Brain structure and the relationship with neurocognitive functioning in schizophrenia and bipolar disorder

MRI studies

Cecilie Bhandari Hartberg, M.D.

Division of Mental Health and Addiction, Institute of Clinical Medicine,

Faculty of Medicine, University of Oslo

Oslo, 2011

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1173

ISBN 978-82-8264-038-1

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Unipub.
The thesis is produced by Unipub merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.

Table of contents

Abstract

Brain structural abnormalities as well as neurocognitive dysfunction, are found in schizophrenia and in bipolar disorder. Based on the fact that both brain structure and neurocognitive functioning are significantly heritable and affected in both schizophrenia and bipolar disorder, relationships between them are expected. However, previous studies report inconsistent findings. Also, schizophrenia and bipolar disorder are classified as separate disease entities, but demonstrate overlap with regard to symptomatology and genetic liability. Few studies have directly compared brain structure abnormalities or relationships between brain structure and neurocognitive functioning between the diseases and, it remains unclear if findings are similar or different between patients with schizophrenia or bipolar disorder. The aims of the thesis were 1) to characterize brain structure and the relationships with neurocognitive performance in schizophrenia and bipolar disorder and healthy control subjects and, 2) to investigate these characteristics for differences and similarities between the subject groups.

Two independent subject samples from two similar ongoing research projects at Karolinska Institutet in Sweden (HUBIN) and at the University of Oslo in Norway (TOP), were included. The participants were patients with schizophrenia or bipolar disorder, and healthy control subjects. All subjects were characterized using magnetic resonance imaging (MRI) of the brain and neuropsychological test methods. Brain cortical thickness and surface area measurements, as well as subcortical structure volumes were obtained using automated computer image analysis methods.

Schizophrenia and bipolar disorder type 1 patients demonstrated cortical thinning in overlapping prefrontal and temporo-parietal brain regions compared with healthy controls, and schizophrenia and bipolar disorder patients demonstrated similar findings of subcortical volume abnormalities, compared to healthy controls. The identified abnormalities were more pronounced among schizophrenia patients. Cortical thickness and surface area in predominantly frontal and temporal regions, but also occipital regions, and several of the subcortical structure volumes, were related to neurocognitive performance in both patients and healthy controls. Between-group comparisons showed that some structure/function relationships were specific to schizophrenia and/or bipolar disorder.

In conclusion, the results demonstrate numerous similar brain structure abnormalities in schizophrenia and bipolar disorder, consistent with a common underlying pathophysiology. Mostly similar brain structure/function relationships were found between patients and controls. Few relationships were found to be similar in schizophrenia and bipolar disorder, but different from healthy controls. Consequently, our findings do not indicate that the neurocognitive dysfunction found in both schizophrenia and bipolar disorder have common brain structural correlates. Some disease-specific relationships were found between brain structure and neurocognition, possibly reflecting disruptions in brain regions that contribute to specific cognitive functions and, could be of relevance to the pathophysiology in schizophrenia and bipolar disorder.

List of studies

Study I

Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. Hartberg, C.B., Lawyer, G., Nyman, H., Jonsson, E.G., Haukvik, U.K., Saetre, P., Bjerkan, P.S., Andreassen, O.A., Hall, H. and Agartz, I., 2010. Psychiatry Research. 182, 123-133.

Study II

Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Rimol, L.M., Hartberg, C.B., Nesvag, R., Fennema-Notestine, C., Hagler, D.J., Jr., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, P.H., Melle, I., Andreassen, O.A., Dale, A.M. and Agartz, I., 2010. Biological Psychiatry. 68, 41-50.

Study III

Brain cortical thickness and surface area correlates of neurocognitive performance in patients with schizophrenia, bipolar disorder and healthy control subjects. Hartberg, C.B., Sundet, K, Rimol, L., Haukvik, U., Lange, E., Nesvåg, R., Dale, A.M., Melle, I., Andreassen, O.A, Agartz, I. Submitted.

Study IV

Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls. Hartberg, C.B., Sundet, K, Rimol, L., Haukvik, U., Lange, E., Nesvåg, R., Melle, I., Andreassen, O.A, Agartz, I. Submitted.

