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Though this be madness, yet there is method in't

William Shakespeare,
Hamlet

Danksagung

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Chapter 1: General Introduction:

Schizophrenia is the most severe and chronic form of mental illness. It ranks among the ten most frequent causes for disability in developed countries (Rossler et al., 2005) and affects roughly one percent of the world's population (Saha et al., 2005; McGrath, 2007). Understanding the etiology of schizophrenia has been one of the primary motivations of psychiatric research during the last one hundred years. For a good part of the last century Kraepelin's claim that schizophrenia or *dementia praecox* has a strong biological basis (Kraepelin, 1899) was disputed (Szasz, 1961), not least because of the failure to unambiguously identify a neurobiological substrate. The methodological advances in neuroscience particularly in the last two decades have provided convincing evidence for neuroanatomical, neurochemical and neurophysiological alterations in schizophrenia (Lewis and Lieberman, 2000). However, so far no clear picture of its pathophysiology has emerged. This lack of knowledge has prevented the development of biomarkers for a timely and reliable diagnosis of schizophrenia (Pantelis et al., 2009) and also remains the biggest obstacle on the way to causal treatments (Lewis and Gonzalez-Burgos, 2006).

The search for the biological underpinnings of schizophrenia is primarily impeded by its complexity and heterogeneity, which is already evident in its phenomenology.

1.1 The clinical profile of schizophrenia

Psychopathologically schizophrenia is characterized by psychotic symptoms like hallucinations, delusions and thought disorder, also referred to as positive symptoms, and by negative symptoms like anhedonia, avolition, social withdrawal and thought poverty (Andreasen, 1982; Andreasen and Olsen, 1982). Patients with schizophrenia also exhibit marked cognitive deficits in a wide variety of domains (Gruzelier et al., 1988; Braff et al., 1991; Gold et al., 1999; Mohamed et al., 1999; Bilder et al., 2000; Kuperberg and Heckers, 2000). However, cognitive dysfunction is not recognized in the current psychiatric classification systems, ICD-10 and DSM-IV.

Instead, the diagnosis of schizophrenia is based exclusively on the clinical symptomatology with a stronger emphasis on positive symptoms (APA, 2000; WHO et al., 2008). This largely mirrors the categorization of first- and second-rank symptoms by Kurt Schneider (Schneider, 1939). While they typically occur together, the extent of each symptom cluster varies considerably across patients (Tamminga and Holcomb, 2005). The heterogeneity of schizophrenia was already acknowledged in Eugen Bleuler's revision of Kraepelin's concept of Dementia praecox, as indicated by the title of his seminal work "Dementia praecox or the group of schizophrenias" (Bleuler, 1911). It is also evident in the clinical subtyping of schizophrenia into a paranoid, disorganized, katatonic and undifferentiated type as well as the distinction of schizoaffective disorder, which is characterized by the additional phasic occurrence of manic or depressive symptoms.

In addition to narrowly defined schizophrenia and schizoaffective disorder, a number of *schizophrenia spectrum disorders* are described (Levinson and Mowry, 1991). These conditions, like schizotypal personality disorder or delusional disorder, share many of the clinical characteristics of schizophrenia but in an attenuated and less persistent form.

Recent findings also point to a surprisingly high prevalence of the clinical symptoms of schizophrenia in the general population (Hanssen et al., 2005; Loewy et al., 2007; Rossler et al., 2007). For instance, in a community sample studied in the United States, 28.4 % of the participants endorsed one or more of the psychosis screening questions (Kendler et al., 1996a). Auditory verbal hallucinations occur in approximately 10 to 15 % of the population (Tien, 1991; Verdoux et al., 1998; Poulton et al., 2000). Only a small portion of these individuals ever develop schizophrenia or a schizophrenia spectrum disorder. In the vast majority of individuals these symptoms are either transitory or remain subclinical (Hanssen et al., 2005).

This line of evidence points to the existence of a continuum of psychotic phenomena, which ranges from mild and often brief subclinical psychotic experiences on one end to the full blown psychotic symptoms encountered in patients with schizophrenia on the other (Johns and van Os, 2001). Such a continuum would argue against the currently used categorical or dichotomous classification of mental disorders and in favor of a dimensional system

(Esterberg and Compton, 2009; Linscott and van Os, 2010), in which psychotic disorders would be defined by a number of continuously varying symptom dimensions. However, both approaches have certain limitations. It has been argued, that a categorical approach would help to increase diagnostic reliability, a dimensional approach would lead to greater diagnostic validity (Esterberg and Compton, 2009). A dimensional approach to the classification of mental disorders would also be unique among medical disciplines, because the medical field is strongly committed to categories, which are thought to reflect discrete disease entities (Dalal and Sivakumar, 2009).

This ongoing and unresolved debate underscores the unique problems associated with the diagnosis of mental disorders. Furthermore, the considerable phenomenological variability and the existence of a broader schizophrenia spectrum all point to the possibility that – rather than constituting a single disease entity – schizophrenia might actually be a group of related disorders (Crow, 1981; Carpenter et al., 1988).

1.2 The course and outcome of schizophrenia

This notion is also supported by its highly variable course and outcome. The onset of schizophrenia typically occurs during late adolescence or early adulthood (an der Heiden and Hafner, 2000) but schizophrenia can also manifest before the age of 10 (McClellan and McCurry, 1999) or as late as the age of 60 (Howard et al., 2000). Interestingly, men have a higher risk to develop schizophrenia than women (1.4 : 1) (Aleman et al., 2003). Sometimes illness onset occurs in an abrupt fashion generally indicative of a comparably benign and episodic course with little or no residual symptoms and a good level of psychosocial functioning (Tamminga and Holcomb, 2005). In the majority of cases the overt manifestation of schizophrenia is preceded by a prodromal phase (an der Heiden and Hafner, 2000). At the beginning of this time period patients primarily suffer from depressive and negative symptoms (Yung and McGorry, 1996; an der Heiden and Hafner, 2000) and show declining intellectual performance (Fuller et al., 2002; Reichenberg et al., 2005) and reduced psychosocial functioning (White et al., 2006). During this stage, positive symptoms are mostly intermittent and attenuated but intensify towards the end of the prodrome (an der Heiden and Hafner, 2000).

On average, the prodromal phase last for approximately five years, but its duration can also be considerably longer (an der Heiden and Hafner, 2000). Such a slow and insidious development of the disorder often signals a more severe and unremitting course and outcome (Tamminga and Holcomb, 2005). Deterioration, i.e. increasing negative symptoms (Carpenter et al., 1988) and declining psychosocial functioning, is even more apparent in the first three years of active illness (McGlashan, 1988; McGlashan and Fenton, 1993). It often leads to profound impairments (Lieberman, 1999b).

Kraepelin's initial concept of progressively deteriorating *dementia praecox* (Kraepelin, 1899) was based on the notion, that this decline would continue throughout the course of the illness in the vast majority of patients. In contrast, current research shows, that after the first years of illness, a lower plateau is reached and no further deterioration occurs (McGlashan, 1988). Likewise, the long-term course and outcome of schizophrenia is not uniformly poor. Overall, 10 to 20 % of patients achieve a good level of remission (Robinson et al., 2004), while about 15 to 20 % of patients have a very poor outcome and respond only minimally to treatment (McGlashan, 1988). Notably, a poor outcome is found more frequently in men (Perala et al., 2007). About 5 % of all patients commit suicide, predominantly near illness onset (Palmer et al., 2005).

The majority of patients recuperates at least partially but continues to suffer from residual symptoms and relapses of acute psychotic episodes (Ciompi and Müller, 1976; Bleuler, 1978). Longitudinal studies have shown that these patterns of recurring psychotic exacerbations and the level of residual symptoms in between episodes vary noticeably (Huber et al., 1979; Harding et al., 1987b, a). Additionally, these studies demonstrated a marked improvement of symptoms in a number of patients after the age of 50 (Harding et al., 1987b, a).

1.3 Etiological hypotheses

Kraepelin's concept of dementia praecox also implied a neurodegenerative etiology of schizophrenia. Conversely, the complex and variable pattern of most schizophrenia spectrum disorders discovered since then clearly differs from the progressive decline observed in typical neurodegenerative disorders like Alzheimer's disease (Braak and Braak, 1991) or Parkinson's disease (Halliday

and McCann). Nevertheless, the possibility of a neurodegenerative background of schizophrenia is still favored by some contemporary researchers (Lieberman, 1999a; Mathalon et al., 2001). However, to date no clear neuropathological signs of neurodegeneration, e.g. gliosis, have been observed in schizophrenia (Harrison, 1999), which remains the strongest argument against this hypothesis (Marenco and Weinberger, 2000; Weinberger and McClure, 2002).

In contrast, a neurodevelopmental etiology of schizophrenia (Weinberger, 1986, 1987; Lewis and Levitt, 2002) is supported by several lines of evidence. Children, who later develop the disorder, already display behavioral, cognitive and motor abnormalities (Jones et al., 1994; Cannon et al., 1999; Erlenmeyer-Kimling et al., 2000; Cannon et al., 2002b). The rate of minor physical anomalies is increased in patients (Schiffman et al., 2002; Weinberg et al., 2007) especially in the midline (Buckley et al., 2005). Neuropathological studies have reported evidence for disturbances of neuronal migration (Akbarian et al., 1993; Rioux et al., 2003).

Yet, schizophrenia also differs from archetypal neurodevelopmental disorders like mental retardation or autism spectrum disorders, which have a very early onset but a steadier course. In schizophrenia abnormalities in brain development seem to occur already during pregnancy and around birth, starting as early as the second trimester (Marenco and Weinberger, 2000; Lewis and Levitt, 2002). However, the disruption of later stages of neurodevelopment, for instance cortical maturation during adolescence, also seems to be an important factor (Rapoport et al., 2005).

These findings suggest, that disturbances during subsequent critical stages of brain development in the first two decades of life are responsible for the manifestation of the disorder (Pantelis et al., 2005). Abnormal brain development, which could be the result of both genetic (Jones and Murray, 1991) and environmental influences, is thought to predispose individuals toward the development of schizophrenia through subtle alterations of neuronal circuits and an increased vulnerability to psychosocial stress (Nuechterlein and Dawson, 1984) and other environmental stressors (Andreasen, 1999). This could explain the fact, that in the majority of cases the actual illness manifests only about twenty years after birth. However, the nature of the profound deterioration observed in many patients around illness onset remains unclear.

Explanations of this phenomenon include infectious agents (Torrey and Yolken, 2000) or neurodegeneration (Lieberman, 1999a). The latter hypothesis is based on the finding that the duration of untreated psychosis and the number of relapses into active psychosis are associated with poorer outcome and increasing treatment resistance (Loebel et al., 1992; Lieberman et al., 1993; Lieberman et al., 1996). This could indicate a neurotoxic effect of active psychosis (Wyatt, 1991). On the other hand, this deterioration could be the result of changes in synaptic plasticity (Weinberger and McClure, 2002; McGlashan, 2006).

This controversy illustrates that the complex and variable illness pattern of schizophrenia currently defies any attempts at categorization. Despite the fact, that current evidence favors a neurodevelopmental over a neurodegenerative origin of schizophrenia, so far neither hypothesis has lead to the development of viable treatment options. The pharmacological treatment of schizophrenia is still mostly confined to the use of antipsychotic drugs. However, their development was primarily the result of accidental findings rather than a hypothesis-driven discovery (Iversen and Iversen, 2007). Only the subsequent discovery of their exact mechanism of action, the blockade of dopamine receptors, led to the formulation of the dopamine hypothesis (Carlsson and Lindqvist, 1963; Carlsson and Carlsson, 2006).

1.4 The dopamine hypothesis

Based on the dopamine hypothesis, a final common pathophysiological pathway for schizophrenia has been proposed, namely an increase in striatal dopamine release (Howes and Kapur, 2009). This is supported by several lines of research. Elevated striatal dopamine release seems to develop during the prodromal phase (Howes et al., 2009). It is closely linked to both prodromal symptoms (Howes et al., 2009) and to the positive symptoms of full blown schizophrenia (Hietala et al., 1995; Laruelle and Abi-Dargham, 1999; Laruelle et al., 1999). It is also the primary target of antipsychotic drugs (Farde et al., 1988; Nordstrom et al., 1993).

The mechanism of counteracting this increase in dopaminergic neurotransmission – primarily through dopamine receptor 2 (D2) antagonism and only slightly modified with the introduction of the second-generation

antipsychotic drugs (Miyamoto et al., 2005) – remains the most effective biological treatment for schizophrenia (Lewis and Lieberman, 2000). The close link between abnormal dopaminergic neurotransmission and schizophrenia has been strengthened by a large number of studies, which have illuminated the functional role of dopaminergic signals in the striatum (Berridge and Robinson, 1998; McClure et al., 2003; Schultz, 2007; Duzel et al., 2009) especially its ventral part. The ventral striatum, which includes the nucleus accumbens, is a central part of the reward system (Voorn et al., 2004). Dopaminergic signals in the ventral striatum are closely involved in the reward and reinforcement of behavior (Schultz, 2007). In a broader sense, they are thought to mediate the motivational salience of stimuli and their associations (Berridge and Robinson, 1998), to facilitate the formation of novel associations and to signal their behavioral relevance (Wise, 2004).

According to the influential model by Kapur (Kapur, 2003; Kapur et al., 2005), increased dopaminergic signaling in schizophrenia results in an abnormal sense of novelty as well as an aberrant assignment of salience to external stimuli and internal representations. Within this framework, psychotic symptoms like hallucinations and delusions can be explained as cognitive schemes to explain these experiences of aberrant salience. The model can thus account for the antipsychotic action of antidopaminergic drugs and the general dampening of motivational salience which often coincides with neuroleptic treatment. It also exemplifies, that all currently available antipsychotic drugs are a symptomatic treatment which can only diminish part of the symptoms of schizophrenia.

The dopamine hypothesis has been extended to a model of an imbalance between cortical and striatal dopaminergic neurotransmission (Davis et al., 1991) to incorporate evidence for reduced cortical dopaminergic neurotransmission, primarily through the D1 receptor (Okubo et al., 1997; Abi-Dargham and Moore, 2003). Reduced cortical dopaminergic neurotransmission, particularly in the prefrontal cortex, seems to be related to the negative symptoms of schizophrenia and to cognitive dysfunction (Tamminga, 2006). There is also increasing evidence that it may lead to a disinhibition of dopaminergic neurotransmission in the striatum (Pycock et al., 1980; Meyer-Lindenberg et al., 2002; Winterer and Weinberger, 2004; Meyer-Lindenberg et al., 2005a).

1.5 Abnormalities in other neurotransmitter systems

However, the dopamine hypothesis can only account for some of the clinical aspects of schizophrenia (Howes and Kapur, 2009). Abnormalities in other neurotransmitter systems like serotonin (Geyer and Vollenweider, 2008) and acetylcholine (Lisman et al., 2008) have also been implicated. More importantly, there is strong evidence for a role of glutamate (Moghaddam, 2003; Lewis and Moghaddam, 2006) and γ-aminobutyric acid (GABA) (Lewis et al., 2005) in the pathophysiology of schizophrenia. Changes in glutamatergic neurotransmission have been implicated for quite some time based on evidence that the blockade of N-methyl D-aspartate (NMDA) receptors induces many of the clinical symptoms of schizophrenia including hallucinations, thought disorder and negative symptoms (Javitt, 2004). Both glutamate and GABA are also directly involved in the control of dopaminergic neurotransmission to the striatum (Winterer and Weinberger, 2004). Alterations in both neurotransmitter systems might therefore play a role in the proposed disinhibition of striatal dopamine release. Preliminary clinical trials also indicate that their modulation may have a therapeutic effect in schizophrenia (Patil et al., 2007; Lewis et al., 2008). These neurotransmitter-based models of schizophrenia remain the most important approach for the development of new pharmacological treatment strategies for schizophrenia. Although their relevance is indisputable, these models represent just one important aspect of the disorder.

1.6 The disconnection hypothesis

In contrast, current more universal concepts of schizophrenia have emphasized the role of a widespread disturbance of neuronal connectivity in schizophrenia as the basis of the disorder. According to this so called disconnection hypothesis (Friston, 1998; Andreasen, 1999), the cognitive and psychopathological symptoms of schizophrenia arise due to the disruption of brain circuits both on the micro- and macroscopic level. Such a “disconnection syndrome” provides an elegant conceptual framework which integrates the evidence for a neurodevelopmental etiology with the known neurochemical changes and the phenomenology of the disorder. It is supported by the increasing body of evidence for alterations of white matter in schizophrenia, which indicates a disturbance of both short- and long-range connectivity

(Kubicki et al., 2007). In the context of the disconnection hypothesis, abnormal dopaminergic, glutamatergic and GABAergic neurotransmission represent disturbances of connectivity on the synaptic level (Friston, 1998). Interestingly, disturbances in any of these neurotransmitter systems can to lead to abnormal brain development (Kellendonk et al., 2006; Di Cristo, 2007; du Bois and Huang, 2007). On the other hand, there is also increasing evidence from animal models, that these neurotransmitter systems themselves can be altered by disruptions of normal brain development (Lewis and Levitt, 2002; Di Cristo, 2007). However, in addition to aberrant neurotransmission, disconnection is thought to arise from aberrant brain development through abnormalities in mechanisms such as neuronal migration, synaptogenesis, synaptic pruning and myelination, which on the molecular level are believed to be caused by changes in protein function and gene expression as a result of genetic abnormalities (Andreasen, 1999). This concept implies that a combination of disturbances in a potentially large number of cellular pathways ultimately lead to the full-blown disconnection syndrome.

1.7 Genetics of schizophrenia

This is also well in line with the notion that the genetic architecture of schizophrenia is extremely complex (Gottesman and Shields, 1967). It is now well established, that schizophrenia has a strong genetic background, with an estimated average heritability of about eighty percent (Cardno et al., 1999; Owen et al., 2003). Relatives of patients have an elevated risk for developing schizophrenia or schizophrenia spectrum disorders, which is directly associated with the degree of biological relatedness, i.e. the amount of shared genes (Gottesman, 1991). It should be noted however, that even for a monozygotic twin of a schizophrenic patient the risk only approaches fifty percent (Gottesman and Shields, 1972; Gottesman, 1991) and that about sixty percent of all patients do not have a first- or second-degree relative with the disorder (Gottesman and Erlenmeyer-Kimling, 2001).

These findings highlight the importance of environmental risk factors (Tsuang et al., 2001) for the etiology of schizophrenia. Furthermore, it suggests that like other common disorders, e.g. diabetes, coronary artery disease or rheumatoid arthritis, schizophrenia has a complex polygenetic background (Risch and

Baron, 1984; Risch, 2000) except for rare cases of familial schizophrenia (Kendler et al., 1996b). Genetic risk in complex genetic disorders is most likely mediated by a substantial number of genetic variations common in the general population, the majority of which confer only a slight increase in risk. This implies that no particular genetic constellation will be characteristic of most individuals. However, additive or epistatic interactions between a larger number of these genes (Straub and Weinberger, 2006) as well as gene-environment interactions (Nicodemus et al., 2008; van Os et al., 2008) would drastically increase susceptibility for schizophrenia (Gottesman and Shields, 1967).

A number of potential risk genes have been identified, among them neuregulin (NRG1) (Stefansson et al., 2002; Stefansson et al., 2003), dysbindin (DTNBP1) (Straub et al., 2002; Benson et al., 2004), disrupted in schizophrenia 1 (DISC1) (Millar et al., 2000), the brain isoform of K^+ channel KCNH2 (Huffaker et al., 2009), regulator of G protein signaling 4 (RGS4) (Chowdari et al., 2002; Talkowski et al., 2006), metabolic glutamate receptor 3 (GRM3) (Fujii et al., 2003; Egan et al., 2004), D-amino acid oxidase activator (DAOA) (Chumakov et al., 2002), glutamic acid decarboxylase (GAD1) (Addington et al., 2005; Straub et al., 2007), proline dehydrogenase (PRODH) (Liu et al., 2002; Kempf et al., 2008), the dopamine D2 receptor (DRD2) (Glatt et al., 2009) and catechol-O-methyl transferase (COMT) (Egan et al., 2001b). These genes have plausible links to purported illness mechanisms like synaptic transmission or neurodevelopment (Harrison and Owen, 2003; Straub and Weinberger, 2006; Lovestone et al., 2007). However, because effects sizes have been rather small and negative findings for most of these genes have also been reported, their relevance for the pathophysiology of schizophrenia remains uncertain. Allelic diversity and locus heterogeneity across individuals, a typical features of complex genetic disorders, increase the likelihood of false positives and make the unambiguous identification of genetic risk factors considerably more difficult (Straub and Weinberger, 2006).

Only very recently, genome-wide association studies, which include several thousand patients, have reported more robust genetic alterations (International Schizophrenia Consortium, 2008; O'Donovan et al., 2008; Stefansson et al., 2008; Walsh et al., 2008; Green et al., 2009; McCarthy et al., 2009; Purcell et al., 2009; Shi et al., 2009; Nyegaard et al., 2010). Among the potential risk

genes identified in these genome-wide studies, several are involved in brain development, such as Notch homolog 1 (NOTCH1), p21-activated kinase 7 (PAK7), transcription factor 4 (TCF4). Other risk genes seem to be associated either directly or indirectly with neuronal signaling, among them the zinc finger protein 804A (ZNF804A), neurexin-1-alpha (NRXN1), contactin-associated protein-like 2 (CNTNAP2), neurogranin (NRGN) and the alpha 1C subunit of the L type voltage-dependent calcium channel (CACNA1C). There have also been several independent reports of alterations in the major histocompatibility locus (MHC) among these genome wide studies, which supports evidence for a role of the immune system in the etiology of schizophrenia (Eaton et al., 2006).

Interestingly, some of these studies (International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Walsh et al., 2008; McCarthy et al., 2009) reported an association of schizophrenia with rare microduplications and microdeletions of genomic sequences. Compared to single nucleotide polymorphisms (SNPs), these so called copy number variations (CNVs) (Redon et al., 2006) seem to influence the risk for schizophrenia more strongly (Owen et al., 2009). Several CNVs have specifically been associated with rare forms of familial schizophrenia (Xu et al., 2009).

These findings are also in line with a well known association between schizophrenia and the 22q11.2 deletion syndrome, also known as velo-cardio-facial syndrome or DiGeorge syndrome. This rare microdeletion is associated with severe developmental abnormalities such as congenital heart disease, cleft palate and learning disability (Good et al., 1969). It also leads to a 20- to 30-fold increase of risk for schizophrenia (Bassett et al., 2003) and can be found in about 1 percent of patients while its prevalence in the general population is estimated to be about 0.0025 percent (Horowitz et al., 2005). Finally, another severe genetic defect, namely a balanced translocation between chromosomes 1 and 11, which disrupts the DISC1 gene on chromosome 11, also segregates with schizophrenia in a single large Scottish family with a high density of schizophrenia (Millar et al., 2000).

These findings imply a causal role for rare genetic variations with a high penetrance in some forms of the schizophrenia. However rare genetic variation are confined to just a small fraction of cases (Williams et al., 2009). Despite the growing body of evidence for both rare and common genetic variations

associated with schizophrenia, clear molecular pathways have yet to be identified.

1.8 Environmental risk factors

Furthermore, in the vast majority of cases, environmental risk factors also play a crucial role (Tsuang et al., 2001). There is strong evidence for an association of obstetric complications like hypoxia and brain damage (Cannon et al., 2002a), an urban environment during development (Mortensen et al., 1999), migration (Cantor-Graae and Selten, 2005) and cannabis use (Grant et al., 2006) with an increased risk for schizophrenia. Prenatal maternal infections (Babulas et al., 2006), childhood abuse or neglect (Spauwen et al., 2006) and stressful life events (van Os et al., 1994) have also been implicated, although metaanalytical evidence is inconclusive (van Os et al., 2008). Additionally, schizophrenia is more prevalent in developed countries than emerging and poorly developed countries (Saha et al., 2005). Some environmental risk factors, i.e. obstetric complications, can be clearly linked to the hypothesized neurodevelopmental etiology of schizophrenia (Cannon et al., 2002c). There have also been reports of an interaction between adolescent cannabis use and a risk allele in the COMT gene (Caspi et al., 2005). In most cases the exact pathophysiological mechanisms of environmental risk factors – especially their interaction with genetic risk factors – remain elusive (Caspi and Moffitt, 2006; van Os et al., 2008). Knowledge about these mechanisms would be crucial for prevention and treatment of schizophrenia (McGrath, 2007).

1.9 The relationship between genotype and phenotype

However, identifying genetic and environmental risk factors for schizophrenia as well as their interactions critically depends on a clearly defined phenotype. It has repeatedly been noted, that the phenomenology of schizophrenia, which forms the basis of its current diagnostic criteria does not characterize such suitable phenotypes. The fact, that the clinical symptoms of schizophrenia do not seem to properly reflect the underlying pathophysiology, is regarded as a major obstacle for research in this area (Gottesman and Gould, 2003; Heinrichs, 2004).

This problem is not surprising, given the heterogeneous nature of schizophrenia. Likewise, schizophrenia susceptibility genes do not code for psychopathological symptoms but rather for alterations in protein function and expression which lead to changes in brain circuits and ultimately brain function (Meyer-Lindenberg and Weinberger, 2006). Furthermore, epigenetic alterations which partly mediate the impact of environmental risk factors should have similar effects. The relationship between these abnormalities at the molecular level and psychopathology is most likely very complex and indirect, which might in many cases obscure associations with genetic and nongenetic risk factors (Gottesman and Gould, 2003).

1.10 Structural neuroimaging and schizophrenia

To get a more complete understanding of the pathophysiology of schizophrenia, the use of neuroimaging for the in vivo study of the underlying brain changes is crucial.

Since the first computer aided tomography studies, which reported enlarged ventricular size in chronic schizophrenia (Johnstone et al., 1976; Weinberger et al., 1979), structural neuroimaging has provided increasingly detailed insights into the structural brain alterations associated with schizophrenia, particularly since the advent of magnetic resonance imaging (MRI). In addition to ventricular enlargement, these include volume reductions in the medial temporal lobe, particularly in the hippocampus, in the superior temporal gyrus, in the frontal and parietal lobe and in thalamus but increased volume of the basal ganglia (Shenton et al., 2001).

Changes in cortical volume can already be found during the prodromal phase (Pantelis et al., 2003; Borgwardt et al., 2007), in neuroleptic naïve patients (Gur et al., 1999), in schizophrenia spectrum disorders (Dickey et al., 1999; Dickey et al., 2002; Koo et al., 2006) and in unaffected relatives (Staal et al., 2000; Cannon et al., 2002c; Gogtay et al., 2003). There is also evidence for a progression of these structural abnormalities in the first years of illness (Kasai et al., 2003a; Kasai et al., 2003b; Salisbury et al., 2007; Takahashi et al., 2009), which correlates with the clinical and functional deterioration that occurs during this time period (Lieberman et al., 2001; Ho et al., 2003). Furthermore, a number of studies have demonstrated a widespread reduction of cortical

thickness (Thompson et al., 2001; Kuperberg et al., 2003; Narr et al., 2005; Goldman et al., 2009), which also appears to be progressive (Thompson et al., 2001).

The observation of disseminated and progressive structural abnormalities particularly during the early stages of the disorder has important implications for pathophysiological models of schizophrenia. Similar to the clinical and functional deterioration, they have been interpreted as evidence for a neurodegenerative process (Lieberman et al., 2001; Csernansky, 2007). As outlined above, this hypothesis is not supported by neuropathological evidence (Harrison, 1999). Following its increase during childhood, a widespread gradual decline of gray matter volume after its peak at the inception of puberty, seems to be a central mechanism of normal brain development (Paus, 2005). Interestingly, animal models have provided clear evidence for the distributed and delayed effects of disruptions in specific brain structures like hippocampus during early brain development on brain maturation and function (Tseng et al., 2009). It has been proposed that environmental factors like hypoxia during birth, infections or stress could interact with genetic alterations to affect neuronal migration and plasticity, synaptic pruning and axonal myelination in schizophrenia (Lewis and Levitt, 2002; Weinberger and McClure, 2002; Pantelis et al., 2005). Abnormal neurodevelopmental trajectories triggered by these factors might thus underlie the apparent excessive loss of gray matter observed in schizophrenia. This hypothesis is supported by neuropathological evidence of a decrease in dendritic spine density (Garey et al., 1998), neuropil (Selemon et al., 1995) and synaptic markers (Eastwood et al., 2000). Still, it remains unclear, how these changes could lead to a measurable decrease in cortical volume in schizophrenia, because even the neurobiological underpinnings of the physiological decline of cortical volume remain poorly understood (Paus et al., 2008).

However, these neurodevelopmental abnormalities, especially decreased synaptic density, could lead to a disturbance of neuronal communication as implied by the disconnection hypothesis.

Structural neuroimaging studies also indicate that the asymmetric organization of the planum temporale, which appears to underlie the typical left hemispheric dominance for language (Geschwind and Levitsky, 1968; Geschwind and

Galaburda, 1985), is disturbed in schizophrenia. In patients, the typical gray matter volume asymmetry of the planum temporale appears to be attenuated or even reversed (Kwon et al., 1999; Hirayasu et al., 2000). Abnormalities of planum temporale asymmetry have been linked to impaired language processing (Crow, 2008) and the severity of auditory hallucinations (Oertel et al., 2010). Additionally, the normal torque of the right frontal and left occipital petalias also appears be reduced or reversed in schizophrenia (Bilder et al., 1994; Sharma et al., 1999). Reduced or reversed asymmetry has also been observed in other cortical areas (Bilder et al., 1994; Narr et al., 2001). Interestingly, relatives of patients with schizophrenia show similar but less pronounced changes of cortical asymmetry in the planum temporale (Oertel et al., 2010) and other cortical structures (Sharma et al., 1999). These findings have contributed to the influential theory that schizophrenia arises due to a genetically mediated failure of normal cerebral lateralization (Crow, 2000, 2008).

Another important structural neuroimaging method is diffusion tensor imaging (DTI). DTI enables researchers to detect white matter tracts due to their inherent restriction of water diffusion. It has been increasingly used to detect changes of structural connectivity in schizophrenia (Kubicki et al., 2007). These studies have provided evidence for a widespread disruption of structural connectivity affecting frontal, temporal, parietal and occipital cortex (Kyriakopoulos and Frangou, 2009) in support of the disconnection hypothesis. There is also preliminary evidence for disturbances of white matter integrity in schizophrenia spectrum disorders (Nakamura et al., 2005) and in unaffected relatives (Hao et al., 2009). So far, compared to studies on gray matter abnormalities, results from DTI studies have been less consistent (Kanaan et al., 2005; Kyriakopoulos and Frangou, 2009). Part of this inconsistency may be attributable to methodological problems concerning spatial resolution and analysis algorithms (Kanaan et al., 2005; Kyriakopoulos and Frangou, 2009), and further advances in this field should lead to a much clearer picture of white matter changes in schizophrenia.

1.11 Cognitive dysfunction in schizophrenia

Although structural brain alterations are undoubtedly an important aspect of schizophrenia, the disorder is ultimately characterized by abnormal brain function (Andreasen, 1999). This is underscored by the profound level of cognitive impairment typically observed. Patients with schizophrenia consistently score about one and a half standard deviations lower than healthy controls in tests of a wide variety of cognitive functions including attention, executive function, verbal fluency, working and long-term memory (Gruzelier et al., 1988; Braff et al., 1991; Gold et al., 1999; Mohamed et al., 1999; Bilder et al., 2000; Kuperberg and Heckers, 2000) independent of medication status (Saykin et al., 1994). Not surprisingly, impaired cognition strongly influences a patient's level of functioning and quality of life, and has a greater predictive value for the long-term outcome of schizophrenia than most clinical symptoms (Green, 1996; Green et al., 2000; Kuperberg and Heckers, 2000; Bowie et al., 2006).

Cognitive deficits can already be observed during the prodromal phase (Hambrecht et al., 2002; Hawkins et al., 2004; Keefe et al., 2006; Lencz et al., 2006) even before the emergence of overt psychopathology (Reichenberg et al., 2002; Reichenberg et al., 2005; Osler et al., 2007). After the initial decline they remain largely unchanged throughout the course of the illness even after positive symptoms might have subsided (Heaton et al., 2001). Impairments in cognitive function are also present to a lesser extent in patients with schizophrenia spectrum disorders (Farmer et al., 2000; Voglmaier et al., 2000) and in patients' siblings, especially in first-degree relatives (Cannon et al., 1994; Hans et al., 1999; Egan et al., 2001a; Schubert and McNeil, 2005).

The abnormal neuropsychological profile of schizophrenia had been known for a long time (Chapman, 1979). Nevertheless, cognitive dysfunction has only more recently been recognized as a cardinal feature of schizophrenia (Andreasen, 1999). The timing of onset of cognitive deficits in schizophrenia many years before any signs of illness, their presence in unaffected relatives and their stability over the course of the illness clearly indicate that they are not a secondary consequence of the disorder. Rather they can be regarded as a direct consequence of abnormal brain function and a primary correlate of the pathophysiology of schizophrenia (Andreasen, 1999).

Although structural brain changes have in some cases been linked in a plausible way to cognitive impairments (Onitsuka et al., 2003; Antonova et al., 2005), in most cases the relationship between brain structure and function is a complex one. Structural neuroimaging techniques provide at best indirect information about the functional organization of the human brain and its disturbance in schizophrenia.

1.12 Functional neuroimaging in schizophrenia

In order to directly study the complex and dynamic brain circuits, which support human cognition, functional neuroimaging methods such as single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), electroencephalography (EEG) or magnetoencephalography (MEG), are required. They allow to measure brain activation noninvasively either indirectly through metabolic (SPECT, PET) or neurovascular (fMRI) signals, or directly (EEG, MEG).

Metabolic neuroimaging studies of schizophrenia were the first to provide direct evidence of altered brain function in schizophrenia. Due to the severely limited temporal and poor spatial resolution of SPECT, PET and similar methods, these studies predominantly reported static dysfunctions in circumscribed brain regions such as the prefrontal cortex (Berman et al., 1986; Weinberger et al., 1986) and the hippocampus (Heckers et al., 1998). In some cases these regional abnormalities were associated with the clinical symptoms. For instance, a correlation between prefrontal hypoactivation and the severity of negative symptoms (Volkow et al., 1987; Wolkin et al., 1992) and global cognitive functioning (Paulman et al., 1990) was demonstrated. Also, a correlation between activation in the left parahippocampal gyrus and global psychopathology was observed (Friston et al., 1992).

This approach was strongly influenced by neuropsychological theories derived from the study of patients with circumscribed brain lesions. This was also reflected in the cognitive paradigms employed, i.e. the Wisconsin Card Sorting Test (Weinberger et al., 1986) and the Tower of London (Andreasen et al., 1992). Similarly, schizophrenia was conceptualized as the result of focal brain “lesions”. For instance, the influential “hypofrontality” theory implicated a general hypometabolism of the prefrontal cortex as a crucial neurophysiological

mechanism of schizophrenia and as the central cause for impaired executive function and negative symptoms (Weinberger and Berman, 1988).

The dramatic increase of knowledge about human brain function over the past two decades spurred by the advances in the field of cognitive neuroscience has led to a refinement of these models and the emergence of the disconnection hypothesis. Advances in the field of functional neuroimaging, particularly the advent of fMRI (Ogawa et al., 1990) have also contributed to this development. Many of the molecular disturbances related to altered neuronal connectivity in schizophrenia, e.g. changes at the synaptic level, elude the currently available structural neuroimaging techniques. In contrast, the neurophysiological correlates of altered connectivity can be assessed more easily with functional neuroimaging methods (Petersson et al., 1999; Friston, 2002; Goebel et al., 2003; Horwitz, 2003; Koenig et al., 2005).

