First episode schizophrenia: functional MRI findings and treatment response

Nicoletta van Veelen

Colofon:

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First episode schizophrenia: functional MRI findings and treatment response

Eerste episode schizofrenie:
bevindingen uit functionele MRI
en behandel response
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
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geboren op 18 april 1966
te Utrecht

Promotoren
Prof. Dr. R.S. Kahn
Prof. Dr. N.F. Ramsey

Co-promotor
Dr. M. Vink

Magnetic resonance imaging scanner

2.
En dan ziet u hier heel mooi
dat dit gebied rood wordt, donkerrood,
de neuronen vuren hier als gekken
er gebeurt van alles, en het bijzondere is
dat niet alleen dit gebied actief is!
Ook linksboven kleurt het nu
toch wel heel intens oranje!
Als een bosbrand slaat de opwinding
in het brein om zich heen, we zien
de herten wegrennen, we horen de
schrille wanhoop van de vogels, het
knetteren van dierenhuid.

1.
Stil lig je in de witte buis
een tunnel van sneeuw waar je
geen engel in kunt maken
je bent heel kalm
totdat de zwarte letters komen

geef aan welk woord er niet
sterft smeekt stijgt stevent
welke is niet
stout stevig stoer slim
volgende opgave
rechts staat tot links als boven staat
tot diepte, 2+2=5, probeer zo snel mogelijk
druk op de

0.
Naar het instituut.
U neemt de tweede afslag links en loopt over de parkeerplaats.
De hoofdingang is aan uw rechterkant.

Uit "Eiland op sterk water" van Floor Buschenhenke, oktober 2009.
(met toestemming van de auteur)

Contents

Chapter 1

General Introduction

Introduction

1. General Introduction

The research presented in this dissertation aims to elucidate some of the pathophysiological and treatment aspects of schizophrenia. The studies center on patients suffering their first psychotic episode of schizophrenia. There are two main reasons to focus research on this patient group.

Firstly, the illness is less affected by confounding factors during the first episode than in the chronic phase. When the illness progresses after the first-episode and takes a chronic course this will have some inherent consequences. For instance, the majority of patients will be treated on a continuous base with antipsychotic agents, with all their known and unknown side effects. Moreover, patients may not be able to hold a job or live independently. These factors will undoubtedly interfere with the evaluation of the pathology and treatment of schizophrenia in chronic patients. The best way to unravel these secondary effects from the primary disease is to study patients who have just become ill, and have not yet been treated: first-episode medication-naive patients.

The second reason to study first-episode schizophrenia is related to treatment. The vast majority of treatment studies describe effects in chronic patients. By consequence, their findings may not necessarily apply to first episode patients. Indeed, patients in the early stages of the illness appear to differ in some important aspects from chronic patients. For example, it is suggested that response to treatment may vary by between first-episode and chronic patients. In young patients lower doses of antipsychotic drugs are probably sufficient and susceptibility to adverse effects may be higher (Ohlsen et al., 2004;Chatterjee et al., 1995). In addition, first-episode schizophrenia patients represent a more heterogeneous group than chronically ill patients. Clinical trials with chronically ill patients may have an entry bias, favoring inclusion of patients with a more severe form of the illness, or who responded poorly to treatment (Kahn et al., 2008; Robinson et al., 1999). Therefore research findings may not be interchangeable between both patients groups.

Optimal treatment in the early stages of the illness is of particular importance in view of two findings: firstly, the majority of the social and biological deterioration occurs in the first five years of the illness, and secondly, treatment appears to be the least effective in chronically ill patients (Birchwood and Macmillan, 1993;Carpenter, Jr.and Strauss 1991). This implies that treatment early in the disease may be more successful. Future hope is that if we manage to optimally treat the early stages of the illness, this may prevent decline in function in later stages of the illness (McGorry et al., 1996).

Conducting research in first-episode medication-naive patients gives rise to practical and ethical problems. Firstly, patients present themselves regionally over various treatment facilities. They have to be identified and, preferably, be admitted to the institute conducting the research, in order to participate in the study, before treatment is commenced. Secondly, they have to be able to participate in the study while being psychotic and untreated, since treatment will be commenced only after baseline measurements are taken. Despite these problems, we were able to include a fairly large sample of such patients, and most of them were able to perform the experiments, even inside an MRI scanner.

The research presented in this dissertation is divided into two parts. Part I describes neuroimaging studies in first-episode medication-naive schizophrenia patients. The aim of this part is to test two hypotheses concerning schizophrenia: reduced language lateralization and frontal lobe dysfunction. Performance data and functional MRI data obtained from patients are compared to those of closely matched healthy control subjects. Part II describes treatment studies in recent onset schizophrenia patients. In these studies, the effects of two second-generation antipsychotics on cognitive as well as clinical improvement are compared. Similar to the patients described in Part I, these patients are still in the acute phase of the illness: their mean duration of illness was about one year. However, most of them had already been briefly treated with antipsychotics (mean exposure to medication was about three weeks). Before discussing studies and their background, a brief overview of schizophrenia is provided.

Schizophrenia

2.1. Epidemiology

Schizophrenia is a mental disorder with a major impact on the life of patients and of their families. It is a relatively common disorder with a life time prevalence of 0.7-1% (van Os and Kapur, 2009;Bromet and Fennig, 1999). The typical onset is in early adulthood for men, while for women this is around ten years later (Leung, 2000;Castle et al., 2000). The average life expectancy of individuals with the disorder is 12 to 15 years less than that of the normal population, as a result of increased physical health problems and a higher suicide rate (van Os and Kapur, 2009;Saha et al., 2007).

2.2. Symptomatology

The symptoms of schizophrenia manifest themselves along two dimensions: positive (psychotic) and negative symptoms. Positive symptoms, such as delusions (persecutory, delusions of reference, somatic, religious) and abnormal perceptions (especially auditory hallucinations, but also other hallucinations) are commonly present in recurrent episodes, with periods of florid psychosis alternating with periods of remission. Negative symptoms, such as blunt or flat affect, lack of volition or lack of initiative, are by nature more enduring. Notably, more severe negative symptoms have repeatedly been linked to worse functional outcome (Milev et al., 2005;Blanchard et al., 2005;Puig et al., 2008).

Although not included in the definition of the illness in the DSM-IV (American Psychiatric Association, 2000) cognitive problems are often seen as part of the illness. Some authors in fact argue that in schizophrenia a cognitive dimension (or a dimension of disorganization) should be included, in addition to the positive and negative dimensions (Johnstone and Frith, 1996;Grube et al., 1998;Chemerinski et al., 2006).

2.3. Diagnosis

The clinical presentation of schizophrenia varies both between individuals and over time. The variability of the clinical presentation of the illness has triggered the debate as to whether the diagnosis represents a single disorder or a number of discrete syndromes (Insel, 2010; van Os and Kapur, 2009). At present, the diagnosis of schizophrenia is based on symptom profiles and is descriptive of nature, formulated in the DSM-IV (American Psychiatric Association, 2000).

2.4. Etiology

The etiology of schizophrenia is not clarified; no single (organic) cause has been explicitly related to schizophrenia. The general understanding nowadays is that schizophrenia is for a large part genetically determined, but that other (environmental) factors also contribute , and that these environmental factors interact with the genetic factors (Sullivan et al., 2003). Examples of these environmental factors are obstetric complications (Cannon et al., 2002), prenatal infections (Brown and Patterson, 2010), psychological /stress factors (Khashan et al., 2008;Norman and Malla, 1993), social factors (upbringing in urbanized area (Pedersen and Mortensen, 2001), (parental) socioeconomic status (Cantor-Graae, 2007) and cannabis use (Caspi et al., 2005). At present it is not completely understood how these risk factors eventually contribute to the development of schizophrenia.

2.5. Treatment

The treatments applied in schizophrenia involve psycho-education, rehabilitation, cognitive/behavioral psychotherapy and medication. Pharmacological treatments have been widely used since the first antipsychotic chlorpromazine was discovered in the 1960s, and form the cornerstone of treating an acute episode of psychosis. Nowadays, both the older conventional (typical) antipsychotics as well as newer second-generation (atypical) antipsychotics are in use, although for the past 15 years, second-generation antipsychotic drugs have been the most frequently prescribed of the two. Conventional antipsychotics are characterised by their antagonistic effect and high affinity for dopamine receptors (particularly D2 receptors), which is believed to be associated with the ability of these agents to reduce the positive symptoms. Second-generation antipsychotics, in contrast, are antagonistic for both dopamine (D2) and serotonin (5-Hydroxytryptamine, 5-HT). Importantly, the second-generation antipsychotics have a lower risk of causing extrapyramidal symptoms (EPS) or tardive dyskinesia.

While antipsychotic agents in general provide a good symptomatic treatment of positive symptoms in most patients, there is much less evidence that they improve negative symptoms or cognitive deficits (Robinson et al., 2004; Buckley and Stahl, 2007,Goldberg et al. 2007;Kraus and Keefe, 2007). Hence, they cannot provide a curative treatment for the illness (Carpenter, Jr., 2001;Simpson et al., 2010).

2.6. Outcome

Research reporting on long-term outcome may vary according to definitions used, but roughly indicates that approximately 75% of people with schizophrenia have ongoing disability with relapses, while the other 25% recover or regain good social functioning (Smith et al., 2010; Warner, 2009;Emsley et al., 2006;Robinson et al., 2004;Menezes et al., 2006).

At first presentation of patients it is difficult to predict which course the illness will take in later stages. The major deterioration in schizophrenia occurs within the first five years following onset rather than over the remaining course (Carpenter, Jr. and Strauss, 1991). The course over the first few years of the illness is therefore the best predictor of long-term courses.

Part I. Functional MRI studies

In the first part of this thesis functional MRI studies are included that focus on two well described hypotheses regarding schizophrenia: reduced frontal lobe function (chapter 3,4) and reduced language lateralization (chapter 2). These hypotheses are tested in first-episode medication-naive patients, as to prevent effects of illness and treatment from confounding the results.

3.1. Reduced language lateralization

In the human brain, various functions and structures are found to be asymmetrically distributed across the hemispheres (Rakic and Yakovlev,1968; LeMay, 1976;Galaburda and Geschwind, 1981; Springer et al., 1999; Frost et al., 1999; Steele, 2000;Annett, 2002). For example, right-handed individuals generally show larger right frontal and left occipital cortical areas (referred to as the "developmental torque") (Rakic and Yakovlev, 1868; LeMay, 1976), a larger thalamus on the left side, and a smaller planum temporale on the right side (Geschwind and Levitsky, 1968; Galaburda and Geschwind, 1981). The best known examples of asymmetry in brain functions are those of language and handedness: the left hemisphere typically controls the processing of language (Galaburda and Geschwind, 1981: Springer et al., 1999;Frost et al., 1999) and the dexterity of the right hand (Steele, 2000; Annett 2002; MacNeilage et al., 2009). In the human population about nine out of ten adults are right handed (Annett 1972). For language function the left cerebral hemisphere is dominant in 90% of right-handed people and 70 % of left handed people (Woods et al., 1988;Pujol et al., 1999). The anatomical asymmetry of the brain and lateralization for language and handedness are clearly interrelated, but their influences on one another are complex and not completely understood.

An increasing number of reports on brain and behavioral lateralization have put forward lateralization as a natural phenomenon in animals, illustrating that cerebral lateralization is not strictly limited to humans (Tommasi, 2009; Vallortigara and Rogers, 2005; Ghirlanda and Vallortigara, 2004).

It is believed that asymmetry of brain structure and function is a result of normal hemispheric specialization during neurodevelopment (Hutsler and Galuske, 2003; Falkai and Bogerts, 1991). When reduced or reversed lateralization of brain functions or structures occurs, this can be understood as an expression of normal variation in human biology or a trait in certain families. However, when it occurs more frequently in a specific patient group, it could be a sign of pathology. This was specifically proposed for the reduced lateralization found in schizophrenia; the neurodevelopmental pathology of the illness may give rise to aberrant asymmetry (and therefore specialization).

In schizophrenia, a reduction of anatomical asymmetry is found in the temporal lobe volume (Collinson et al., 2009) and the planum temporale (Clark et al., 2010). In addition, reduced functional lateralization is present, as evidenced by an excess of mixed-handedness (Green et al., 1989;Nelson et al., 1993;Cannon et al., 1995;Orr et al., 1999;Sommer et al., 2001;Collinson et al., 2004;Crow et al. 1996), as well as reduced language lateralization in chronic patients (Li et al., 2007;Sommer et al., 2001;Sommer et al, 2004;Dollfus et al., 2005;Spaniel et al., 2007;Razafimandimby et al., 2007;Sakuma et al., 1996; Li et al., 2009).

Crow (1996) proposed that the delay in establishing dominance in one hemisphere could be a critical factor in the predisposition for schizophrenia. He specifically formulated a hypothesis concerning language lateralization stating that "Schizophrenia originates from a deficit in the hemispheric specialization for language" (Crow et al., 1996) and that reduced left hemispheric dominance causes language related symptomatology such as hallucinations and thought disorder (Crow, 2008). While reduced language lateralization was repeatedly found in chronic patients, it is not clear at what stages of the illness the reduced (language) lateralization actually occurs, and how it relates to the development of schizophrenia.

In this thesis (Chapter 2), research is presented that investigates whether language lateralization is reduced already in the first-episode of schizophrenia, before medical treatment is installed, and explores whether it is related to specific symptomatology.

3.2. Frontal lobe dysfunction

Over a century ago, Kraepelin made a distinction between dementia praecox (what would later become "schizophrenia") and manic-depressive illness based on symptomatology and course of the illness (Kraepelin, 1899;Kraepelin, 1919). He characterized dementia praecox with the occurrence of disorganization of thought and behavior, the disturbance of volition and as an illness following a progressive course for all patients. Furthermore, he related dementia praecox to pathology of the frontal lobe (Kraepelin 1896 and 1899, Kraepelin, 1919).

Consistent with this central importance of the frontal lobe first proposed by Kraepelin are later findings in structural (Pantelis et al., 2005, 2007; Ho et al., 2003;Job et al., 2005; Hazlett et al., 2008; Hulshoff Pol and Kahn, 2008;Antonova et al., 2004;Gur et al., 1998) and functional (Weinberger et al., 1992; Andreasen et al., 1992., Yurgelun-Todd et al., 1996; Buchsbaum et al., 1992; Ragland et al., 1998; Karlsgodt et al., 2007; Jansma et al., 2001) neuroimaging studies. These studies report abnormalities of the frontal lobe, that are related to the severity of negative symptoms (and cognitive dysfunction)(Hazlett et al., 2008; Cahn et al., 2006; Hulshoff Pol and Kahn, 2008; Antonova et al., 2004) and poor outcome (Hulshoff Pol and Kahn, 2008; Weinberger et al., 1992; Andreasen et al., 1992; Yurgelun-Todd et al., 1996).

It is not clear at which stage of the illness frontal lobe dysfunction becomes apparent and whether antipsychotic treatment affects frontal lobe function. As both negative symptoms and cognitive symptomatology have shown limited improvement to antipsychotic treatment, one may expect that patients with impaired frontal lobe function show diminished response to antipsychotic treatment. We will address the hypothesis of frontal lobe dysfunction and how it is related to symptomatology and treatment response in chapter 3 and 4 of this thesis.

3.3. Functional Magnetic Resonance Imaging

3.3.1. Background

Functional Magnetic Resonance Imaging (fMRI) allows the visualization of task related brain activation. It was first developed in the early 1990's (Belliveau et al., 1991;Ogawa et al., 1992) and has since become one of the main techniques to map activity of the brain. The technique has certain advantages over other brain imaging techniques such as positron emission tomography (PET): it is non-invasive, subjects are not exposed to radiation, it has a relatively good spatial resolution (millimeters) and temporal resolution (seconds), and gives the possibility to provide anatomical information within the same scanning session. It has also some advantages over EEG and MEG: it has a better spatial resolution (but a smaller temporal resolution) and the ability to record signals from all regions of the brain, instead of only the cortical surface.

3.3.2. How does Magnetic Resonance Imaging work?

MR imaging uses a large magnet with a field strength (B_0) of around 1.5-7 Tesla. When a subject is placed in the magnetic field of the scanner some protons (hydrogen nuclei) in the body will align with the field (B_0). A radio frequency (RF) pulse is used to excite the protons (away) from their resting state into a higher energy state (protons start to "spin"). After the field is turned off, the protons return to their original state, with the emission of an electromagnetic signal ("echo") that the scanner detects using a receiver coil. This receiver coil is placed as close as possible to the head of the subject to minimize signal loss. The time that it takes for hydrogen atoms to lose 67 percent of their energy is called 'T2' relaxation time. An image can be constructed because the protons in different tissues have different 'T2' relaxation times.

A radio frequency pulse sequence can be used to create contrast between different types of body tissue, as in anatomical imaging, or a contrast between other properties, as in fMRI. In fMRI scanning, the scanner is tuned to resonate as in conventional MRI, but with different (T2*) relaxation times.

3.3.3. How does BOLD-fMRI work?

The most commonly used fMRI technique is called BOLD-fMRI. It uses the so called 'Blood Oxygen Level-Dependent' (BOLD)-contrast (Ogawa and Lee, 1990). It does not directly measure neuronal activation, but maps the hemodynamic response (change in relative oxygenation in blood flow) related to neural activity in the brain. Increased neural activity causes an increased demand for oxygen, provided for by an increase in cerebral blood flow. The vascular system actually overcompensates for the decrease in oxygen, delivering an oversupply for oxygenated blood (Fox and Raichle, 1986), increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Deoxy- and oxyhemoglobin have different magnetic properties; deoxyhemoglobin is *paramagnetic* and introduces an inhomogeneity into the nearby magnetic field (and lowers the measured fMRI signal), whereas oxyhemoglobin is *diamagneticly weaker* and has little effect. The changing concentrations of oxyhemoglobin vs. deoxyhemoglobin constitute the basis of the BOLD effect (Kwong et al., 1992;Ogawa et al., 1992). The precise nature of the relationship between neural activity and the BOLD signal, the neurovascular coupling, however, is still a matter of debate. It involves multiple vascular, metabolic, and neural processes, but is as yet not fully understood.

In fMRI the task-related signal changes are typically in the order of 1- 5% (at 1.5 Tesla). In order to obtain 'significant' changes in the signal-to-noise ratio per voxel (i.e. the smallest unit of the brain from which signal is sampled), repetitive scans are required. Setting up an fMRI study requires one to choose a task design which maximizes task-related signal changes.

3.3.4. Behavioral task design in fMRI

The most frequently used study design in fMRI is the block design, because this potentially yields the strongest task-related fMRI signal. This is also the design used in the experiments described in this thesis (chapters 2-4).

In a block design, two or more conditions are alternated in blocks of, for example, 20 seconds, over the course of the scanning. The experimental condition contains the function of interest while the control condition involves a similar set of functions except for the one of interest. Alternatively, the control condition can be fixation while not performing any task at all (i.e. rest). By subtracting activation during the control task from that obtained during the experimental condition, activation related to the function of interest can be obtained. This is known as the subtraction paradigm (Grabowski and Damasio, 1996).

A practical issue regarding research investigating cognitive function is that the MRI signal is very sensitive to head movement. As talking induces head movement, this limits the possibility to collect verbal responses. In addition, the MRI scanner is very

noisy. This limits the possibility to present auditory stimuli. In the studies described in this thesis, we therefore required subjects to make a response by pressing a button on an MRI-compatible button-box, and use silent vocalization.

3.3.5. Data acquisition

The acquisition technique used in the studies described in this thesis is 3D PRESTO-fMRI (Principle of Echo Shifted Train of Observations). The PRESTO imaging technique is based on the conventional multi-slice echo planar imaging (2D EPI) technique, however with this method a whole volume is exited simultaneously, rather than scans built from two-dimensional slices. This way fast three dimensional scans can be obtained. The advantage of this technique is that it is less sensitive to signal effects from inflowing and draining blood vessels, which improves accuracy of the localization of brain activity. The 3D PRESTO technique has been extensively described in earlier papers (van Gelderen et al., 1995;Ramsey et al., 1996;Ramsey et al.,1998).

Part II. Treatment studies of olanzapine versus ziprasidone.

In this thesis we compare the efficacy of two second-generation antipsychotics, olanzapine and ziprasidone. The specific binding sites within the class of second-generation antipsychotics vary: they generally have additional affinities for a variety of neurotransmitter subtypes. Olanzapine, for instance has a higher affinity for histamine H1 receptors and several muscarinic receptors, and a lower affinity for dopamine D2 receptors than ziprasidone. The specific binding profile of different antipsychotic agents may contribute to their distinct efficacy and safety profiles.

4.1. Cognitive function

Over 85% of patients with schizophrenia show clinically significant impairment in one or more domains of cognition (Palmer et al., 1997; Keefe et al., 2006). In spite of this frequent occurrence, no single test or cognitive construct completely discriminates patients with schizophrenia from healthy controls (Zakzanis, 1999). The cognitive domains that are commonly found as deficient include attention, action planning, memory, executive function and processing speed (Nuechterlein et al., 2004;Heinrichs and Zakzanis, 1998; Albus et al., 2006). The same generally holds true for the cognitive domains in first-episode patients (Friis et al., 2002; Rodriguez-Sanchez et al., 2008) and in medication-naive patients (Saykin et al., 1994; Mohamed et al., 1999).

Schizophrenia patients not only show cognitive impairments compared to healthy controls, but also compared to patients with mood disorders. Whereas cognitive impairments in mood disorders have shown variability depending on the phase of illness (Keefe and Fenton, 2007; Hill et al., 2008), the cognitive deficits in schizophrenia are more stable throughout the course of the illness (Albus et al., 2002; Keefe, 2007; Kopelowicz et al., 2005). Moreover, the cognitive impairments are usually more severe in schizophrenia than in people with bipolar disorder (Keefe and Fenton, 2007;Krabbendam et al., 2005).

While the cognitive deficits in schizophrenia are modestly associated with negative and disorganized symptom dimensions in schizophrenia, they are not consistently related to positive symptoms (Brazo et al., 2002;Heydebrand et al., 2004).

As it has been repeatedly demonstrated that cognitive deficits contribute to poor functional outcomes in schizophrenia (Green, 1996; 2000;Harvey et al.,1998; Velligan et al., 2000; Kraus and Keefe,2007), they have formed an important target of treatment in the past decade. In the course of this thesis we will compare the effects of two antipsychotic medications on neurocognitive functioning in recent-onset schizophrenia, specifically in chapter 5.

In our research we use a large battery of cognitive tasks that are widely used and validated.

4.2. Symptomatology and tolerability

Earlier (open) studies comparing olanzapine and ziprasidone showed an increased risk of olanzapine for metabolic side-effects and weight gain, while ziprasidone was associated with akathisia (Kahn et al., 2008;Lieberman et al., 2005). Reports on clinical efficacy were less consistent: some showed similar improvement for both olanzapine and ziprasidone (Simpson et al., 2005;Kahn et al., 2008) and one study showed greater improvement for psychopathology for olanzapine (Breier et al., 2005). Another large open treatment trial comparing second-generation antipsychotics suggested superiority of olanzapine, in that the "time to discontinuing treatment" was longer for olanzapine than for ziprasidone. This effect however was not significant after correction for multiple comparisons (Lieberman et al., 2005).

In the research presented, clinical efficacy was measured with scales using patient interviewing and observation, aimed at measuring the severity of psychosis and negative symptoms (PANSS, the Positive and Negative Syndrome Scale), depression (CDSS, Calgary Depression Scale for Schizophrenia), severity of illness and functioning (CGI, Clinical Global Impression, GAF, Global Assesment of Functioning Scale) and quality of life (HQLS, Heinrich Quality of Life Scale). As described earlier, it is important to investigate effects of treatment in specific patients groups, such as first-episode patients, and establish superiority of one antipsychotic drug over the other, or else determine what agent has the best benefit/risk ratio for these patients.

Outline of this thesis

Part I of this thesis describes fMRI investigation of language lateralization and frontal brain function in first-episode medication-naive schizophrenia patients (**Chapter 2-4).** Part II of this thesis is focussed on the effects of treatment (**Chapter 5 and 6).** Here we compare the difference in cognitive as well as clinical improvement between two atypical antipsychotics in recent onset schizophrenia.

The objective of the study described in **Chapter 2** is to test for differences in the level of language lateralization using fMRI in first-episode medication-naive schizophrenia patients and matched healthy controls. Subjects performed three language tasks while being scanned. We used predefined Regions of Interest (ROIs), including the main language-related areas and their contralateral homologues to investigate language related activation. Using these activations, a Lateralization Index (LI) was calculated so that the asymmetry of language function across the hemispheres could be examined. The lateralization index was compared to that of the healthy control subjects and related to symptomatology.

In **Chapter 3** a study is presented that probes frontal lobe function, using fMRI. Medication-naive male schizophrenia patients in their first episode of illness were compared to matched healthy subjects. To test frontal lobe function, a working memory task was administered while fMRI data were acquired. This set up allowed us to study frontal brain function without the effects of medication, and to relate symptomatology to frontal lobe dysfunction.

Chapter 4 is a follow-up study to the one described in chapter 3, and aims to determine the effects of medication and to determine whether frontal lobe dysfunction is of predictive value for clinical outcome. After the initial scan described in chapter 3, patients started treatment with an atypical antipsychotic. Severity of symptomatology and subsequent improvement was recorded using the PANSS.

In **Chapter 5 and 6** we describe a treatment study in which two second-generation antipsychotics are compared. The study is an eight -week, double-blind, randomized, and controlled multicenter trial. The purpose of the study described in **Chapter 5** is to compare the effect of two second-generation antipsychotic drugs (olanzapine and ziprasidone) on the cognitive performance of patients with recent onset schizophrenia (mean illness duration of illness about 1 year, mean exposure to medication about 3 weeks). Cognitive tests were performed within five cognitive domains (speed of processing, attention, visual learning and memory, verbal learning and memory and executive functioning). Subsequently patients started short term treatment with

olanzapine or ziprasidone, which they were randomly assigned to. After eight weeks of treatment, neurocognitive performance was tested again, and improvement was compared between both antipsychotics.

The study described in **Chapter 6** compared clinical efficacy and tolerability of the two second-generation antipsychotics (olazapine and ziprasidone) in patients described in chapter 5. Efficacy of ziprasidone and olanzapine was measured using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) Scale, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS); tolerability assessments included laboratory assessments, body weight, and electrocardiography. These measurements were taken at randomization and after eight weeks of treatment, and compared between both agents.

Finally, **Chapter 7** provides a brief summary of the study results. Implications for future research are also discussed.

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Chapter 2

Reduced language lateralization in first-episode medication-naive schizophrenia

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Abstract

Diminished functional lateralization in language-related areas is found in chronic schizophrenia. It is not clear at what stage of illness these abnormalities in lateralization arise, or whether they are affected by medication. In addition, it is hypothesized that reduced language lateralization is related to positive symptoms of schizophrenia, but studies addressing this issue have yielded contradictory results.

In this study we used functional MRI to measure language lateralization in 35 first-episode medication-naive schizophrenia patients and 43 matched healthy controls. Subjects performed three language tasks: a paced verb generation task, an antonym generation task, and a semantic decision task. Lateralization Index (LI) was calculated, using a relative threshold technique, in seven Regions of Interest (ROIs), including the main language-related areas and their contralateral homologues. In addition, we investigated whether language lateralization was correlated with psychotic symptoms.

Across all ROIs, LI was significantly reduced in patients ($p<0.001$) compared to controls. Post-hoc tests revealed that this reduction was most prominent in the inferior frontal gyrus (part of Broca's area) ($p=0.003$) and the superior temporal gyrus (part of Wernicke's area) ($p< 0.001$). LI was not correlated with the positive subscale of the PANSS, nor with hallucinations or disorganization. This is the first study to report reduced LI at the onset of schizophrenia, before medical treatment is initiated.

1. Introduction

Brain asymmetry is a sign of hemispheric specialization of various brain functions and is a feature of normal neurodevelopment (Falkai and Bogerts, 1992;Hutsler and Galuske, 2003). Right-handed individuals show larger right frontal and left occipital cortical areas (referred to as the "developmental torque") (Rakic and Yakovlev, 1968;LeMay, 1976) and a decrease in the size of the right planum temporale (Geschwind and Levitsky, 1968;Galaburda and Geschwind, 1981). Typically, the left hemisphere controls the processing of language (Galaburda and Geschwind, 1981;Springer et al., 1999;Frost et al., 1999) and the dexterity of the right hand (Steele, 2000;Annett, 2002).

Various disorders are associated with reduced lateralization to the left side of the brain, such as autism (Minagawa-Kawai et al., 2009;Kleinhans et al., 2008), dyslexia (Spironelli et al., 2008), unipolar and bipolar affective psychosis (Sommer et al., 2007) and schizophrenia (Shenton et al., 2001;Sommer et al., 2001).