Abbreviations

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AP	Antipsychotic
BD I	Bipolar Disorder type 1
BD II	Bipolar Disorder type 2
BDNF	Brain-Derived Neurotrophic Factor
BOLD	Blood-Oxygen-Level dependent
COMT	Catechol-O-Metyltransferase
CNV	Copy Number Variation
CT	Computer Tomography
CVLT-II	California Verbal Learning Test II
D-KEFS	Delis-Kaplan Executive Function System
DTI	Diffusion Tensor Imaging
DSM	Diagnostic and Statistical Manual of Mental Disorders
FDR	False Discovery Rate
FEP	First episode psychosis
FES	First episode schizophrenia
GAF	Global Assessment of Functioning Scale
GLM	General Linear Model
IDS	Inventory of Depressive Symptomatology
HUBIN	Human Brain Informatics
ICD	International Classification of Diseases
ICV	Intracranial volume
MRI	Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
RAVLT	Rey Auditory Verbal Learning Test
RF	Radiofrequency
ROI	Region of interest
SBM	Surface based method
SCID I	Structured Clinical Interview for DSM-IV Axis I disorders
TMT B	Trail Making Test B
TOP	Thematically Organized Psychosis
VBM	Voxel-based morphometry
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
YMRS	Young Mania Rating Scale

Acknowledgements

The work in this thesis was conducted at the University of Oslo in collaboration with Karolinska Institutet, with financial support from the Research Council of Norway, the South-Eastern Norway Regional Health Authority, the Wallenberg Foundation and the Swedish Medical Research Council. The current studies were part of the larger TOP (Thematically Organized Psychosis) and HUBIN (Human Brain Informatics) research studies.

I would like to thank all patients and controls who contributed with their time and effort to the collection of the large amounts of data, making our research possible.

I am also grateful to a number of people who have supported me and who have contributed directly or indirectly to this thesis, including my supervisors, the senior scientists, and all co-authors.

First, I would like to thank my main supervisor, professor Ingrid Agartz for giving me the opportunity to do my PhD under her skilled and patient supervision. Ingrid´s blend of pragmatism and enthusiasm has motivated sustained progress throughout the three years of work. My co-supervisor, professor Kjetil Sundet has contributed with knowledgeable advice on statistical, and more importantly, neuropsychological issues, and in general has been very supportive.

Furthermore, I wish to thank professors Ole Andreassen and Ingrid Melle, who initiated the ongoing and continuously growing TOP study, and who have retained a personal and direct involvement in the separate parts of the study, including this dissertation. I am also grateful to psychiatrist Erik Jönsson and neuropsychologist Håkan Nyman, who generously shared data from the HUBIN study.

From the Institute of Psychiatry at Vinderen, I would especially like to thank Lars Morten Rimol and Glenn Lawyer for invaluable knowledge on advanced neuroimaging processing and analysis, and for including me in their ongoing projects. My fellow PhD students Unn Haukvik and Elisabeth Lange have been my closest colleagues throughout this period of work. Unn´s constant optimism and Elisabeth´s clinical experience have in different ways been especially important for this project. Moreover, I am grateful to Ragnar Nesvåg, Ørjan Bergmann, Petr Bjerkan, Peter Saetre, Merete Øibakken and Martin Furan for close collaboration, and for scientific, practical, and technical assistance beyond what is expected. Also, my appreciation goes to all my

other colleagues at the Institute of Psychiatry at Vinderen for contributing to an inspiring and scientific-minded workplace.

I would like to thank all the people at TOP who have been great fun to work with, in particular Carmen Simonsen, Monica Juuhl-Langseth, Christian Thoresen, Akiah Berg, Beth Barrett, Aina Holmén, Kristin Lie Romm, Trine Vik Lagerberg, Thomas Bjella and Eivind Bakken. Anders Dale contributed with high-quality imaging tools, and has shared valuable expertise with our group. I am grateful to Torgeir Husby at the Department of Psychiatry at Vinderen for the opportunities I have been given with clinical work during and after the writing of this thesis. Thanks to Nargis Bhandari for the careful and time-consuming language editing.

