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Hirnfunktionelle Korrelate der Aufmerksamkeitsorientierung bei Patienten mit schizophrenen Psychosen mittels funktioneller MR-Tomographie

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Die dieser Arbeit zugrunde liegenden Prozessschritte von der Probandenrekrutierung, über die Planung und Durchführung der Datenaquisation, bis hin zur Dateneingabe und -pflege sind nach Rücksprache mit Herrn Prof. Dr. J. Daumann von mir mit Unterstützung durch Herrn Dr. Dr. D. Wagner und Dr. P. Köster durchgeführt worden. Die statistische Auswertung und Interpretation der Daten habe ich unter Einbeziehung fruchtbarer Diskussionen mit den oben genannten Koautoren eigenständig durchgeführt.

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Glossary

AIMS	Abnormal involuntary movement scale
AMDP	Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie
ANOVA	analysis of variance
BA	Brodmann Area
BOLD signal	blood oxygenation level dependent signal
COVAT	Covert Orienting of Visual Attention Task
CPT	Continuous Performance Test
CT	computerized tomography
DMT	Dimethyltryptamin
EPI	echoplanar imaging
EPS scale	Extrapyramidal Symptom Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
ICD	International Statistical Classification of Diseases and Related Health Problems
IOR	Inhibition of Return
MRI	magnetic resonance imaging
PET	positron emission tomography
RT	reaction time
SAPS	Scale for the Assessment of Positive Symptoms
SANS	Scale for the Assessment of Negative Symptoms
SC	superior colliculus
SD	standard deviation
SOA	stimulus onset asynchrony
SMA	supplementary motor area
VF	visual field

1 Introduction

This thesis deals with spatial orienting in patients with paranoid-type schizophrenia and its neural correlates.

Cognitive deficits are well documented in schizophrenia and have also been reported in terms of spatial orienting (Addington & Addington, 1998a; Fuentes et al., 1999; Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2007). One factor that has been the object of intensive research is a phenomenon called “Inhibition of Return” (IOR). It occurs in orienting of attention tasks and has been shown to be disturbed in patients with schizophrenia (Carter et al., 1994; Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2006; Huey & Wexler, 1994; Larrison-Faucher et al., 2002; Sapir et al., 2001). Additionally there were findings, suggesting a connection between IOR and activated brain regions that are supposed to participate in the formation of IOR (Lepsien & Pollmann, 2002; Mayer et al., 2004a; Mayer et al., 2004b; Rosen et al., 1999; Zhou & Chen, 2008).

In this study we wanted to investigate whether blunted or delayed Inhibition of Return in patients with schizophrenia is reflected in an altered cortical activation pattern.

1.1 Schizophrenia

1.1.1 Historical development

In the early 19th century all types of psychosis were seen as one disease with different manifestations. In 1860 Bénédict Morel (1809 - 1873), a French physician, described “démence précoce”, a psychosis with progressive characteristics. It included social withdrawal, bizarre mannerisms and self-neglect, onset in early adulthood and later resulted in intellectual impairments. This term was picked up by Emil Kraepelin (1856 – 1926) in 1896, latinized to “Dementia praecox” and distinguished from bipolar disorders. Kraepelin was the first person who tried to ascertain specific diagnostic criteria and defined hallucinations, attentional deficits, reduced curiosity, illogical thinking, delusional

ideas, affective flattening, negativism and stereotypies as indicative of the illness. The term “schizophrenia” was later established by Eugen Bleuler (1857 – 1939) in 1908. He declared that neither dementia nor precocity were necessary components for a diagnosis of the disorder, but that schizophrenia could be seen as a disruption of the psychic functions. He defined fundamental symptoms including autism, ambivalence and disturbances of associations and affect, as well as accessory symptoms including hallucinations, delusion and catatonia, which he described as less important than the basic symptoms. In 1959 the German psychiatrist Kurt Schneider (1887 – 1967) devised diagnostic criteria, which formed the general basis for the DSM-IV and ICD-10 criteria that are used in diagnosing today. He distinguished between first-rank symptoms and second-rank symptoms; the latter being less specific (Sartory, 2007; Scharfetter, 2006).

<u>First-rank symptoms included:</u>

- Audible thoughts, voices arguing, discussing or commenting on one's action
- Somatic passivity experiences
- Thought withdrawal, thought insertion or thought broadcasting
- Delusional perceptions

<u>Second-rank symptoms included amongst others:</u>

- Other forms of hallucinations
- Depressive or euphoric mood changes
- Perplexity
- Delusional ideas

These criteria marked the first step in order to create tools for the diagnosis of schizophrenia and have been adopted in a modified form for the diagnostic criteria that are in use today.

1.1.2 Epidemiology

The incidence of schizophrenia is approximately between 16 and 42 per 100,000 residents per year depending on the nation and between 7 and 14 per 100,000 residents with a more constrictive definition of schizophrenia (Sartorius et al., 1986). The prevalence amounts to about 5 per 1,000 population, whereas the lifetime prevalence is 1% similarly for male and female persons. The mean age of onset is 26.5 years in male patients and 30.6 years in female patients, which shows an earlier onset at an average of about 4 years in males (Easton & Chen, 2006; Huber, 2005; Häfner, 2003).

1.1.3 Etiology

Causes for the development of schizophrenia have not been completely clarified, but it is a matter of common knowledge that the genesis is multifactorial. Genetic and environmental aspects can influence the risk to develop a schizophrenic psychosis and interact with each other.

In 1977 Zubin and Spring tried to explain the complex pathogenesis by their vulnerability hypothesis (Zubin & Spring, 1977), which was later advanced by Nuechterlein and Dawson to a vulnerability-stress model (Nuechterlein & Dawson, 1984a). It says that every person has individual vulnerability characteristics and is influenced by different environmental stimuli and that special constitutions have a high risk for the development of a schizophrenic psychosis. Promotive vulnerability factors are, for example reduced social competence, deficits in information processing and insufficient coping strategies. Environmental factors that influence the development of schizophrenia comprise, inter alia, social stressors and deficient social support. If a person has a high vulnerability, there is less stress needed to effect the development of schizophrenia as if the individual predisposition is of low risk. It has been shown that the most important risk factor is a first-degree relative, who is affected by schizophrenia. If for example one parent is suffering from schizophrenic psychosis, the risk for each child increases from 1% to 5 – 15%. However it has been shown that the risk of contracting the disease is not completely determined by the genotype. There have been studies with

monozygotic twins, which present a concordance rate of only 50%. This demonstrates that environmental factors must have an influence on the genesis of schizophrenia as well (Spitzer, 2006).

In order to detect significant environmental influencing factors there have been several studies, which examined prenatal parameters, obstetric complications and lifestyle. Interestingly concerning lifestyle there were findings which suggest a correlation between schizophrenia and parental unemployment, low socio-economic status and urban birth (Byrne et al., 2004). Also cannabis consumption has been associated with an increased risk of developing schizophrenia (Andreasson et al., 1987; Henquet et al., 2005; Zammit et al., 2002). Additionally the risk for schizophrenia seems to be raised by fetal hypoxia (Cannon et al., 2000) and maternal diabetes (Van Lieshout & Voruganti, 2008). Furthermore maternal depression during gestation significantly increases the risk for schizophrenia in the offspring if one parent suffers from psychotic disorder (Mäki et al., 2010).

The vulnerability-stress model seems to be an adequate theory trying to understand the complex pathogenesis of schizophrenia, even if it still requires investigation and the environmental factors seem to be at least of the same variety as our genome.

1.1.4 Diagnostics

Today there are two established classification systems used to diagnose schizophrenia. On the one hand there is the ICD-10 (International Statistical Classification of Diseases and Related Health Problems), which is constituted by the World Health Organization and on the other hand there is the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders), which is defined by the American Psychiatric Association and whose criteria have been used in our study.

DSM-IV criteria include:

A. Characteristic symptoms:

1. delusions
2. hallucinations
3. disorganized speech
4. grossly disorganized or catatonic behavior
5. negative symptoms

B. Social/occupational dysfunction

C. Duration: 6 months

D. Schizoaffective and Mood Disorder exclusion

E. Substance/general medical condition exclusion

F. Relationship to a Pervasive Developmental Disorder

Additionally the DSM-IV system contains a classification into five subtypes: Paranoid Type, Catatonic Type, Disorganized Type, Undifferentiated Type and Residual Type. Patients with paranoid-type schizophrenia participated in our study. This type is characterized by prominent delusional ideas and hallucinations.

Furthermore there is a differentiation of the symptoms of positive and negative. Positive symptoms are behaviors that are normally absent in the general population and comprise delusions, hallucinations, disorganized speech/thinking, grossly disorganized behavior and catatonic behaviors. However negative symptoms are behaviors and cognitions that normally appear in healthy persons, but are disturbed or weakened in schizophrenic patients and contain social and cognitive deficits such as affective flattening, alogia, anhedonia, avolition and attentional dysfunctions (Braus, 2005; Mitchell et al., 2001).

1.1.5 Cognitive Deficits

Patients with schizophrenia exhibit dysfunctions in all fields of cognition. It has been shown that 60-80% of the patients have serious deficits independent of

state and medical treatment. Especially memory, attention and executive functions can be affected (Aleman et al., 1999; Braus, 2005; Spitzer, 2006). Cognitive impairments can already occur prior to the manifestation of clinical symptoms (Jones et al., 1994).

Attention comprises visual, auditory and motor parts and can be directed to a stimulus automatically or intentionally. The selective part enables us to drive our attention to certain locations deliberately, whereas the other part is an automatic mechanism. The latter provides a status of general activity and allows the processing of notably relevant information. One explanation for deficits in cognitive functioning in schizophrenia is the Faulty-Filter theory, which states that the patients are unable to filter insignificant from significant stimuli and that this would lead to an “information overload” (Broadbent, 1958).

This study concentrates on spatial orienting as a part of visual attention.

1.1.6 Neuroanatomical alterations

Schizophrenic patients additionally show structural changes concerning neuroanatomical conditions. One frequent finding is the dilatation of the lateral ventricles, especially the temporal horns (Braus, 2005; Harrison, 1999; Sartory, 2007). In particular the dilatation of the left temporal horn has been shown to be associated with positive symptoms such as hallucinations, whereas a bilateral enlargement of the lateral ventricles shows a correlation with negative symptoms such as attentional dysfunctions (Bogerts, 1997; Braus, 2005; Marsh et al., 1997). Interestingly it has been shown that if one twin of monozygotic twins suffers from schizophrenia, only the affected one has dilated ventricles, whereas the second one shows normal neuroanatomical structures (Harrison, 1999; Sartory, 2007). Another finding is the decrease in volume of different cerebral structures including the temporal and frontal lobe and the thalamus. Temporal parts that have been observed to be reduced are the superior temporal gyrus and the medial temporal lobe including hippocampus, parahippocampus, amygdala, planum temporale and the entorhinal cortex (McCarley et al., 1997; Wright et al., 2000). The prefrontal cortex of the frontal lobe seems to be diminished in volume and also shows a decrease in the

density of neurons, which led to the term “hypofrontality” (McCarley et al., 1997; Pakkenberg, 1993; Sartory, 2007). Reduced volume of the prefrontal cortex has been shown to be associated with negative symptoms, such as cognitive deficits (Sanfilipo et al., 2000).

As reported, the neuroanatomical alterations in schizophrenic patients are not observed all over the brain, but ascertained regions seem to be affected. Until now there has been evidence for a progressive genesis, but there also appear to be indications for a developmental hypothesis. It is only known that the aforementioned brain areas are involved in cognitive functions such as attention, verbal memory, problem solving, speech and spatial orienting.

1.2 Spatial orienting of attention

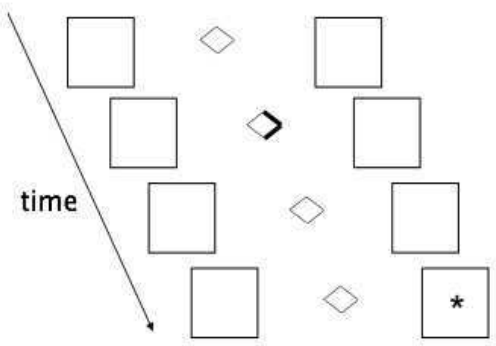
Over the last few centuries there has been much research concerning attention and its mechanisms. Posner was a central figure within the investigations on spatial orienting and defined different components of attention: Alertness, selectivity and vigilance (Posner & Rafal, 1987). Alertness can be seen as unfocused attention that describes the regulation of general physical and psychical responsiveness and is responsible for faster reactions to stimuli due to increased preparedness to reaction. Selectivity demonstrates the goal-directed attention and allows processing of a certain stimuli while others are ignored. Vigilance is defined as the ability to sustain attention deliberately over a period of time. Furthermore Posner and Rafal describe spatial orienting as a part of attention, which enables us to move our attention spatially, with or without moving the eyes to the specific point of attention. In addition Posner engaged in processing capacity and the problem of processing more than one stimulus at once (Posner & Boies, 1971).