In schizophrenia, reduced functional lateralization is evidenced by an excess of mixed-handedness (Orr et al., 1999;Sommer et al., 2001;Collinson et al., 2004) (although this was not confirmed in a recent study by Deep-Soboslay et al. (Deep-Soboslay et al., 2010)) and reduced language lateralization (Li et al., 2007;Sommer et al., 2001; Sommer et al., 2004;Dollfus et al., 2005;Spaniel et al., 2007;Razafimandimby et al., 2007;Sakuma et al., 1996;Li et al., 2009). Moreover, Crow (Crow, 1997a;Crow, 1997b;Crow, 2008) proposed that the main symptoms of schizophrenia (hallucinations and thought disorders) arise from this reduced left hemispheric dominance for language. Indeed, several studies reported an association between the level of language lateralization and severity of hallucinations (Sommer et al., 2001;Weiss et al., 2006), delusions (Sommer et al., 2003), and formal thought disorder (Kircher et al., 2002). However, other studies failed to find a correlation between reduced language lateralization and psychotic symptoms (Bleich-Cohen et al., 2009;Razafimandimby et al., 2007;Sommer et al., 2007), or with a lifetime history of auditory verbal hallucinations (Sommer et al., 2007).

So far, language lateralization has most often been studied in chronic, medicated, patients. It is therefore not clear if reduced hemispheric dominance for language is already present at illness-onset, and whether medical treatment influences language lateralization.

To date, only two functional MRI studies have partially addressed these issues. Weiss et al. (Weiss et al., 2006) reported reduced language lateralization in seven medication-free patients (not all medication-naive) compared to healthy controls, whereas Bleich-Cohen et al.(Bleich-Cohen et al., 2009) found reduced lateralization in 12 medicated first-episode patients compared to 12 healthy controls.

In the current study, we examine language lateralization using functional MRI in the

largest cohort to date of medication-naive patients with first-episode schizophrenia (n = 35) and matched healthy controls (n = 43). In addition, we examine whether reduced language lateralization and psychotic symptoms are related. We hypothesize that language lateralization is reduced at illness-onset prior to the initiation of medical treatment, and that it is not related to specific symptomatology.

2. Methods

2.1. Participants

Patients were recruited from the Department of Psychiatry at the University Medical Center Utrecht, as well as from other psychiatric facilities in the area of Utrecht, The Netherlands. Healthy controls were recruited via local advertisements. The study was approved by the Ethics Committee of the University Medical Center of Utrecht. Written informed consent was obtained from all subjects prior to participation in the study. The sample included 35 first-episode medication-naive schizophrenia patients and 43 healthy comparison subjects (see table 1). Patients fulfilled DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorder, assessed with a standardized clinical interview (Structured Clinical Interview for DSM-IV, SCID (First et al., 1996) or The Comprehensive Assessment of Symptoms and History, CASH (Andreasen et al., 1992). First episode of illness was defined as an onset within 2 years prior to inclusion. Diagnoses were confirmed after half a year. Healthy controls were screened using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and had neither a prior psychiatric or medical history nor any first degree relatives with a psychotic disorder. Participants with a diagnosis of substance abuse within the three months before the experiment were excluded. Patients and healthy controls were matched on age and parental education. All subjects were right handed (assessed by the Edinburgh Handedness Inventory) (Oldfield, 1971). Symptom ratings in patients were recorded using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression (CGI) (Guy, 1976) prior to scanning.

2.2. Language paradigm

While being scanned using functional MRI, subjects performed three language tasks: a categorical semantic decision task (Kapur et al., 1994), a paced verb generation task (Xiong et al., 1998;Benson et al., 1999) and an antonym generation task (Benson et al., 1996). These language tasks were previously used in our group (Ramsey et al., 2001;Rutten et al., 2002;van Rijn et al., 2008). All tasks consisted of five language blocks (29 s) which were alternated with non-language control blocks (29 s). During the language blocks a word was presented on the screen every 3 seconds. In the cat-

egorical semantic decision task, subjects had to indicate whether the word signified an animal by a button press with the right hand. During the control blocks of this task, subjects had to indicate whether asterisks presented on the screen corresponded to a cue (three or five asterisks).
In the verb generation task, subjects had to generate an appropriate verb for the presented word (e.g. apple → eating). To prevent artefacts from jaw movement, silent vocalization (i.e. without overt articulation) was used.
In the antonym generation task, subjects had to think of a word with an opposite meaning of the presented word (e.g. large → small). In both the verb generation and the antonym generation task, the control condition consisted of the presentation of five squares at the same frequency as the words, requiring passive viewing.
Accuracy in the categorical decision task was registered during scanning using a computer. Performance during the verb generation and antonym generation task could not be directly monitored, but subjects were trained prior to scanning so that they were familiar with the tasks. Only subjects who could perform all three tasks were included in the study. Two patients failed to perform the tasks adequately and were not included in the analysis.

2.3. Analysis of behavioral data

Accuracy (percentage of correctly identified targets and non-targets) during the semantic decision task was compared between patients and healthy controls using a two-sample t-test.
In addition, to test for correlations between LI and behavioural measures, we performed correlation analyses with LI and accuracy levels.

Scanning

2.4.1. Functional MRI data acquisition

A navigated echo 3D-PRESTO pulse sequence was used on a 1.5-T Philips ACS-NT MRI scanner (van Gelderen P. et al., 1995). Functional images were obtained with the following parameter settings: Echo Time/Repetition Time 35/2.4 s, flip angle 9°, FOV 256 × 204 × 104 mm^3, matrix 64 × 52 × 26, voxel size 4 mm isotropic, scan time per volume 2.43 s. A reference image with the same specifications as the functional scans, but with more anatomical contrast (flip angle 30 degrees; (Ramsey et al., 1998)) was also acquired to facilitate coregistration to the anatomical image. Following the fMRI procedure, an anatomical T1-weighted scan was acquired (voxel size 1 mm isotropic).

2.4.2. Functional MRI analysis

Pre-processing and statistical analyses were done using SPM5 (Welcome Department of Cognitive Neurology, London, UK). All functional volumes were realigned to the reference scan. Next, the anatomical scan was coregistered to the reference scan, so that the anatomical scan was aligned with all functional volumes. Using unified segmentation the structural scan was segmented and normalization parameters were estimated. Subsequently, all scans were registered to a MNI T1-standard brain using these normalization parameters. Finally, functional scans were spatially smoothed using an 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

For each individual subject, the pre-processed data were analysed using the General Linear Model (GLM) approach with a factor matrix modelling the three language tasks and their associated movement parameters as separate sessions within the same model. These factors were convolved with a canonical hemodynamic response function (Friston et al., 1995). The analysis of the three language tasks together has proven to yield more reliable results (Ramsey et al., 2001).To correct for drifts in the signal, a high-pass filter was applied to the data with a cut-off frequency of 0.0086 Hz.

This resulted in a b-map (containing the regression coefficients for each voxel) and a t-map for the contrast between language blocks (across the three tasks) and the non-language control blocks.

2.4.3. Regions of Interest

We used Regions of Interest (ROIs) determined in an earlier study of our group (Sommer et al., 2008b). In this study a mask of these ROIs was created using the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) and included the main language-related areas and their contralateral homologues (see Sommer et al., 2008b). These language areas were the insula, middle temporal gyrus (MTG), superior temporal gyrus (STG), supramarginal gyrus, angular gyrus and the inferior frontal gyrus pars triangularis (IFG). This latter region was extended to include the inferior frontal gyrus pars opercularis. Furthermore, we included the rolandic operculum, as this area is implicated in speech production or phonological processing (Veroude et al., 2010;Fink et al., 2009;Ischebeck et al., 2008). For an overview of the resulting seven ROIs, see figure 1.

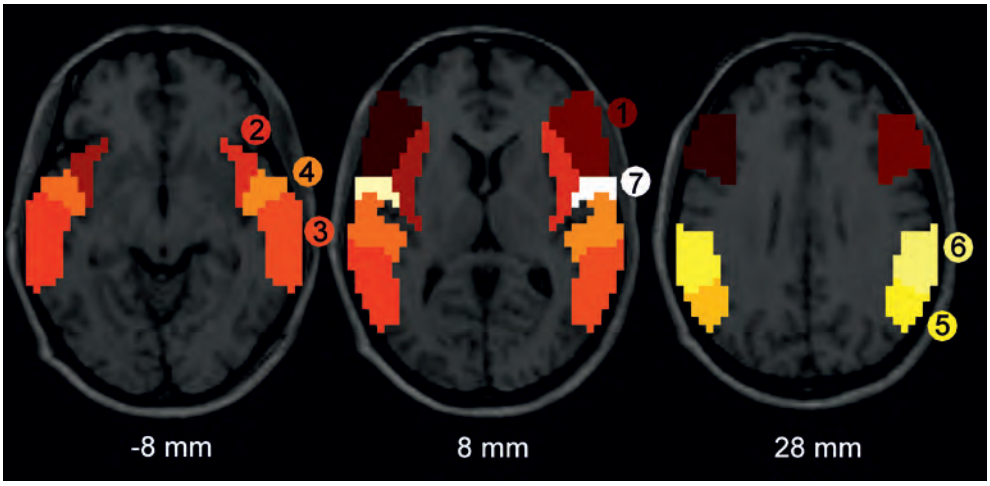

Fig.1. Regions of Interest (ROIs) included the main language-related areas and their contralateral homologues: 1. inferior frontal gyrus (pars triangularis and opercularis) (IFG), 2. insula, 3. middle temporal gyrus (MTG), 4. superior temporal gyrus (STG), 5. angular gyrus, 6. supramarginal gyrus, 7. Rolandic operculum. Slices are in radiological orientation (left side is right hemisphere and vice versa).

2.5. Lateralization Index

The Lateralization Index (LI) was defined as the difference in (thresholded) signal intensity changes in the left versus the right hemisphere (within the selected language regions) divided by the total sum of signal intensity changes. Lateralization indices were calculated for each individual subject and for each ROI separately. To prevent confounds resulting from the use of a static threshold for voxel selection, we applied a relative thresholding technique proposed by Jansen et al. (Jansen et al., 2006) which has been used previously in our group (Sommer et al., 2008b). Using this procedure, the mean activation value for each ROI was calculated in those 5% of voxels showing the highest level of activation (as expressed in b-values) in that ROI. Subsequently, the threshold for inclusion in the calculation of the LI was set at 50% of this average maximum activation value. Only voxels with b-values that exceeded this relative threshold were used to calculate the lateralization index, according to this formula: LI= (number of active voxels left- number of active voxels right)/(total number of active voxels).

A repeated-measures GLM with ROI (seven levels) as within-subject factor and group (two levels) as between-subject factor was performed to investigate differences in LI between the groups. Post-hoc t-tests, Bonferroni corrected for multiple comparisons, were performed to investigate in which ROIs the LI differed significantly between groups.

2.6 Correlation with symptoms

To test for correlations between LI and symptomatology, we performed correlation analyses with LI, the total positive PANSS-subscore and the items "hallucinations" and "disorganization". Similar correlation analyses were performed for left and right activation levels in of ROIs with a significant different LI between groups.

3. Results

3.1. Participants

Demographic and illness related data of all subjects are presented in table 1. Patients were moderately to severely ill with an average total PANSS score of 72 (±11) (PANSS positive: 21±4, negative: 16±4, general: 36±7), and had an illness duration of 5.2 (±4.3) months.

Table 1. Demographic and illness related items for patients and healthy controls.

	Healthy controls (n=43)	Patients (n=35)	*p*
Male	39	32	0.91
Age (yrs)	24.08 (±4.65) (range: 18.59-36.76)	24.18 (±4.24) (range 18.08-34.20)	0.92
EHI	0.97 (±0.05)	0.94 (±0.11)	0.28
Parental education (yrs)	12.90 (±3.27)	13.03 (±3.10)	0.87
Education (yrs)	13.05 (±2.26)	11.91 (±2.86)	0.06
Illness duration (months)		5.20 (±4.32) (range: 0.25-18)	
Diagnose schizophrenia		19	
Diagnose schizophreniform		15	
Diagnose schizoaffective		1	
PANSS-total		71.86 (±11.27)	
PANSS-positive		20.51 (±3.94)	
PANSS-negative		15.63 (±4.34)	
PANSS-general		35.71 (±6.51)	
CGI		4.97 (±0.82)	

Values are indicated as means ± SD. SD: standard deviation. EHI: Edinburgh Handedness Inventory, (Oldfield, 1971d), PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987), CGI: Clinical Global impression (Guy, 1976).

3.2. Behavioral measures

Accuracy levels during the categorical semantic decision task were equal for patients (91% ± 9.85) and controls (90% ± 9.74) (t(71)=0.54, p= 0.59).
There was no significant correlation between the LI in IFG and STG and accuracy levels (IFG: r=-0.13, p=0.25, STG: r=-0.02, p=0.85).

3.3. Neuroimaging

3.3.1. Lateralization and hemispheric activation.

Over all ROIs, the LI was significantly smaller in schizophrenia patients (LI: 0.07) compared to healthy controls (LI: 0.18) (main effect of group (F(1, 71)= 13.96, p< 0.001). The interaction between group and ROI was not significant (F (6, 71)= 1.70, p=0.13). Post-hoc t-tests (thresholded at p = (0.05 / 7) = 0.007 using the Bonferroni-correction for multiple comparisons) showed a decreased LI in patients compared to controls in the inferior frontal gyrus (IFG, Broca's area) (LI patients: 0.12, LI controls 0.24; t(76)= -3.10, p=0.003) and the superior temporal gyrus (STG, Wernicke's area) (LI patients: 0.02, LI controls: 0.23; t(76)= -4.77 , p< 0.001).
Subsequent comparison of left and right sided activation in these areas revealed no significant differences between patients and healthy controls, suggesting that both sides contributed to the differences in the lateralization index (t-test for activation differences between patients and controls: STG, left: t(76)= -1.12, p= 0.27 and right: t(76)= 1.70, p= 0.09; IFG left: t(76)= -1.64, p= 0.11 and right: t(76)= 0.52, p= 0.60). Brain activation data and lateralization indices for these areas are presented in table 2.

Table 2. Left- and right sided activation and lateralization index in the superior temporal gyrus and frontal inferior cortex

	left		*p*	right		*p*	LI		*p*
	SZ n = 35	HC n = 43		SZ	HC		SZ	HC	
STG	0.29 (±0.16)	0.34 (±0.19)	0.27	0.27 (±0.12)	0.22 (±0.15)	0.09	0.02 (±0.19)	0.23 (±0.20)	< 0.001
IFG	0.38 (±0.17)	0.44 (±0.15)	0.11	0.30 (±0.14)	0.28 (±0.14)	0.60	0.12 (±0.19)	0.24 (±0.16)	0.003

Brain activation (b-value) in mean ± SD.
STG: superior temporal gyrus, IFG: inferior frontal gyrus, SZ: schizophrenia, HC: healthy control, SD: standard deviation.

3.3.2. Correlation with PANSS (sub)-scores and hallucinations

There was no significant correlation between the LI in IFG and STG and the positive subscale of the PANSS (IFG: r=-0.07, p=0.70, STG: r=-0.20, p=0.26) nor with hallucinations (IFG: r=-0.24, p=0.16, STG: r=-0.06, p=0.73) or disorganization (IFG: r=-0.80, p=0.65, STG: r= 0.12, p=0.48). In addition, activation in neither STG (left, right), nor in IFG (left, right) was correlated with any of these clinical measures.

4. Discussion

We used functional MRI to investigate language lateralization in 35 first-episode medication-naive patients and 43 matched healthy controls. Lateralization, as expressed by the Lateralization Index (LI), was significantly reduced in patients compared to healthy controls in language related areas, indicating reduced left hemisphere dominance in schizophrenia patients. This reduction was most prominent in the inferior frontal gyrus (part of Broca's area) and the superior temporal gyrus (part of Wernicke's area). Whereas the ratio of the left and right sided activation (LI) was decreased, the left and right sided activation levels in these regions in itself did not differ between patients and healthy controls. In addition, the level of lateralization was not related to specific symptomatology. These findings suggest that language lateralization is impaired already in the first episode of the illness and is not a confound of medication use.

Our findings are in line with previous studies demonstrating reduced language lateralization in chronic patients with schizophrenia (Sommer et al., 2001;Sommer et al., 2003;Kircher et al., 2002;Dollfus et al., 2005;Dollfus et al., 2008;Spaniel et al., 2007;Razafimandimby et al., 2007;Bach et al., 2009) as well as in patients in their first episode (Bleich-Cohen et al., 2009), and medication-free patients (Weiss et al., 2006). Importantly, our findings replicate and extent this finding by showing reduced lateralization in a larger sample of first episode as well as medication-naive schizophrenia patients.

In our study, reduced lateralization was not specifically caused by significant activation changes in the left or right hemisphere. This may indicate that it is the left-right ratio, rather than the left- or right sided activation that is critical to the illness. Previous studies on language related activation in schizophrenia changes have yielded inconsistent results; it is not clear whether reduced language lateralization in schizophrenia is primarily driven by increases in right sided activation or decreases in left sided activation. Whereas some studies report a relative increase of right sided

activation (Sommer et al., 2001;Bleich-Cohen et al., 2009;Sommer et al., 2004;Whyte et al., 2006), others found decreased left sided activation (Dollfus et al., 2005;Razafimandimby et al., 2007), or bilateral activation changes (Weiss et al., 2006;Artiges et al., 2000). These differences may be due not only to the use of varying in methods to calculate the LI (Rutten et al., 2002;Jansen et al., 2006) but also to the effects of medication and selection of patient groups.
Indeed, whereas we found bilateral activation changes in first-episode medication-naive patients, Bleich-Cohen et al (Bleich-Cohen et al., 2009) reported a right sided increase in activation in first-episode but medicated patients.
So far, only one other study has addressed the effects of medication on LI and included medication–free schizophrenia patients (Weiss et al., 2006). Consistent with our results reduced lateralization was found due to bilateral activation changes during a verbal fluency task. However, only seven patients were tested, and the task performance of the patients was significantly lower compared to the controls.

Differences in activation patterns underlying reduced LI may also be caused by the selection of patient groups. Li et al. (Li et al., 2007a;Li et al., 2007b) proposed that activation changes take place during the course of the disease and especially during the first episode of illness. Li et al. (2007a) investigated subjects at high (genetic) risk for schizophrenia as well as chronic patients and found a reduced LI in both groups. In the high-risk cohort, however, the decreased LI was linked to decreased activation in the left hemisphere, while chronic schizophrenia patients displayed an increased activation in the right hemisphere.

In the current study, LI as well as activation levels in the IFG and STG were not significantly correlated with clinical measures as the PANSS positive subscale, or the PANSS items "disorganization" and "hallucinations". Although there are some studies that did report a relationship between reduced LI and hallucinations or positive symptoms (Weiss et al., 2006;Sommer et al., 2001;Sommer et al., 2003;Oertel et al., 2010), other studies failed to find such an association (Sommer et al., 2004;Sommer et al., 2007;Razafimandimby et al., 2007). Combined with the finding of reduced LI in high-risk subjects (Li et al., 2007b), and in unaffected monozygotic co-twins of patients with schizophrenia (Li et al., 2007a;Sommer et al., 2004), we take our data to suggest that reduced language lateralization may constitute a trait characteristic associated with the vulnerability for schizophrenia (or psychosis in general), rather than being related to clinical state. Reduced language lateralization may be a stable finding over time in schizophrenia, while psychotic symptoms may fluctuate over time. This may explain inconsistent results when correlating symptomtology to language lateralization.

There are a few limitations to consider with respect to the current study. First, only a small number of female patients participated. As symptomatology, but also language processing may be different between sexes, our results may have potentially limited generalizability. However, an earlier study (Sommer et al., 2003) and a meta-analysis of our group (Sommer et al., 2008a) did not find an effect of gender on lateralization. A second limitation is that performance data could be obtained for only one of the three tasks (categorical semantic decision). Accuracy for this task was equal for both groups, but we cannot rule out that performance was significantly different on the verb generation task or the antonym generation task. However, all subjects were trained on the tasks prior to scanning, to ensure good performance in the scanner. Furthermore, activation levels of patients were at the same level as that of controls, suggesting that all patients were similar to controls engaged in language processing.

Thus, we present data on language lateralization in the largest cohort to date of first-episode medication-naive patients. We did not only replicate the findings of reduced functional lateralization for language processing in schizophrenia, but build on these by showing a reduction in first-episode schizophrenia patients, prior to initiation of medical treatment.

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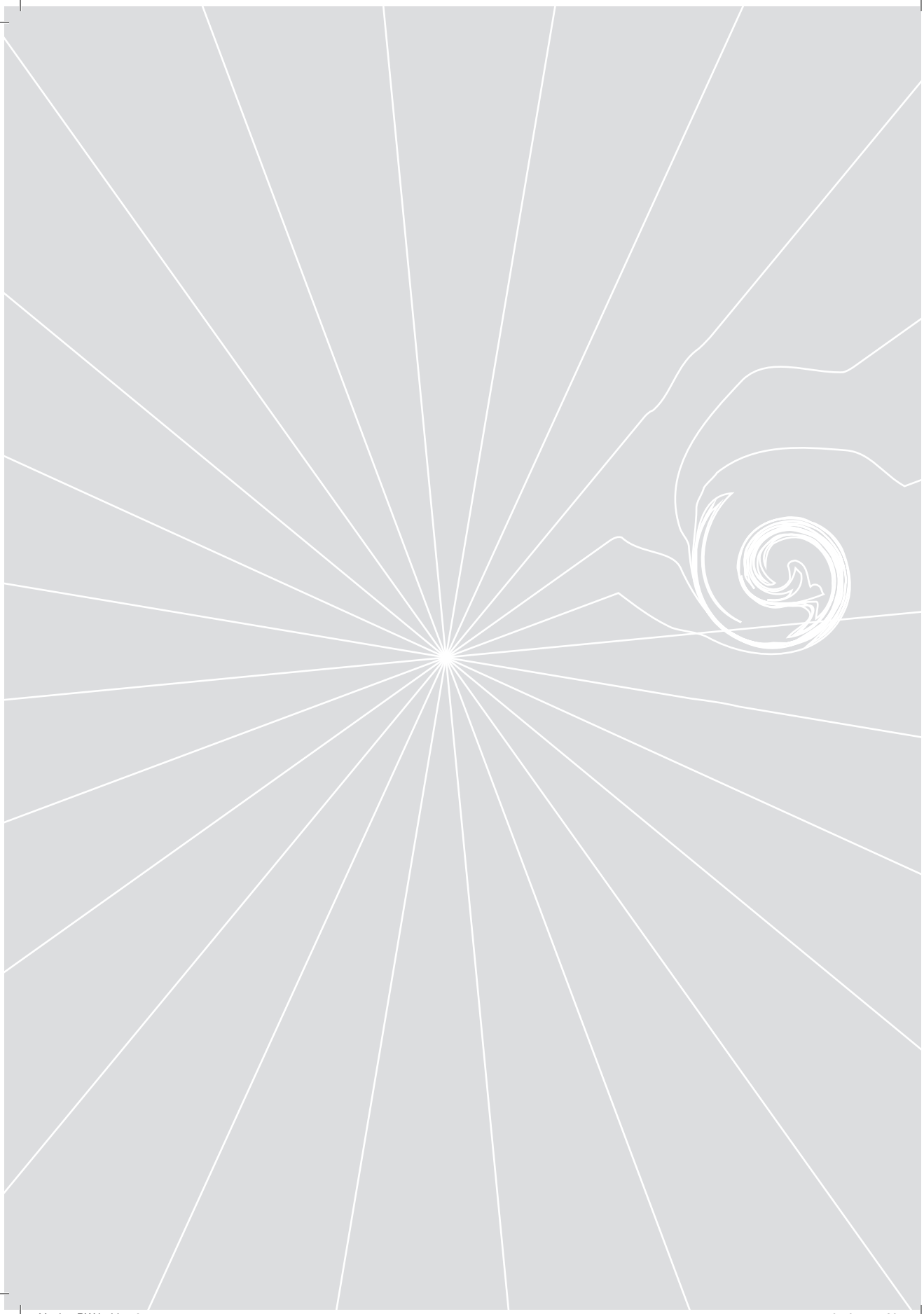

Chapter 3

Left dorsolateral prefrontal cortex dysfunction in medication-naive schizophrenia

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Abstract

Abnormalities in the frontal lobe are considered to be central to the pathology of schizophrenia. Neuroimaging studies indeed report abnormal function of the frontal lobe in schizophrenia patients. However, the nature of these functional abnormalities is unclear, in particular whether they are affected by medication. We therefore investigated whether frontal functioning is already abnormal in first-episode medication-naive schizophrenia, and if so, if this dysfunction is related to symptomatology. Thirty medication-naive male patients with first-episode schizophrenia and 36 matched healthy controls performed a modified working memory task while fMRI data were acquired. During the task, subjects were presented with novel task (NT) and practiced task (PT) memory sets. Compared to controls, patients showed reduced performance during NT and PT. However, both groups performed better during PT, indicating that practice improved performance. Importantly, practice reduced brain activation in both patients and controls, but this effect of practice was significantly smaller in patients compared to controls, specifically in the left dorsolateral prefrontal cortex (DLPFC; $p=0.01$). The reduced effect of practice on brain activation was related to the severity of negative symptoms and disorganization. These results suggest that DLPFC function is deficient in the early phases of schizophrenia and cannot be attributed to the use of antipsychotics.

1. Introduction

Abnormalities of the frontal lobe have been thought to be central to the pathology of schizophrenia. Indeed, magnetic resonance imaging (MRI) studies report volume decrements in the frontal lobes even in the early stages of the illness (Pantelis et al., 2005;Ho et al., 2003;Job et al., 2005;Pantelis et al., 2007). This volume loss appears to be functionally relevant, since several studies find the loss of frontal brain matter to be related to the severity of negative symptoms (Hazlett et al., 2008;Cahn et al., 2006;Hulshoff Pol and Kahn, 2008) and to cognitive dysfunction such as poor attention and reduced working memory capacity (Antonova et al., 2004;Gur et al., 1998).

Findings from functional MRI studies are generally consistent with those examining brain structure in schizophrenia: abnormal frontal lobe function is found in most studies, although the nature of these changes is inconsistent, varying from hypoactivation (Weinberger et al., 1992;Andreasen et al., 1992b;Yurgelun-Todd et al., 1996;Buchsbaum et al., 1992;Ragland et al., 1998;Karlsgodt et al., 2007) to hyperactivation (Callicott et al., 2000;Manoach et al., 2000;Jansma et al., 2004). This inconsistency may be due to several factors of which the cognitive tasks used, the cognitive load (Goldberg et al., 1998;Callicott et al., 1999;Manoach, 2003) and the effects of medication are probably the most important. Indeed, frontal lobe activity has not been adequately studied in medication-free (let alone medication-naive) schizophrenia patients.

Here we investigate frontal lobe function in the largest cohort to date of medication-naive schizophrenia patients in their first episode of illness in comparison to matched healthy subjects. To test frontal lobe function, we employ a modified Sternberg working memory task previously used in our group (Jansma et al., 2001;Ramsey et al., 2004;Jager et al., 2006;van Raalten et al., 2008). The modified version of the task allows to test the effects of practice on performance and brain activation. Functional neuroimaging studies in healthy controls have demonstrated that practice of working memory tasks induces improved performance accompanied by a significant decrease in brain activation, especially in the dorsolateral prefrontal cortex (Jansma et al., 2001;Milham et al., 2003;Landau et al., 2004).We hypothesized that if schizophrenia is associated with deficient frontal functioning, then the benefits of practice will be smaller, even in the early course of the illness. Furthermore, we hypothesized that this reduced frontal functioning is likely to be associated with predominantly negative symptoms and disorganization.

2. Methods

2.1. Participants

Forty-five patients were recruited from the Department of Psychiatry at the University Medical Center Utrecht. Forty-two controls were recruited through advertisements. The study was approved by the Ethics Committee of the University Medical Center of Utrecht. Written informed consent was obtained from all subjects prior to participation in the study. DSM-IV diagnosis of schizophrenia, schizoaffective or schizophreniform disorder was assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992a), and confirmed after half a year. Controls with a history of psychiatric (or neurological) disorder (assessed by the Mini International Neuropsychiatric Interview (MINI)(Sheehan et al., 1998) or with any first degree relative with a psychotic disorder were excluded. Participants with a diagnosis of substance abuse within the previous three months were also excluded. Patients were in their first episode of illness defined as an onset of illness (first psychotic symptoms) <2 years. Patients and healthy controls were matched on age, gender and parental education. In addition, all subjects were right handed (assessed by the Edinburgh Handedness Inventory (Oldfield, 1971)). Prior to scanning symptom ratings in patients were recorded using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression (CGI).

2.2. Working memory task

All subjects performed a modified Sternberg working memory task (figure 1) (Sternberg, 1966;Jansma et al., 2001;Ramsey et al., 2004;Jager et al., 2006;van Raalten et al., 2008). Stimuli were presented in blocks, each lasting 32 seconds. At the beginning of each task block, a set of five consonants was presented and the subjects were instructed to memorize them. Next, ten consonants were presented as probes (one second apart). Subjects had to indicate, by a button-press, whether this letter was part of the memorized set. Of the ten probes, five were present in the set (target) and five were different (non-target). Prior to scanning, subjects practised the task for 20 minutes, using a memory set that did not change throughout the practice session. During scanning, eight blocks with the practiced memory set (Practiced Task, PT) were semi-randomly mixed with eight blocks with a novel memory set (Novel Task, NT). In addition, eight blocks of a Control Task (CT) were included during which subjects pressed a button when the symbol '< >' appeared. In total, 24 blocks were presented. The focus of the current study was on the effect of practice, i.e. the difference in performance and brain activity between Practiced and Novel Task blocks.

