnen geht ?	SA
21.	Sind Sie sich manchmal sicher, daß andere Menschen Ihre Gedanken lesen können ?	MD
22.	Wenn Sie einen Menschen anschauen oder sich selbst im Spiegel betrachten, haben Sie jemals beobachtet, daß sich das Gesicht vor ihren Augen verändert?	UW
23.	Manchmal denken andere Leute, daß ich ein bißchen merkwürdig bin.	EV
24.	In Gegenwart anderer Menschen bin ich meistens ganz still.	KEF
25.	Ich vergesse manchmal, was ich gerade zu sagen versuche.	US
26.	Ich lache oder lächle selten.	EA
27.	Machen Sie sich manchmal Sorgen darüber, ob Freunde oder Kollegen wirklich redlich und vertrauenswürdig sind?	AW
28.	Haben Sie jemals ein gewöhnliches Ereignis oder einen gewöhnlichen Gegenstand bemerkt, das oder der für Sie ein besonderes Zeichen darstellte?	RI
29.	Wenn ich Menschen zum ersten Mal begegne, werde ich ängstlich.	SA
30.	Glauben Sie an das Hellsehen?	MD
31.	Ich höre oft eine Stimme meine Gedanken laut aussprechen.	UW
32.	Manche Menschen denken, dass ich eine sehr wunderliche Person bin.	EV
33.	Ich finde es schwierig, einen engen emotionalen Kontakt zu anderen Menschen zu haben.	KEF
34.	Beim Sprechen schweife ich oft zu sehr ab.	US
35.	Meine "nicht-sprachliche" Kommunikation (z.B. Nicken oder Lächeln im Gespräch) ist nicht sehr ausgeprägt.	EA
36.	Ich spüre, daß ich selbst bei meinen Freunden auf der Hut sein muß.	AW
37.	Sehen Sie manchmal besondere Bedeutungen in Anzeigen, Schaufenstern oder in der Art, wie Dinge um Sie herum angeordnet sind ?	RI

38.	Fühlen Sie sich oft angespannt, wenn Sie sich in einer Gruppe fremder Menschen befinden ?	SA
39.	Können andere Menschen Ihre Gefühle fühlen, auch wenn sie gar nicht anwesend sind ?	MD
40.	Haben Sie jemals Dinge gesehen, die für andere Menschen unsichtbar waren ?	UW
41.	Sind Sie der Meinung, daß es außerhalb Ihrer engsten Verwandtschaft niemanden gibt, dem Sie wirklich nahe stehen, oder daß es niemanden gibt, dem Sie vertrauen können oder mit dem Sie über persönliche Probleme reden können ?	KEF
42.	Manche Menschen finden, daß ich im Gespräch etwas unbestimmt und schwer zu begreifen bin.	US
43.	Höflichkeiten und gesellige Gesten kann ich nicht gut erwidern.	EA
44.	Erkennen Sie in dem was andere sagen oder tun oft versteckte Drohungen oder Demütigungen ?	AW
45.	Haben Sie während des Einkaufens das Gefühl, daß andere Menschen Notiz von Ihnen nehmen ?	RI
46.	Unter Menschen, die ich nicht näher kenne, fühle ich mich sehr unwohl.	SA
47.	Hatten Sie bereits Erfahrungen mit Astrologie, Vorhersehen der Zukunft, UFOs, übersinnlicher Wahrnehmung oder dem Sechsten Sinn ?	MD
48.	Erscheinen alltägliche Gegenstände ungewöhnlich groß oder klein ?	UW
49.	Briefe an Freunde zu schreiben bringt mehr Schwierigkeiten als Gewinn.	KEF
50.	Ich benutze Worte manchmal in einer unüblichen Weise.	US
51.	Wenn ich mich mit anderen unterhalte, neige ich dazu, den Blickkontakt zu vermeiden.	EA
52.	Haben Sie die Erfahrung gemacht, daß es am besten ist, andere Leute nicht zu viel über Sie wissen zu lassen ?	AW
53.	Wenn Sie sehen, daß andere Menschen sich unterhalten, fragen Sie sich dann öfters, ob sie sich über Sie unterhalten ?	RI
54.	Ich würde mich sehr ängstlich fühlen, wenn ich vor einer großen Gruppe von Menschen eine Rede halten müßte.	SA
55.	Haben Sie jemals das Gefühl gehabt, mit einer anderen Person mittels	MD

	Gedankenübertragung zu kommunizieren ?	
56.	Wird Ihr Geruchssinn manchmal ungewöhnlich sensibel ?	UW
57.	Bei geselligen Ereignissen neige ich dazu, im Hintergrund zu bleiben.	KEF
58.	Neigen Sie in einem Gespräch dazu, vom Thema abzukommen ?	US
59.	Ich habe oft das Gefühl, daß andere es auf mich abgesehen haben.	AW
60.	Haben Sie manchmal das Gefühl, daß andere Menschen Sie beobachten ?	RI
61.	Fühlen Sie sich jemals plötzlich von entfernten Geräuschen abgelenkt, die Sie normalerweise nicht wahrnehmen ?	UW
62.	Enge Freunde zu haben bedeutet mir nicht viel.	KEF
63.	Haben Sie manchmal das Gefühl, daß die Leute über Sie reden ?	RI
64.	Sind Ihre Gedanken manchmal so stark, daß Sie sie fast hören können ?	UW
65.	Müssen Sie oft darauf acht geben, daß andere Sie nicht übervorteilen ?	AW
66.	Haben Sie das Gefühl, daß Sie mit anderen Menschen nicht "warm" werden können ?	KEF
67.	Ich bin eine merkwürdige, ungewöhnliche Person.	EV
68.	Meine Art zu reden ist weder ausdrucksvoll noch lebendig.	EA
69.	Ich finde es schwierig, meine Gedanken anderen klar mitzuteilen.	US
70.	Ich habe ein paar exzentrische Gewohnheiten.	EV
71.	Mir ist sehr unbehaglich zumute, wenn ich mit Leuten spreche, die ich nicht gut kenne.	SA
72.	Die Leute sagen gelegentlich, daß das Gespräch mit mir verwirrend ist.	US
73.	Ich neige dazu, meine Gefühle für mich zu behalten.	EA
74.	Manchmal starren mich die Leute wegen meines sonderbaren Auftretens an.	EV

SPQ-G Auswertungsbogen

Name: Alter: Untersuchungsdatum:

Alle mit „Ja" beantworteten Items werden mit 1 verrechnet. Der Gesamtwert ist die Summe aller Subskalenwerte.