These techniques and can provide very detailed information about the functional architecture and the temporal dynamics of brain networks and their disturbance in schizophrenia.

1.13 Functional neuroimaging techniques

1.13.1 Electroencephalography

The EEG signal is typically recorded with scalp electrodes and provides the most direct measurement of neuronal activity of all functional neuroimaging techniques (Berger, 1938). It reflects the summation of the synchronous activity of many thousands of neurons which share a similar spatial orientation. The main contribution to the EEG signal comes from post-synaptic potentials generated by dendrites located in the superficial cortical layers, on gyral crests directly adjacent to the skull, and radial to the skull. In contrast, dendrites, which are located deeper in the cortex, inside sulci, in midline or deep structures, e.g. the hippocampus, or dendrites which produce currents that are tangential to the skull, have far less contribution to the EEG signal. EEG recordings suffer from considerable signal blurring by the tissues between neurons and the scalp electrodes such as the skull and the dura mater and by the cerebrospinal fluid. Overall this results in a poor spatial resolution. Additionally, attempts to localize the sources of the EEG signal suffer from the “inverse problem” posed by the infinite number of source distributions, which can explain the scalp EEG data.

Despite these drawbacks, EEG is ideally suited to study the temporal dynamics of neuronal populations during cognitive processes due to its excellent temporal resolution. For this purpose, event related potentials (ERPs) are the most commonly used method (Coles and Rugg, 1996; Luck, 2005a). They are derived from the averaging of a large number of events – usually more than 100 – in recorded EEGs, i.e. the response to the presentation of a stimulus. It is typically assumed that an ERP represents the sum of individual events that occur with a fixed latency and polarity, independently of the rest of the EEG, and that the averaging process removes background EEG activity, which is considered to be noise (Coles and Rugg, 1996). However, neuronal activity elicited by an external stimulus or a cognitive event is not the only source of ERPs. It has been shown, that multiple independent processes, probably occurring within compact cortical domains, which are partially reset by the occurrence of a stimulus produce averaged ERPs (Makeig et al., 2002; Makeig et al., 2004). Thus, the ERP seems to arise in no small part due to the 'phase resetting' of ongoing EEG activity.

ERPs have been used to study a variety of cognitive processes, such as perception, attention, memory and language processing (Luck, 2005a; Fabiani et al., 2007). A number of different potentials have been identified on the basis of their typical latency, polarity and relationship to specific events.

These include visual EPRs such as the P100 (Hillyard and Munte, 1984; Mangun, 1995), a positive potential, which originates from extrastriate visual cortical areas (Noesselt et al., 2002) with a peak around 80 to 130 milliseconds after the onset of a visual stimulus. The P100 does not reflect the first cortical response to a visual stimulus, which has been linked to the C1 component originating from primary visual cortex (Mangun et al., 1993). However it still seems to reflect an early stage of perceptual processing. Notably, it can already be modulated by selective attention (Hillyard and Munte, 1984) and appears to be caused partly by feedback from higher cortical areas such as prefrontal cortex (Barcelo et al., 2000).

The P300 is another widely studied ERP, which is elicited by infrequent, task-relevant stimuli with a latency of 300 to 600 milliseconds (Ritter and Vaughan, 1969). The P300 is usually elicited using the oddball paradigm in which low-probability target items are inter-mixed with high-probability non-target (or

"standard") items. However, it can also be observed in the context of other cognitive processes. In a broad sense, the P300 is thought to reflect the evaluation or categorization of stimuli (Kok, 2001). It seems to be generated by a number of areas including lateral frontal and parietal cortex (Linden, 2005).
In addition to the classical P300 component, also termed P3b, a slightly earlier P3a component can also be distinguished (Friedman et al., 2001). The P3b component seems to be associated with the cognitive processes of context updating, context closure and event categorization (Kok, 2001). In contrast, the P3a component appears to reflect the orienting response towards a stimulus (Friedman et al., 2001). It has been shown, that the P3b component is mainly generated by parietal and inferior temporal areas, while premotor cortex together with the insula contribute predominantly to the P3a component (Bledowski et al., 2004).
Using the ERP technique allows researchers to investigate different processing stages, e.g. the stages related more to perceptual processing represented by the P100 as well as subsequent stages related more to the cognitive processing represented by the P300 subcomponents, with high temporal resolution and to gain insight into the mental chronometry of cognitive processes such as working memory (Bledowski et al., 2006).

1.13.2 Functional magnetic resonance imaging

In contrast to EEG, fMRI captures neuronal activity indirectly by utilizing the coupling between neuronal activity and hemodynamic in the brain. This is usually accomplished by measuring the blood-oxygenation level dependent (BOLD) effect (Ogawa et al., 1990). The BOLD effect is the result of a local increase of the ratio between oxygenated hemoglobin (HbO2) and deoxygenated hemoglobin (dHb), which differ slightly in their magnetic susceptibility: dHb is paramagnetic and introduces an inhomogeneity into the magnetic field of the surrounding tissue. HbO2 is diamagnetic and has little effect (Ogawa et al., 1990).
In the brain, the ratio between HbO2 and dHb in a blood vessel, in particular in the venoles, is tightly coupled with the energy consumption of adjacent neurons. When activity of neurons increases, their increased energy consumption leads to higher oxygen extraction from the blood vessel. Within the first few seconds

the resulting decrease of diamagnetic HbO2 compared to paramagnetic dHb results in a decrease of the T2* weighted signal used for fMRI measurements. Following this so called initial dip (Buxton, 2001), the increased energy consumption of the neuron leads to a compensatory increase of regional cerebral blood flow. This hemodynamic response alters the relative concentration of HbO2 and dHb in the blood in the favour of HbO2. The relative decrease in dHb associated with neural activity leads to an increase in the local homogeneity of the magnetic field which in turn results in an increase of the T2*-weighted signal. The increased T2*-weighted fMRI signal due to the BOLD effect – also termed the BOLD signal – has been widely used as a measure of the local neural activity.

The BOLD signal has been shown to reliably reflect both increases (Logothetis et al., 2001) and decreases (Shmuel et al., 2002; Shmuel et al., 2006) of neuronal activity. It correlates most strongly with changes in the local field potential (Logothetis et al., 2001), which reflects the synaptic input into an ensemble of neurons, rather than spiking activity. However, our understanding of the biological mechanisms underlying the BOLD signal and neurovascular coupling remains incomplete (Sirotin and Das, 2009).

The main advantage of BOLD fMRI is its excellent spatial resolution, the possibility to study subcortical areas such as the basal ganglia, thalamus or the cerebellum, whose activity cannot be reliably captured with EEG, and the high number of channels that can be recorded simultaneously. However, due to the sluggishness of the hemodynamic response in the order of several seconds and because the BOLD signal integrates over a considerable number of neuronal events, the temporal resolution of BOLD fMRI is quite limited. Additionally, in conventional blocked-design procedures the BOLD signal is temporally integrated across a number of trials, which more or less eliminates the possibility to study the temporal sequence of neuronal events.

The advent of event-related fMRI (Buckner, 1998) has allowed researchers to isolate subcomponents of cognitive tasks and to overcome to a certain degree the limited temporal resolution of BOLD fMRI. This methodological advance has been instrumental in the study of complex cognitive functions such as working memory (Courtney et al., 1997) and long term memory (Brewer et al., 1998; Wagner et al., 1998).

1.13.2.1 Cortex-based intersubject alignment

The comparison of structural and functional MRI data across subjects and across groups of subjects requires a common coordinate system, which accurately co-registers corresponding locations across brains. Three-dimensional normalization methods which align imaging data to Talairach space (Talairach and Tournoux, 1988) or similar coordinate systems are most commonly used. The main advantages of this approach are its ease of use and the possibility to simultaneously co-register all brain structures.

However, three-dimensional normalization methods do not take into account the inherent structure of the cerebral cortex, which in its unfolded state equals that of a two-dimensional sheet several millimeters thick (Fischl et al., 1999a). Due to the columnar organization of the cerebral cortex, many of its functional dimensions such as retinotopy, orientation tuning, ocular dominance, somatotopy and tonotopy, vary predominantly in the two dimensions parallel to its surface (Knudsen et al., 1987). Because of the high degree of “buried” cortex estimated to be in the range of 60 to 70 percent (Van Essen and Drury, 1997), measuring the distance between two points on the cortical surface in 3-D space will in many cases substantially underestimate its real distance along the cortical sheet.

Consequently, the anatomical accuracy, which can be achieved by methods such as normalization to Talairach space, is rather poor. The accuracy of these procedures is further impaired by the considerable between-subject variability in the location of cortical landmarks, which lies in the order of several centimeters even after normalization (Hunton et al., 1996; Van Essen and Drury, 1997). This issue is critical because of the relatively good association of the major gyral and sulcal landmarks with the location of functional areas. Many of these areas are less than two centimeters wide (Fischl et al., 1999b). Therefore in many cases a three-dimensional normalization is not sufficiently accurate to distinguish neighboring but functionally distinct cortical regions. This also limits the probability to detect these areas across subjects in fMRI studies.

This problem is particularly relevant for the study of pathological conditions, which are associated with an abnormally high interindividual anatomical variability. In this case, it represents a systematic confound, which may bias the results of group comparisons. It has been demonstrated, that schizophrenia is

associated with an increased interindividual anatomical variability (Park et al., 2004). Therefore, observations such as decreased activation of the dorsolateral prefrontal cortex in schizophrenia may at least partly be confounded by the anatomical normalization procedure. This may lead to an overestimation of the degree of hypoactivation in patients (Manoach, 2003). It could also cause an artificial group difference or even mask a stronger activation of functionally homologous areas in patients.

Several solutions have been proposed in order to achieve a more precise intersubject alignment. These include the use of high-dimensional warpings which use several million degrees of freedom to morph one three-dimensional anatomical volume into another (Miller et al., 1993b; Ashburner, 2007). However, even such a high degree of three-dimensional warping does not ensure the accurate alignment of the sulcal and gyral folding patterns. Cortical surface based alignment techniques, which use explicit representations of the cortical surface, can overcome this limitation. Some of these methods work with flattened representations, which are aligned by fluid deformation driven by a small number of manually labeled anatomical landmarks (Drury et al., 1998; Van Essen et al., 1998). However, alignment precision for brain regions distant from these landmarks may be suboptimal. This approach also requires a high amount of user interference. Additionally, the creation of these flattened cortical representations without major distortions requires several incisions in the cortical surface. This is problematic, because the exact positions of these incisions greatly affect the outcome of this procedure and because of the difficulty to make these incisions at equivalent points in different subjects.

These methodological difficulties can be avoided by using spherical representations, which respect the topological structure of the original cortical surface and minimize metric distortions (Fischl et al., 1999b). The mapping of cortical representations into a common spherical space also provides a latitude and longitude coordinate system, which indexes the corresponding point on each individual surface. In contrast to a Cartesian coordinate system such as Talairach space, this spherical coordinate system allows to accurately measure the distance between different cortical regions. This way, functional data can also be smoothed without the introduction of noise due to neighboring

noncortical voxels and grey matter voxels, whose proximity in Cartesian space is solely the result of cortical folding.

After the mapping into spherical space, the individual cortical folding patterns are aligned to a target folding pattern, which is typically derived from a single subject. This has been shown to be an effective way to increase the localization accuracy of structural and functional features of the human brain (Fischl et al., 1999b). However, this approach critically depends on the selection of a suitable target folding pattern. Large discrepancies between individual cortical folding patterns and the specified target may lead to suboptimal alignment. Alternatively, the target could be derived from an average of all cortical folding patterns. Although this does not completely eliminate the problem of outliers, it should overall minimize differences between individual cortical folding patterns and the target.

Such an approach has been developed by Goebel et al. (Goebel et al., 2006). It operates in several steps. The folded, topologically correct cortex representation of each hemisphere, which is generated through segmentation and three-dimensional reconstruction, is used as the input of the alignment procedure. Initially, each folded cortex representation is morphed into a spherical representation. This way a parameterizable surface well suited for nonrigid alignment across subjects is generated. Each vertex on the sphere, i.e. in the spherical coordinate system, corresponds to a vertex of the folded cortex, i.e. in the Cartesian coordinate system, and vice versa. This way the curvature information of the folded representation is preserved on the spherical representation. The curvature information containing the sulcal and gyral folding pattern is smoothed along the surface to provide spatially extended gradient information. This information drives the intercortex alignment which aims to minimize the mean squared differences between the curvature of a source and a target sphere.

The alignment itself is achieved by an iterative procedure following a coarse-to-fine matching strategy. It starts with highly smoothed curvature maps and progresses to only slightly smoothed curvature representations. Starting with a coarse alignment as provided by Talairach space, this ensures that the smoothed curvatures of the two cortices overlap sufficiently for a locally operating gradient-descent procedure to converge without user interference.

A moving target group averaging approach is used, which does not require the selection of a specific target sphere. Rather, a “moving target brain” is computed repeatedly during the alignment process as the average curvature across all hemispheres at a given alignment stage. This procedure starts with the coarsest curvature maps. The next finer curvature maps are used and averaged with the obtained alignment result of the previous level. Finally, the established correspondence mapping between cortical vertices is used to align the subjects’ functional data.

This completely data-driven method reliably aligns the cortical folding patterns across subject, leading to a substantial increase in the alignment precision of both structural and functional MRI data (Goebel et al., 2006). The use of this method should minimize the impact of increased anatomical variability in patients with schizophrenia and should decrease the likelihood of an artificial hypoactivation in patients as a result of this confound. It could also help to localize dysfunctional cortical areas more precisely, which might in turn inform post-mortem studies searching for changes in cytoarchitecture (Harrison, 1999) and gene expression (Mirnics et al., 2001).

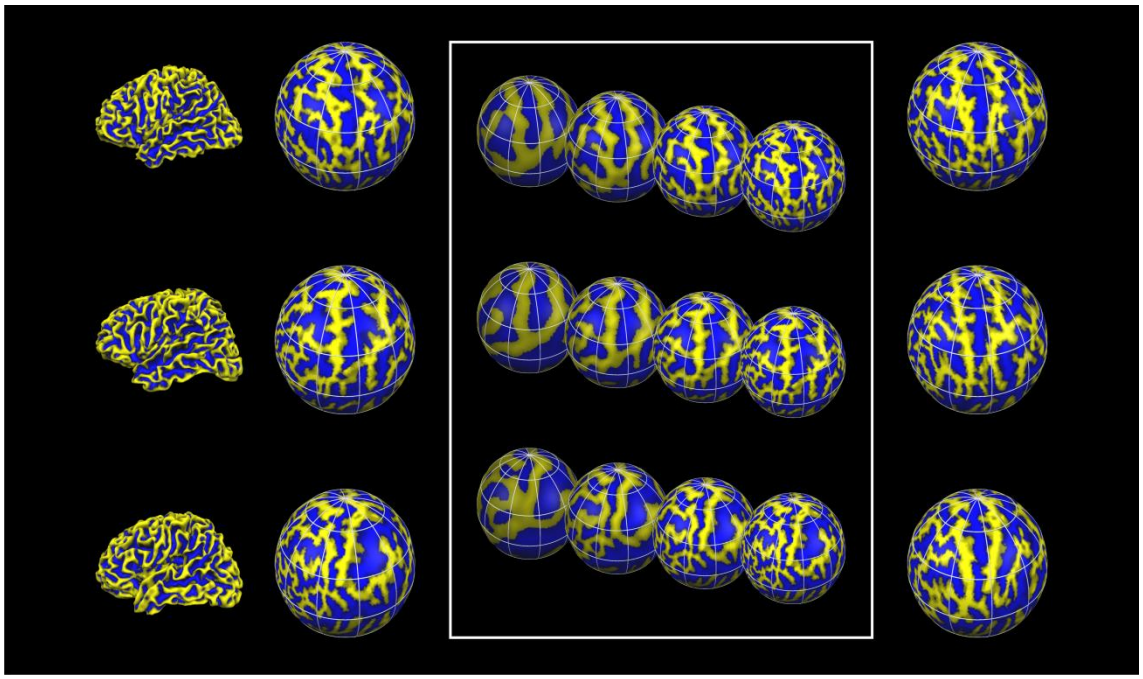

Figure 1. Cortex-based intersubject alignment.

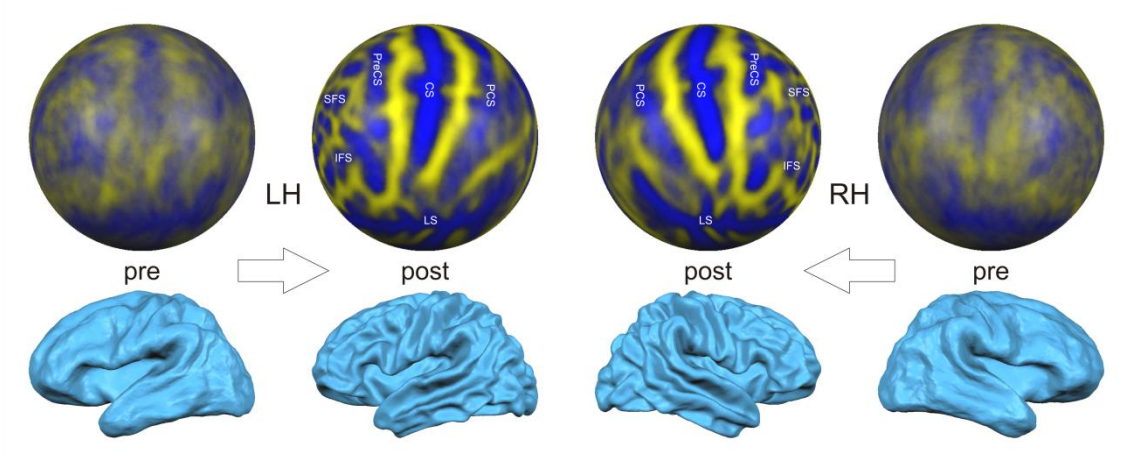

Figure 2. Effects of cortex-based intersubject aligment.

1.13.2.2 Measuring functional connectivity

In addition to studying where in the brain information is processed, i.e. functional segregation, fMRI is also increasingly used to investigate interactions between activated brain regions, i.e. functional integration. Because brain function relies on the coordinated interaction of neuronal populations in distributed networks, the possibility to investigate brain connectivity with fMRI (Horwitz, 1991; Friston et al., 1995; McIntosh and Gonzales-Lima, 1995; Buchel and Friston, 2000) constitutes a significant methodological advance. Importantly, changes in brain connectivity may be particularly sensitive to pathological brain alterations found in psychiatric disorders such as schizophrenia (Meyer-Lindenberg, 2009). In the light of the disconnection hypothesis, this is especially relevant for the study of schizophrenia.

In functional neuroimaging, two forms of connectivity can been distinguished: functional and effective connectivity. Functional connectivity can be defined as “the temporal correlations between remote neurophysiological events” (Friston et al., 1995), whereas effective connectivity refers to “the influence one neural system exerts over another” (Friston et al., 1995).

Granger causality mapping (Goebel et al., 2003; Roebroeck et al., 2005) has been proposed a method to study both functional and effective connectivity using fMRI. This approach is based on Granger causality (Granger, 1969, 1980), a technique which was originally developed for economics. It allows to determine, whether one time series is useful in forecasting another. In the

context of fMRI these time series x[n] and y[n] are taken from two different brain regions or voxels. If incorporating past values of x improves the prediction of the current value of y, it can be said that x Granger causes y.

It has to be noted however, that despite its name, Granger causality does not imply true causality. If both X and Y were driven by a common third process, their measure of Granger causality might still be statistically significant, but manipulation of one process would not change the other. In its original form, it was designed to handle pairs of variables, and may produce misleading results when the true relationship involves three or more variables. However, it can be extended to cases involving more variables using vector autoregression.

This approach has been implemented by Roebroeck et al. (Roebroeck et al., 2005). Here, the discrete zero-mean vector time-series x[n] = (x1[n], . . . , xM[n])T is modeled as a vector autoregressive (VAR) process of order p (Kay, 1988):

Equation 1:
$$x[n] = -\sum_{i=1}^{p} A[i]x[n-i] + u[n]$$

where u[n] is (multivariate) white noise. The matrices A[i] are called the autoregression coefficients because they regress x[n] onto its own past. The VAR model can be thought of as a linear prediction model that predicts the current value of x[n] based on a linear combination of the most recent past p values. Consequently, the current value of a component xi[n] is predicted based on a linear combination of its own past values and the past values of the other components. This shows the value of the VAR model in quantifying Granger causality between (groups of) components.

Granger causality uses temporal precedence to identify the direction of causality from information in the data. Thus, given two time series x[n] and y[n], one can independently identify both influence from x to y, and influence in the reverse direction with suitable models. A measure of linear dependence Fx,y between x[n] and y[n] has been proposed by Geweke (Geweke, 1982) which implements Granger causality in terms of VAR models.

Geweke's dependence measure Fx,y can be defined using the (zero-lag) autocorrelation matrices of the residuals of the following three VAR models involving the K-dimensional series x[n] and L-dimensional series y[n]:

Equation 2: $$x[n] = -\sum_{i=1}^{p} A_x[i]x[n-i] + u[n] \quad \text{var}(u[n]) = \sum_1$$

Equation 3: $$y[n] = -\sum_{i=1}^{p} A_y[i]y[n-i] + v[n] \quad \text{var}(v[n]) = T_1$$

and with

Equation 4: $$q[n] = \begin{bmatrix} x[n] \\ y[n] \end{bmatrix}:$$

Equation 5: $$q[n] = -\sum_{i=1}^{p} A_q[i]q[n-i] + w[n] \quad \text{var}(w[n]) = Y$$

$$= \begin{bmatrix} \sum_2 & C \\ C^T & T_2 \end{bmatrix}$$

where q[n] is O-dimensional (with O = K + L), ∑1 and ∑2 are K by K, T1 and T2 are L by L, and Y is O by O. Although both x[n] and y[n] can both be vector time series, they are typically both scalar time series, that is, K = L = 1. The residual correlation matrices ∑1, ∑2, and Y, quantify how well current values of x and y can be predicted from their past values. The measures of total linear dependence between x and y, linear influence from x to y, linear influence from y to x, and instantaneous influence between x and y are defined to be, respectively (Geweke, 1982):

Equation 6: $$F_{x,y} = \ln(|\sum_1| \cdot |T_1|/|Y|)$$

Equation 7: $$F_{x \to y} = \ln(|T_1|/|T_2|)$$

Equation 8: $$F_{y \to x} = \ln(|\sum_1|/|\sum_2|)$$

Equation 9: $$F_{xy} = \ln(|\sum_2| \cdot |T_2|/|Y|)$$

where |∑| is the determinant of ∑. From these definitions, it can be seen that it holds that:

Equation 10: $$F_{x,y} = F_{x \to y} + F_{y \to x} + F_{x.y}$$

Fx,y is a measure of the total linear dependence between the time series x and y. If nothing of the value at a given instant of one time series can be explained by a linear model containing all the values (past, present, and future) of the other time series, Fx,y will equal zero. Fx→y is a measure of linear directed influence from x to y. If past values of x improve the prediction of the current

value of y, then $F_{x\rightarrow y} > 0$. A similar interpretation applies to $F_{y\rightarrow x}$. Thus, the two directed components, $F_{x\rightarrow y}$ and $F_{y\rightarrow x}$, use the arrow of time to decide on the direction of influence.

It has to be noted though, that in most cases the total linear dependence between x and y does not consist fully of these directed components. A large portion of the total linear dependence can be contained in the undirected instantaneous influence $F_{x.y}$ between x and y. $F_{x.y}$ quantifies the enhancement in the prediction of the current value of x (or y) by including the current value of y (or x) in a linear model already containing the past values of x and y. $F_{x.y}$ represents residual correlations in the data that cannot be assigned to causally directed influence based on the information in the data. In practice, nonzero values of $F_{x.y}$ can be caused by directed influence between x and y at a finer time-scale than that at which x and y are observed (Granger, 1969, 1980).

While it has been shown in simulations, that Granger causality mapping is able to detect directed influence between neuronal populations in the fMRI signal to some extent even in these cases, the sensitivity to such interactions decreases with increasing sampling interval (Roebroeck et al., 2005). For typical fMRI experiments, during which the whole brain is scanned this implies that if the TR approaches 2000 ms, $F_{x\rightarrow y}$ and $F_{y\rightarrow x}$ approach zero and $F_{x,y}$ is exclusively determined by the instantaneous term $F_{x.y}$. Since $F_{x.y}$ does not contain information about the directionality of influence, $F_{x,y}$ only provides a measure of functional connectivity.

One important characteristic of Granger causality mapping is its exploratory nature. It assesses the strength of connectivity between a brain region of interest and every other brain voxel, without making any a priori assumptions about the underlying brain networks. In contrast, other techniques such as structural equation modeling (McIntosh and Gonzales-Lima, 1994; Buchel and Friston, 1997) or dynamic causal modeling (Friston et al., 2003) require the pre-selection of the interacting regions as well as assumptions about the existence and direction of influence between any two regions. While these pre-specified models can be used to test a specific hypothesis regarding interactions between a particular set of brain regions, a misspecification of these models such as the omission of an area, which mediates or initiates interactions, may result in erroneous conclusions (Roebroeck et al., 2009). Thus, the results of these

types of analyses are limited by the quality of the underlying connectivity models. Given the heterogeneity of findings regarding aberrant structural connectivity (Kyriakopoulos and Frangou, 2009) in schizophrenia, the empirical basis for the generation of suitable models for functional or effective connectivity studies is most likely insufficient. The exploratory approach of Granger causality mapping should therefore be particularly suited to study the relationship between abnormal connectivity and cognitive dysfunction in schizophrenia.

1.14 Working memory

To use these functional neuroimaging methods to full effect in the study of cognitive dysfunction, it is crucial to identify those cognitive impairments, which are the most relevant for schizophrenia and provide the most information about the underlying neurophysiological abnormalities. Disturbances in working memory are widely regarded as such a core cognitive deficit (Goldman-Rakic, 1994; Silver et al., 2003; Lee and Park, 2005). Working memory is an essential cognitive ability, which allows individuals to transiently store a limited amount of information for further cognitive processing (Atkinson and Shiffrin, 1968; Baddeley and Hitch, 1974; Baddeley, 1992). In their influential model Baddeley and Hitch have proposed the existence of two content specific storage systems for visuospatial and verbal information, i.e. the visuospatial sketch pad and the phonological loop (Baddeley and Hitch, 1974). Both buffers have been partitioned into a passive store, which decays over time, and an active rehearsal mechanism used to refresh this decaying information. According to the model of Baddeley and Hitch, both the visuospatial sketch pad and the phonological loop are under the control of the central executive a third element of the model with limited attentional capacity. Subsequently, a fourth element in the form of the episodic buffer has been added (Baddeley, 2000), which is forms an interface between the phonological loop, the visuospatial sketchpad and long term memory. It is thought to subserve the storage of integrated material, e.g. events or scenes, in a multimodal code. Another influential theory has been developed by Cowan (Cowan, 1999, 2001). Cowan emphasizes the essential role of attention for working memory. According to his model, working

memory operates by bringing and holding information stored in long-term memory into the focus of attention.

These theories underscore the cognitive complexity of working memory. Furthermore, a number of component processes can also be distinguished. Independent of the type of information, working memory always involves the encoding, maintenance and retrieval of information. This is exemplified by the task developed by Sternberg (Sternberg, 1966). In this classical paradigm subjects were shown a series of digits for 1.2 seconds each, which had to be maintained in memory for 2 seconds. After this delay period a test digit was presented, which could either be novel or match one of the previously shown digits. Variations of this paradigm have been widely used in working memory research including functional neuroimaging studies.

Working memory forms the basis for a number of higher order cognitive processes such as learning and language (Baddeley, 2003). Consequently, working memory dysfunction in schizophrenia might account for a number of deficits in related cognitive processes (Silver et al., 2003). However, the presence of differential cognitive deficits in domains such as working memory in schizophrenia has been challenged. It has been argued, that such an observation might be an artifact of differences in discriminating power of the tasks used to asses different cognitive functions coupled with a generalized cognitive impairment of the patients (Chapman and Chapman, 1973). The use of cognitive models and experimental paradigms generated by cognitive psychologists, and the carefull definition of cognitive processes based on these models has been proposed as a solution to overcome this problem (Knight and Silverstein, 2001). This approach has been successfully used to identify areas of preserved cognitive function in schizophrenia (Gold et al., 2009), which argues against the existence of a generalized cognitive deficit.

Working memory impairment is closely linked to a number of key findings in schizophrenia. There is a large body of evidence (Fuster and Alexander, 1971; Goldman-Rakic, 1995; Cohen et al., 1997; Courtney et al., 1997; Goldman-Rakic, 1999; D'Esposito et al., 2000) which indicates that the prefrontal cortex is a key region supporting working memory. The dopaminergic modulation of prefrontal neurons also appears to be a crucial mechanism for the successful maintenance of information in working memory (Goldman-Rakic, 1995; Wang et

al., 2004). For that reason, working memory deficits have long been particularly associated with prefrontal cortical dysfunction and disturbances in prefrontal dopaminergic neurotransmission (Goldman-Rakic, 1999; Weinberger et al., 2001). This has led to the view, that the executive component of working memory is predominantly impaired (Tan et al., 2007). The focus on the prefrontal cortex is somewhat reminiscent of the early “neuropsychological” models of schizophrenia. These models may not be sufficient to explain working memory dysfunction in schizophrenia, because they considerably underestimate the cognitive and neurophysiological complexity of working memory. An alternative approach is to focus on the component processes of working memory.

1.15 Outline of studies

The studies presented in the following three chapters aim to elucidate the neurophysiological mechanisms underlying the working memory component processes of encoding, maintenance and retrieval and their dysfunction in schizophrenia. All studies employ a modified version of the Sternberg paradigm (Sternberg, 1966) using abstract visual shapes.

The first study investigates the neurophysiological substrates of visual working memory capacity and its limitations in healthy subjects during encoding, maintenance and retrieval using event-related fMRI. Working memory capacity limitations place severe constraints on human cognition by restricting the amount of information that can be held in working memory. Illuminating the neurophysiological mechanisms of this phenomenon is crucial for a better understanding of both intact cognition as well as cognitive dysfunction in schizophrenia.

The second study examines the contribution of early perceptual processing deficits during encoding and retrieval to working memory dysfunction in patients with schizophrenia compared to healthy control subjects using EEG and event-related fMRI. The detailed perceptual processing of information is an important prerequisite for the successful encoding of information into working memory. The same applies to the comparison of information stored in working memory with newly presented information. Therefore, disturbances of the early stages of perceptual processing in schizophrenia might impair working memory. This

would provide a link between deficits in basic perceptual and higher order cognitive processes found in schizophrenia.

The third study, which is based on the same data set as the second study, investigates abnormal cortical activity and connectivity in patients with schizophrenia compared to healthy control subjects during the working memory component processes of encoding, maintenance and retrieval using event-related fMRI. There is increasing evidence from behavioral studies, that working memory dysfunction is caused by deficits during both working memory encoding and working memory maintenance. Clarifying the role of dysfunctions in prefrontal and other cortical areas as well as the role of abnormal functional connectivity in these impairments is essential in order to reconcile behavioral and neurophysiological models of working memory dysfunction.

Chapter 2: Experiment 1

Cortical Capacity Constraints for Visual Working Memory: Dissociation of fMRI Load Effects in a Fronto-parietal Network

Based on:
Linden D.E., Bittner R.A., Muckli L., Waltz J.A., Kriegeskorte N., Goebel R., Singer W., Munk M.H.J. *Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network.* Neuroimage. 2003 Nov;20(3):1518-30.

2.1 Abstract

Working memory capacity limitations and their neurophysiological correlates are of special relevance for the understanding of higher cognitive functions. Evidence from behavioral studies suggests that restricted attentional resources contribute to these capacity limitations. In an event-related functional magnetic resonance imaging (fMRI) study, we probed the capacity of the human visual working memory system for up to four complex non-natural objects using a delayed discrimination task (DDT).

A number of prefrontal and parietal areas bilaterally showed increased blood oxygen level-dependent (BOLD) activity, relative to baseline, throughout the task when more than one object had to be held in memory. Monotonic increases in response to memory load were observed bilaterally in the dorsolateral prefrontal cortex (DLPFC) and the pre-supplementary motor area (pre-SMA). Conversely, activity in the frontal eye fields (FEF) and in areas along the intraparietal sulcus (IPS) peaked when subjects had to maintain only two or three objects and decreased in the highest load condition.

This dissociation of memory load effects on cortical activity suggests that the cognitive operations subserved by the IPS and FEF, which are most likely related to attention, fail to support visual working memory when the capacity limit is approached. The correlation of brain activity with performance implies that only the operations performed by the DLPFC and pre-SMA, which support an integrated representation of visual information, helped subjects to maintain a reasonable level of performance in the highest load condition. These results indicate that at least two distinct cortical subsystems are recruited for visual

working memory, and that their interplay changes when the capacity limit is reached.

2.2 Introduction

Working memory is thought to be an essential cognitive ability that allows the encoding and storing of information for short periods of time, thus making it available for manipulation and for the active guidance of behavior (Baddeley, 1992). Electrophysiological studies in monkeys (Fuster and Alexander, 1971; Funahashi et al., 1989; Miller et al., 1996; Pesaran et al., 2002) along with functional neuroimaging studies in humans (Cohen et al., 1997; Courtney et al., 1997; Smith and Jonides, 1999) have identified a distributed network of cortical areas engaged during working memory tasks including areas in the dorsolateral and ventrolateral prefrontal cortex (DLPFC, VLPFC) and the superior and inferior parietal lobule (SPL, IPL). Whether these areas display a functional segregation according to the type of information to be stored remains controversial.

While some studies have found differences in the recruitment of dorsal and ventral lateral prefrontal areas for the storage of visuospatial and object features, respectively (for review, see (Haxby et al., 2000; Levy and Goldman-Rakic, 2000)) others have found such a segregation for the type of processing required (e.g., manipulation versus maintenance), rather than the memoranda (for review see (D'Esposito et al., 2000; Owen, 2000)). For the posterior cortex, a dissociation of visual stimulus processing into a dorsal (occipitoparietal) stream for spatial and motion information and a ventral (occipitotemporal) stream for object characteristics has been confirmed in numerous studies on humans and non-human primates (for review see (Ungerleider and Haxby, 1994)). This dissociation has also been found in the encoding phase of human working memory studies (Munk et al., 2002), with inferior temporal areas more responsive to object features and parietal areas more responsive to locations. Regarding the delay phase of working memory tasks, sustained parietal activation was found when the spatial layout of a stimulus display had to be remembered (Munk et al., 2002), while sustained medial temporal activation was observed in a face memory task (Ranganath and D'Esposito, 2001). For other classes of visual objects, evidence for sustained temporal activation, as could be expected on the basis of monkey electrophysiology (Miller et al., 1993a), is still lacking.