1.2.1 Covert Orienting of Visual Attention Task and Inhibition of Return

Orienting of attention is part of the selective attention and can take place in two different ways. The first one known as “overt orienting” occurs by moving

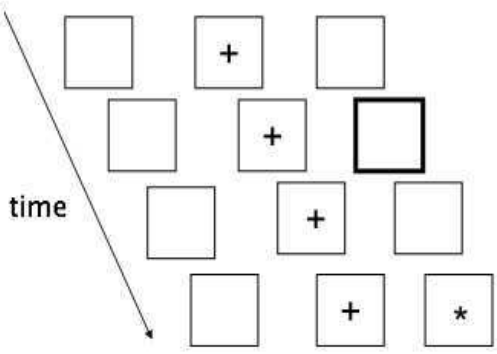
attention in collaboration with the eyes or the head to a specific location. The second one, in which attention is directed to a place of interest, but the eyes keep fixed to another place, is called “covert orienting” (Johnson & Proctor, 2004; Posner, 1988a). In order to investigate the mechanisms of covert orienting, Posner established the “Covert Orienting of Visual Attention Task” (COVAT) (Posner et al., 1982). In this task subjects have to maintain fixation on a centrally presented cross of a screen. If a special stimulus (target, e.g. an asterisk) appears in a peripheral box on the right or left side of this cross, the subject is instructed to react as rapidly as possible by pressing a single key. Prior to the target there is another stimulus, a so-called cue, which attracts attention to the periphery. This cue can be either endogenous or exogenous. Endogenous cues are positioned in the centre of the visual field and demonstrate an arrow that can point into different directions. However exogenous cues are located in the periphery and are most times presented by a luminance change (e.g. brightening) of one of the boxes. Endogenous (central) cues attract attention deliberately, because the arrow first needs to be interpreted, whereas exogenous (peripheral) cues lead to an automatic shift of attention to the peripheral visual field. The cues can either direct the attention to that direction where the target is going to appear (valid cue) or to the opposite side (invalid cue). The time between the appearance of the cue and the appearance of the target (cue-target interval) is called “stimulus onset asynchrony” (SOA) and is relevant for the performance of the subjects.

Figure 1: Example for a COVAT with endogenous cues



The figure shows a COVAT with an endogenous cue. This example demonstrates a valid-cued target on the right side.

Figure 2: Example for a COVAT with exogenous cues



The figure shows a COVAT with an exogenous cue. This example demonstrates a valid-cued target on the right side.

Posner showed that reaction times (RTs) are already shortened by neutral cues that appear prior to the target. That is a brightening of the central box in the exogenous COVAT or a brightening of both sides of the arrow in the endogenous COVAT. He named this effect “facilitation” (Posner & Cohen, 1984). Using endogenous, i.e. central cues, reaction times are always facilitated at trials with valid cues compared to trials with invalid cues independent from the length of the SOA. This indicates that RTs can be shortened if attention is directed to the “right” side where the target is going to appear. On the other hand invalid cues result in longer RTs because attention has to be detached from the cued location and driven to the other side (disengagement and reorienting of attention) (Posner et al., 1985). In Covert Orienting of Visual Attention Tasks with exogenous, i.e. peripheral cues RTs are also facilitated in valid compared to invalid trials if the SOA is shorter than 200 ms. But if the SOA is longer than about 300 ms the facilitation effect reverses and results in shorter RTs in invalid trials compared to valid trials. This phenomenon is called “Inhibition of Return” (IOR) (Posner & Cohen, 1984) and does not come up in trials with endogenous cues. The meaning and function of IOR are not entirely understood, but a widespread hypothesis says that IOR presents a mechanism to filtrate relevant from irrelevant information. If attention is drawn to one direction (e.g. by the cue), the organism expects a significant stimulus at this location. But if no stimulus appears within a certain period (e.g. SOA longer than 300 ms), attention is withdrawn from the location and inhibited from

returning there. This leads to a delayed reaction to that previously scanned location. This inhibitory mechanism could be able to save the organism from being distracted by insignificant stimuli and thus prevent it from information overload (Klein, 2000; Posner & Cohen, 1984; Sapir et al., 1999).

1.2.2 Neural correlates of spatial orienting

Regarding neuronal activation patterns there have been many studies using functional brain imaging in combination with a COVAT. Concerning this matter the results have been inconsistent. Some of them indicated that endogenous and exogenous orienting may rely on common neural networks (Kim et al., 1999; Nobre et al., 1997; Rosen et al., 1999), whereas others achieved contrary results (Klein, 2000; Mayer et al., 2004b). Apart from that there were diverse findings regarding the activation pattern. Some found an overlap of activated areas for endogenous and exogenous orienting (parietal and dorsal premotor regions (frontal eye fields, FEF), left sensorimotor cortex, anterior cingulate areas (supplementary motor area, SMA), bilateral temporoparietal junction and cerebellum), but also specific activations for the endogenous task in the right dorsolateral prefrontal cortex and the globus pallidus and for the exogenous task in the left thalamus (Rosen et al., 1999). Other results suggest a complete overlap of activated areas in both tasks (the lateral premotor areas (FEF), the medial frontal lobe (SMA), the posterior parietal lobes, the cingulate gyrus, the temporo-occipital cortex, the insula, the dorsolateral prefrontal cortex and the left sensorimotor cortex), but with differences in extension and asymmetry (Kim et al., 1999). There has also been investigation concerning Inhibition of Return and activated areas linked to that phenomenon. An involvement of frontal premotor (oculomotor) and parietal areas, the temporoparietal junction, the ventrolateral nucleus of the thalamus and the cerebellum has been suggested on the basis of different findings (Lepsien & Pollmann, 2002; Mayer et al., 2004a; Mayer et al., 2004b; Rosen et al., 1999). Furthermore the superior colliculus (SC) seems to play a decisive role in the generation of IOR (Fecteau et al., 2004; Sapir et al., 1999) and an influence of the visual cortex can also not be excluded due to recent research results (Müller & Kleinschmidt, 2007).

This section shows the complexity of the neural correlates underlying spatial orienting, but it also indicates that ascertained brain regions are most probably involved in attentional functions.

1.3 Spatial orienting in schizophrenia patients

Spatial orienting is one important sub-function of attention and has been the subject of intense investigations since the late 1980s. Posner et al. reported about schizophrenic patients with asymmetries between the visual fields in a Covert Orienting of Visual Attention Task (Posner et al., 1988b). The patients had to respond manually to targets presented in either the right or the left visual field and showed significantly slower reaction times if the target appeared on the right side compared to the left side in invalid cueing paradigms. This means that the subjects showed longer RTs if a cue appeared on the left side and the target appeared on the right side subsequently than if there was a right-positioned cue and a following left-positioned target. They interpreted it as a deficit of the left cerebral hemisphere in schizophrenia and presumed a dysfunction of the disengagement of attention. In later studies these findings could mostly not be replicated. Some authors could just find this result of “higher costs of left visual field invalid cueing” in unmedicated or neuroleptic-naive patients and partially using predictive cues (e.g. 80% valid cues and 20% invalid cues, so that the probability of the target appearing at the same location as the cue is 80%) (Maruff et al., 1995; Moran et al., 1996; Potkin et al., 1989; Wigal et al., 1997). Indeed others were not able to obtain any asymmetrical/lateralized results (Gold et al., 1992; Gouzoulis-Mayfrank et al., 2006; Strauss et al., 1992; Strauss et al., 1991). However all these studies had one thing in common. Almost exclusively they obtained slower RTs in the patient group than in the control group in all task conditions. This indicates a general impairment in target detection and reaction.

Concerning Inhibition of Return current data are at least as heterogeneous as results concerning visual fields. Huey and Wexler described a dysfunction of that phenomenon in schizophrenic patients compared to healthy controls with

later onset and diminished magnitude (Huey & Wexler, 1994). This finding could be replicated in different studies (Larrison-Faucher et al., 2002; Sapir et al., 2001). Others compared patients with paranoid-type schizophrenia to patients with undifferentiated schizophrenia and also found a reduction of IOR, but only in the paranoid-type group (Carter et al., 1994). The results of further studies indicate deficits or a total lack of IOR independent from psychopathology, disease history, and type of neuroleptic medication (Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2006). In contrast other authors observed a normal pattern of Inhibition of Return (Carter et al., 1992; Fuentes & Santiago, 1999; Fuentes et al., 1999; Maruff et al., 1998). Interestingly their methodical procedures showed small differences compared to those who reported about a dysfunction in IOR. Either they used predictive cues with 80% probability for the condition being valid or very long stimulus onset asynchronies (1200 ms between appearance of cue and target). Another discrepancy is that some of them employed a so-called cue-back mechanism. That is a second cue appearing in the centre of the screen (e.g. a brightening of the central box) after the peripheral cue had disappeared. After this second cue the target arises either on the same side as the first cue or opposite to it (valid or invalid trial respectively). This procedure enhances the development of IOR and could lead to a compensation of the deficits in schizophrenia. In this context Sapir et al. compared a COVAT with a single-cue condition to a COVAT with a cue-back manipulation in schizophrenic patients and demonstrated that a dysfunction in IOR could merely be observed in the normal condition with one peripheral cue (Sapir et al., 2001).

1.4 Functional neuroimaging in schizophrenia

In order to find out whether cognitive deficits are represented in disturbed cortical functions, there have been several studies analyzing neural correlates of cognitive functions in patients with schizophrenia. Cognition comprises, inter alia, perception, problem solving, motor functions, memory, working memory, language, executive functions and attention. As previously mentioned, all these functions can be disturbed in patients suffering from schizophrenic psychosis.

Due to the magnitude of studies and results, only studies engaging in attention can be mentioned here.

Several cerebral regions were found to be disordered linked to attentional tasks.

Liddle and colleagues studied selective attention in schizophrenic patients compared to healthy controls. They found less activation in the dorsolateral prefrontal cortex, the insula, the anterior cingulate gyrus and in subcortical structures such as amygdala, ventral striatum, thalamus and cerebellum (Liddle et al., 2006), as well as in the right temporo-parietal-occipital junction, the intraparietal sulci, the dorsal frontal cortex and the basal ganglia (Laurens et al., 2005). However other investigations on attention resulted in further underactivated regions as the medial prefrontal cortex and the cingulate (Volz et al., 1999).

While many neuroimaging studies investigating cognitive functions in schizophrenia have provided evidence for diminished activation in different brain areas (Liddle et al., 2006; Polli et al., 2008; Weiss et al., 2007), others found an increase of cortical activity (Callicott et al., 2000; E. Weiss et al., 2003) or even simultaneously higher and less activated areas (Gur et al., 2007). Interestingly, compared to controls, patients showed raised activity on less difficult attentional tasks and decreased activity on more demanding tasks (Karch et al., 2009). Furthermore altered activation pattern could be observed in healthy siblings of schizophrenic patients despite the absence of deficits in an attentional task. In particular they showed a significantly increased activation of the left insula and the inferior frontal gyrus during incorrect responses and a significantly reduced activation during correct responses (Sepede et al., 2010).

One attentional task that has been part of many imaging studies with schizophrenic patients is the Continuous Performance Test (CPT) addressing selective attention. Different studies showed a deficient activation in the dorsolateral prefrontal cortex (MacDonald & C. Carter, 2003; Volz et al., 1999). Barch et al. demonstrated that this effect was not linked to antipsychotic medication and could also be seen in neuroleptic-naive patients (Barch et al., 2001).

However Keedy et al. arranged a study comparing a control group to patients

suffering from psychosis before and after antipsychotic therapy for 4-6 weeks. The subjects had to react to nonpredictive targets by performing a saccade. Before medical treatment the patients showed reduced activation in frontal and parietal eye fields and cerebellum, as well as in sensory and ventromedial prefrontal cortex. These disturbances were absent or at least less in magnitude after antipsychotic treatment. Interestingly they found hypoactivation in different brain regions after medication such as the dorsal prefrontal cortex, dorsal striatum and dorsomedial thalamus (Keedy et al., 2009).

Weiss et al. also examined selective attention by the use of a modified verbal Stroop Task in patients with schizophrenia and healthy controls. By pressing a key the subjects had to decide whether the meaning of a presented word conforms to its color (e.g. the word RED printed in red, the word YELLOW printed in red). They found that patients showed a significant increase in brain activation in the left and right inferior frontal cortex and the anterior cingulate cortex. Both groups showed activated prefrontal cortex, but interestingly the controls recruited predominantly the left hemisphere and in contrast the patients showed a bilateral activation (Weiss et al., 2003).

In another sample with unmedicated patients in an acute episode they found less activation in dorsolateral prefrontal, anterior cingulate and parietal areas and an increase in activation in temporal regions and posterior cingulate compared to the control group (Weiss et al., 2007).

As it can be seen, inter alia the prefrontal cortex seems to play an important role in attentional disturbances of schizophrenic patients. Since there is a great variety of attentional tasks and task conditions such as medication it is still difficult to define disturbed brain regions associated with attention in psychosis. Even if a task is realized two times by the same study group there seem to be many factors influencing the result, so that a conclusion about disturbed cerebral regions during attention tasks in schizophrenia is quite difficult.

Despite the huge quantity of investigations until now there is no study about IOR-associated cerebral activations in patients with schizophrenia compared to healthy controls.