2.3. Functional MRI data acquisition

A navigated echo 3D-PRESTO pulse sequence (van Gelderen P. et al., 1995) was used on a 1.5-T Philips ACS-NT MRI scanner. Functional images were obtained with the following parameter settings: Echo Time /RT 35/24 msec, flip angle 9 degrees, FOV 256x120x208 mm, data matrix 64x52, voxel size 4 mm isotropic, 30 slices.

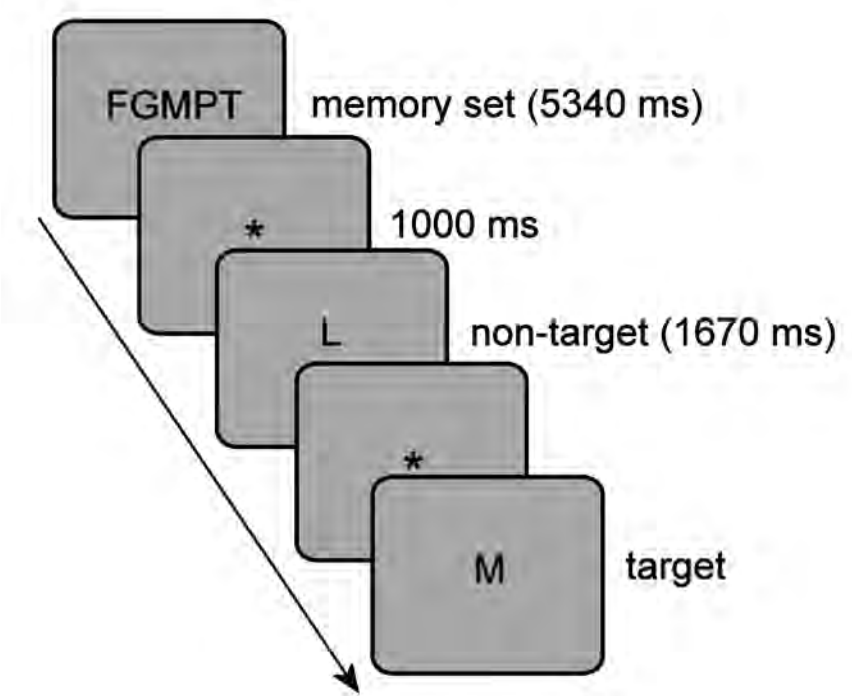

Fig. 1. Schematic display of the modified Sternberg working memory task.
Each task block starts with the presentation of a memory set (here FGMPT) and is followed by ten probes, each presented one second apart. Five probes were part of the memory set (target) and five were not (non-target).

A single run of 384 scans was acquired over a period of 18 minutes. A reference image with the same specifications as the functional scans, but with more anatomical contrast (flip angle 30 degrees) (Ramsey et al., 1998) was also acquired in order to facilitate coregistration to the anatomical image.

2.4. Data analysis: behavioral data

Reaction times (RT) of all correctly identified targets, accuracy (i.e. percentage of correctly identified targets and non-targets) and the effect of practice (performance PT – performance NT) was compared between patients and controls using univariate ANOVAs.

2.5. Data analysis: imaging data

Data analysis and pre-processing was performed using SPM5 (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm).

First, all functional scans were registered to the reference image so that all functional images were spatially aligned. Next, the reference and the structural image were coregistered, aligning the functional images with the structural image. Next, the structural scan was segmented using unified segmentation and normalization parameters were estimated. Subsequently, all scans were registered to a MNI T1-standard brain using these normalization parameters. Finally, all functional images were smoothed with an 8 mm full-width at half maximum isotropic Gaussian Kernel.

Second, the preprocessed functional images were submitted to a general linear model (GLM) regression analysis. The design matrix contained factors modeling the onsets and durations of the NT, PT and CT blocks as well as the memory sets that were presented during the task. These factors were convolved with a canonical hemodynamic response function (Friston et al., 1995). To correct for head motion, the six realignment parameters were included in the design matrix as regressors of no interest. To correct for drifts in the signal, a high-pass filter was applied to the data with a cut-off frequency of 0.003 Hz.

Third, to test for the effects of practice on brain activation, we used Regions of Interest (ROIs) determined in an independent sample (van Raalten et al., 2008). This sample consisted of 18 schizophrenia patients and 18 matched healthy controls. ROIs were regions showing activation in a group t-map calculated for the contrast NT-CT in both patients and controls (threshold of $p<0.05$ corrected). This resulted in five ROIs: left fusiform gyrus, left and right superior parietal cortex, anterior cingulate cortex and left dorsolateral-prefrontal cortex (see table 1, figure 2). By using these ROIs, we avoided biasing of our results via data selection as described by Kriegeskorte et al (Kriegeskorte et al., 2009).

Fourth, the average level of brain activation (i.e. b-value) over all voxels per ROI was obtained for NT and PT for each subject. These data were entered into a repeated-measures GLM analysis to test the effect of practice (NT -PT) in all five ROIs between patients and controls. Furthermore, a correlational analysis was performed between symptomatology and the effect of practice on brain activation in those ROIs showing a significant group difference (using PANSS sub-scores and the item "conceptual disorganization" of the PANSS).

Table 1. Regions identified in the t-map of the modified sternberg task (NT versus CT contrast, for the patients and controls combined) (van Raalten et al., 2008)

Region	Brodmann area	Number of voxels	X	Y	Z	Maximum t-value
Left fusiform gyrus	37	14	45	−59	−11	10.53
Left dorsolateral prefrontal cortex	9/46	193	46	11	29	14.36
Left superior parietal cortex	7	133	33	−56	41	10.31
Right superior parietal cortex	7	56	−32	−60	42	8.77
Anterior cingulate cortex	6/24	57	4	23	53	18.52

The MNI-coordinates of the voxel with the highest statistical value (group-map t-score) within each region are listed under X, Y and Z (Collins et al., 1994).

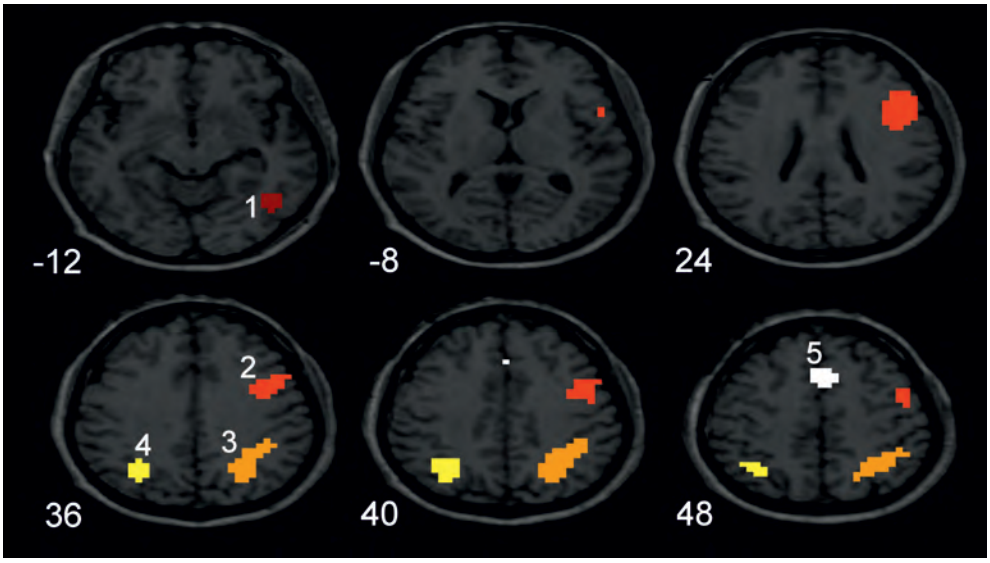

Fig. 2. Regions of Interest (ROIs) determined in an independent sample in an earlier study of our group (van Raalten et al., 2008): activity map of 18 patients and 18 controls combined of the STERN task (NT versus CT contrast), showing the following regions: 1. left fusiform gyrus LFG, 2. left dorsolateral prefrontal cortex DLPFC, 3. left superior parietal cortex LSPC, 4. right superior parietal cortex RSPC, 5. anterior cingulate cortex ACC. The numbers in the slices correspond to MNI z-coordinates (Collins et al., 1994). Threshold for significance corresponded to 0.05 Bonferroni-corrected, with a minimum cluster size of 10 voxels. Slices are in radiological orientation (left side is right hemisphere and vice versa).

3. Results

3.1. Participants

The sample included 45 first-episode schizophrenia patients and 42 healthy controls. Four patients were discarded for further analysis due to poor scan quality or- movement artefacts (>3 mm), two patients were discarded due to performance at chance level and four patients were discarded due to a change in diagnosis in the subsequent half year (3 bipolar disorder, 1 obsessive compulsive disorder). Two healthy control subjects were excluded due to poor scan quality or movement artefacts. In addition, to increase homogeneity of the sample, we excluded female participants (2 patients and 4 healthy controls) and three patients who were medication-free. So, the final analysis was performed on data of 30 medication-naive patients and 36 healthy controls.

Demographic and illness-related details are shown in table 2.

Table 2. Demographic and clinical characteristics of patients and healthy controls included in the analysis

Characteristics	Healthy Controls (male) (n=36)	Patients (male) (n=30)	*p*
Mean age(years) (SD)	24.3 (4.6) Range: 18.6-36.7	24.7 (4.2) Range: 18.6-34.2	0.74
Mean parental education (years) (SD)	12.9 (3.2)	12.7 (3.1)	0.80
Mean subject education (years) (SD)	13.2 (2.4)	11.7 (2.8)	0.03
EHI *	0.97 (0.06)	0.96 (0.11)	0.58
Diagnosis**: schizophrenia	n=17		
Diagnosis**: schizophreniform disorder	n=13		
Illness duration (months)		Mean: 5.08 (0.84) Range: 0.25-18.00	
PANSS total		73.3 (11.4)	
PANSS positive		20.8 (4.1)	
PANSS negative		16.4 (4.7)	
PANSS general		36.2 (6.4)	
CGI		5.0 (0.9)	

*EHI: Edinburgh Handedness Inventory (Oldfield, 1971). ** Diagnosis at inclusion.

3.2. Behavioral measures

The data are presented in table 3. Reaction times of patients were significantly longer than those of controls for the Novel Task (NT: F (1, 60) =4.27), p=0.04) and near significantly longer for the Practiced Task (PT: F (1, 60) =3.76, p=0.06). In addition, patients were less accurate during NT (F (1, 60) =19.98, p<0.001) and PT (F (1, 60) =10.64, p=0.002).

Practice significantly reduced response times (main effect of practice (F (1, 59) =98.26, p<0.001) and this effect was the same for both groups (group by practice interaction: F (1, 59) =0.01, p=0.94). Accuracy also improved with practice (main effect of practice (F (1, 59) =64.02, p<0.001), but this was different for patient and controls (group by practice interaction: F (1, 59) =6.92; p=0.01), with patients showing a larger improvement than controls. This is, however, probably caused by a ceiling effect in controls, as their accuracy for the NT was already 94%.

Table 3. Behavioural measures

	Novel Task		*p*	Practiced Task		*p*	Effect of practice		*p*
	SZ n = 30	HC n = 36		SZ	HC		SZ	HC	
reaction times (msec)	802 (±126)	744 (±95)	0.04	737 (±132)	680 (± 99)	0.06	64 (±45)	63 (±53)	0.94
accuracy (percentage)	84 (±11)	94 (±6)	<0.001	94 (±8)	99 (±2)	0.002	10 (±9)	5 (±5)	0.02

Performance data, in means ± SD

Effect of practice: improvement after practice, SD: standard deviation, SZ: schizophrenia, HC: healthy controls.

3.3. Neuroimaging

3.3.1. Activations

The data are presented in table 4. Practice significantly reduced brain activity in all ROIs in both groups (main effect of practice (F (1, 64) =311.73; p<0.001). Practice induced a smaller drop in brain activity in patients than in controls (group by practice interaction (F (1, 64) =3.82; p=0.05).This remained significant after controlling for behavioral differences in the effect of practice (F (1, 58) =4.07; p=0.04). Post-hoc ANOVAs for all ROIs indicated that this group difference was present only in the left DLPFC (F (1, 60) =6.60, p=0.01). This difference remained significant after correct-

ing for the difference in practice effect on accuracy by including it as a covariate (F (2, 54) =4.35, p=0.02). In addition, the difference in practice effect between the groups was not caused by a difference in left DLPFC activation during either the NT or the PT (F (2, 57) =2.03, p =0.14, and F (2, 57) =1.43, p=0.25, respectively).

Table 4. Brain activation levels and the effect of practice.

	Novel Task		*p*	Practiced Task		*p*	Effect of practice		*p*
	SZ n=30	HC n=36		SZ	HC		SZ	HC	
LFG	0.29 (±0.50)	0.30 (±0.27)	0.54	0.13 (±0.48)	0.18 (±0.23)	0.66	0.16 (±0.19)	0.11 (±0.19)	0.57
DLPFC	0.22 (±0.22)	0.34 (±0.21)	0.14	0.05 (±0.22)	0.06 (±0.18)	0.25	0.17 (±0.22)	0.29 (±0.16)	0.02
LSPC	0.26 (±0.19)	0.28 (±0.19)	0.33	0.09 (±0.18)	0.04 (±0.17)	0.55	0.17 (±0.14)	0.24 (±0.17)	0.14
RSPC	0.22 (±0.26)	0.25 (±0.24)	0.58	0.05 (±0.21)	0.04 (±0.23)	0.72	0.17 (±0.16)	0.21 (±0.20)	0.70
ACC	0.28 (±0.32)	0.43 (±0.27)	0.04	0.10 (±0.27)	0.24 (±0.23)	0.09	0.17 (±0.13)	0.20 (±0.20)	0.26

Brain activation levels (b-values) during task conditions and the effect of practice (±SD).
SZ: schizophrenia patients, HC: healthy Controls, Effect of practice: reduction of brain activation after practice.
LFG: left fusiform gyrus, DLPFC: left dorsolateral prefrontal cortex, LSPC: left superior parietal cortex, ACC: anterior cingulated cortex.

3.3.2. Correlations

The effect of practice on brain activation in the left DLPFC was negatively correlated with the total PANSS score (r=-0.38, p=0.04), the total Negative PANSS score (r=-0.44, p=0.02) and the item "conceptual disorganization" (r=-0.52, p<0.005), but not with the total General PANSS score (r=-0.32, p=0.09) nor with the total Positive PANSS score (r=-0.05, p=0.79).

4. Discussion

This study examined the effects of practice on brain activation using a modified Sternberg working memory task in 30 first-episode, medication-naive, male schizophrenia patients. Results were compared to those of 36 matched healthy subjects. During the task, subjects were presented with novel task (NT) and practiced task (PT) memory sets. Both groups performed better during PT, indicating that practice improved performance. Compared to controls, patients showed similar levels of brain activation during both NT and PT, although their overall performance was reduced. Practice was associated with a reduction in frontal brain activation in both patients and healthy controls. This decrease, however, was significantly smaller in patients than in controls in the left dorsolateral prefrontal cortex (DLPFC). This reduced effect of practice on left DLPFC activation was found to be related to the severity of negative symptoms and conceptual disorganization. Taken together, these results suggest that frontal lobe function particularly that of the left DLPFC, is significantly impaired in schizophrenia patients during their first episode and unrelated to antipsychotic treatment.

Consistent with our current findings, previous imaging studies in healthy controls have shown a pattern of decreased activation after short-term practice (e.g. 20 minutes), using the same paradigm as in the current study (Jansma et al., 2001), or other working memory paradigms (spatial working memory task (Sayala et al., 2006;Garavan et al., 2000), face working memory task (Landau et al., 2004) or an adapted version of the Tower of London Task (Beauchamp et al., 2003)). Notably, practice of working memory tasks in these studies was not accompanied by a shift of activation to other brain areas over the course of learning. Therefore, the decrease of activation with practice in healthy controls is hypothesized to reflect increased neural efficiency, whereby practice builds a more efficient neural route through the modification of neural connectivity. As a result fewer neurons or neural circuits are recruited (Kelly et al., 2006;Garavan et al., 2000).

The reduced effect of practice on brain activation that we observed in the first-episode medication-naive schizophrenia patients may therefore indicate inefficient neuronal processing. That is, like controls, patients improved performance after practice, but their reduction in activation levels in the left DLPFC was significantly smaller.

To our knowledge, this is the first study investigating the effects of practice on working memory in first-episode medication-naive patients. We previously performed a study using the same working memory paradigm in outpatients stable on medication (van Raalten et al., 2008). These patients had an average length of illness of 5.2 years (± 4.4 years) and a lower total PANSS score as compared to the current patients (51

versus 73, respectively). In that study, activation levels during the PT were similar for patients and controls, consistent with the results presented here. However, in the previous study, not a smaller, but rather an increased effect of practice in the DLPFC was found, as indicated by a larger difference between NT and PT activation in patients relative to controls. This larger practice effect was caused by a hyperactivation in patients compared to controls during NT in both the DLPFC and the left superior parietal cortex (van Raalten et al., 2008), whereas NT activation levels in the current study did not differ between patients and controls. Patient performance levels on NT were also different. Patients in the previous study performed at an equal level as the controls did (95% vs. 97% accuracy in NT for patients and controls respectively), while patients in the current study performed significantly worse than controls (85% vs. 94%). However, these differences in activation levels and performance may in fact be linked and can be explained based on previous research in this field.
First, it has been shown that brain activation levels are influenced by task performance levels (see (Manoach, 2003;Callicott et al., 1999) for a meta-analysis). In addition, this relationship between performance and brain activation is likely to be different for healthy controls and patients (Callicott et al., 2003;Karlsgodt et al., 2007). To account for such differences, Karlsgodt et al. (Karlsgodt et al., 2007) proposed the Cross-Over Between-Subjects Model, which predicts that high performing patients show higher activation levels, not only compared to patients with low task performance, but also in comparison to high performing healthy controls. This model was confirmed by findings of the same group (Karlsgodt et al., 2009). The results of our previous and current study, at first glance appear to be contradictory, are in line with this model. As predicted by the model, high performing patients showed hyperactivation in the DLPFC compared to controls with the same accuracy (van Raalten et al., 2008), while patients in the current study, with a significantly lower accuracy had similar activation levels as controls with good performance.

The relationship between frontal lobe dysfunction and the severity of negative symptoms and disorganization as we found here is in line with findings from earlier structural MRI studies (Hazlett et al., 2008;Cahn et al., 2006;Hulshoff Pol and Kahn, 2008;Molina et al., 2003) as well as with findings of functional imaging studies. Decreased frontal brain function was related to disorganization (Callicott et al., 2000;Snitz et al., 2005) and to negative symptoms (Liddle, 1992;Lahti et al., 2001;Snitz et al., 2005) by some but not al studies (Honey et al., 2003;Arce et al., 2006). Moreover, in an fMRI study by Sanz et al (Sanz et al., 2009) lower levels of activation during a working memory task across left frontal and parietal regions covaried with poorer role functioning as well as greater severity of negative and disorganized symptoms.

A significant strength of our study is the fact that we included the largest cohort of medication-naive patients to date. This is important, as the use of medication may influence brain activation levels, although the results of studies investigating these effects are not conclusive (Meisenzahl et al., 2006;Wolf et al., 2007;Snitz et al., 2005). Only a few studies have been performed with medication-naive patients, and these studies did not investigate the effect of practice (Andreasen et al., 1992;Barch et al., 2001;Riehemann et al., 2001). Our results are consistent with those of Barch et al. (Barch et al., 2001), who investigated brain activation during working memory in 14 first-episode medication-naive patients and 12 healthy controls. Their results match ours in that they found patients to display deficits in brain activation in the DLPFC, but not in other regions important for task performance.

The underlying mechanisms of the inefficient processing within the DLPFC found in this study are largely unknown and may be heterogeneous. It has been hypothesized that abnormal apoptosis and/or synaptic pruning (Glantz et al., 2006;Jarskog et al., 2005) play a role in the pathogenesis of schizophrenia. Furthermore, schizophrenia is associated with reduced cortical neuropil (for a review, see (Selemon and Goldman-Rakic, 1999)), specifically in the DLPFC (Selemon et al., 2003), possibly leading to reduced connectivity (Selemon et al., 2003), and in turn impaired neural synchrony, as hypothesized by Williams et al. (Williams et al., 2009). Alternatively, reduced neuronal efficiency may be the result of deficient GABA-mediated inhibition in the DLPFC in schizophrenia (Gonzalez-Burgos and Lewis, 2008). Finally, it has been hypothesized that this inefficiency is primarily caused by aberrant NMDA-receptor mediated synaptic plasticity which is the result of abnormal regulation of neuromodulatory transmitters like dopamine, serotonin, and acetylcholine (Stephan et al., 2009).

Several of the present study limitations should be considered. First, our sample consisted of male patients, reducing the generalizability of our results. However, Schmidt et al. (Schmidt et al., 2009) did not find gender differences for verbal working memory at the behavioural or neural level in healthy controls. Furthermore, a recent review of 45 meta-analyses by Hyde (Hyde, 2005) showed that gender differences are generally smaller than intra-gender differences in many cognitive domains.
Another limitation is that patients were not very ill: the average total PANSS score was 73.3. Patients more severely ill proved to be unable to adhere to the functional MRI procedure (lying still, in a confined space, paying attention to a cognitive task during twenty minutes, with adequate performance).
Finally, we matched subjects on parental education level as the illness typically impedes maximum educational attainment in patients. As a consequence, it is impossible to disentangle the effects of illness from that of a lower education level on task performance.

In conclusion, both controls and patients improved performance of a working memory task with practice. Practice was associated with a reduction in brain activation in both groups, but this effect was smaller in patients, specifically in the left DLPFC. This deficiency was found to be correlated with the severity of negative symptoms and disorganization. Our results therefore suggest that DLPFC function is deficient in the early phases of schizophrenia and cannot be attributed to the use of antipsychotics.

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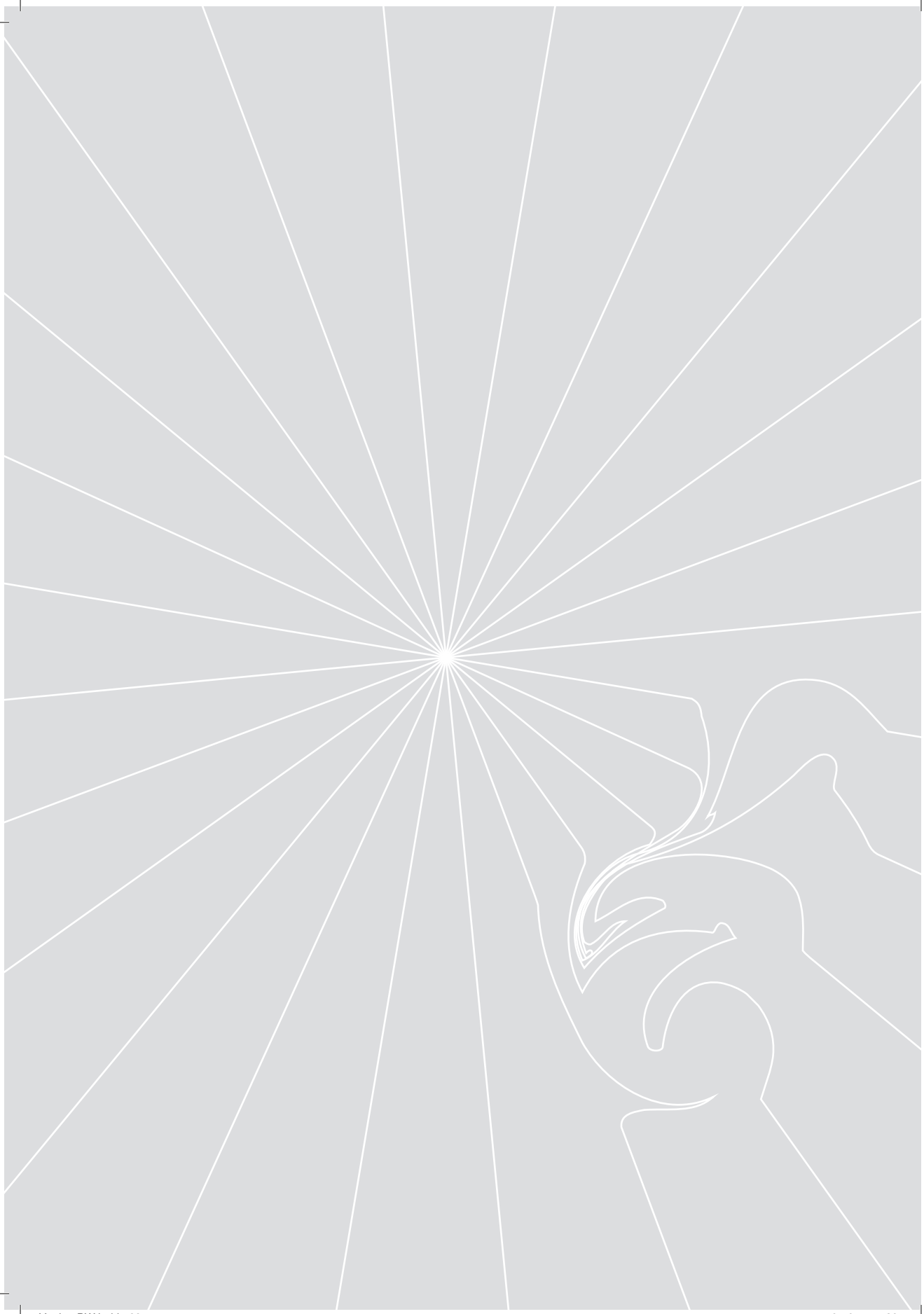

Chapter 4

Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia

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Abstract

Dysfunction of the frontal lobe is considered to be central to the pathology of schizophrenia. However, the nature of these abnormalities is unclear, in particular whether they are affected by treatment. In an earlier functional MRI study of our group we found dorsolateral prefrontal lobe (DLPFC) dysfunction to be present in medication-naive first-episode patients. In this follow-up study, we investigated whether treatment with atypical antipsychotics had an effect on DLPFC functioning, and whether (change in) DLPFC functioning was related to treatment response.

Twenty-three medication-naive, first-episode male schizophrenia patients and 33 matched healthy controls were scanned at baseline and were re-scanned after ten weeks, while performing a modified Sternberg working-memory task. We specifically investigated the effect of practice on brain activation, defined as the signal change between a novel and practiced working-memory task. After the baseline scan, patients were treated with atypical antipsychotics. Based on their symptom change after ten weeks, patients were divided into responders and non-responders

We found DLPFC function did not change after ten weeks in healthy controls or in patients who received treatment. However, while patients who responded to treatment did not differ from controls, non-responders showed a reduced practice effect in the DLPFC that was present already at baseline, which did not change after treatment. A reduced practice effect in the DLFPC at baseline was found to be predictive of poor treatment response at ten weeks.

These results suggest that prefrontal lobe dysfunction reflects a distinct neuropathological substrate in a subgroup of treatment non-responsive schizophrenia patients.

1. Introduction

From the first description of the illness by Emil Kraepelin over a century ago, abnormalities of the frontal lobe have been thought to be central to the pathology of schizophrenia. Indeed, structural (Pantelis et al., 2007;Ho et al., 2003;Job et al., 2005;Pantelis et al., 2005;Hazlett et al., 2008;Hulshoff Pol and Kahn, 2008;Antonova et al., 2004;Gur et al., 1998) as well as functional magnetic resonance imaging (MRI) studies (Weinberger et al., 1992;Andreasen et al., 1992b;Yurgelun-Todd et al., 1996;Buchsbaum et al., 1992;Ragland et al., 1998;Karlsgodt et al., 2007;Jansma et al., 2001) report abnormalities of the frontal lobe. In a previous functional MRI study, we found dorsolateral prefrontal lobe (DLPFC) dysfunction to be present already in first-episode patients who were medication-naive (van Veelen et al., 2010). This was found to be related to the severity of negative symptoms and disorganization.

We now extend this study and investigate whether subsequent treatment with atypical antipsychotics has an effect on DLPFC functioning. As it is evident that not all patients respond to antipsychotic treatment (Robinson et al., 2005;Leucht et al., 2007) and that the outcome of the illness is heterogeneous (Van Os and Kapur, 2009), we also test if treatment response is related to DLPFC functioning. For example, structural MRI studies have shown that more pronounced progressive brain changes in the frontal lobes are associated with poor outcome (Hulshoff Pol and Kahn, 2008;Weinberger et al., 1992;Andreasen et al., 1992b;Yurgelun-Todd et al., 1996). Furthermore, one may expect patients with impaired prefrontal lobe function to show diminished response to antipsychotic treatment since these drugs have been found to have limited effects on improving negative symptoms (Buckley and Stahl, 2007;Erhart et al., 2006;Alphs, 2006) and cognitive performance (Keefe, 2007;Goldberg et al., 2007), both having been related to prefrontal lobe function.