One central characteristic of working memory is its limited capacity. While Miller originally proposed that this capacity is seven plus or minus two chunks (Miller, 1956), a large body of evidence indicates that the actual storage size in humans is restricted to about four items (Luck and Vogel, 1997; Cowan, 2001; Wheeler and Treisman, 2002). Whereas functional imaging has contributed greatly to the question of where in the brain different classes and features of visual objects are stored and manipulated, the neurophysiological basis of working memory capacity limitations is still poorly understood. Functional imaging studies that used a parametric variation of memory load in n-back tasks (Braver et al., 1997; Cohen et al., 1997) have found corresponding increases in prefrontal activation. However, in order to distinguish the brain activation patterns related to encoding and retention with fMRI, delayed discrimination tasks (DDT) are often used in a trial-based design (Zarahn et al., 1997). A number of fMRI studies that varied the memory load of a DDT have also found increases of activity mainly in prefrontal areas (Rypma and D'Esposito, 1999; Rypma et al., 2002). Yet, it has been suggested that BOLD activity might decline again under conditions of high working memory demand (Callicott et al., 1999). Such an “inverted U-shape” response has also been implicated in the limitation of the capacity to shift visual attention (Beauchamp et al., 2001). A global decrease in activation in conditions of high memory or attentional demand is difficult to interpret because it might merely indicate that the subjects were not equally engaged by the task, perhaps due to frustration with their declining performance. Local decreases, however, especially when accompanied by continuous increases in other areas, could inform us about the localization of capacity constraints and potential compensatory strategy shifts.

A number of previous behavioral and neuroimaging studies provide indications as to where in the working memory network such decreases might be observed when the memory capacity limit is approached. Several models implicate restricted attentional resources as a cause for working memory capacity constraints (Cowan, 2001; Kane et al., 2001; Wheeler and Treisman, 2002). It has also been shown that visual attention is particularly sensitive to interference from working memory requirements in conditions of high memory load (de Fockert et al., 2001). One way to overcome limits in the sequential attentional scanning of visual objects would be to form symbolic representations of the

visual material especially in the high memory load conditions. This would lead to increased prefrontal activation, which has also been reported for supracapacity verbal memory conditions (Rypma and Gabrieli, 2001), while activation of the classical visual attention-related network comprising the posterior parietal cortex and the frontal eye fields (Corbetta et al., 1998; Goebel et al., 1998; Culham et al., 2001; Yantis et al., 2002), would decrease as the capacity limit is approached.

In the present fMRI study, we therefore used a delayed visual discrimination task with parametric variation of memory load from one to four objects. We presented complex non-natural shapes that could not easily be verbalized in order to reduce the immediate accessibility of symbolic representations and increase the demand on visual attention. We expected to observe a monotonic increase of reaction times and drop of accuracy with increasing memory load and a dissociation of monotonic increases and inverted U-shape patterns of the BOLD signal according to the hypotheses laid out in the preceding paragraph.

2.3 Methods

2.3.1 Subjects

All twelve subjects (eight males, four females) were right-handed and had no history of neurological or psychiatric disorder. The mean age was 27.3 years (SD: 2.4 years, age range: 24 to 31 years). All subjects gave written informed consent to participate in the study.

2.3.2 Behavioral task

A delayed visual discrimination task was implemented on a personal computer using custom-developed software (Figure 1*A*). Non-natural objects (BORTS: blurred outlines of random tetris shapes), presented on the center of the computer monitor, were used as visual stimuli. One to four sample objects were presented for 500ms each (*encoding* phase). Thus the length of the encoding phase varied between 500 and 2000ms. After a delay of 12s (*delay* phase), a test stimulus was presented for 2s at the center of the monitor (*retrieval* phase). Subjects responded with a left or right hand button press to indicate a test that matched or did not match one of the sample objects. The inter-trial interval lasted between 8s and 9.5 s, ensuring that a new trial would start every 24 seconds. The experiment was preceded by a training session which allowed subjects to complete as many trials as necessary to familiarize themselves with the structure and timing of the task. During scanning, the computer display was projected onto a mirror mounted on the head coil. Stimuli subtended 4° of visual angle. Subject's responses were registered by a custom-made fiber-optic response box. Subjects were asked to fixate upon the cross at the center of the monitor throughout the experiment. Each of the subjects completed 96 trials of the DDT (24 for each of the four memory load conditions) during fMRI data acquisition. Eye movement control was performed with separate electroencephalographic recording sessions on 4 of the subjects (for EEG/EOG parameters see (Linden et al., 1999)).

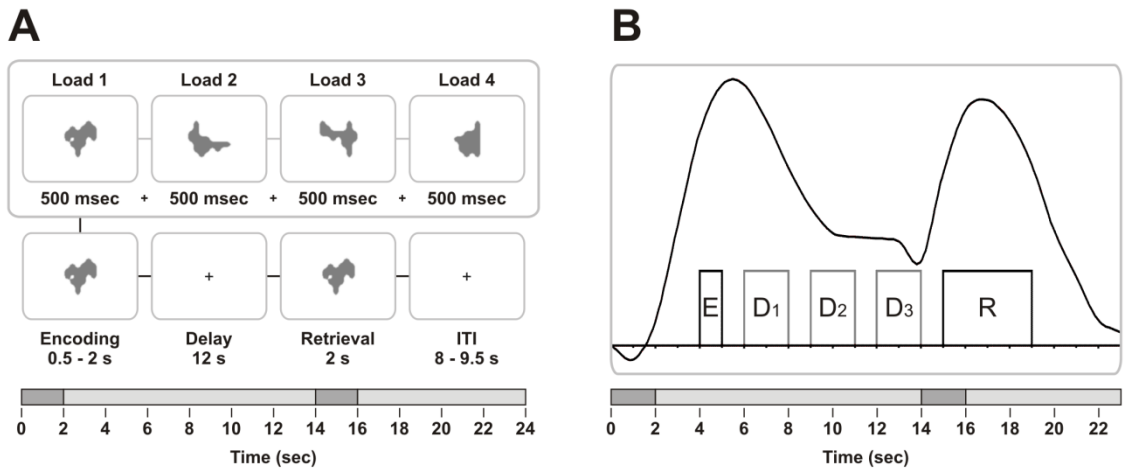

Figure 1. Paradigm and design matrix. *A*: The delayed visual discrimination task. Non-natural objects (blurred outlines of random tetris shapes: BORTS) were used as stimuli. Load was varied by presenting one to four objects for 500msec each for encoding. After a 12s delay interval a probe stimulus was presented for 2s and subjects had to judge by button press whether it was part of the sample set. *B*: Predictors modeling the different task phases shifted by 4s. The graph represents a paradigmatic time course from right IPS. E: encoding; $D_{1,2,3}$: early, middle, late delay; R: retrieval.

2.3.3 Analysis of behavioral data

Values for accuracy and reaction times were compared between memory load conditions with an analysis of variance (ANOVA). The number of stored items was calculated for individual behavioral data according to Pashler's method for estimating memory capacity (Pashler, 1988; Luck and Vogel, 1997):

$$s = n\frac{(h-g)}{(1-g)}$$

with s being the number of stored items, n the number of items in the display (1 in memory load 1, 2 in memory load 2 etc.), h the hit rate (correctly identified matches), g the rate of false alarms (non-matches incorrectly identified as matches).

2.3.4 fMRI data acquisition

fMRI data were acquired with a Siemens 1.5 T Magnetom Vision MRI scanner using a gradient echo EPI sequence (8 axial slices; TR = 1000ms; TE = 60; FA = 90°, FOV = 210 x 210 mm^2, voxel size: 3.1x3.1x7 mm^3). Functional images were acquired in four runs in a single session. Each run comprised the acquisition of 580 volumes and contained 24 trials (6 of each memory load condition). The slices covered large parts of the occipital, temporal, parietal, and frontal lobes (z coordinate range from -5 to 45 at y=-50 and from 10 to 65 at

y=20, Talairach coordinates). Stimulus presentation was synchronized with the fMRI sequence at the beginning of each run. Each scanning session included the acquisition of a high-resolution T1-weighted three-dimensional volume (voxel size: 1x1x1 mm^3) for co-registration and anatomical localization of functional data.

2.3.5 Data preprocessing and cortex based statistics

Functional data were preprocessed and analyzed using the BrainVoyager 4.9 package (www.brainvoyager.com). The first four volumes of each run were discarded to allow for T1 equilibration. 3D motion correction and Talairach transformation was performed for the remaining set of functional data of each subject. Data pre-processing furthermore comprised spatial smoothing with a Gaussian kernel (FWHM=8mm), and temporal high pass filtering (high pass: 5 per functional run of 580 volumes). The cortical sheets of the individual subjects were reconstructed as polygon meshes based on the high-resolution T1-weighted structural three-dimensional recordings. The white-gray matter boundary was segmented, reconstructed, smoothed, and morphed (Kriegeskorte and Goebel, 2001). Based on the gray-white matter boundary, a cortex mask for each subject was created, that indexed all grey matter voxels. These twelve individual masks were then combined to produce a group mask.

The cortex based general linear model (GLM) of the experiment was computed from the 48 (12 subjects, four runs per subject) z-normalized volume time courses. For each of the four memory load conditions five task phases were defined representing encoding, early, middle and late delay, and retrieval (Figure 1*B*). The signal values during these phases were considered effects of interest. The corresponding predictors, obtained by shifting an ideal box-car response (assuming a value of 1 for the volumes of the respective task phase and a value of 0 for the remaining time points) by four seconds to account for the hemodynamic delay, were used to build the design matrix of the experiment. The delay phase was modeled by three predictors of 3s duration each. This approach was chosen in order to avoid an overlap with the ascending slope of retrieval-related BOLD activity (Figs. 1*B*, 5). The retrieval phase was modeled by one predictor of 5s (although test stimulus presentation was only 2s) in order to cover the entire task period without gaps and to capture fully the BOLD

response evoked by the test stimulus (Figure 1*B*). The global level of the signal time-courses in each session was considered to be a confounding effect, and a fixed effects analysis was employed. Effects are only shown, if the associated p value yielded p' < 0.05. The obtained p-values were corrected for multiple comparisons using a cortex-based Bonferroni adjustment, i.e., the number of comparisons considered was reduced by limiting the analysis to gray matter voxels, as defined by the group mask (Trojano et al., 2000; Muckli et al., 2002). The resulting 3D statistical maps for the predictors of the higher memory load conditions (memory load 2-4) were projected on the flattened surface reconstruction of a template brain (courtesy of the MNI). Each of the maps was associated with a color of the red-green-blue (RGB) system (*red:* memory load 2; *green:* memory load 3; *blue:* memory load 4). Colors were superimposed and areas of overlap (cortical regions showing activation during more than one condition) received the appropriate mixed color. The resulting *superposition maps* enabled us to display those areas particularly involved in the maintenance of multiple objects and to illustrate changes in the degree of activation and the extent of recruitment of these areas for the different memory load conditions and phases of the experiment. Four maps were created, showing activity during encoding, early delay, middle and late delay, and retrieval. Analysis of middle and late delay were combined in order to maximize statistical power for the detection of delay activity under the assumption that these predictors, in a box car model like ours, capture activity uncontaminated by encoding or retrieval (Figure 1*B*) (Zarahn et al., 1997; Rypma et al., 2002).

2.3.6 Load-response functions

Load response functions were created for the cortical areas revealed by the superposition map of the middle and late delay predictors, i.e. those areas that were most closely associated with the maintenance of the stimuli. However, in order to assess the memory load-dependent activity at encoding in the inferior temporal cortex (which did not show sustained activity), the cluster selection for this area was based on the encoding map. The beta values of the encoding and all delay predictors (corrected for serial correlations) were plotted to visualize effects of memory load. Contrasts between predictors of each memory load condition were calculated with Student's t-test ($p<0.05$).

2.3.7 Correlation with behavioral data

The individual differences in the number of stored items in memory load conditions three and four, as estimated with Pashler's equation, were correlated with the beta values of individual fMRI data sets (Pearson's correlation coefficient).

2.4 Results

2.4.1 Behavioral data

For the behavioral data recorded during the experiment, the ANOVA revealed a significant main effect of memory load on reaction time and accuracy (Figure 2) ($p<0.05$). Accuracy decreased and reaction times increased monotonically with the number of objects. Reaction times were significantly longer for each increase in memory load. Accuracy was significantly lower for memory load three and four than for memory load one and two. However, even in the highest memory load condition, accuracy was above chance level (mean accuracy 67.0%, SEM 10%), indicating that subjects were still engaged in the task. The number of stored items (mean of individual subjects/ SEM) for the four memory load conditions was as follows: 0.93/0.09 (memory load one); 1.60/0.26 (memory load two); 1.91/0.54 (memory load three); 1.90/0.97 (memory load four).

2.4.2 Eye movements

Horizontal and vertical saccades > 2° were detected and compared between memory load conditions. A Friedman test revealed no significant main effect of memory load (chi-square = 2.036; df = 3; p = 0.565). This result was confirmed by a Kendall-W-test (Kendall-W = 0.170; df = 3; p = 0.565). Each possible combination of conditions was also compared using the Wilcoxon-test, which showed no significant difference between any pair of conditions.

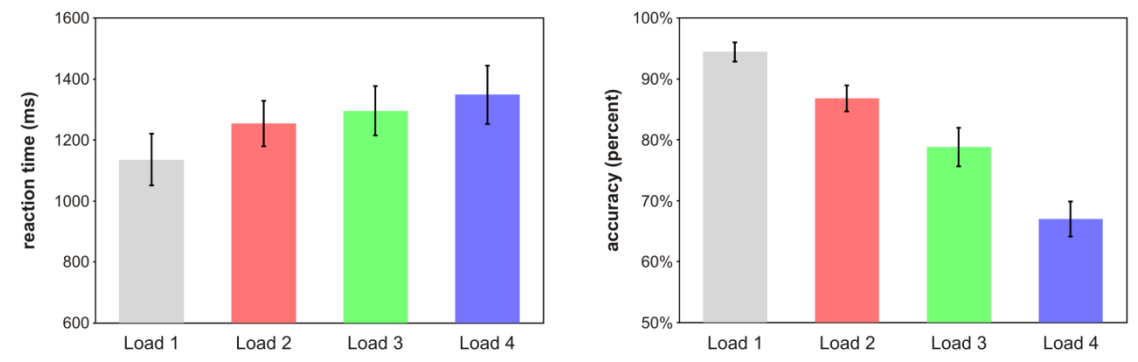

Figure 2. Behavioral data. Reaction times and accuracy plotted against memory load conditions. Error bars indicate standard error of the mean.

2.4.3 Encoding activity

The *superposition map* of the encoding predictors (Figure 3*C*) shows activation in a widespread cortical network of early and higher visual areas that included the occipitotemporal and occipitoparietal pathways. Bilateral activation was also observed in the IPS, the FEF, the SMA and the prefrontal cortex.

2.4.4 Delay activity

The *superposition map* of the early delay predictor (Figure 3*D*) shows a pattern of activity very similar to encoding. A sub-set of the fronto-parietal network remained active during the middle and late delay, including the IPS, the left POS, the left SMG and the right PCS in the parietal lobe, as well as the DLFPC, FEF, SMA and pre-SMA bilaterally in the frontal lobe (Table 1). The color-coding of the memory load conditions with significant beta values reveals a segregation of areas where more variance was explained by the memory load 4 predictor (DLFPC and pre-SMA bilaterally) and areas where more variance was explained by the memory load 2 or 3 predictors (parietal areas, FEF, SMA) (Table 2).

Region of activation	Left/ right	From Map	Cluster size (voxels)	Talairach coordinates (mm)			Brodmann area
				x	y	z	
IT	L	Encoding	5867	-40	-64	-6	19/37
	R		5383	46	-61	1	37
DLPFC	L	Middle & late delay	9546	-37	15	30	9
	R		1990	32	28	33	9
FEF	L		2112	-25	-10	52	6
	R		823	25	-11	50	6
pre-SMA	L		164	-6	17	41	6/32
	R		173	8	12	37	6/32
SMA	L		1905	-6	-2	49	6
	R		265	10	-4	42	6
RS	L		394	-49	4	30	4/6
PCS	R		1096	33	-34	40	2
SMG	L		732	-44	-44	37	40
IPS	L		2516	-36	-47	41	19/40
	L		992	-28	-64	35	19
	R		977	33	-46	42	19/40
POS	L		804	-18	-68	35	19

Table 1. Talairach coordinates. Values are given for clusters from the middle and late delay surface map shown in **Figure 3** (and of the IT cluster from the encoding map).

2.4.5 Retrieval activity

The *superposition map* of the retrieval predictor (Figure 3*F*) shows widespread activation in occipitotemporal, frontal and parietal cortex. The prominent bilateral sensorimotor cortex activity is most probably related to the button presses.

2.4.5 Load response functions

The load response functions (LRFs) revealed a principal difference in the amount of cortical activation between the single and multiple object conditions (Figure 4). This was confirmed by the corresponding beta value contrasts (Table 2). Two main types of LRFs were identified: a *memory load-dependent monotonic increase* with a significant increase in activity beyond memory load two and a peak at memory load four (Figure 4*A,C*), and an *inverted U-shape response* with a peak at memory load two or three and a significant decrease towards the highest memory load conditions (Figure 4*B*). During encoding, a monotonic increase was observed most prominently in IT, while the parietal cortex and FEF demonstrated an inverted U-shape response. During delay, a monotonic increase was observed in the DLFPC and pre-SMA bilaterally, while an inverted U-shape response was found in IPS and FEF bilaterally. A similar pattern was observed for retrieval. Selected time courses of BOLD signal change are shown for left DLFPC and left FEF (Figure 5) in order to illustrate the time courses of memory load effects at finer temporal resolution.

2.4.6 Correlation of BOLD signal and behavioral data

The correlation of the difference in stored items in memory load conditions three and four with that of the beta values at the single subject level yielded a significant correlation ($p<0.05$) or trend ($p<0.1$) for left and right DLFPC and pre-SMA, mainly in the early delay. A negative correlation was observed for left and right FEF and IPS, mainly at encoding and during the middle and late delay. Finally a negative correlation in left and right FEF, left IPS but also left DLFPC was found for retrieval (Table 3).

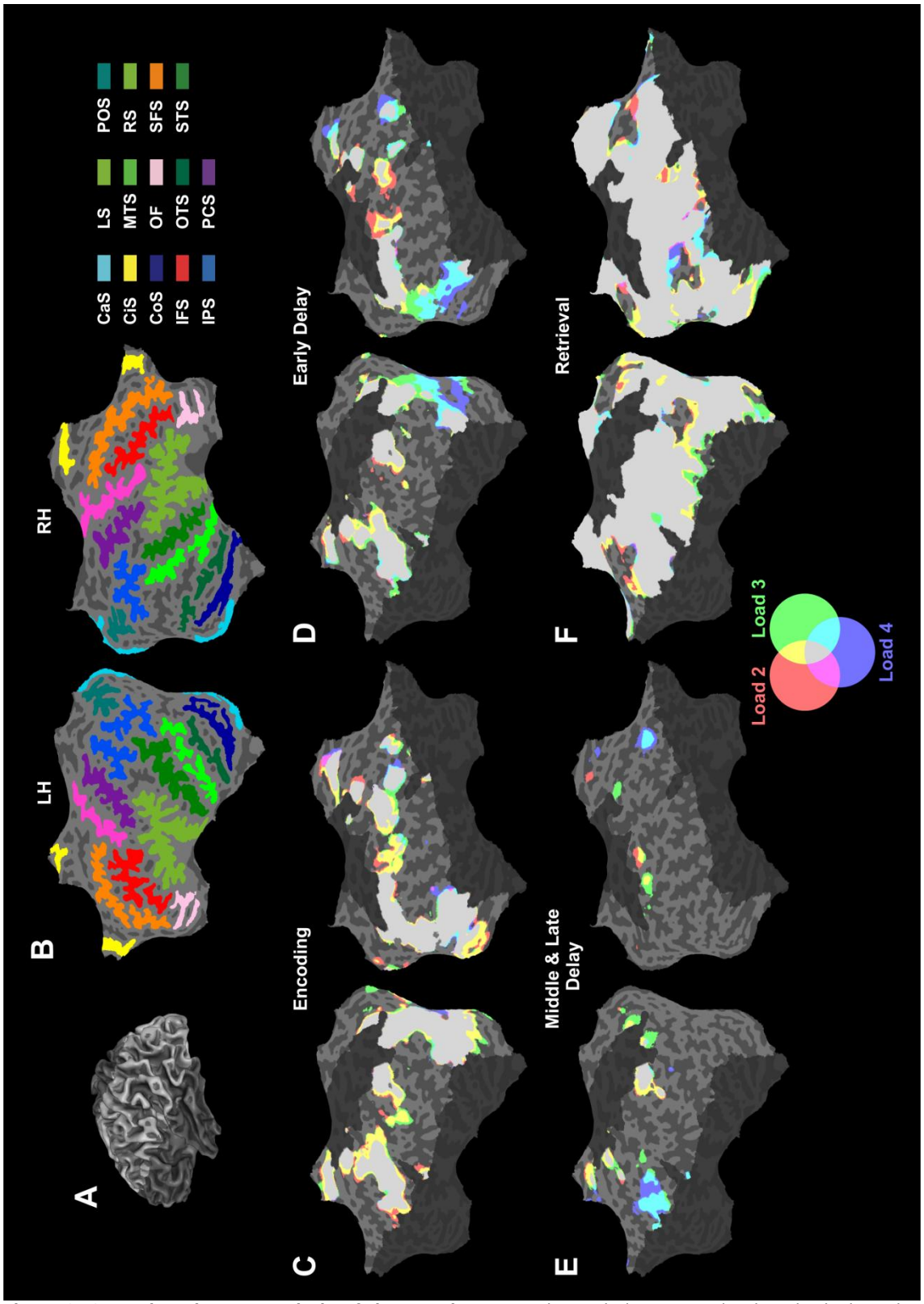

Figure 3. Cortex-based group analysis of the experiment. *A*: The analysis was restricted to the brain region commonly imaged in all twelve subjects (highlighted on each brain or flatmap). *B*: Sulcal topography on the cortical flatmap of the MNI template brain used for visualization. *C-F*: Superposition maps of the predictors modeling higher memory load conditions during encoding, delay and retrieval. Effects were only shown if the associated p value yielded p'<0.05 (corrected for multiple comparisons). The three resulting 3D statistical maps were then projected on the flattened surface reconstruction of the MNI template brain. Each of the maps was associated with a color of the red-green-blue system (red: load 2; green: load 3; blue: load 4). Colors were superimposed and areas of overlap (cortical regions showing activation during more than one condition) received the appropriate mixed color.

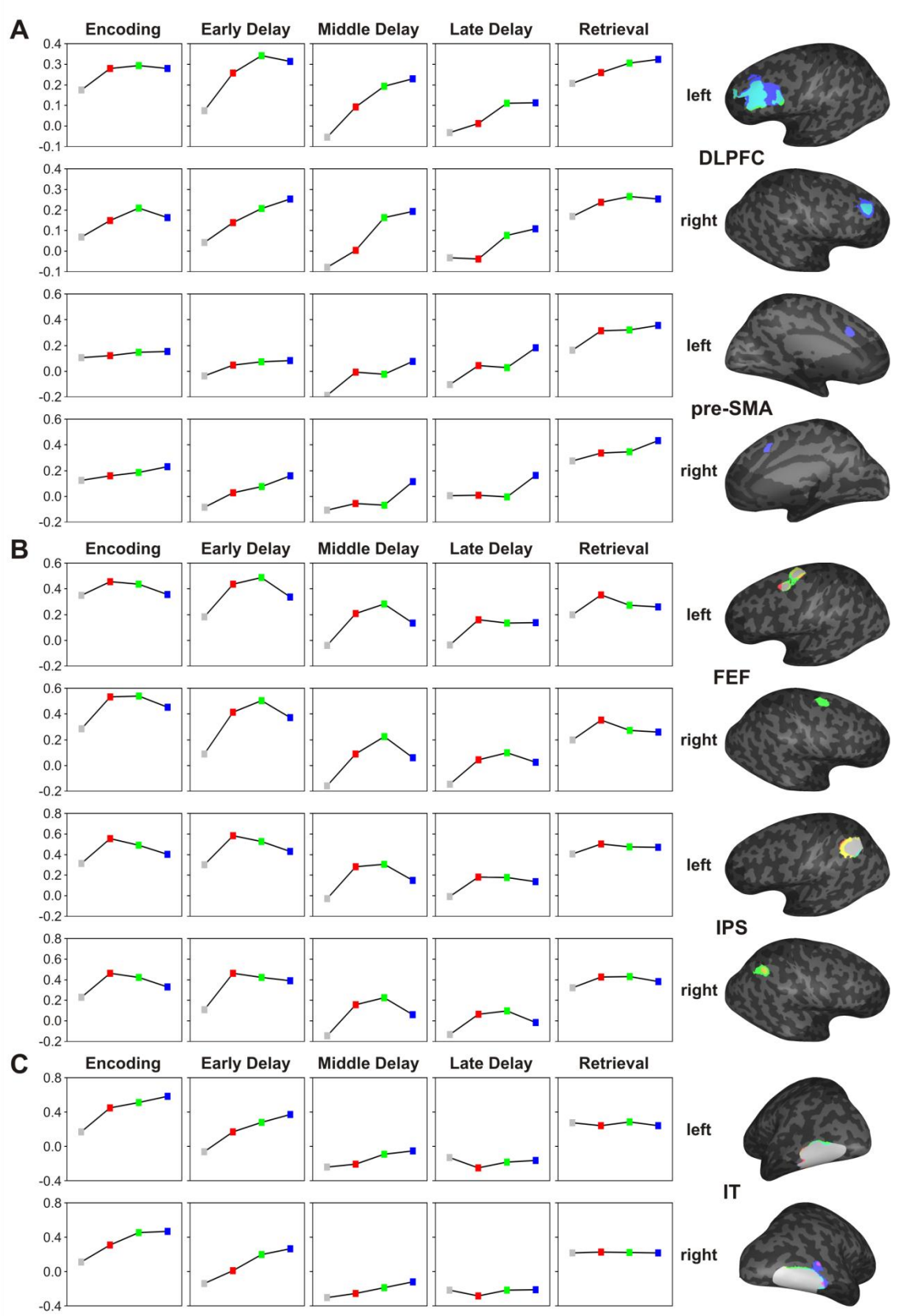

Figure 4. Load response functions. *A*: Response profiles of areas showing a load-dependent monotonic increase during delay. *B*: Response profiles of areas showing an inverted U-shape response. *C*: Response profiles of bilateral IT, showing a load-dependent monotonic increase mainly at encoding. Conditions are coded as follows: load 1: grey, load 2: red, load 3: green, load 4: blue. Regions of interest used for the generation of load response functions are shown on inflated cortical reconstructions of the MNI template brain. The extraction of these regions was based on the superposition maps of encoding (*C*) or middle and late delay respectively (*A* and *B*).

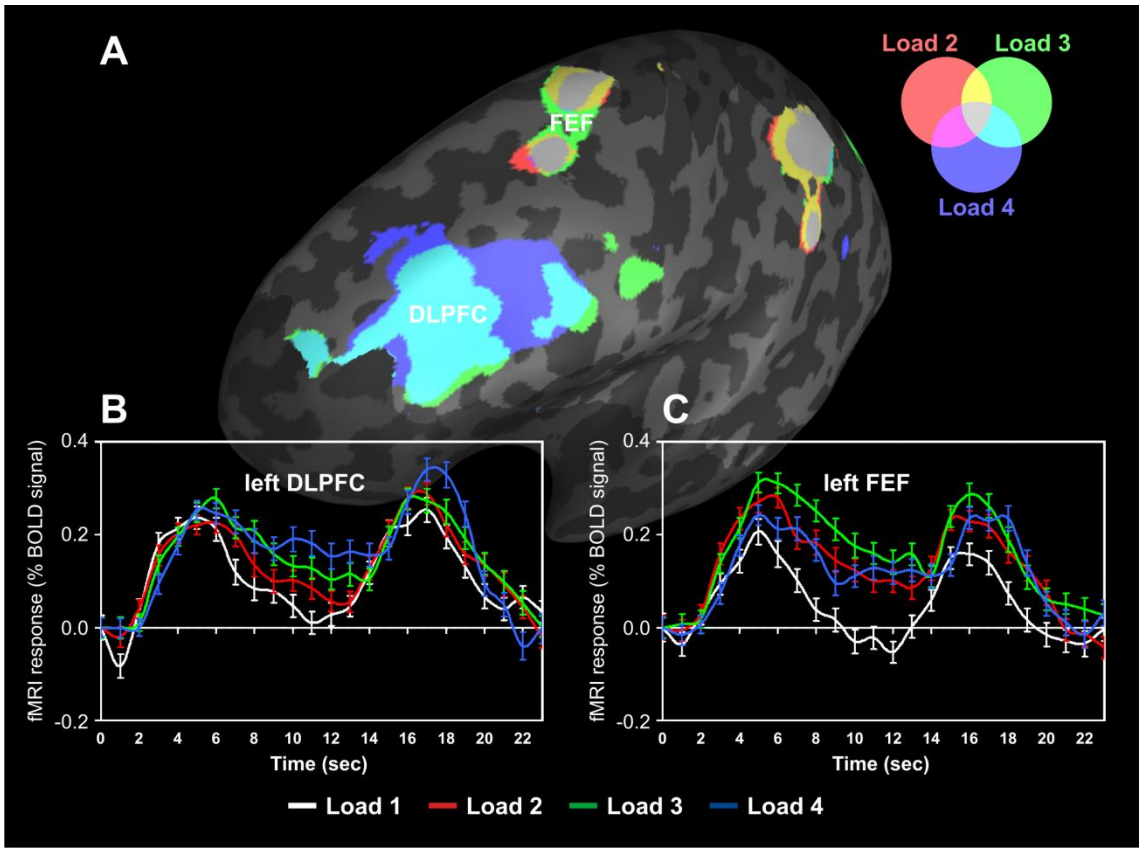

Figure 5. Averaged timecourses. *A*: Regions of interests for which averaged timecourses were derived. *B*: Averaged timecourse of the left DLPFC representative for areas showing a *load-dependent response*. *C*: Averaged timecourse of the left FEF representative for areas showing an *inverted U-shape response*. Conditions are coded as follows: load 1: white, load 2: red, load 3: green, load 4: blue. Error bars indicate standard error of the mean.

	Left DLFPC					Right DLFPC				
	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
4 vs. 3										
4 vs. 2			*0.03*	0.09			0.06	*0.002*	*0.02*	
3 vs. 2			0.09	0.09				*0.009*	0.06	
4 vs. 1	0.07	*10^{-4}*	*10^{-5}*	*0.02*	*0.01*		*0.001*	*10^{-5}*	*0.02*	0.06
3 vs. 1	*0.04*	*10^{-5}*	*10^{-4}*	*0.02*	*0.03*	*0.02*	*0.007*	*10^{-4}*	0.08	*0.04*
2 vs. 1	0.07	*0.002*	*0.02*							

	Left pre-SMA					Right pre-SMA				
	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
4 vs. 3			0.09	*0.008*				*0.002*	*0.005*	*0.05*
4 vs. 2				*0.02*			*0.03*	*0.005*	*0.009*	*0.03*
3 vs. 2									*0.008*	*0.001*
4 vs. 1		*0.05*	*10^{-5}*	*10^{-6}*	*10^{-5}*	0.09	*10^{-4}*	*0.001*		
3 vs. 1		0.07	*0.006*	*0.03*	*0.001*		*0.008*			
2 vs. 1			*0.003*	*0.02*	*0.001*		0.06			

	Left FEF					Right FEF				
	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
4 vs. 3		***0.007***	***0.007***		***0.01***		***0.02***	***0.003***		***0.01***
4 vs. 2		***0.08***			***0.005***					***0.002***
3 vs. 2							0.09	*0.02*		
4 vs. 1		*0.005*	*0.002*	*0.002*		*0.008*	*10^{-6}*	*10^{-4}*	0.003	
3 vs. 1			*10^{-6}*	*0.002*	*0.03*	*10^{-4}*	*10^{-6}*	*10^{-6}*	*10^{-5}*	0.09
2 vs. 1	0.09		*10^{-5}*	*0.001*	*0.02*	*10^{-4}*	*10^{-6}*	*10^{-5}*	*0.001*	*0.03*

	Left IPS					Right IPS				
	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
4 vs. 3		**0.09**	***0.006***					***0.005***	***0.05***	
4 vs. 2	***0.02***	***0.007***	***0.02***			***0.04***		**0.09**		
3 vs. 2										
4 vs. 1		*0.02*	*0.002*	*0.009*	0.09		*10^{-6}*	*0.001*	*0.05*	
3 vs. 1	*0.006*	*10^{-4}*	*10^{-6}*	*0.001*	0.08	*0.003*	*10^{-6}*	*10^{-6}*	*10^{-4}*	*0.007*
2 vs. 1	*10^{-4}*	*10^{-6}*	*10^{-6}*	0.001	*0.02*	*0.001*	*10^{-6}*	*10^{-6}*	*0.001*	*0.01*

	Left IT					Right IT				
	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
4 vs. 3										
4 vs. 2	*0.02*	*0.001*	*0.008*			*0.006*	*10^{-5}*	*0.03*		
3 vs. 2		0.06	*0.05*			*0.01*	*0.002*			
4 vs. 1	*10^{-6}*	*10^{-6}*	*0.002*			*10^{-6}*	*10^{-6}*	*0.002*		
3 vs. 1	*10^{-6}*	*10^{-6}*	*0.01*			*10^{-6}*	*10^{-6}*	*0.04*		
2 vs. 1	*10^{-6}*	*10^{-4}*				*0.001*	*0.009*			

Table 2. Contrasts between the predictors documented in **Figure 4**. The contrasts that reached a p<0.1 are documented. Significant values (p<0.05) are reported in italics. P-values in bold indicate that the beta weight was higher for the lower load condition.

	Encoding	Early Delay	Middle Delay	Late Delay	Retrieval
left DLPFC		0.09			***0.04***
right DLPFC	0.08				
left pre-SMA		0.06			**0.09**
right pre-SMA		*0.02*	*0.04*		
left FEF	**0.08**		**0.06**	***0.03***	***0.03***
right FEF	**0.09**			***0.05***	***0.006***
left IPS	***0.003***		**0.07**	**0.08**	**0.09**
right IPS	***0.02***	***0.04***	***0.05***	***0.05***	
left IT					
right IT					

Table 3. Correlation between behavioral data (change in number of stored items between load three and load four) and individual beta weights. Correlation that reached a p<0.1 are documented. Significant values (p<0.05) are reported in italics. P-values in bold indicate a negative correlation.

2.5 Discussion

The present study used a paradigm involving the manipulation of the number of non-natural objects that had to be stored in visual working memory. We found that activity in the previously described fronto-parietal working memory network was consistently higher in the multiple than in the single object conditions, which conforms to the results of previous fMRI studies (Cohen et al., 1997; Jha and McCarthy, 2000). This effect was present at encoding and continued through the entire delay and retrieval period. However, the amplitude of the BOLD signal (represented by the beta weights of the general linear model of the experiment) did not increase monotonically with memory load in all of these areas. Our hypothesis was confirmed in that we observed dissociation between cortical areas in which activity increased monotonically and areas in which it declined as memory load increased beyond a certain level.

2.5.1 Frontal cortex: DLFPC and pre-SMA

The middle frontal gyri and pre-SMA of both hemispheres showed an increase of the BOLD response with the number of presented objects beyond memory load three and thus did not appear to be influenced by supposed capacity constraints. It has been argued that the regions in lateral prefrontal cortex are likely to subserve the symbolic representation and executive processes required for working memory (Postle et al., 1999; Wagner et al., 2001). A recent study of verbal memory demonstrated increased activity in these areas as a correlate of memory organization processes that facilitated the maintenance of very large amounts of information (Rypma et al., 2002). Increasing prefrontal activation, in both lateral and mesial structures, has been shown previously in conditions of high integrative demand (Prabhakaran et al., 2000). In the highest memory load conditions of our study, subjects might have been forced to rely on the rehearsal of more integrated representations to compensate for their inability to retain the increasing amount of detail in the same manner as they managed to do in the easier conditions.