1.5 Objectives

This thesis deals with spatial orienting in schizophrenic patients and its purpose is to point out whether disturbed Inhibition of Return results in an altered cortical activation pattern. Different neuroimaging studies found dysfunctions in several cortical and subcortical areas, but to our knowledge until now there was no study, which addressed neural correlates of the phenomenon Inhibition of Return in visual attention tasks in schizophrenia. Merely Daumann et al. (Daumann et al., 2008) arranged an fMRI study and tried to imitate schizophrenic psychosis by using hallucinogenic drugs in healthy adults. In that study the same methodical procedures as in our experiments (COVAT with two different SOAs: 100 ms and 800 ms) were used. Concerning the Dimethyltryptamin (DMT, hallucinogenic drug) model, which is used to imitate paranoid-type schizophrenia, they found blunted Inhibition of Return, but no differences in the cortical activation pattern compared to a placebo. In contrast the ketamine model, which is thought to be an appropriate model for undifferentiated psychosis, showed a normal pattern of Inhibition of Return, but significantly increased IOR-associated activations in the right superior frontal gyrus, the left superior temporal gyrus and the right midfrontal gyrus. This result might suggest that increased cerebral activation could result in a normal pattern of IOR, at least in a model of pschosis. As it is impossible to preclude drug-specific influences and differences to real schizophrenia, the next stage had to be to examine patients in order to find out whether their dysfunctions in Inhibition of Return show differences in the cortical activation pattern.

Therefore our objectives were to find neural correlates of spatial orienting of attention in schizophrenic psychosis. We wanted to discover whether blunted Inhibition of Return might be influenced by specific cerebral regions or whether increased brain activity might even be able to normalize attentional performance. Besides, it was interesting to find out whether the results of Daumann et al. (Daumann et al., 2008) could be replicated and thus indicate that models of psychosis are an adequate tool to investigate schizophrenia.

Based on our results, it should be possible to identify brain regions or cerebral networks taking part in altered attentional mechanisms in patients with schizophrenia. This should help to draw better conclusions on neurocognitive fundamentals of psychosis and shed more light on potential causes of the genesis of this illness.

2 Materials and methods

2.1 Subjects

Twenty patients diagnosed with paranoid-type schizophrenia participated in the study. They were recruited shortly after confinement to inpatient treatment in the psychiatric department of the University Hospital of Cologne. We only included male subjects to the study in order to avoid gender-specific differences in the performances.

Further inclusion criteria were:

- Majority age
- Capacity to consent

Following exclusion criteria were constituted:

- Further psychiatric disorder
- Neurological and severe somatic illness
- Craniocerebral injury or other relevant cerebral lesion (e.g. stroke, hemorrhage, encephalitis) in anamnesis
- Subjects under centrally effective medication
- Compulsory hospitalization (by PsychKG)
- Gravidity
- Cardiac pacemaker or different electronic implants
- Intracorporeal ferromagnetic contaminant
- Claustrophobia
- Left-handed subjects

Five of the patients had to be excluded from the study because of extensive head movements exceeding one voxel (>3 mm) during the examination.

15 exactly matched healthy controls without an anamnesis of any neurological or psychiatric disorders were matched for age and years of education. Exclusion and inclusion criteria were also considered.

Paranoid-type schizophrenia (ICD-10: F20.2, DSM-IV: 295.3x) was diagnosed

by SCID I, a Structured Clinical Interview for DSM IV Axis I Disorders. Additionally the patients had been treated for at least 6 months as in- or outpatient in the psychiatric department prior to the fMRI examination. Eleven of the 15 patients were diagnosed with schizophrenia for the first time. Four patients were stabilized on atypical antipsychotic treatment whereas eleven of them had never received any antipsychotic medication (table 1). By using the Extrapyramidal Symptom Scale (EPS Scale, Simpson & Angus, 1970) and the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976), extrapyramidal adverse effects could be ruled out.

The subjects were screened with different rating scales (Scale for the assessment of positive symptoms SAPS, Scale for the assessment of negative symptoms SANS, (Andreasen et al., 1995) and the AMDP (AMDP, 2000), which was developed by the Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie) in order to reveal differences in psychiatric symptoms between the subjects. General psychotic symptoms and passive symptoms were evaluated by the SAPS and the SANS using items 1 – 7 to assess hallucinations (1 Auditory Hallucinations, 2 Voices Commenting, 3 Voices Conversing, 4 Somatic or Tactile Hallucinations, 5 Olfactory Hallucinations, 6 Visual Hallucinations, 7 Global Rating of Severity of Hallucinations) and item 15 – 19 to assess passive symptoms (15 Delusions of Being Controlled, 16 Delusions of Mind Reading, 17 Thought Broadcasting, 18 Thought Insertion, 19 Thought Withdrawal) amongst others. The extent of symptoms ranges from 0 (none) to 5 (severe). The AMDP comprises 88 symptoms including passivity symptoms (53 Derealization, 54 Depersonalization, 55 Thought Broadcasting, 56 Thought Withdrawal, 57 Thought Insertion, 58 (Other) Experiences of Alien Control). In our elevation, 58 coded for bodily experiences of alien control. The extent of symptoms ranges from 0 (absent) to 3 (severe). In order to enhance the acquisition of passivity symptoms, we summed the values of each passivity symptom within the scales. Thereafter the score intervals for passivity symptoms were expanded from 0 – 5 to 0 – 25 in the SAPS and from 0 – 3 to 0 – 18 in the AMDP (table 2). It was possible that a subject reached a different score in those two scales because the AMDP does not include the level “questionable”.

The study was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2004) and was approved by the ethics committee at the Medical Faculty of the University of Cologne, Germany. All subjects were informed about the experimental procedure and gave their written consent being aware of the possibility to withdraw from the study at any time without having to explain the reasons.

2.2 Experimental Procedure

After the psychiatric interviews the subjects had some time to recover.

The stimuli were then projected onto a screen in an fMRI scanner, which was approximately 29 cm from the subject away. We used a Covert Orienting of Visual Attention Task (COVAT) with nonpredictive peripheral cues and eight different stimuli (figure 1).

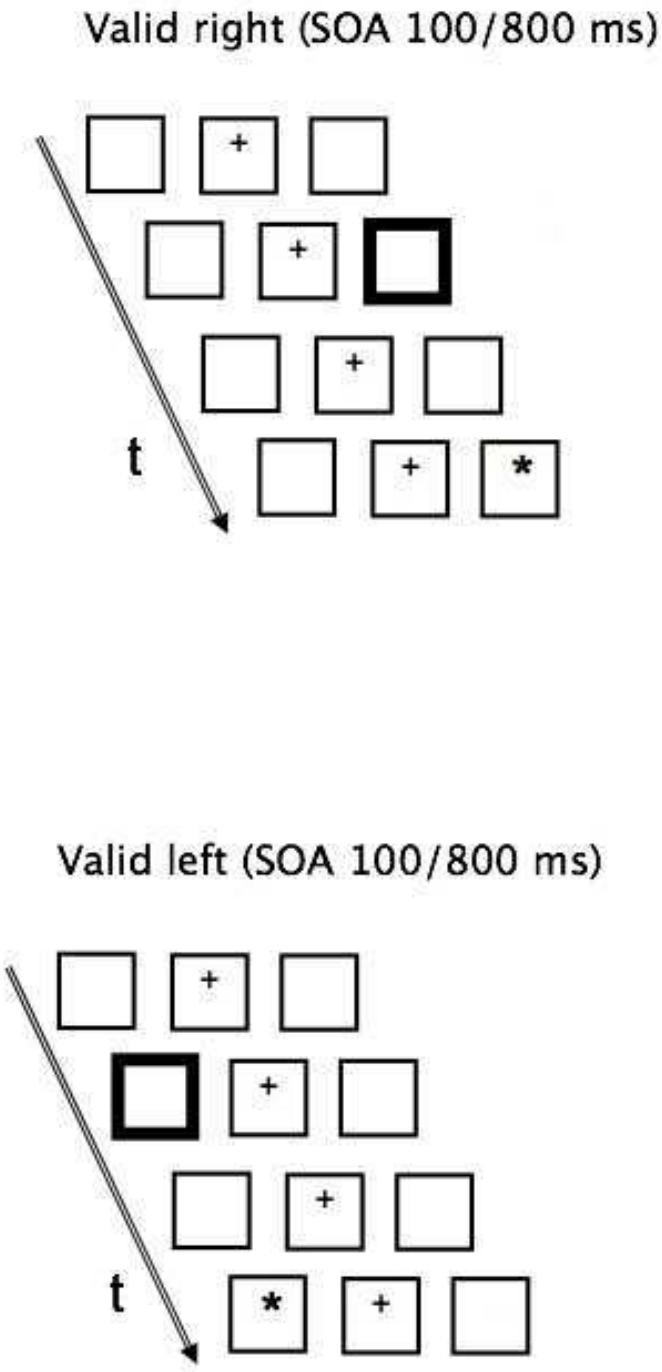
There were three squared boxes on the screen next to each other. The central box contained a cross on which the subjects were instructed to maintain fixation throughout the task. Before they entered the fMRI scanner, they passed a practice experiment of 40 trials without recording of the reaction times (RTs). The task consisted of 200 trials each presented every 2000 ms and lasted altogether 400s. 40 of those trials were baseline trials where no cues and targets were presented (null events). The meaning of those null events is to prevent accumulation of the BOLD (blood oxygenation level dependent) signal so that the hemodynamic response function is set back to its baseline. The other 160 trials started with a brightening of either the right or the left peripheral box (cue). Then a target, which was presented as a star appearing inside one of the peripheral boxes about 5° right or left from the fixation cross, followed the cue after 100 or 800 ms (Stimulus onset asynchrony, SOA). It turned up either in the brightened square or opposite to it (valid or invalid trial respectively) and remained for 200ms. All factors occurred randomly and with equal probability.

This enables eight different task stimuli:

1. Right cue, 100 ms SOA, valid target
2. Right cue, 100 ms SOA, invalid target
3. Right cue, 800 ms SOA, valid target
4. Right cue, 800 ms SOA, invalid target
5. Left cue, 100 ms SOA, valid target
6. Left cue, 100 ms SOA, invalid target
7. Left cue, 800 ms SOA, valid target
8. Left cue, 800 ms SOA, invalid target

The subjects had to respond as fast as possible when they noticed the target by pressing a single key. Eye movements were monitored by an MR-compatible infrared eye tracker (ASL Model 540, Applied Science, Bedford, MA, USA).

Figure 3: Schematic illustration: COVAT with nonpredictive peripheral cues



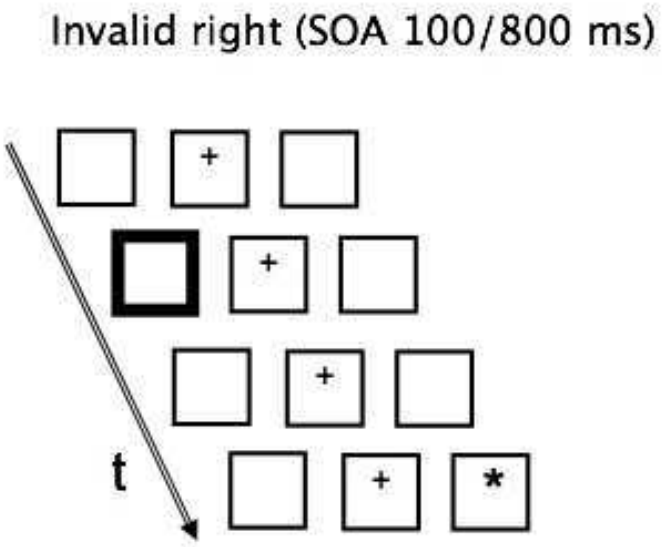


Illustration of the Covert Orienting of Visual Attention Task (COVAT) with nonpredictive peripheral (exogenous) cues.
The subjects have to focus on the centrally located cross. The brightening of one peripheral box demonstrates the cue and the asterisk appearing inside one of the peripheral boxes presents the target
t = time

2.3 Functional magnetic resonance imaging (fMRI)

2.3.1 Basic principles of MRI

Atomic nuclei containing positive charged protons and neutral neutrons are the basis of magnetic resonance imaging (MRI). Especially the atom hydrogen is used for imaging with the MRI scanner, because it consists of one proton and no neutrons. Protons show a spin which generates a small magnetic field. Naturally in the human body these fields show into different directions and therefore neutralize each other. MRI scanners contain a coil which generates a powerful magnetic field and leads to same-directed protons. Applying a high-frequency pulse to that field then, tilts the protons and brings them to former position if the pulse is deactivated again. Thus different signals are generated dependent on the moisture content of the tissue. The computer illustrates these signals as two-dimensional layers consisting of small cubes, called voxels. Each voxel is attributed to a different grey scale value depending on the moisture content of the respective tissue (Walter, 2005).

2.3.2 Functional imaging

Functional magnetic resonance imaging (fMRI) is a newer method of functional imaging. It enables the measurement of signals which depend on the oxygen content of the blood (BOLD = blood oxygenation level dependent). It utilizes the fact that oxygenated blood (oxyhemoglobin) shows different magnetic characteristics than desoxygenated blood (deoxyhemoglobin). Neuronal activity leads to an increase in local blood flow, but just to a minor increase in oxygen consumption and therefore to a change of the oxygenation level. For this reason, functional measuring can be used to examine connections between different stimuli (e.g. attentional tasks, auditory impulses) and activated brain regions. In contrast to positron emission tomography (PET) and computerized tomography (CT) anatomical or functional imaging with MRI does not implicate radioactive exposure (Handels, 2009; Walter, 2005).

