Challenges of brain imaging in psychiatry: understanding brain structure and function in schizophrenia

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chapter

General Introduction
General Introduction

Recent advances in brain imaging have provided an excellent opportunity for neuroscientists and psychiatrists to explore the neurobiological mechanisms of schizophrenia and related disorders. Decades of extensive research in schizophrenia have significantly contributed to increase our knowledge of this severe mental disorder. However, the neural substrates underlying the psychopathology of schizophrenia are still not fully understood.

Schizophrenia has been subject of research for more than one century. Already in 1893 psychiatrist Emil Kraepelin hypothesised that dementia praecox (an earlier operationalization of schizophrenia) was closely related to brain abnormalities. Together with Alois Alzheimer they investigated the neuroanatomical substrates of this illness. However, in those days conflicting findings of post-mortem brain studies were disappointing and interest in biological research in schizophrenia decreased. Only from 1976 schizophrenia research gained a new impulse with the first non invasive in vivo brain imaging investigation by computer assisted tomography (CT). CT studies confirmed earlier x-ray and pneumoencephalography findings of enlarged lateral ventricles in schizophrenia (Haug, 1962; Johnstone et al., 1976). Subsequently, there were significant advances in brain imaging methods in the years that followed, particularly in magnetic resonance imaging (MRI). In 1984 the first MRI study visualized the schizophrenia brain with much greater detail than with CT scans.
(Smith et al., 1985). Subsequent MRI reports showed volume reductions in several brain regions. Since then MRI has become a powerful research tool for in vivo investigation of brain structure and function that may be related to schizophrenia and other mental disorders (Fusar-Poli et al., 2012; Mueller et al., 2011).

### 1.1 Schizophrenia

Schizophrenia is a chronic and disabling mental illness characterized by abnormalities in perception, disruption of thought processes and feelings, and a marked decline in social and occupational functioning in the vast majority of cases. Schizophrenia has serious consequences not only for the well-being of patients but also for their families. The onset of clinical symptoms typically emerges during late adolescence or early adult life, the estimated lifetime prevalence is approximately 0.3–0.7% (McGrath et al., 2008). The incidence is significantly higher in males than in females and onset of the disease occurs later in women (Abel et al., 2010).

Psychotic symptoms play a central role in the schizophrenia but the clinical picture is highly heterogeneous with a variety of symptoms. Emil Kraepelin (1893) and Eugen Bleuler (1908) were the first who attempted to cluster the symptoms of schizophrenia. Kraepelin first described the disorder as dementia praecox, but the term was later changed to ‘schizophrenia’ by Bleuler. Since then many attempts have been made to refine the diagnostic criteria of schizophrenia. These have resulted in the development of several classification systems such as the international classification of diseases (ICD) (World Healthy Organization, 1992) and the Diagnostic and Statistical manual of mental disorders (DSM). Initially, the symptoms were clustered in two categories: positive and negative symptoms. Positive symptoms include hallucinations, delusions and thought disorganization. Negative symptoms include lack of motivation, anhedonia, affective flattening, reduction in spontaneous speech and social withdrawal. But often cognitive impairments such as difficulties in memory, attention, and executive functioning are present as well which may comprise a third dimension of symptoms (Keefe et al., 2005) and
are often associated with negative symptoms. At this moment diagnosis of schizophrenia is based on the DSM-IV criteria and requires an illness duration of at least six months with at least one month of active symptoms. However, diagnosis and treatment is not always straightforward because schizophrenia has shared clinical symptoms and genetic causes with other psychotic disorders (e.g. bipolar disorder and major depression with psychotic symptoms) and with autism. The next editions of the DSM-V (http://www.dsm5.org) and the ICD-11 (http://www.who.int/classifications/icd/revision/en/) scheduled for 2013 and 2015 (respectively), try to find solutions for several diagnostic issues and will possible combine more valid definitions from both a categorical point of view and a continuous or dimensional concept.

The aetiology of schizophrenia is complex. Genetic factors and structural and functional brain abnormalities play a crucial role. The current view is that genetic factors and environmental interact and affect neurodevelopment (van Os and Kapur, 2009). Environmental factors include pre- and perinatal events (viral infections, obstetric complications), urbanicity, social isolation, developmental trauma, cannabis use (van Os, 2008; Mueser and McGurk, 2004; Murray et al., 2008). Family history and thus genetic transmission is amongst the most consistent risk factors for schizophrenia with an estimated heritability of approximately 80%. Genetic transmission does not appear to follow single gene mendelian patterns. But, multiple polymorphisms and copy number variants have been identified that are associated with schizophrenia (van Winkel et al., 2010). For instance, susceptibility genes for schizophrenia playing a significant role in neurodevelopment include neuroregulin, dysbindin, DISC1 and COMT.