2.5.2 Frontal cortex: FEF and SMA

The frontal regions showing a decrease in fMRI activity beyond memory load three (and thus an “inverted U-shape” response) were located along the

precentral and superior frontal sulci (presumed site of the human FEF) and in the posterior part of the superior mesial frontal cortex (SMA). Both regions are believed to be part of the cortical system for directing visual attention (Corbetta et al., 1998) and have consistently been found to be active in studies of visual working memory (Postle et al., 2000; Munk et al., 2002). This overlap of cortical networks for visual attention and working memory has been taken as an indication that both cognitive processes rely on shared resources (LaBar et al., 1999). There is indeed converging evidence from functional imaging and behavioral studies that selective attention is crucial for maintenance of information in visual working memory (Awh et al., 1998; Awh and Jonides, 2001; Wheeler and Treisman, 2002). Consistent with our hypothesis, we observed an inverted U-shape pattern of BOLD activity mainly in frontal and parietal (see below) attention-related regions and a negative correlation with performance. This might indicate that subjects reached a limit of their capacity to covertly scan the detailed visual features of the objects and consequently shifted to a different strategy, which relied more on the prefrontal regions that showed a continuing monotonic increase of the BOLD signal. This interpretation is supported by the observation that the “inverted U-shape” pattern, if present at all, started to manifest itself early in the task (encoding or early delay), indicating a failure of the initial scanning process (Figure 4; Table 2).

2.5.3 Parietal cortex

Like the FEF, various parietal regions, mainly along the IPS, showed an “inverted U-shape” pattern of BOLD activity in association with memory load. The IPS is another region, where considerable overlap between attention and working memory-related activity has been demonstrated (LaBar et al., 1999). Several previous fMRI studies of working memory using non-natural geometric stimuli similar to ours also reported substantial activation of parietal regions (Postle and D'Esposito, 1999; Nystrom et al., 2000). The IPS region is believed to play an essential role in the processing of spatial object representations in the absence of visual stimulation (Trojano et al., 2000; Formisano et al., 2002; Sack et al., 2002). The performance of working memory tasks with visual content certainly depends critically on this ability. Additionally, when multiple objects have to be maintained, the shifting of attention between different object

representations becomes crucial, and both the FEF and the IPS have been shown to be highly involved in this process (Goebel et al., 1998; Culham et al., 2001). Thus, the pattern of activity observed in our study might very well reflect a rehearsal procedure involving the repeated covert scanning of multiple objects. Such a strategy places great demands on the attention network. The observation of decreasing parietal activity in the memory load four condition as compared to the memory load three condition during all phases of the delay suggests that both the initial scanning process and the attention-based rehearsal mechanism were affected by capacity limitation.

The absence of parietal inverted U-shape responses in earlier event-related functional imaging studies of memory load effects (e.g.: (Cohen et al., 1997; Jha and McCarthy, 2000; Leung et al., 2002)) might be explained by the less complex visual characteristics of the stimuli used (e.g., letters). Also, the level of difficulty in these studies as indicated by both the number of items to be maintained and the accuracy of the participants was clearly below the level of difficulty in our study. Thus these studies most likely did not reach the capacity limit of working memory.

2.5.4 Temporal cortex

BOLD activity in inferior temporal cortex (IT) was most prominent during the encoding phase and returned to baseline during the middle and late delay, confirming the results of earlier fMRI studies of DDT paradigms (Munk et al., 2002). A memory load-dependent monotonic increase was observed at encoding, indicating that the higher visual areas of the ventral stream, unlike those of the parietal lobe, were able to maintain the same level of visual information processing in the memory load four as in the memory load three condition. Why our and most other fMRI studies of visual working memory did not find sustained activity in the temporal lobe in contrast to single unit recordings (Miller et al., 1993a) remains an open question.

2.5.5 Correlation with behavioral data

We interpret the dissociation of load effects as indicating that subjects compensated for the inability to retain the increasing amount of detail by shifting to more integrated representations. Such an interpretation is supported by the

correlation analyses between BOLD signal time courses and measures of behavior, which showed that the number of items individual subjects were able to store correlated positively with activity in prefrontal areas during delay, while it was inversely correlated to activity in the FEF and parietal lobes. These results confirm previous studies that correlated prefrontal delay activity with subsequent memory performance and also found a positive correlation (Pessoa et al., 2002; Rypma et al., 2002; Sakai et al., 2002). This effect disappeared at retrieval when active rehearsal was not required any more. Instead, we observed a negative correlation between left DLPFC activity and performance. This latter effect is compatible with the observation by Rypma et al. (Rypma and D'Esposito, 1999) that prefrontal retrieval activity is inversely correlated with retrieval performance.

By analyzing the cortical BOLD responses associated with increasing memory load, we found evidence for correlates of capacity limitations in visual working memory. We observed dissociation between brain activity patterns in several prefrontal areas, in which activity continued to increase up to the maximum memory load condition of the paradigm, and regions of the visual attention network, in which activity started to decline as the behavioral capacity limit was approached. While these findings confirm the implicated role of attention as a cause of working memory capacity constraints, the exact influence of attention on working memory is not fully understood. Whether the limits of the attention network, as such, or rather those of the capacity for fronto-parietal cooperation (Sakai et al., 2002), constrain working memory capacity cannot be decided on the basis of the present data. However we were able to show that event-related fMRI can detect gradual changes in activity patterns within distributed cortical networks in response to increasing task demands. With fMRI we can thus study the neural correlates of cognitive capacity limitations. Further studies, combining behavioral and functional imaging techniques, will be needed to explore explicitly the interplay of attention and storage mechanisms in working memory

Chapter 3: Experiment 2

Impaired early-stage visual processing contributes to working memory dysfunction in adolescents with schizophrenia – a study with event-related potentials and functional magnetic resonance imaging

Based on:
Haenschel C., Bittner R.A., Haertling F., Rotarska-Jagiela A., Maurer K., Singer W., Linden D.E. *Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia – a study with event-related potentials and functional magnetic resonance imaging.* Archives of General Psychiatry. 2007 Nov;64(11):1229-40.

3.1 Abstract

Context

Working memory deficits in schizophrenia have mainly been associated with prefrontal dysfunction. However, the contribution of perceptual deficits and abnormalities in sensory areas has not been explored. The present study closes this important gap in our understanding of working memory dysfunction in schizophrenia, by monitoring neural activity during both working memory encoding and retrieval with event-related potentials (ERPs).

Objective

Here we investigate the relationship between the ERP components P1, P3a, P370 and P570 and working memory in early-onset schizophrenia to elucidate the neurophysiological changes contributing to working memory impairment in early-onset schizophrenia at both perceptual and cognitive stages.

Design and Setting

EEG data were acquired during a visual delayed discrimination task. Participants encoded up to three abstract shapes that were presented sequentially for 600 ms each, and decided after a 12 s delay interval, whether a probe matched one of the sample stimuli. We also obtained fMRI data from visual areas from the same participants.

Participants

Seventeen adolescents with early-onset schizophrenia according to DSM-IV and 17 matched controls participated in the study.

Results

P1 amplitude was reduced in patients during encoding and retrieval. The amplitude of the P1 increased with memory load during encoding only in controls. In this group a stronger P1 amplitude increase predicted better working memory performance. The P1 reduction was mirrored by reduced activation of visual areas in patients in fMRI. P370 during encoding and retrieval was also reduced in patients.

Conclusions

P1 reduction indicates an early visual deficit in adolescents with schizophrenia. Our findings suggest that P1 is of particular relevance for successful working memory encoding. Early visual deficits contribute to impaired working memory in schizophrenia in addition to deficits in later memory related processes.

3.2. Introduction

Working memory deficits are a core feature of schizophrenia (Goldman-Rakic, 2001; Silver et al., 2003; Lee and Park, 2005), often develop before the first clinical symptoms (Hambrecht et al., 2002; Wood et al., 2003; Lencz et al., 2006) and also affect first-degree relatives of patients (Park et al., 1995; Conklin et al., 2000). Most studies have focussed on maintenance and executive processes and prefrontal cortex (PFC) dysfunction, which has consistently been reported in functional magnetic resonance imaging (fMRI) studies of patients (Callicott et al., 2000; Barch et al., 2001; Manoach, 2003) and their first-degree relatives (Callicott et al., 2003b).

However, recent behavioural (Tek et al., 2002; Gold et al., 2003; Hartman et al., 2003; Lencz et al., 2003; Lee and Park, 2005; Kim et al., 2006) and fMRI (Cairo et al., 2006; Johnson et al., 2006) evidence indicates that abnormal encoding also contributes to working memory impairment in schizophrenia. Parallel neurophysiological evidence from steady-state visual evoked potentials and time-frequency analysis of EEG signals also indicates dysfunctional early-stage visual processing (Butler et al., 2001; Butler et al., 2005; Uhlhaas et al., 2006).

Here we use event-related potentials (ERPs) in order to distinguish between the mechanisms that reflect different stages of visual working memory, using the temporal resolution of ERPs to probe both the early perceptual stages and the later, memory-related operations (Bledowski et al., 2006).

Early visual processing is related to the P1 component (Luck, 2005b). It indexes the suppression of irrelevant information (Luck et al., 1994; Martinez et al., 2006), a mechanism which seems to be necessary for efficient working memory encoding (Conway et al., 2001). It is also sensitive to spatial attention (Luck et al., 1994; Martinez et al., 2001; Noesselt et al., 2002; Di Russo et al., 2003; Martinez et al., 2006), which is required for subsequent processing of object features (Duncan, 1993). Although the perceptual and cognitive processes probed by the P1 are thus highly relevant in the context of working memory, most previous studies have shown no working memory related P1 amplitude effects (Pratt et al., 1989). Conversely, the classical ERP component associated with memory processes is the P3 (Kok, 2001; Bledowski et al., 2006). The P3 can be divided into a frontocentral P3a and a parietocentral P3b (Squires et al., 1975). The P3a has been regarded as an index of the novelty of information

and may be the neurophysiological correlate of the orienting response (Soltani and Knight, 2000), whereas the P3b is elicited by expected (but rare) task-relevant stimuli (Linden, 2005). The P3b complex is similar during encoding and retrieval in its latency and duration (Wolach and Pratt, 2001). Several studies found that the P3b amplitude decreased and the P3 latency increased with memory load in delayed discrimination tasks like the one used in the present study (Verleger, 1997; Kok, 2001; Bledowski et al., 2006). In contrast to the P3b evoked with oddball paradigms, the P3b elicited by a working memory task can be divided into two peaks – the first reflecting most likely stimulus evaluation and the second consolidation during encoding and template matching during retrieval (Kok, 2001; Bledowski et al., 2006).

The classical view that only late components like the P3 are abnormal in schizophrenia while early visual processing is unimpaired (Vianin et al., 2002; van der Stelt et al., 2004) has recently been challenged (Foxe et al., 2001; Doniger et al., 2002; Butler and Javitt, 2005; Foxe et al., 2005). A growing body of evidence indicates abnormalities in schizophrenia of both the P3 (Roth et al., 1986; Ford et al., 2002; Jeon and Polich, 2003) and changes in early potentials, such as the auditory P50 (Light and Braff, 1998) and the visual P1 (Foxe et al., 2001; Doniger et al., 2002; Butler and Javitt, 2005; Foxe et al., 2005).

To minimize the confounds of chronic illness and long term medication we investigated ERP changes during the performance of a working memory task in adolescents with a recent onset of schizophrenia (mean illness duration 1.4 years). Compared to adult-onset schizophrenia, early-onset schizophrenia (EOS), the manifestation of the illness by the age of 18 (McClellan and McCurry, 1999; Kumra et al., 2004) seems to represent a rarer, more homogeneous form of the disorder with a higher genetic loading (Asarnow et al., 2001) and a more severe and unremitting outcome (Hollis, 2000). Its study might thus lead to more salient and consistent findings.

We investigated ERP responses related to early visual and subsequent memory related processes during working memory encoding and retrieval in adolescent EOS patients. We designed a delayed discrimination task using abstract visual shapes as stimuli and manipulated memory load by varying the number of ‘sample’ stimuli in the encoding period. We focused on the following components: P1, P3a, and the early and late P3b peaks (P370 and P570). We

aimed to identify ERP components sensitive to increasing memory load and group differences and clarify which processing stages are disrupted.

If early perceptual dysfunction contributes to working memory deficits, we expect reduced P1 responses to the sample stimuli. If switching from the encoding of the already presented stimulus (i.e. the first stimulus of load 2 and the first and second stimulus of load 3) to that of the subsequently presented stimuli (i.e. the second stimulus of load 2 and the second and third stimulus of load 3) is impaired, we would expect a reduced P3a to the subsequently presented stimuli in the patient group. If stimulus evaluation or consolidation is abnormal, we expect a reduction in the first or second P3b peak. Furthermore, we assess whether analogous impairments are also present during retrieval.

We were specifically interested in the possible contribution of early visual processing deficits. Given that combined EEG-fMRI analyses have consistently reported P1 generators in the middle occipital gyrus, the fusiform gyrus and posterior temporal areas (Luck et al., 1994; Martinez et al., 2001; Noesselt et al., 2002; Di Russo et al., 2003), we used fMRI, to provide complementary information about group differences in these areas.

3.3 Methods

3.3.1 Participants

Seventeen patients with EOS according to DSM-IV criteria and seventeen control participants (Table 1) participated in the study. DSM-IV diagnosis of schizophrenia was established with the German version of the Structured Clinical Interview for DSM-IV (SCID) (Sass and Wittchen, 2003) and by thorough chart review. Current psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients with a history of substance abuse in the 6 months preceding the study or those with additional neuropsychiatric diagnoses were excluded from the study. Seventeen control participants matched for age, gender, handedness and premorbid IQ were recruited through local advertisements. Controls with a history of mental illness or substance abuse were excluded. All participants and, for participants under 18 years, parents provided informed consent prior to the study. Ethical approval was obtained from the local ethics committee.

Variable	Patients (n=17)	Controls (n=17)	*P* Value
Age (range)	17.9 (15.2–20.4)	17.5 (15.1–19.9)	$t_{(32)}$=0.87, p=0.48
Sex (male/female)	11/6	11/6	χ^2 (1)=0, p=1
Handedness (right/left)	13/4	13/4	χ^2 (1)=0, p=1
Mean Premorbid IQ	96 (SD 16)	97 (9)	$t_{(32)}$=-0.21, p=0.83
Years of Illness	1.4 (SD 0.9)		
Age at Onset	16.5 (SD 1.2)		
Mean PANSS Score	44.92 (SD 18.38)		
Antipsychotic Medication:	Quetiapine 10; Risperidone 2; Clozapine 1; Olanzapine 1; Aripiprazole 2; Perphenazine 1;		
Mean Chlorpromazine Equivalents	188.7 mg/d (SD 166)		

Table 1. Demographic and clinical characteristics of schizophrenia patients and controls. Premorbid IQ was measured with the MWT, the German equivalent of the Spot the Word Test.

3.3.2 Stimuli and task

A delayed discrimination task that probes load effects in visual working memory (Linden et al., 2003) was implemented on a personal computer using the Experimental-Run-Time-System (ERTS) software (www.erts.de) (Figure 1). Thirty-six non-natural visual objects were presented in the center of the computer monitor (visual angle: 1.34 degrees). Working memory load was

manipulated by presenting either one, two or three sample stimuli for 600 ms each with an ISI of 400 ms (*encoding* phase). After a delay of 12s (*maintenance* phase), a probe stimulus was presented for 3s (*retrieval* phase). Participants had to indicate whether it was part of the initial sample set by button press. The inter-trial interval was 12s. The three memory load conditions were randomly intermixed within each run. The experiment was preceded by a training session that allowed participants to complete as many trials as necessary to familiarize themselves with the structure and timing of the task. Subjects participated in two EEG sessions on consecutive days, each comprising three 10 minute blocks, and one fMRI session, comprising two 12 minute blocks.

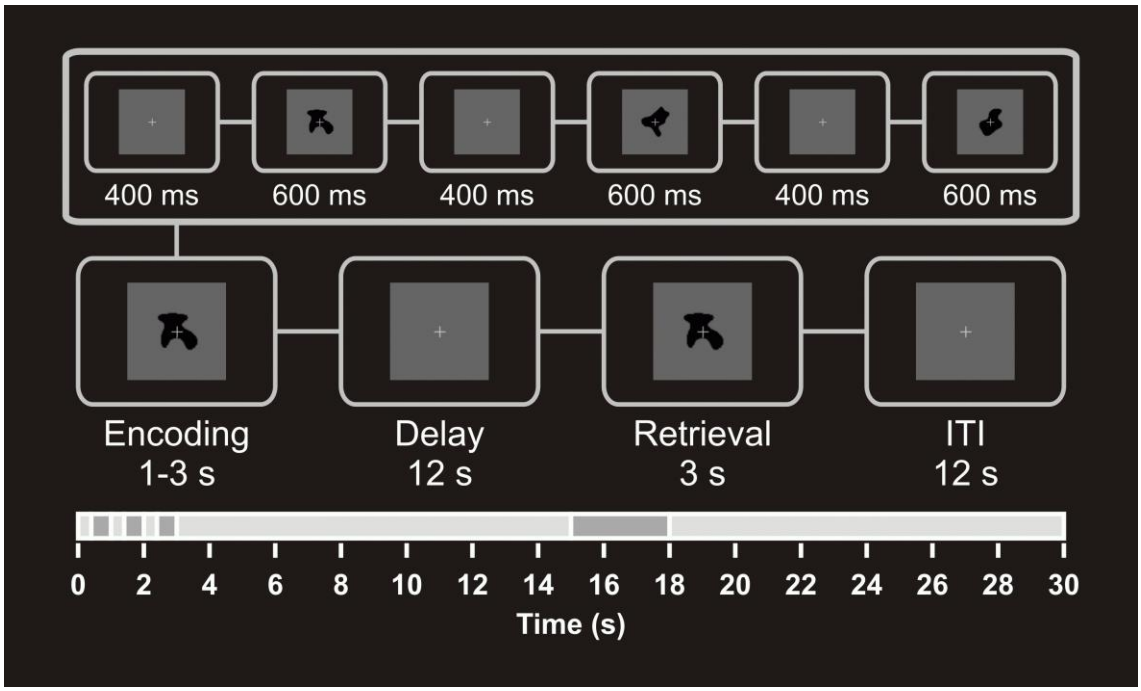

Figure 1. Working Memory Paradigm. The visual delayed discrimination task using abstract shapes. memory load was varied by presenting either one, two or three objects for encoding for 600 msec each with an interstimulus interval of 400 msec. After a 12 second delay interval, a probe stimulus was presented for 3 seconds. Participants had to judge whether or not it was part of the initial sample set by pressing a button.

3.3.3 ERP data acquisition, processing and analysis

An electrode-cap with 64 channels was fitted to the participants' head with the ground electrode at position AFZ, the reference electrode at Cz and an additional vertical electrooculogram electrode below the right eye. For analysis data were re-referenced to the average reference. Recording, digitization and

processing of the EEG data were carried out with a BrainAmp amplifier and the BrainVision Recorder software (Brain Products, Munich, Germany). The EEG was recorded at a sampling rate of 500 Hz with a system bandpass between 0-100 Hz. Impedance was kept below 5 kΩ.

EEG data during encoding and retrieval were analysed for ERPs using the BrainVision Analyser software. EEG data were averaged in intervals from -300 ms before to 1000 ms after stimulus onset and baseline corrected from -100 ms to stimulus onset. Epochs were excluded automatically if the amplitudes exceeded a threshold of ±100 μV. Only correct trials were entered into the analysis. To assess encoding, we analysed the final sample stimulus in each memory load condition, i.e. the first stimulus for a load of 1, the second stimulus for a load of 2 and the third for a load of 3. This ensured an equal number of stimuli for each condition and more importantly, maximised the effect of prior processing in the memory load conditions.

Averaged ERPs were filtered with a high frequency cut off at 30 Hz (roll-off: 12 dB/oct) before further processing. Peak amplitudes and latencies of P1 at electrode O1, Oz and O2 were defined in the interval between 80-160 ms and P3a at C1, Cz, C2 were defined in the time window between 200-400 ms. We defined the first and the second P3b peaks according to peak latency: P370 and P570. The P370 component at P3, Pz, P4 were defined in the time window between 200-400ms and the second P3b peak, the P570 component at P3, Pz, P4 between 450-750 ms.

Repeated-measures multivariate analysis of variance (MANOVA) was used to test the effects within- (electrode, working memory load) and between-participants (participant group) on all dependent measures (P1 and P3a & P370 and P570 amplitude and latency). Load by Group interactions were reported only if significant. In cases of significant group effects we correlated amplitudes with accuracy for each load condition. We used polynomial contrasts to determine linear or quadratic trends in order to measure if the increase in memory load resulted in a monotonic increase of the component amplitude. In cases of significant linear effects of memory load we used linear regression to measure if amplitudes in addition to memory load can predict accuracy.

3.3.4 fMRI data acquisition, processing and analysis

Images were acquired with a Siemens 1.5 T Magnetom Vision MRI scanner using a gradient echo EPI sequence (16 axial slices, TR=2000ms, TE=60, FA=90°, FOV=220 x 220 mm^2, voxel size: 3.43x3.43x5 mm^3, gap 1 mm, 350 volumes). Data analysis was performed with BrainVoyager QX 1.8.6 (Brain Innovation, Maastricht, The Netherlands). The first four volumes of functional runs were discarded to allow for T1 equilibration. Data preprocessing included slice scan time correction, 3D motion correction, spatial smoothing with a Gaussian kernel (FWHM=8mm), linear trend removal and temporal high pass filtering (high pass: 3 cycles per functional run), manual alignment to a high resolution anatomy and transformation into Talairach coordinate space (Talairach and Tournoux, 1988).

Multi-subject statistical analysis was performed by voxel-wise multiple linear regression of the blood oxygenation level dependent (BOLD) signal. For each of the three memory load conditions four box-car predictors were defined representing the different phases of the task: encoding, early delay, late delay and retrieval. They were adjusted for the hemodynamic delay by convolution with a canonical hemodynamic response function (Boynton et al., 1996). 3D group statistical maps were generated by associating each voxel with the F-value corresponding to the specific set of predictors and calculated on the basis of the least mean squares solution of the general linear model with a random-effects model. The obtained beta weights were entered into a second-level random-effects repeated-measures ANOVAs with memory load as a within-subjects factor and group as a between-subjects factor. We searched for areas which showed a main-effect of group ($p<0.000005$, minimum cluster size of 10 mm^3) during encoding or retrieval within a 15 mm radius of the P1 coordinates reported by Noesselt and colleagues (Noesselt et al., 2002) (left hemisphere: -39, -74, 4; right hemisphere: 32, -75, 6; Talairach space (Talairach and Tournoux, 1988)).

3.4 Results

3.4.1 Behavior

Figure 2 shows the average response times and the proportion of correct responses (accuracy) across both groups. Reaction time increased with memory load for both groups ($F_{(2,31)}$=111.96, p<0.001). The interaction between memory load and group showed a trend to significance ($F_{(2,31)}$=2.56, p=0.092), which is attributable to the control group demonstrating a greater increase from load 1 to Load 2 than patients. The linear contrasts confirmed the monotonic increase in both groups with memory load (controls: $F_{(1,15)}$=114.32, p<0.001; patients: $F_{(1,15)}$=59.47, p<0.001).

The overall accuracy was lower in patients than controls (group: $F_{(1,32)}$=24.98, p<0.001). With an increase in working memory load, the accuracy decreased in both groups ($F_{(2,31)}$=10.06, p=0.003). The linear contrast confirmed a trend towards a significant interaction between memory load and group (linear contrast: $F_{(2,31)}$=3.32, p=0.078) showing that the decrease in accuracy was more pronounced in patients. There was no correlation between chlorpromazine equivalents and accuracy or reaction time.

3.4.2 Broad-Band ERPs

As no interaction between group and electrode location was significant for the amplitudes of the various ERP components during encoding [P1: ($F_{(2,31)}$=1.61, p=0.21); P3a: ($F_{(2,31)}$=1.04, p=0.36); P370: ($F_{(2,31)}$=0.17, p=0.83); P570: ($F_{(2,31)}$ =0.36, p=0.69)] and only for P3a during retrieval [P1: ($F_{(2,31)}$=1.56, p=0.22); P3a: ($F_{(2,31)}$=4.14, p=0.02); P370: ($F_{(2,31)}$=0.5, p=0.59); P570: ($F_{(2,31)}$=0.4, p=0.95)], results will be reported only for midline electrodes (for P1 electrode Oz, for P3a electrode Cz, for P370 and P570 electrode Pz). There was no correlation between chlorpromazine equivalents and any of the amplitude or latency measures in patients.

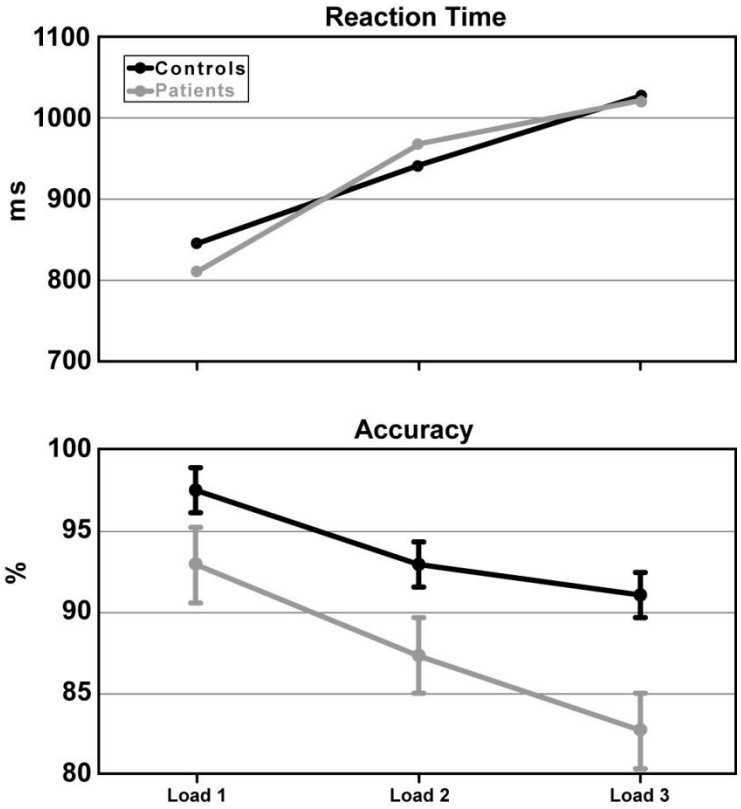

Figure 2. Behavioural Data (Reaction Time and Accuracy). Mean Reaction Time (top row) and Mean Accuracy (bottom row) (percent of correct answers) in response to memory load of 1, 2 or 3 in controls (black line) and patients (grey line). Error bars represent standard error (SE).

3.4.3 Encoding:

P1

The grand mean ERPs to memory load 1, 2 and 3 during encoding in controls (left side) and patients (right side) are illustrated in Figure 3. The sample stimuli evoked a P1 component with a mean latency of 132 ms (SD 17) in controls and 140 ms (SD 24) in patients at the central occipital electrode (Oz) (Figure 3, 4). There was no significant effect of group ($F_{(1,32)}$=2.09, p=0.16) or load ($F_{(2,31)}$=0.32, p=0.73) on latency. P1 amplitude was significantly reduced in patients compared to controls ($F_{(1,32)}$=5.53, p=0.025) and increased with memory load ($F_{(2,31)}$=3.43, p=0.04, Table 2). Post-hoc tests showed that this increase was explained by a linear amplitude increase with memory load from 1 to 3 in controls (linear contrast: $F_{(1,15)}$=6.42, p=0.02). Conversely, patients showed neither a linear (linear contrast: $F_{(1,15)}$=0.94, p=0.35) nor a significant quadratic trend (quadratic contrast: $F_{(1,15)}$=1.4, p=0.25). In addition, P1 amplitude correlated with accuracy for memory load 3 in controls (r=0.52, p=0.03), but there was no correlation for any of the memory load conditions in

patients. Stepwise linear regression analyses were then computed in order to test if accuracy can be predicted by memory load and by P1 amplitude. We found a significant effect of both variables ($F_{(2,48)}$=8.38, p=0.001) in controls but not in patients. Whereas accuracy was negatively correlated with memory load (beta: -0.512, p<0.001), it was positively correlated with P1 amplitude (beta: 0.264, p=0.046). A higher P1 amplitude increase with increasing memory load predicted better performance.

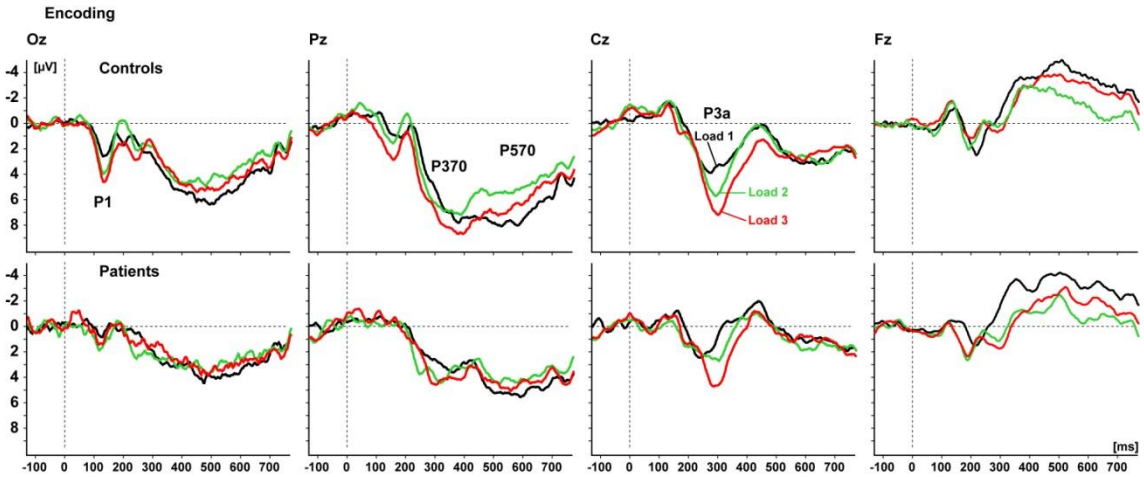

Figure 3. ERPs during working memory encoding. The ERP responses following the first sample stimulus for memory load 1 (black line), the second stimulus for memory load 2 (green line) and the third stimulus for memory load 3 (red line) are shown at the central occipital electrode (Oz), the central parietal electrode (Pz), the vertex electrode (Cz) and the central frontal electrode (Fz) for controls (top row) and patients with early-onset schizophrenia (bottom row). P1 can be seen at Oz, P3a at CZ and P370 and P570 at Pz. Please note that the ERPs at Fz are shown for illustrative purposes.

P3a

The sample stimuli evoked a P3a component measured between 200 and 450 ms with a mean latency of 280 ms (SD 40) in controls and 288 ms (SD 57) in patients at the midline central electrode (Cz). P3a mean amplitude did not differ between groups (group: $F_{(1, 32)}$=0.81, p=0.37) (Figure 3, 4, Table 2). The mean amplitude increased with memory load (Cz: main effect load: $F_{(2,31)}$=9.49, p<0.001). Post-hoc tests showed that this increase was explained by a linear increase with memory load in patients (linear contrast: $F_{(1,15)}$=5.01, p=0.04) and a quadratic increase in controls ($F_{(1,15)}$=9.46, p=0.04). There was no difference in latency at the midline central electrode (group: ($F_{(1,32)}$=0.7, p=0.41); working memory load: ($F_{(2, 31)}$=2.24, p=0.12)). There was no significant correlation

between P3a and accuracy. In the linear regression model with memory load and P3a amplitude, P3a did not predict accuracy.

P370

The P370-component measured between 200 and 450 ms peaked with a mean latency of 372 ms (SD 53) in controls and 359 ms (SD 44) in patients at the central parietal electrodes (Pz) (Figure 3, 4). Latency did not differ across groups ($F_{(1,32)}$=0.99, p=0.33), but there was a significant difference in latency with working memory load: ($F_{(2, 31)}$=3.48, p=0.05)
(Table 2). The mean P370 amplitude was significantly smaller in patients ($F_{(1,32)}$=6.36, p=0.017, Figure 4), but did not increase with memory load ($F_{(2, 31)}$=1.9, p=0.16). A positive correlation between P370 amplitude and accuracy was significant for memory load 2 (r=0.58, p=0.014) and memory load 3 (r=0.8, p<0.001) in controls but there was no correlation for any of the memory load conditions in patients.

P570

The sample stimuli evoked a P570-component with a mean latency of 568 ms (SD 75) in controls and 568 ms (SD 73) in patients at the central parietal electrodes (Pz) (Figure 3, Table 2). Latency did not differ significantly between groups ($F_{(1,32)}$=0.001, p=0.98) or across load conditions ($F_{(2,31)}$=0.81, p=0.44). There were no effects of group on amplitude ($F_{(1,32)}$=2.68, p=0.11). The P570 mean amplitude (measured between 450 and 750 ms) showed a significant decrease with memory load ($F_{(2,31)}$=28.24, p<0.001, Figure 4). This quadratic decrease was significant both in controls ($F_{(1,15)}$=45.59, p<0.001) and in patients ($F_{(1,15)}$=15.92, p=0.001**)**. In addition, we found a significant correlation between P570 amplitude and accuracy in memory load 3 (r=0.67, p=0.003) in controls.

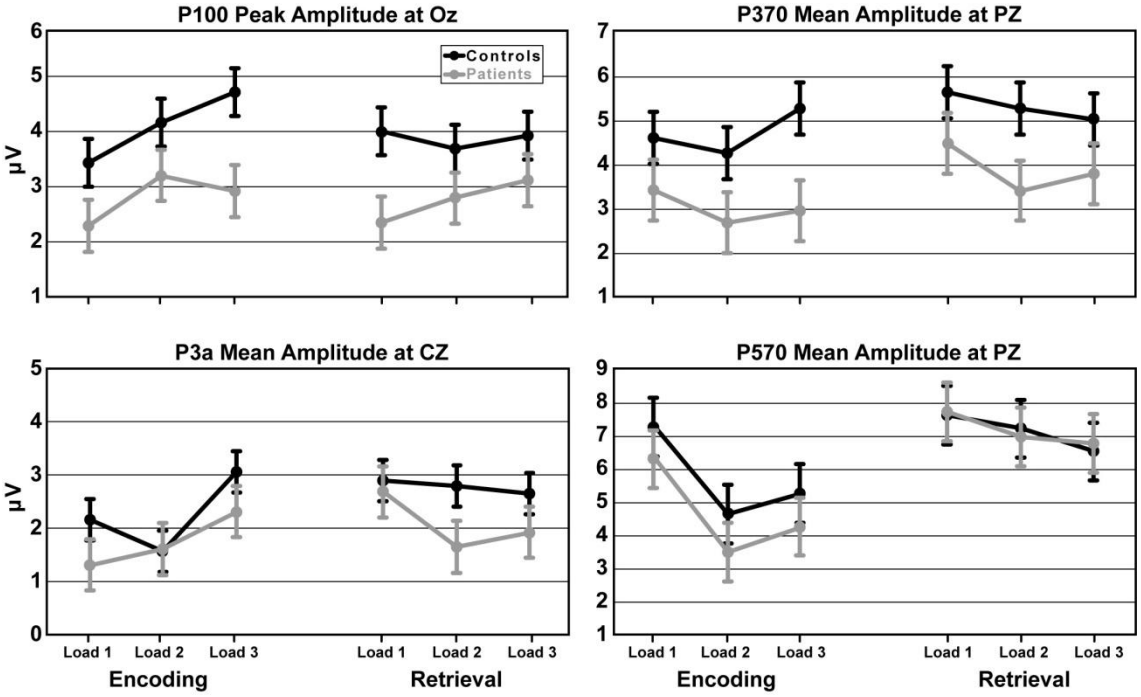

Figure 4. Peak and Mean ERP Amplitudes. P1 peak amplitude at the central occipital electrode (Oz), P3a mean amplitude at the vertex electrode (Cz), P370 and P570 mean amplitude for the central parietal electrode (Pz) in response to memory load 1, 2 or 3 for encoding (left) and retrieval (right) in controls (black line) and patients (grey line). Error bars represent SE.