Rohwerteberechnung und z-Transformation

RW	z-♀	z-♂	z
RI	Referenzideen		
SA	(Exzessive) soziale Angst		
MD	Ungewöhnliche Glaubensinhalte / Magisches Denken		
UW	Ungewöhnliche Wahrnehmungen		
EV	Ungewöhnliches oder exzentrisches Verhalten		
KEF	Keine engen Freunde		
US	Ungewöhnliche Sprache		
EA	Eingeschränkter Affekt		
AW	Argwohn / Wahnähnliche Vorstellungen		
SPQ-G	Gesamtwert		

FAKTOR I (kognitiv-perzeptuell) FAKTOR II (interpersonell)

Recruiting

Möchten Sie wissen, wie Ihr Gehirn von innen aussieht und dafür noch bezahlt werden?

Sind Sie zwischen 35 und 65 Jahren alt?

Haben Sie möglichst keinen Universitätsabschluss?

Sie können einen wertvollen Beitrag zur wissenschaftlichen Forschung leisten ! Unsere Forschungs-Studie wird im Zentrum der Psychiatrie, Universitätsklinikum Frankfurt, durchgeführt. Sie besteht aus einer Kernspin-Messung und Fragebögen aus dem Bereich Wahrnehmung und Imagination. Die Studie wird anonym durchgeführt und dauert circa 1 ½ Stunden.

Wenn Sie bei uns teilnehmen, erhalten Sie neben einer Aufwandsentschädigung als Danke schön interessante Bilder von Ihrem Gehirn, die wir Ihnen erklären und die Sie anschließend mit nach Hause nehmen können.

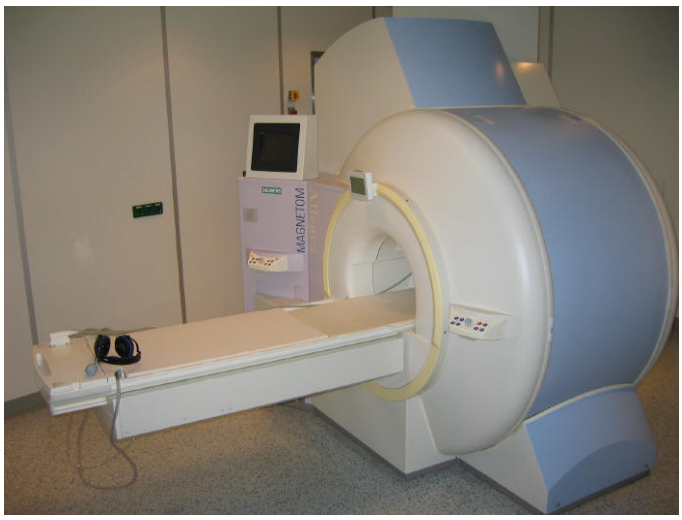
Wenn Sie ein bisschen Zeit und Interesse mitbringen, melden Sie sich bitte bei

Dipl.-Psych. Viola Oertel,

Dipl.-Psych. Anna Rotarska unter Tel.:

069/6301/7634

E-Mail: Viola.Oertel@kgu.de



Probanden für Studie zur Schizophrenie gesucht

Forschungsprojekt am Frankfurter Uniklinikum untersucht die Imaginationsfähigkeit von Personen mit Schizophrenie und deren Verwandten.
Die Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Klinikums der Johann Wolfgang Goethe-Universität Frankfurt am Main sucht Probanden für eine Studie zur Imaginationsfähigkeit bei Personen mit Schizophrenie. Die Frage ist, ob bestimmte Aspekte der Wahrnehmung und der Vorstellungskraft einen Einfluss auf die Leistungsfähigkeit und die Bewältigung des Lebensalltags haben. Es gilt herauszufinden, ob Verwandte von Patienten mit psychotischen Erlebnissen über eine andere Wahrnehmungs- und Imaginationsfähigkeit verfügen als Personen, die keine besonderen Wahrnehmungsphänomene haben. Von Erkenntnissen hierzu verspricht sich die Forschungsgruppe bessere Möglichkeiten in der Diagnostik und Behandlung von Erkrankungen aus dem schizophrenen Formenkreis abzuleiten.

Die Studie umfasst eine circa 2-stündige Untersuchung, in der Fragebögen zur mentalen Vorstellungskraft, zur Leistungsfähigkeit bei Wahrnehmungsaufgaben und zum Selbstbild ausgefüllt werden.
Anschließend werden allgemeine Fragen wie Alter, Geschlecht oder Anzahl der Bildungsjahre abgefragt, was circa 60 Minuten in Anspruch nimmt. In einer zweiten Sitzung wird eine Kernspin-Tomographie (MRT) des Kopfes erstellt. Diese moderne bildgebende Technik ermöglicht die Darstellung des Gehirns mittels Magnetfeldern und Radiowellen. Die circa 30-minütige Untersuchung erfolgt ohne eine Strahlenbelastung für den Patienten. Die Bilddaten der MRT werden anschließend ausgewertet, mit dem Probanden besprochen und können als CD-Rom mit nach hause genommen werden.

Die Projektleitung liegt bei Professor Dr. med. Konrad Maurer, Direktor der Klinik für Psychiatrie, Psychosomatik und Psychotherapie an der Uniklinik Frankfurt. Die Studie läuft bis April 2006 und erfolgt in Kooperation mit dem Brain Imaging Center Frankfurt (BIC).

Interessenten wenden sich bitte unter der Rufnummer 069 - 6301 7634 an Dipl.-Psych. Anna Rotarska-Jagiela. Unter gleicher Telefonnummer oder per Email (Viola.Oertel@kgu.de) steht Dipl.-Psych. Viola Oertel vom Labor für Neurophysiologie und Neuroimaging an der Klinik für Psychiatrie, Psychosomatik und Psychotherapie der Johann Wolfgang Goethe-Universität Frankfurt am Main für Anfragen zur Verfügung.
Die Fahrtkosten der Studienteilnehmer werden erstattet.