Here, we investigate medication-naive first-episode male schizophrenia patients before and after an open ten week treatment trial with (atypical) antipsychotic treatment, using a modified Sternberg working memory task (Jansma et al., 2001;Ramsey et al., 2004;Jager et al., 2006;van Raalten et al., 2008;van Veelen et al., 2010). Patients are matched with healthy controls, and all subjects are scanned twice. Based on their symptom change after ten weeks of treatment, patients are categorized as responder or non-responder. In this way, we can examine whether treatment affects DLPFC function in patients and whether dysfunction in this region is related to treatment response.

2. Materials and methods

2.1. Participants

All subjects were part of a larger cohort, described previously, in which 30 medication-naive first-episode patients and 36 matched healthy controls participated (van Veelen et al., 2010). The diagnosis of schizophrenia or schizophreniform disorder in patients was assessed with the Structured Clinical Interview for DSM-IV (First et al., 1996) or The Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992a) and confirmed after six months.

The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used to exclude controls with a history of psychiatric or neurologic disorder, or with any first degree relatives with a psychotic disorder. Participants with a diagnosis of substance abuse within the previous three months were excluded.

In the current study we obtained functional MRI data from 23 patients and 33 healthy controls, who were scanned at baseline prior to treatment (see (van Veelen et al., 2010) and after 10 weeks (10.1± 2.2 weeks). The seven patients who did not have a second scan did not differ from those patients who were scanned at both time points in demographic and clinical measures at baseline

Patients were started on atypical antipsychotic treatment after the baseline scan (van Veelen et al., 2010); the use of concomitant antidepressant medication and mood stabilisers was prohibited. Prior to each scan, symptom ratings were recorded using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). After ten weeks of treatment, patients were categorized as responder or non-responder based on the change in total PANSS score. Treatment response was defined as a reduction of more than 30 percent in total PANSS score (Leucht et al., 2005).

The study was approved by the Ethics Committee of the University Medical Center of Utrecht. Written informed consent was obtained from all subjects prior to participation in the study.

2.2. Working memory task

Subjects performed a modified Sternberg working memory task with a practiced (PT) and a Novel (NT) memory set. Task design and experimental procedure were identical to those described previously (van Veelen et al., 2010) and are briefly explained in figure 1.

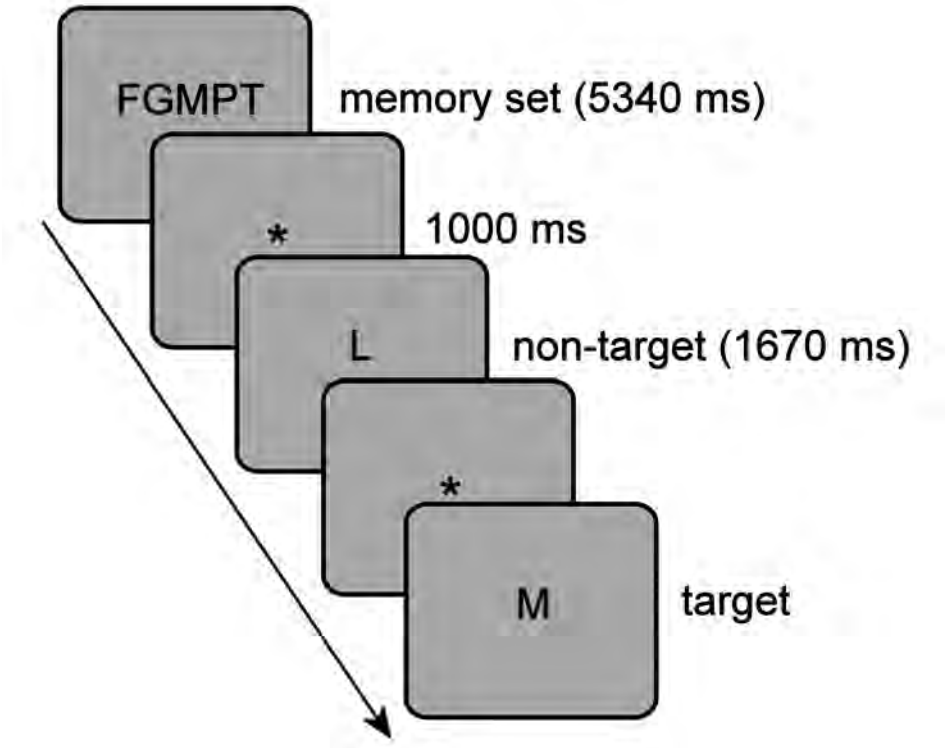

Fig. 1. Schematic display of the modified Sternberg working memory task (Sternberg, 1966;Jansma et al., 2001;Ramsey et al., 2004;Jager et al., 2006;van Raalten et al., 2008;van Veelen et al., 2010). Each task block starts with the presentation of a memory set (here FGMPT) and is followed by ten probes, each presented one second apart. Five probes were part of the memory set (target) and five were not (non-target). Subjects had to indicate, by pressing a button, whether this letter was part of the memorized set. Prior to scanning, subjects practised the task for 20 minutes, using a predefined memory set that did not change throughout the practice session. During scanning, task blocks with the practiced memory set (Practiced Task, PT) were semi-randomly mixed with task blocks with a novel memory set (Novel Task, NT). In addition, a Control task (CT) was included during which subjects had to press a button when the symbols '< >' appeared. The entire experiment lasted about 18 minutes and consisted of the pseudo-randomized presentation of eight blocks (memory set and ten probes) for each condition (total 24 blocks) interleaved with resting periods. For the second scan-session, a new set of letters was used for the PT. The focus of the current study was on the effect of practice, i.e. the difference between activation during PT versus NT blocks.

2.3. Functional MRI data acquisition

For the image acquisition, a navigated echo 3D-PRESTO pulse sequence (van Gelderen P. et al., 1995;Ramsey et al., 1998) was used, on a 1.5-T Philips ACS-NT MRI scanner. The following parameter settings were used: Echo Time /Repetition Time

35/24 msec, flip angle 10.5 degrees, Field of View: 256x120x208 mm, data matrix 64x52, voxel size 4 mm isotropic, 30 slices. A single run of 384 scans was acquired over a period of 18 minutes. A reference image with the same specifications as the functional scans, but with more anatomical contrast (flip angle 30 degrees) was also acquired to facilitate coregistration to the anatomical image. Finally, an anatomical T1-weighted scan was acquired (voxel size 1mm isotropic).

2.4. Treatment

Patients were treated with olanzapine (n=13, mean dose 15 ±4.8 mg), risperidone (n=4, mean dose 4 ±1.4 mg), quetiapine (n=3, mean dose 733 ±567 mg), or ziprasidone (n=3, mean dose 65 ±19.2 mg).

2.5.1. Data analysis: behavioral data

Reaction times (RT) of all correctly identified targets, as well as accuracy (i.e. percentage correctly identified targets and non-targets) were tested with a repeated-measures GLM analysis with time (baseline, second scan-session) and task (NT, PT) as within-subject and group (either patients and controls or responders and non-responders) as between-subject factor.

2.5.2. Data analysis: imaging data

Data analysis and pre-processing was performed using SPM5 (Wellcome Trust Centre for Neuroimaging, London, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing and first-level statistical analyses were performed as described previously (van Veelen et al., 2010). In brief, preprocessing involved realignment for head motion correction, coregistration of functional images to the anatomical image, spatial normalization to the Montreal Neurological Institute template brain, and spatial smoothing (8 mm FWHM) of functional images.

The functional data were then analysed voxel-wise, using a general linear model (GLM) including regressors modelling the onsets and durations of the NT, PT and Control Task (CT) blocks as well as the memory sets that were presented at the beginning of each taskblock. These factors were convolved with a canonical hemodynamic response function (Friston et al., 1995). To correct for head motion, the six realignment parameters were included in the design matrix as regressors of no interest. To correct for drifts in the signal, a high-pass filter was applied to the data with a cut-off frequency of 0.003 Hz.

To test for the effects of practice (NT – PT) on brain activation, we used Regions of Interest (ROIs) that included the Left Fusiform Gyrus (LFG), Left and Right Superior Parietal Cortex (LSPC and RSPC), Anterior Cingulate Gyrus (ACC) and the left Dorsolateral Prefrontal Cortex (DLPFC) (see table 1, figure 2). These predefined

ROIs were determined in an independent sample performing the same task (van Raalten et al., 2008), to avoid biasing of our results via data selection as described by Kriegeskorte et al (Kriegeskorte et al., 2009) and were identical to the regions used in our previous report on the baseline scan (van Veelen et al., 2010).
For each subject, the average level of brain activation (i.e. b-value) over all voxels per ROI was obtained for NT and PT. These data were entered into a repeated-measures GLM analysis with time (baseline, second scan-session), task (NT, PT) and ROI as within-subject factors and group (patients, controls) as between-subject factor. In this way, the effects of illness and the effect of treatment and/or retesting could be tested. A similar analysis was performed for responders and non-responders. Furthermore, to determine whether frontal lobe activation at baseline was predictive of clinical outcome after ten weeks, a regression analysis was performed with PANSS improvement as dependent variable and the practice effect on brain activation in the DLPFC as independent variable.

Table 1. Regions of Interest.

Region	Brodmann area	Number of voxels	X	Y	Z	Maximum t-value
Left fusiform gyrus	37	14	45	−59	−11	10.53
Left dorsolateral prefrontal cortex	9/46	193	46	11	29	14.36
Left superior parietal cortex	7	133	33	−56	41	10.31
Right superior parietal cortex	7	56	−32	−60	42	8.77
Anterior cingulate cortex	6/24	57	4	23	53	18.52

Regions of Interest identified in the group t-map of the modified sternberg task (NT versus CT contrast, for the patients and controls combined) (van Raalten et al., 2008)
The MNI-coordinates of the voxel with the highest statistical value (group-map t-score) within each region are listed under X, Y and Z (Collins et al., 1994).

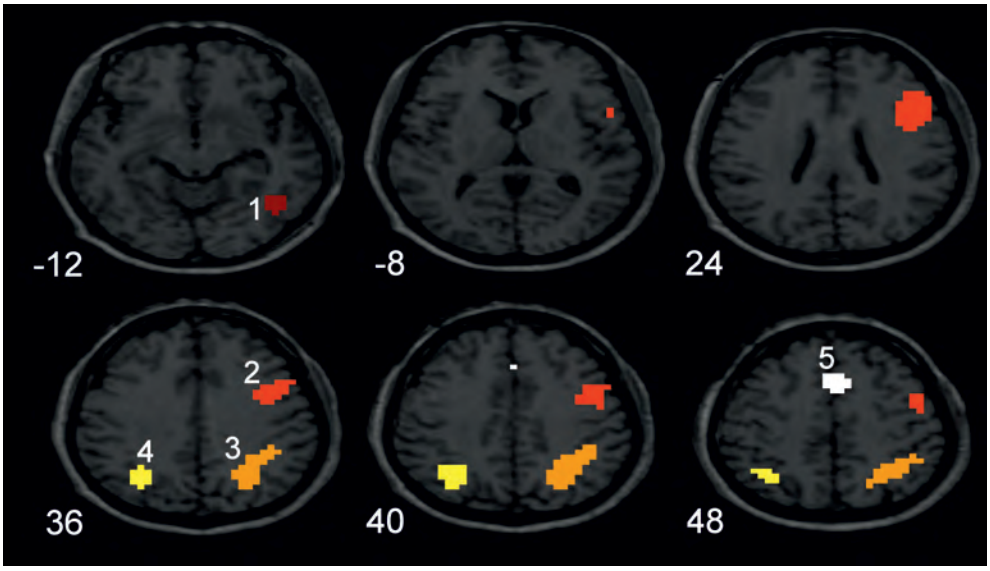

Fig. 2. Regions of Interest (ROIs) determined in an independent sample in an earlier study of our group, obtained from the Novel Task versus Control Task contrast (for details, see table 1). 1. left fusiform gyrus (LFG), 2. left dorsolateral prefrontal cortex (DLPFC), 3. left superior parietal cortex (LSPC), 4. right superior parietal cortex (RSPC), 5. anterior cingulate cortex (ACC). The numbers in the slices correspond to MNI z-coordinates (Collins et al., 1994). Threshold for significance corresponded to 0.05 Bonferroni-corrected, with a minimum cluster size of 10 voxels. Slices are in radiological orientation (left side is right hemisphere and vice versa).

3. Results

3.1. Participants

Patients were moderately ill with a mean total PANSS score of 75.0 (±11.4) and had a mean duration of illness of 4.9 (±4.4) months at inclusion (see table 2). After ten weeks of treatment, 11 patients were classified as responder and 12 as non-responder. Responders and non-responders did not differ in socio-demographic features or in the PANSS scores at the baseline scan (see table 3). Two patients used benzodiazepines (<20 mg oxazepam) at baseline scanning, one responder, one non-responder.

Table 2. Demographic and clinical characteristics of participants at baseline.

Characteristics	Healthy controls (n=33) Mean (± SD)	Patients (n=23) Mean (± SD)	*p*
Mean age in years	24.5 (±4.7)	25.3 (±4.6)	0.53
Mean parental education in years	12.9 (±3.2)	12.6 (±2.6)	0.78
Mean subject education in years	13.2 (±2.4)	11.2 (±2.7)	0.006
EHI	0.97 (±0.1)	0.93 (±0.1)	0.15
Illness duration (months)		4.9 (±4.3)	
Diagnose schizophreniform disorder		11	
Diagnose schizophrenia		12	
PANSS total		75.0 (±11.4)	
PANSS positive		21.7 (±4.0)	
PANSS negative		16.4 (±5.1)	
PANSS general		37.0 (±5.9)	

Note. Values enclosed in parentheses represent standard deviation (SD). PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987), EHI: Edinburgh Handedness Index (Oldfield, 1971). (Significance of differences is calculated using t-tests). All participants were male.

Table 3. Demographic and clinical characteristics of responders and non-responders at baseline.

Characteristics	Responders (n=11) Mean (± SD)	Non-responders (n=12) Mean (± SD)	*p*
Mean age in years	23.9 (±4.1)	26.5 (±4.8)	0.11
Mean parental education in years	13.2 (±2.3)	11.9 (±2.9)	0.50
Mean subject education in years	11.5 (±2.6)	10.8 (±2.9)	0.60
EHI	0.98 (±0.1)	0.88 (±0.2)	0.09
Illness duration	5.3 (±5.2)	4.5 (±3.4)	0.80
PANSS total	71.1 (±12.2)	78.6 (±9.9)	0.12
TOTAL positive	20.4 (±4.8)	22.9 (±2.9)	0.17
TOTAL negative	15.9 (±5.5)	16.8 (±5.0)	0.61
TOTAL general	34.8 (±5.1)	38.9 (±6.2)	0.12
Haldol doses equivalent mg/day (at time of second scan-session)	5.2 (±2.1)	6.3 (±1.7)	0.21

Note. Values enclosed in parentheses represent standard deviation (SD). PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987), CGI: EHI: Edinburgh Handedness Index (Oldfield, 1971). (Significance of differences is calculated using t-tests). Responders had a reduction of more than 30 percent on total PANSS (after subtracting the minimum score of 30 of the total PANSS) after 10 weeks (Leucht et al., 2005).

3.2. Behavioral data

Patients versus controls

Data are presented in table 4. Patients were slower than controls (main effect of group: F(1,45)=6.10, p=0.02). However, the improvement in response speed with practice (PT versus NT) was equal for patients and controls (group by task interaction: F(1,45)=0.26, p=0.61) and was not affected by time (main effect of time: F(1,45)=0.01, p=0.93), group by time interaction: F(1,45)=1.19, p=0.28, group by task by time interaction: F(1,45) =1.99, p=0.17).

Patients and healthy controls did not differ in accuracy (effect of group: F(1,45)=2.43, p=0.13). More importantly, the improvement in accuracy with practice (main effect of task: F(1,45)=43.21, p<0.001) was equal in patients and controls (group by task interaction: F(1,45)=1.73, p=0.20), and was not affected by time (main effect of time: F(1,45)=0.96, p=0.33, group by time interaction: F(1,45)=1.18, p=0.29, group by task by time interaction: F(1,45)=0.37, p=0.55).

Table 4. Behavioral measures patients and healthy controls.

	Novel Task		***Practiced Task***		***Effect of practice***	
Behavioural measures baseline scan	**SZ n = 23 Mean (± SD)**	**HC n = 33**	**SZ**	**HC**	**SZ**	**HC**
reaction times (ms)	822 (±25)	746 (±16)	752 (±25)	683 (±18)	70 (±10)	63 (±10)
accuracy (percentage)	85 (±2)	93 (±1)	94 (±02)	98 (±0.2)	9 (±1)	5 (±1)
Behavioral measures second scan						
reaction times (ms)	800 (±23)	755 (±14)	769 (±28)	697 (±16)	30 (±19)	58 (±10)
accuracy (percentage)	89 (±3)	92 (±2)	97 (±0.8)	95 (±1.8)	8 (±3)	3 (±2)

Performance data, in means (± SD)

Effect of practice= improvement after practice, SD= standard deviation, SZ= schizophrenia, HC= healthy controls.

Responders versus non-responders

Data are presented in table 5. The improvement of response speed with practice (main effect of task: F(1,13)=19.34, p=0.001) did not differ between the patient groups (group by task interaction: F(1,13)=0.05, p=0.82) and was not affected by time (main effect of time: F(1,13)=0.37, p=0.55, group by time interaction: F(1,13)=0.05, p=0.82, group by task by time interaction: F(1,13)=0.18, p=0.68).

There was no difference between responders and non-responders in overall RT (effect of group: F(1,13)=, p=0.52). The improvement in accuracy with practice (main effect of task: F(1,13)=11.44, p=0.005) did not differ between the groups (group by task interaction: F(1,13 =0.54, p=0.48) and was not affected by time (main effect of time: F(1,13)=0.50, p=0.50, group by time interaction: F(1,13)=1.12, p=0.31, group by task by time interaction: F(1,13)=0.16, p=0.70). There was no difference between responders and non-responders in overall accuracy (effect of group: F(1,13)=2.35, p=0.15).

Table 5. Behavioral measures responders and nonresponders.

	Novel Task		*Practiced Task*		*Effect of practice*	
Behavioural measures baseline scan	**resp n = 11 Mean (± SD)**	**nonresp n = 12**	**resp**	**nonresp**	**resp**	**nonresp**
reaction times (ms)	788	852	729	772	59	80
	(±28)	(±38)	(±31)	(±40)	(±12)	(±16)
accuracy (percentage)	87	82	97	92	10	10
	(±3)	(±3)	(±0.4)	(±1.6)	(±2)	(±3)
Behavioral measures second scan						
reaction times (ms)	784	810	740	787	44	23
	(±26)	(±34)	(±30)	(±41)	(±24)	(±27)
accuracy (percentage)	90	87	98		8	10
	(±3)	(±4)	(±1.7)	97 (±0.8)	(±2)	(±4)

Performance data, in means (± SD)
Effect of practice= improvement after practice, SD= standard deviation, resp= responders, schizophrenia patients responding to treatment, nonresp: nonresponders, schizophrenia patients not responding to treatment.

3.3. Neuroimaging data

Patients versus controls

Activation levels for NT and PT were not significantly different between the groups (main effect of group: F(1,54)=0.17, p=0.70). Across all ROIs, activation for NT was significantly higher than for PT (main effect of task F(1,54)=290.51, p<0.001. This differed between the groups (group by task interaction: (F(1,54)=6.57, p=0.01), indicating a smaller reduction of activation with practice for patients compared to controls. In addition, the group by task by ROI interaction was significant (F(4,51)=3.57, p=0.01), suggesting that the difference in the effect of practice on brain activation between the groups was different across ROIs. Consistent with our previous report

which included these patients, post-hoc t-tests revealed that the difference between patients and controls was significant in the left DLPFC (t(54)=-2.83, p=0.007) and bilateral SPC cortex (left: t(54)=-2.34, p=0.23, right: t(54)=-3.13, p=0.003), with patients showing a smaller reduction in activation with practice (see figure 3a).

There was no effect of time on brain activation levels (F(1,54)=2.51, p=0.12), nor was any interaction with time significant, indicating that treatment in patients had no additional effect over test-retest effects in controls in any of the ROIs (time by task interaction: F(1,54)=1.23, p=0.27, time by group interaction: F(1,54)=2.19, p=0.15, time by task by group interaction (F(1,54)=0.24, p=0.62, time by task by group by ROI interaction (F(4,51)=1.53, p=0.21).

Responders versus non-responders

Activation levels for NT and PT were not significantly different between the groups (main effect of group: F(1,21)=1.02, p=0.33). Across all ROIs, activation for NT was significantly higher than for PT (main effect of task: F(1,21)=136.46, p<0.001), but this differed between the groups (group by task interaction: (F(1,21)=6.42, p=0.02), indicating a decrease in activation with practice for responders but not for non-responders. Furthermore, the group by task by ROI interaction was significant (F(1,21)=3.40, p=0.03), suggesting that the difference in the effect of practice on brain activation between the groups was different across ROIs. Post-hoc t-tests revealed that the difference between responders and non-responders was significant in the left DLPFC (t(21)=3.56, p=0.002), and right SPC (t(21)=2.11, p=0.05) with non-responders showing a smaller decrease in activation with practice. Importantly, the reduced effect of practice on brain activation in non-responders was already evident at the baseline scan session when compared to responders (t(21)=2.35, p=0.03), as well as healthy controls (t(43)=3.48, p=0.001) in the left DLPFC, but not in any other ROI. Responders and controls did not differ in the left DLPFC (t(42)=-0.31, p=0.76) or any other ROI (see figure 3b).

Similar to the analysis of patients versus controls, there was no effect of time on brain activation levels (F(1,21)=0.01, p=0.96), nor did any interaction with time reach significance, indicating that treatment response itself had no additional effect over test-retest effects in any of the ROIs (time by group interaction: F(1,21)=0.07, p=0.80, time by task interaction: F(1,21)=0.16, p=0.70, time by task by group: F(1,21)=0.59, p=0.45, time by task by group by ROI interaction: F(4, 18)=1.81=0.14).

To assess the predictive value of the baseline scan for clinical outcome we conducted a regression analysis with activity reduction with practice in the five ROIs as independent variables, and reduction in PANSS scores as dependent variable. This analy-

sis showed that the effect of practice on brain activation in the working memory network at the baseline scan session was predictive of clinical outcome at ten weeks ($F(5,17)=3.93$, $p=0.02$) with smaller clinical improvement associated with a smaller pretreatment practice effect on brain activation. This was caused by the effect in the left DLPFC, which had the only regression coefficient differing significantly from zero ($t(22)=3.24$, $p=0.005$; see figure 3c). When excluding the patient that had a substantial increase of symptoms over time, this effect remained significant ($t(21) = 2.35$, $p=0.03$). Running the other previous analyses without this patient did not change significances of the results.

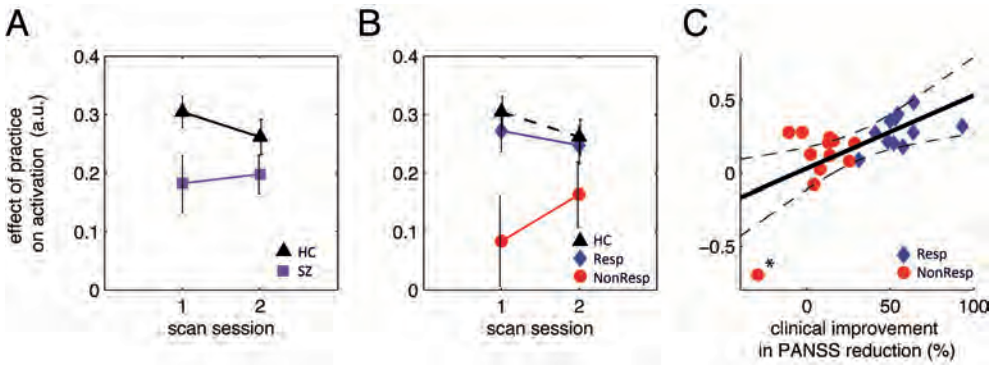

Fig.3

A. The effect of practice on brain activation (activation during the Novel task (NT) versus Practiced task (PT), in B-values) in the left dorsolateral prefrontal cortex (DLPFC) for healthy controls (HC) and schizophrenia patients (SZ) at the baseline scan and at the second scan. The effect of practice in the DLPFC was significant smaller in schizophrenia patients ($p=0.007$) and did not change over time.

B. The effect of practice on brain activation in the DLPFC for responders (Resp), and non-responders (NonResp). Data from the controls is added as a reference, but not included in the analysis. The effect of practice of non-responders was significantly smaller than for responders ($p=0.002$) and did not change over time. The effect of practice at baseline was significant smaller for non-responders compared to responders ($p=0.03$) and healthy controls ($p=0.001$).

C. Scatter plot of the relation between the effect of practice on brain activation in the DLPFC and clinical improvement between baseline and second session (PANSS reduction in percent). The effect of practice on activation in the left DLPFC was predictive of clinical outcome ($p=0.005$).* Even after excluding the patient that had a substantial increase of symptoms over time, this effect remained significant ($p=0.03$).
PANSS : positive and negative syndrome scale (Kay et al., 1987).

4. Discussion

This study examined whether prefrontal lobe dysfunction in medication-naive schizophrenia is altered by antipsychotic treatment, and whether prefrontal lobe dysfunction is related to treatment response. Medication-naive first-episode schizophrenia patients were scanned prior to and after 10 weeks of antipsychotic treatment. Results were compared to those of closely matched healthy subjects.
While being scanned subjects performed a modified Sternberg working memory task with a practiced and a novel memory set to test for the effect of practice on brain activation.
As we have shown in our previous paper (van Veelen et al., 2010), function of the left dorsolateral prefrontal cortex (DLPFC) was significantly impaired in medication-naive schizophrenia patients: while practice was associated with a reduction in brain activation in healthy controls, this decrease in activation did not occur in the patients. In the current follow-up study, we now show that antipsychotic treatment does not change this dysfunction of the DLPFC.
Interestingly, the prefrontal dysfunction observed in patients was far from uniform: the abnormal left DLPFC function was almost entirely accounted for by the subgroup of patients who failed to respond to antipsychotic treatment. In contrast, in patients who responded to treatment left DLPFC activation levels were not different from that of the healthy subjects. Moreover, reduced effect of practice in the DLPFC at baseline was predictive of poor clinical outcome at 10 weeks. Importantly, while DLPFC activity differentiated responders from non-responders, these groups could not be discriminated by their test performance, suggesting that the difference in functional brain activity is not merely an artefact of poor performance in patients non-responsive to treatment. Moreover, differences could not be explained by symptom severity, as responders and non-responders did not differ on total PANSS or PANSS sub-scores at the baseline scan. Taken together, these findings suggest that prefrontal lobe dysfunction is a stable trait characteristic of treatment non-responsive (first-episode) patients.

Our finding of reduced DLPFC as well as parietal function in schizophrenia patients in the early phase of their illness is consistent with most functional MRI studies in chronic patients (Callicott et al., 2000;Manoach et al., 2000;Karlsgodt et al., 2007;Jansma et al., 2004;Barch and Csernansky, 2007;Koch et al., 2008) and in early schizophrenia (Barch et al., 2001;Pantelis et al., 2007;Snitz et al., 2005) reporting abnormal activation within DLPFC and within the functional cortical networks involving the DLPFC, such as the fronto-parietal network.

The lack of effect of antipsychotic treatment on prefrontal lobe function in our study is in line with findings from a study of Schlagenhauf et al. (Schlagenhauf et al., 2008) who reported no effects on frontal activation levels in patients (n=10) compared to controls (n=10) four weeks after switching from conventional drugs to olanzapine. Furthermore, our data are consistent with a longitudinal fMRI study by Snitz and colleagues (Snitz et al., 2005), in which controls and patients performed a task designed to probe DLPFC and anterior cingulate cortex functioning. In this study medication-naive patients (n=11) were rescanned after four weeks of treatment with atypical antipsychotic medication. Interestingly, although treatment improved functioning in the anterior cingulate cortex, it did not affect activity in the DLPFC. The effect of retesting for controls however, was not explicitly mentioned in this study.
There are a number of studies which do report normalization or even an increase of activation levels due to neuroleptic medication. For example, Honey et al. (Honey et al., 1999) tested chronic schizophrenia patients on a working memory task while they were on typical antipsychotics, and six weeks later after having switched to risperidone. They reported increased activation in the right prefrontal cortex, supplemental motor area, and the posterior parietal cortex. Meisenzahl et al. (Meisenzahl et al., 2006) found increased activation in the left prefrontal cortex during a working memory task in 12 medication-free patients after quetiapine treatment for 12 weeks. Finally, Wolf et al. (Wolf et al., 2007) found increased activation in the frontotemporal cortex in ten patients after treatment with atypical antipsychotics (including clozapine) during eight weeks. In these studies however, no repeat scan was performed on healthy controls, which makes it impossible to disentangle treatment effects from test-retest effects (Zandbelt et al., 2008).