Encoding		**Amplitude in µV (SE)**			**Latency in ms (SE)**		
		WM load 1	WM load 2	WM load 3	WM load 1	WM load 2	WM load 3
P1	Controls	3.55 (0.53)	4.32 (0.44)	4.91 (0.51)	125 (5)	132 (3)	137 (5)
	Patients	2.32 (0.59)	3.3 (0.59)	2.99 (0.56)	149 (6)	136 (5)	134 (6)
Effect size		d=0.53,	d=0.51	d=0.87			
P3a	Controls	2.15 (0.37)	1.53 (0.41)	3.07 (0.45)	282 (14)	264 (10)	292 (5)
	Patients	1.27 (0.37)	1.57 (0.56)	2.31 (0.64)	285 (15)	277 (16)	302 (11)
P370	Controls	4.59 (0.47)	4.24 (0.55)	5.26 (0.73)	387 (12)	353 (13)	374 (14)
	Patients	3.39 (0.37)	2.63 (0.55)	2.9 (0.65)	399 (11)	320 (10)	360 (11)
Effect size		d=0.70	d=0.72	d=0.81			
P570	Controls	7.28 (0.7)	4.6 (0.42)	6.37 (0.63)	556 (13)	555 (17)	593 (24)
	Patients	6.3 (0.7)	3.42 (0.73)	4.21 (0.87)	555 (14)	596 (23)	552 (17)

Table 2. Peak amplitude and latency for P1 at the central occipital electrode and mean amplitude and latency for P3a at vertex electrode, and P370 and P570 at central parietal electrode to Load 1, Load 2 and Load 3 sample stimuli during encoding. (SE=Standard Error). Effect sizes are calculated for significant group differences.

3.4.4 Retrieval:

P1

The grand mean ERPs to memory load 1, 2 and 3 during retrieval in controls (left side) and patients (right side) are illustrated in Figure 5. The probe related P1 activity peaked at 135 ms (SD 16) in controls and at 129 ms (SD 23) in patients. The P1 peak amplitude was in trend reduced in patients relative to controls ($F_{(1,32)}$=3.8, p=0.06, Figure 4, 5, Table 3). There was no effect of memory load on P1 peak amplitude ($F_{(2,31)}$=1.44, p=0.25) and latency ($F_{(2,31)}$=1.1, p=0.89). There was no significant correlation between P1 amplitude and accuracy in any of the memory load conditions.

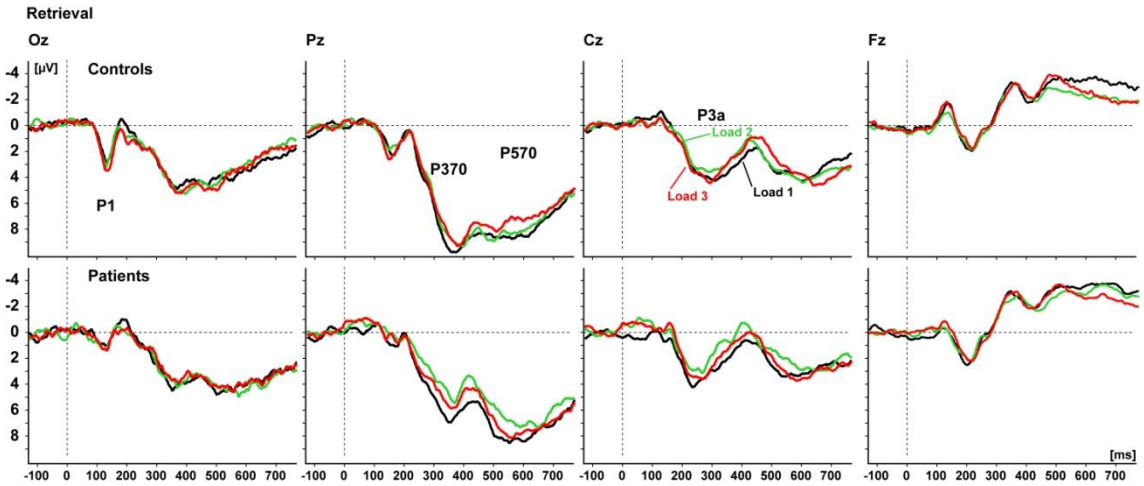

Figure 5. ERPs during working memory retrieval. The ERP responses following the test stimulus for memory load 1 (black line), memory load 2 (green line) and memory load 3 (red line) are shown at the central occipital electrode (Oz), the central parietal electrode (Pz), the vertex electrode (Cz) and the central frontal electrode (Fz) in controls (top row) and patients with schizophrenia (bottom row). P1 can be seen at Oz, P3a at Cz and P370 and P570 at Pz. Please note that the ERPs at Fz are shown for illustrative purposes.

P3a

P3a peaked with a mean latency of 291 ms (SD 51) in controls and 293 ms (SD 72) in patients. There was neither a significant difference in latency ($F_{(1,32)}$=0.005, p=0.94) nor in mean amplitude ($F_{(1,32)}$=1.16, p=0.29) between groups. The mean amplitude decreased significantly with memory load ($F_{(2, 31)}$=4.9, p=0.01) (see Figure 4 & 5, Table 3). There was a trend to a Load by Group interaction for P3a during retrieval ($F_{(2,31)}$=2.72, p=0.074). Post-hoc tests showed that this interaction was explained by a quadratic decrease with

memory load in patients ($F_{(1,15)}$=7.07, p=0.02), but not in controls ($F_{(1,15)}$=0.01, p=0.92). There was no significant correlation between P3a amplitude and accuracy in any of the memory load conditions.

P370

The P370 component peaked with a mean latency of 375 ms (SD 49) in controls and 369 ms (SD 62) in patients. This difference was not significant ($F_{(1,32)}$=0.17, p=0.68). The mean amplitude was significantly smaller in patients than in controls (group: $F_{(1,32)}$=4.12, p=0.05). Mean amplitude decreased significantly with increasing memory load ($F_{(2, 31)}$=5.78, p=0.006) (see Figure 4, 5, Table 3). The load-dependent decrease was only significant in patients (quadratic contrast: patients: $F_{(1,15)}$=10.09, p=0.006, linear contrast: $F_{(1,15)}$=3.62, p=0.075) but not in controls (quadratic contrast: $F_{(1,15)}$=0.05, p=0.82, linear contrast: $F_{(1,15)}$=2.64, p=0.12). There was a significant correlation between P370 amplitude and accuracy at memory load 3 (r=0.7, p=0.002).

P570

The P570 peaked significantly later in patients than in controls ($F_{(1,32)}$=6.48, p=0.02) with a mean latency of 533 ms (SD 63) in controls and 574 ms (SD 59) in patients. In contrast to P370, the P570 amplitude was not significantly different between groups ($F_{(1,32)}$=0.001, p=0.98). The P570 at Pz decreased in mean amplitude with increasing memory load ($F_{(2,31)}$=12.43, p<0.001) (see Figure 4, 5, Table 3). Post-hoc tests showed that this linear decrease was significant in both groups (linear contrast: controls: $F_{(1,15)}$=10.12, p=0.006**)** , patients: ($F_{(1,15)}$=15.92, p=0.001). There was no significant correlation between P570 and accuracy in any of the memory load conditions. In the linear regression model with memory load and P570 amplitude, P570 did not predict accuracy.

Retrieval		Amplitude in µV (SE)			Latency in ms (SE)		
		WM load 1	WM load 2	WM load 3	WM load 1	WM load 2	WM load 3
P1	Control	4.15 (0.41)	3.81 (0.47)	4.07 (0.41)	128 (5)	139 (4)	137 (2)
	Patients	2.39 (0.4)	2.86 (0.55)	3.20 (0.55)	133 (5)	125 (6)	130 (6)
Effect size		d=1.1	d=0.45	d=0.47			
P3a	Control	2.9 (0.47)	2.81 (042)	2.66 (0.5)	297 (12)	298 (14)	282 (11)
	Patients	2.68 (0.63)	1.62 (0.49)	1.90 (0.5)	279 (17)	314 (20)	280 (14)
P370	Control	5.64 (0.63)	5.27(0.49)	5.02 (0.61)	375 (13)	376 (12)	372 (11)
	Patients	4,46 (0.51)	3.37 (0.45)	3.76 (0.52)	376 (14)	364 (16)	364 (15)
Effect size		d=0.47	d=0.99	d=0.55			
P570	Control	7.67 (0.85)	7.24 (0.8)	6.53 (0.79)	534 (15)	533 (15)	532 (15)
	Patients	7.75 (0.8)	6.99 (0.83)	6.79 (0.83)	559 (12)	583 (18)	581 (14)

Table 3. Peak amplitude and latency for P1 at the central occipital electrode and mean amplitude and latency for P3a at vertex electrode, and P370 and P570 at central parietal electrode to Load 1, Load 2 and Load 3 test stimuli during retrieval. (SE=Standard Error). Effect sizes are calculated for significant group differences.

3.4.5 fMRI Data

Behavioral parameters closely matched those acquired during EEG recordings. For encoding, a main effect of group was observed in the middle occipital gyrus bilaterally, in the left middle and superior temporal gyrus and in the right inferior temporal gyrus (Figure 6a, Table 4). For retrieval, clusters in the middle occipital gyrus bilaterally the left middle temporal gyrus and the right inferior temporal gyrus were found (Figure 6b, Table 4). Group differences during retrieval were more confined in terms of the number of voxels than during encoding. However, 49% of voxels showing a group effect during retrieval also showed a group effect during encoding. Post-hoc two-tailed t-tests were computed to examine group differences for each memory load condition within individual clusters (Table 4). For encoding, all clusters showed significantly greater activation for memory load 2 and 3 for controls. For retrieval, greater activation for controls was found in all clusters. Differences in activation were most pronounced for memory load 1 and declined towards the highest memory load conditions.

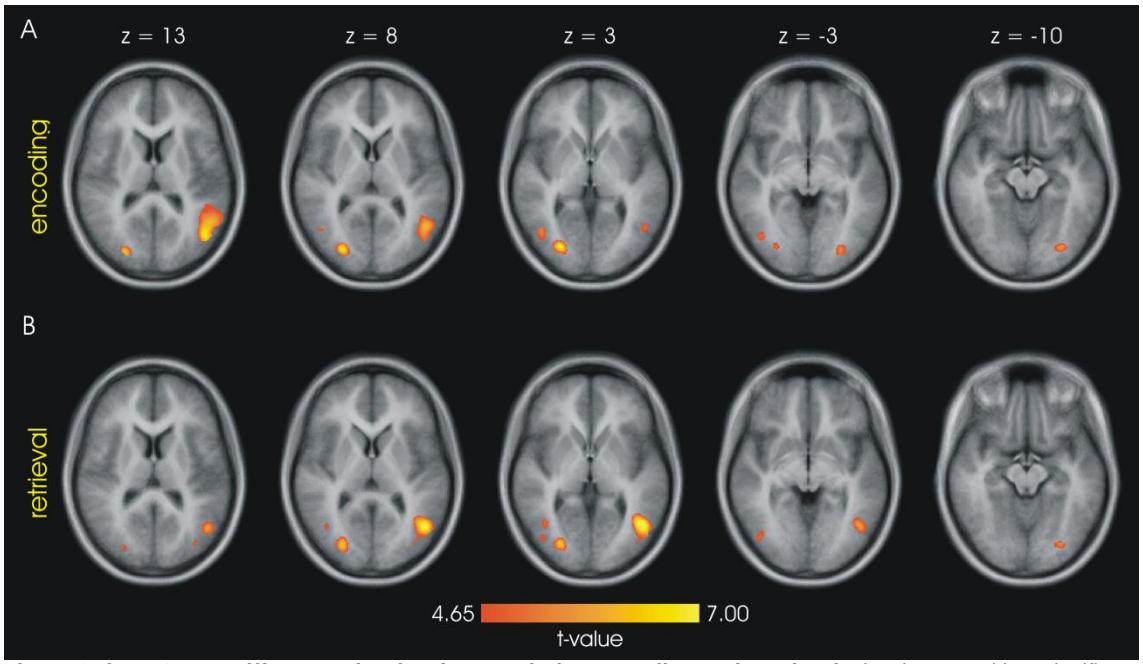

Figure 6. fMRI Group Differences in Visual Areas during Encoding and Retrieval Visual areas with a significant main-effect of group during encoding or retrieval (p<0.000005, minimum cluster size of 10 mm^3) in the fMRI analysis depicted on the average brain of all participants. Only brain areas within a 15 mm radius of the P1 coordinates derived from an established dipole model (left hemisphere: -39, -74, 4; right hemisphere: 32, -75, 6; Talairach space) are shown.

Task Phase	ROI	BA	Talairach x	Talairach y	Talairach z	Cluster size (mm^3)	ROI based group conrasts (t-value) WM load 1	WM load 2	WM load 3
Encoding	left GOm	19	-28	-78	-8	1010	0.01	3.12**	2.68*
	right GOm	19	26	-77	6	1585	0.29	3.26**	2.74*
	left GTs/GTm	22/39	-47	-57	14	5726	0.65	3.1**	3.59**
	right GTi	37	42	-65	2	658	-0.03	2.25*	2.74*
Retrieval	left GOm	18/19	-28	-77	-10	224	2.79**	2.44*	1.64
	left GOm	19	-35	-76	13	135	2.48*	2.06*	2.34*
	right GOm	19	26	-77	6	1102	4.13**	3.01**	1.83
	left GTm	37	-44	-62	5	3716	3.98**	2.64*	2.34*
	right GTi	37	40	-66	1	679	3.19**	3.67**	1.03

Table 4. Visual areas with a significant main-effect of group during encoding or retrieval (p<0.000005, minimum cluster size of 10 mm^3) in the fMRI analysis. *p<0.05, **p<0.01 Abbreviations: Talairach=standard brain space as defined by Talairach and Tournoux (x,y,z), GOm: middle occipital gyrus, GTi: inferior temporal gyrus, GTm: middle temporal gyrus, GTs: superior temporal gyrus. T-values are listed for ROI-based two-tailed t-tests comparing group differences for individual memory load conditions.

3.5 Discussion

We examined the neural substrates of visual working memory encoding and retrieval in patients with EOS and compared the results to those obtained from healthy controls. Accuracy was significantly lower and decreased more steeply with memory load in patients than in controls. Reaction times increased with working memory load, but were not slowed in our sample of adolescent patients in contrast to findings in chronic patients.

Compared to controls, the patients showed reduced amplitudes in P1 and P370 components during encoding. During retrieval P1 showed a strong trend towards a reduction in patients with a large effect size for memory load 1. P370 was again reduced in patients. There was no correlation between individual chlorpromazine equivalents and any of the dependent measures in line with evidence that both P1 and P3 deficits occur irrespective of medication (Foxe et al., 2001; Jeon and Polich, 2003). Several of the investigated ERP components were sensitive to memory load. During encoding P1 and P3a amplitude increased and P570 decreased with increasing memory load in controls. We found correlations of P370 amplitudes with performance in controls for the higher memory load conditions during encoding and retrieval. A similar effect was found for the P1 and P570 only for encoding. Thus, both early activity of sensory areas, reflected by the P1, and later cognitive processes, as indexed by the subcomponents of the P300, seem to be crucial for effective memory performance in healthy controls. However, linear regression analysis revealed that a stronger P1 amplitude augmentation with increasing memory load predicted better performance. This suggests that P1 is of particular relevance for successful working memory encoding.

This working memory load-dependent modulation of component amplitudes was absent or greatly attenuated in the patients with the exception of a linear memory load effect on the P3a component. P3a is elicited by items for which no memory template is available but for which reorienting is required (Fabiani and Friedman, 1995), which suggests that patients were still able to refocus on each new stimulus. In contrast, the P370 was significantly smaller in patients, which suggests a deficit in the categorisation or evaluation of the stimuli.

During retrieval there was no effect of memory load on P1 in either group. Only patients demonstrated a decrease in P3a and P370 amplitude with increasing memory load. Both groups showed a linear decrease in P570. The amplitude

reduction of P370 during retrieval suggests that patients have a deficit in the evaluation of the probe stimulus against the stimulus representations held in memory. The normal amplitude and the prolonged latency of the second peak (P570) suggests that template matching takes longer but that the neuronal substrate for this matching process is probably unimpaired.

One possible confound is the sensitivity of the P3 components to probability effects. The intermixed sequence of memory load conditions in our experiment may thus have had an influence on the P3 load effects. However, we did not find any significant load by group interaction effects during encoding. Thus the P3 deficit in patients cannot be attributed to reduced expectancy (Duncan-Johnson et al., 1984; Ford, 1999).

Importantly, a neural deficit in patients was already evident for the P1 during both encoding and retrieval. In our complimentary fMRI analysis of extrastriate visual areas we observed reduced activation for patients both during encoding and retrieval in highly overlapping brain areas. During *encoding*, group differences were particularly pronounced for the highest memory load conditions, which matched the P1 deficit. During *retrieval* group differences were more pronounced for the lowest memory load conditions, again mirroring the P1 data. The considerable overlap of group effects for encoding and retrieval in visual areas in the fMRI data show that mostly the same brain regions contribute to the P1 deficit irrespective of the precise behavioural relevance of the stimuli. However, this overlap might also point to impaired stimulus encoding during both sample and probe presentation in patients.

Reduced P1 amplitudes in schizophrenia have been reported in several studies (Foxe et al., 2001; Doniger et al., 2002; Butler and Javitt, 2005; Foxe et al., 2005), but this is the first study to do so for early-onset schizophrenia. The decreased BOLD signal in extrastriate visual areas observed in our patients implicates reduced neuronal activity as a reason for the P1 deficit. There is recent evidence for a reduction in total neuron number (Dorph-Petersen et al., 2007) in visual cortex in schizophrenia as well as disruptions of occipital white matter (Kumra et al., 2004) which seem to be related to reduced ERP amplitudes (Butler et al., 2005). However other factors may also play a role, for instance increased neuronal response variability (Haenschel et al., 2004; Winterer et al., 2004) in patients. Deficits in magnocellular stream processing

have been linked to the P1 attenuation (Foxe et al., 2001; Doniger et al., 2002; Butler and Javitt, 2005; Foxe et al., 2005). This could lead to reduced precision with which temporal transients are signalled and thus to reductions in response timing (synchrony) (Spencer et al., 2003; Uhlhaas et al., 2006; Uhlhaas and Singer, 2006). Furthermore dysfunctions in thalamo-cortical circuits have been associated with reduced inhibition of irrelevant information (Knight and Grabowecky, 1995) and could give rise to reduced alpha phase reset that in part generates the P1 (Klimesch et al., 2007).

This is the first report of a memory load dependent increase of P1 during encoding. Such a modulation implies a role of P1 related processes for working memory. Indeed, better performance could be predicted by a larger P1 increase with memory load. The use of semantically accessible stimuli, e.g. letters or numbers, could explain why earlier studies failed to find an effect of memory load on P1 (Pratt et al., 1989). Our complex visual shapes probably required more detailed processing to establish perceptual representations for subsequent working memory encoding. This would include the inhibition of irrelevant information, spatial shifts of attention required for object feature processing, as well as feedback from higher intra- and supramodal areas (Bullier, 2001). These operations have been associated with the P1 component (Heinze et al., 1990; Luck et al., 1994; Barcelo et al., 2000; Simon-Thomas et al., 2003; Martinez et al., 2006) and seem to be necessary for further object processing (Duncan, 1993) and encoding into working memory (Conway et al., 2001). The rapid presentation of up to three objects makes these processes particularly demanding. This should increase the likelihood that deficits in patients reflected by reduced P1 amplitude contribute to disturbed working memory encoding. However, since P1 is only modulated by spatial selective attention to a small degree, it is unlikely that impaired spatial attention in patients is at the root of their marked P1 deficit.

Finally, the increase in P1 with presenting stimuli in succession could reflect the sequential build-up of a sensory memory trace. Future studies need to investigate if the memory load dependent P1 increase is due to sensitisation of sensory processes (Haenschel et al., 2005).

In summary, adolescents with early-onset schizophrenia demonstrated an attenuated P1 component, an absence of a P1 memory load modulation and

reduced BOLD activation in early visual areas during working memory. This highlights the relevance of early sensory deficits for higher-level cognitive dysfunction in schizophrenia. These early processing deficits might also reduce encoding efficiency for other forms of memory, such as long term visual memory (Tracy et al., 2001) and auditory sensory memory (Baldeweg et al., 2004). While sufficient stimulus presentation time may facilitate encoding and normalize working memory performance (Kim et al., 2006), impairments of working memory maintenance still persists when encoding difficulty is adjusted for by reducing stimulus complexity (Lencz et al., 2003). The influence of impaired encoding on working memory maintenance may be further illuminated by analyzing slow potentials (Vogel and Machizawa, 2004) or time-frequency patterns (Tallon-Baudry et al., 1998; Schmiedt et al., 2005). An integration of the present ERP approach with anatomical connectivity (Agartz et al., 2001; Ardekani et al., 2003; Kumra et al., 2004) and EEG measures of functional connectivity (Ford et al., 2002; Uhlhaas et al., 2006) will be paramount to further elucidate the underlying neural deficits.

Both impaired P1 generation (Yeap et al., 2006) and working memory dysfunction (Park et al., 1995; Conklin et al., 2000) have been found in unaffected first-degree relatives of patients with schizophrenia. Future studies should address the extent to which these putative endophenotypes (Lee and Park, 2005; Yeap et al., 2006; Gur et al., 2007a) overlap with each other, and whether their integration into a composite endophenotype might provide a more robust marker of genetic vulnerability for schizophrenia (Turetsky et al., 2007).

Chapter 4: Experiment 3

Experiment 3: Cortical dysfunction during working memory component processes in adolescents with schizophrenia

Based on:

Bittner R.A., Linden D.E., Roebroeck A., Haertling F., Rotarska-Jagiela A., Goebel R., Singer W., Maurer K., Haenschel C. *Cortical dysfunction during working memory component processes in adolescents with schizophrenia - A functional magnetic resonance imaging study.* In preparation.

4.1 Abstract

Context

Working memory dysfunction in schizophrenia is caused by impairments of both encoding and maintenance processes. The relationship of these deficits with prefrontal cortical dysfunction, disturbances in other brain regions and abnormal connectivity is unclear. The current study addresses these crucial issues in order to reconcile behavioral with neurophysiological models of working memory impairment.

Objective

To examine patterns of abnormal cortical activation and connectivity during encoding, maintenance and retrieval with functional magnetic resonance imaging (fMRI).

Design

Case-control study.

Setting

Hospital-based research units and outpatient clinic.

Participants

Seventeen adolescent patients with schizophrenia and seventeen matched controls.

Main Outcome Measures

working memory capacity, regional brain activation and functional connectivity as measured by fMRI during a delayed discrimination task with varying levels of memory load.

Results:

Patients had reduced working memory capacity. During encoding activation in the left ventrolateral prefrontal cortex (VLPFC) and extrastriate visual cortex was reduced in patients but positively correlated with working memory capacity in controls. During early maintenance patients switched from hyper- to hypoactivation with increasing memory load in a fronto-parietal network which included left dorsolateral prefrontal cortex. During late maintenance abnormally increased suppression of default mode areas in patients was correlated with working memory capacity. During retrieval right inferior VLPFC hyperactivation was correlated with encoding-related hypoactivation of left VLPFC in patients. Cortical dysfunction in patients during encoding and retrieval was accompanied by abnormal functional connectivity between fronto-parietal and visual areas.

Conclusions

Patients showed a primary encoding deficit largely independent of working memory load, caused by a dysfunction of VLPFC and visual areas. Prefrontal hyperactivation during retrieval seems to be a secondary consequence of this deficit. In contrast, a memory load dependent fronto-parietal dysfunction and the dysregulation of default mode areas seem to contribute to impaired working memory maintenance. Isolating the component processes of working memory leads to more specific markers of cortical dysfunction in schizophrenia.

4.2 Introduction

Impairments in working memory have long been regarded as a central characteristic of schizophrenia and a fundamental cognitive deficit (Goldman-Rakic, 1994; Silver et al., 2003; Lee and Park, 2005) with important prognostic implications (Cervellione et al., 2007; Heinrichs et al., 2008). Their presence during the prodromal phase (Wood et al., 2003; Simon et al., 2007), in spectrum disorders (Roitman et al., 2000; Mitropoulou et al., 2005; Robles et al., 2008), in high-risk populations (Erlenmeyer-Kimling, 2001) and in unaffected relatives (Park et al., 1995) indicates a close relationship with the pathophysiology of schizophrenia. working memory dysfunction has therefore gained increasing interest as a target of psychological and pharmacological interventions (Green et al., 2004; Greenwood et al., 2005; Barch and Smith, 2008; Barch et al., 2009) and as an intermediate phenotype in the search for the genetic causes of the disorder (Meyer-Lindenberg and Weinberger, 2006; Gur et al., 2007a). These translational strategies critically depend upon a clear understanding of the underlying cognitive and neurophysiological disturbances. Yet, behavioral and neuroimaging studies have largely focused on different aspects of working memory dysfunction and an integrated approach is still lacking.

Behavioural studies indicate that working memory is already compromised during the initial encoding of information (Tek et al., 2002; Hartman et al., 2003; Lencz et al., 2003; Kim et al., 2006; Lee and Park, 2006; Javitt et al., 2007; Fuller et al., 2009). Nevertheless, the observation of additional impairments during maintenance (Dreher et al., 2001; Reilly et al., 2006; Stephane and Pellizzer, 2007; Badcock et al., 2008) and retrieval (Dreher et al., 2001) suggests a combination of deficits in these three basic component processes.

Yet, the use of blocked experimental designs – often in conjunction with the n-back task – has prevented their isolation in the majority of fMRI studies. Although these studies have consistently implicated dysfunction of the prefrontal cortex (PFC) as a central cause for working memory impairment (Goldman-Rakic, 1999; Weinberger et al., 2001; Glahn et al., 2005), both decreased (Stevens et al., 1998; Barch et al., 2001; Perlstein et al., 2001; Perlstein et al., 2003) and increased prefrontal cortical activation (Manoach et al., 1999; Callicott et al., 2000; Manoach et al., 2000) have been reported. This discrepancy has been explained by models of a dynamic memory load

dependent dysfunction of prefrontal cortex: while low memory load should give rise to prefrontal hyperactivation in patients signifying inefficient processing, high memory load should lead to hypoactivation caused by a failure to sustain activation in prefrontal circuits (Callicott et al., 2003a; Manoach, 2003; Jansma et al., 2004).

However, these models fail to account for the modularity and relative specialization of the prefrontal cortex (PFC) (D'Esposito et al., 2000; Levy and Goldman-Rakic, 2000; Munk et al., 2002), which also applies to the major working memory component processes. More specifically, the dorsolateral prefrontal cortex (DLFPC) seems to control the flow of information within the working memory network (Rypma and D'Esposito, 1999; Druzgal and D'Esposito, 2001; Curtis and D'Esposito, 2003) and its top-down influence over premotor and superior parietal areas appears to be crucial for the successful maintenance of visuospatial information (Sakai et al., 2002; Edin et al., 2009). The latter areas together with the superior part of the ventrolateral prefrontal cortex (VLPFC) seem to be critical for the encoding of visuospatial information (Bor et al., 2003; Mayer et al., 2007). By contrast the inferior portion of the VLPFC appears to be particularly involved in the facilitation of working memory retrieval (Bledowski et al., 2006; Nee and Jonides, 2008). Notably, a corresponding differential effect of memory load on activation in these prefrontal areas during encoding, maintenance and retrieval has also been demonstrated (Linden et al., 2003; Bledowski et al., 2006; Edin et al., 2009).

These findings imply that impairments in a specific working memory component process may be the result of disturbances in the corresponding prefrontal modules rather than a global dysfunction of the PFC. It also has to be noted, that the imbalanced prefrontal cortical dopamine D1:D2 receptor activation ratio found in schizophrenia (Okubo et al., 1997; Abi-Dargham et al., 2002; Winterer and Weinberger, 2004) seems to differentially affect prefrontal cortical activation during working memory encoding, maintenance and retrieval (Wang et al., 2004; Gibbs and D'Esposito, 2005; Durstewitz and Seamans, 2008; Rolls et al., 2008). Therefore, abnormal prefrontal cortical activation patterns in schizophrenia might differ markedly across component processes. Although several recent event-related fMRI studies investigated disturbances during the encoding (Johnson et al., 2006; Schlosser et al., 2007; Driesen et al., 2008;

Schlosser et al., 2008; Potkin et al., 2009), maintenance (Driesen et al., 2008; Lee et al., 2008; Schlosser et al., 2008) and retrieval (Johnson et al., 2006; Schlosser et al., 2008; Brown et al., 2009; Potkin et al., 2009) of spatial and verbal information separately, no clear association between deficits in these component processes and altered prefrontal cortical activation patterns has been established.

Most importantly, it remains unclear whether prefrontal cortical dysfunction already contributes to encoding deficits, which have been implicated as a primary cause for working memory impairment (Lee and Park, 2005; Haenschel et al., 2007). It is not known, which parts of the PFC might be disturbed during encoding and whether the response profile of the prefrontal areas in patients is consistent with models of a memory load dependent dysfunction. Alternatively, a prefrontal hyper- or hypoactivation independent of memory load might also be found. The former could be interpreted as an inefficient compensatory engagement of the PFC. In contrast the latter finding could indicate a primary dysfunction of prefrontal circuits that perturbs the formation of durable mnemonic representations in line with the psychophysical evidence for a principal encoding deficit (Tek et al., 2002; Hartman et al., 2003; Lencz et al., 2003; Lee and Park, 2005; Kim et al., 2006; Lee and Park, 2006; Javitt et al., 2007; Fuller et al., 2009). Moreover, such an impairment during encoding might in turn lead to compensatory hyperactivation of prefrontal areas during maintenance and retrieval.

Yet, the working memory network is highly distributed comprising not only prefrontal but also parietal (Linden et al., 2003; Todd and Marois, 2004; Xu and Chun, 2006; Mayer et al., 2007) and – for visuospatial working memory – visual areas (Furey et al., 2000; Druzgal and D'Esposito, 2001; Pasternak and Greenlee, 2005; Nee and Jonides, 2008; Harrison and Tong, 2009). While deficits in early visual areas seem to impair encoding and retrieval (Haenschel et al., 2007), abnormal parietal activation (Quintana et al., 2003; Glahn et al., 2005; Brahmbhatt et al., 2006; Barch and Csernansky, 2007; Schneider et al., 2007) has not been linked to specific component processes.

Such widespread cortical dysfunctions could be a reflection of disturbed interactions between brain areas as proposed by the disconnection hypothesis (Friston, 1998; Andreasen, 1999). The latter interpretation is supported by

reports of altered functional connectivity in schizophrenia during working memory (Meyer-Lindenberg et al., 2001; Kim et al., 2003; Schlosser et al., 2003; Meyer-Lindenberg et al., 2005b; Tan et al., 2006; Kim et al., 2009), but it remains to be clarified how abnormal interactions within the cortical working memory network affect individual working memory component processes.

In the current study we investigated differences in cortical activation and their relationship to working memory capacity as well as abnormal functional connectivity in adolescents with early-onset schizophrenia (EOS) with a relatively short illness duration (mean 1.4 years) and matched controls during the performance of a visual delayed discrimination task under varying levels of memory load with event-related fMRI (Figure 1).

Our main hypothesis was that cortical dysfunction would manifest itself differentially during the different component processes. Specifically, we expected a dysfunction during encoding in cortical areas closely involved in this component process especially in the PFC. We hypothesized that such a primary encoding deficit should in turn lead to compensatory changes in later task phases. We also predicted component process specific changes in functional connectivity between task relevant areas, in line with the disconnection hypothesis of schizophrenia.

4.3 Methods

4.3.1 Subjects

Seventeen patients with EOS according to DSM-IV criteria and seventeen control participants matched for age, gender, handedness and premorbid IQ (Table 1) participated in the study. Event-related potential data (Haenschel et al., 2007), fMRI results on extrastriate visual areas (Haenschel et al., 2007) and EEG time frequency results(Haenschel et al., 2009) obtained from the same group of patients have been reported previously. Patients were assessed with the German version of the Structured Clinical Interview for DSM-IV (SCID) (Sass and Wittchen, 2003) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Handedness was determined with the Edinburgh Handedness Inventory (Oldfield, 1971). Premorbid IQ was assessed with MWT,(Lehrl, 1995) the German equivalent of the Spot-the-Word Test (Baddeley et al., 1993). Exclusion criteria for patients were a history of other neuropsychiatric conditions or substance abuse in the six months preceding the study. Control participants were recruited through local advertisements. Controls were excluded if they had any history of mental illness or substance abuse. All participants and, for participants under 18 years, also their parents provided informed consent prior to the study. Ethical approval was obtained from the ethics committee of Frankfurt Medical School.

4.3.2 Stimuli and task

A delayed visual discrimination task was implemented on a personal computer using the Experimental-Run-Time-System (ERTS) software (www.erts.de) (Figure 1). Non-natural objects, presented at the center of the computer screen, were used as visual stimuli (Linden et al., 2003). One to three sample objects were presented for 600 ms each with an interstimulus interval of 400 ms (*encoding* phase). After a delay of 12 s (*maintenance* phase), a test stimulus was presented for 3s at the center of the screen (*retrieval* phase). Subjects had to indicate whether it was part of the initial sample set by button press. The inter-trial interval lasted 12 s. The three memory load conditions were randomly intermixed within each run. Prior to the scanning session all participants were given instruction and practice with the task.

Variable	Patients (n=17)	Controls (n=17)	*P* Value
Age (range)	17.9 (15.2–20.4)	17.5 (15.1–19.9)	$t_{(32)}$=0.87, p=0.48
Sex (male/female)	11/6	11/6	χ^2 (1)=0, p=1
Handedness (right/left)	13/4	13/4	χ^2 (1)=0, p=1
Mean Premorbid IQ	96 (SD 16)	97 (9)	$t_{(32)}$=-0.21, p=0.83
Years of Illness	1.4 (SD 0.9)		
Age at Onset	16.5 (SD 1.2)		
Mean PANSS Score	44.92 (SD 18.38)		
Antipsychotic Medication:	Quetiapine 10; Risperidone 2; Clozapine 1; Olanzapine 1; Aripiprazole 2; Perphenazine 1;		
Mean Chlorpromazine Equivalents	188.7 mg/d (SD 166)		

Table 1. Demographic and clinical characteristics.

During scanning, the computer display was projected onto a mirror mounted on the head coil. Stimuli subtended 1.34° of visual angle. Subject's responses were registered by a custom-made fiber-optic response box. Subjects were asked to fixate upon the cross at the center of the screen throughout the experiment. Each of the subjects completed a total of 48 trials of the task (16 trials per memory load condition).

4.3.3 Analysis of behavioral data

We computed estimates of subjects working memory capacity for each memory load condition using Cowan's formula (Cowan et al., 2005): k = N * (H + CR -1) where k is working memory capacity, N is the number of items displayed (one, two or three), H is the hit rate (correctly identified matches), and CR is the correct rejection rate (correctly identified non-matches). K values and reaction time were entered in separate repeated-measures analyses of variance (ANOVAs) to test for main effects of group (controls and patients) and memory load condition (load 1, load 2 and load 3). Significant main effects and interactions were decomposed using t-tests.