2.3.3 Data acquisition

Imaging data were acquired on a Philips Gyroscan NT Intera – MRI scanner (Philips, Eindhoven, Netherlands) operating at 1,5 T. Changes in blood oxygenation level dependent (BOLD) T_2*-weighted MR signal were measured during the task using a gradient echo-planar imaging (EPI) sequence (repetition time = 2,5 s; echo time = 66 ms; matrix size = 64 x 64; pixel size = 3.12 x 3.12 mm^2; flip angle 90°). The 172 volumes of 24 4-mm thick axial slices were acquired sequentially with a 0,8 mm gap. Additionally a high resolution T_1-weighted image was collected for anatomic reference. We used a T1-FFE sequence (imaging parameters: TR = 30 ms, TE = 4,5 ms, matrix size 256 x 256; field of view 256 mm x 256 mm; flip angle = 30°; 70 slices; slice spacing 2 mm).

We used foam pads and Velcro straps to minimize head movements. Images were acquired using a standard head coil.

2.4 Analysis

2.4.1 Reaction times

Reaction times were recorded in milliseconds. If RTs were less than 100 ms, they were not included in the analysis because they were interpreted to be due to anticipation. Furthermore RTs exceeding 1,000 ms were excluded because they were supposed to reflect general inattention to the task. Subjects with more than 10% (20 trials) of those errors were completely suspended from analysis. The data were evaluated statistically using SPSS 16 (SPSS Inc., Chicago, Illinois, USA).

First median RT values for each subject and task condition were calculated. These data were then used for calculation of mean values and standard deviations (SD) for each group and type of trial. Reaction times were analyzed by means of repeated-measures analysis of variance (ANOVA) using the within-subject factors cue (valid, invalid), stimulus onset asynchrony (100 ms, 800 ms) and visual field in which the target appeared (right, left) and the between-subject factor group (patients, controls).

Afterwards, we performed paired *t*-tests for each group, testing the reaction times of the valid vs. the invalid trials of the long SOA (800 ms).

In order to demonstrate differences in reaction times at valid-cued trials compared to invalid-cued trials depending on the SOA, the so-called validity effect was generated. It can be calculated by subtracting the reaction time of a valid cue from the reaction time of an invalid cue:

Validity in ms = $RT_{invalid}$ - RT_{valid}

In peripheral cues the result depends on the SOA. If the SOA is short (up to 250 ms), the result is positive, which shows that the subjects reacted faster to valid-cued trials that to invalid-cued trials (facilitation) and that IOR has not yet occurred. But if the SOA lasts more than 300 ms, the result becomes negative, which reflects the phenomenon IOR.

In a final step validity effects were also analyzed by repeated-measures ANOVA using the within-subject factors visual field (VF) and SOA and the between-subject factor group.

2.4.2 fMRI data

Data were preprocessed with Statistical Parametric Mapping software SPM2 (Wellcome Department of Cognitive Neurology, London, UK). The first six volumes were discarded to allow T_1 equilibration. Preprocessing of images included realignment to the first volume to correct for inter-scan head movements, correction of slice-timing and normalization to a standard EPI template volume (resampled to 3 mm x 3 mm x 3 mm voxel size). Subsequently the data were smoothed using a Gaussian kernel of 9 mm full-width half-maximum to accommodate anatomical variability between the subjects.

Analysis of functional data was also processed with SPM2 implemented in Matlab 6 (Mathworks, Sherborn, Massachusetts, USA). Patients and controls were incorporated into one design matrix each having eight different event types (see 2.2).

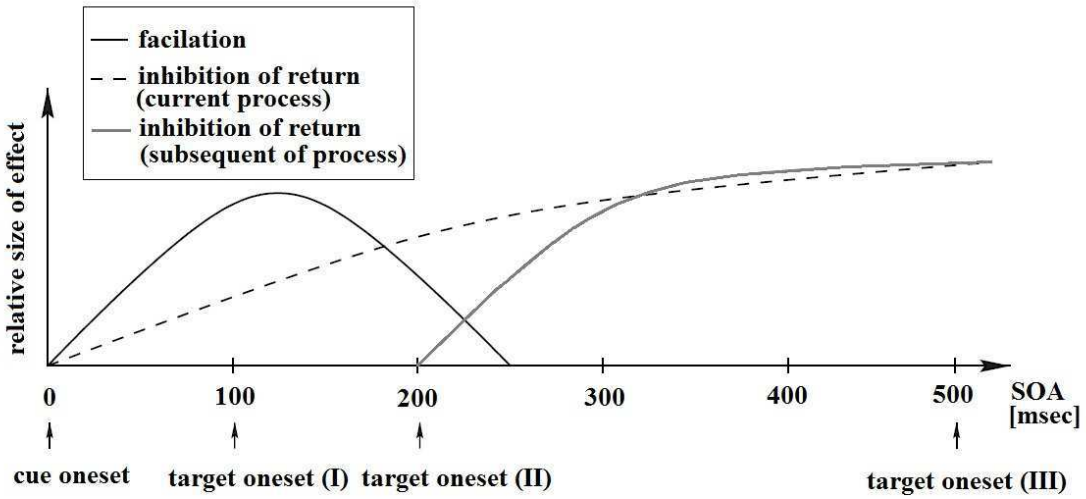
We analyzed the main effect of SOA (Lepsien & Pollmann, 2002) in order to

identify the brain regions involved in the generation of IOR. The underlying basic concept was that brain activity associated with IOR would accumulate over time independent from the validity of the target. This theory supposes that facilitation and inhibition occur at the same time and that the inhibitory mechanism is prolonged and first covered by the facilitatory process (figure 4). For this purpose we summed the results (significantly activated brain areas) of invalid and valid targets of the 100 ms condition and subtracted it from the sum of invalid and valid targets of the 800 ms condition independent from side of target presentation:

(valid/SOA 800 ms + invalid/SOA 800ms) – (valid/SOA 100 ms + invalid/SOA 100ms)

Stimuli with long SOA were directly compared to stimuli with short SOA because IOR-related activity should accumulate over time, which is supposed to be independent from the validity of the cues. In order to detect differences between patients and controls, their computed contrasts were entered into an unpaired t-test using a threshold of p = 0.001 uncorrected.

Figure 4: Illustration of the hypothetical time course of the facilitatory and inhibitory mechanisms



(Figure taken from Lepsien & Pollmann, 2002)
The figure demonstrates the theory of the time course of initial facilitation and prolonged inhibition. In the beginning the inhibitory mechanism is outweighed by the facilitatory effect. With a delay the inhibition can be observed because it is prolonged. The arrows indicate the onset of cue and targets with different SOAs.

3 Results

3.1 Demographic and clinical data

Demographic and clinical data of the patients are presented in table 1 and 2.

Five of the 20 initially recruited patients had to be excluded from further analysis due to head movements exceeding 3 mm. Data from 15 patients and 15 matched controls could be evaluated. The mean age was 30.27 years (standard deviation (SD) ± 9.04) in the patient group and 30.80 (SD ± 7.71) in the control group. The mean of the educational years was 11.47 years (SD ± 1.46) during the patients and 12.2 (SD ± 1.37) during the controls. Patients and controls did not differ significantly in age (*t*-test, p = 0.86) and educational years (*t*-test, p = 0.17).

Four of the 15 patients were treated with atypical antipsychotics, whereas the others had never received any medication. Eleven patients were diagnosed with schizophrenia for the first time (table 1).

As already mentioned the patients were screened with different rating scales. The mean results were 24.1 (SD ± 10.6) for the SAPS and 20.9 (SD ± 19.5) for the SANS. Concerning the SAPS passivity symptoms were found in eight patients with a range from 2 to 10 (mean 2.6, SD ± 3.2). However using the AMDP scale passivity symptoms were found in nine patients ranging from 1 to 5 (mean 1.4, SD ± 1.6). Thus seven patients were free of passivity according to the SAPS (SAPS = 0) while six patients did not show passivity according to the AMDP (AMDP = 0) (table 2).

Passivity symptoms, receipts of antipsychotic medication and time of initial diagnosis did not show any significant correlation to cognitive performance and fMRI results (p > 0.05).

Table 1: Demographic and clinical data

Patient	Age (years)	Years of education	Time of initial diagnosis	Antipsychotic medication
1	19	10	At present	–
2	35	13	2 years	–
3	28	13	At present	–
4	22	10	At present	Aripiprazole
5	19	10	At present	–
6	53	12	20 years	Risperidone
7	27	10	4 years	Risperidone
8	26	13	At present	–
9	39	10	At present	–
10	36	13	At present	–
11	39	12	At present	–
12	26	13	At present	–
13	26	10	6 years	Quetiapine
14	26	13	At present	–
15	33	10	At present	–
Mean	30.27	11.47		
Standard Deviation	9.04	1.46		

Table 1 demonstrates demographic and clinical data of the patients. It comprises age (column 2), years of education (column 3), time of initial diagnosis (column 4) and antipsychotic medication (column 5). The bottom two rows show mean and standard deviation of age and years of education.

Table 2: Results of the symptom scales

Patient	AMDP 53 – 58 passivity	SAPS 15 – 19 passivity	SAPS 1 – 7 hallucinations	SAPS all sum	SANS all sum
1	1	3	16	25	1
2	0	0	7	23	35
3	0	0	3	24	9
4	0	0	0	19	33
5	0	0	0	25	0
6	0	0	9	35	8
7	4	10	0	41	67
8	5	8	9	23	20
9	2	3	4	21	4
10	2	0	5	9	53
11	1	3	3	19	8
12	0	0	7	43	24
13	3	5	8	35	23
14	1	2	0	10	6
15	2	5	0	10	22
Mean	1.4	2.6	4.7	24.1	20.9
Standard Deviation	1.6	3.2	4.7	10.6	19.5

Columns 2 and 3 present scores of passivity symptoms, column 4 represents the reached scores of hallucinations as part of the SAPS and columns 5 and 6 list the sum of the scores for the SANS and SAPS

3.2 Cognitive performance

3.2.1 Reaction times

Reaction times less than 100 ms or exceeding 1,000 ms were observed in 1.8 % of the trials in the patient group and in 0.6 % of the trials in the control group. Thus these data were not included in the analysis.

The results of the mean RTs of the patient group and the control group are presented in table 3 and figure 5 and 6.

Table 3: Reaction times (RTs) of the COVAT with peripheral cues

	Invalid 100	Valid 100	Invalid 800	Valid 800
Patients left VF	386.41 ± 71.48	375.60 ± 43.66	344.22 ± 63.23	375.30 ± 51.34
Controls left VF	382.66 ± 69.25	364.58 ± 63.50	364.43 ± 72.69	413.98 ± 56.78
Patients right VF	386.75 ± 77.04	368.45 ± 52.23	348.63 ± 59.05	386.64 ± 73.80
Controls right VF	381.16 ± 59.78	353.82 ± 60.83	358.80 ± 73.86	400.05 ± 58.74

Mean RTs and standard deviation (group mean ± standard deviation) of the COVAT with peripheral cues in ms for patients with schizophrenia (n=15) and for healthy controls (n=15).
Left VF = The target appeared in the left visual field
Right VF = The target appeared in the right visual field
100 = Stimulus onset asynchrony of 100 ms
800 = Stimulus onset asynchrony of 800 ms
Valid = Valid target
Invalid = Invalid target

While the controls showed faster RTs in valid and invalid trials of the condition with a stimulus onset asynchrony of 100 ms compared to the patients, latter reacted faster to valid and invalid trials when the SOA was 800 ms. This reaction time pattern can be observed in both visual fields. In the task with the 100 ms SOA the two groups show shorter reaction times in valid trials versus invalid trials. Looking at the performance of the 800 ms condition it appears that the result is reversed. The subjects reacted faster to invalid trials than to valid ones. This is caused by the phenomenon IOR and can also be seen during the patient group.

Controls showed faster reaction times in the right visual field compared to the left visual field independent of SOA and validity. However, except for the valid condition of the 100 ms SOA, patients showed shorter reaction times in the left visual field.

In the ANOVA for the reaction times we found no significant main effects for the within-subject factors cue ($F = 3.65$, $p = 0.067$), SOA ($F = 0.014$, $p = 0.908$) and visual field ($F = 0.54$, $p = 0.467$) or the between-subject factor group ($F = 0.09$, $p = 0.769$). During the interactions merely cue x SOA showed a highly significant effect ($F = 58.41$, $p < 0.001$). This demonstrates the facilitation and inhibition of the RTs depending on the SOA. The interactions SOA x group ($F = 3.45$, $p = 0.074$) and visual field x SOA x group ($F = 3.09$, $p = 0.09$) approached significance.

Comparing valid with invalid trials at the long SOA (800 ms), paired *t*-tests showed significant results for both visual fields for the patients (left VF: $t = -2.62$, $p = 0.02$; right VF: $t = -4.74$, $p < 0.001$) and the controls (left VF: $t = -4.94$, $p < 0.001$; right VF: $t = -5.34$, $p < 0.001$).