Furthermore, although this is the first study to report diminished prefrontal lobe function in relation to poor treatment outcome in first episode patients using fMRI, our findings are in agreement with those of Wood et al. (Wood et al., 2006). In this study, using Magnetic resonance Spectroscopy, a reduction in the NAA/CR ratio (a measure to indicate neural loss) in the left prefrontal cortex was found in patients showing poor functional outcome after 18 months of treatment. In addition, McIntosh et al. (McIntosh et al., 2010) found greater prefrontal tissue loss in high-risk subjects who became unwell compared to those who did not. These findings supports the idea that the group of patients with reduced prefrontal lobe function (non-responders) may be characterized by progressive (frontal) brain loss, a phenomenon that has been associated with poor outcome in several longitudinal neuroimaging studies in schizophrenia (DeLisi et al., 2004;van Haren et al., 2007;van Haren et al., 2008).

The present study has several limitations which should be considered. Clinical outcome in the current study was measured after ten weeks of treatment, which may be regarded as a relatively short period. It is however unlikely that non-responding patients would respond to the same drug after a more prolonged treatment period (Leucht et al., 2007;Emsley et al., 2006), as recent studies show that longer term treatment response is already evident after two weeks of treatment (Kinon et al., 2008). Therefore, our results may be extrapolated to longer term outcome of first episode schizophrenia patients. Furthermore, only male patients participated in the study. Therefore, the generalizability of our results across gender is limited, since symptomatology and course of the disease are more favourable in females as compared to males (Leung and Chue, 2000). Finally, our finding that there were no intersession differences over groups should be interpreted with caution, as the various atypical antipsychotics prescribed may have a differential effect, and because test-retest reproducibility of fMRI may be poor (Gradin et al., 2010;Gountouna et al., 2010;Suckling et al., 2010;Raemaekers et al., 2007). As such, our results should be taken as preliminary and should be replicated in larger samples.

In conclusion, dysfunction of the DLPFC was present in first-episode medication-naive schizophrenia patients and was not affected by subsequent antipsychotic treatment. Furthermore, dysfunction of the DLPFC at baseline was predictive of treatment response, with patients showing a reduced benefit of practice on activation levels in the DLPFC at baseline. Our findings may be both theoretically and clinically relevant. They support the notion that prefrontal lobe dysfunction is not a unitary concept in schizophrenia (Wood et al., 2006), explaining some of the inconsistent findings on prefrontal lobe function in this illness. Our data suggest that prefrontal lobe dysfunction may reflect a distinct neuropathological substrate in a subgroup of schizophrenia patients who are clinically characterized by non-response to treatment with dopamine antagonists. Subsequent genetic and neuroimaging studies should further characterize this group of patients unravelling some of the diverse neuropathological causes of schizophrenia.

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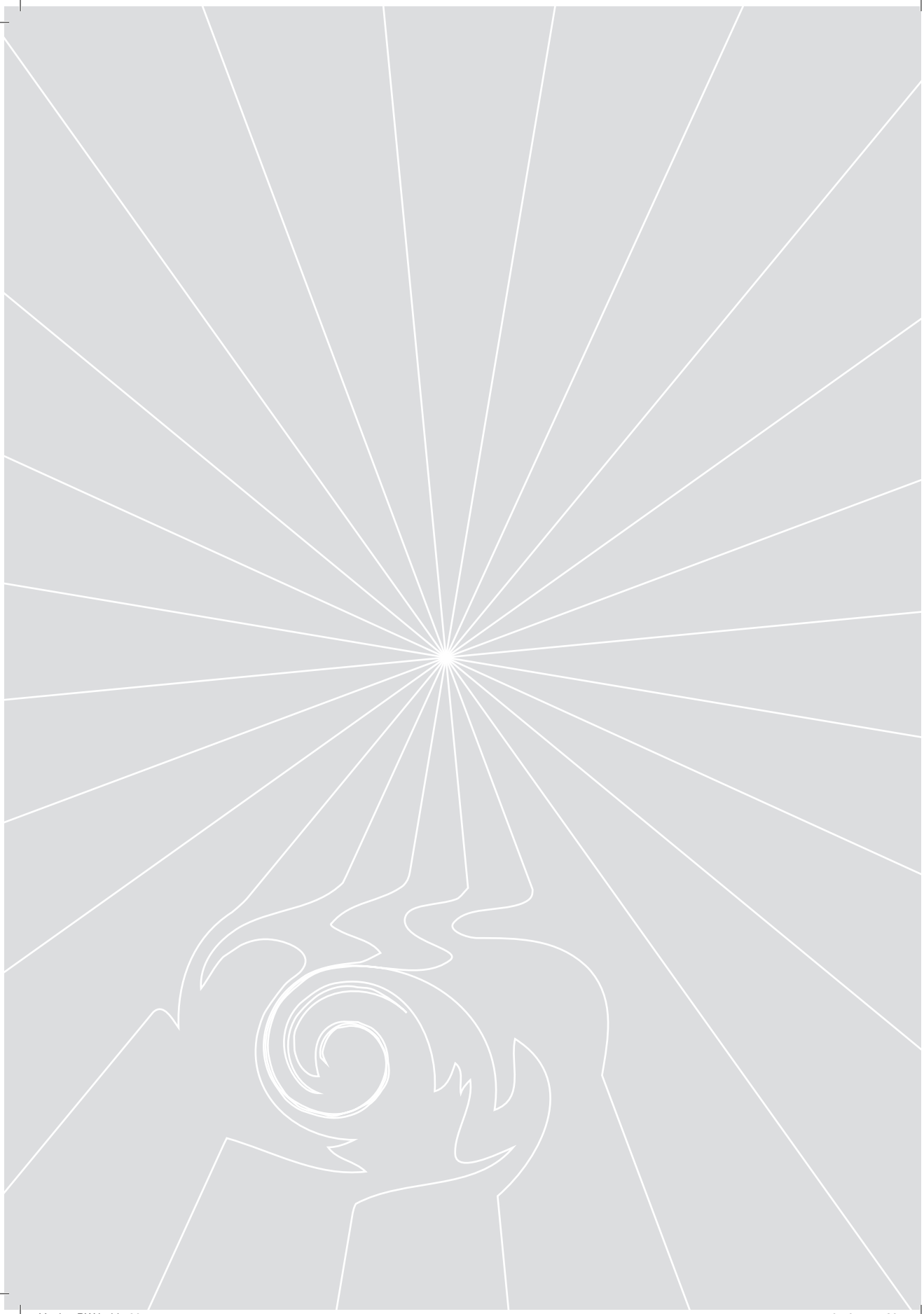

Chapter 5

Short term neurocognitive effects of treatment with ziprasidone and olanzapine in recent-onset schizophrenia

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Abstract

Background: Cognitive deficits are a core feature in schizophrenia. Cognitive deficits appear to be present at the onset of schizophrenia and persist after remission of psychotic symptoms. As cognitive deficits are associated with poor functional outcome, they form an important focus of treatment. There are relatively few head-to-head comparisons of the effects of second generation antipsychotics on cognition in recent onset schizophrenia. This is the first study to compare the effects of a short term treatment of olanzapine versus ziprasidone on cognitive functioning in recent onset schizophrenia. An earlier study conducted in chronic patients revealed an enhancement of cognition after treatment for both agents, but the extent of improvement was not significantly different between ziprasidone and olanzapine. Method: Patients with recent onset schizophrenia with limited previous exposure to medical treatment underwent a double blind randomized controlled treatment trial. Fifty-six patients completed the neuropsychological testing procedure prior to randomization and after eight weeks of treatment and were included in the analysis. We tested cognitive functioning in general and verbal memory in particular. We calculated a single unweighted composite score based on nine cognitive tests to determine general cognitive functioning. Results: Cognition appeared enhanced after treatment, but was not significantly different between treatment groups, neither for the verbal memory measures, nor for the neurocognitive composite score. Furthermore, cognitive enhancement did not correlate to clinical improvement.

Conclusion: cognitive deficits are not a reason for preferentially prescribing one of the two second generation antipsychotics tested over the other.

1. Introduction

Cognitive impairments are a core feature of schizophrenia (Lewis, 2004;Heinrichs, 2005;Keefe et al., 2006a;Heinrichs and Zakzanis, 1998). Over 85% of patients with this disorder show clinically significant impairment in some domains of cognition (Palmer et al., 1997;Keefe et al., 2006a). While these cognitive deficits are modestly associated with negative and disorganized symptom dimensions (Dominguez et al., 2009;Rund et al., 2004;Heydebrand et al., 2004), they are not consistently related to positive symptoms (Brazo et al., 2002;Heydebrand et al., 2004) and continue to be present after remission of psychosis (Albus et al., 2002;Keefe, 2007;Kopelowicz et al., 2005). Cognitive deficits are present in medication naive patients (Saykin et al., 1994;Mohamed et al., 1999), early in the course of schizophrenia (Oie and Rund, 1999;Rund et al., 2004;Rund et al., 2007;Hoff et al., 1999;Bilder et al., 2000;Gonzalez-Blanch et al., 2008) and are found preceding the manifestation of psychosis (Lencz et al., 2006;Keefe et al., 2006;Freedman et al., 1998;Erlenmeyer-Kimling et al., 2000). Importantly, there is considerable evidence that cognitive deficits are associated with functional disability and impaired outcome (Green, 1996;Green et al., 2000;Harvey et al., 1998;Velligan et al., 2000;Kraus and Keefe, 2007), underlining the relevance of treating the cognitive deficits in schizophrenia.

Although cognitive deficits are a core feature of schizophrenia, no single test or cognitive construct completely discriminates patients with schizophrenia from healthy controls (Zakzanis, 1999). The cognitive domains that are commonly described as deficient and that discriminate patients from healthy controls include attention, memory, executive function and processing speed (Nuechterlein et al., 2004;Heinrichs and Zakzanis, 1998;Albus et al., 2006). These domains are particularly affected in first episode schizophrenia (Friis et al., 2002;Rodriguez-Sanchez et al., 2008) and deficits are substantial, often 1-2 standard deviations below that of healthy comparison subjects (Saykin et al., 1994;Mohamed et al., 1999;Bilder et al., 2000;Hoff et al., 1999;Albus et al., 2002).
In the current study, we tested general cognitive functioning in recent onset schizophrenia, administering cognitive tests within five cognitive domains (speed of processing, attention, visual learning and memory, verbal learning and memory, and executive functioning). Moreover, we focussed on verbal learning and memory since these domains have been specifically implicated as a mediator of poor clinical outcome in schizophrenia (Green, 1996;Green et al., 2000) and are among the most severe cognitive impairments in chronic schizophrenia (Aleman et al., 1999;Heinrichs and Zakzanis, 1998;Leeson et al., 2009;Hill et al., 2004;Paulsen et al., 1995;Saykin et al., 1994).

An increasing number of studies have addressed the question of the potential benefit of antipsychotic medication on cognitive dysfunction. Initial results of clinical trials (Keefe et al., 2004;Keefe et al., 2006c;Harvey et al., 2005) and meta-analyses (Woodward et al., 2005;Woodward et al., 2007) favoured second generation antipsychotics (SGA's) over first generation antipsychotics (FGA's) in the enhancing effects on cognitive functioning in schizophrenia. Later studies however have not confirmed these findings (Keefe, 2007;Keefe et al., 2007a;Davidson et al., 2009).
Olanzapine is possibly the best studied SGA in respect of cognitive improvement in schizophrenia. However, the current study is the first double blind study to compare the effect of olanzapine and ziprasidone, both SGA's, on cognition in recent onset schizophrenia.
Olanzapine has been shown to improve cognitive function in both chronic (Bilder et al., 2002;Sharma et al., 2003;Gurpegui et al., 2007;Keefe et al., 2007a) and first episode patients (Keefe et al., 2007b;Keefe et al., 2004;Cuesta et al., 2009;Crespo-Facorro et al., 2009;Davidson et al., 2009). Ziprasidone is less frequently studied, but has also been found to improve cognitive function in chronic patients suffering from schizophrenia (Harvey et al., 2004;Gibel and Ritsner, 2008;Keefe et al., 2007a). Head to head comparisons of olanzapine and ziprasidone were conducted exclusively in chronic patients with schizophrenia (Harvey et al., 2004;Harvey et al., 2006). In a double-blind randomized controlled trial of six weeks comparing the effect of olanzapine and ziprasidone on cognition, no differences in cognitive change were found in the domains of attention, memory, executive functioning or verbal fluency (Harvey et al., 2004). The six month extension of this study did not reveal statistically significant differences in the enhancement of cognition either (Harvey et al., 2006).

There are still relatively few studies that compare the effects of SGA's on cognition in first episode schizophrenia head-to-head in double blind randomized trials (Cuesta et al., 2009;Crespo-Facorro et al., 2009;Keefe et al., 2007b).
The aim of this study was to compare the effects of an eight week treatment trial of ziprasidone versus olanzapine on cognitive functioning in general and on verbal memory in particular, in recent onset schizophrenia.
The advantage of studying cognitive deficits in early episode psychosis is that confounding factors such as long-term prior exposure to antipsychotic drug treatment, the effects of institutionalisation and chronicity of illness can be excluded.

2. Methods

2.1. Study design

The study was an eight-week, double blind, double-dummy, parallel-group, randomized, controlled multicenter trial. The effects on clinical measures are described elsewhere (Grootens et al., 2009). This study was part of a larger study with a follow-up period of 52 weeks (the extended part of the study had a cross-over design and will be described elsewhere).

After a screening period of less than ten days, patients were tapered off medication, if applicable, and were drug free for ≥12 hours after which they were randomized to one of the two treatment groups. Patients received a fixed dose of either ziprasidone 40 mg twice a day (b.i.d.) or olanzapine 10 mg once a day (q.d.) the first two days. From day three onwards the medication regimen was flexible in three doses ('low', 'medium', high': ziprasidone 40, 60 or 80 mg b.i.d., or olanzapine 10, 15 or 20 mg/day).

Neurocognitive tests were administered at baseline, before drug treatment was commenced, and at week eight, or at discontinuation of the study (at >7 weeks from baseline). At week eight, four subtests of the WAIS-III were administered to estimate intelligence. Clinical ratings (PANSS (Kay et al., 1987)) and the Heinrich Quality of Life Scale (QoLs) (-interpersonal relations element) (Heinrichs et al., 1984) were obtained on the day of neurocognitive testing. The Global Assessment of Functioning (GAF) (Luborsky L., 1962;Endicott et al., 1976) was obtained at baseline and at 52 weeks follow-up (of the extended part of the study). When patients dropped out during the 52 weeks follow-up GAF score was obtained at the final visit.

When needed, anticholinergic agents or propranolol was administered. For patients using stable doses of anticholinergic agents prior to randomization, the anticholinergic agents were withdrawn a week after randomization. If additional sedation was necessary, temazepam or oxazepam up to 20 mg/day was permitted. Concurrent treatment with psychopharmacological agents was not allowed, whereas washout periods were permitted depending on the type of pharmacological agent (antidepressants or mood stabilizers ≥7days of randomization, MAO-inhibitors ≥2 weeks, fluoxetine ≥5 weeks, oral antipsychotics≥12 hours, depot agents ≥2 weeks or one cycle).

2.2. Subjects

Patients were recruited from four centers in the Netherlands and Belgium. All patients gave informed written consent before screening took place. A diagnosis of schizophreniform disorder, schizophrenia or schizo-affective disorder was confirmed using the Structured Clinical Interviews for DSM-IV (SCID-I) (First et al., 1996). Patients were 18-40 years of age at randomization and were included when the duration of illness was less than five years, the CGI-severity score was >4 ('moderately ill') and the maximum life time exposure to antipsychotics was less than 16 weeks.

Patients were excluded when they had a DSM-IV diagnosis of substance dependence within three months before screening or when they had a positive urine drug screen for amphetamines, cocaine or opioids at screening. Furthermore, patients were excluded if they had an organic mental disease, mental retardation, clinically significant physical illness, abnormal laboratory values, significant EEG abnormalities, including a QTc ≥500 milliseconds or medication that prolongs the QT interval. Moreover, women who were pregnant, breast-feeding or not using reliable contraceptive methods were excluded. Patients who were unlikely to follow the study protocol or were at immediate risk of harming themselves or others were excluded as well.

2.3. Neurocognitive measures

Several measures of the California Verbal Learning Test (CVLT) were selected as the primary outcome measure of the study. A larger cognitive battery was administered for which a composite score was developed. The dependent measures used in this study are given in the following section.

2.3.1. VERBAL LEARNING and MEMORY:

- *California Verbal Learning Test (CVLT)* (Dutch version) (Mulder J.L. et al., 1996).
  Dependent measures: Total number correct immediate recall (list A), number correct short delay free recall list A, number correct long delay free recall list A.

- *Wechsler memory Scale-Revised: Verbal Paired Associates (WMS-R, Verbal Paired Associates)* (Dutch version) (Wechsler D, 1987;Reitan R.M., 1992).
  Dependent measure: Total number of correct easy and hard associations.

2.3.2. SPEED OF PROCESSING:

- *Trail Making Test – part A* (*TRAILS A)* (Reitan R.M., 1992).
  Dependent measure: Time to complete test (connect digits).
- *Fluency:*
  Category fluency (Dutch version) (Luteyn F. and Van der Ploeg F.A.E., 1983).
  Dependent measure: total number of correct words generated.

  Letter fluency (Benton A.L. and Hamsher K., 1976).
  Dependent measure: total number of correct words generated.

2.3.3. ATTENTION:

- *Continuous Performance Test - identical pairs version (CPT-IP)* (Cornblatt et al., 1988).
  Dependent measure: Response sensitivity (d-prime).

2.3.4. VISUAL MEMORY:

- *Wechsler Memory Scale-Revised, visual reproduction with delayed recall (WMS-R, visual reproduction)* (Wechsler D., 1987;Wechsler D., 1987).
  Dependent measure: scores from the immediate and delayed recall.

2.3.5. EXECUTIVE FUNCTIONING:

- *Wisconsin Card Sorting Test (WCST)* (Heaton R.K. et al., 1993;Heaton R.K. et al., 1993).
  Dependent measure: Number of perseverative errors.
- *Trail Making Test- part B* (*TRAILS B*) (Reitan R.M., 1992).
  Dependent measure: Time to complete test.
- *Stroop Color Word Test (STROOP)* (Dutch version) (Hammes J.G.W., 1971)
  Dependent measure: Interference (i.e. time condition III (color-word) – condition II (color))

IQ:

An estimation of full scale IQ was calculated from four subscales of the WAIS-III: Information, Block Design, Arithmetic & Digit Symbol - Coding (Blyler et al., 2000;Wechsler D., 1997).

2.4 Statistical analysis

The two treatment groups were tested for differences in demographic, clinical or cognitive measures at baseline.

Two tailed t-test comparisons were performed over CVLT change-scores (raw scores, week eight-baseline). In addition to the analysis of the CVLT, an exploratory analysis on the other cognitive measures was done. To facilitate comparison between the two groups, a single unweighted composite score was developed based on adjusted z-scores of the nine cognitive tasks. The raw scores were transformed into z scores (mean=0 [SD=1]) based on the means and standard deviations on the baseline assessments of the entire sample. For neurocognitive tasks with more than one measure, a summary score was calculated by averaging z scores from individual measures, resulting in nine neurocognitive test summary scores.The effect size of improvement over eight weeks was also calculated for each treatment group (Cohen's formula, using the pooled standard deviation).

To rule out the confounding effect of anticholinergic medication on cognitive functioning (Silver and Geraisy, 1995) additional analyses were run excluding patients on anticholinergic medication from the analysis. An additional ancova was performed to rule out the effect of baseline antipsychotic treatment.

Additionally, paired sample t-tests were run to examine if cognitive scores improved over eight weeks in the separate treatment groups.

We explored the association between clinical (improvement on PANSS total scores) and cognitive changes through Pearson's correlational analysis.

3. Results

3.1. Patient characteristics

Eighty-one patients were screened for eligibility, of them 74 were randomized, 39 to ziprasidone and 35 to olanzapine.

Eighteen patients discontinued treatment during the first eight weeks, or did not have follow-up neurocognitive testing. These patients were not significantly different from those completing the eight weeks study in terms of demographic data, clinical -or cognitive measures (see table 1).

Table 1. Demographic and clinical data of patients included in the study and drop-outs.

Demographic and clinical data	Drop out (n=18) Mean (SD)	Continued (n=56) Mean (SD)	p-value
Male			
Age	23.17 (4.65)	23.91 (4.42)	p= 0.54
CGI severity score	5.39 (0.85)	5.00 (0.76)	p= 0.07
Global Assessment of Functioning Scale (GAF)	28.89 (7.77)	34.13 (12.76)	p= 0.11
Subtotal positive PANSS	21.28 (4.95)	21.75 (4.56)	p= 0.71
Subtotal negative PANSS	21.56 (6.93)	19.07 (5.60)	p= 0.13
Subtotal general PANSS	39.89 (6.63)	39.22 (7.42)	p= 0.73
PANSS total score	82.72 (13.26)	80.04 (13.67)	p= 0.47
CDSS total score	3.78 (3.37)	5.11 (3.87)	p= 0.19
Schizophreniform disorder	8	19	
Schizophrenia, paranoid type	5	24	
Schizophrenia, disorganized type	2	5	
Schizophrenia, undifferentiated type	2	3	
Schizoaffective disorder	1	5	
Reason for discontinuation:			
Adverse event	zip:n=5 olanz: n=2		
No longer willing to participate	zip: n=4 olanz: n=3		
Protocol violation	zip: n=3 olanz: n=1		

Demographic and clinical data of patients who continued the study ≥ 7 weeks and of patients who discontinued before this visit. The 18 patients that did not continue with medical treat-

ment were not significant different from those who did continue on demographic data, clinical data or cognitive measures.

Fifty-six patients (olanzapine, n=29, ziprasidone, n=27) continued study treatment, performed neuropsychological testing and were included in the analyses. The mean exposure to antipsychotics before randomization of the patients completing the study was 20.66 (± 3.52) days. There were no significant differences between the two groups in the baseline characteristics in terms of demographic features, severity of symptoms, co-medication at baseline. However, the use of anticholinergic medication at week eight testing was significantly more frequent in the ziprasidone group (see table 2). The antipsychotics used at baseline are presented in table 2. The percentage of patients who were randomized to the same antipsychotic they used at baseline was 4.8% for olanzapine. Ziprasidone was not used before randomization.

Baseline neurocognitive functioning (CVLT and composite score) was not significantly different between the two groups (see table 3).

Table 2. Demographic characteristics and clinical data of patients included in the final analyses.

Demographic and clinical data	Olanzapine (n=29) Mean (SD)	Ziprasidone (n=27) Mean (SD)	p-value
Male	26	20	
Age	23.38 (4.67)	24.48 (4.15)	p= 0.36
CGI severity score	4.97 (.78)	5.04 (.77)	p= 0.73
Global Assessment of Functioning Scale (GAF)	32.79 (13.94)	35.56 (11.40)	p= 0.42
subtotal positive PANSS	21.89 (3.76)	21.59 (5.33)	p= 0.81
subtotal negative PANSS	18.89 (5.73)	19.26 (5.57)	p= 0.81
subtotal general PANSS	38.36 (7.30)	40.11 (7.57)	p= 0.38
PANSS total score	79.14 (13.24)	80.96 (14.29)	p= 0.63
CDSS total score	4.29 (3.67)	5.96 (3.95)	p= 0.11
Schizophreniform disorder	10	9	
Schizophrenia, paranoid type	13	11	
Schizophrenia, disorganized type	4	1	
Schizophrenia, undifferentiated type	1	2	
Schizoaffective disorder	1	4	
IQ at 8weeks	89.63 (3.39)	90.39 (3.82)	p= 0.88
Illness duration prior to randomization (months)	13.08 (16.34)	14.65 (15.98)	p= 0.70
Exposure to antipsychotics before randomization (days)	17.90 (3.97)	23.63 (5.95)	p= 0.42
Antipsychotics prior to randomization:			p= 0.31
Haloperidol	1	3	
Risperidone	7	3	
Quetiapine	1	1	
Olanzapine	6	3	
Thioridazide	1		
Zuclopenthixol	4		
Amisulpride	1		
Benzodiazepine (at baseline testing) (n)	1	2	p= 0.54
Anticholinergic (at baseline testing) (n)	0	3	p= 0.08
Benzodiazepine (at week 8 testing) (n)	1	1	p= 0.98
Anticholinergic (at week 8 testing) (n)	0	7	p= 0.005

Demographic characteristics at baseline (or at eight weeks) of patients included in the final analyses on neurocognitive measures (n= 56) (indep t-test).

3.2. Neurocognitive change

Change scores on the CVLT:

Cognitive change scores after eight weeks of treatment were not significantly different for ziprasidone or olanzapine on any measure of the CVLT (CVLT immediate recall: p=0.59, CVLT short delay free recall: p=0.67, CVLT long delay free recall: p=0.41, see table 3).

Discarding the seven patients (all in the ziprasidone treatment arm) who used anticholinergic medication at eight weeks from the analysis did not significantly alter results: CVLT immediate recall: patients on ziprasidone (without an anticholinergic): mean: 5.06 (±9.65), olanzapine: mean: 6.31 (±7.94), t(45)= -0.50, p= 0.63. CVLT short delay free recall: ziprasidone: mean:1.14 (±1.65), olanzapine: mean:1.21(±2.43), t(43) =-0.92, p=0.36. CVLT long delay free recall: ziprasidone: mean:1.44 (±2.7), olanzapine: mean: 0.86(±2.44), t(45) =0.75, p=0.45. Ancova with baseline antipsychotics (medication before randomization identical to baseline medication) as covariate did not alter results (CVLT immediate recall p=0.28, CVLT short delay free recall p=0.71, CVLT long delay free recall p=0.76).

After eight weeks, CVLT immediate recall and short delay free recall improved significantly in both the ziprasidone- and the olanzapine-treated group (respectively p=0.006, and p= <0.0001 for immediate recall, and p= 0.017 and p=0.014 for short delay recall). For the long delay free recall, the ziprasidone-treated group improved significantly (p=0.011) while for the olanzapine-treated group this did not reach significance (p=0.068).

Change scores of the composite score:

The composite score for cognitive change after eight weeks was not significantly different between ziprasidone: mean: 0.25(± 0.45) and olanzapine: mean: 0.20(± 0.43), t(54)= 0.42, p=0.67 (see table 3. In this table the outcome of the explorative analysis of the separate cognitive tasks (raw scores) are also described).When excluding patients who used anticholinergic medication at week eight during testing, results were not significantly different: patients on ziprasidone without an anticholinergic: mean: 0.27(± 0.48) vs. patients in the olanzapine arm: mean: 0.20(± 0.43), t(45)= 0.55, p=0.58. Ancova with baseline antipsychotics did not significantly alter results (p= 0.84).

After eight weeks, the composite score for the ziprasidone-treated group as well as the olanzapine treated-group improved significantly (respectively p=0.001 and p=0.005). Effect sizes are also indicated in table 3.

Table 3. Baseline cognitive scores and cognitive change scores after eight weeks of treatment.

variabele	ziprasidone			olanzapine				ziprasidone			olanzapine			
	n	baseline		n	baseline			Change from baseline		Effect size	Change from baseline		Effect size	
		M	SD		M	SD	*p*	M	SD		M	SD		*p*
Domain: verbal learning and memory														
CVLT:														
immediate recall	27	44.15	12.25	29	44.55	11.62	0.9	5.11	8.92	0.42	6.31	6.94	0.52	0.59
Short delay free recall	27	8.96	2.82	29	9.24	3.90	0.76	0.88	3.25	0.28	1.21	2.55	0.37	0.67
Long delay free recall	27	8.81	3.13	29	9.21	4.00	0.68	1.44	2.74	0.43	0.86	2.44	0.24	0.41
WMS-R, verbal paired associates (easy&hard pairs)	26	17.23	3.66	27	18.18	3.69	0.35	1.65	2.95	0.43	0.92	2.54	0.25	0.36
Domain: speed of processing														
TRAILS A	27	34.66	15.01	29	39.96	34.48	0.47	-5.14	12.64	0.34	-10.52	34.02	0.42	0.45
Verbal fluency:														
Category fluency	26	16.72	4.00	28	15.86	4.47	0.47	0.63	3.05	0.26	1.00	2.78	0.27	0.65
Letter fluency	27	9.06	3.41	29	8.81	2.80	0.76	0.93	2.64	0.17	0.71	2.27	0.17	0.74
Domain: attention/vigilance														
CPT-IP (d-prime)	27	1.48	0.69	27	1.14	2.14	0.42	0.48	0.62	0.29	0.65	2.50	0.22	0.74
Domain: visual memory														
WMS-R, visual reproduction														
Immediate recall	27	32.59	5.76	29	34.24	6.10	0.30	1.58	4.98	0.3	1.24	5.21	0.23	0.81

variabele	ziprasidone			olanzapine				ziprasidone			olanzapine			
	n	baseline		n	baseline			Change from baseline		Effect size	Change from baseline		Effect size	
		M	SD		M	SD	*p*	M	SD		M	SD		*p*
Domain: problem solving/executive functioning														
WCST (perseverative errors)	25	15.16	10.21	27	22.41	14.36	0.04	-3.42	11.27	0.35	-5.92	10.79	0.39	0.43
TRAILS B	26	70.04	29.58	29	83.37	66.04	0.35	-8.59	23.06	0.33	-17.61	60.85	0.35	0.48
STROOP (interference)	27	34.26	21.84	27	38.66	33.98	0.57	-2.15	21.43	0.08	-6.57	39.19	0.16	0.61
composite score neurocognitive tasks	27	-0.02	0.39	29	0.05	0.43	0.52	0.25	0.45	0.31	0.20	0.43	0.28	0.67

Baseline cognitive scores and cognitive change scores after eight weeks of treatment. Means, standard deviations (sd) and significance for neurocognitive tests (raw scores) and composite score (expressed in z-scores) for ziprasidone and olanzapine at baseline, and as change score after eight weeks of treatment. Effect sizes are also indicated (Scores were adjusted so that positive scores reflect improvement).