4.3.4 Acquisition of fMRI data

Functional MRI data were acquired with a Siemens 1.5 T Magnetom Vision MRI scanner using a gradient echo EPI sequence (16 axial slices; TR = 2000ms; TE = 60; FA = 90°, FOV = 220 x 220 mm^2, voxel size: 3.43 x 3.43 x 5 mm^3, gap 1 mm).

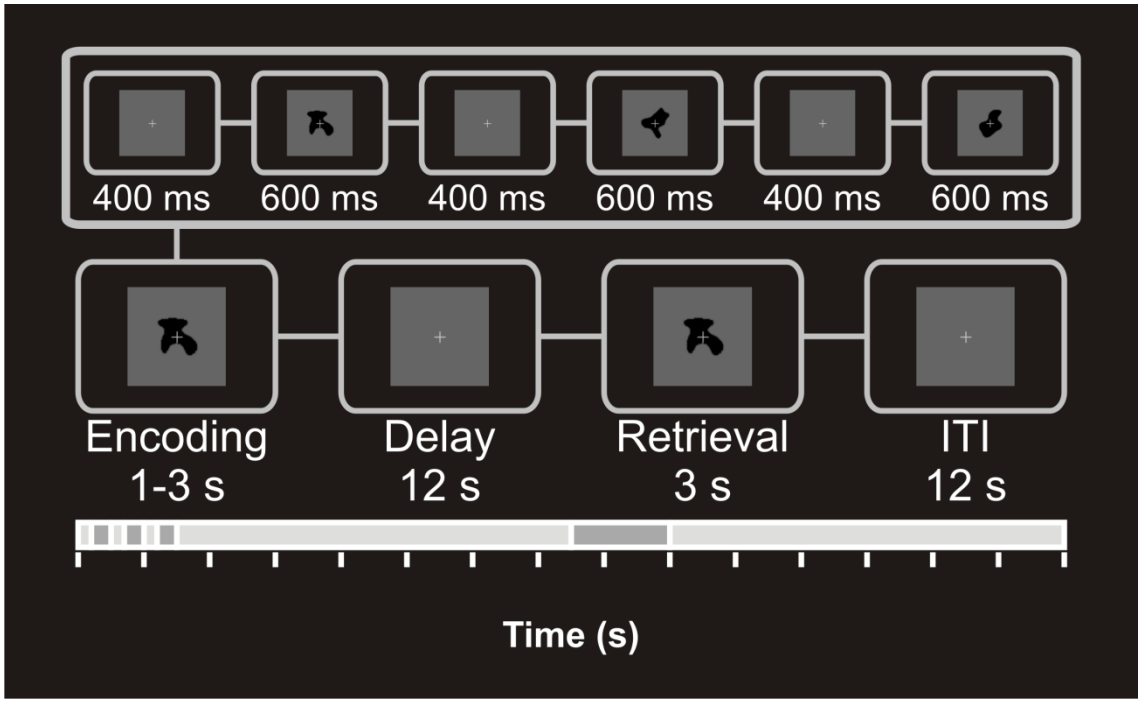

Figure 1. Working memory paradigm. The delayed discrimination task with random shapes. memory load was varied by presenting one to three objects for encoding for 600 msec each with an interstimulus interval of 400 msec. After a 12 second delay interval a probe stimulus was presented for 3 seconds. Subjects had to judge whether or not it was part of the initial sample set by pressing a button. The intertrial interval was 12 seconds.

Slices were positioned parallel to the anterior-commissure posterior-commissure plane. Functional images were acquired in two runs in a single session, each comprising the acquisition of 350 volumes. Stimulus presentation was constantly synchronized with the fMRI sequence. Head motion was minimized with pillows. A high-resolution T1-weighted three-dimensional volume using a fast low-angle shot (T1-FLASH) sequence (voxel size: 1x1x1 mm^3) was acquired for co-registration of functional data.

4.3.5 Analysis of behavioral data

We computed estimates of subjects working memory capacity for each memory load condition using Cowan's formula (Cowan et al., 2005): k = N * (H + CR -1) where k is working memory capacity, N is the number of items displayed (one, two or three), H is the hit rate (correctly identified matches), and CR is the correct rejection rate (correctly identified non-matches). K values and reaction time were entered in separate repeated-measures analyses of variance (ANOVAs) to test for main effects of group (controls and patients) and memory

load condition (memory load 1, memory load 2 and memory load 3). Significant main effects and interactions were decomposed using t-tests.

4.3.6 Functional image preprocessing

Functional data were analyzed using BrainVoyager QX 1.10.4 (Brain Innovation, Maastricht, The Netherlands) and the BrainVoyager QX Matlab Toolbox. The first four volumes of each run were discarded to allow for T1 equilibration. Functional data preprocessing included slice scan time correction, 3-dimensional motion correction, linear trend removal and temporal high pass filtering (high pass: 0.00867 Hz), manual alignment to the T1-FLASH anatomical scans and transformation into Talairach coordinate space (Talairach and Tournoux, 1988).

We applied a high-resolution, multiscale cortex alignment procedure, which reliably aligns corresponding gyri and sulci across subjects (Fischl et al., 1999b; Goebel et al., 2006) to reduce the impact of the increased variability of cortical topology in schizophrenia (Manoach, 2003; Park et al., 2004). Anatomical scans were segmented along the white–gray matter boundary. Cortical hemispheres were reconstructed (Kriegeskorte and Goebel, 2001) and morphed into spherical representations. Each cortical folding pattern was then aligned to a dynamically updated group average through iterative morphing following a coarse-to-fine matching strategy. Based on the vertex-to-vertex referencing from the folded, topologically correct meshes to the aligned spherical representations, the functional data was then mapped into a common spherical coordinate system (Fischl et al., 1999a; Fischl et al., 1999b) and spatially smoothed using a nearest neighbor interpolation (FWHM 5 mm).

4.3.7 Analysis of intrascan motion

To assess differences in intra-scan motion between patients and controls, the standard deviations for the six estimates of motion obtained during motion correction (translation in x, y, z direction and rotation around x, y, z axis) were computed separately and averaged over the two runs of each subject. These data were entered into a repeated-measures ANOVA with group as the between-factor and standard deviation for the six motion estimates as the within-factor (Morey et al., 2005). This yielded no significant group differences

($F_{1,32}$=0.47, p=.50) and no significant group by motion interaction ($F_{5,160}$=1.93, p=.15).

4.3.8 Cortex-based group fMRI analysis

Multi-subject statistical analysis was performed by multiple linear regression of the BOLD signal. For each memory load condition four task phases of interest were modeled by ideal box-car functions, which covered the first, third, fifth and eighth volume of each trial, respectively, convolved with a synthetic two-gamma function. While encoding-related activity was captured by the first and retrieval-related activity by the fourth regressor, the second and third regressor reflected activity during the early and later parts of the maintenance phase. However, due to the sluggishness of the BOLD-signal, the early maintenance regressor might still be contaminated by activity related to the visual stimulation (Zarahn et al., 1997).

These predictors were used to build the design matrix of the experiment. Individual statistical maps were generated by associating each voxel with the F-value corresponding to the specific set of predictors and calculated on the basis of the least mean squares solution of the general linear model. The obtained beta weights were entered into a second-level random-effects repeated-measures ANOVA.

Only correctly answered trials were entered into the analysis to control for the impact of performance differences between groups (Manoach, 2003). For the control group a number of correct trials equal to the number of correct trials of the patient group on the respective memory load level were randomly selected from its total number of correctly answered trials.

For each task phase of interest, we performed a random-effects level repeated-measures ANOVA with memory load condition (load 1, load 2 and load 3) as within-factor and group (controls and patients) as between-factor. Maps for the main effect of group and for the group by memory load interaction were computed at a voxel-wise threshold of p<.01 corrected for multiple comparisons using a cluster-level threshold of p<.05 (Forman et al., 1995). For each region of interest (ROI) derived from these maps post-hoc t-tests were performed on the extracted beta-values to test for the direction of group differences in individual memory load conditions.

4.3.9 Correlation between BOLD signal and working memory capacity

Beta values of the respective task phase were extracted from all ROIs with a main effect for group or a group by load interaction in the ANOVA. They were entered into a planned post-hoc correlation with subjects' working memory capacity as estimated by Cowan's K (Spearman's rank correlation coefficient). α was set at 0.00129 (Bonferroni corrected for the total number of 39 ROIs).

4.3.10 Cortex-based functional connectivity analysis

Prefrontal, parietal and visual ROIs derived from the ANOVA were used for the functional connectivity analysis which was based on the instantaneous influence term of Granger causality mapping (Goebel et al., 2003; Roebroeck et al., 2005). Because we were specifically interested in the relationship between abnormal connectivity and working memory component processes, correct trials from all memory load conditions were pooled. For each subject, functional connectivity maps for each ROI and the respective task phase were generated. Differences in functional connectivity were analyzed using t-tests (random effects level) with a voxel-wise threshold of $p<.01$, corrected for multiple comparisons using a cluster-level threshold of $p<.05$ (Forman et al., 1995).

4.4 Results

4.4.1 Behavioral Performance and working memory capacity estimates

Figure 2 depicts the working memory capacity estimates and the average response times for patients and controls. Working memory capacity was lower for patients ($F_{(1,32)}$=14.31, p<0.001), with no interaction between memory load and group ($F_{(2,64)}$=2.46, p=0.093). Two-tailed t-tests showed that patients had lower estimated working memory capacity in each memory load condition (memory load 1: t=2.65, p<0.05; memory load 2: t=3.76, p<0.001; memory load 3: t=2.39, p<0.05). Reaction times increased with memory load in both groups ($F_{(2,64)}$=23.26, p<0.001). There was no difference in reaction times between the groups ($F_{(1,32)}$=2.49, p=0.12) and no memory load by group interaction ($F_{(2,64)}$=0.26, p= 0.95).

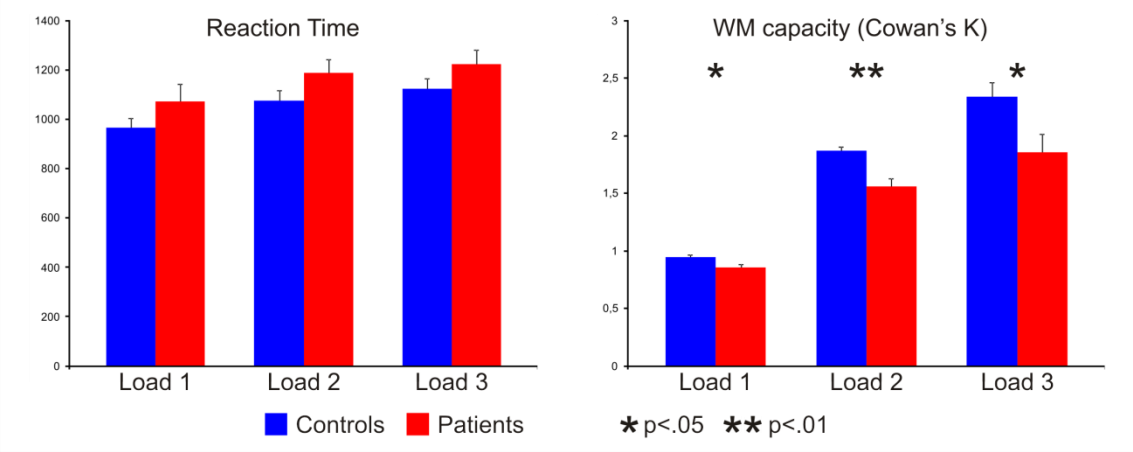

Figure 2. Behavioral data (reaction time and working memory capacity). The mean reaction time (left) and the mean working memory capacity as estimated by Cowan's K (right) for each memory load condition are shown for controls (blue) and patients (red). Error bars represent SEM. *p<.05, **p<.01.

4.4.2 Encoding

The results of the ANOVA for encoding are illustrated in Figure 3 and Table 2. The beta-values of all regions of interest for encoding and subsequent task phases are depicted in the supplementary material (Figures S1-S4).

A main effect for group was found in the left VLPFC and left inferior parietal lobule (IPL). Post-hoc t-tests indicated significantly higher activation for controls for all three memory load conditions in both regions.

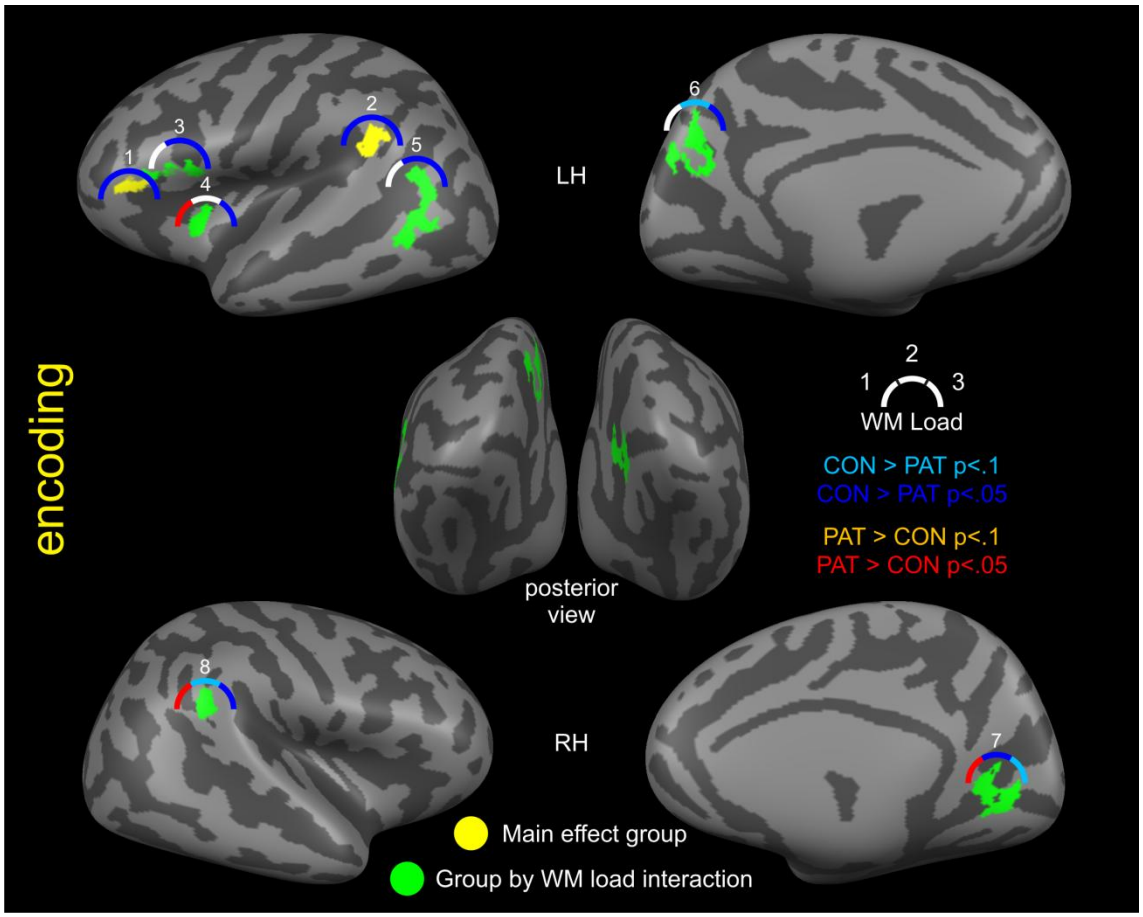

Figure 3. ANOVA results encoding. F-maps of the ANOVA for encoding thresholded at p<.01 (p<.05 corrected for multiple comparisons). Areas, which showed a main effect of group, are depicted in yellow, areas, which showed a group by memory load interaction, are depicted in green. The results of the two-tailed t-tests for group differences for each memory load condition are displayed in the half circle above each region. Trends and significant differences are indicated by light blue and blue for higher activation in controls compared to patients, and by orange and red for higher activation in patients compared to controls respectively. The numbers correspond to the respective indices in Table 2 which provides further details for each region.

Map Index	Name		BA	No of Vertices	Talairach coordinates			WM Load 1	WM Load 2	WM Load 3
					x	y	z	$t_{(32)}$	$t_{(32)}$	$t_{(32)}$
1	left	inferior frontal gyrus (VLPFC)	45	56	-48	25	12	2.91[c]	2.88[c]	3.79[c]
2	left	inferior parietal lobule	40	126	-54	-43	26	2.55[b]	3.61[c]	4.52[c]
3	left	inferior frontal gyrus (VLPFC)	44	97	-48	11	12	0.32	2.75[c]	3.71[c]
4	left	insula	13	79	-34	4	6	-2.15[b]	0.51	2.99[c]
5	left	middle temporal gyrus	37	197	-50	-55	7	-1.21	2.06[b]	3.12[c]
6	left	precuneus	31	195	-6	-68	27	-1.63	1.90[a]	2.85[c]
7	right	lingual gyrus	18	181	18	-56	4	-2.41[b]	2.06[b]	1.92[a]
8	right	inferior parietal lobule	40	101	57	-41	26	2.12[b]	1.79[a]	2.05[b]

Table 2. ANOVA results encoding. [a]p<.1 (trend), [b]p<.05, [c]p<.01

A group by memory load interaction was observed in the left VLPFC caudally of the region showing a main effect of group, the left insula, left middle temporal gyrus (MTG), left precuneus, the right IPL and right lingual gyrus.

Post-hoc t-tests indicated significantly higher activation for controls than for patients for memory load 2 and 3 in the left VLPFC and the left MTG. The left precuneus showed a similar pattern, a trend for memory load 2 and significantly higher activation for memory load 3. In contrast the left insula, the right IPL and the right lingual gyrus showed a pattern compatible with a memory load dependent cortical dysfunction. For memory load 1 significantly higher activation in patients than in controls was observed in these regions. For memory load 3 the condition was reversed and these regions showed significantly higher activation in controls than in patients. The right lingual gyrus which only showed a trend at memory load 3 did, however, exhibit significantly stronger activation in controls than in patients at memory load 2.

The relationship between these findings and our previous report of abnormal activation in early visual areas during encoding (Haenschel et al., 2007) is detailed in the supplementary material (Figure S5).

4.4.3 Early maintenance

The results of the ANOVA for early maintenance are illustrated in Figure 4 and Table 3.

A main effect of group was observed in the following areas: the posterior cingulate cortex (PCC), precuneus and middle occipital gyrus (MOG) bilaterally, the left insula and left MTG, the right central sulcus, right supramarginal gyrus (SMG), right superior temporal gyrus (STG) and right lingual gyrus. Post-hoc t-tests revealed significantly higher activation for controls for all three memory load conditions in all of these areas.

A group by memory load interaction was observed in the superior parietal lobule (SPL) bilaterally as well as in the left DLPFC, the left frontal eye field (FEF), and two areas in the left intraparietal sulcus^(IPS). Post-hoc t-tests revealed significantly higher activation in controls than in patients in the left DLPFC, the right SPL and the two regions in the left IPS for memory load 3 and a trend in

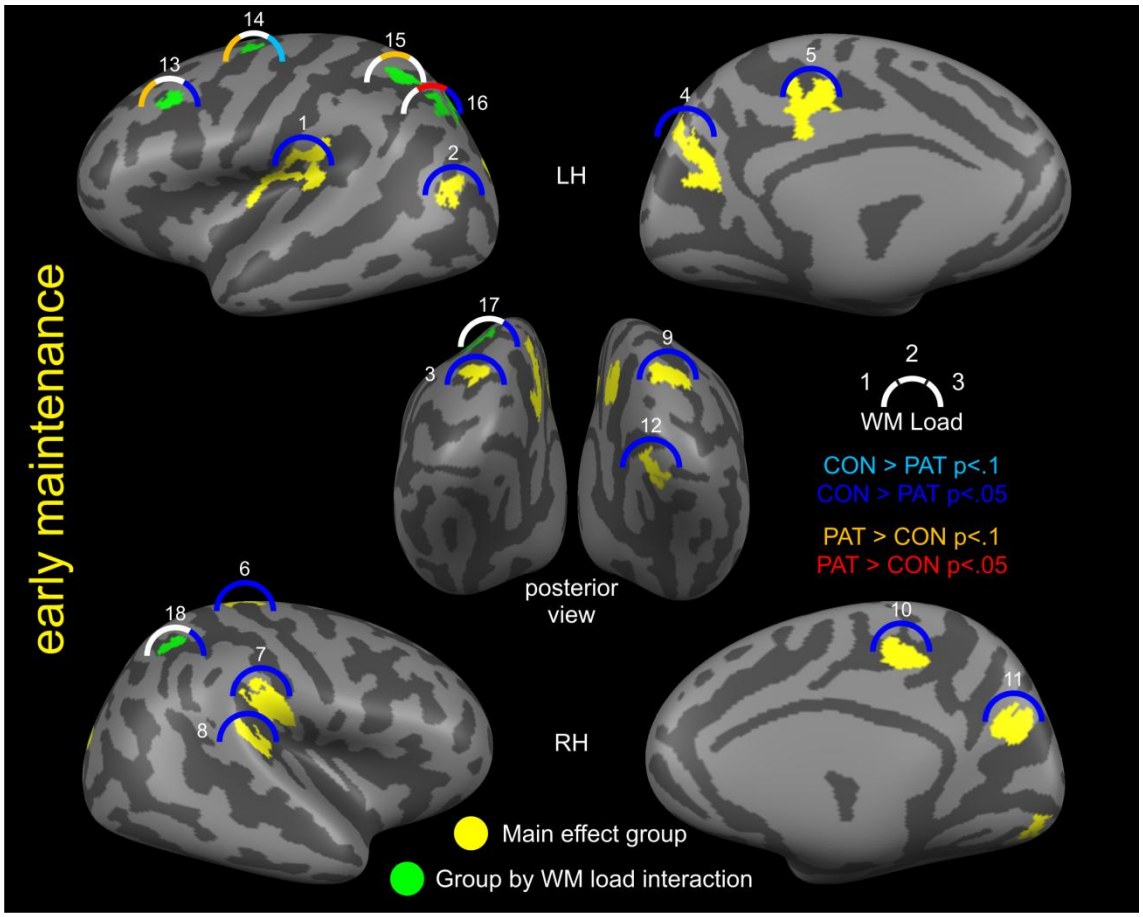

Figure 4. ANOVA results early maintenance. F-maps of the ANOVA for early maintenance thresholded at p<.01 (p<.05 corrected for multiple comparisons). Areas, which showed a main effect of group, are depicted in yellow, areas, which showed a group by memory load interaction, are depicted in green. The results of the two-tailed t-tests for group differences for each memory load condition are displayed in the half circle above each region. Trends and significant differences are indicated by light blue and blue for higher activation in controls compared to patients, and by orange and red for higher activation in patients compared to controls respectively. The numbers correspond to the respective indices in Table 3 which provides further details for each region.

the same direction in the left FEF. Three of these regions showed a pattern compatible with a memory load dependent cortical dysfunction: in the more lateral left IPS cluster, patients had significantly higher activation than controls for memory load 2, in the left DLPFC, patients showed a strong trend towards higher activation than controls (p=0.056) for memory load 1 and in the left FEF a similar but weaker trend was observed.

Map Index	Name	BA	No of Vertices	Talairach coordinates			WM Load 1	WM Load 2	WM Load 3
				x	y	z	$t_{(32)}$	$t_{(32)}$	$t_{(32)}$
1	left insula	13	418	-40	-26	17	2.94[c]	3.14[c]	3.86[c]
2	left middle temporal gyrus	19	83	-45	-63	13	1.11	2.31[b]	3.49[c]
3	left middle occipital gyrus	19	79	-24	-81	14	3.15[c]	3.80[c]	3.63[c]
4	left precuneus	31	240	-5	-68	23	3.39[c]	4.45[c]	3.75[c]
5	left posterior cingulate cortex	31	230	-10	-33	38	2.64[b]	4.28[c]	3.20[c]
6	right central sulcus	1,2	125	19	-32	58	2.68[b]	3.64[c]	2.55[b]
7	right supramarginal gyrus	40	286	51	-25	24	2.46[b]	3.63[c]	3.95[c]
8	right superior temporal gyrus	41	152	51	-29	16	2.92[c]	2.61[b]	3.56[c]
9	right middle occipital gyrus	19	116	24	-80	16	3.88[c]	3.84[c]	4.83[c]
10	right posterior cingulate cortex	31	134	12	-30	41	2.07[b]	3.95[c]	2.28[b]
11	right precuneus	31	187	7	-65	25	2.42[b]	4.58[c]	3.41[c]
12	right lingual gyrus	18	78	8	-76	-11	2.12[b]	4.60[c]	4.11[c]
13	left middle frontal gyrus (DLFPC)	9	47	-37	10	38	-1.98[a]	1.58	3.47[c]
14	left precentral gyrus (FEF)	6, 9	48	-26	-12	51	-1.84[a]	-1.53	1.86[a]
15	left superior parietal lobule	7	126	-31	-50	44	-1.47	-1.70[a]	1.59
16	left intraparietal sulcus	19	131	-30	-62	37	-0.29	-2.56[b]	2.05[b]
17	left intraparietal sulcus	7	96	-23	-67	35	-0.05	-0.37	2.68[b]
18	right superior parietal lobule	7	107	31	-49	42	-0.14	-0.79	2.75[c]

Table 3. ANOVA results early maintenance. [a]p<.1 (trend), [b]p<.05, [c]p<.01

4.4.4 Late Maintenance

The results of the ANOVA for late maintenance are illustrated in Figure 5 and Table 4.

Three areas exhibited a significant main effect of group. In the left STG and the left PCC activation was higher for controls at memory load 2 and 3. This effect was due to a deactivation in patients which increased with increasing memory load and was not observed in controls. Conversely, patients had significantly stronger activation than controls in all memory load conditions in the dorsal portion of the left FEF (Linden et al., 2003; Tark and Curtis, 2009). There was no area, which showed a group by memory load interaction.

4.4.5 Retrieval

The results of the ANOVA for retrieval are illustrated in Figure 6 and Table 5.

A significant main effect of group was observed for the anterior cingulate cortex (ACC), inferior VLPFC and IPL bilaterally as well as for the left anterior PFC. Post-hoc t-tests indicated that all of these regions were significantly more activated in patients than in controls, particularly at memory load 2 and 3. For memory load 1 patients also had significantly higher activation than controls in

the IPL bilaterally with the left anterior PFC and the right VLPFC showing a trend in the same direction.

A memory load by group interaction was found in the left fusiform gyrus and the right ACC. Post-hoc t-tests indicated that in the left fusiform gyrus controls had higher activation for memory load 1 than patients with no group differences for the other memory load conditions. The right ACC showed a pattern compatible with a memory load dependent cortical dysfunction: for memory load 1 controls had higher activation than patients, while the reverse was the case for memory load 2 and for memory load 3, where only a trend was found.

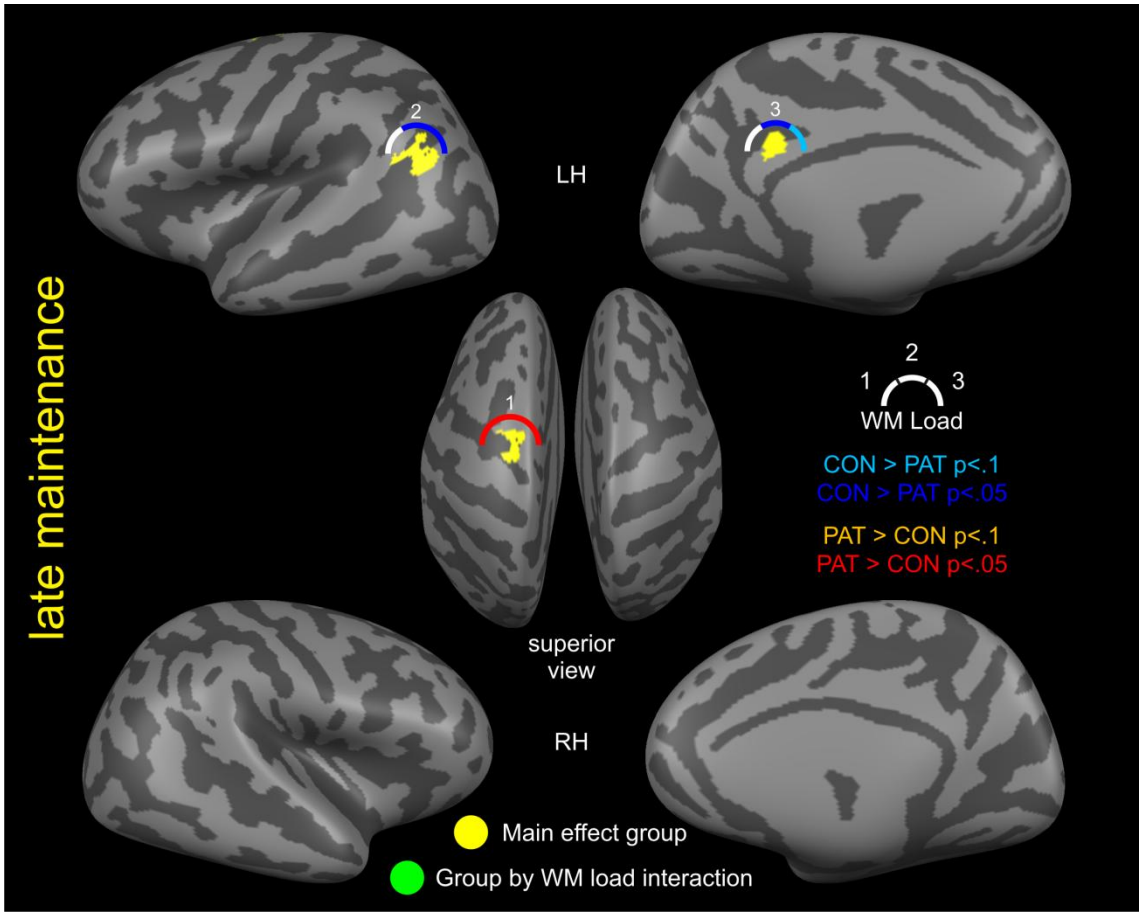

Figure 5. ANOVA results late maintenance. F-maps of the ANOVA for late maintenance thresholded at p<.01 (p<.05 corrected for multiple comparisons). Areas, which showed a main effect of group, are depicted in yellow, areas, which showed a group by memory load interaction, are depicted in green. The results of the two-tailed t-tests for group differences for each memory load condition are displayed in the half circle above each region. Trends and significant differences are indicated by light blue and blue for higher activation in controls compared to patients, and by orange and red for higher activation in patients compared to controls respectively. The numbers correspond to the respective indices in Table 4 which provides further details for each region.

Map Index	Name	BA	No of Vertices	Talairach coordinates			WM Load 1	WM Load 2	WM Load 3
				x	y	z	$t_{(32)}$	$t_{(32)}$	$t_{(32)}$
1	left superior frontal gyrus (FEF)	6	83	-16	-14	62	-3.01[c]	-2.18[b]	-3.25[c]
2	left superior temporal gyrus	39	185	-45	-54	20	1.61	3.58[c]	2.22[b]
3	left posterior cingulate cortex	31	63	-5	-41	29	1.18	4.14[c]	1.91[a]

Table 4. ANOVA results late maintenance. [a]p<.1 (trend), [b]p<.05, [c]p<.01

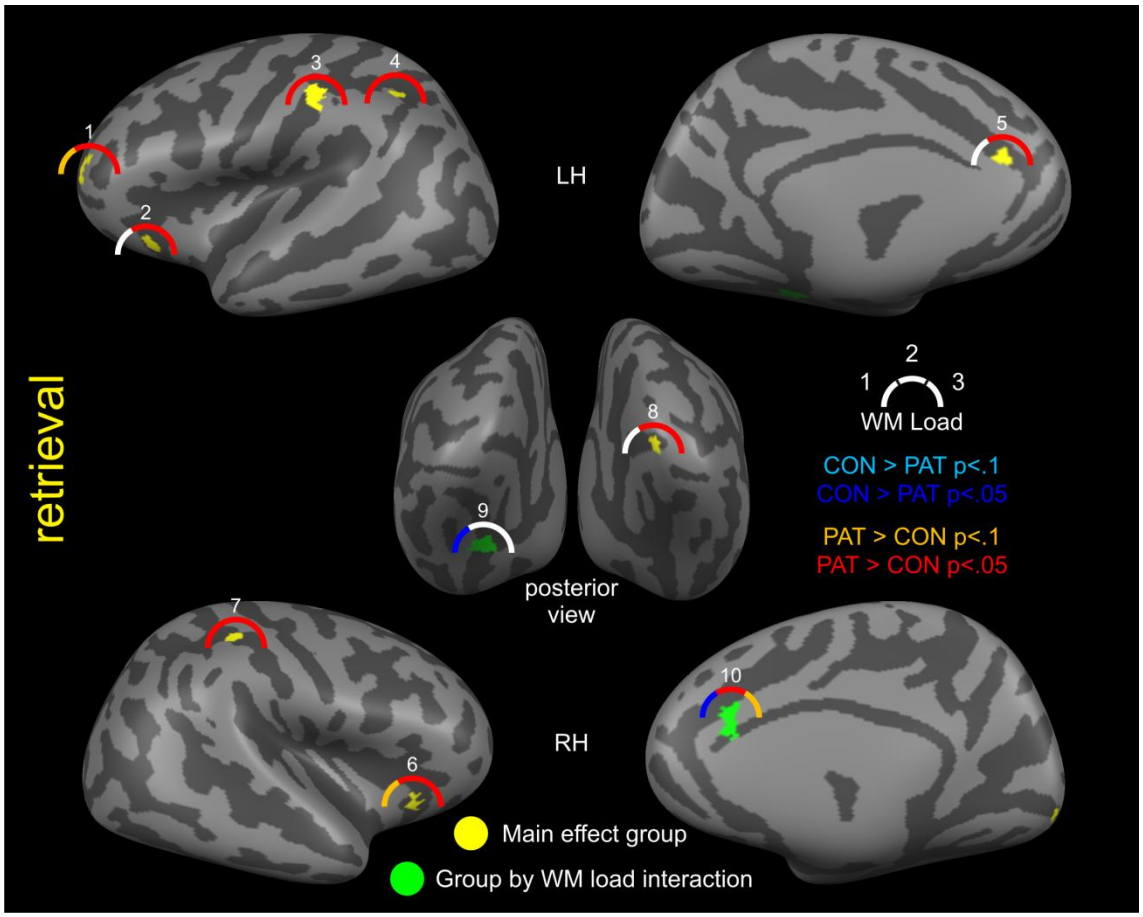

Figure 6. ANOVA results retrieval. F-maps of the ANOVA for retrieval thresholded at p<.01 (p<.05 corrected for multiple comparisons). Areas, which showed a main effect of group, are depicted in yellow, areas, which showed a group by memory load interaction, are depicted in green. The results of the two-tailed t-tests for group differences for each memory load condition are displayed in the half circle above each region. Trends and significant differences are indicated by light blue and blue for higher activation in controls compared to patients, and by orange and red for higher activation in patients compared to controls respectively. The numbers correspond to the respective indices in Table 5 which provides further details for each region.