Frankfurt am Main, Oktober 2005

APPENDIX D

Tables of results

(Chapter 2, 3; SPSS-output-files)

Factorial structure

Table A4: *Factor analysis for the QMI, the RHS, the SPQ and the PANSS.*

	Patients	Low-Schizotypy	High-Schizotypy	Relatives
RHS	6-factors: 73.93% Strongest: 33.09%	6-factors: 67.328 % Strongest: 21.164%	7-factors: 77.248% Strongest: 20.384%	6-factors: 79.73 % Strongest: 26.24%
QMI	4-factors: 77.842% Strongest: 58.64%	5-factors: 80.743% Strongest:56.962 %	9-factors: 79.328 % Strongest: 38.637%	9-factors: 85.40 % Strongest: 44.08%
SPQ		4-factors: 66.401% Strongest: 23.897%	3-factors: 60.097% Strongest: 30.630%	3-factors: 71.06% Strongest: 34.45%
PANSS	9-factors: 77.58% Strongest: 30.20%			

RELIABILITY ANALYSIS

QMI:	Nr. of cases =180;	Nr. of items = 35,	Cronbach`s Alpha = .98
SES:	Nr. of cases =192;	Nr. of items: 16,	Cronbach`s Alpha = .74
PANSS:	Nr. of cases =44	Nr. of items: 31,	Cronbach`s Alpha = .91
RHS:	Nr. of cases =138	Nr. of items: 20	Cronbach`s Alpha = .88

GROUP COMPARISON AND ANALYSIS OF VARIANCE

Table A5: *Task performance in all subject groups for QMI, RHS, LPS 10, LPS 11, LPS 12.*

	0 = patient, 1 = low score (< 8), 2 = high score (=> 8), 4 = relatives	Mean value	SD	N
QMI	SZ patients	86.81	37.95	47
	Low-schizotypy	73.85	17.54	43
	High-schizotypy	64.48	23.45	43
	Relatives	64.48	23.44	42
	Sum	89.06	38.92	175
RHS	SZ patients	34.78	10.11	47

	Low-schizotypy	24.61	2.57	43
	High-schizotypy	29.95	3.52	43
	Relatives	26.48	4.99	42
	Sum	28.89	7.20	175
LPS 10	SZ patients	20.19	8.27	47
	Low-schizotypy	28.86	5.30	43
	High-schizotypy	26.65	5.51	43
	Relatives	23.95	5.48	42
	Sum	25.01	7.17	175
LPS 11	SZ patients	17.46	4.50	47
	Low-schizotypy	20.50	1.95	43
	High-schizotypy	20.30	3.34	43
	Relatives	18.62	2.99	42
	Sum	19.26	3.62	175
LPS 12	SZ patients	19.65	7.44	47
	Low-schizotypy	25.46	2.38	43
	High-schizotypy	23.75	4.23	43
	Relatives	24.11	4.07	42
	Sum	23.26	5.46	175

Table A6: *Comparison of task performance in QMI, RHS; LPS 10, LPS 11, LPS 12 between patients, low- and high schizotypy controls and relatives (multivariate ANOVA)*

Source	Dependent variable	df	F	significance
Corrected model	QMI	3	19.13	.00
	RHS	3	21.72	.00
	LPS 10	3	18.31	.00
	LPS 11	3	8.91	.00
	LPS 12	3	12.92	.00
Intercept	QMI	1	1197.16	.00
	RHS	1	3776.65	.00
	LPS 10	1	2650.58	.00
	LPS 11	1	5639.64	.00
	LPS 12	1	3733.05	.00
SPQ group	QMI	3	19.08	.00
	RHS	3	21.66	.00
	LPS 10	3	18.81	.00
	LPS 11	3	8.96	.00
	LPS 12	3	12.99	.00
Mistake	QMI	134		
	RHS	134		
	LPS 10	134		
	LPS 11	134		
	LPS 12	134		

Sum	QMI	138		
	RHS	138		
	LPS 10	138		
	LPS 11	138		
	LPS 12	138		
Corrected sum	QMI	137		
	RHS	137		
	LPS 10	137		
	LPS 11	137		
	LPS 12	137		

Table A7: *Task performance in all subject groups for primary, secondary and tertiary scales of the CCBS (primary: SK, P, I, C; secondary: SKI, PC; tertiary: SKI PC).*

		N	**Mean score**	**SD**
CCBS SK	Patients	52	26.54	30.48
	Low-Schizotypy	44	35.91	2.96
	High-schizotypy	48	33.98	3.59
	Relatives	44	32.61	5.78
CCBS P	Patients	52	25.27	5.27
	Low-Schizotypy	44	24.50	4.93
	High-schizotypy	48	27.04	6.55
	Relatives	44	23.77	5.75
CCBS I	Patients	52	29.15	5.72
	Low-Schizotypy	44	29.70	40.4
	High-schizotypy	48	30.81	6.30
	Relatives	44	32.07	5.55
CCBSC	Patients	52	24.52	3.21
	Low-Schizotypy	44	20.09	3.62
	High-schizotypy	48	24.65	5.67
	Relatives	44	24.07	7.12
CCBS SKI I	Patients	52	55.69	6.83
	Low-Schizotypy	44	65.61	50.49
	High-schizotypy	48	64.79	7.87
	Relatives	44	64.68	9.09
CCBS PC	Patients	52	49.79	6.90
	Low-Schizotypy	44	44.59	6.69
	High-schizotypy	48	51.69	9.25
	Relatives	44	47.84	11.64
CCBS SKI PC	Patients	52	5.90	9.13
	Low-Schizotypy	44	21.02	9.52
	High-schizotypy	48	13.10	11.84
	Relatives	44	16.84	17.55

Table A8: *Comparison of task performance in the CCBS scales between patients, low- and high schizotypy controls and relatives (multivariate ANOVA)*