Correlations:
-Improvements on CVLT measures were not significantly correlated with improvement on the total PANSS score: CVLT immediate recall: r= 0.04, p= 0.77 and CVLT free recall delayed: r= 0.17, p= 0.21.
-The correlation between change in the cognitive composite score and the change in total PANSS score from baseline to the eight-week follow-up was not significant, r=0.06 p= 0.66.
-Improvement on the CVLT immediate recall correlated to improvement on the GAF (r=0.29, p=0.03). (The mean time for GAF baseline visit-GAF final visit was 7.9 (± 4.3) months). Other CVLT measures were not significantly correlated.
-Improvement on the composite score correlated to the improvement on the QoLs (-interpersonal relations element) (r=0.27, p=0.05).

4. Discussion

This is the first randomized controlled double blind trial comparing the effects of olanzapine and ziprasidone on neurocognitive functioning in patients with recent onset schizophrenia. Neurocognitive performance was measured at randomization and at eight weeks follow-up, in patients who had limited previous exposure to antipsychotic medication (mean of 20.66 (± 3.52) days). The primary outcome measure of the study was the California Verbal Learning Test (CVLT). In addition, a larger cognitive battery was administered for which a composite score was developed based on adjusted z-scores of differential cognitive tests. The cognitive tests included were Trailmaking Test - part A, Verbal fluency (Category fluency and Letter fluency), CPT-IP, WMS-R Visual Reproduction, WMS-R Verbal Paired associates, California Verbal Learning Test, Wisconsin Card Sorting Test, Trailmaking Test - part B and Stroop Color-Word Test.
We found a considerable effect-size for the change in CVLT scores. Specifically, effect sizes ranged between 0.4 and 0.6 for total and free delayed recall respectively. However, these effects were not different for the two drugs tested. The effect size for the change in the composite score for ziprasidone and olanzapine (0.31 and 0.28 respectively) were not significantly different either. Importantly, the cognitive enhancement in this study was unrelated to the improvement in clinical symptoms, since neither the composite change-score nor the CVLT change-scores were correlated with symptom amelioration. Although the use of anticholinergic medication was significantly different between groups, it did not affect the results of the study. We found a (weak) correlation between the CVLT immediate recall and GAF improvement, as well as a correlation between the composite change score and the QoLs(-interpersonal rela-

tions element). This may indicate that cognitive improvement confers to improvement of functional outcome, independently from clinical measures.

Our findings are consistent with the two previous studies finding no differential effect of ziprasidone and olanzapine in chronic patients (Harvey et al., 2004;Harvey et al., 2006). Our results also corroborate findings from earlier studies where no differences were found between SGA's on cognition in recent onset schizophrenia (Crespo-Facorro et al., 2009;Keefe et al., 2007;Crespo-Facorro et al., 2009;Davidson et al., 2009). Moreover, the effect size found in our study is similar to that reported in studies examining cognitive enhancement in first episode schizophrenia. Goldberg (Goldberg et al., 2007) after a six weeks treatment trial, found an effect size of the composite score of 0.36 and an effect size of the CVLT (total trials) of 0.40. Crespofacorro et al (Crespo-Facorro et al., 2009), using the Rey Auditory Verbal Learning Test, found an effect size of 0.48 in the olanzapine and of 0.30 in the risperidone treated group respectively, after a six month treatment trial.
Our results need to be interpreted in the context of several limitations. Firstly, we cannot rule out that the improvement in cognitive functioning was (partly) due to a practice effect, since no healthy comparison subjects were included. Indeed, Goldberg et al. (Goldberg et al., 2007) addressed the problem of retesting in cognitive functioning comparing first episode schizophrenia patients and healthy controls in a six week trial of olanzapine versus risperidone. The cognitive improvements observed in patients in this trial were consistent in magnitude with practice effects observed in healthy controls, with effect sizes of 0.36 for patients versus 0.33 for healthy controls. In that study, only visual reproduction/memory and trail making performance gains of patients exceeded the improvement in healthy controls. In addition, Crespo-Facorro et al. (Crespo-Facorro et al., 2009) studied cognitive change in first episode patients who were treated with haloperidol, risperidone or olanzapine and healthy controls during treatment of a year. Likewise, they found that all three treatment groups improved significantly across time, without significant differences in cognitive enhancement between groups. When comparing patients to healthy controls, the Trailmaking Test – part B, the Rey Complex Figure Test and the Finger Tapping Test showed a rate of improvement above practice effects. Other measures, like the Verbal Fluency Test and the Rey Auditory Verbal Learning Test, did not differ between patients and healthy controls. Since both studies were conducted in first episode patients, this may indicate a practice effect on at least some cognitive variables in our study. However, even if the enhancement in cognitive performance can be (in part) explained by a practice effect, the practice effect does not explain the absence of a differential effect on cognition by both drugs.
Secondly, we cannot be beyond doubt that the results are partly explained by a lack

of statistical power, although the effect sizes we found are consistent with those described previously. In conclusion, although both ziprasidone and olanzapine improved cognition in recent onset schizophrenia in this eight-week double-blind, randomized trial they did not differ significantly in this effect.

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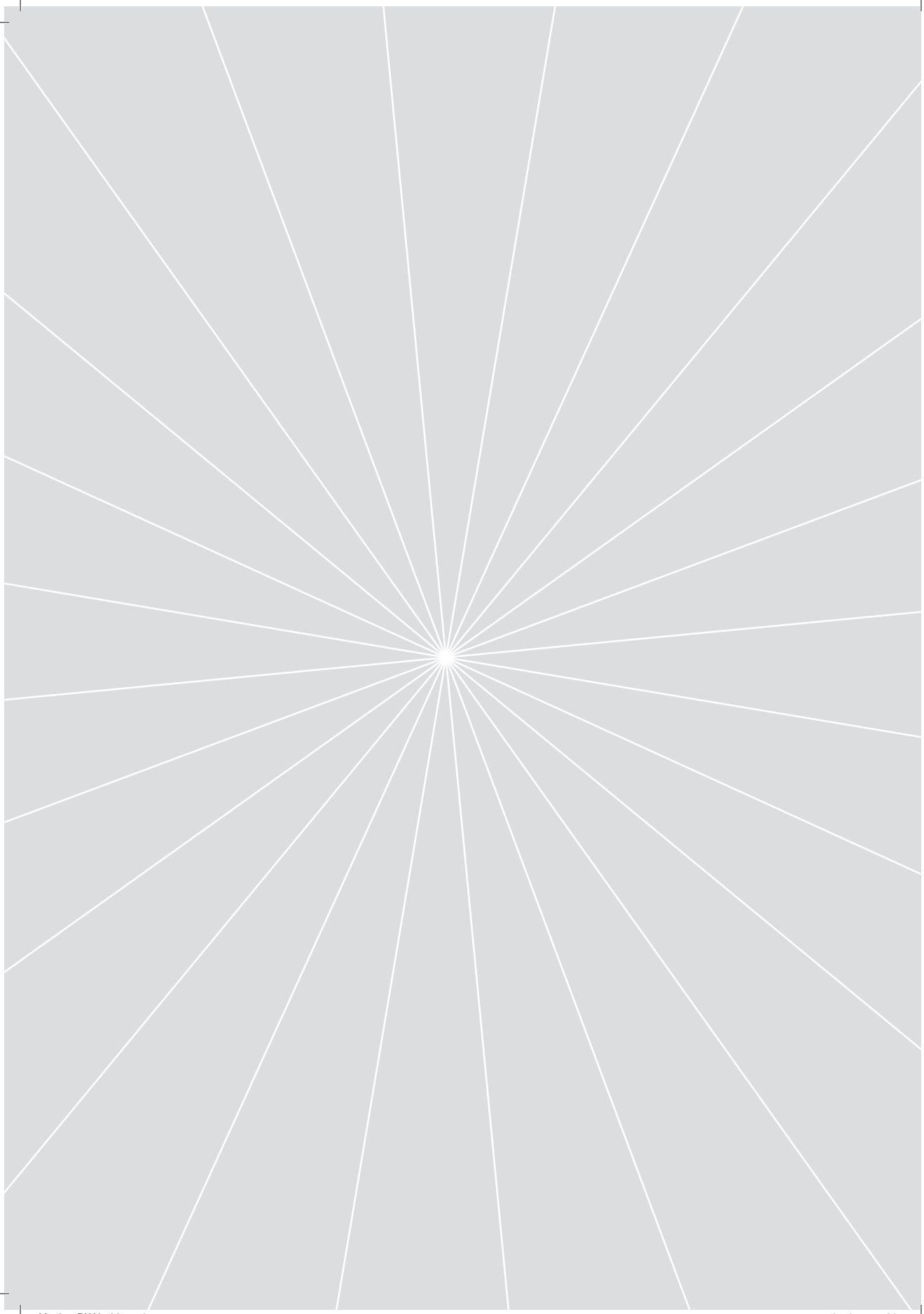

Chapter 6

Ziprasidone vs Olanzapine in Recent-Onset Schizophrenia and Schizoaffective Disorder: Results of an 8-Week Double-Blind Randomized Controlled Trial

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Abstract

Head-to-head comparisons of antipsychotics have predominantly included patients with chronic conditions. The aim of the present study was to compare the efficacy and tolerability of ziprasidone and olanzapine in patients with recent-onset schizophrenia.

The study was an 8-week, double-blind, parallel-group, randomized, controlled multicenter trial (NCT00145444 ClinicalTrials.gov). Seventy-six patients with schizophreniform disorder, schizophrenia or schizoaffective disorder (diagnosis < 5 years), and a maximum lifetime antipsychotic treatment <16 weeks participated in the study. Efficacy of ziprasidone (80–160 mg/day) and olanzapine 10–20 mg/day was measured using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) Scale, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS); tolerability assessments included laboratory assessments, body weight, and electroencephalogram.

Olanzapine (n = 34) and ziprasidone (n = 39) showed equal efficacy as measured by the PANSS, CDSS, CGI, and HQLS. However, mean weight gain was significantly higher in the olanzapine group (6.8 vs 0.1 kg, $p < 0.001$). Ziprasidone was associated with decreasing levels of triglycerides, cholesterol, and transaminases, while these parameters increased in the olanzapine group (all p values < 0.05). There were no significant differences in fasting glucose and prolactin levels or in cardiac or sexual side effects. Patients on ziprasidone used biperiden for extrapyramidal side effects more frequently ($p < 0.05$).

The results of this study indicate that ziprasidone and olanzapine have comparable therapeutic efficacy but differ in their side effect profile. However, there is a risk of a type II error with this sample size. Clinically significant weight gain and laboratory abnormalities appear early after initiating treatment and are more prominent with olanzapine, while more patients on ziprasidone received anticholinergic drugs to treat extrapyramidal symptoms.

1. Introduction

The second-generation antipsychotics (SGAs) have established a prominent role in the treatment of schizophrenia due to better treatment adherence and a lower risk of extrapyramidal side effects (Leucht et al., 2003). On the other hand, SGAs also have side effects that have major impact on compliance, such as sedation, weight gain, anticholinergic effects, sexual dysfunction, and metabolic syndrome (Picchioni and Murray, 2007). The high attrition rates due to side effects in randomized controlled trials (RCTs) and "practical trials" in chronic schizophrenia patients indicate that there are limitations to the use of SGAs in daily practice, despite their efficacy (Lieberman et al., 2005). Therefore, head-to-head comparisons between antipsychotics are necessary to answer the question which antipsychotic drug has the best benefit/risk ratio (Robinson et al., 2005).

In the present study, we compared the effects of two SGAs: olanzapine and ziprasidone. Olanzapine has a profile of good efficacy but with a risk of considerable weight gain (Duggan et al., 2005). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, olanzapine and other SGAs were compared with perphenazine in 1493 chronic schizophrenia patients. The results of the CATIE trial suggest that olanzapine is superior to other antipsychotics in terms of treatment adherence and improvement of psychopathology (Lieberman, 2006). Ziprasidone is a relatively new antipsychotic drug that has shown to have comparable efficacy in comparison to conventional antipsychotics (Bagnall et al., 2000).

So far, four head-to-head RCTs comparing ziprasidone and olanzapine have been published. Breier et al found greater improvement in psychopathology and a higher response and completion rate for olanzapine, whereas ziprasidone had a better profile for lipid profiles and weight gain (Breier et al., 2005). In contrast, Simpson et al did not detect differences in efficacy but did find a favorable metabolic profile for ziprasidone, including less weight gain and lower fasting insulin, triglycerides, and cholesterol (Simpson et al., 2005;Simpson et al., 2004). In the CATIE study, the time to discontinuing treatment was longer for olanzapine than for ziprasidone ($p = 0.028$ but not significant because of correction for multiple comparisons), whereas the improvement in psychopathology was similar for both antipsychotics. Ziprasidone had higher rates of insomnia, while olanzapine had more metabolic effects and greater weight gain (Lieberman et al., 2005). Recently, the results of the European First Episode Schizophrenia Trial (EUFEST) study, an open RCT of SGAs vs haloperidol in 498 patients with schizophrenia, were published. In the EUFEST study, ziprasidone and olanzapine showed a comparable treatment discontinuation, but there was more weight gain in the olanzapine group and higher levels of akathisia in the ziprasidone group (Kahn et al., 2008).

In addition, two studies were published with a crossover design. A significant improvement was found in an open-label study when stable patients on olanzapine were switched to ziprasidone (Weiden et al., 2003). The follow-up results of the CATIE study indicate, on the contrary, that among patients who had discontinued another atypical antipsychotic, switching to olanzapine was more effective than switching to ziprasidone. Metabolic effects and weight gain favored ziprasidone, but ziprasidone had more serious adverse events and higher levels of insomnia (Stroup et al., 2006).
It is important to underline that all these comparative studies, except for the EUFEST study, included mostly patients in the chronic stages of the illness. Previous research suggests that first-episode patients respond better to treatment and are more susceptible to side effects such as dystonia and prolactin increase (Fleischhacker et al., 2005). So far, it is unknown whether this holds true for the drug-induced metabolic syndrome as well. As schizophrenia is often a progressive disorder, it is important for clinicians to know which antipsychotic can reduce the symptoms at an earlier stage. Few trials have addressed this question yet (Rummel et al., 2003).
Furthermore, there are two methodological complications of studying patients with chronic schizophrenia. First, previous use of antipsychotics, comorbidity, or ageing may confound outcome variables such as metabolic effects. Second, there is potential study entry bias in chronic patients, favoring the inclusion of more severe, hospitalized patients who are nonresponsive or noncompliant. The higher response rates in first-episode patients are in accordance with this observation (Robinson et al., 1999).
The aim of the present study was to compare the clinical efficacy and side effects of ziprasidone and olanzapine in patients with recent-onset schizophrenia.

2. Methods

2.1 Patients: Inclusion and Exclusion Criteria

Male or female patients, 18–40 years of age, were recruited from 4 academic and nonacademic hospitals in The Netherlands and Belgium. The large majority of the included subjects were acutely ill inpatients. All patients gave written informed consent before screening took place. A diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder was confirmed in Structured Clinical Interviews for DSM-IV). Patients were included if the maximum lifetime exposure to antipsychotics was < 16 weeks, duration of illness was < 5 years, and Clinical Global Impression Severity (CGI-S) score was ≥ 4 (ie, at least "moderately ill").
Patients were excluded if they had a DSM-IV diagnosis of substance dependency ≤ 3 months prior to screening or a positive drug screen for amphetamines, cocaine, or opioids at screening. Furthermore, patients were excluded if they had epilepsy, an

organic mental disease (including mental retardation), a history of psychosurgery or any significant medical illness, abnormal laboratory values, electroencephalogram (ECG) abnormalities (including heartrate-corrected QT-interval [QTc] ≥ 500 msec), or medication that prolongs the QT interval. Women who were pregnant, breast-feeding, or not using reliable contraceptive methods were excluded as well. Concurrent treatment with psychopharmacological agents was not allowed, whereas washout periods were permitted depending on the type of pharmacological agent (antidepressants: ≥ 7 days, monoamine oxidase inhibitors: ≥ 2 weeks, fluoxetine: ≥ 5 weeks, oral antipsychotics: ≥ 12 hours, depot agents: one cycle [at least 2 wk]). There were no further guidelines for tapering off the previous medication. Patients who were deemed unlikely to follow the study protocol and those at immediate risk of harming themselves or others were excluded as well. Previous treatment with 1 of the 2 study drugs (eg, nonresponding) did not serve as an exclusion criterion.

2.2. Study Design

The study was an 8-week, double-blind, parallel-group, randomized, controlled multicenter trial (NCT00145444 ClinicalTrials.gov). Effects on cognitive measures will be published elsewhere (van Veelen N. et al., 2010). Patients who completed the 8-week study were offered to continue or to cross over to different medication. The results of this second phase are beyond the scope of the present article and will be described in another article. The study protocol was approved by the local ethical committee and was carried out in accordance with the Declaration of Helsinki.

Following the screening period of < 10 days, patients were tapered off their psychotropic treatment. Patients were randomized to 1 of the 2 treatment groups in the ratio 1:1, receiving a fixed dose for the first 2 days of either ziprasidone 40 mg twice a day or olanzapine 10 mg/day. From day 3 onward, the dose regimen was flexible and consisted of 3 doses ("low," "medium," and "high": ziprasidone 40, 60, or 80 mg twice a day or olanzapine 10, 15, or 20 mg/day respectively). The medication was dispensed in a double dummy design to keep the allocation double blinded.

Patients were assessed on day 1, day 3, week 1, week 2, week 4, and week 8 and in between if necessary due to adverse events. In case of akathisia, propranolol was permitted. In patients receiving stable doses of anticholinergic agents prior to randomization, the anticholinergic agents were withdrawn a week after randomization. If sedation was necessary, temazepam or oxazepam up to 20 mg/day was permitted. Any concomitant drug treatment remained constant during the study, and no such drug was started during the study unless considered medically necessary (ie, antidepressants for comorbid depression).

The sample size was determined on the base of the California Verbal Learning Test, the primary cognitive outcome measure: Using a 2-sided test, a sample size of ap-

proximately 37 patients per treatment group would assure 80% power to detect a difference of at least 1.6 points in change ($\alpha = .05$) assuming an SD of 2.4 (according to interim results at wk 6 from studies R-0554 and R-0555, data on file) (Daniel et al., 1999).

2.3. Efficacy Assessments

Clinical efficacy was assessed on the basis of a reduction from baseline to week 8 in the total score of the Positive and Negative Syndrome Scale (PANSS), the CGI-S Scale, Clinical Global Impression Improvement (CGI-I) Scale, and the Calgary Depression Scale for Schizophrenia (CDSS).(Addington et al., 1993) The PANSS was administered at baseline, week 4, and week 8 (or end visit);(Kay et al., 1987) the CGI-S and CGI-I were administered at every visit. The interpersonal relations element of the Heinrich Quality of Life Scale (HQLS) was used to evaluate quality of life at baseline and week 8 (Heinrichs et al., 1984).

In addition to the continuous data, the percentages of patients with clinical response were compared, with response criteria set a priori at 20% reduction in the total PANSS scores. The results from the PANSS were also considered in terms of proposed remission criteria ("mild" or less on items P1, P2, P3, N1, N4, N6, G5, G9). The criterion "maintenance over a 6-month period" could not be applied in the present study (Andreasen et al., 2005). The percentage of patients who fulfilled these remission criteria was calculated as well.

2.4. Safety and Tolerability Measures

All adverse events, regardless of the causal relationship, were monitored and assessed on severity. Vital signs and body weight were checked at baseline, week 4, and week 8. All patients underwent ECG evaluation by a cardiologist at baseline and at week 1. Laboratory safety assessments at baseline and week 8 included cholesterol, triglycerides, fasting glucose, prolactin, and the transaminases serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT).

Extrapyramidal side effects were monitored with the St Hans Rating Scale (SHRS) (Gerlach et al., 1993), Barnes Akathisia Scale (BAS)(Barnes, 1989) and Abnormal Involuntary Movement Scale (AIMS) (guy, 1976). All participating researchers were trained in the administration and scoring of the instruments for efficacy and safety in consensus meetings, with an independent expert and with high interrater reliability.

Where considered necessary by the investigator, biperiden was administered in case of dyskinisia, parkinsonism, or dystonia, whereas propranolol was administered for akathisia. Temazepam and oxazepam were allowed for insomnia or additional sedation.

2.5. Patients' Opinion

The Drug Attitude Inventory (DAI)-10 was used to assess patients' opinion on the study treatment (baseline, wk 4, and wk 8) (Hogan et al., 1983).

2.6. Discontinuation

Primary reasons for early discontinuation were recorded. The compliance was checked every visit by counting the unused blisters. Patients unable to adequately comply with medication (compliance <80% or >120% since the previous study visit) were withdrawn from the study. Patients with marked liver function abnormalities were immediately withdrawn from the study (SGOT/SGPT ≥ 3 x upper limit of the norms, alkaline phosphates ≥ 1.5 x upper limit, total bilirubin ≥ 2 x upper limit). The difference between the two antipsychotics in treatment discontinuation was tested with a Kaplan-Meier analysis.

2.7. Statistical Analysis

The description of demographic data and the description and analyses of safety data were based on all subjects who were randomized and who were known to have taken at least one dose of study medication. The analyses of efficacy and effectiveness data were based on the intention-to-treat population with the last observation carried forward.

For continuous data outcome measures, an analysis of covariance (ANCOVA) model was used to test the effect of treatment at week 8 vs baseline. Dependent measures in the ANCOVA analyses were the PANSS total score (primary outcome measure) and subscores, CDSS, CGI, and QLS. The subject's score at baseline included a covariate in order to control for the initial value. "Treatment center" was set as an extra independent variable. Analyses of CGI-I scores did not include baseline terms because a baseline CGI-I score could not be determined.

As with the efficacy analysis, ANCOVA was used with treatment center as the factor and baseline levels as covariates. An additional baseline-to-maximum analysis was performed for the side effect scales BAS, AIMS, and SHRS. In order to gain more insight into the clinical consequences of the study intervention, we performed additional analyses on proportions of patients with clinically significant abnormalities based on international consensus (e.g., 7% weight increase). For dichotomous data, Fisher exact tests were used. All statistical tests were 2 tailed (superiority design), with a 5% level of significance. SPSS 14.0 was used for the statistical analysis.

3. Results

3.1. Characteristics and Disposition of Patients

A total of 81 patients were screened for eligibility, of whom 74 were randomized to either the ziprasidone arm (n = 39) or the olanzapine arm (n = 35) (figure 1). There were no significant differences in the baseline characteristics between the 2 groups (tables 1 and 2). Seven of the patients in the ziprasidone group and 8 patients in the olanzapine group were exposed to olanzapine before. None of the patients were exposed to ziprasidone before. The mean study dose was 14 mg for olanzapine and 104 mg for ziprasidone. During the first 8 weeks of treatment, 11 out of 39 patients in the ziprasidone arm and 6 out of 34 in the olanzapine arm discontinued the study; this difference was not statistically significant (Fisher exact test, p = 0.28). The Kaplan-Meier analysis for treatment discontinuation in time revealed no significant difference either (p = 0.22).

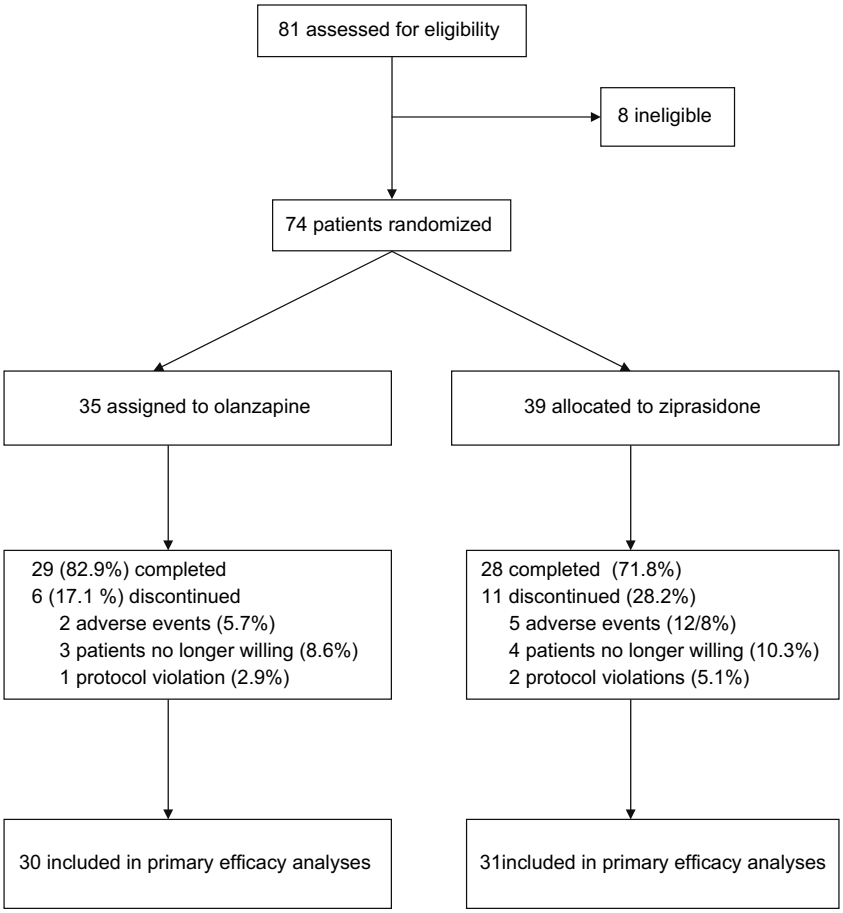

Fig 1. Patient Disposition and Reasons for discontinuation.

Table 1. Baseline Characteristics of All Randomized Patients (n = 74).

Variable	Olanzapine (n=35), N (%)	Ziprasidone (n=39), N (%)
Diagnosis		
Schizophreniform disorder	13 (37)	14 (36)
Schizophrenia, paranoid type	15 (43)	14 (36)
Schizophrenia, disorganized type	5 (14)	2 (5)
Schizophrenia, residual type	0 (0)	1 (3)
Schizophrenia, undifferentiated type	1 (3)	3 (8)
Schizoaffective disorder	1 (3)	5 (13)
Gender		
Male	30 (86)	31 (79)
Female	5 (14)	8 (21)
Number of hospitalizations during the past year		
0 times	8 (23)	9 (23)
1 time	25 (71)	25 (64)
2 times	2 (6)	4 (10)
> 2 times	0	1 (3)
Psychotropic medication stopped before study		
Antipsychotics	22 (63)	22 (56)
SSRI's	1 (3)	1 (3)
Lithium	0 (0)	1 (3)

Table 2. Baseline Characteristics of All Randomized Patients (n = 74).

	Olanzapine (n=35)	Ziprasidone (n=39)	Statistic
	Mean (SD)	Mean (SD)	(*F, df, p*)
Age (years)	23.1 (4.4)	24.3 (4.5)	F(1.72) = 1.52 p= 0.22
Days since onset clinical symptoms	476 (544)	463 (524)	F(1.72) < 0.01 p= 0.96
Positive and Negative Symptoms Syndrome Scale (PANSS):total score	80.8 (12.8)	80.5 (14.3)	F(1.72) = 0.16 p= 0.90
Calgary Depression Scale for Schizophrenia (CDSS)	4.2 (3.6)	5.3 (3.9)	F(1.72) = 1.64 p= 0.20
Clinical Global Impression severity scale (CGI-s)	5.0 (0.8)	5.2 (0.8)	F(1.72) = 0.45 p= 0.50
Global Assessment of Functioning scale (GAF)	32.0 (13.09)	33.6 (10.88)	F(1.72) = 0.31 p= 0.58
Body Mass Index (BMI)	21.7 (2.6)	22.2 (2.2)	F(1.72) = 0.84 p= 0.36
Prior lifetime antipsychotics use (days)	19.1 (23.5)	22.1 (35.0)	F(1.72) = 0.17 p= 0.68

3.2. Efficacy

Changes in efficacy measures are listed in table 3. Patients from both groups had a similar decrease in PANSS score, the primary outcome measure, compared with baseline (p = 0.68) (table 4). The percentage of patients showing a clinical response (≥20% improvement on the PANSS) was 61% for olanzapine and 60% for ziprasidone (p = 1.00). Thirty-five percent of the olanzapine patients and 40% of the ziprasidone patients fulfilled the remission criteria (p = 0.80). Group differences on depression symptoms (CDSS), quality of life (HQLS), and clinical impression (CGI) were also nonsignificant.