Map Index		Name	BA	No of Vertices	Talairach coordinates x	y	z	WM Load 1 $t_{(32)}$	WM Load 2 $t_{(32)}$	WM Load 3 $t_{(32)}$
1	left	middle frontal gyrus (anterior PFC)	10	31	-33	48	18	-1.72[a]	-3.74[c]	-2.70[b]
2	left	inferior frontal gyrus (VLPFC)	47	37	-27	20	-3	-1.65	-2.80[c]	-3.19[c]
3	left	inferior parietal lobule	2, 40	94	-49	-25	35	-4.12[c]	-2.72[b]	-3.17[c]
4	left	inferior parietal lobule	40	36	-37	-48	37	-2.73[b]	-2.80[c]	-2.40[b]
5	left	anterior cingulate gyrus	32	19	-8	27	26	-1.18	-3.61[c]	-2.56[b]
6	right	inferior frontal gyrus (VLPFC)	47	36	28	19	2	-1.92[a]	-3.02[c]	-2.29[b]
7	right	inferior parietal lobule	2, 40	50	38	-30	41	-2.62[b]	-3.39[c]	-2.92[c]
8	right	lingual gyrus	18	16	11	-86	-7	-1.35	-3.85[c]	-2.48[b]
9	left	fusiform gyrus	37	88	-30	-38	-11	2.62[b]	-1.4	0.77
10	right	anterior cingulate gyrus	32	47	5	22	28	2.04[b]	-2.79[c]	-1.73[a]

Table 5. ANOVA results retrieval. [a]p<.1 (trend), [b]p<.05, [c]p<.01

4.4.6 Correlation with behavioral data

For encoding controls but not patients showed a significant positive correlation between BOLD activity and working memory capacity in the left posterior VLPFC (ρ =0.445, p<.05, corr.), the left insula (ρ=0.549, p<.01, corr.) and the right lingual gyrus (ρ=0.44725, p<.05, corr.). In contrast, for late maintenance only patients but not controls showed a significant negative correlation between BOLD activity and working memory capacity in the left STG (ρ=-0.603, p<.001, corr.) and the left PCC (ρ=-0.543, p<.01, corr.). For early maintenance and retrieval no significant correlation was observed in either group between working memory capacity and BOLD activity.

4.4.7 Correlation of activation across task phase

We were also interested in the question, whether prefrontal hypoactivation in patients during encoding might lead to prefrontal hyperactivation during retrieval independent of working memory capacity. This would strengthen our hypothesis of a primary encoding deficit. To this end we conducted post-hoc partial correlations which controlled for individual differences in working memory capacity between the two left hemispheric VLPFC clusters, for which patients showed hypoactivation during encoding, and the bilateral clusters in inferior VLPFC, for which patients showed hyperactivation during retrieval. A correlation across component processes was observed in both groups between the more posterior lefthemispheric VLPFC cluster from the encoding map and the right inferior VLPFC cluster from the retrieval map. However, while patients showed

a negative correlation (ρ=-0.361, p=.01) controls showed a significant positive correlation (ρ=0.326, p<.05).

4.4.8 Functional connectivity analysis

Encoding

Significant differences in functional connectivity between groups were found for two of the eight tested seed regions: the left VLPFC and the right lingual gyrus (Figure 7). In patients, the left VLPFC had reduced functional connectivity with the left precentral gyrus and an area in the left MOG corresponding to the lateral occipital complex (LOC) (Malach et al., 1995; Larsson and Heeger, 2006) Similarly, the right lingual gyrus had reduced functional connectivity with a region in the left calcarine sulcus.

Early and late Maintenance

No differences in functional connectivity emerged for any of the seed regions.

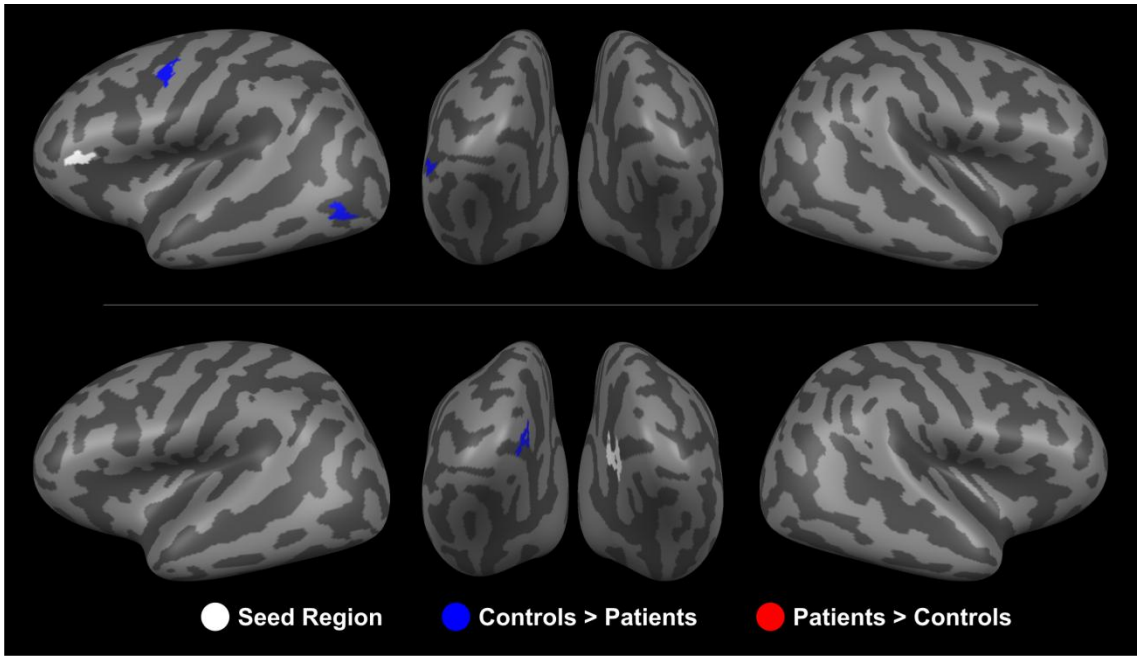

Figure 7. Functional connectivity results encoding. Contrast maps for significant group differences in the strength of functional connectivity during encoding thresholded at p<.01 (p<.05 corrected for multiple comparisons). Blue areas indicate significantly stronger connectivity with the seed region for controls, red areas indicate significantly stronger connectivity with the seed region for patients (two-tailed t-tests, random effects level).

Retrieval

Significant differences in functional connectivity between groups were found for three of the ten tested seed regions. Patients showed increased functional connectivity between a large number of areas. The left IPL interacted more strongly with the fusiform gyri in both hemispheres and the right inferior VLPFC (Figure 8), while the right IPL showed enhanced connectivity with the left SPL and the right inferior VLPFC. Finally, the right lingual gyrus interacted more strongly with the fusiform gyri in both hemispheres.

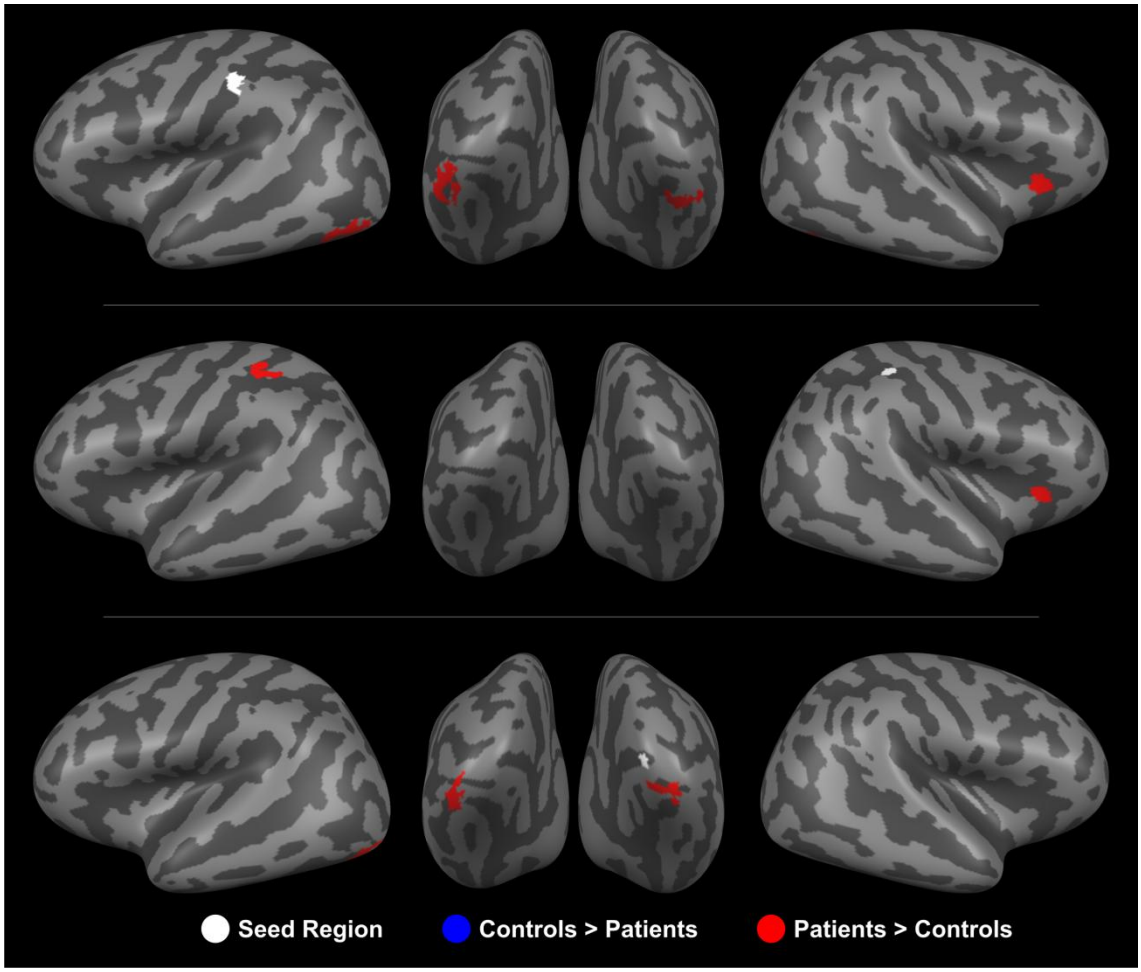

Figure 8. Functional connectivity results retrieval. Contrast maps for significant group differences in the strength of functional connectivity during retrieval thresholded at p<.01 (p<.05 corrected for multiple comparisons). Blue areas indicate significantly stronger connectivity with the seed region for controls, red areas indicate significantly stronger connectivity with the seed region for patients (two-tailed t-tests, random effects level).

Encoding

Seed region	Name		BA	No of Vertices	Talairach coordinates x	y	z
left inferior frontal gyrus (VLPFC)	left	precentral gyrus	6	68	-45	-6	43
	left	middle occipital gyrus	19	50	-44	-60	-4
right lingual gyrus	left	calcarine sulcus	17, 18	62	-5	-77	3

Retrieval

Seed region	Name		BA	No of Vertices	Talairach coordinates x	y	z
left inferior parietal lobule	left	fusiform gyrus	19	173	-42	-65	-13
	right	fusiform gyrus	19	91	34	-59	-16
	right	inferior frontal gyrus (VLPFC)	47	83	30	21	10
right inferior parietal lobule	left	intraparietal sulcus	7, 40	147	-38	-36	44
	right	insula	13	60	30	22	10
right lingual gyrus	left	fusiform gyrus	19	91	-39	-74	-14
	right	fusiform gyrus	19	67	21	-78	-16

Table 6. Functional connectivity results.

4.5 Discussion

We studied the neurophysiological correlates of cortical dysfunction in patients with EOS compared to healthy control subjects during the encoding, maintenance and retrieval stages of a visual working memory task in which memory load was varied in three steps. Patients differed from controls in that they had significantly lower working memory capacity and exhibited abnormal activity patterns in key regions of the fronto-parietal network and in extrastriate visual areas. As predicted, these patterns were specific for the different working memory component processes. Patients also showed disturbed functional connectivity during encoding and retrieval.

Abnormal activity patterns within the fronto-parietal network during encoding were largely indicative of a general disturbance of this component process independently of memory load. Patients underactivated two clusters within the left VLPFC, particularly at higher memory load. This part of the VLPFC is thought to support the structured encoding of visuospatial information into working memory (Bor et al., 2003). The involvement of the VLPFC in encoding is further underscored by the correlation between individual working memory capacity and its activation in controls. Patients also failed to activate the left IPL, which is also closely involved in encoding (Linden et al., 2003; Mayer et al., 2007). Overall, these findings confirm our hypothesis of a primary encoding deficit in patients.

Interestingly, the hypoactivation of the VLPFC during encoding preceded the hyperactivation of the left DLPFC during the early maintenance phase, which switched to hypoactivation with increasing memory load. A similar switch from hyper- to hypoactivation was found in the left FEF and the left IPS, both of which are part of a network involved in the control of selective visual attention (Corbetta and Shulman, 2002) and the maintenance of object information (Linden et al., 2003; Todd and Marois, 2004; Xu and Chun, 2006; Mayer et al., 2007). The DLPFC has been shown to support the maintenance of multiple object representations (Linden et al., 2003; Edin et al., 2009). Hyperactivation of this network during low memory load could reflect a compensatory process to overcome preceding encoding problems while its relative hypoactivation with increasing memory load could be due to a saturation of compensation capacity. Apparently patients had to mobilize more attentional resources than controls

already at low memory load but were unable to adequately increase the engagement of the fronto-parietal retention network with increasing memory load.

During retrieval patients showed bilateral hyperactivation in inferior VLPFC, ACC, and the IPL. As the VLPFC and the ACC are crucial for working memory retrieval (Druzgal and D'Esposito, 2001; Bledowski et al., 2006; Nee and Jonides, 2008), the increased activation might reflect a compensatory mechanism for impaired working memory encoding. This interpretation is supported by the negative correlation between the hypoactivation of left VLPFC during encoding with the hyperactivation of the right inferior VLPFC during retrieval in patients. Finally, the higher activation of the left anterior PFC in patients could reflect an increased demand for high-level cognitive control processes (Miller and Cohen, 2001; Koechlin and Hyafil, 2007).

During encoding patients exhibited reduced activation in the higher memory load conditions in several visual areas. These included the left MOG and the right lingual gyrus adjacent to primary visual cortex, for which activation was positively correlated with working memory capacity in controls. Stronger activation for memory load 1 in patients in the right lingual gyrus may indicate a compensatory mechanism, which failed as memory load increased. This area also showed reduced functional connectivity with the left early visual cortex in patients. Reduced functional connectivity was also observed in patients between the left LOC, a visual area essential for the detailed processing of object information (Malach et al., 1995; Grill-Spector et al., 1998) and the left VLPFC. These findings suggest deficits of encoding already at early stages of visual processing and in addition a disruption of communication between the ventral visual pathway and the VLPFC (Ungerleider et al., 1998). Thus mechanisms critical for object recognition (Sehatpour et al., 2008) and object working memory (Goldman-Rakic, 1995; Ungerleider et al., 1998) seem to be affected. This extends our previous reports of abnormal ERP (Haenschel et al., 2007) and evoked oscillatory responses (Haenschel et al., 2009) during encoding in the same patients. These results are compatible with the view that impaired perceptual processing contributes to working memory dysfunction (Haenschel et al., 2007; Koychev et al., in press).

Working memory maintenance seems to be associated with sustained activity in visual areas (Furey et al., 2000; Pasternak and Greenlee, 2005; Harrison and Tong, 2009). The reduced bilateral activation of the MOG in patients during the early maintenance phase could thus be a correlate of an additional malfunction of maintenance mechanisms. Accordingly, the enhanced activity in the PFC and the increased functional connectivity between visual areas, VLPFC and IPL in patients during retrieval could reflect the enhanced engagement of read out mechanisms in order to compensate for impaired encoding and maintenance.

During early maintenance, patients showed an abnormally strong deactivation in parts of the default mode network (DMN) (Gusnard et al., 2001; Raichle et al., 2001) including the PCC and the precuneus bilaterally which in controls was either absent or much smaller in magnitude. During late maintenance a similar effect was observed in the left STG and the left PCC and the patients' level of remaining activity was inversely correlated with working memory capacity. This could point to a preserved mechanism in patients, which supports maintenance processes. On the other hand, there is increasing evidence for disturbances of the DMN in schizophrenia (Kim et al., 2009; Zhang and Raichle, 2010), which have been linked to working memory dysfunction (Whitfield-Gabrieli et al., 2009). Therefore, our results might also indicate that maintenance deficits in schizophrenia partly result from a dysregulation of the DMN.

In summary our results indicate, that working memory deficits in schizophrenia are a consequence of disturbances in several of the cortical networks that are engaged during the component processes of working memory. While abnormalities in fronto-parietal and visual areas are strongly suggestive of an encoding deficit, some of the disturbances found during later stages of the task, especially prefrontal hyperactivation during retrieval, can be interpreted as consequences of this primary impairment. The use of a cortex alignment procedure may have increased our power to detect these specific patterns of abnormal activity. They might have been obscured in many previous studies, which examined the neurophysiological and genetic (Egan et al., 2001b; Bertolino et al., 2006; Meyer-Lindenberg and Weinberger, 2006) basis of working memory dysfunction. Consequently, investigating the heritability of working memory component process impairments and the related

neurophysiological abnormalities could help to define more valid endophenotypes.

We conclude that studying the impact of deficits in individual component processes on cortical activation and connectivity appears to be crucial for our understanding of the complex cognitive, neurophysiological and genetic architecture of working memory dysfunction in schizophrenia. This might ultimately lead to the development of reliable biomarkers and improved cognitive remediation strategies (Olincy et al., 2006; Wykes et al., 2007).

4.6 Supplementary Material

In a previous analysis of our data set (Haenschel et al., 2007) we focused on group differences in early visual cortex related to reduced P1 amplitudes. To this end we computed a group contrast (t-statistics) and searched for significant group differences within a 15 mm radius of the coordinates of an established P1 dipole model published by Noesselt et al. (Noesselt et al., 2002). We observed reduced bilateral activation in early visual areas in patients both during encoding and retrieval.

We aimed to compare the results of this Talairach space based analysis with our cortex-based approach. We created a mask, which restricted our ANOVA to all vertices within a 15 mm radius of the coordinates of the P1 generators according to the dipole model published by Noesselt et al. (left hemisphere: −39, −74, 4; right hemisphere: 32, −75, 6; Talairach space). The resulting maps were thresholded at $p<.01$, uncorrected (Figure S5).

For encoding we observed a bilateral region in the middle occipital gyrus which showed a main effect of group. Bilaterally these clusters showed a high degree of overlap with areas which showed a group by memory load interaction. Because of the high degree of overlap they were combined into a single region of interest for each hemisphere. In both regions, activation increased with memory load only in controls. In the left middle occipital gyrus controls had significantly higher activation than patients for memory load 2 and 3. In the right middle occipital gyrus controls had significantly higher activation than patients for memory load 3.

For retrieval a main effect of group was found in the left middle occipital gyrus and right middle temporal gyrus. In both areas controls had significantly higher activation than patients in all memory load conditions with the exception of memory load 1 in the left middle occipital gyrus, where only a trend was detected.

These results mirror our initial analysis in Talairach space. In our cortex-based analysis, group differences during encoding in the lower memory load conditions were less pronounced. This might be due to reduced anatomical variability in patients as a consequence of the cortex-based alignment.

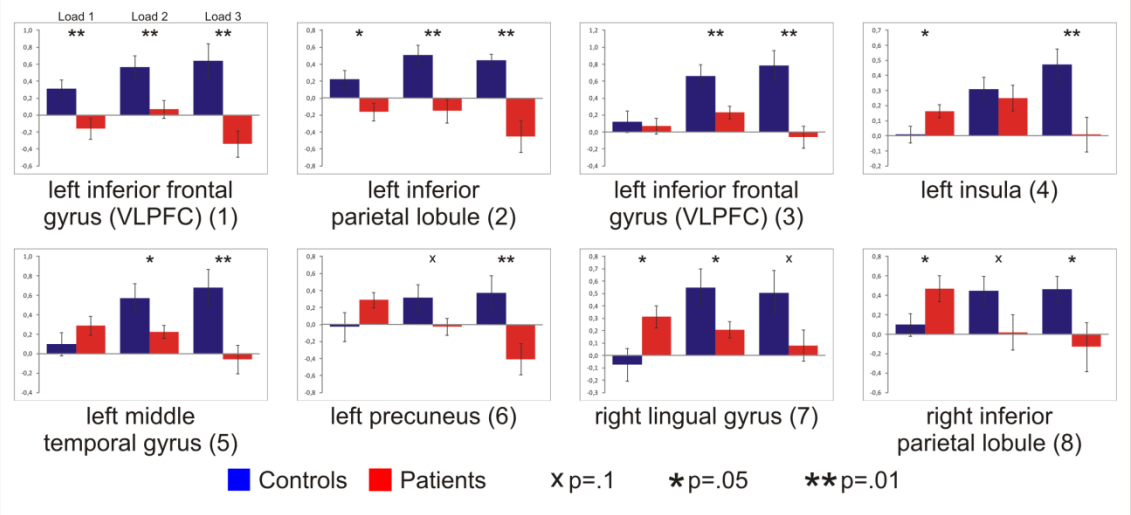

Figure S1. Beta values encoding. Beta values for the regions of interest derived from the ANOVA for encoding for controls (blue) and patients (red). The number for each region corresponds to its index in Figure 3 and Table 2. Error bars represent SEM. ^{x}p<.1, *p<.05, **p<.01.

Importantly, all of the visual areas, which we report in our whole brain analysis, lie beyond the 15 mm radius around the P1 dipoles. Therefore, they are probably not directly related to the abnormalities of the P1 we observed in our patients.

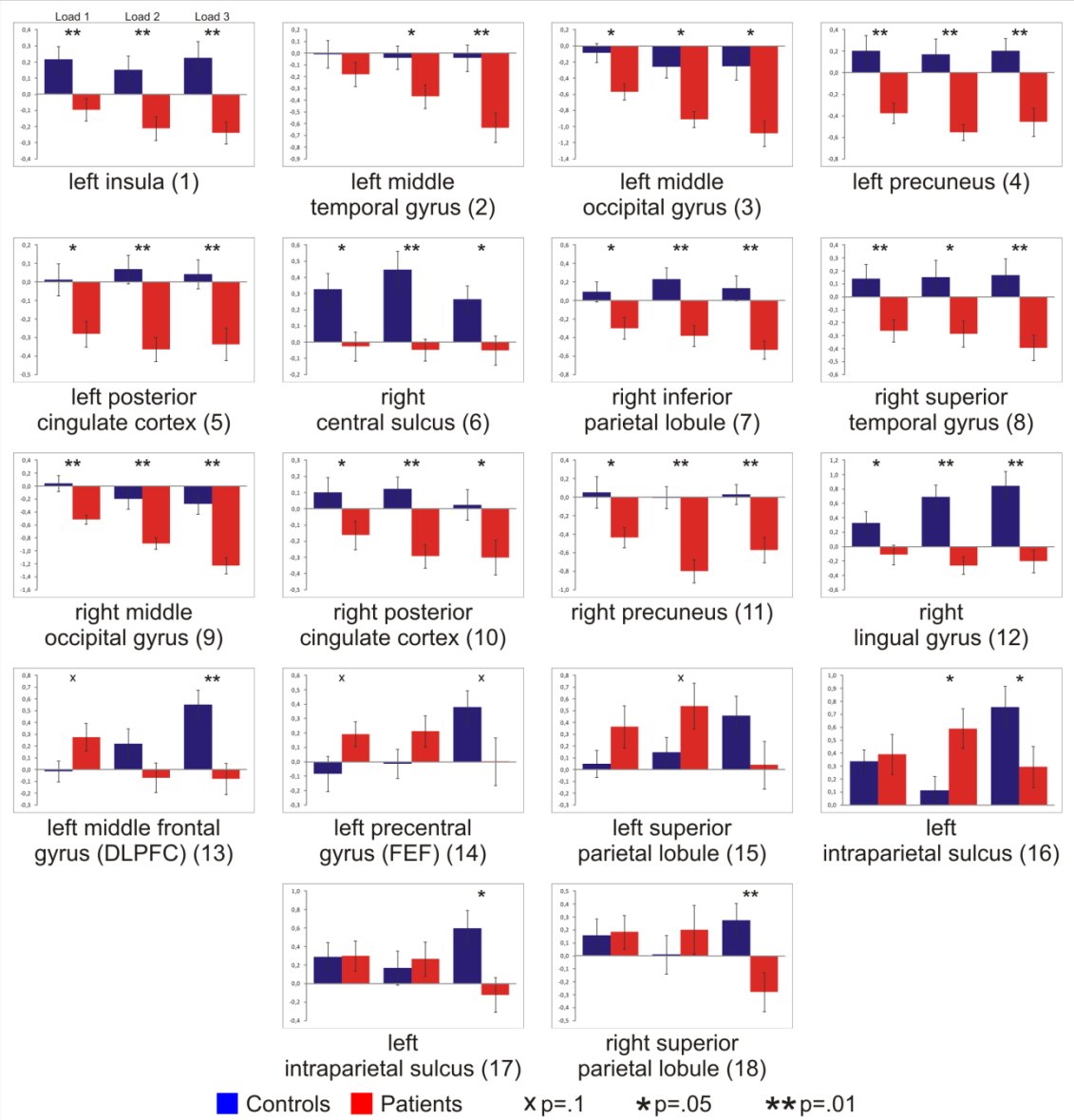

Figure S2. Beta values early maintenance. Beta values for the regions of interest derived from the ANOVA for early maintenance for controls (blue) and patients (red). The number for each region corresponds to its index in Figure 4 and Table 3. Error bars represent SEM. ^{X}p<.1, *p<.05, **p<.01.

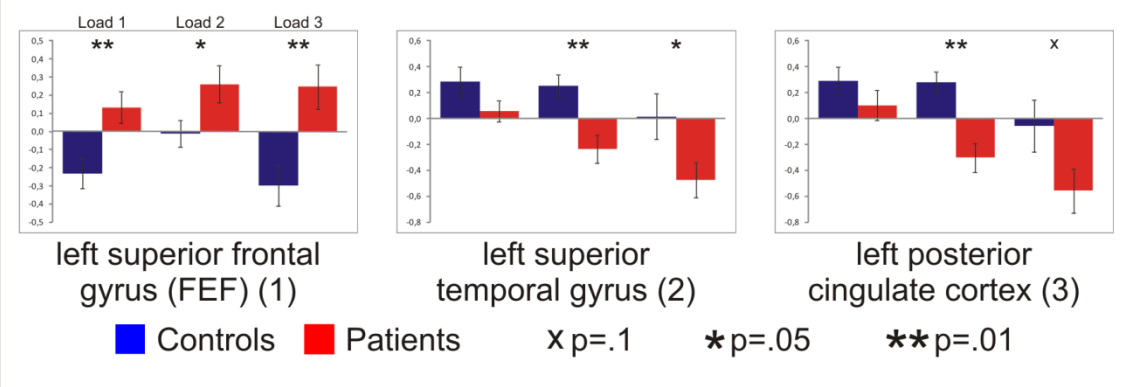

Figure S3. Beta values late maintenance. Beta values for the regions of interest derived from the ANOVA for late maintenance for controls (blue) and patients (red). The number for each region corresponds to its index in Figure 5 and Table 4. Error bars represent SEM. ^{X}p<.1, *p<.05, **p<.01.

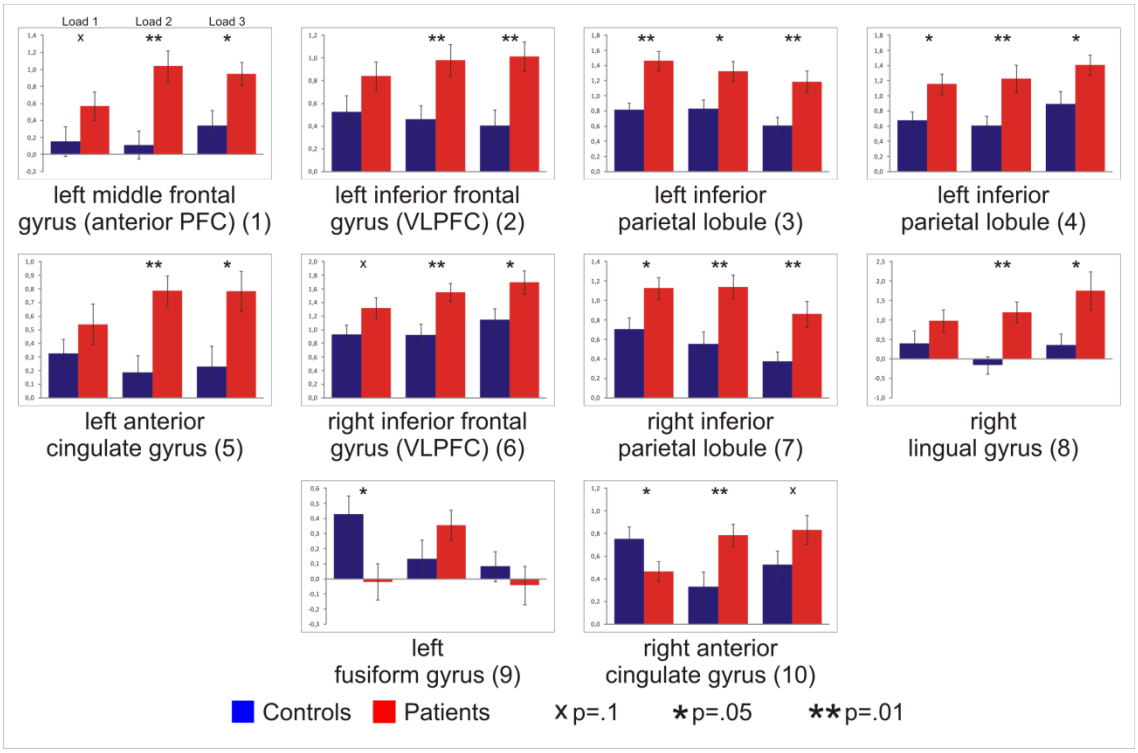

Figure S4. Beta values retrieval. Beta values for the regions of interest derived from the ANOVA for retrieval for controls (blue) and patients (red). The number for each region corresponds to its index in Figure 6 and Table 5. Error bars represent SEM. ^{X}p<.1, *p<.05, **p<.01.

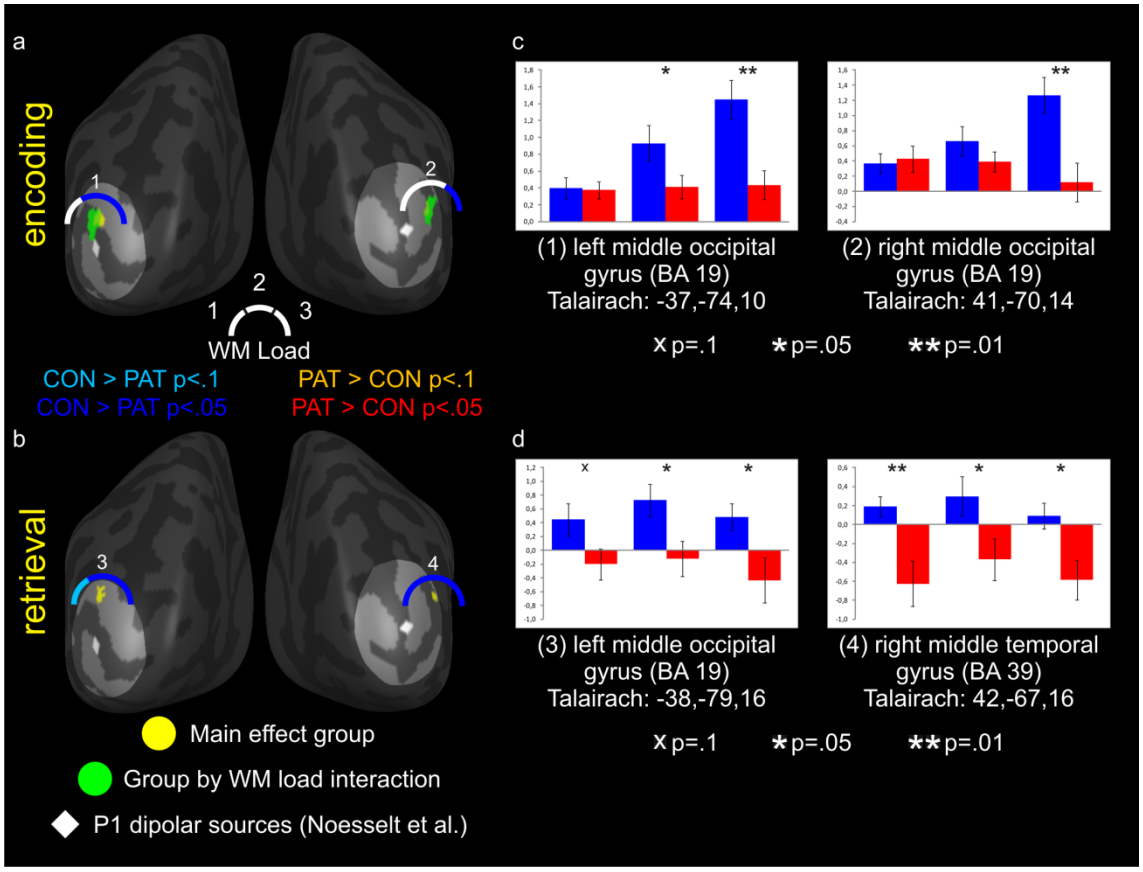

Figure S5. Abnormal activation related to reduced P1 amplitudes. F-maps of the ANOVA for encoding (a) and retrieval (b) thresholded at p<.01, uncorrected. White diamonds indicate the position of the P1 dipoles derived from the model of Noesselt et al. (left hemisphere: −39, −74, 4; right hemisphere: 32, −75, 6; Talairach space) which were used in our previous analysis of early visual areas. The analysis was restricted to a radius of 15 mm around these coordinates. Areas, which showed a main effect of group, are depicted in yellow, areas, which showed a group by memory load interaction, are depicted in green. Overlapping regions were combined into a single region. The results of the two-tailed t-tests for group differences for each memory load condition are displayed in the half circle above each region. Trends and significant differences are indicated by light blue and blue for higher activation in controls compared to patients, and by orange and red for higher activation in patients compared to controls respectively. c) and d): Beta values and Talairach coordinates of each regions for encoding and retrieval respectively.

Chapter 5: General Discussion

The general aim of this dissertation was to investigate the cortical networks supporting visual working memory and their disturbance in schizophrenia. To this end, the effect of a parametric increase of memory load on different parts of the cortical working memory networks during working memory encoding, maintenance and retrieval was assessed in all three studies. This main experimental manipulation was carried out in order to elucidate the neurophysiological underpinnings of working memory capacity limitations and to test the hypothesis of a differential effect of increasing memory load on abnormal cortical activation patterns in schizophrenia.

5.1 The neurophysiological basis of working memory capacity constraints

The results of the first study point to a crucial role of attentional processes for the limited capacity of working memory. This interpretation is based on the observation of a bilateral inverted U-shape pattern of BOLD activity with increasing memory load in areas closely linked with selective attention, i.e. the FEF and areas around the IPS. In both regions, the increase of the number of stored items from memory load three to memory load four was negatively correlated with the increase of BOLD activity from memory load three to memory load four. This correlation was already observed during encoding.

A number of more recent fMRI studies also reported a close association between BOLD activity in the posterior parietal cortex and working memory capacity (Todd and Marois, 2004, 2005; Xu and Chun, 2006). In contrast, activity in the superior parietal cortex and the LOC has been shown to reflect not the number of objects stored in working memory but rather object complexity and the total amount of information which can be encoded and maintained in working memory (Xu and Chun, 2006). These findings extend our own observation and indicate that attentional mechanisms supported by distinct parietal areas limit both the number of items which can be simultaneously stored in working memory and the level of complexity of these items. This is also in line with psychophysical evidence, that both the visual information load and the number of objects impose capacity limits on visual working memory (Alvarez and Cavanagh, 2004). Further support for the association of neuronal

activity in parietal cortex and working memory capacity comes from a recent MEG study (Palva et al., 2010). This study reported a correlation between working memory capacity and neural synchrony in the alpha- and beta-band in frontoparietal networks centered on the left and right IPS.