Source	Dependent variable	df	F	significance
Corrected model	CCBS SK	3	48.98	.00
	CCBS P	3	2.85	.03
	CCBS I	3	77.54	.06
	CCBS C	3	8.24	.00
	CCBS SKI	3	19.94	.00
	CCBS PC	3	5.45	.00
	CCBS SKIPC	3	13.07	.00
Intercept	CCBS SK	1	117.25	.00
	CCBS P	1	368.89	.00
	CCBS I	1	559.29	.00
	CCBS C	1	392.89	.00
	CCBS SKI	1	133.61	.00
	CCBS PC	1	569.56	.00
	CCBS SKI PC	1	248.50	.00
SPQ GRUP	CCBS SK	3	48.98	.00
	CCBS P	3	2.85	.03
	CCBS I	3	2.50	.06
	CCBS C	3	8.24	.00
	CCBS SPI	3	19.94	.00
	CCBS PC	3	5.45	.00
	CCBS SKI PC	3	13.07	.00
Fehler	CCBS SK	134		
	CCBS P	134		
	CCBS I	134		
	CCBS C	134		
	CCBS SKI	134		
	CCBS PC	134		
	CCBS SKI PC	134		
Sum	CCBS SK	138		
	CCBS P	138		
	CCBS I	138		
	CCBS C	138		
	CCBS SKI	138		
	CCBS PC	138		
	CCBS SKI PC	138		
Corrected sum	CCBS SK	137		
	CCBS P	137		
	CCBS I	137		
	CCBS C	137		
	CCBS SKI	137		
	CCBS PC	137		

	CCBS SKI PC	137		

Table A9: *Task performance in all subject groups for the ESI and the subscales ESI AS, ESI AU, ESI IR and ESI DP.*

ESI	Patients	52	23.81	12.73
	Low-schizotypy	42	1.43	1.55
	High-schizotypy	47	8.87	9.68
	Relatives	44	4.54	4.20
ESI AS	Patients	52	7.29	3.78
	Low-schizotypy	42	0.69	0.90
	High-schizotypy	47	2.83	2.66
	Relatives	44	1.77	2.08
ESI AU	Patients	52	6.08	3.80
	Low-schizotypy	42	0.21	0.56
	High-schizotypy	47	1.64	2.82
	Relatives	44	0.77	0.80
ESI IR	Patients	52	4.86	2.87
	Low-schizotypy	42	0.05	0.22
	High-schizotypy	47	1.36	1.90
	Relatives	44	0.36	0.61
ESI DP	Patients	52	5.67	30.45
	Low-schizotypy	42	0.48	1.06
	High-schizotypy	47	3.04	3.59
	relatives	44	0.73	0.84

Table A10: *Comparison of task performance in the ESI scales between patients, low- and high schizotypy controls and relatives (multivariate ANOVA).*

Source	**Dependent variable**	**df**	**F**	**significance**
Corrected model	ESI AS	3	58.05	.00
	ESI AU	3	55.25	.00
	ESI IR	3	71.54	.00
	ESI DP	3	39.81	.00
	ESI	3	64.39	.00
	ESI AS	1	258.36	.00
	ESI AU	1	137.73	.00
	ESI IR	1	15.46	.00
	ESI DP	1	160.01	.00
	ESI	1	231.13	.00
SPQ GRUP	ESI AS	3	58.05	.00
	ESI AU	3	55.26	.00
	ESI IR	3	71.54	.00
	ESI DP	3	39.81	.00
	ESI	3	64.39	.00
Mistake	ESI AS	134		
	ESI AU	134		

	ESI IR	134		
	ESI DP	134		
	ESI	134		
Sum	ESI AS	138		
	ESI AU	138		
	ESI IR	138		
	ESI DP	138		
	ESI	138		
Corrected Sum	ESI AS	137		
	ESI AU	137		
	ESI IR	137		
	ESI DP	137		
	ESI	137		

Table A11: *Task performance in all subject groups for the SPQ total score and factor I (cognitive-perceptuell) and factor II (interpersonal).*

		N	Mean score	SD
SPQ	Low-Schizotypy	44	1.57	1.14
	High-schizotypy	48	24.50	7.25
	Relatives	44	12.07	6.38
SPQ I	Low-Schizotypy	44	1.95	1.58
	High-schizotypy	48	19.05	5.52
	Relatives	44	6.45	4.03
SPQ II	Low-Schizotypy	44	0.42	0.61
	High-schizotypy	48	4.104	1.97
	Relatives	44	5.10	3.76
	Gesamt	136	30.47	3.22

BIVARIATE CORRELATION ANALYSES

Table A12: *Correlations between QMI, RHS, LPS, MWT-B and trail-making tests in the patient group.*

	QMI	RHS	LPS 10	LPS 11	LPS 12	MWT-B	TMT
QMI	1	-.23(.11)	-.05 (.77)	-.05 (.75)	-.24 (.11)	-.28 (.07)	-.03 (.84)
RHS	-.23 (.11)	1	-.03 (.83)	-.09 (.56)	-.03 (.83)	-.23 (.12)	.04 (.78)
LPS 10	-.04 (.77)	-.03 (.83)	1	.63 (.00**)	.67 (.00**)	.23 (.05)	-.53 (.00**)
LPS 11	-.04 (.75)	-.09 (.56)	.63 (.00**)	1	.76 (.00**)	.40 (.01**)	-.52 (.00**)
LPS 12	-.24 (.11)	-.03 (.83)	.67 (.00**)	.76 (.00**)	1	.4 (.00**)	-.52 (.00**)
MWT-B	-.28 (.07)	-.23 (.12)	.29 (.05)	.40 (.01**)	0.48 (.01**)	1	-.15 (.32)
TMT	-.03 (.84)	.04 (.78)	-.53 (.00**)	-.52 (.00**)	-.52 (.00**)	-.15 (.3 219)	1

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A13: *Correlations between QMI, RHS, LPS, MWT-B and trail-making tests in the relative group.*

	QMI	RHS	LPS 10	LPS 11	LPS 12	MWT-B	TMT
QMI	1	-.08 (.63)	.22 (.18)	.15 (.36)	.03 (.83)	.08 (.63)	-.17 (.31)
RHS	-.08 (.63)	1	.06 (.73)	.19 (.24)	.23 (.16)	-.23 (.14)	-.120 (.47)
LPS 10	.22 (.18)	.06 (.73)	1	0.42 (.01**)	.56 (.00**)	.03 (.86)	-.67 (.00**)
LPS 11	.15 (.36)	.19 (.24)	0.42 (.01**)	1	.56 (.00**)	-.03 (.86)	-.38 (.02*)
LPS 12	.03 (.83)	.23 (.16)	.56 (.00**)	.56 (.00**)	1	.11 (.51)	-.41 (.01*)
MWT-B	.08 (.63)	-.23 (.14)	.03 (.86)	-.03 (.86)	.11 (.51)	1	-.05 (.75)
TMT	-.17 (.31)	-.12 (.47)	-.67 (.00**)	-.38 (.02*)	-.41 (.01*)	-.05 (.75)	1