Table 3. Changes in Clinical Measures

	Baseline	Difference score at end-point	Difference between groups		
	Mean (SD)	Mean (SD)	*F*	*df*	*p*
PANSSa Positive Symptoms Scale					
Olanzapine (N= 30)	21.95 (3.69)	-7.32 (3.69)	0.001	1. 52	0.98
Ziprasidone (N= 31)	20.87 (5.54)	-6.37 (4.54)			
PANSS Negative Symptom Scale					
Olanzapine (N= 30)	19.68 (6.03)	-2.71 (4.23)	0.41	1.52	0.84
Ziprasidone (N= 31)	19.00 (5.85)	-2.37 (5.01)			
PANSS General Psychopathology Scale					
Olanzapine (N= 30)	39.03 (7.32)	-8.06 (6.47)	0.38	1.52	0.54
Ziprasidone (N= 31)	39.57 (7.77)	-7.57 (7.09)			
PANSS Grand Total Scale					
Olanzapine (N= 30)	80.65 (13.41)	-17.45 (10.38)	0.05	1.52	0.82
Ziprasidone (N= 31)	79.43 (15.16)	-16.30 (13.01)			
Clinical Global Impressions Severity scale					
Olanzapine (N= 30)	5.00 (0.78)	-0.97 (0.84)	0.21	1.52	0.65
Ziprasidone (N= 31)	5.00 (0.75)	-0.97 (0.81)			
Heinrich Quality of Life Scale					
Olanzapine (N= 28)	25.96 (8.15)	-1.11 (6.24)	0.41	1.44	0.53
Ziprasidone (N= 25)	28.44 (9.96)	-2.44 (5.85)			
Calgary Depression Scale for Schizophrenia					
Olanzapine (N= 30)	4.42 (3.71)	-1.35 (4.11)	1.71	1.52	0.20
Ziprasidone (N= 31)	5.83 (3.99)	-0.30 (4.52)			
		Endpoint score	Difference between groups		
		Mean (SD)	*F*	*df*	*p*
Clinical Global Impressions Improvement scale			0.11	1.56	0.75
Olanzapine (N= 30)	-	2.82 (0.81)			
Ziprasidone (N= 31)		2.94 (0.74)			
Drug Attitude Inventory			1.19	1.56	0.28
	-	3.07 (3.89)			
Olanzapine (N= 22)		1.86 (4.55)			
Ziprasidone (N= 18)					

Note: Endpoint is at 8 weeks with last observation carried forward
a = Positive and Negative Symptoms Scale for Schizophrenia.

3.3. Safety and Tolerability

The percentages of patients who reported adverse events and required concomitant drugs are shown in table 4. Treatment with olanzapine was associated significantly more often with weight gain and increased appetite. Treatment with ziprasidone led to more frequent use of biperiden as comedication and more frequent use of antidepressants and propranolol.

Table 4. Patient-Reported Adverse Events[a] and Concomitant Psychotropics

	Olanzapine (n=35) N (%)	Ziprasidone (n=39) N (%)	P (Fischer exact)
Any adverse events	33 (94.3)	3(92.3)6	1.0
Gastrointestinal disorders	11 (31.4)	18 (46.2)	0.23
Fatigue/sedation	16 (45.8)	22 (56.4)	0.49
Sexual side effects	5 (14.3)	5 (12.8)	1.0
Hypersalivation	2 (5.7)	5 (12.8)	0.44
Headache	7 (20.0)	11 (28.2)	0.43
Weight gain	20 (57.1)	5 (12.8)	<0.001 *
Increased appetite	5 (14.3)	0 (0)	0.02*
Extrapyramidal symptoms and tremor	20 (57.1)	20 (51.3)	0.65
Psychiatric symptoms	13 (37.1)	9 (23.1)	0.61
Suicide attempt/suicidality	4 (11.4)	1 (2.6)	0.18
Concomitant medication			
Biperiden	7 (20.0)	17 (43.6)	<0.05 *
Propranolol	0 (0.0)	5 (12.8)	0.06
Benzodiazepines	11 (31.4)	16 (41.0)	0.64
Lithium	0 (0.0)	1 (2.6)	0.47
Antidepressants	0 (0.0)	5 (12.8)	0.06

[a]Table only includes those adverse events that occured at statistically different proportions in the two groups, or in at least 10% of one of the groups
* p< 0.05

3.4. Metabolic Side Effects

The analyses revealed significant differences between the two study groups in terms of metabolic risk (figure 2). Olanzapine patients had a mean weight increase of 6.8 kg, whereas ziprasidone patients only had an increase of 0.1 kg ($p < 0.001$). Additional analyses showed that 64.5% of the olanzapine patients had a weight gain of more than 7%, while this occurred in 3.3% of the ziprasidone group ($p < 0.001$). Treatment with olanzapine was associated with an increase in levels of cholesterol, triglycerides, and liver transaminases, whereas treatment with ziprasidone led to lower levels of choles-

terol, triglycerides, and liver transaminases (p values < 0.001) (table 6). There were no group differences in fasting glucose and glycosylated hemoglobin (Hb1ac).

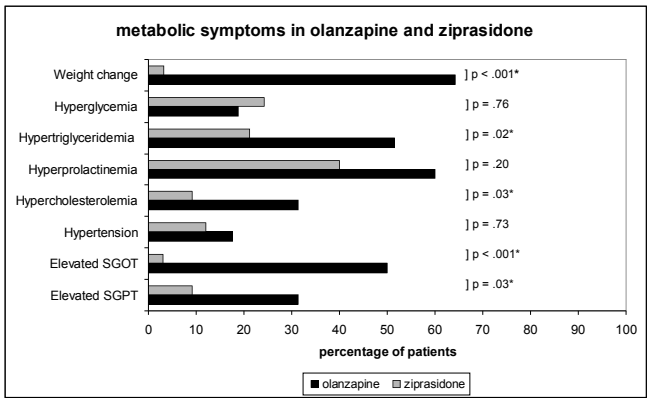

Fig. 2. Percentage of Patients on Olanzapine and Ziprasidone with Clinically Significant Metabolic Symptoms at 8 wk. Weight change ≥ 7% increase of total body weight. Hyperglycemia ≥ 5.5 mmol/l. Hypertriglyceridemia > 1.69 mmol/l. Hypercholesterolemia > 5.17 mmol/l. Hypertension > 130/85 mm Hg. Elevated SGPT > 37 U/l. Elevated SGOT (>40 U/l). *p < 0.05. Hyperprolactinemia ♂ > 18 ng/l, ♀ > 25 ng/l.

3.5. Movement Disorders

There were no differences between the two groups in any of the extrapyramidal side effect scales (table 5). Additional analyses comparing the proportion of patients with clinically significant values (≥ "moderate" on one of the SHRS items) revealed no significant differences either (5 patients in each group). However, significantly more patients in the ziprasidone group used as needed biperiden to relieve extrapyramidal symptoms (table 4).

3.6. Sexual Dysfunction

As shown in table 5, there were no differences in the UKU Scale for sexual side effects. In both groups, there were 8 patients with at least one moderate score on one of the items. As a substantial proportion of the patients were on antipsychotics before the study entry, there was a decrease in prolactin levels that was similar in both groups. Nevertheless, 60% and 40% of patients on olanzapine and ziprasidone, respectively, met the criteria for hyperprolactinemia at end point (figure 2).

Table 5. Changes in Metabolic Parameters

	Baseline Mean (SD)	Difference score at endpoint Mean (SD)	Difference between groups		
			F	*df*	*p*
Weight (kg)					
Olanzapine (n-33)	69.6 (11.2)	6.8 (4.1)	24.1	1.53	<.001 *
Ziprasidone (n=35)	68.4 (10.4)	0.1 (3.6)			
QTc (msec)					
Olanzapine (n=33)	400.4 (15.5)	-1.7 (21.1)	0.06	1.59	0.80
Ziprasidone (n=35)	394.3 (16.1)	5.2 (18.2)			
Systolic blood pressure (mmHg)					
Olanzapine (n=34)	120.5 (10.4)	0.7 (15.3)	3.9	1.58	0.05
Ziprasidone (n=33)	116.2 (12.2)	-0.9 (10.2)			
Diastolic blood pressure (mmHg)					
Olanzapine (n=34)	75.9 (7.6)	0.7 (9.2)	1.2	1.60	0.28
Ziprasidone (n=35)	75.5 (8.4)	3.1 (9.3)			
Heart rate (beats per min)					
Olanzapine (n=32)	71.3 (10.7)	2.3 (14.5)	1.1	1.56	0.30
Ziprasidone (n=33)	73.8 (13.0)	-1.6 (12.1)			
SGOT / ASAT (U/l)					
Olanzapine (n=32)	23.4 (6.8)	8.0 (13.9)	10.6	1.56	0.02*
Ziprasidone (n=33)	35.0 (54.4)	-10.7 (51.5)			
SGPT / ALAT (U/l)					
Olanzapine (n=32)	26.5 (14.1)	21.8 (37.9)	14.0	1.56	<0.001 *
Ziprasidone (n=33)	28.6 (25.1)	- 7.3 (21.9)			
Cholesterol (mmol/l)					
Olanzapine (n=30)	4.47 (0.94)	0.48 (0.72)	12.5	1.56	0.001 *
Ziprasidone (n=31)	4.47 (1.15)	-0.24 (0.87)			
Triglycerides (mmol/l)					
Olanzapine (n=30)	1.42 (1.04)	0.41 (1.00)	7.5	1.55	0.008 *
Ziprasidone (n=31)	1.70 (1.50)	-0.21 (1.41)			
Fasting glucose (mmol/l)					
Olanzapine (n=30)	5.50 (1.54)	0.06 (0.90)	2.1	1.56	0.15
Ziprasidone (n=31)	5.75 (2.14)	0.10 (0.99)			
Glycosylated hemoglobin (Hb1Ac)					
Olanzapine (n=31)	5.12 (0.35)	0.0 (0.35)	0.72	1.55	0.94
Ziprasidone (n=33)	5.13 (0.34)	-0.3 (0.35)			
Prolactin (U/l)					
Olanzapine (n=28)	0.81	-0.17	1.83	1.49	0.18
Ziprasidone (n=30)	0.69	-0.40			

Note: Endpoint is at 8 weeks with last observation carried forward.
* $p<0.05$.

Table 6. Changes in Extrapyramidal Side Effects and Sexual Side effects

	Baseline to endpoint					Baseline to maximum score			
	Baseline	Change in score	Difference between groups			Change in score	Difference between groups		
	Mean (SD)	Mean (SD)	*F*	*df*	*p*	Mean (SD)	*F*	*df*	*p*
Barnes Acathisia rating scale, overall score									
Ziprasidone (n=34)	1.36 (2.16)	0.03 (3.18)	0.03	1.56	0.95	-0.38 (2.92)	0.0	1.56	0.99
Olanzapine (n=33)	0.61 (1.27)	-0.30 (2.05)				-0.55 (1.95)			
Abnormal Involuntary Movement Scale (AIMS), total score									
Ziprasidone (n=34)	1.06 (2.55)	0.58 (3.19)	2.07	1.58	0.16	-0.15 (3.13)	0.41	1.58	0.84
Olanzapine (n=33)	0.39 (1.09)	-0.97 (2.47)				-1.09 (2.37)			
St. Hans Rating Scale, total score									
Ziprasidone (n=34)	6.94 (11.32)	1.59 (11.67)	0.30	1.58	0.86	-0.15 (8.60)	0.81	1.58	0.37
Olanzapine (n=33)	6.76 (10.92)	-0.21 (9.05)				-1.88 (8.39)			
UKU sexual side effects*									
Ziprasidone (n=25)	2.72 (3.84)	0.92 (3.40)	0.41	1.47	0.53	-	-	-	-
Olanzapine (n=31)	1.23 (2.20)	0.00 (0.89)							

Note: Endpoint is at 8 weeks with last observation carried forward.

*= The Antipsychotics and Sexual Functioning Questionaire (ASFQ), based upon items of UKU side effect scale.

3.7. Cardiac Side Effects

There were no ECG abnormalities in any of the patients. Group differences in QTc were not statistically different.

3.8. Patient's Opinion

The results of the DAI-10 indicate that there was no significant difference in the patients' opinion regarding their medication (table 3).

4. Discussion

This study is the first head-to-head, double-blind comparison of olanzapine and ziprasidone in patients with recent-onset schizophrenia. The results suggest that both agents have comparable clinical efficacy but show differences in the side effects profile.

About two-thirds of the patients in both groups met the response criteria, defined as ≥ 20% improvement on the PANSS, and one-third fulfilled remission criteria defined by Andreasen et al (Andreasen et al., 2005). The high response rates in our study are consistent with the literature on recent-onset schizophrenia (Kahn et al., 2008). The attrition rates did not differ significantly between the two groups, but numerically there were more completers on olanzapine. Effects on the depression and quality-of-life scales were marginal in both groups, which may be explained by the low baseline values and the short period of treatment.

We realize that we have included a relatively small number of patients in this study. However, the differences between the two patient groups in the primary outcome measure, the difference score on the total PANSS score, are extremely small (effect size $d = 0.10$, $p = 0.82$). A sample of more than 3000 patients would have been required to find this small effect significant at the 0.05 level. We conclude that the primary results are not biased by insufficient statistical power. Several secondary outcome measures, such as the DAI-10 and the dropout rate, may be prone to type II error. The present difference in dropout rate would have been statistically significant at the 0.05 level if we had included at least 590 patients in our study.

The weight gain findings in the olanzapine group are consistent with the literature (Newcomer, 2007). However, the mean increase of 6.8 kg we found in the olanzapine group is high in comparison with other studies. The relatively high mean dose of 14 mg olanzapine may have contributed to the higher weight gain. The recent onset of the symptoms and the limited history of antipsychotics in our patient population may explain the difference with previous data as well. This study showed that half of the olanzapine patients had laboratory abnormalities within 8 weeks, whereas this proportion was lower with ziprasidone treatment. This pattern has been previously

described in chronic patients as well (Meyer et al., 2008). We also found a differential effect on transaminases; to our knowledge, this is the first recent-onset study reporting effects on liver enzymes. The increase in transaminases seen with olanzapine may be a transient effect, but it would be worthwhile exploring its clinical implications in future studies. This holds for the increase in prolactin levels as well, although it should be noted that the blood samples were taken in the morning (levels are relatively high at that time of the day).

Significantly more anticholinerigc drugs were administered for extrapyramidal symptoms in patients treated with ziprasidone. This concomitant medication appeared to relieve the symptoms, as there were no differences in the number of patients with clinically manifest extrapyramidal symptoms. However, long-term biperiden use may result in other problems, such as lower cognitive function (Silver and Geraisy, 1995). The prescription of other concomitant drugs in both groups did not differ significantly. Although there were more prescriptions of antidepressants in the ziprasidone group, this did not reach statistical significance. Nonetheless, this deserves further attention because the association between depression and ziprasidone has been made previously (Kaptsan et al., 2007).

It is important to underline that our study population had a recent onset of the syndrome. In this way, there is a smaller chance of a patient selection bias, ie, including subpopulations of severe, untreatable patients. Moreover, studies with recent-onset schizophrenia populations offer the opportunity to examine the effectiveness without the confounding effects of long-term medication use (Robinson et al., 2005).

Recently, metabolic syndrome has been the focus of considerable attention. Unfortunately, we were not able to determine the prevalence of metabolic syndrome in our sample because we did not evaluate waist circumference, low-density lipoprotein, and high-density lipoprotein. The metabolic syndrome is considered a constellation of cardiovascular risk factors linked by insulin resistance, which include obesity, dyslipidemia, glucose tolerance, and hypertension. Antipsychotics, especially those from the second generation, increase the risk of cardiovascular incidents in schizophrenia. This risk is already higher in this population due to heavy smoking, low treatment adherence for somatic medication, less access to medical care, and a (genetic) higher prevalence of diabetes. It is estimated that patients with schizophrenia have a 20% reduced life expectancy compared with the general population and that two-thirds of schizophrenia patients die of cardiovascular incidents (Hennekens et al., 2005).

Taken together, ziprasidone and olanzapine have comparable efficacy, resulting in remission rates of around 40% within 8 weeks. This study further demonstrates that abnormalities of metabolic parameters, which are risk factors for developing metabolic syndrome in the long term, can be detected in substantial proportions of recent-onset schizophrenia patients at an early stage of treatment.

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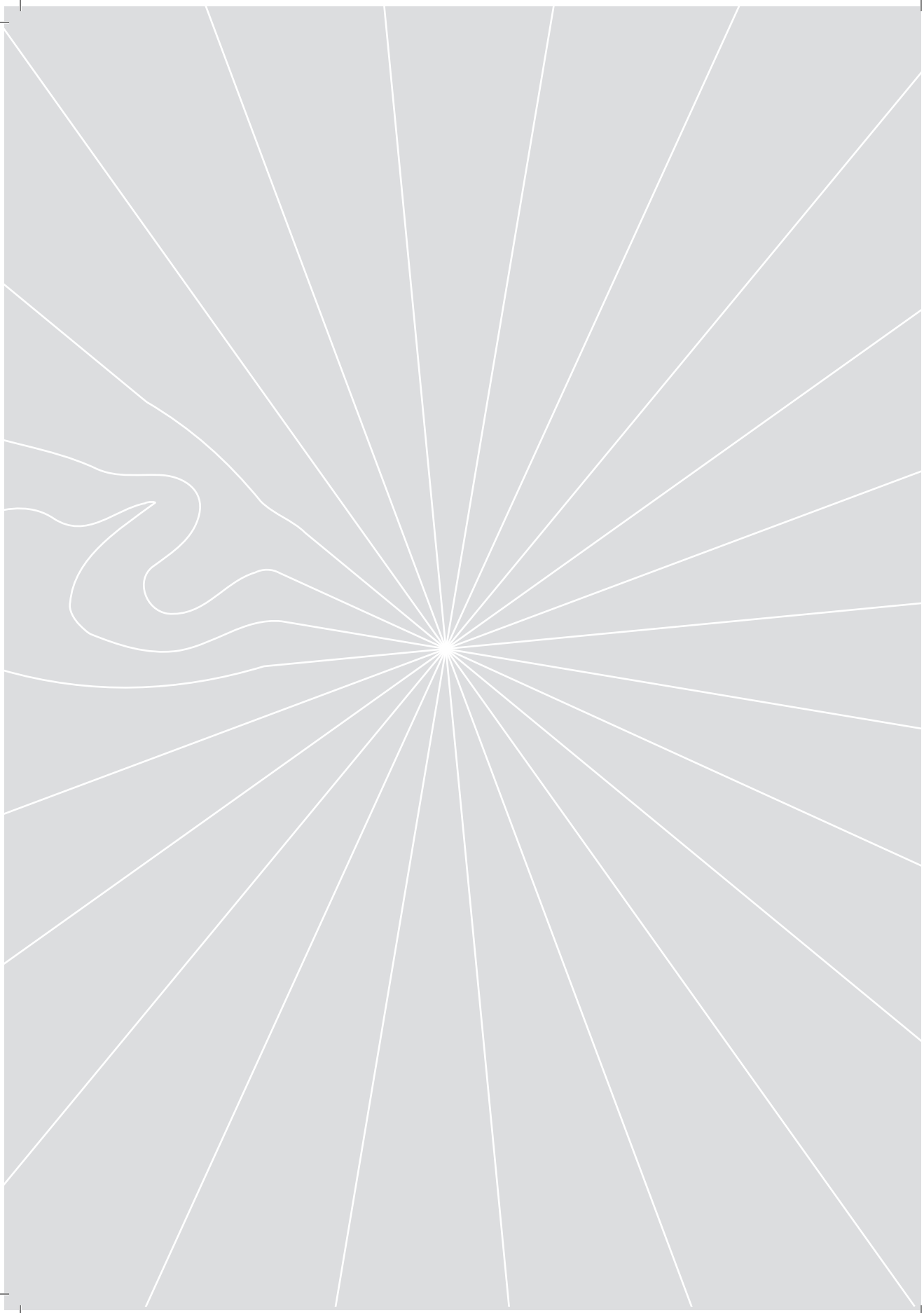

Chapter 7

Summary and concluding words

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The research of this thesis centers on the investigation of first-episode medication-naive and recent onset schizophrenia patients.
In the first part of this thesis (chapter 2-4) we used functional MRI to investigate two hypotheses concerning the pathophysiology of schizophrenia: (1) schizophrenia is characterized by reduced language lateralization, and (2) frontal lobe dysfunction is related to schizophrenia, in particular to negative symptoms and disorganization.
In the second part of this thesis (chapter 5 and 6) we compare the short term treatment effects (clinical efficacy and cognitive improvement) of two atypical antipsychotics in patients who have recently fallen ill.

Part I. Functional MRI studies

1.1. Reduced language lateralization

The purpose of the study described in **Chapter 2** was to test for differences in the degree of language lateralization in first-episode schizophrenia and healthy controls, using functional MRI. Reduced language lateralization has been demonstrated earlier in chronic schizophrenia patients, but not in first-episode medication-naive patients. We expected that language lateralization was reduced at illness-onset, prior to the initiation of medical treatment.
To test language lateralization, subjects performed three language tasks: a categorical semantic decision task, a paced verb generation task and an antonym generation task while being scanned. We used six Regions of Interest (ROIs) that included the main language-related areas and their contralateral homologues, and subsequently calculated the lateralization index. Symptomatology was measured using the PANSS. Results demonstrated that lateralization was significantly reduced in medication-naive first-episode patients. This reduction was most prominent in the inferior frontal gyrus (part of Broca's area) and the superior temporal gyrus (part of Wernicke's area). However, in our study population, the level of lateralization was not related to specific symptomatology. We concluded that language lateralization is impaired already in the first episode of the illness and is not a confound of medication use.

1.2. Reduced language lateralization -concluding remarks

These results confirm the hypothesis postulated by Crow (Crow 2008) that states that language lateralization is reduced in schizophrenia. We did however fail to support his notion that reduced language lateralization was related to specific symptomatology, such as hallucinations or thought disorder. This could be interpreted as an indication

that reduced lateralization points to a fundamental impairment in schizophrenia or a risk factor to the illness, rather than a phenomenon accompanying psychotic symptoms which generally display a more cyclic course. This interpretation is consistent with findings of reduced lateralization in non-psychotic high-risk subjects (Li et al., 2007) and in unaffected monozygotic co-twins (Li et al., 2007; Sommer et al., 2004).
It is not clear how lateralization arises in the healthy brain, and when and how aberrant asymmetry arises. Genetic (Badzakova-Trajkov et al., 2010; Geschwind et al, 2002) as well as environmental factors (Tommasi et al., 2009) are likely to be of importance in the development of asymmetry. Anatomical asymmetry is present already in the embryonic brain, supposedly due to genetic factors (Kasprian et al., 2010). Subsequent environmental factors have been identified that can influence lateralization. These are general factors, such as acquiring language skills (Holland et al, 2007;Friederici, 2006) or the ability to read (Porta et al., 2010). There are also more specific factors that have been identified. For instance, high concentrations of prenatal testosterone (review: (Pfannkuche et al., 2009) and perinatal stress were associated with differences in lateralization (Llaurens et al., 2009, Orlebeke et al., 1996).
Moreover, several toxic agents are associated with aberrant anatomical asymmetry. Heavy alcohol use (Medina et al., 2007;Nagel et al., 2005) during adolescence as well as prolonged cannabis use (Yucel et al., 2008) were associated with changes in asymmetry of the hippocampus (reduction on the left side) and changes in the left sided (language related) areas (Bava et al., 2009).

It is important to note that environmental factors may influence the left and right hemisphere differentially. In the foetal period, the right hemisphere appears to develop more rapidly than the left hemisphere (hence the good perceptual abilities of a new born) (Zhu et al., 2011; Schaafsma et al., 2009). After birth, the left hemisphere still develops more slowly, and the left frontal cortex is the last brain area to mature in adulthood (Zhu et al., 2011). It was suggested that the left hemisphere can therefore be exposed to (harmful) environmental factors for a much more extended period (Roberts, 1991). The fact that various developmental diseases are associated with reduced lateralization (learning-and language disabilities (Rodriguez et al., 2010;Llaurens et al., 2009) autism (Knaus et al., 2010;Herbert et al., 2005), ADHD (Shaw et al., 2009) and altered immune function (Hermans et al., 2009;Quaranta et al., 2006;Koch et al., 2006) is consistent with this notion.
As multiple mechanisms appear to influence cerebral lateralization (Liu et al., 2009) it is hard to determine whether our finding of reduced language lateralization is specifically related to (the genetic vulnerability for) schizophrenia, or that other, abovementioned factors have an additive or interactional effect. A way to further proceed this research is to investigate factors that are related to reduced lateralization prior

to the onset of the illness (high-risk patients), and to extend such a research to other diseases that are related to reduced lateralization.
Finally, patients should be tested repeatedly to investigate stability of lateralization over time.

1.3. Frontal lobe dysfunction

In **Chapter 3** results are presented of a functional MRI study that aimed to investigate frontal lobe function in 30 male first-episode medication-naive patients and 36 matched healthy comparison subjects.
To test frontal lobe function, we applied a modified Sternberg working memory task, which comprised a novel (NT) and practiced task (PT). An earlier study conducted in healthy controls indicated that brain activation was decreased after practice. This was hypothesized to reflect increased neural efficiency, whereby practice builds a more efficient neural route through the modification of neural connectivity (Garavan et al.,2000;Kelly et al., 2006). In the current study, we expected patients to show a limited profit from practice in terms of brain activation, expressing inefficient neuronal processing in schizophrenia. In addition, we expected this dysfunction to be associated to negative symptoms and disorganization, as these symptoms have been related to frontal lobe function previously.
Subjects performed the modified working memory task while they were being scanned with functional MRI. We investigated five predefined Regions of Interest (ROIs) that were used in an earlier study (van Raalten et al., 2008), and conducted a repeated measurement analysis for task (NT and PT) and ROI.
Results indicated that after practice, both groups increased their performance equally. Frontal brain activation was reduced after practice in controls as well as in patients. In patients however, this decrease was significantly smaller than in controls in the left dorsolateral prefrontal cortex (DLPFC), in spite of equal improvement in performance. Furthermore, this reduced effect of practice in left DLPFC activation was found to be related to the severity of negative symptoms and conceptual disorganization. Taken together, the results of this study were in accordance with our expectation, implying that frontal lobe function (particularly that of the left DLPFC), is already impaired at the first-episode of schizophrenia and not as a consequence of antipsychotic treatment.

In **Chapter 4** we describe a follow-up study to the study reported in chapter 3. The objective of this study was to determine whether frontal dysfunction was influenced by subsequent medical treatment, and furthermore to test whether frontal brain dysfunction could be of predictive value in first episode schizophrenia.
Of the subjects described in chapter 3, 23 male patients and 33 comparison subjects

participated and were rescanned after ten weeks, using the same working memory paradigm as applied during the baseline scan. After the baseline scan, patients were started on atypical antipsychotic medication, and clinical measures (PANSS) were taken at both scanning points. Results again showed that function of the left DLPFC was significantly impaired: while practice was associated with a reduction in brain activation in healthy controls, this decrease in activation did not occur in the patients. Interestingly, the abnormal left DLPFC function was almost entirely explained for by the subgroup of patients who failed to respond to antipsychotic treatment. In contrast, in patients responding to medical treatment the activation levels after practice were similar to those of the healthy subjects. Importantly, responders and non-responders could not be discriminated by their test performance. Furthermore, the antipsychotic treatment that was applied did not alter the function of the DLPFC. In addition, a regression analysis was performed with PANSS improvement as dependent variable and the practice effect on brain activation in the DLPFC as independent variable. Results showed that reduced effect of practice in the DLPFC at baseline was predictive of poor clinical outcome at ten weeks.
We concluded that dysfunction of the DLPFC was present in first-episode medication-naive schizophrenia patients, that DLPFC function was not affected by subsequent antipsychotic medication and that DLPFC dysfunction at baseline was predictive of treatment response. Taken together, our results indicate that prefrontal lobe dysfunction reflects a distinct neuropathological substrate in a subgroup of schizophrenia patients that does not respond to treatment with dopamine antagonists.

1.4. Frontal lobe dysfunction – concluding remarks

The data presented in **chapters 3 and 4** point to a disturbed function of the left prefrontal lobe in first-episode medication-naive schizophrenia patients. This dysfunction was related to negative symptoms and disorganization. This frontal lobe dysfunction was most prominent in patients who did not improve clinically after treatment (non-responders). These non-responders may be closest to the original description of Kraepelin for schizophrenia or 'dementia praecox'. In fact, they may represent a separate treatment non-responsive, subgroup of (first-episode) schizophrenia patients.

Different approaches can be pursued to further characterize this prefrontal lobe dysfunction.
An obvious step for further research would be to combine the imaging information with the genetic information from the subjects, for instance the dopamine regulating gene, catechol-o-methyltransferase (COMT). Variations in this gene should be tested, as these were associated with prefrontal inefficiency in healthy controls (Mey-

er-Lindenberg et al.,2006) as well as in schizophrenia patients (Molero et al., 2007, Bertolino et al., 2004, Diaz-Asper et al., 2008), and possibly with treatment response (Bertolino et al., 2004).

An alternative approach would be assessing treatment effects of other agents than D2 antagonists as used in the current study. The group of patients with inefficient frontal lobe function we identified in our research may be characterized by progressive (frontal) brain loss, a phenomenon that has been associated with poor treatment response in several longitudinal neuroimaging studies in schizophrenia (van Haren et al., 2008, Hulshoff Pol and Kahn, 2008). Since progressive brain changes have been suggested to result from glutamatergic pathology (Theberge et al., 2007), these patients may benefit from (novel) treatments targeting metabotropic glutamate receptors (Patil et al., 2007).