The latter results and observation of figure 5 compared to figure 6 indicate that in fact there is no absence of IOR in the patient group, but a diminished magnitude of the inhibitory effect in the left visual field.

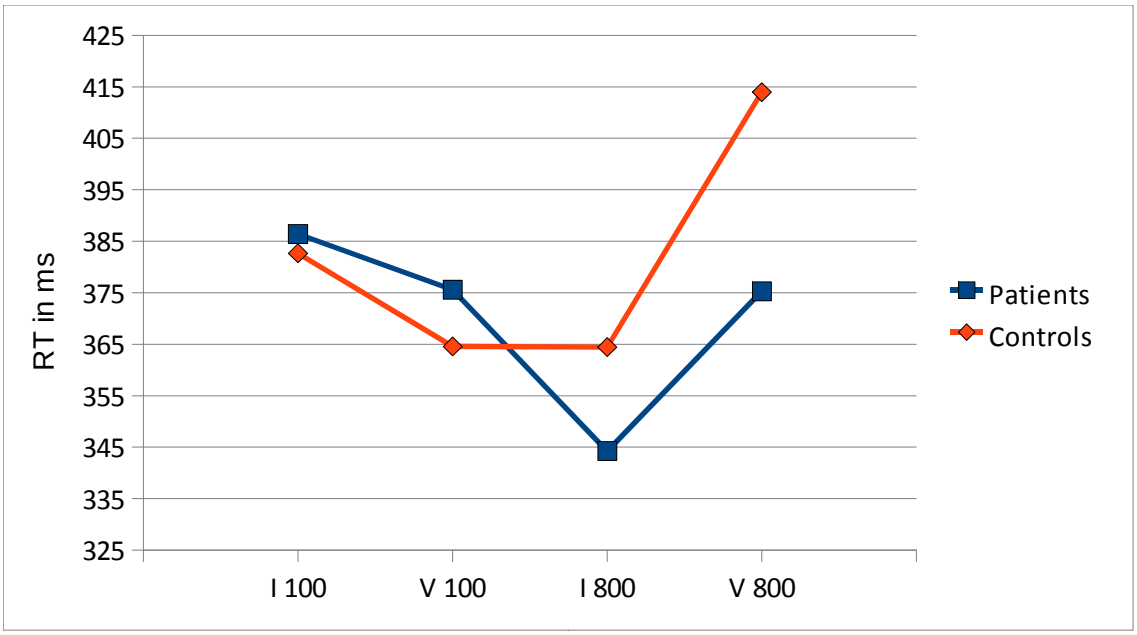
First the result of the paired *t*-test at the long SOA is significant for both visual fields in the patient group, but the result in the right visual field reaches high significance ($p < 0.001$), while the left visual field is merely significant ($p = 0.02$). However the control group shows a highly significant result in both visual fields.

Second figure 5 and 6 indicate that the result of the patients in the validly cued trial of the 800 ms SOA deviates in greater extent from the control group than it can be observed in the right visual field. This also indicates that the patients show a smaller magnitude of IOR in the left visual field. In the right visual field the graphs of both groups at the long SOA run almost parallel suggesting a homogeneous inhibitory effect in that visual field for both subject groups.

Interpreting these results and observing figure 5 and 6 it can be seen that the patients in our study did not show deficient IOR. Descriptive data show that they reacted faster to invalid than to valid trials at the SOA of 800 ms. This pattern

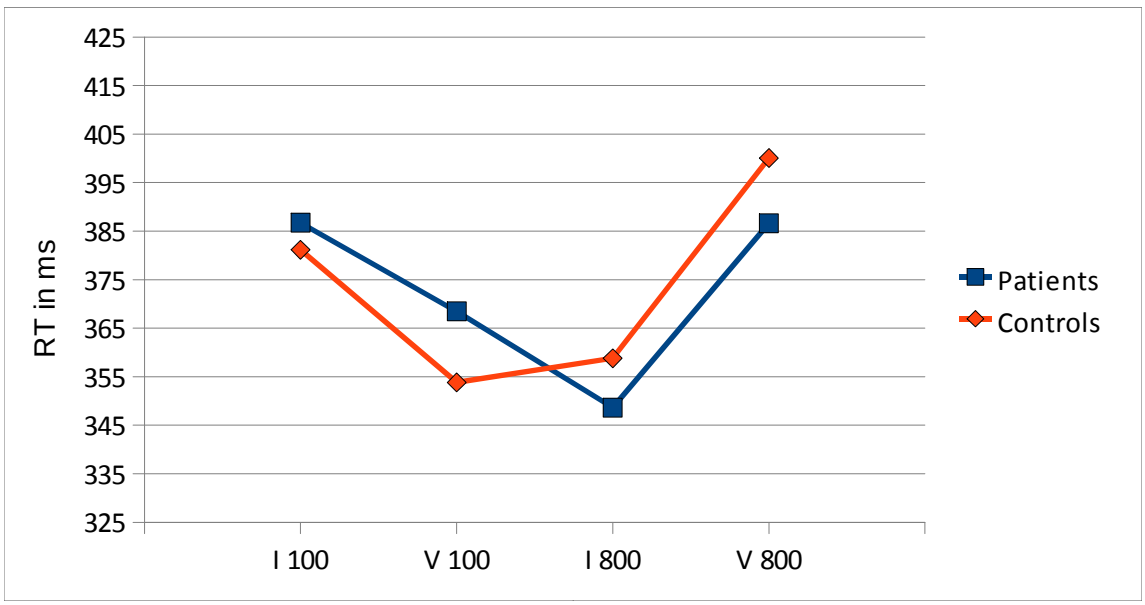
can also be seen in the control group and reflects the inhibitory attentional mechanism. The finding of a normal reaction pattern is also supported by the insignificant results of the ANOVA. There are no significant differences between the two groups in matters of SOA and visual field. Indeed the paired *t*-tests displayed that the difference between valid and invalid trials at the long SOA was less for the left visual field in the patient group, but it still reached significance ($p = 0.02$).

Figure 5: Reaction times (RTs) of the targets in the left visual field



Mean RTs in milliseconds of the targets appearing in the left visual field in patients with schizophrenia (n=15) and in healthy controls (n=15).
100 = Stimulus onset asynchrony of 100 ms; 800 = Stimulus onset asynchrony of 800 ms
V = Valid target; I = Invalid target

Figure 6: Reaction times (RTs) of the targets in the right visual field



Mean RTs in milliseconds of the targets appearing in the right visual field in patients with schizophrenia (n=15) and in healthy controls (n=15).
100 = Stimulus onset asynchrony of 100 ms; 800 = Stimulus onset asynchrony of 800 ms
V = Valid target; I = Invalid target

3.2.2 Validity effects

Validity effects (median RT in invalid trials – median RT in valid trials) are illustrated in table 4 and figure 7 and 8.

Table 4: Validity effects of the COVAT with peripheral cues

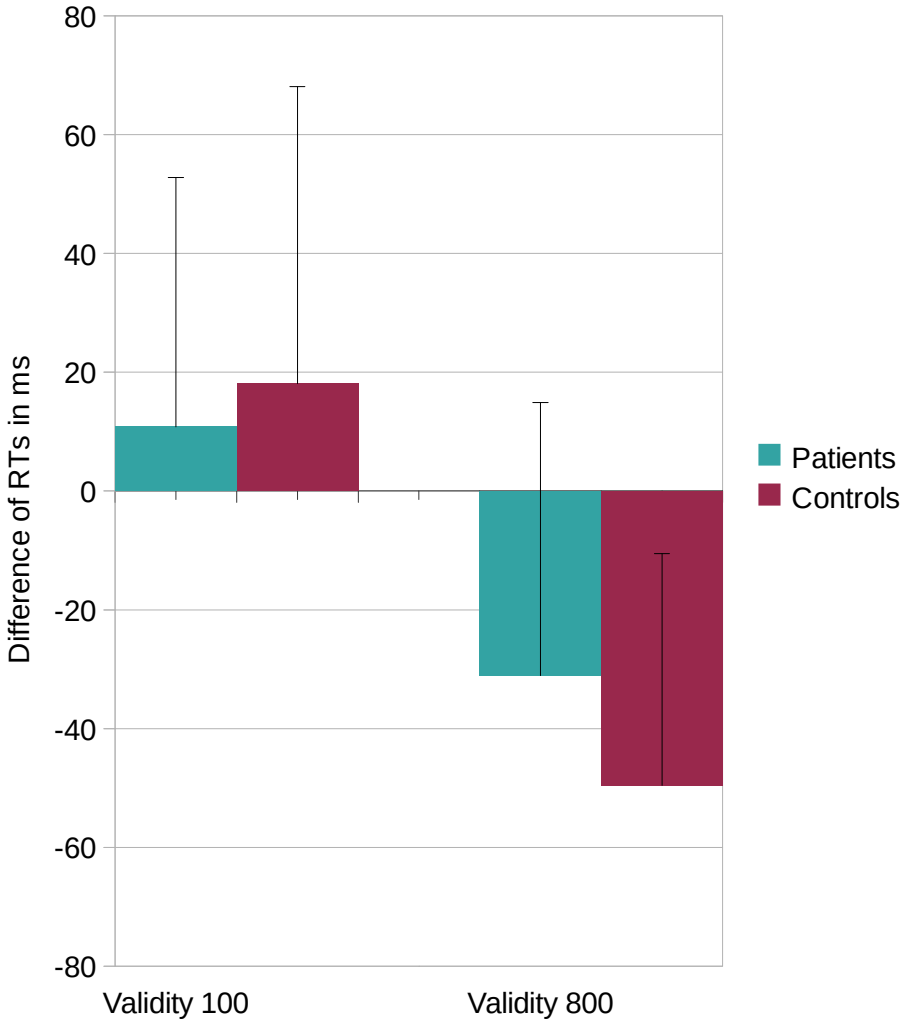
	SOA 100 ms	SOA 800 ms
Patients left VF	10.80 ± 41.73	-31.08 ± 45.92
Controls left VF	18.08 ± 50.18	-49.55 ± 38.87
Patients right VF	18.30 ± 42.62	-38.01 ± 31.08
Controls right VF	27.35 ± 49.37	-41.24 ± 29.90

The table shows the results (group mean ± standard deviation) of the validity effects (RT invalid – RT valid) for patients with schizophrenia (n=15) and for healthy controls (n=15) in the left and right visual field for the different SOAs.
SOA = Stimulus onset asynchrony
VF = Visual field

At the short SOA (100 ms) the validity effects showed positive values independent of group and visual field. This demonstrates the facilitation of valid versus invalid trials at short stimulus onset asynchronies. However the validity effects of the long SOA (800 ms) were consistently negative, because the subjects reacted faster to invalid-cued trials than to valid-cued ones. In the right visual field there is not much difference between patients and controls at the 800 ms SOA, while the values of the left visual field show a bigger deviance at the long SOA.

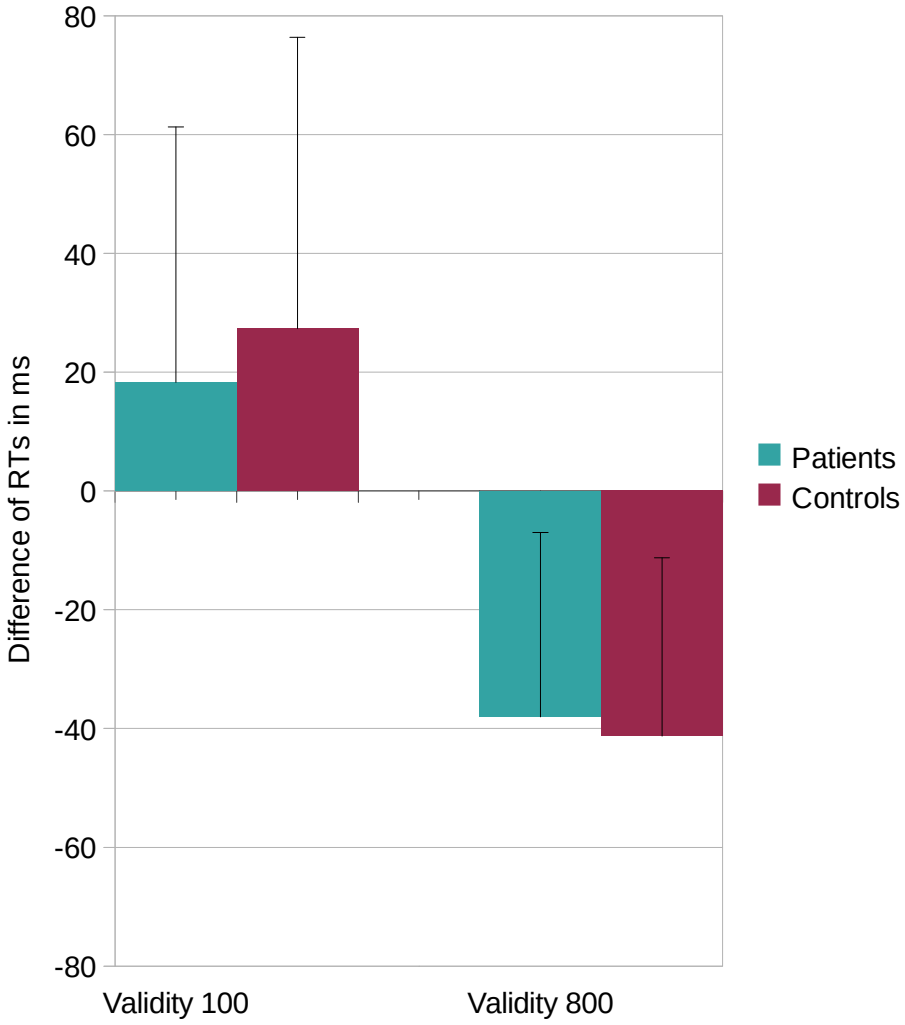
In the ANOVA of the validity effects we found a significant main effect for SOA ($F = 58.41$, $p < 0.001$), but not for the visual field ($F = 0.653$, $p = 0.426$). The effect of the between-subject factor group ($F = 0.014$, $p = 0.905$) and all interactions between the factors were insignificant ($p > 0.05$).