1.2 22q11 Deletion Syndrome

22q11 deletion syndrome (22q11DS) also known as velo-cardio-facial syndrome or diGeorge syndrome is the most recurrent copy number variation (CNV) disorder (Karayiorgou et al., 2010) with an approximate prevalence of 1:4000 live births (Botto et al., 2003; Kobrynski and Sulli-
People with this syndrome have a deletion on the long arm of chromosome 22 (Shprintzen et al., 1978). The 22q11 deleted region contains about 25-40 genes that are probably related to the anomalies seen in patients. The length of deletion varies from 1.5 to 3.0 megabases (Mb) with most subjects (90%) having a 3.0Mb deletion, 7% have a 1.5 Mb and others an atypical deletion (Edelmann et al., 1999). This syndrome is associated with a variety of clinical features; typical abnormalities of 22q11DS include facial dysmorphism, speech and palatal problems, cardiovascular anomalies (congenital heart defects), immune disorders, learning difficulties (Papolos et al., 1996). 22q11DS is also associated with increased incidence of psychiatric disorders (Gothelf et al., 2008). Several studies have reported anxiety and mood disorders, attention deficits, deficit hyperactivity disorder (ADHD), autism and obsessive-compulsive disorders (OCD) in children and adolescents with 22q11DS. However, with the exception of schizophrenia, most of these diagnoses may not meet the criteria set forth in the literature (Flint, 1998; Karayiorgou et al., 2010). In adulthood, about 30% of the patients develop schizophrenia-like psychosis. The genetic deletion of chromosome 22q11 is the third-highest risk factor for the development of schizophrenia, after being the child of two parents with schizophrenia or the monozygotic co-twin of an affected individual. Of patients with schizophrenia, approximately 1–2% have a 22q11 deletion (Karayiorgou et al., 2010). In conclusion, 22q11DS represents an excellent model for studying the effect of a genetic deletion on the development of brain structure and function, and on the emergence of schizophrenia-like psychotic disorder.

In fact, 22q11DS has been in the focus of psychiatric research for the past 15 years. We now know that people with 22q11DS have an increased incidence of neuro-anatomical abnormalities (Gothelf et al., 2008). Also, haplo-insufficiency of one or more genes on 22q11 such as COMT (Lachman 1996; Graf 2001; Gothelf 2008) and PRODH (Li et al., 2004; Paterlini et al., 2005) may expose 22q11DS patients to dysfunctional dopaminergic and glutamatergic neurotransmission contributing to high rates of psychosis and other psychiatric disorders. Moreover, copy number variation has also been associated with 22q11DS and with schizophrenia (Cook, Jr. and Scherer, 2008; Karayiorgou et al., 1995; St, 2009; Stefansson et al., 2008). However, the neurobiological mechanisms of the 22q11DS syndrome related to the vulnerability to schizophrenia are yet poorly understood.
MRI has facilitated the studies investigating the neurobiology of psychiatric disorders. Studies employing a variety of MRI methods such as voxel based morphometry (VBM), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), functional and pharmacological magnetic resonance imaging (fMRI, PhMRI) have documented several neuroanatomical, neurochemical and neurofunctional abnormalities in schizophrenia. In 22q11DS the available MRI studies, although fewer than in schizophrenia, also indicate that people with 22q11DS have altered brain morphology and function.