Another way to broaden our understanding of the neural deficits underlying our functional MRI results is the use of different imaging –or analysing techniques. We were able to determine disturbances in localized brain activity, but the prefrontal cortex does not work in isolation (nor do the language related areas). The prefrontal cortex may have a key function when performing a working memory task but it is also clear that the neural system supporting working memory engages other distant cortical areas (e.g. the posterior parietal cortex, the inferotemporal cortex, the cingulate gyrus and hippocampus) (Jonides et al., 1998;Goldman-Rakic, 1999). Functional MRI, as performed in the current research, enables us to visualize activation, but it does not show how activation in one area is related to the other, nor does it yield information about the temporal order in which activation occurs. Performing an effective or functional connectivity analysis could further clarify our findings.
Finally, our understanding of prefrontal lobe dysfunction may be further elucidated by studying high-risk subjects, so that we can determine when these deficits arise, and what environmental and genetic factors are involved. One such environmental factor may be stress, as the effects of stress on the frontal lobe during development for instance have been described as deleterious (Weber and Reynolds, 2004;Carrion et al., 2010).
Moreover, using an alternative diagnostic approach, based on endophenotypes (such as prefrontal lobe dysfunction), could be helpful in research in high risk as well as first-episode patients, since this is a way to reduce the extended heterogeneity of symptoms and syndromes in schizophrenia (Gottesman and Gould, 2003;Braff et al., 2007).

Part II. Treatment studies of olanzapine versus ziprasidone.

2.1. Cognitive function

In **Chapter 5** we describe a study that compares the effects of short-term treatment of two atypical antipsychotics on cognitive function in recent-onset schizophrenia. The rationale of the study was that cognitive impairments are a prominent feature in schizophrenia, and that there is considerable evidence that they are associated with poor outcome. The (early) treatment of these impairments is thus relevant. There are still relatively few studies that compare the effects of atypical antipsychotic medication on cognition specifically in first episode schizophrenia in double blind randomized trials (Cuesta et al., 2009, Crespo-Facorro et al., 2009, Keefe et al. 2007). This is the first study to compare the effects of a short term treatment of olanzapine versus ziprasidone on cognitive functioning in recent onset schizophrenia.

The primary outcome measure of the study was the California Verbal Learning Test (CVLT). This task was chosen since verbal learning and memory have been specifically implicated as a mediator of poor clinical outcome in schizophrenia (Green, 1996, Green et al., 2000) and are among the most severe cognitive impairments in chronic schizophrenia (Aleman et al., Heinrichs and Zakzanis, 1998, Leeson et al., Hill et al., Paulsen et al., Saykin et al., 1994). In addition, we administered a larger cognitive battery consisting of nine neurocognitive tests, for which a composite score was developed to determine general cognitive functioning and avoid multiple testing. We evaluated 56 patients and tested neurocognitive performance at randomization and at eight weeks follow-up. In addition we administered symptom scales and a scale for psychosocial functioning.

Results indicated that after eight weeks of treatment cognition was enhanced, with considerable effect sizes for both the verbal memory measures and the neurocognitive composite score. This improvement however, was not significantly different between the two treatment groups. Furthermore, the cognitive enhancement did not correlate with clinical improvement, but we did find a (weak) correlation with (psychosocial) functioning. From our research we concluded that cognitive deficits in recent onset schizophrenia were not a reason for preferentially prescribing one of the two second generation antipsychotics tested over the other.

2.2. Symptomatology and tolerability

The study in **Chapter 6** sets out to compare the clinical efficacy and tolerability of two second-generation antipsychotic drugs (ziprasidone and olanzapine) in recent onset schizophrenia.

Seventy-six patients were evaluated in this 8-week, double-blind, randomized,

controlled multicenter trial. Clinical efficacy was measured using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) Scale, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS). Tolerability was determined using laboratory assessments, body weight, and electrocardiography.

Results showed that while clinical improvement was virtually the same in both treatment groups, the adverse effects differed between groups. The weight change from baseline was highest for patients in the olanzapine group (patients on olanzapine had a mean weight increase of 6.8 kg, whereas those assigned to ziprasidone only had an increase of 0.1 kg ($P < 0.001$)). Ziprasidone was associated with decreasing levels of triglycerides, cholesterol, and transaminases, while these parameters increased in the olanzapine group. In addition, patients on ziprasidone were more likely to be prescribed anticholinergic drugs for extrapyramidal side effects. There were no significant differences in prolactin levels or in cardiac or sexual side effects.

We concluded that ziprasidone and olanzapine have comparable therapeutic efficacy but differ in their side effect profile. Clinically significant weight gain and laboratory abnormalities appear early after initiating treatment and are more prominent with olanzapine, while more patients on ziprasidone received anticholinergic drugs to treat extrapyramidal symptoms.

2.3. Concluding remarks

In **chapters 5 and 6** of this thesis we found that short term treatment with both ziprasidone and olanzapine has a comparable effect on symptomatology and cognitive function, but that they differ in side effects. Our findings replicate findings of other (open) treatment studies comparing atypical antipsychotics in first-episode patients (Crespo-Facorro et al., 2009, Davidson et al., 2009, Kahn et al, 2008).

It appears from both studies that while receptor profiles of both drugs differ, the effect of these differences are mainly apparent in the side effects they exert, and not in their therapeutic effect. This implies that the choice of antipsychotic is guided by patient preference and tolerability.

The current drugs leave some symptoms and therapy-resistant patients "untreated". More extensive research of specific subgroups of patients, for instance in those with prefrontal dysfunction, as mentioned above, may eventually lead to more diverse treatment options, other that D2 receptor antagonists.

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Nederlandse Samenvatting

Nederlandse Samenvatting

Het centrale thema van dit proefschrift betreft het onderzoek naar eerste episode (medicatie naïeve) patiënten met schizofrenie.
In het eerste deel van dit proefschrift (Hoofdstuk 2-4) onderzochten we met behulp van functionele MRI twee hypothesen aangaande de pathofysiologie van schizofrenie: (1) schizofrenie wordt gekarakteriseerd door verminderde taallateralisatie, en (2) frontaal kwab dysfunctie is gerelateerd aan schizofrenie, en dan m.n. aan negatieve symptomen en desorganisatie.
In het tweede deel van dit proefschrift (Hoofdstuk 5 en 6) vergelijken we de korte termijn behandeleffecten (klinische effectiviteit en cognitieve verbetering) van twee atypische antipsychotica in patiënten met schizofrenie die kort tevoren ziek werden.

Deel 1. Functionele MRI studies

1.1. Verminderde taallateralisatie

Het doel van de studie beschreven in **Hoofdstuk 2** was het vergelijken van de mate van taallateralisatie in eerste episode schizofrenie patiënten en gezonde controles, met behulp van functionele MRI. Verlaagde taallateralisatie was eerder aangetoond bij chronische patiënten, maar niet bij eerste episode medicatie naïeve patiënten. Onze verwachting was dat taal lateralisatie ook verlaagd zou zijn gedurende de eerste episode van de ziekte, voordat medicamenteuze behandeling gestart was.
Om taallateralisatie te kunnen testen, voerden deelnemers 3 taaltaken uit (een "categorical semantic decision task", een "paced verb generation task" en een "antonym generation task") terwijl ze werden gescand. We bepaalden hersenactivatie patronen van de 6 belangrijkste taal gerelateerde gebieden en van de 6 contralaterale homologe hersengebieden (ROIs), en berekenden daarvan vervolgens een lateralisatie index. De ernst van symptomen werd gemeten door middel van een vragenlijst (PANSS).
Taallateralisatie bleek significant geringer te zijn in patiënten vergeleken met gezonde proefpersonen. Dit verschil was m.n. aanwezig in de inferieure frontale gyrus (waar het gebied van Broca zetelt) en in de superieure temporale gyrus (waar het gebied van Wernicke zetelt). Bovendien vonden we dat in deze onderzoeksgroep, taallateralisatie niet gerelateerd was aan specifieke symptomatologie. We concludeerden dat taallateralisatie reeds verstoord was gedurende de eerste episode van de ziekte, en geen verstorende variabele was van medicatie gebruik.

1.2. Verminderde taallateralisatie –conclusies en verder onderzoek

We bevestigden de theorie van Crow ea (2008) dat taallateralisatie verminderd is in schizofrenie. We vonden echter geen bevestiging voor zijn stelling dat verminderde taal lateralisatie gerelateerd is aan specifieke symptomatologie, zoals hallucinaties of een denkstoornis. Dit zou een indicatie kunnen zijn dat verminderde taallateralisatie als een risico factor of een stabiele factor gezien moet worden en niet een factor die specifiek met psychotische symptomen gepaard gaat, die over het algemeen een cyclisch verloop hebben. Dit komt ook overeen met andere bevindingen, zoals gedaalde taal lateralisatie in niet-psychotische hoog risico personen (Li et al., 2007) en in niet-aangedane monozygote tweelingen (Li et al., 2007;Sommer et al., 2004).

Het is niet duidelijk hoe lateralisatie in het brein precies ontstaat. Waarschijnlijk spelen zowel genetische (Badzakova-Trajkov et al., 2010:McManus et al., 1991, Geschwind et al., 2002, Liu et al., 2010) als omgevingsfactoren (Annet, et al., 1985; Klar et al., 1996; Tommasi et al., 2009) een rol.

Anatomische asymmetrie is al aangetoond in het embryonale brein en verondersteld wordt dat deze onder genetische invloed ontstaat (Kasprian et al., 2010). Er zijn diverse omgevingsfactoren gevonden die lateralisatie of taallateralisatie beïnvloeden. Dit zijn algemene factoren zoals het zich eigen maken van taal (Holland et al.,2007, Friederici et al., 2006) en lezen (Porta et al., 2010). Er zijn ook meer specifieke invloeden van belang. Hoge concentraties prenataal testosteron (review: Pfannkuche 2009) en perinatale stress zijn eveneens geassocieerd met verschillen in lateralisatie (Soper & Satz 1984, Orlebeke 1996, Geschwind &Galaburda 1985, Coren 1993, Llaurens 2009). Ook enkele toxische stoffen werden geassocieerd met anatomische asymmetrie. Zwaar alcoholgebruik (Medina et al., 2007, Nagel 2005) in de adolescentie evenals langdurig cannabis gebruik (Yucel et al., 2008) werden geassocieerd met veranderingen in asymmetrie van de hippocampus (links kleiner) en veranderingen in de linker (taal gerelateerde) hersen gebieden (Bava et al., 2009).

Van belang is dat deze omgevingsfactoren een verschillend effect kunnen hebben op de linker en de rechter hersenhelft. In de foetale periode blijkt de rechter hemisfeer zich sneller te ontwikkelen dan de linker (vlak na de geboorte zijn de perceptuele functies bij een baby dan ook al goed ontwikkeld) (Zhu et al., 2011, Schaafsma et al., 2009). Ook na de geboorte ontwikkeld de linker hemisfeer zich langzamer, en de linker frontale cortex is als laatste volgroeid is bij het volwassen worden (Zhu et al., 2011). Een veronderstelling is daarom dat de linker hersenhelft gedurende een veel langere periode aan (beschadigende) omgevingsfactoren bloot staat (Coren & Halpern 1991). Dat diverse ziektebeelden geassocieerd zijn met verminderde lateralisatie (leer-en taal stoornissen, (Satz et al., 1985, Rodriguez et al., 2010, Llaurens et al., 2009) autisme (Knaus et al., 2010, Rubia et al., 2000) en ADHD (Herbert et al., 2005),

gewijzigde immuunfunctie (Hermans et al.,2009, Meador et al., 2004, Koch et al., 2006 Quaranta et al., 2006)) kan met deze gebeurtenissen samenhangen.
Omdat cerebrale lateralisatie door multipele mechanismen wordt beïnvloed (Liu et al., 2009) is het moeilijk vast te stellen of in onze studie verminderde lateralisatie specifiek gebonden is aan (genetische kwetsbaarheid voor) schizofrenie, of dat andere, bovengenoemde factoren een additief of interactioneel effect hebben. Vervolg onderzoek zou zich kunnen richten op onderzoek van factoren gerelateerd aan verminderde taallateralisatie in de fase voordat de ziekte zich openbaart (in hoog-risico patiënten). Eveneens kan het zinvol zijn het onderzoek uit te breiden naar andere ziekten die gerelateerd zijn aan verminderde taallateralisatie. Ten slotte, patiënten zouden herhaaldelijk getest moeten worden, om de stabiliteit van lateralisatie over de tijd vast te stellen.

1.3 Frontaal kwab dysfunctie

In **Hoofdstuk 3** worden resultaten gepresenteerd van onderzoek waarin door middel van functionele MRI de frontale hersenfunctie werd vergeleken van 30 mannelijke 1e episode medicatienaïeve patiënten en 36 gezonde controles.
Om frontale hersenfunctie te testen, werd een aangepaste versie van de "Sternberg werkgeheugen taak" toegepast, die bestond uit een nieuwe versie en een geoefende versie (NT en GT). Uit een eerdere studie waar alleen gezonde proefpersonen werden getest, bleek dat hersenactivatie daalde na oefening. Dit werd uitgelegd als een toegenomen neurale efficiëntie, waarbij door oefening de neurale overdracht efficiënter wordt door toegenomen neurale connectiviteit (Kelly et al., 2006;Garavan et al., 2000). In de huidige studie verwachtten wij dat patiënten minder zouden profiteren van oefening wat betreft hersenactivatie, dan gezonde proefpersonen, als uiting van inefficiënte neuronale verwerking in schizofrenie. Tevens verwachtten wij dat deze dysfunctie geassocieerd zou zijn met negatieve symptomen en desorganisatie, omdat deze symptomen eerder werden gerelateerd aan frontale dysfunctie.
Subjecten voerden de werkgeheugen taak uit terwijl ze in de scanner lagen. We bekeken activatiepatronen in 5 van te voren vastgestelde hersengebieden (ROIs), en voerden een test voor herhaalde metingen over deze ROIs en deze taken (NT en GT) uit. Het bleek dat patiënten en proefpersonen niet significant verschilden wat betreft hun prestatie op de taak, ze hadden een vergelijkbaar scoringspercentage. In beide groepen nam de hersenactivatie af na oefening. In patiënten was de afname van hersenactivatie echter veel kleiner dan bij de proefpersonen in de linker dorsolaterale prefrontale cortex (DLPFC), terwijl hun scoringspercentage dus gelijk was. Bovendien was het activatie verschil in de DLPFC gerelateerd aan de ernst van de negatieve symptomen en desorganisatie. Samenvattend kwamen onze bevindingen overeen met onze hypothese: frontale hersenfunctie (mn die in de linker DLPFC) is al verstoord

is gedurende de eerste episode van schizofrenie, en dus geen gevolg van behandeling antipsychotische medicatie.

In **Hoofdstuk 4** wordt een vervolg op de studie van hoofdstuk 3 beschreven.
Het doel van deze studie was om vast te stellen of frontale hersenactivatie patronen worden beïnvloed door medicamenteuze behandeling, en tevens of frontale dysfunctie van voorspellende waarde kan zijn in eerste episode schizofrenie.
Drieëntwintig mannelijke patiënten en 33 vergelijkbare proefpersonen die deelnamen aan de studie beschreven in hoofdstuk 3 werden geïncludeerd en werden voor een tweede keer gescand. Er werd hetzelfde werkgeheugen paradigma gebruikt als bij de baseline scan.
Na de baseline scan begonnen patiënten met behandeling met atypische antipsychotische medicatie. Er werden symptoomschalen (PANSS) afgenomen rond beide scan momenten. Opnieuw bleek, als beschreven onder hoofdstuk 3, dat de linker DLPFC functie verminderd was: na oefening verminderde de hersenactiviteit van gezonde proefpersonen, maar bij patiënten trad deze vermindering niet op. Het opvallende was dat deze abnormale linker DLPFC functie bijna geheel verklaard werd door de subgroep van patiënten die niet verbeterden op de medicatie. Bij de patiënten die wel verbeterden op medicatie, was het activatie patroon na oefening gelijk aan dat van gezonde proefpersonen. Dit verschil in activatie patroon tussen patiënten die wel en die niet goed op medicatie reageerden werd niet veroorzaakt door een slechtere taakscore door non-responders: de taakscore was gelijk voor beide patiënten groepen. Er bleek bovendien dat de antipsychotische medicatie die na de baseline scan was gestart, geen effect had op dit frontale hersenactivatie patroon.
Wij voerden tevens een regressie analyse uit met verbetering op de PANSS als afhankelijke variabele, en het effect van oefening op hersenactivatie in de DLPFC onafhankelijke variabele. Het bleek dat het gedaalde effect van oefening in de DLPFC wat gemeten was gedurende de baseline scan, voorspellend was voor een slechte klinische uitkomst na 10 weken.
We concludeerden dat dysfunctie van de DLPFC aanwezig was in eerste-episode medicatie naïeve patiënten met schizofrenie, dat deze niet beïnvloed werd door medicatie die gestart was, en dat deze dysfunctie voorspellend was of een patiënt zou responderen op medicatie. We veronderstellen dat dysfunctie van de prefrontale hersenkwab een onderscheidend neuropathologisch substraat kan zijn voor een subgroep van patiënten die niet verbeteren op een behandeling met dopamine antagonisten.

1.4 Frontaal kwab dysfunctie –conclusies en verder onderzoek

De resultaten gepresenteerd in **hoofdstuk 3 en 4** wijzen op een verstoorde functie van de linker prefrontale kwab in eerste episode schizofrenie patiënten. Deze dysfunctie was gerelateerd aan negatieve symptomen en desorganisatie, en was voornamelijk te toe te schrijven aan de groep niet responderende patiënten. Dit is de patiënten groep die bij benadering past bij oorspronkelijke beschrijving van Kraepelin voor schizofrenie of 'dementia praecox'. Het lijkt in elk geval een aparte niet-op behandeling responderende subgroep van (eerste-episode) patiënten te zijn.

Verschillende benaderingen kunnen worden gevolgd om deze prefrontale dysfunctie verder te karakteriseren.

Een logische stap voor verder onderzoek is het combineren van genetisch en neuroimaging onderzoek in deze subjecten. Er zou bv. gekeken kunnen worden naar variaties van een dopamine regulerend enzym, catechol-o-methyltransferase (COMT), omdat dit enzym geassocieerd is met prefrontale inefficiëntie in gezonde proefpersonen (Meyer-Lindenberg et al., 2006) en in patiënten met schizofrenie (Diaz Asper et al., 2008;Molero et al., 2007;Bertolino et al., 2004), en mogelijk ook met (verlaagde) therapie respons (Bertolino 2004, 2006).

Een andere mogelijkheid voor verder onderzoek zou kunnen zijn om de behandeleffecten van andere middelen dan de in deze studie gebruikte D2 antagonisten vast te stellen. Wellicht is de prefrontale dysfunctie die we in een subgroep van de patiënten vast stelden gerelateerd aan progressief (frontaal) hersenverlies. In diverse longitudinale studies naar schizofrenie werd progressief hersenverlies geassocieerd met verminderde behandelings respons (van Haren et al., 2008;Hulshoff Pol and Kahn, 2008). Aangezien van progressieve hersenveranderingen wordt vermoed dat deze samenhangen met verstoringen in het glutamaterge systeem (Therberge et al., 2007), zouden deze patiënten wellicht kunnen profiteren van nieuwe middelen die met name aangrijpen op glutamaat receptoren (Patil et al., 2007).

Een andere manier om de neuronale deficiten die ten grondslag liggen aan onze functionele MRI bevindingen verder te karakteriseren is door gebruik te maken van nieuwere beeldvormende technieken –of analyses. We konden in het huidige onderzoek verstoringen in locale hersenactiviteit vaststellen, maar de prefrontale cortex werkt vanzelfsprekend niet als een geïsoleerd gebied (net zo min als de taalgerelateerde gebieden). De prefrontale cortex heeft een sleutelfunctie bij de uitvoering van werkgeheugentaken, maar het is tevens duidelijk dat ook andere corticale gebieden zijn betrokken bij de uitvoering van een dergelijke taak (bv de posterieure parietale cortex, de infero-temporale cortex, de gyrus cingulate en de hippocampus) (Cavada & Goldman-Rakic, 1989; Fuster, 1997; Goldman-Rakic, 1988, 1999; Jonides et al., 1998; Petrides & Pandya, 1984; Selemon & Goldman-Rakic, 1985). Functionele MRI uitgevoerd zoals in dit onderzoek, laat activatie zien, maar geeft geen inzicht in hoe de

activiteit van het ene gebied samenhangt met dat in het andere, noch laat het zien wat de tijdsrelatie is tussen activatie van verschillende gebieden. Een effectieve of functionele connectiviteitsanalyse zou onze bevindingen verder kunnen verhelderen. Tenslotte, onderzoek bij hoog risico patiënten zou verder kunnen verhelderen, wanneer deze afwijkingen als verminderde lateralisatie en prefrontale dysfunctie nu eigenlijk ontstaan, en welke factoren hierbij een rol spelen. Een omgevingsfactor die onderzocht zou kunnen worden is bv. stress, aangezien schadelijke effecten zijn beschreven van stress op de linker frontaal kwab gedurende de ontwikkeling (Teicher et al.,1997, Weber et al., 2004, Carrion et al., 2010).
Tevens zou een alternatieve diagnostische benadering, die meer gebaseerd is op endophenotypes (zoals bv dysfunctie van de prefrontale cortex), behulpzaam kunnen zijn om de uitgebreide heterogeniteit van de symptomen en syndromen binnen schizofrenie te reduceren (Gottesman and Gould, 2003; Braff et al., 2007).

Deel II. Behandelstudies van olanzapine versus ziprasidone

2.1. Cognitieve functie

In **Hoofdstuk 5** worden de effecten op cognitief functioneren van een kortdurende behandeling van olanzapine versus ziprasidone vergeleken in patiënten die recent schizofrenie ontwikkelden.
De rationale achter de studie was dat cognitieve problemen een belangrijk probleem vormen bij schizofrenie, en dat er aanzienlijk bewijs is dat deze cognitieve problemen gerelateerd zijn aan een slechte uitkomst van de ziekte. De (vroege) behandeling van deze problemen is dus relevant. Het aantal studies dat behandeleffecten juist in deze vroege fase onderzoekt is echter beperkt (Cuesta et al., 2009;Crespo-Facorro et al., 2009;Keefte et al., 2007). Dit is de eerste studie die de effecten van olanzapine en ziprasidone op cognitief functioneren vergelijkt in eerste episode schizofrenie patiënten.
De primaire uitkomstmaat van de studie was de California Verbal Learning Test (CVLT). We richtten ons op het verbale leren en geheugen omdat m.n. deze domeinen tot de meest aangedane cognitieve functies behoren in schizofrenie (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; Leeson et al., 2009; Paulsen et al., 1995; Saykin et al., 1994) en omdat ze gerelateerd zijn aan een ongunstige klinische uitkomst in schizofrenie (Green et al., 1996;2000). Tevens namen we een uitgebreidere neuropsychologische testbatterij af, bestaande uit 9 testen, waarvoor een samengestelde score werd berekend. Hiermee kon een meer algemeen beeld van het neurocognitief functioneren worden vastgesteld, en werd voorkomen veel herhaalde metingen te doen.

Er werden gegevens van 56 patiënten geanalyseerd die na randomisatie in de studie en na 8 weken follow-up neuropsychologisch getest werden. Tevens werden symptoomschalen en schalen t.a.v. het psychosociaal functioneren afgenomen.
Na 8 weken behandeling bleek het cognitieve functioneren aanzienlijk te zijn verbeterd, zowel op de verbaal geheugen maten als voor de samengestelde neurocognitieve score. Deze verbetering verschilde echter niet tussen de 2 behandelgroepen. Daarnaast bleek dat de verbetering op neurocognitieve taken niet gerelateerd was aan de reductie van symptomen, wel werd er een zwakke correlatie gevonden met het (psychosociaal) functioneren. We concludeerden dat er geen verschil in behandeleffectiviteit is op neurocognitief functioneren tussen zyprexa danwel ziprasidone.

2.2. Symptomen en bijwerkingen

In **Hoofdstuk 6** wordt een onderzoek beschreven dat de effectiviteit en bijwerkingen vergelijkt van twee atypische antipsychotica (ziprasidone and olanzapine) in patiënten die recent schizofrenie hadden ontwikkeld.
Zes en zeventig patiënten werden geëvalueerd in deze dubbelblinde, gerandomiseerde, mulitcenter studie van 8 weken. Klinische effectiviteit werd gemeten met behulp van de Positive and Negative Syndrome Scale (PANSS), de Clinical Global Impression (CGI) Scale, de Calgary Depression Scale for Schizophrenia (CDSS), en de Heinrich Quality of Life Scale (HQLS). Bijwerkingen werden vastgesteld met behulp van bloedonderzoek, gewichtsmeting, en een elektrocardiogram.
Resultaten lieten zien dat in beide behandelgroepen de symptoom reductie vrijwel gelijk was, op alle klinische schalen. De bijwerkingen verschilden echter per groep.
De gewichtstoename na randomisatie was het grootse in de groep behandeld met olanzapine (gemiddeld een toename van 6.8 kg bij behandeling met olanzapine, een gewichtstoename van 0.1 kg ($P < 0.001$) bij patiënten behandeld met ziprasidone). Ziprasidone behandeling ging gepaard met een verlaging van de triglycerides, cholesterol, en transaminases, terwijl deze parameters stegen in de groep behandeld met olanzapine. Wel hadden patiënten die behandeld werden met ziprasidone een grotere kans om anticholinerge middelen voorgeschreven te krijgen. Er waren geen significante verschillen in de hoogte van prolactine of cardiale of sexuele bijwerkingen.
We concludeerden dat de klinische effectiviteit van ziprasidone en olanzapine vergelijkbaar is maar dat hun bijwerkingen profiel verschilt. Klinisch significante gewichtstoename en afwijkende laboratorium waarden ontstaan vroeg na het starten van de behandeling met olanzapine, terwijl meer patiënten met ziprasidone anticholinergica kregen voor extrapiramidale bijwerkingen.

2.3. Conclusies en verder onderzoek

In **Hoofdstuk 5 en 6** van dit proefschrift vonden we dat de korte termijn effecten van behandeling met ziprasidone en olanzapine op symptomatologie en cognitief functioneren vergelijkbaar waren, maar dat de bijwerkingen verschilden. Onze bevindingen komen overeen resultaten van eerdere (open) behandel studies waarin diverse atypische antipsychotica werden vergeleken (Crespo-Facorro et al., 2009;Davidson et al., 2009;Kahn et al., 2008).

Uit beide studies in dit proefschrift blijkt dat hoewel de receptor profielen van beide medicamenten verschilt, dit mn tot uiting komt in verschillende bijwerkingen, en niet in hun therapeutisch effect. Dit betekent dat de keuze voor een bepaald antipsychoticum voornamelijk bepaald wordt door de voorkeur van een patiënt en het bijwerkingen profiel van het medicament.

De huidige antipsychotica laten een aantal symptomen en therapieresistente patiënten onbehandeld. Meer uitgebreid onderzoek naar specifieke subgroepen van patiënten, bv de groep met prefrontale dysfunctie, zou uiteindelijk kunnen leiden tot meer diverse behandelopties, naast de receptor D2 antagonisten.

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Let's party!

List of publications

Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia
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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 18 april 1966 te Utrecht. In 1885 behaalde zij het V.W.O. diploma aan het Christelijk Lyceum te Zeist. Aansluitend studeerde zijn Geneeskunde aan de Vrije Universiteit van Amsterdam, en volgde aan deze Universiteit een aantal bijvakken van de studie Antropologie. In de wachttijden voor coschappen liep zij een aantal keuze stages, ondermeer chirurgie en KNO aan het National Kenyatta Hospital te Nairobi, Kenia, Oogheelkunde bij l'hôpital Nianakoro Fomba de Ségou, Mali, tevens oogheelkundig veldondezoek in de region Niono, Mali en advanced psychiatry aan het Mc.Lean Hospital te Boston, USA. Na het behalen van het artsexamen in 1993 werkte zij als arts assistent chirurgie in Ziekenhuis de Heel, te Zaandam. Tevens was zij werkzaam als Onderzoeker In Opleiding bij het Antoni van Leeuwenkoek Ziekenhuis /NKI te Amsterdam. In 1994 begon zij met een keuzejaar op de kliniek voor schizofrenie en startte haar opleiding tot psychiater in het Universitair Medisch Centrum, Utrecht, met als opleider Prof.dr. Kahn. De stage stage sociale Psychiatrie werd gevolgd bij de Riagg Amersfoort 1998-1999, met als opleider B. van de Goot. Eind 1999 werd zij geregistreerd als psychiater. Sindsdien is zij werkzaam als psychiater in het Universitair Medisch Centrum Utrecht. Zij werkte hier achtereenvolgens op de polikliniek voor schizofrenie, de kliniek voor schizofrenie en op de zorglijn schizofrenie, alwaar ook dit promotie onderzoek werd verricht. Zij is gehuwd met Erik Blom met wie zij drie dochters heeft.