Figure 7: Validity effects in the left visual field



Group means and standard deviations of the validity effects (in ms) in the left visual field in patients with schizophrenia (n=15) and in healthy controls (n=15).
Validity 100 = Validity effects (RT invalid – RT valid) of the 100 ms SOA
Validity 800 = Validity effects (RT invalid – RT valid) of the 800 ms SOA

Figure 8: Validity effects in the right visual field



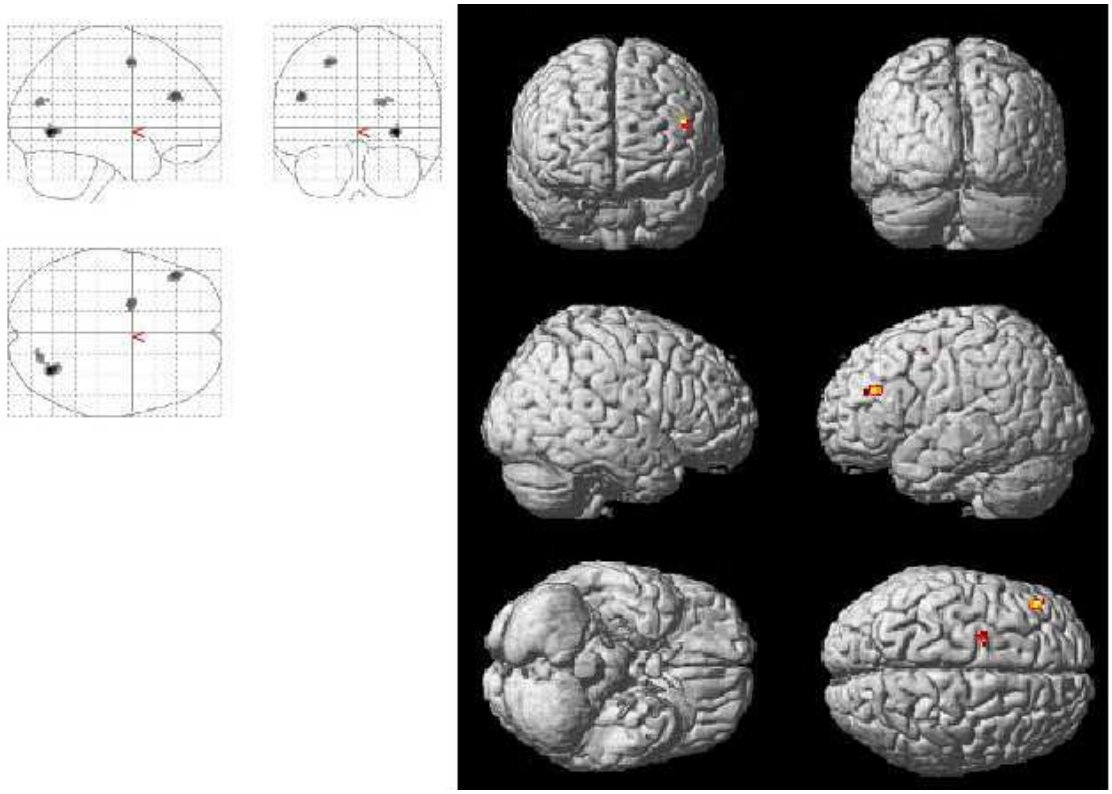
Group means and standard deviations of the validity effects (in ms) in the right visual field in patients with schizophrenia (n=15) and in healthy controls (n=15).
Validity 100 = Validity effects (RT invalid – RT valid) of the 100 ms SOA
Validity 800 = Validity effects (RT invalid – RT valid) of the 800 ms SOA

3.3 fMRI results

The summary of the results of the fMRI analysis is presented in figure 9. The MRI scans showed normal-structured brains without any evidence for focal brain lesions or anatomical alterations.

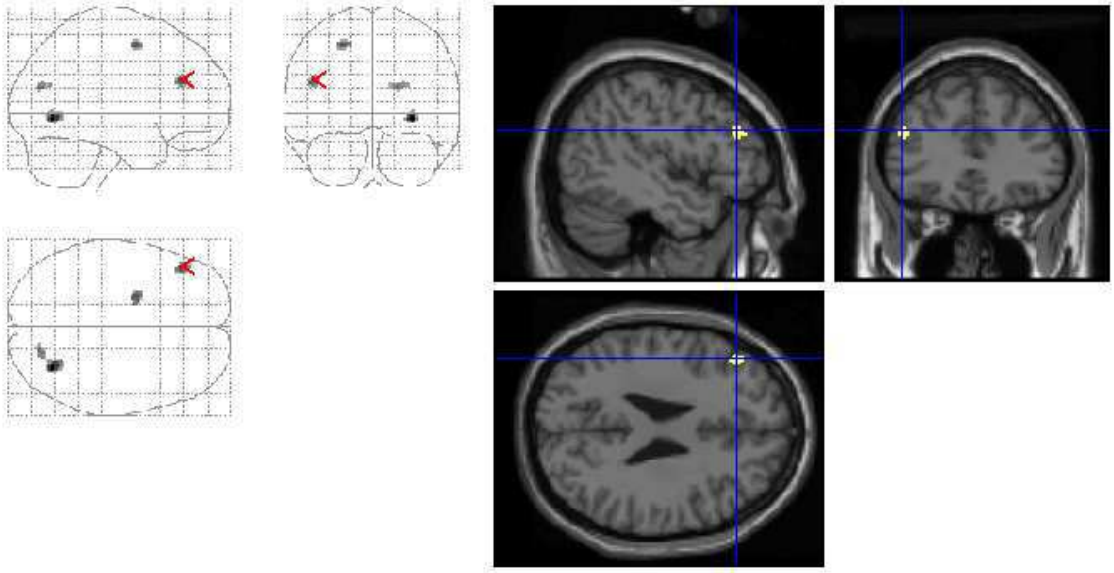
As already mentioned the computed contrasts ((valid/SOA 800ms + invalid/SOA 800ms) – (valid/SOA 100ms + invalid/SOA 100ms)) of the patients and the controls were entered into an unpaired *t*-test using a threshold of p = 0.001 uncorrected. The result showed significant activations in the frontal and the occipital lobe of the patients' brain compared to the controls' brain. In the occipital area activation increased significantly in the right fusiform gyrus (Brodmann Area (BA) 19, Z = 3.94) and the right cuneus (BA 18, Z = 3.45), whereas the BOLD response in the frontal lobe was increased in the left middle frontal gyrus (BA 46, Z = 3.63) and in the Brodmann Area 6 in direct proximity to the left precentral gyrus and the middle frontal gyrus (BA 6, Z = 3.56). Significant hypoactivations compared to the controls were not found. Similarly there were no significant effects in the opposed contrast.

Figure 9: Summary of the fMRI results for the IOR condition



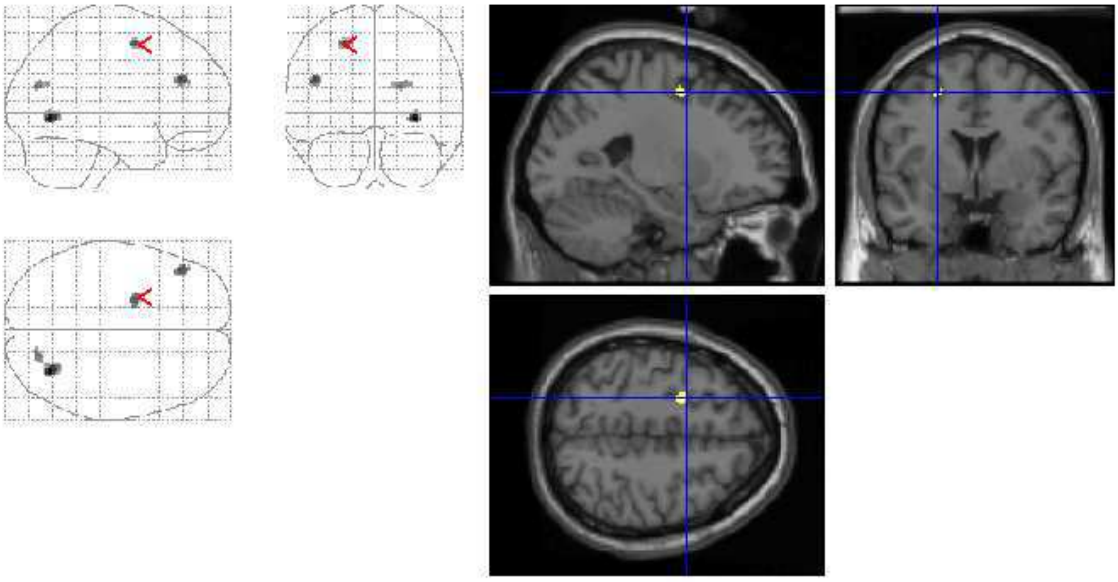
Hyperactivations in the patients' brain compared to the controls' brain for the IOR condition (events with long SOA of 800ms – events with short SOA of 100ms) demonstrating significant increased activations in the right fusiform gyrus (maximum located at Talairach coordinates 30, -66, -4; BA 19), the right cuneus (maximum located at Talairach coordinates 18, -76, 20; BA 18), the left middle frontal gyrus (maximum located at Talairach coordinates -46, 34, 26; BA 46) and in the Brodmann Area 6 in direct proximity to the left precentral gyrus and the middle frontal gyrus (maximum located at Talairach coordinates -24, -2, 52; BA 6).

Figure 10: Hyperactivation in Brodmann area 46



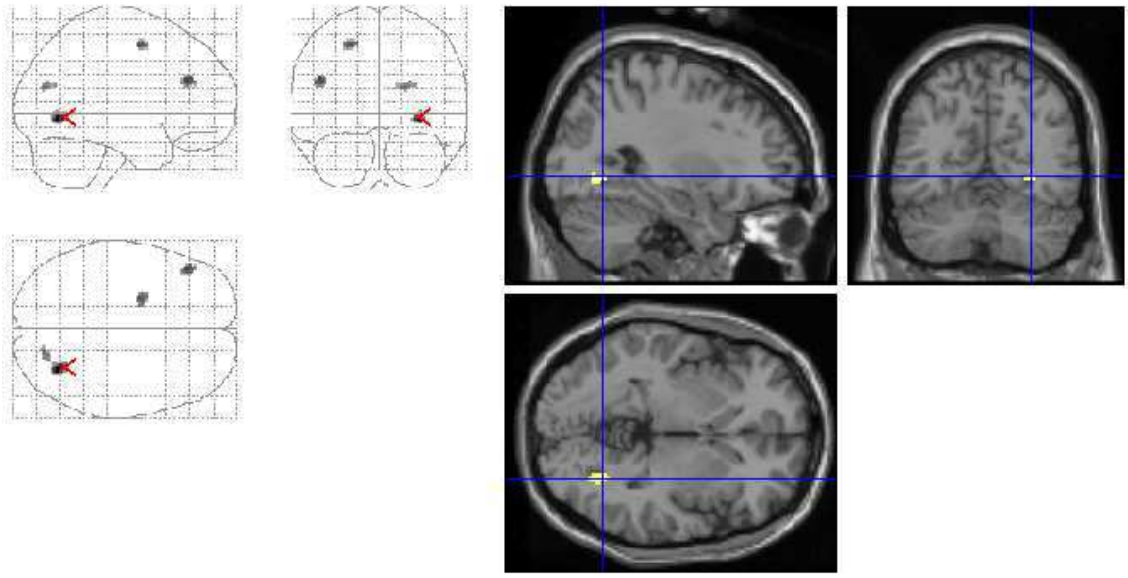
Hyperactivation in the Frontal Lobe of the patients' brain compared to the controls' brain for the IOR condition (events with long SOA of 800ms – events with short SOA of 100ms) demonstrating significant increased activation in the left middle frontal gyrus (maximum located at Talairach coordinates -46, 34, 26; BA 46).