Two ERP studies have also investigated the neurophysiological substrates of working memory capacity limits. The first study (Vogel and Machizawa, 2004) demonstrated that subjects working memory capacity was correlated with their ERP amplitude at lateral occipital and posterior parietal electrodes during the maintenance phase. In the second study (Vogel et al., 2005), which examined the same ERP waves, subjects also had to filter out distracting stimuli which were presented simultaneously with target items in an array. Subjects with high working memory capacity could be distinguished from subjects with low working memory capacity based on their ERP amplitude in the presence of distracting stimuli. In subjects with high working memory capacity EPR amplitude was correlated with the number of target stimuli whereas in subjects with low working memory capacity ERP amplitude closely reflected the total number of stimuli.

Interestingly, it has been shown in another recent fMRI study, that the prefrontal cortex and the left basal ganglia seem to be closely involved in the filtering of irrelevant information (McNab and Klingberg, 2008). Activity in these regions was positively correlated with individual working memory capacity scores and negatively correlated with activity in the right IPS when subjects had to suppress distracting information during the encoding of spatial information.

These findings indicate that working memory capacity is at least partially determined by the ability to efficiently control access to working memory during the encoding stage, a process which is highly dependent on selective attention (Cowan and Morey, 2006). It has also been shown, that during encoding selective attention and working memory draw upon common neuronal resources in a number of brain regions including the FEF and the IPS (Mayer et al., 2007). Taken together, these studies indicate a strong overlap between working memory and selective attention not only for maintenance processes but also for the encoding of information.

This fits nicely with the association between the level of BOLD activation in attention related areas – particularly in the left IPS – and working memory

capacity during encoding in this study. However, in contrast to subsequently published fMRI studies (Todd and Marois, 2004, 2005; Xu and Chun, 2006), which reported a positive correlation in the IPS, a negative correlation was observed in the data presented in this dissertation.

This discrepancy might be explained by differences in task design and stimulus material. The studies cited above employed a variety of change detection paradigms which required subjects to encode arrays of simultaneously presented items. These items were characterized by one or more elementary features, e.g. color, orientation, and basic shapes such as squares. Successful performance of these task required subjects to encode all of the relevant features.

In contrast subjects may have relied on a chunking strategy to recode the complex but distinct abstract visual shapes used in the present study when memory load was exceeding their capacity. Chunking refers to the use of “chunks”, existing long-term memory representations, to recode information stored in working memory (Miller, 1956; Gobet et al., 2001). Chunks have been defined as a collection of elements having strong associations with one another, but weak associations with elements within other chunks (Gobet et al., 2001). Chunking allows subjects to memorize an amount of information considerably larger than their working memory capacity. Such a strategy should reduce the attentional demand which would explain the decrease of activation in the FEF and IPS regions at memory load 4. It has been shown that chunking specifically engages the left PFC (Bor et al., 2003). This observation is in line with the increase of activity in the left PFC from memory load 3 to memory load 4. Thus, the findings of the present study are compatible with the interpretation, that those subjects which were able to store relatively large amounts of information successfully used a chunking strategy.

In contrast, the stimuli used in the subsequently published fMRI studies (Todd and Marois, 2004, 2005; Xu and Chun, 2006) probably do not lend themselves to a chunking strategy, because their elementary features do not correspond well to distinct long-term memory representations. Therefore, the use of complex abstract visual shapes might have certain limitations, because it does not control for changes in strategy, i.e. the use of chunking, with increasing memory load.

The findings presented in this dissertation and the results of subsequently published studies indicate that limited attentional resource might constrain working memory capacity in a number of ways. The close correspondence between working memory and attention observed in the current study has already been pointed out by Allen Baddeley (Baddeley, 1995), who argued that working memory could also be termed “working attention”. Further research is needed in order to fully understand the degree of overlap and the distinguishing features of these two cognitive processes.

5.2 The neurophysiological basis of working memory deficits in schizophrenia

5.2.1 The relevance of working memory component processes

The second and third study presented in this dissertation provide converging evidence for an impairment of encoding as a main cause of working memory dysfunction in schizophrenia. Abnormal ERP responses were observed during both early and late stages of working memory encoding, but P1 amplitude was the strongest predictor of performance in healthy controls. In the fMRI data, reduced activation was observed both in early visual areas as well as in the frontoparietal network, especially in the left PFC. The reduced functional connectivity between the left PFC and the left LOC suggests a strong relationship between these deficits. Our findings also underscore that impaired working memory encoding is not the result of a dysfunction within a circumscribed region such as the PFC but rather the consequence of complex disturbances in the cortical networks supporting this process, which affect both its early and later stages.

While our data poins for the first time to the particular relevance of early perceptual processing deficits for working memory impairment, their relationship to deficits during subsequent stages of working memory encoding as well as to working memory maintenance remains to be elucidated.

Psychophysical evidence indicates that the later stage of working memory consolidation is impaired in schizophrenia (Fuller et al., 2005; Fuller et al., 2009). Working memory consolidation is conceptualized as an attention demanding process during encoding required for the formation of durable mnemonic representations (Jolicoeur and Dell'Acqua, 1998; Vogel et al., 2006)

which is an independent process from working memory maintenance(Woodman and Vogel, 2005). It has been shown, that delayed or disturbed working memory consolidation leads to a delayed onset of or a reduced amplitude of the P300 respectively (Vogel and Luck, 2002). Thus, the patients reduced P3 amplitudes in the current study could be interpreted in part as a neurophysiological correlate of impaired consolidation of information in working memory.

Presently, it is unclear, how impaired early perceptual processing of visual information might influence the subsequent consolidation of this information in working memory. One could hypothesize, that impaired early perceptual processing might increase the likelihood that the resulting object representations are not adequately consolidated in working memory. This hypothesis could be tested by selectively manipulating perceptual difficulty, e.g. by varying the degree of noise in the presented stimuli. Also, through the use of a staircase procedure perceptual difficulty for each control and each patient could be equalized. This way the impact of early perceptual processing deficits could be minimized in order to investigate directly, to which degree impaired working memory consolidation is independent from these deficits. Analogous research strategies need to be applied in order to investigate, to which degree the maintenance of information after successful perceptual processing and consolidation is impaired.

The observation of distinct patterns of prefrontal cortical dysfunction during different working memory component processes in the fMRI data demonstrates the power of event-related study designs for the investigation of the neurophysiological disturbances underlying cognitive dysfunction in schizophrenia. These findings have implications for models of prefrontal cortical dysfunction in schizophrenia.

Notably, previous fMRI studies that reported prefrontal hyperactivation employed working memory tasks that required the repeated retrieval of information from working memory (Callicott et al., 2000; Manoach et al., 2000). Two event-related studies specifically observed prefrontal hyperactivation during retrieval (Johnson et al., 2006; Potkin et al., 2009). However, even the latter findings were not interpreted in light of existing evidence regarding deficits in individual working memory component processes. The results of the current

study show that prefrontal hyperactivation constitutes to some extent a compensatory mechanism for prefrontal hypoactivation during working memory encoding. Thus, current concepts of prefrontal cortical inefficiency signified by hyperactivation (Winterer et al., 2004; Tan et al., 2007; Potkin et al., 2009) appear to apply only to working memory retrieval and to a lesser degree to working memory maintenance. The present results indicate that maintenance and retrieval related recruitment of prefrontal circuits is “inefficient”, but that prefrontal hyperactivation might not necessarily represent a primary dysfunction. This inefficiency might rather be a secondary consequence of a primary failure of prefrontal circuits to sufficiently process information during encoding. Finally, the impact of memory load on prefrontal cortical dysfunction might not be as relevant as previously suggested (Callicott et al., 2003a; Manoach, 2003), since it was only evident during the early maintenance phase. It has to be noted however, that increasing memory load did lead to a switch from hyper- to hypoactivation in several areas outside prefrontal cortex, even during encoding, e.g. in the left insula and in right early visual cortex. It is tempting to speculate, that this might partly be a compensatory recruitment of areas whose function is not compromised to the same degree as the prefrontal cortex.

5.2.2 Working memory dysfunction and the dopamine dual-state theory

The observation of distinct patterns of prefrontal cortical dysfunction during different working memory component processes ties in nicely with the current dual-state theory of prefrontal dopaminergic neurotransmission (Durstewitz and Seamans, 2008; Rolls et al., 2008). The dual-state theory implies that prefrontal dopaminergic neurotransmission can change dynamically between a state dominated by D1 receptor activation and a state of predominant D2 receptor activation. It is based on the observation that neurons originating in the ventral tegmental area considerably increase the release of dopamine in prefrontal cortex during working memory maintenance (Durstewitz and Seamans, 2008; Rolls et al., 2008). Because of the predominantly peri- and extrasynaptic location of D1 receptors and the intrasynaptic location of D2 receptors, only relatively high levels of prefrontal dopamine lead to a preferential activation of D1 over D2 receptors. D1 receptors act antagonistically to D2 receptors. They

increase intracellular cAMP and activate DARPP32, a key enzyme in the intracellular dopaminergic signaling cascade. This amplifies NMDA-receptor induced excitatory postsynaptic potentials (EPSPs) in prefrontal pyramidal neurons as well as GABAa-receptor induced inhibitory postsynaptic potentials (IPSPs) (Seamans et al., 2001b; Seamans et al., 2001a; Durstewitz and Seamans, 2008). Together, these mechanisms amplify and stabilize recurrent activity in prefrontal circuits related to the maintenance of information in working memory while suppressing irrelevant neuronal signals (Durstewitz and Seamans, 2008; Rolls et al., 2008). Conversely, the comparatively lower level of prefrontal dopamine during retrieval changes the D1:D2 receptor activation ratio in favor of the D2 receptor, which facilitates the flexible processing of new information and the initiation of an adequate behavioral response (Durstewitz and Seamans, 2008; Rolls et al., 2008).

The putative reduced prefrontal dopaminergic neurotransmission in schizophrenia (Okubo et al., 1997; Abi-Dargham et al., 2002; Winterer and Weinberger, 2004) would alter the D1:D2-receptor activation ratio in favor of the D2 receptor. Interestingly, amplified D2-receptor signaling has been shown to reduce prefrontal activity during encoding but leads to increased prefrontal activity during retrieval (Gibbs and D'Esposito, 2005). Attenuating D1 receptor activation has been shown to disturb the sustained firing of prefrontal neurons during working memory maintenance (Wang et al., 2004). These findings broadly match the results of the current study, implying that altered dopaminergic neurotransmission contributes to the distinct abnormal activation patterns observed in our patients. It has to be noted however, that all patients in our study received antipsychotic medication. The antidopaminergic properties of this medication most likely had an impact as well. Therefore, the current results need to be interpreted cautiously and future studies in medication naïve patients during the prodromal phase or at the beginning of the first psychotic episode are required.

While the dual-state theory underscores the necessity to isolate individual working memory component processes, a number of open questions remain. Although the density of dopaminergic synapses in the prefrontal cortex is particularly high, dopaminergic synapses can be found throughout cortex (Lewis et al., 1998; Lewis et al., 2001; Muller and Huston, 2007). Yet it is not known,

how other more posterior cortical areas are regulated by dopaminergic signals during working memory. Currently, the dual-state theory is founded mostly on empirical data and computational models of working memory maintenance and retrieval. Since the encoding of information into working memory is emerging as the primary deficit in schizophrenia, it will be crucial to extend the dual-state theory to this component process as well. If multiple items have to be encoded, the neuronal signatures of these items have to be stabilized while simultaneously allowing the flexible processing of further information, which might be accidentally suppressed under strong D1 receptor influence. Therefore, the tuning of dopaminergic neurotransmission during working memory encoding might have to be particularly fine both on the temporal and the spatial scale. This complexity might explain to some extent why encoding is disturbed in schizophrenia.

5.2.4 Working memory dysfunction and abnormal neural oscillations

The results of the patient study are also relevant with regard to the concepts of neural oscillations and neural synchrony. The synchronization of neural oscillations appears to be an important mechanism for the coordination of distributed neuronal activity in the brain (Singer, 1999; Varela et al., 2001). A large body of evidence from electrophysiological recordings in animals and humans as well as EEG and MEG studies indicates that synchronous oscillatory activity in the theta-, alpha-, beta- and gamma-band is associated with a variety of cognitive functions such as attention, long-term memory, sensory-motor integration and also with consciousness (Singer, 1999; Varela et al., 2001; Kaiser and Lutzenberger, 2003; Jensen et al., 2007).

In EEG and MEG data two types of oscillatory activity are commonly distinguished: evoked oscillations which are time-locked to an external stimulus and induced oscillations which appear with a jitter in latency and seem to represent endogenous oscillatory activity (Tallon-Baudry and Bertrand, 1999).

Disturbances of oscillations and neuronal synchrony might lie at the heart of the disconnection syndrome (Uhlhaas and Singer, 2010). They could offer a parsimonious explanation for important aspects of the clinical phenotype such as hallucinations (Ford et al., 2007; Heinks-Maldonado et al., 2007). They have also been linked to a number of cognitive impairments (Spencer et al., 2003;

Spencer et al., 2004; Cho et al., 2006; Uhlhaas et al., 2006). Working memory, which has been associated with neural oscillations in a number of frequency bands, especially the gamma frequency band (Tallon-Baudry et al., 1998; Jensen et al., 2007), might also be impaired due to disturbed neural oscillations. To test this hypothesis, oscillatory activity during working memory component processes was investigated with EEG in a subset of 14 patients and controls, derived from the sample presented in this dissertation. The results of this analysis have been published in a separate paper which is not part of this dissertation (Haenschel et al., 2009). In patients pronounced deficits in oscillatory activity were observed during all phases of the task. During the encoding of visual information, they showed reduced evoked oscillatory activity in the theta, alpha and beta band over posterior electrodes. During the later maintenance phase of the task, induced oscillatory activity in the gamma-band over anterior electrodes was stronger in patients for a memory load of two items. However, patients failed to sustain this level of gamma-band activity for a memory load of three items, where gamma-band power dropped below the level of controls. During retrieval, evoked and induced anterior theta as well as induced posterior gamma-band activity was significantly reduced. In controls but not in patients, evoked posterior beta, alpha and anterior theta activity during encoding predicted working memory capacity as estimated by Cowan's K. Whereas working memory capacity was negatively correlated with evoked beta and theta oscillatory activity, it was positively correlated with evoked alpha activity.

The distinct abnormalities in oscillatory activity during the different working memory component processes, particularly the observation of an early posterior deficit during encoding are well in line with the fMRI results. The correlation between oscillatory activity over posterior electrodes and working memory capacity during encoding in controls nicely corresponds to the correlation between P100 and performance and the correlation in between BOLD activity and working memory capacity in the right early visual cortex. However, the detection of additional correlations between working memory capacity in the left posterior VLPFC and the left insula in the fMRI data underscore the advantages of the high spatial resolution of fMRI. The switch from increased (memory load 2) to decreased (memory load 3) frontal induced gamma oscillatory activity in

patients during the maintenance phase mirrors to some extent the prefrontal findings in the fMRI data during the same component process. However, here a switch from hyper- to hypoactivation was observed between memory load 2 and 3. This discrepancy and the divergent results during retrieval may be attributable to the poor spatial resolution of EEG.

For future studies, the full integration of fMRI and EEG/MEG data (Bledowski et al., 2006) is attractive for a number of reasons. The study of abnormal functional or effective connectivity with fMRI is limited by the poor temporal resolution of this method. On the other hand functional and effective connectivity can be readily assessed in EEG or MEG data using the Granger causality approach, which should massively benefit from the high temporal resolution offered by these methods. Also the neurophysiological basis of abnormal functional or effective connectivity cannot be determined with fMRI. In contrast EEG and MEG are ideally suited to investigate, whether altered neural synchrony within and across specific frequency bands might be related to these findings. One has to bear in mind though that measures of connectivity based on fMRI Granger causality mapping and measures of neural synchrony in EEG or MEG data differ drastically not only in terms of the temporal and spatial resolution of the data but also in terms the methods used to generate these measures. It remains to be investigated, whether these approaches provide corresponding or complimentary information. Despite these methodological issues, combining fMRI and EEG or MEG should provide a more complete assessment of the disconnection syndrome found in schizophrenia. Additionally, such a combination can improve the source localization of EEG/MEG data (Fujimaki et al., 2002; Bledowski et al., 2004; Bledowski et al., 2006).

Linking fMRI data of working memory dysfunction with changes of neural oscillations is also attractive because of the relationship between the latter changes and specific alterations in GABAergic interneurons which have been discovered in post-mortem studies of prefrontal cortical brain slices of patients with schizophrenia. These changes are regarded as particularly important due to the central role of the affected GABAergic interneurons in the generation of neural oscillations (Pouille and Scanziani, 2001; Klausberger et al., 2003). Abnormalities in distinct subtypes of cortical GABAergic interneurons have been identified in schizophrenia which might have detrimental effects on neuronal

oscillations (Lewis et al., 2005). Fast spiking parvalbumin (PV)-containing chandelier cells which form a network linked by both chemical and electrical synapses in the middle layers of cortex seem to influence oscillatory gamma-band activity via inhibitory synaptic input on the axon initial segments of pyramidal neurons (Tamas et al., 2000). In prefrontal PV-positive neurons of patients mRNA expression of the 67kDa isoform of the GABA synthesizing enzyme glutamic acid decarboxylase 1 (GAD67) is diminished (Akbarian et al., 1995; Volk et al., 2000; Lewis et al., 2005). The resulting decrease in extracellular prefontal GABA levels should lead to reduced gamma-band activity and impairments in working memory. This notion is supported by a PET study using [11C]Flumazenil which showed that higher capacity to increase extracellular GABA predicts greater gamma-band power during the performance of a working memory-cognitive control task (Frankle et al., 2008). Additionally, in patients with schizophrenia a significant reduction of prefrontal gamma-band power during the performance of the same task was reported (Cho et al., 2006). Other alterations – decreased PV expression, reduced GABA transporter 1 (GAT1) expression and up-regulation of post-synaptic GABAa receptors containing the α2 subunit – may be compensatory attempts to augment the presynaptic release of GABA and the duration and amplitude of inhibitory postsynaptic postsynaptic potentials (IPSPs) respectively (Lewis et al., 2005). In another class of interneurons, cholecystokinin (CCK)-containing basket cells, GABA synthesis seems to be reduced in a similar fashion (Hashimoto et al., 2008b). Like chandelier neurons they regulate the output of pyramidal neurons primarily through GABAa receptors containing the α2 subunit but target pyramidal cell bodies and proximal dendrites. Recent data indicates that alterations in GABAergic interneurons are conserved across cortical regions – even in primary visual cortex (Hashimoto et al., 2008a).

These post-mortem findings provide a convincing link between alterations of gene expression and cortical microstructure on the one hand and widespread changes of brain activation and connectivity on the other. Additionally, the excitability of fast-spiking prefrontal interneurons seems to be increased specifically by D1 receptor activation (Kroner et al., 2007). Together with the D1 receptor mediated amplification of both the NMDA-receptor and the GABAa-receptor (Seamans et al., 2001b; Seamans et al., 2001a), this should aid the

generation of neural oscillations (Cunningham et al., 2006; Roopun et al., 2008). These findings suggest that abnormalities of dopaminergic, glutamategic and GABAergic neurotransmission in schizophrenia might converge to disturb neural oscillations and neural synchrony. Integrating the study of these neurotransmitter systems, e.g. by using PET, with fMRI and EEG or MEG measures of working memory dysfunction would allow to test this hypothesis.

5.3 Directions for future research

5.3.1 The endophenotype strategy

Functional neuroimaging might also offer a solution for the fact that the phenotype of schizophrenia does not correspond well to the underlying genetic alterations (Gottesman and Gould, 2003; Meyer-Lindenberg and Weinberger, 2006). This poor genotype-phenotype relationship might considerably hamper genetic studies. The use of endophenotypes has been proposed as solution to this problem (Gottesman and Shields, 1972; Gottesman and Shields, 1973; Gottesman and Gould, 2003). Endophenotypes are conceptualized as distinct traits formed along the pathway from genotype to disease. In contrast to the clinical phenotype, these traits constitute relatively less complex and more clearly biologically based phenotypes. The endophenotype concept implies that the decomposition of the clinical phenotype into measurable components should ultimately lead to more successful genetic analyses (Heinrichs, 2004). Five indicators have been proposed (Gottesman and Gould, 2003) to identify potential endophenotypes. (1) An endophenotype is associated with illness in the population. (2) It is heritable. (3) It is primarily state-independent, i.e. it can be found in an individual whether or not illness is active. (4) Within families, endophenotype and illness co-segregate. (5) The endophenotype found in affected family members is found in unaffected family members at a higher rate than in the general population.

Importantly, cognitive dysfunction seems to fulfill these criteria (Gur et al., 2007a; Gur et al., 2007b). There have indeed been several successful links of specific cognitive deficits to putative schizophrenia risk genes. These include executive function and COMT (Goldberg et al., 2003), long- and short-term memory and DISC1 (Cannon et al., 2005; Hennah et al., 2005), attention and DTNBP1 as well as spatial working and NRG1 (Stefanis et al., 2007). However,

none of these putative risk loci were confirmed by recent genome-wide association studies (GWAS).

While more reliable and parametrizable than clinical symptoms, impairments in cognitive processes constitute behavioral phenotypes as well and their association with specific genotypes remains very indirect (Meyer-Lindenberg and Weinberger, 2006). In contrast, the direct measurement of abnormalities in brain structure and function through the use of neuroimaging techniques should yield endophenotypes more proximal to the genetic underpinnings of schizophrenia (Meyer-Lindenberg and Weinberger, 2006).

A growing number of fMRI studies have used neurophysiological signatures of working memory dysfunction as an endophenotype and were able to provide evidence for an association with a variety of putative schizophrenia risk genes such as COMT (Egan et al., 2001b; Meyer-Lindenberg et al., 2006), GRM3 (Egan et al., 2004), GAD1 (Straub et al., 2007), DTBN1 (Wolf et al., 2009) and ZNF804A (Esslinger et al., 2009) (with only the last locus derived from GWAS). However, most of these studies did not use event-related designs and were therefore unable to associate these genetic alterations with a specific working memory component process. This makes the result of these studies hard to interpret with regards to the neurophysiological mechanisms through which these putative risk genes exert their effect. Separating the component processes of working memory would be crucial in order to reduce its cognitive and neurophysiological complexity and to use the endophenotype strategy to full effect. A first step will have to be to investigate the heritability of the neurophysiological markers of working component process deficits in relatives of patients with schizophrenia.

5.3.2 Functional neuroimaging as a biomarker and diagnostic tool

Another promising avenue for research concerns the use of fMRI for the development of biomarkers to improve the early diagnosis of schizophrenia. A longer duration of untreated psychosis has a detrimental effect on the prognosis of schizophrenia (Loebel et al., 1992). Reducing or eliminating this time period should therefore improve outcome. To this end the early detection of people in the prodromal stages of schizophrenia, also referred to as the ultra high risk clinical state, and the evaluation of early interventions have become the focus of

intensive research during the past decade (Cannon et al., 2007). At the moment the identification of people at ultra high risk for developing schizophrenia relies primarily on the presence of prodromal symptoms such as attenuated psychotic symptoms, neurotic or mood-related symptoms (Yung and McGorry, 1996) or “basic symptoms” like thought interference or thought perservation (Klosterkotter et al., 2001). Currently, early intervention strategies suffer from a lack of predictive markers for the conversion of ultra high risk patients to full blown schizophrenia. Such knowledge could improve the process of selecting those patients who are in a particular need for psychotherapeutic or pharmacological interventions. There is preliminary evidence that impairments in some cognitive abilities, e.g. verbal and working memory, might have a predictive value for the conversion from an ultra high risk clinical state to schizophrenia (Brewer et al., 2005; Keefe et al., 2006; Lencz et al., 2006). The development of biomarkers based on fMRI data might help to further improve this process.

Supervised multivariate techniques such as support vector machines may be particularly suited for this purpose. In contrast to standard univariate MRI analysis methods, which only consider one voxel at a time, these techniques jointly analyze data from multiple voxels. Thus, they focus on the analysis and comparison of patterns of activity. This approach has been widely used in the field of “brain reading” (Haxby et al., 2001; Haynes et al., 2005; Kamitani and Tong, 2005; Haynes and Rees, 2006; Harrison and Tong, 2009). Here, classifiers generated from a set of training data are used to decode specific mental states or representational content, e.g. different categories such as faces, houses and objects (Haxby et al., 2001) from fMRI activity patterns. Likewise, instead of distinguishing between different classes of visual objects, classifiers could also be trained to distinguish between different populations, e.g. patients with schizophrenia and healthy controls. For this purpose, classifiers need to achieve a good generalization performance. An overfitting classifier which learns correctly all input classes but performs at chance level for new data would be of little use. Support vector machines produce a decision boundary which provides an optimal separation between the data points of two classes in a multidimensional feature space based on the principle of large-margin separation. The margin is the distance of the separation line to the

closest point of each class. A support vector machine selects the separation line producing the largest margin. Because of that, overfitting of the data can be avoided, which ensures a good generalization performance (De Martino et al., 2008).

Interestingly, it has recently been demonstrated using support vectors machines that changes in cortical volume during the prodromal phase can identify people at risk for schizophrenia and predict the conversion from the prodromal phase to schizophrenia with high accuracy (Koutsouleris et al., 2009). Similar results have been demonstrated for other neuropsychiatric disorders such as Alzheimer's disease (Kloppel et al., 2008; Gerardin et al., 2009). It remains to be seen whether these results can be successfully extended to fMRI in longitudinal studies of prodromal patients.

5.4 Conclusion

These developments and the results of the studies presented in this dissertation indicate that non-invasive techniques such as EEG and fMRI are powerful tools that have the power to connect genetic and neurochemical alterations with abnormal brain function and cognition as well as the clinical phenomenology. This approach should be essential in the process of refining and possibly redefining our conceptualization of complex neuropsychiatric disorders like schizophrenia.

Summary

The pathophysiology of schizophrenia is still poorly understood. Investigating the neurophysiological correlates of cognitive dysfunction with functional neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) is widely considered to be a possible solution for this problem. Working memory impairment is one of the most prominent cognitive impairments found in schizophrenia. Working memory can be divided into a number of component processes, encoding, maintenance and retrieval. They appear to be differentially affected in schizophrenia, but little is known about the neurophysiological disturbances which contribute to deficits in these component processes. The aim of this dissertation was to elucidate the neurophysiological underpinnings of the component processes of working memory and their disturbance in schizophrenia.

In the first study the the neurophysiological substrates of visual working memory capacity limitations were investigated during encoding, maintenance and retrieval in 12 healthy subjects using event-related fMRI. Subjects had to encode up to four abstract visual shapes and maintain them in working memory for 12 seconds. Afterwards a test stimulus was presented, which matched one of the previously shown shapes in fifty percent of the trials. A bilateral inverted U-shape pattern of BOLD activity with increasing memory load in areas closely linked with selective attention, i.e. the frontal eye fields and areas around the intraparietal sulcus, was observed already during encoding. The increase of the number of stored items from memory load three to memory load four in these regions was negatively correlated with the increase of BOLD activity from memory load three to memory load four. These results point to a crucial role of attentional processes for the limited capacity of working memory.

In the second study, the contribution of early perceptual processing deficits during encoding and retrieval to working memory dysfunction was investigated in 17 patients with schizophrenia and 17 healthy control subjects using EEG and event-related fMRI. A slightly modified version of the working memory task used in the fist study was employed. Participants only had to encode and maintain up to three items. In patients the amplitude of the P1 event-related potential was significantly reduced already during encoding in all memory load conditions. Similarly, BOLD activity in early visual areas known to generate the

P1 was significantly reduced in patients. In controls, a stronger P1 amplitude increase with increasing memory load predicted better performance. These findings indicate that in addition to later memory related processing stages early visual processing is disturbed in schizophrenia and contributes to working memory dysfunction by impairing the encoding of information.

In the third study, which was based on the same data set as the second study, cortical activity and functional connectivity in 17 patients with schizophrenia and 17 to healthy control subjects during the working memory encoding, maintenance and retrieval was investigated using event-related fMRI. Patients had reduced working memory capacity. During encoding activation in the left ventrolateral prefrontal cortex and extrastriate visual cortex was reduced in patients but positively correlated with working memory capacity in controls. During early maintenance patients switched from hyper- to hypoactivation with increasing memory load in a fronto-parietal network which included left dorsolateral prefrontal cortex. During retrieval right ventrolateral prefrontal hyperactivation was correlated with encoding-related hypoactivation of left ventrolateral prefrontal cortex in patients. Cortical dysfunction in patients during encoding and retrieval was accompanied by abnormal functional connectivity between fronto-parietal and visual areas. These findings indicate a primary encoding deficit in patients caused by a dysfunction of prefrontal and visual areas.

The findings of these studies suggest that isolating the component processes of working memory leads to more specific markers of cortical dysfunction in schizophrenia, which had been obscured in previous studies. This approach may help to identify more reliable biomarkers and endophenotypes of schizophrenia.

Zusammenfassung

Die Pathophysiologie der Schizophrenie ist noch immer weitgehend unverstanden. Die Untersuchung der neurophysiologischen Grundlagen kognitiver Störungen mit den Methode der funktionellen Bildgebung wie der Elektroenzephalographie (EEG) und der funktionellen Magnetresonanztomographie (fMRT) wird als mögliche Lösung für dieses Problem angesehen. Störungen des Arbeitsgedächtnisses sind eines der bedeutendsten kognitive Defizite der Schizophrenie. Das Arbeitsgedächtnis kann in eine Reihe von Subprozessen eingeteilt werden, die Enkodierung, das Halten und das Abrufen von Information. Diese Subprozesse scheinen bei der Schizophrenie in differenzieller Weise beeinträchtigt zu sein, über die zugrundeliegenden neurophysiologischen Störungen ist jedoch sehr wenig bekannt. Das Ziel dieser Dissertation ist die Untersuchung der neurophysiologischen Grundlagen dieser Arbeitsgedächtnissubprozesse und ihrer Störung bei der Schizophrenie.

In der ersten Studie wurden die neurophysiologischen Korrelate der Kapazitätsbegrenzungen des Arbeitsgedächtnisses während der Enkodierung, des Halten und des Abrufen von Information in 12 gesunden Probanden mittels fMRT untersucht. Die Probanden mußten bis zu vier abstrakte Figuren enkodieren und für 12 Sekunden im Arbeitsgedächtnis behalten. Anschließend wurde ein Testreiz präsentiert, der in fünfzig Prozent der Fälle mit einem der vorher gezeigten Figuren übereinstimmte. Während der Enkodierung zeigte sich mit steigender Arbeitsgedächtnisbelastung in den frontalen Augenfeldern und im Bereich des Sulcus intraparietalis, die beide eng mit selektiver Aufmerksamkeit verknüpft sind, beidseits ein Aktivierungsmuster in Form eines invertierten U. Für den Anstieg der Anzahl der erfolgreich gespeicherten Objekte fand sich in den beiden schwierigsten Bedingungen eine negative Korrelation mit dem Aktivierungsanstieg in diesen Regionen. Diese Ergebnisse weisen auf eine wichtige Rolle von Aufmerksamkeitsprozessen für die Begrenzung der Arbeitsgedächtniskapazität hin.

In der zweiten Studie wurde die Rolle von Störungen früher perzeptueller Verarbeitungsschritte während der Enkodierung und dem Abrufen von Information aus dem Arbeitsgedächtnis mittels EEG und fMRT bei 17 Patienten mit Schizophrenie und 17 gesunden Kontrollprobanden untersucht. Es wurde

eine leicht modifizierte Variante der Aufgabe der ersten Studie verwendet, bei der die Versuchspersonen maximal drei Objekte enkodieren mußten. Bei den Patienten fand sich eine reduzierte Amplitude der P1 während der Enkodierung unabhängig von der Zahl der zu merken Objekte. In frühen visuellen Arealen, die für die Entstehung der P1 verantwortlich sind, zeigte sich ebenso eine verminderte Hirnaktivität. Bei den Kontrollprobanden war eine stärkerer P1 Amplitudenanstieg mit steigender Zahl der Objekte mit einer höheren Antwortrichtigkeit assoziiert. Dies Befunde weisen darauf hin, daß zusätzlich zu späteren Gedächtnisprozessen die führe visuelle Verarbeitung bei der Schizophrenie gestört ist und die Enkodierung von Informationen beeinträchtigt.
In der dritten Studie, die auf dem gleichen Datensatz wie die zweite Studie basiert, wurde die kortikale Hirnaktivität sowie die funktionelle Konnektivität während der Enkodierung, dem Halten und dem Abrufen von Information mittels fMRT bei 17 Patienten mit Schizophrenie und 17 gesunden Kontrollprobanden untersucht. Die Arbeitsgedächtniskapazität der Patienten war reduziert. Während der Enkodierung war die Aktivität des linken ventrolateralen präfrontalen Kortex und des extrastriatären visuellen Kortex bei den Patienten reduziert. Bei den Kontrollprobanden fand sich in diesen Arealen eine positive Korrelation zwischen Hirnaktivität und Arbeitsgedächtniskapazität. Während der frühen Haltephase wechselten die Patienten mit steigender Objektzahl von einer präfrontalen Über- zu einer Minderaktivierung eines frontoparietalen Netzwerks, welches den linken dorsolateralen präfrontalen Kortex mit einschloss. Die Überaktivierung des rechten ventrolateralen präfrontalen Kortex während der Abrufphase korrelierte bei den Patienten mit der Minderaktivierung des linken ventrolateralen präfrontalen Kortex während der Enkodierung. Während der Enkodierung und dem Abrufen fand sich eine gestörte funktionellen Konnektivität zwischen frontoparietalen und visuellen Arealen. Diese Befunde weisen auf ein primäres Enkodierungsdefizit als Folge einer Dysfunktion präfrontaler und visueller Areale bei den Patienten hin.
Die Ergebnisse der Studien deuten darauf hin, daß die getrennte Untersuchung der Arbeitsgedächtnissubkomponenten zu spezifischeren Markern kortikaler Dysfunktion bei den Patienten führen, die in früheren Studien verdeckt geblieben waren. Dieser Ansatz könnte dabei helfen, reliablere Biomarker und Endophäntoypen für die Schizophrenie zu identifizieren.

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

The Neurophysiological Correlates of
Working Memory Dysfunction in Schizophrenia

in der Klinik für Psychiatrie, Psychosomatik und Psychotherapie unter Betreuung und Anleitung von Herrn Prof. Dr. Dr. David Linden ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden (oder werden) in folgendem Publikationsorgan veröffentlicht:

1. Linden D.E., Bittner R.A., Muckli L., Waltz J.A., Kriegeskorte N., Goebel R., Singer W., Munk M.H.J. *Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network.* Neuroimage. 2003 Nov;20(3):1518-30.

2. Haenschel C., Bittner R.A., Haertling F., Rotarska-Jagiela A., Maurer K., Singer W., Linden D.E. *Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia – a study with event-related potentials and functional magnetic resonance imaging.* Archives of General Psychiatry. 2007 Nov;64(11):1229-40.

3. Bittner R.A., Linden D.E., Roebroeck A., Haertling F., Rotarska-Jagiela A., Goebel R., Singer W., Maurer K., Haenschel C. *Cortical dysfunction during working memory component processes in adolescents with schizophrenia - A functional magnetic resonance imaging study.* In preparation.

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