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A14: *Correlations between QMI, RHS, LPS, MWT-B and trail-making tests in the low-schizotypy group.*

	QMI	RHS	LPS 10	LPS 11	LPS 12	MWT-B	TMT
QMI	1	-.25 (.10)	-.04 (.82)	.02 (.88)	.04 (.81)	.13 (.41)	-.13 (.38)
RHS	-.25 (.10)	1	-.09 (.55)	.06 (.70)	-.26 (.07)	.07 (.66)	.14 (.36)
LPS 10	-.03 (.82)	-.09 (.55)	1	.58 (.00**)	.54 (.00**)	.47 (.00**)	-.29 (.06)
LPS 11	.023 (.88)	.06 (.70)	.58 (.00**)	1	.26 (.09)	.39 (.01)	.16 (.28)
LPS 12	.04 (.81)	-.26 (.09)	.54 (.00**)	.26 (.09)	1	.15 (.31)	-.42 (.01**)
MWT-B	.127 (.41)	.07 (.66)	.41 (.00**)	.25 (.09)	.15 (.32)	1	-.15 (.34)
TMT	-.13 (.38)	.14 (.36)	-.28 (.05)	.16 (.28)	-.42 (.01**)	-.15 (.34)	1

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A15: *Correlations between QMI, RHS, LPS, MWT-B and trail-making tests in the high-schizotypy group.*

	QMI	RHS	LPS 10	LPS 11	LPS 12	MWT-B	TMT
QMI	1	-.21 (.28)	.23 (.10)	.20 (.15)	-.00 (.98)	-.32 (.02*)	-.27 (.06)
RHS	-.21 (.17)	1	.16 (.29)	.13 (.38)	.16 (.29)	.46 (.00**)	.05 (.72)
LPS 10	.23 (.10)	.16 (.29)	1	.39 (.00**)	.10 (.49)	-.12 (.40)	-.44 (.00**)
LPS 11	.20 (.15)	.13 (.38)	.39 (.00**)	1	.38 (.00**)	-.16 (.27)	-.09 (.51)
LPS 12	-.00 (.98)	.16 (.29)	.10 (.49)	.38 (.00**)	1	.37 (.00**)	-.27 (.06)

MWT-B	-.32 (.02*)	.46 (.00**)	-.12 (.40)	-.16 (.27)	.37 (.00**)	1	.02 (.86)
TMT	-.27 (.06)	.05 (.72)	-.44 (.00**)	-.09 (.51)	-.27 (.06)	.02 (.86)	1

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A16: *Bivariate correlations between QMI, RHS, LPS and the PANSS in the patient group.*

Test	QMI	RHS	LPS 10	LPS 11	LPS 12
PANSS	- .06 (.69)	.06 (0.66)	-.01 (.90)	-.17 (.24)	-.18 (.21)
PANSS N	.09 (.56)	-.07 (0.63)	.03 (.83)	-.17 (.23)	-.07 (.62)
PANSS P	-.12 (0.42)	.32 (.07)	-.12 (.42)	-.10 (.47)	-.18 (.22)
PANSS H	-.11 (0.47)	.55 (0.06)	-.11 (.45)	-.23 (.12)	-.12 (.40)
PANSS G	-.08 (0.57)	-.02 (.89)	.01 (.90)	-.15 (.31)	-.18 (.22)

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A17: *Bivariate correlation analysis between the PANSS score and his subscales and the ESI questionnaire.*

Test	ESI	ESIS AS	ESI AU	ESI IR	ESI DP
PANSS	.02 (.85	-.04 (.76)	.01 (.89)	.21 (.14)	-.11 (.43)
PANSS N	-.11 (.23)	-.07 (.60)	-.17 (.25)	-.03 (.80)	-.31 (.03*)
PANSS P	.16 (.27)	.13 (.38)	.15 (.31)	.28 (.05)	.09 (.54)
PANSS H	.28 (.05)	.25 (.09)	.27 (.06)	.36 (.01*)	.22 (.14)
PANSS G	.05 (0.70)	.05 (.71)	.04 (.76)	.26 (.07)	-.09 (.55)

* The correlation is significant (2-tailed; Pearson) at the 0.05-level.
** The correlation is significant (2-tailed; Pearson) at the 0.01-level.

Table A18: *Bivariate correlation analysis between the PANSS score and his subscales and the CCBS scales.*

	CCBS SK	CCBS P	CCBS I	CCBS C	CCBS SKI	CCBS PC	CCBS SKI PC
PANSS	-.09 (.51)	0.22 (.13)	.16 (.28)	.00 (.95)	.08 (.59)	.17 (.23)	-.07 (.63)
PANSS POS	-.10 (.48)	.08 (.56)	-.03 (.81)	-.08 (.56)	-.08 (.57)	.02 (.86)	-.08 (.58)
PANSS N	-.00 (.97)	.10 (.49)	.16 (.27)	.03 (.80)	.13 (.37)	.09 (.51)	.02 (.85)
PANSS G	-.11 (.43)	.29 (.04 *)	.21 (.15)	.04 (.77)	.11 (.44)	.25 (.09)	-.10 (.51)
PANSS H	.066 (.66)	.01 (.92)	.14 (.33)	-.19 (.20)	.15 (.29)	-.08 (.59)	.17 (.23)
CCBS SK	1	-.00 (.95)	.04 (.75)	.06 (.63)	.54 (.00**)	.02 (.85)	.39 (.00**)
CCBS P	-.00 (.95)	1	.11 (.40)	.28 (.04*)	.09 (.50)	.89 (.00**)	-.60 (.00**)
CCBS I	.04 (.75)	.11 (.40)	1	.06 (.62)	.86 (.00**)	.12 (.38)	.55 (.00**)

CCBS C	.06 (.63)	.28 (.04*)	.06 (.62)	1	.09 (.51)	.68 (.00**)	-.44 (.00**)
CCBS SKI	.54 (.00**)	.09 (.50)	.86 (.00**)	.09 (.51)	1	.11 (.41)	.66 (.00**)
CCBS PC	.02 (.85)	.89 (.00**)	.12 (.38)	.68 (.00**)	.11 (.41)	1	-.67 (.00**)
CCBS SKI PC	.39 (.00**)	-.60 (.00**)	.55 (.00**)	-.44 (.00**)	.66 (.00**)	-.67 (.00**)	1

* The correlation is significant (2-tailed; Pearson) at the .05-level.
** The correlation is significant (2-tailed; Pearson) at the .01-level.