Figure 11: Hyperactivation in Brodmann area 6



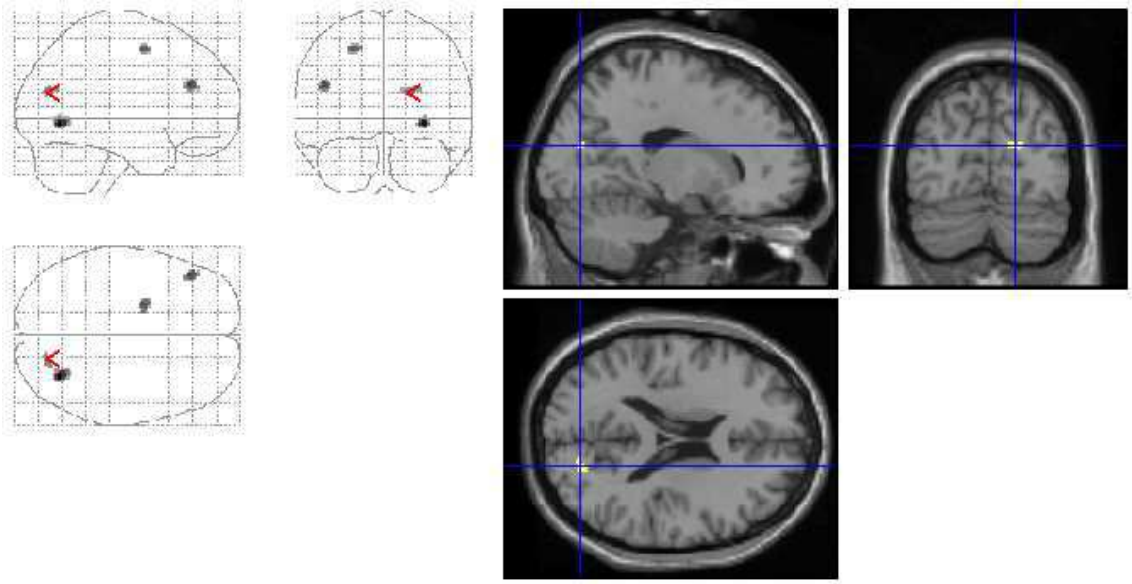
Hyperactivation in the Frontal Lobe of the patients' brain compared to the controls' brain for the IOR condition (events with long SOA of 800ms – events with short SOA of 100ms) demonstrating significant increased activation in in the Brodmann Area 6 in direct proximity to the left precentral gyrus and the middle frontal gyrus (maximum located at Talairach coordinates -24, -2, 52; BA 6).

Figure 12: Hyperactivation in Brodmann area 19



Hyperactivation in the Occipital Lobe of the patients' brain compared to the controls' brain for the IOR condition (events with long SOA of 800ms – events with short SOA of 100ms) demonstrating significant increased activation in the right fusiform gyrus (maximum located at Talairach coordinates 30, -66, -4; BA 19).

Figure 13: Hyperactivation in Brodmann area 18



Hyperactivation in the Occipital Lobe of the patients' brain compared to the controls' brain for the IOR condition (events with long SOA of 800ms – events with short SOA of 100ms) demonstrating significant increased activation in the right cuneus (maximum located at Talairach coordinates 18, -76, 20; BA 18).

4 Discussion

4.1 Objectives of the study

This study analyzed functional correlates of the brain of spatial orienting of attention in patients with schizophrenia. Our objectives were to find out whether schizophrenics show disturbed performance and whether it might result in altered activation patterns. In particular, the phenomenon Inhibition of Return (IOR) as a part of orienting of attention was interesting to us. Previous investigations indicated disturbed IOR in psychosis (Gouzoulis-Mayfrank et al., 2006; Gouzoulis-Mayfrank et al., 2004; Huey & Wexler, 1994; Larrison-Faucher et al., 2002; Sapir et al., 2001). In order to find evidence for causes of potential deficits and the neurofunctional origin of schizophrenia we implemented a neuroimaging study with schizophrenic patients.

We analyzed data of 15 patients suffering from paranoid-type schizophrenia and 15 healthy controls which were matched for age and years of education. The subjects had to pass a Covert Orienting of Visual Attention Task (COVAT) with peripheral (exogenous) cues and two different stimulus onset asynchronies (SOAs, 100 ms and 800 ms). During the examination an fMRI scanner recorded changes in the BOLD (blood oxygenation level dependent) signal and thus showed changes in neuronal activity.

4.2 Summary of the results

While the controls showed faster RTs in valid and invalid trials in the condition with a stimulus onset asynchrony of 100 ms compared to the patients, latter reacted faster to invalid and valid trials in the 800 ms SOA condition. This reaction time pattern could be observed in both visual fields.

In the task with the 100 ms SOA we found shorter reaction times in valid trials versus invalid trials in both groups. This represents the facilitating effect of valid cues at the short SOA and reproduces previous findings (Carter et al., 1992; Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2006; Huey &

Wexler, 1994; Larrison-Faucher et al., 2002; Maruff et al., 1995; Posner et al., 1988b).

Considering the performance of the 800 ms condition the result is reversed. The subjects reacted faster to invalid trials than to valid ones. This is caused by the phenomenon IOR and could also be demonstrated in the patient group. The ANOVA of reaction times did not result in significant main effects for the within-subject factors cue, SOA and visual field or the between-subject factor group. Merely the interaction between cue and SOA showed a highly significant effect. This demonstrates facilitation and inhibition of the reaction times depending on the SOA. The interactions between SOA and group or visual field, SOA and group approached significance.

Comparing valid to invalid trials at the long SOA (800 ms), paired *t*-tests showed significant results for both visual fields for the patients and the controls.

Interpreting these results the patients in our study did not show blunted or deficient IOR. Descriptive data show that they reacted faster to invalid than to valid trials at the SOA of 800 ms. This pattern could also be demonstrated in the control group and reflects the inhibitory attentional mechanism IOR. The finding of a normal reaction pattern is also supported by the above mentioned insignificant results of the ANOVA.

Interestingly throughout literature heterogeneous results can be found. Several studies, however, demonstrated a lack of Inhibition of Return in patients with schizophrenia (Carter et al., 1994; Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2006 ; Huey & Wexler, 1994), while others could not find disturbed IOR in schizophrenics (Carter et al., 1992; Fuentes et al., 1999; Fuentes & Santiago, 1999; Maruff et al., 1998; Sapir et al., 2001). However Fuentes and Santiago used a so-called cue-back mechanism. This is a centrally presented second cue drawing attention back to the fixation point (Fuentes & Santiago, 1999). Maruff and his colleagues used predictive cues indicating the side where the target is going to appear with a probability of 80% (Maruff et al., 1998). In order to find out whether the generation of normal IOR in schizophrenia patients might be stimulated by a cue-back mechanism Sapir et al. compared both task paradigms and found a normal Inhibition of Return at

cue-back, but blunted IOR at single-cue paradigm (Sapir et al., 2001). In contrast another study considered both single-cue and cue-back mechanisms and demonstrated normal IOR for both conditions in patients with psychosis (Fuentes et al., 1999). In contrast to our experimental procedure they used very long SOAs (1200 ms) at single-cue paradigm. Accordingly Larrison-Faucher and his colleagues detected a normal magnitude of IOR, but with a delay of onset (Larrison-Faucher et al., 2002). To our knowledge only one investigation did not find disturbed IOR using the same methodical framework as we did (peripheral non-predictive cues, single-cue paradigm, short SOA of 100 ms, long SOA of 800 ms) (Carter et al., 1992).

Indeed the paired t-tests of the reaction times of valid and invalid trials at the long SOA displayed that the difference between valid- and invalid-cued trials was less for the left visual field in the patient group, but it still reached significance. Additionally the graphs suggest a smaller inhibitory effect in the left visual field. It might be suspected that patients showed a non-significant reduced magnitude of IOR in the left visual field indicating a slight lateralization of visual attention in patients with schizophrenia.

At the short SOA (100 ms) the validity effects showed positive values independent of group and visual field. This demonstrates the facilitation of valid versus invalid trials at short stimulus onset asynchronies. However the validity effects of the long SOA (800 ms) were consistently negative, because the subjects reacted faster to invalid-cued trials than to valid-cued ones. In the right visual field there was a marginal difference between patients and controls at the 800 ms SOA, while the values of the left visual field showed a more distinct deviance at the long SOA. This supports the theory of a slightly blunted IOR-effect in the left visual field suggesting a lateralization of attention in schizophrenia.

In matters of a lateralized attentional disturbance, some authors detected a potential left hemispheric deficit. Compared to the left visual field they found significantly slower reaction times if an invalid-cued target appeared in the right visual field at a short SOA (Carter et al., 1992; Moran et al., 1996; Posner et al., 1988b; Potkin et al., 1989). Others could replicate this finding only in unmedicated patients (Maruff et al., 1995; Wigal et al., 1997) or in patients with

undifferentiated schizophrenia, but not in paranoid-type schizophrenia (Carter et al., 1994). These results diverge from our findings indicating a mild disorder of attentional mechanisms in the left visual field. However, interestingly all but one study (Carter et al., 1994) used predictive cues with a probability of at least 70% for the target appearing at the cued location and thus differ methodologically from our study. Wigal et al. demonstrated a significant validity effect in the right visual field, but not in the left visual field at an SOA of 100 ms in drug-free patients (Wigal et al., 1997) indicating that there might not just be an inhibitory, but a general attentional disturbance with regard to the left visual field. Sapir et al. indeed found a significantly stronger validity effect in the right visual field compared to the left visual field, but he could not show any asymmetry related to Inhibition of Return (Sapir et al., 2001).

Definitely there were also studies demonstrating no differences in the visual fields in patients with schizophrenia (Gold et al., 1992; Gouzoulis-Mayfrank et al., 2006; Gouzoulis-Mayfrank et al., 2004; Strauss et al., 1992; Strauss et al., 1991) and even our results only suggest a slight non-significant attentional asymmetry with respect to IOR. These facts complicate a distinct statement about potential lateralization and hemispheric deficits. For this reason we additionally analyzed fMRI data trying to discover abnormalities of cerebral function in schizophrenics.

The paired t-test of the computed contrasts ((valid/SOA 800 ms + invalid/SOA 800ms) – (valid/SOA 100 ms + invalid/SOA 100ms)) of patients and controls showed significant activations in the frontal and the occipital lobe of the patients' brain compared to the controls' brain. In the occipital area activation increased significantly in the right fusiform gyrus (Brodmann Area (BA) 19) and the right cuneus (BA 18), whereas the BOLD response in the frontal lobe was increased in the left middle frontal gyrus (BA 46) and in Brodmann Area 6 close to the left precentral gyrus and the left middle frontal gyrus. The patients did not show any hypoactivated cerebral regions compared to the control group.

Brodmann Area 6 is commonly associated with voluntary motor control and initiation of motor responses. However Brodmann Area 18 seems to be involved in processing of visual stimuli and spatial orientation. Brodmann area 19 is functionally connected to Brodmann area 18 and participates in object

recognition and orienting of attention. Similarly Brodmann Area 46 is linked to object recognition as well as to control of attention. It allows sustained attention despite the presence of distractors (Bösel, 2006; Hirsch, 2000).

As can be seen, all of the significantly higher activated brain regions seem to play a crucial role in Covert Orienting of Visual Attention Tasks. They are either involved in motor functions, visual processing or in fact take part in attentional mechanisms.

Accordingly Lepsien and Pollmann demonstrated an association of activation in the medial frontal gyrus and the precentral sulcus to IOR in healthy adults. Although the results concerned the right hemisphere, the areas per se match our findings (Lepsien & Pollmann, 2002).

Interestingly our patients did not differ significantly from the controls in terms of Inhibition of Return. Contrary to many studies we did not find deficient IOR in patients with schizophrenia. However, with respect to IOR, analyzing fMRI data we detected four significantly higher activated areas in the patients' brain compared to the controls' brain. These findings suggest that normal cognitive performance might be achieved by increased cerebral activation. This presumption would also explain why the patients in our study did not show overall slower reaction times in the COVAT.

This hypothesis is supported by Ettinger et al. (2011) who conducted a neuroimaging study with schizophrenic patients performing a working memory task. They demonstrated hyperactivations in occipital and lateral prefrontal cortex of the patients compared to controls. They showed that the difference increased dependent on working memory load and good task performance. Thus they suspected that normal performance might be caused by “compensatory neural activity” as well (Ettinger et al., 2011).

Another study by Daumann et al. (2008) could additionally support our hypothesis. They investigated neuronal correlates of a COVAT in two models of psychosis. They used the hallucinogenic drugs dimethyltryptamine (=DMT) and S-ketamine to imitate schizophrenia in healthy adults and compared the two groups to a placebo group. It is assumed that DMT can be used as an adequate model for paranoid-type schizophrenia, while the use of S-ketamine serves as

an appropriate model for undifferentiated schizophrenia (Abi-Saab et al., 1998; Gouzoulis-Mayfrank et al., 2005; Javitt & Zukin, 1991).

Daumann and his colleagues demonstrated that reaction times in the DMT group were significantly longer and that this group showed deficient IOR. However compared to the placebo group the fMRI results did not display any IOR-associated difference. In contrast, the S-ketamine group showed normal reaction times and a normal pattern of IOR, but significantly increased activations in the right superior frontal gyrus, the left superior temporal gyrus and the right middle frontal gyrus in comparison to the placebo group (Daumann et al., 2008). Indeed they could not support our findings in the model for paranoid-type schizophrenia, but the results also indicate that increased BOLD signal might be associated with normal cognitive task performance.