MRI uses a powerful magnetic field and radio waves to create detailed images of the organs and tissues within the body. MRI signals are generated from hydrogen atoms present in the human body proving means of discriminating between grey matter, white matter and cerebral spinal fluid in structural images of the brain. Findings of structural brain abnormalities in schizophrenia include enlarged lateral ventricles, higher prevalence of cavum septum pellucidum, decreases of grey matter, white matter and whole brain volume (Shenton et al., 2001; Wright et al., 2000). Recently, results of a meta-analysis have shown that schizophrenia is associated with progressive structural brain abnormalities, affecting both gray and white matter (Olabi et al., 2011). Reductions in gray matter include bilateral areas of the insula, inferior frontal cortex, superior temporal, anterior cingulate gyrus, medial frontal cortex, thalamus and left amygdala (Bora et al., 2011). In early phases of the disease, volumes are decreased in the hippocampus, thalamus, amygdala, insula and anterior cingulate. Later on, in chronic schizophrenia, extensive volume reductions are observed in medial and dorsolateral prefrontal cortex, and in the temporal lobe (Ellison-Wright et al., 2008). Also volume increases have been documented in striatal regions. Relatives of schizophrenia patients show reductions in hippocampal brain volume indicating the genetic aspect of the disorder (Boos et al., 2007). In addition to volume changes, abnormalities in gyrification and grey matter thickness have been reported. In schizophrenia associated with 22q11DS reduced fronto-temporal grey matter volume and widespread loss of white matter volume has been documented (Chow et al., 2002; van Amelsvoort et al., 2001; van Amelsvoort et al., 2004).
There is also increasing evidence for disrupted white matter in schizophrenia. DTI has been widely used to study the structure and integrity of white matter fibers connecting grey matter. With DTI one can investigate the orientation and integrity of white matter tracts by measuring the amount and direction of water diffusion, which can be isotropic (the same amount in every direction) or anisotropic. The degree of anisotropy in particular tissues is often quantified through its fractional anisotropy (FA) value. It is thought that a lower FA is indicative of lower connectivity or integrity of white matter tracts (Basser, 1995; Beaulieu, 2002) which depends on a number of factors, for instance, myelination, fiber diameter and density. DTI studies in schizophrenia have reported lower FA in frontal and temporal brain regions, commissural and association white matter fibers (Kanaan et al., 2005; Kubicki et al., 2007). Disruptions in white matter have been associated with decreased FA in fibers of the anterior thalamic radiation, inferior longitudinal fasciculi, inferior frontal occipital fasciculi, cingulum and fornix (Bora et al., 2011). Also significant FA reductions have been found in first episode patients but to a lesser extent than chronic patients (Friedman et al., 2008). In children with 22q11DS DTI studies suggest pervasive white matter dysfunction. Reduced FA has been found in frontal, parietal and temporal regions (Barnea-Goraly et al., 2003; Simon et al., 2005; Sundram et al., 2010) and clusters of increased FA from posterior areas of the corpus callosum to the occipital lobes (Barnea-Goraly et al., 2003). Moreover, FA reductions in the parietal lobe correlated with poor arithmetic task performance (Barnea-Goraly et al., 2005) These findings suggest neuropathology of white matter and unusual development of brain connectivity.

$^1$H-MRS is another MRI method used for measurement of a number of brain metabolites that possible reflects the status of important functions of neurons and glial cells. $^1$H-MRS studies have demonstrated altered neurometabolites in psychiatric disorders including schizophrenia. The $^1$H-MRS signal comes from small chemical compounds based on different resonance frequencies (Dager et al., 2008). The $^1$H-MRS signal is transformed to a frequency spectrum and the position of the signal peaks are expressed as ‘chemical shifts’ (shift in resonance frequency that is unique to a given molecule). Neurometabolites measured by $^1$H-MRS include $N$-acetyl-aspartate, creatine, choline, myo-Inositol, lactate, glutamate and glutamine. These metabolites can be related to neuronal integrity, density, energy metabolism and protein synthesis that, if altered, may reflect abnormal neuro-developmental features (Soares and
Law, 2009). In schizophrenia an increasing number of $^1$H-MRS studies have been conducted suggesting abnormal concentration of glutamate (Bartha et al., 1997; Theberge et al., 2002; Theberge et al., 2003) and NAA reductions in several regions implicated in the pathogenesis of schizophrenia. Although there has been much evidence in favor of glutamatergic alterations in schizophrenia accumulated in recent years, the most prominent findings have been decreased NAA in the frontal cortex and the temporal lobes especially in the hippocampus and superior temporal lobe (Bertolino and Weinberger, 1999).

Abnormalities in brain structure and neurochemical composition may consequently lead to abnormal brain function. This can be demonstrated by functional MRI (fMRI), the MRI method used to study brain function. fMRI works by detecting the changes in blood oxygenation and flow that occur in response to neural activity. A brain area that is active consumes more oxygen thereby increasing blood flow. This mechanism is referred to as BOLD (blood-oxygen-level dependent), which cause changes in the T$^*2$ signal providing an indirect measure of neural activity (Logothetis et al., 2001). Investigations with fMRI have shown abnormal brain activity (hypo- and hyperactivity) in several brain regions in schizophrenia patients. For instance, enhanced activity of auditory and speech cortices have been demonstrated during hallucinatory experiences (Dierks et al., 1999). Reduced executive functioning is accompanied by reduced activation of the dorsolateral prefrontal cortex, anterior cingulate and inferior parietal lobule. Dysfunction of brain functions involved in reward related brain activation relying in midbrain dopaminergic neurons projecting to the ventral striatum and dorsolateral prefrontal cortex. In 22q11DS very few fMRI studies in 22q11DS have been reported. These studies have suggested parietal lobe dysfunction during cognitive tasks (Eliez et al., 2001; Kates et al., 2007). Also, reduced fusiform gyrus activation in response to neutral faces compared to houses has been found in 22q11DS with schizophrenia (Andersson et al., 2008) and less activation in the right insula and frontal brain regions and increased activation in occipital regions during an emotional face processing task in adults with 22q11DS (van Amelsvoort et al., 2006).

Finally, PhMRI is a brain imaging modality that combines fMRI with a pharmacological challenge making it possible to explore the effect of a drug agent on the brain. For instance, PhMRI studies assessing the effects of antipsychotic medication, based on blockage of dopamine recep-
tors, have shown that typical antipsychotics probably normalize striatal-related dopaminergic dysfunction in schizophrenia (Juckel et al., 2006; Schlagenhauf et al., 2008).