APPENDIX E

Localizer - project

1. **Software (beside the standard software package)**

- **SPSS 11.5 for Windows**

SPSS Inc. Headquarters,

233 S. Wacker Drive, 11th floor

Chicago, Illinois 60606

www.spss.com

- **Brain Voyager 2000 & QX**

Rainer Goebel

Brain Innovation B.V.

Postbus 1142

6201 BC Maastricht

The Netherlands

E-Mail: Info@BrainVoyager.com

- **Presentation, Version 09**

Neurobehavioral Systems, Inc.

828 San Pablo Ave STE 216

Albany, CA 94706-1564

www.nbs.neuro-bs.com

- **The MathWorks Deutschland Offices**

  Adalperostr. 45

  D-85737 Ismaning

  Deutschland

  E-mail: info@mathworks.de

Localizer-Project (chapter 4)

Fragebogen zu den Texten

Liebe Teilnehmerin / Lieber Teilnehmer,

vielen Dank, dass du dir den Text_____ angehört hast. Ich möchte Dich nun bitten, die folgenden Fragen zu dem zuletzt gehörten Text so genau wie möglich zu beantworten.

Alle Fragen beziehen sich nur auf den **zuletzt** gehörten Text!

1)Welche Emotionen / Gefühle löste der Text in Dir aus?

(Bitte Zutreffendes ankreuzen)

Freude	gar nicht	etwas	sehr viel
Wut	gar nicht	etwas	sehr viel
Ärger	gar nicht	etwas	sehr viel
Traurigkeit	gar nicht	etwas	sehr viel
Anderes Gefühl:_____	gar nicht	etwas	sehr viel

2) Schätze nun bitte den „Emotionsgehalt" des zuletzt gehörten Textes ein:

☐ Neutral (keine Empfindung) ☐ sehr emotional (starker Gefühlsbezug)

Neutral (keine Empfindung) ☐

Sehr emotional (starker Gefühlsbezug) ☐

3)Hat Dich der Text an eigene Erfahrungen / Erlebnisse erinnert?

_____

_____

4)Gibt es für Dich einen persönlichen Bezug zu den Inhalten der Texte?

_____

_____

5)Wie hast Du die Stimme des Sprechers empfunden?

_____

_____

6)War der Inhalt des Textes angenehm/ nicht angenehm?

_____

_____

7)Hat der Text eine bestimmte Wirkung auf Dich gehabt?

_____

_____

8)Wie gut kannst Du Dir den Inhalt des Textes behalten?

Nicht gut ☐ Sehr gut ☐

9)Welches Thema wurde in dem zuletzt gehörten Text besprochen?

_____

_____

10)War die Stimme des Sprechers weiblich oder männlich?

weiblich ☐ männlich ☐

11)War(en) der/die Hauptdarsteller weiblich oder männlich?

weiblich ☐ weiß ich nicht ☐

männlich ☐ gab keine(n) Hauptdarsteller ☐

12)Worauf hast Du beim Hören besonders geachtet?

auf die Stimme ☐ auf meine Gedanken ☐

auf den Inhalt ☐ sonstiges:_____ ☐

13)Hast Du den Text zuvor schon einmal gehört?

ja ☐ nein ☐

Examples for the texts for the auditory stimulation

Dialog 1: Einkaufen

A: - Ich hätte gern ein T-Shirt. Etwas Schickeres für die Arbeit.

B: -Ja, gerne. Welche Größe haben Sie denn ?

A: -Größe 42.

B: -Da habe ich zwei T-Shirts zur Auswahl. In Rosa oder in Blau.

A: -Ja, das Blaue gefällt mir. Wo kann ich es anprobieren?

B: -Die Kabinen sind da hinten links.

A: -Danke.

A: -Das ist aber schön an Ihnen.

B: -Es ist mir etwas zu groß, und die Farbe gefällt mir auch nicht so. Haben Sie etwas in Dunkelblau und etwas kleiner?

A: -Ja, da habe ich hier noch eins in Violett, eine Nummer kleiner und sehr preiswert.

B: -Ja, das müsste passen. Das nehme ich. Wo kann ich bezahlen ?

A: -Da drüben an der Kasse.

Dialog 2: Leute

A: -Und wie war das Wetter? Habt ihr gutes Wetter gehabt?

B: -Das Wetter war ganz okay, aber es hat häufig geregnet.

C: -Ich fand das Wetter gut. Es hat jeden Tag etwas geregnet, aber es gab auch viel Sonne.

B: -Ist das Wetter hier zu Hause auch so?

A: -Also so einen heißen Sommer hatten wir schon lange nicht mehr.

C: -Da habt ihr Glück. Ich habe immer gehofft, dass es aufhört zu regnen. Das hat es dann auch oft.

B: -Wir sind oft nach Hause gegangen, wenn es geregnet hat. Wie soll denn das Wetter am Wochenende werden ?

A: So, wie heute, sehr warm und ohne Regen.

C: -Wenn es am Samstag auch so schön ist, gehen wir ins Schwimmbad.

B: -Da hast Du Recht, da habe ich auch Lust drauf. Kommst Du auch mit ?

A: -Ja, vielleicht. Ruft mich noch einmal an und sagt mir Bescheid. Ich gehe jetzt erstmal einkaufen.

B: -Was willst Du denn einkaufen ?

A: -Ich will zuerst in den Supermarkt. Dort brauche ich Brot, Obst, Salat, Butter und Wurst und Käse.