4.3 Limitations

This study is the first that attempts to analyze neural correlates of the attentional phenomenon “Inhibition of Return” in visual tasks in patients with schizophrenia. However there are methodological limitations that need to be mentioned.

Primarily the sample size was small with two groups of 15 participants. Therefore, the lack of significant differences in the performance between patients and healthy controls could be caused by a lack of statistical power. Furthermore even if the groups were matched for age and years of education, we only included male patients in the study in order to avoid gender-specific differences. Hence the results are not transferable to females or a complete population.

It is quite difficult to recruit a homogeneous patient group and as it can be seen in table 1 and 2 our group of schizophrenic patients is rather inhomogeneous. Eleven patients were diagnosed with schizophrenia for the first time, while the remaining four patients have had their initial diagnosis two, four, six and 20 years ago respectively. Four of the 15 patients were under neuroleptic medication (two patients were taking risperidone, one patient was taking quetiapine and one patient was taking aripiprazole), while the remaining eleven

patients were medication-free. Similarly the results of the symptom scales differed in quite large dimensions among the patients.

As we could not find significant correlations of passivity symptoms, receipts of antipsychotic medication and time of initial diagnosis with cognitive performance, Gouzoulis-Mayfrank et al. did not find a significant interaction of psychopathology, length of illness and type of neuroleptic medication as well (Gouzoulis-Mayfrank et al., 2007; Gouzoulis-Mayfrank et al., 2004). They were able to show that a deficient Inhibition of Return could be found in an acute episode of the illness as well as in partial remission (Gouzoulis-Mayfrank et al., 2004).

Additionally, it seems interesting whether cognitive performance could be influenced by medication and whether blunted IOR might just be a side effect of neuroleptics. Gouzoulis-Mayfrank et al. could not find an association between type of neuroleptic medication and Inhibition of Return (Gouzoulis-Mayfrank et al., 2004; Gouzoulis-Mayfrank et al., 2006). They found an absence of IOR in medicated as well as in unmedicated patients of the same study group (Gouzoulis-Mayfrank et al., 2007). Concerning this matter Carter et al. could demonstrate a normal Inhibition of Return in medication-free patients (Carter et al., 1992), while Maruff et al. found a normal IOR also in patients receiving antipsychotic medication (Maruff et al., 1998). Interestingly in another study Carter and his colleagues could show a disturbed IOR-effect in unmedicated patients suffering from paranoid-type schizophrenia. However this lack could not be found in a group of patients with undifferentiated schizophrenia (Carter et al., 1994). Another study indicated a less pronounced, but still present lack of IOR in unmedicated patients compared to patients receiving antipsychotic treatment. Though, they admitted that any interpretation of the side effects of antipsychotics on the cognitive performance might be restricted by the fact that medication was not allocated to the subjects randomly, but depending on clinical aspects (Gouzoulis-Mayfrank et al., 2006).

Evidently it is quite difficult to differentiate, whether cognitive results might be influenced by side effects of neuroleptic treatment. However as can be seen, blunted IOR has been found in medicated as well as in unmedicated patients, while other authors could demonstrate normal Inhibition of Return in

medication-free patients as well as in patients receiving neuroleptics. Presumably disturbed IOR is not primarily caused by antipsychotic medication, but an intensification of the deficit might be conceivable.

Another limitation might be the influence of neuroleptic medication on the blood oxygenation level dependent (BOLD) signal. Currently there are discussions whether the effect of atypical antipsychotics on serotonin and dopamine receptors might influence cerebral activation patterns. Medicated patients might thereby show an increase or a decrease in BOLD signal in several cerebral regions in comparison to the control group. Concerning this matter Braus et al. conducted a motor task and compared cerebral activation of schizophrenia patients taking typical or atypical antipsychotics to neuroleptic-naive patients and controls. Subjects taking medication showed reduced activation in the supplementary motor area regardless of whether medication was typical or atypical. Furthermore there was a significant hypoactivation in sensorimotor cortices within the patient group medicated with typical antipsychotics (Braus et al., 1999).

Schlagenhof and his colleagues carried out a neuroimaging study with schizophrenics taking neuroleptic medication as well. The subjects had to perform a working memory task, first when they were under typical antipsychotic medication (T1) and a second time after the medication was substituted by olanzapine (T2). Compared to healthy controls, at T1 patients showed reduced activation in the dorsolateral prefrontal cortex. At T2 this previously hypoactivated region showed an increase in BOLD signal during the attentional part of the task, but not during working memory per se (Schlagenhauf et al., 2008). In a second investigation, with similar experimental procedure, patients were switched to aripiprazole and then had to perform the task a second time. The MRI scanner displayed a hypoactivation in the dorsal anterior cingulate gyrus compared to the control group at T1. At T2 patients showed improved task performance and consequently increased activation in the formerly less activated area (Schlagenhauf et al., 2010).

Another neuroimaing study compared schizophrenic patients at baseline and after twelve weeks of antipsychotic treatment with quetiapine in a working memory task. Compared to controls there was a hypoactivation in the

ventrolateral prefrontal cortex at first task performance. After time of medical treatment the BOLD signal in the aforementioned region was significantly increased (Meisenzahl et al., 2006).

Apparently neuroleptic medication in schizophrenia patients seems to influence the BOLD signal. Primarily an increase of activation might be a side effect of antipsychotics and can not completely be excluded. However in our study only four of the 15 patients were treated with atypical antipsychotic medication, reducing the risk of a massive influence on our results. In addition we did not find any significant interaction between medication and cerebral activation making a distortion of the results rather unlikely.

4.4 Conclusion and prospects

Our study is the first attempt to investigate neural correlates of the phenomenon Inhibition of Return in visual attention tasks in patients with schizophrenia. The initial objective was to find out whether disturbed IOR in patients with schizophrenia might result in an altered cerebral activation pattern. Hence we wanted to draw conclusions on potential brain structures that are fundamentally disturbed in schizophrenia and might be involved in genesis of the illness. However the patients in our study did not show significantly slowed reaction times or disturbed IOR even though there seemed to be a slightly non-significant diminution of IOR in the left visual field. Interestingly the fMRI results displayed IOR-associated hyperactivations in the patient group compared to the control group. These areas included the right fusiform gyrus (Brodmann Area (BA) 19), the right cuneus (BA 18), the left middle frontal gyrus (BA 46) and parts of Brodmann Area 6 close to the left precentral gyrus and the left middle frontal gyrus. All of these areas are thought to have functions that are involved in motor functions, visual orienting or attentional mechanisms (Bösel, 2006; Hirsch, 2000). In line with two other studies (Daumann et al., 2008; Ettinger et al., 2011), our results indicate that increased cerebral activation might result in improved task performance and thus might almost normalize cognitive functioning in schizophrenics.

As this is the first neuroimaging study with regard to Inhibition of Return in visual attention tasks in patients with schizophrenia and there is a number of methodological limitations, the questioning requires more precise investigations. In this context it would be rather important to see whether patients, showing disturbed IOR, show a normal brain activation pattern or even less activated areas compared to healthy controls. Further studies might shed more light on the question whether patients suffering from schizophrenia need to activate more cerebral neurons to achieve an equivalent cognitive performance.

5a Summary

Rationale and objectives: Besides other cognitive deficits, spatial orienting of attention has commonly been found to be disturbed in schizophrenia. In particular, a phenomenon called Inhibition of Return (IOR) seemed to be absent or at least blunted in patients suffering from psychosis. It has been hypothesized that IOR might be an automatic inhibitory attentional mechanism, filtrating relevant from irrelevant stimuli. In order to detect whether disturbed IOR might be caused by altered cerebral activation patterns, we implemented a functional neuroimaging study.

Methods: 15 patients with paranoid-type schizophrenia and 15 healthy controls participated in this functional magnetic resonance imaging (fMRI) study. They had to perform a Covert Orienting of Visual Attention Task (COVAT) with exogenous non-predictive cues, while alterations in blood oxygenation level dependent (BOLD) signal indicating changes in cerebral activation, were recorded by an MRI-scanner.

Results: Compared to controls, patients did not show significantly slower reaction times. In addition they presented a normal pattern of Inhibition of Return in the COVAT. However, in the fMRI, in comparison to the control group, schizophrenics offered IOR-associated hyperactivations in the right fusiform gyrus (Brodmann Area (BA) 19), the right cuneus (BA 18), the left middle frontal gyrus (BA 46) and in Brodmann Area 6 in direct proximity to the left precentral gyrus and the left middle frontal gyrus.

Conclusions: The fact that patients showed a normal task performance, but offered increased BOLD signals linked to IOR, might allow the presumption that patients need to recruit more neurons to improve their cognitive performance to a normal level. These findings might help to clarify which cerebral regions could be fundamentally disturbed in schizophrenia and could also have an influence on the genesis of this disease.

5b Zusammenfassung

Hintergrund und Zielsetzung: Neben anderen kognitiven Defiziten wurde in der Schizophrenieforschung häufig von einer gestörten räumlichen Orientierung der Aufmerksamkeit berichtet. Insbesondere ein Phänomen namens “Inhibition of Return” (IOR) fehlte bei Patienten, die an einer Psychose erkrankt waren oder zeigte sich zumindest in abgestumpfter Form. Es wurde vermutet, dass IOR einen automatischen inhibitorischen Aufmerksamkeitsmechanismus darstellt, welcher es ermöglicht, relevante von irrelevanten Reizen zu unterscheiden. Wir führten eine bildgebende Studie durch, um der Fragestellung nachzugehen, ob eine gestörte IOR durch ein verändertes Aktivierungmuster zerebraler Areale verursacht sein könnte.

Methoden: 15 Patienten mit paranoider Schizophrenie und 15 gesunde Kontrollprobanden nahmen an der funktionellen Magnetresonanztomographie (fMRT)-Studie teil. Es wurde jeweils ein “Covert Orienting of Visual Attention Task” (COVAT) mit exogenen Hinweisreizen durchgeführt. Währenddessen wurden Veränderungen im “blood oxygenation level dependent” (BOLD)-Signal, welche auf Änderungen der zerebralen Aktivierung hindeuten, von einem MRT-Gerät gemessen.

Ergebnisse: Im Vergleich zu den Kontrollen, zeigten die Patienten keine signifikant langsameren Reaktionszeiten. Außerdem wiesen sie ein normales Muster der “Inhibition of Return” im COVAT auf. Allerdings zeigte sich im MRT, dass die Schizophrenen im Kontrast zur Kontrollgruppe IOR-assoziierte Hyperaktivierungen im rechten Gyrus fusiformis (Brodmann Areal (BA) 19), im rechten Cuneus (BA 18), im linken Gyrus frontalis medialis (BA 46), sowie im Brodmann Areal 6 in direkter Nähe zum linken Gyrus praecentralis und zum linken Gyrus frontalis medialis aufwiesen.

Schlussfolgerung: Die Tatsache, dass die Patienten eine normale Performance der Aufgabe erreichten, aber eine Steigerung des BOLD-Signals in Bezug auf IOR zeigten, lässt die Schlussfolgerung zu, dass Patienten mehr Neuronen aktivieren müssen, um ihre kognitive Leistung einem normalen Standard anzupassen. Diese Resultate könnten dazu beitragen, Hirnareale zu identifizieren, welche bei Schizophrenen eventuell grundlegend gestört sind und einen Einfluss auf die Entstehung dieser Erkrankung haben könnten.

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7 Appendix

7.1 List of figures

7.2 List of tables

8 Lebenslauf

Name:	Braje
Vorname:	Nikola
Geburtsdatum:	25. März 1987
Geburtsort:	Köln
Familienstand:	ledig
Eltern:	Vater: Wolfgang Braje – kaufm. Angestellter
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Schulischer Werdegang

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08/1997 – 06/2005	Gymnasium der Stadt Kerpen / Europaschule
06/2005	Erwerb der Allgemeinen Hochschulreife

Studium

Seit 10/2005	Studium der Humanmedizin im Modellstudiengang an der Universität zu Köln
09/2007	Erster Abschnitt der ärztlichen Prüfung – Note 2,38
12/2011	Zweiter Abschnitt der ärztlichen Prüfung – Note 2,0

Famulaturen

02/2008 – 03/2008	Allgemeinmedizin, Gemeinschaftspraxis Dr. med. Bauer und Dr. med. Schilling, Hürth
09/2008 – 09/2008	Gynäkologie und Geburtshilfe, St. Elisabeth Krankenhaus, Köln
02/2009 – 03/2009	Anästhesie und Intensivmedizin, St. Franziskus Hospital, Köln
08/2009 – 09/2009	Orthopädie, St. Joseph's Hospital, Koforidua (Ghana)

Praktisches Jahr

08/2010 – 07/2011	1. Tertial: Gynäkologie, Krankenhaus der Augustinerinnen, Köln
	2. Tertial: Innere Medizin, Krankenhaus der Augustinerinnen, Köln
	3. Tertial: Chirurgie, Krankenhaus der Augustinerinnen, Köln

Nebentätigkeiten

04/2006 – 12/2006	Studentische Hilfskraft im Schlaflabor, St. Katharinen-Hospital, Frechen
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Kerpen, den 21.01.2014

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Nikola Braje