1.4 Dopamine and Glutamate Hypothesis of Schizophrenia

Abnormal dopaminergic neurotransmission plays a crucial role in psychosis. The influential dopamine hypothesis of schizophrenia proposes that heightened dopaminergic neurotransmission in the mesolimbic pathway is associated with positive symptoms of schizophrenia, whereas a decreased dopaminergic function in the mesocortical pathway may be related to negative symptoms (Davis et al., 1991; Howes et al., 2012; Toda and Abi-Dargham, 2007). Initial evidence for a role of dopamine in psychosis came from studies of psychostimulant drugs that trigger release of dopamine and psychosis (Angrist et al., 1974; Harris and Batki, 2000). Furthermore, studies of antipsychotic action on dopamine D2 receptor blockade support the role of dopamine in the pathophysiology of schizophrenia (Seeman et al., 1975).

At present the main treatment for psychosis and schizophrenia is antipsychotic medication based on the blocking properties of D2 dopamine receptors (Seeman, 2002; Snyder, 1981). The first-generation antipsychotic medication introduced in the 1950s (chlorpromazine) was effective to moderate the positive psychotic symptoms but often lead to extrapyramidal side-effects. The new, second-generation, antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) were introduced in the past 15 years aiming to improve the psychotic symptoms, and also the negative and cognitive aspects of the syndrome. This treatment is effective for positive symptoms, however an effective treatment against negative and cognitive symptoms remains subject of research.

Despite treatment with dopaminergic antagonists, many patients with schizophrenia remain chronically impaired. Although the dopamine hypothesis has received much support in the past 50 years, several aspects of schizophrenia (e.g. negative and cognitive symptoms) cannot be ex-
plained based upon dopaminergic dysfunction alone. Moreover, modulation of dopaminergic neurotransmission involves other neurotransmitters and their interactions. The need for alternative explanations has brought us to the glutamate theory of schizophrenia, which is based on the ability of N-methyl-D-aspartate (NMDA) receptor antagonists to induce schizophrenia-like symptoms. Available literature suggests disturbances of NMDA related gene expression in schizophrenia (McCullumsmith et al., 2012; Sodhi et al., 2008). Moreover, dopamine and glutamate interactions in controlling synaptic function have been documented in the hippocampus (Lisman and Otmakhova, 2001) and between glutamatergic afferents and subcortical dopaminergic nuclei (Lisman and Grace, 2005). Increasing evidence has also pointed to a dysfunction of glutamatergic neurotransmission, related to NMDA receptor hypofunction which, accounts for positive and negative symptoms, and cognitive deficits (Soares and Innis, 1999; Zhang et al., 2008). Currently, glutamate receptors are targets for drug research and development based on potential pre- and postsynaptic and glial mechanisms leading to NMDA receptor dysfunction.

### 1.5 Aim and Outline of this Thesis

The overall aim of the studies described in this thesis was to increase our understanding of the neurobiological basis of schizophrenia, including schizophrenia associated with 22q11DS. We investigate several aspects of brain structure and function that may be underlying the vulnerability to schizophrenia. We employed structural MRI, DTI, $^1$H-MRS, fMRI and PhMRI to explore brain structure and white matter integrity, glutamatergic and neurometabolism, and dopamine-related brain function in schizophrenia, 22q11DS and healthy individuals.

*Chapter 1* contains a general introduction of this thesis. In *Chapter 2* we report a DTI study in 22q11DS patients with and without schizophrenia compared to ‘idiopathic’ schizophrenia patients and also compared to healthy controls. Our aim was to enhance our understanding of white matter integrity in adults with 22q11DS and its association with schizo-
phrenia. We explored whether measures of white matter integrity differentiates between patients with 22q11DS with and without schizophrenia. In Chapter 3 we describe a $^{1}$H-MRS study in 22q11DS with and without schizophrenia and healthy controls. We expected glutamatergic abnormalities in people with 22q11DS with schizophrenia since glutamate play a crucial role in schizophrenia. In Chapter 4 we review pharmacological MRI studies with atypical antipsychotic medication providing support for the revised dopamine hypothesis of schizophrenia. In Chapter 5 we report a pharmacological challenge study of the brain reward system in healthy individuals. We investigate the effects of dopamine depletion using fMRI and a monetary incentive delay task. In addition to BOLD contrast we assessed the effect of dopamine depletion on peripheral markers for dopamine. Similarly, in Chapter 6 we investigated the effects of dopamine depletion in schizophrenia and how it would interfere with activation of the brain reward system compared to healthy controls. In Chapter 7 we summarize the findings of the studies of this thesis and discuss implications, limitations and future directions of research.

References