C: -Wir wollen auch noch einkaufen gehen. Aber keine Lebensmittel, sondern Sachen zum Anziehen.

B: -Ich brauche dringend eine neue Hose.

A: -Ich war gestern bei C & A und habe mir eine neue Hose gekauft. Die war reduziert.
C: -Wie sieht sie aus ?
A: -Sie ist grün und sitzt gut. Ich fühle mich sehr wohl darin.
B: -Interessierst Du dich sehr für Mode?
A: -Ein bisschen.
C: -Wenn die Hosen schön sind, kaufe ich mir auch eine.
B: -Dann lass uns mal los gehen und gucken. Hast Du Lust mitzukommen ?
A: -Ja, ich habe Lust.
C: -Willst Du erst Deine Lebensmittel kaufen?
A: -Nein, dann mache ich das später.
B: -Wollen wir dann gleich losgehen?
C: -Okay.
A: -In Ordnung.

Monolog 1: Auf in den Garten !

Nachdem der große Regen jetzt vorbei ist, kann vieles im Garten erledigt werden.

- Schneiden Sie abgeblühte Stauden zurück.
- Stark wachsende Hecken, z.B: Buchen- oder Lebensbaumhecken jetzt ein zweites Mal schweren.
- Rasen schneiden, Blumenwiesen mähen.
- Boden lockern, dabei gleich Unkraut jäten.
- Gründünger auf abgeerntete Beete säen.
- Noch kann man Blumenzwiebeln wie Herbstzeitlosen pflanzen, die im Herbst blühen werden.
- Zweijährige Blumen wie Stiefmütterchen und Vergissmeinnicht an den endgültigen Platz setzen.

Monolog 2: Obsternte

Heiß ersehnt sind spätsommerliche Sonnentage auch beim Obst. Frühe Apfelsorten, Frühzwetschgen, Blaubeeren und die ersten Brombeeren und Herbsthimbeeren bekommen Farbe und Süße. Ernten Sie das Obst erst, wenn es sich voll ausgefärbt hat und sich leicht von den Zweigen löst. Bei Brombeeren geht immer auch der Fruchtzapfen mit ab, auf dem die schwarzen Beerchen sitzen, bei Himbeeren dagegen bleibt der Zapfen am Strauch. Fallobst unbedingt aufsammeln! Raupenfangring bei Zwetschgen, Pflaumen und Mirabellen regelmäßig kontrollieren! Johannesbeer- und Stachelbeersträucher nach Abschluss der Ernte streichen.

APPENDIX F

Curriculum vitae

Persönliche Daten

Name:	Viola Oertel
	ledig
	Dipl.-Psychologin
Geburtstag, -ort:	02. Juli 1976 in Langen/Hessen

Schulausbildung

08/1983-06/1987:	Selma-Lagerlöf-Schule, Dreieich (Grundschule)
08/1987-06/1996:	Ricarda-Huch-Schule, Dreieich (Gymnasium)
Abschluss:	Allgemeine Hochschulreife (Note: 1,7)

Hochschulbildung

10/1996-07/2002:	Studium an der Johann Wolfgang Goethe-Universität, Frankfurt / Main
Studiengang:	Psychologie
07/1998:	Vordiplom in Psychologie (Note: 1,5)
07/2002:	Diplom in Psychologie (Note: 1,1)
Thema der Diplomarbeit:	Das Kardinalitätsverständnis von Kindern im Alter zwischen drei und fünf Jahren
Betreuerin:	Frau Prof. Dr. Monika Knopf, Abteilung für Entwicklungspsychologie, Johann Wolfgang Goethe-Universität, Frankfurt / Main

Zusatzausbildung

seit 01/2004	*Doktorandin im Labor für Neurophysiologie und Neuroimaging, Klinik für Psychiatrie, Psychosomatik und Psychotherapie (Leiter: Prof. Dr. K. Maurer), Johann Wolfgang Goethe-Universität, Frankfurt / Main*
seit 04/2003	Teilnehmerin der Weiterbildung zur Psychologischen Psychotherapeutin am Verhaltenstherapeutischen Institut der Johann Wolfgang Goethe-Universität, Frankfurt / Main; Abschluss der Weiterbildung: April 2008
12/2003	Brainvoyager QX Kurs in Maastricht, Niederlande

06/2005	Posterkurs Graduiertenförderungsprogramm, Johann Wolfgang Goethe-Universität, Frankfurt/Main
08/2005	Kurs für das Softwareprogramm „Presentation", Max-Planck-Institut für Hirnforschung, Frankfurt/Main
10/2005	Gehirn-Anatomie-Kurs des Institut der Senkenbergischen Anatomie, Johann Wolfgang Goethe-Universität, Frankfurt / Main
06/2007	Teilnehmerin am Intensivkurs: „Cognitive Behavioral Analysis System of Psychotherapy - Spezifische Psychotherapie Chronischer Depressionen", Freiburg.

Praktika

01/1999-07/1999	Praktikum an der Klinik für Psychiatrie und Psychotherapie I des Klinikums der Johann Wolfgang Goethe-Universität, Frankfurt / Main; Mitarbeit bei einem DFG-Projekt über Suchterkrankungen; Tätigkeitsschwerpunkte lagen im diagnostischen Bereich und bei der Erstellung und Auswertung der Daten mit dem Computerprogramm SPSS
08/1999-09/1999	Praktikum in Mitarbeit mit der Universität Köln; Normierung eines neu entwickelten Intelligenztests (K-TIM/K-NEK)
02/2000-04/2000	Praktikum in der Psychiatrischen Abteilung der Stadtklinik Offenbach; Betreuung und Diagnose von Psychiatriepatienten

Berufstätigkeit

10/1999-06/2002	Hilfswissenschaftliche Mitarbeiterin in der Abteilung Klinische Psychologie und Psychotherapie, Johann Wolfgang Goethe-Universität, Frankfurt / Main
04/2003-01/2004	Psychologin im praktischen Jahr an der Klinik für Psychiatrie und Psychotherapie (Direktor: Prof. Maurer), Klinikum für Psychiatrie, Psychosomatik und Psychotherapie, Johann Wolfgang Goethe-Universität, Frankfurt / Main
10/2003-01/2004	Wissenschaftliche Mitarbeiterin an der Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Bereich Labor für Neurophysiologie und Neuroimaging; Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt / Main

02/2004-01/2005	Wissenschaftliche Mitarbeiterin an der Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt / Main
02/2005-01/2007	Stipendiatin des Frankfurter Graduiertenförderprogramms (Leiter: Prof. Dr. A. Goldberg)
seit 01/2007	Wissenschaftliche Mitarbeiterin der Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Johann Wolfgang Goethe-Universität, Frankfurt / Main.

Ehrenamtliche Tätigkeiten

seit 1992	Schwimmlehrerin in der Schwimmgemeinschaft Dreieich; Tätigkeitsbereiche Kinder- und Jugendbereich, Säuglingsschwimmen, Erwachsenenunterricht
seit 1998	Tätigkeit als Wahlhelferin bei der Stadt Dreieich

Poster- & Abstract-Präsentationen, bisherige Veröffentlichungen

12/2003	Symposium des Max-Planck-Instituts für Hirnforschung, Frankfurt / Main. Poster & Abstract: Oertel, V., Rotarska-Jagiela, A., Van de Ven, V., Formisano, E., Sack, A.T., Linden, D.E.J. Studying the brain correlates of hallucinations.
2003	Bittner, R., Haenschel, C., Maurer, K., Oertel, V., ,Rotarska-Jagiela, A., Linden, D.E.J. (2003). Correlates of visual working memory in Schizophrenia studied with functional magnetic resonance imaging. *Society for Neuroscience Abstracts.*
2004	Van de Ven, V., Rotarska-Jagiela, A., Formisano, E., Prvulovic, D., Bittner, R., Oertel, V., Dierks, T., Linden, D.E.J. (2004). Functionally connected networks underlying auditory verbal hallucinations in schizophrenia. *Human Brain Mapping Conference Abstract.*
2005	Rotarska-Jagiela, A., Oertel, V., Van de Ven, V.G., Formisano, E., Roebroeck, A., Rami, A., De Martino, F., Schoenmeyer, R., Haenschel, C., Maurer, K., Linden, D.E.J. White matter hyperconnectivity and psychopathology of schizophrenia – a diffusion tensor imaging study. *Clinical EEG and Neuroscience 35*, 21.

2005	Rotarska-Jagiela**,** A., Oertel, V., Formisano, E., Roebroeck, A., Rami, A., De Martino, F., Schoenmeyer, R., Haenschel, C., Van de Ven, V.G., Maurer, K., Linden, D.E.J. White matter integrity in chronic schizophrenia patients – a diffusion tensor imaging study. *Society for Neuroscience Abstract 2005*.
07/2005	Posterpräsentation Graduiertenförderung (2. Preis beim Posterwettbewerb). Poster: Oertel, V. Stimmen hören bei der Schizophrenie.
12/2005	Symposium des Max-Planck-Instituts für Hirnforschung, Frankfurt/Main. Poster & Abstract: Oertel, V., Rotarska-Jagiela, A., Haenschel, C., van de Ven, C., Stangier, U., Maurer, K., Linden, D.E.J. Visual Hallucinations in Schizophrenia – combined fMRI and behavioural data- a case report.
02/ 2006	13th Biennial Winter Workshop on Schizophrenia Research, Davos, Schweiz. Abstract & Poster: Oertel, V., Rotarska-Jagiela, A., Haenschel, C., Van de Ven, V., Maurer, K., Linden, D.E.J. Visual Hallucinations in Schizophrenia-combined fMRI and behavioural data- a case report.
03/2006	TEAP (Tagung experimentell arbeitender Psychologen), Mainz. Abstract & Poster: Oertel, V., Rotarska-Jagiela, A., Haenschel, C., Van den Ven, V., Maurer, K., Linden, D.E.J. Perceptual and cognitive trait markers of schizophrenia.
11/2006	DGPPN Konferenz 2006, Berlin. Abstract & Poster: Oertel, V., Rotarska-Jagiela, A., Altmann, C., van de Ven, V., Haenschel, C., Maurer, K., Linden, D.E.J.. Lokalisierung der Aktivität in Gehirnarealen während akustischer Stimulation bei schizophrenen Patienten und ihren Verwandten -untersucht mit fMRI
12/2006	Symposium des Max-Planck-Instituts für Hirnforschung, Frankfurt/ Main; Abstract & Poster: Lokalisierung der Aktivität in Gehirnarealen während akustischer Stimulation bei schizophrenen Patienten und ihren Verwandten - untersucht mit fMRI
09/2007	1. European Conference on Schizophrenia Research, Düsseldorf. Abstract & Poster, oral presentation: Oertel, V., Rotarska-Jagiela**,** A., Lindner, M., Van de Ven, V.G., Altmann, C., Knöchel, C., Haenschel, C., Maurer, K., Linden, D.E.J. Hypoactivity in Wernicke's area bilaterally in Schizophrenia patients and their

	unaffected family members- a fMRY study. *Kompetenznetz Schizophrenie, Düsseldorf.*
12/2007	Symposium des Max-Planck-Instituts für Hirnforschung, Frankfurt / Main. Abstract & Poster: Oertel, V., Rotarska-Jagiela**,** A., Lindner, M., Van de Ven, V.G., Altmann, C., Knöchel, C., Haenschel, C., Maurer, K., Linden, D.E.J. Changes in auditory speech areas in schizophrenia patients and their unaffected familty members.
2007	Publikation: Oertel, V., Rotarska-Jagiela, A., Van de Ven, V.G., Haenschel, C., Maurer, K., Linden, D.E.J. Visual hallucinations in Schizophrenia investigated with functional magnetic resonance imaging. *Psychiatry Research Neuroimaging, 156: 269-273.*
2008	Publikation: Rotarska, Jagiela, A., Schönmeyer, R., Oertel, V., Haensche, C., Vogeley, K., and Linden, D.E. The corpus callosum in schizophrenia - volume and connectivity changes affect specific regions. *NeuroImage,* 39: 1522-1532.
2008	Publikation: Oertel, V., Rotarska-Jagiela, A., Van de Ven, V.G., Haenschel, C., Grube, M., Stangier, U., Maurer, K., Linden, D.E.J. Mental imagery vividness as a trait marker across the schizophrenia spectrum. *Schizophrenia Research, in press.*