I would like to thank my family members and friends who helped with looking after my children, giving me the extra time I needed to finish this thesis. I look forward to spending more time with my children August, Mikkel and Edvard post PhD. Finally, my deepest gratitude goes to my husband Vemund for his infinite patience, love and flexibility and, for sharing my interest in psychiatry.

1. Introduction

Schizophrenia and bipolar spectrum disorders are severe mental illnesses. Both disorders are ranked among the top ten diseases as leading causes of disability on the WHO global burden of disease report (1998). Schizophrenia was first described as *Dementia Praecox* by the German psychiatrist Emil Kraepelin in 1899 (Kraepelin, 1917). Kraepelin suggested dementia praecox was different from manic-depressive insanity, later known as mood disorders. According to Kraepelin, Dementia Praecox was characterized by early onset of disease with subsequent cognitive deterioration and poor outcome, while manic-depressive disorder was characterized by episodicity and better outcome. Since then the clinical picture, rather than aetiology or pathology defined the disorders. In 1911, the Swiss psychiatrist Bleuler introduced the term schizophrenia (Bleuler, 1950), while the German psychiatrist Karl Leonhard was the first to introduce the term bipolar disorder in 1957 (Goodwin et al., 2007). Although the distinction between the two disorders has been under long time debate, schizophrenia and bipolar disorder are still categorized as separate disease entities defined by symptoms, in the current diagnostic systems, DSM-IV (First, 2002) and ICD-10 (World Health Organization, 1993). The diagnostic criteria in the diagnostic systems are important both for clinical work as well as scientific psychiatric research as they provide common nomenclature and increase objectivity and precision. The debate on disease classification has once again been intensified by the upcoming DSM-V and ICD-11 editions, based on the fact that the disorders have, to some extent, overlapping heredity, pathophysiology, clinical features and cognitive dysfunction.

When this thesis was planned, the two disorders had mainly been studied separately, and the current knowledge on differences and similarities between them was based on comparisons across different methodologies. Few scientific studies had directly compared schizophrenia and bipolar disorder. The main focus in this thesis was the pathophysiological characteristics, i.e. brain structure, and the relationship with cognitive dysfunction, in schizophrenia and bipolar disorder, and the similarities and differences between the disorders. Since the disorders are defined as separate diagnostic entities based on symptoms and clinical course, these areas are introduced separately for the two disorders, whereas other aspects such as neurocognitive functioning, aetiology, neurobiology and brain structure abnormalities are presented together with a focus on shared and unique features. In general, schizophrenia has

been more studied in biological psychiatry than bipolar disorder. Consequently the bulk of studies that are cited are skewed towards schizophrenia.

1.1 Schizophrenia spectrum disorders

Definition

The schizophrenia spectrum disorder group consists of several subtypes (Appendix 1). For the present thesis schizophrenia, schizophreniform disorder and schizoaffective disorder were included and based on the DSM-IV criteria (American Psychiatric Association, 1994). The DSM-IV criteria for a diagnosis of *schizophrenia* include (1) presence of characteristic symptoms such as delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, negative symptoms, i.e., affective flattening, alogia, or avolition. Two or more of the symptoms must have been present for one month. Only one symptom suffices if the delusions are bizarre or the hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices converse with each other. (2) For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset. (3) Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (as described above). In order for the schizophrenia criteria to be fulfilled, the symptoms should not be better accounted for by having schizoaffective disorder or mood disorder or be physiological effects of substance abuse or a medical condition. The relationship to pervasive developmental disorder should be considered.

In *schizophreniform* disorder the signs of the disturbance have been present for more than one month, but less than six months, and functional decline need not be present. All other criteria described for schizophrenia must otherwise be met. In *schizoaffective* disorder, there is either a major depressive episode, manic episode or mixed episode concurrent with the characteristic symptoms in schizophrenia. Furthermore, during the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

In the following these three subtypes will collectively be referred to as "schizophrenia".

Prevalence

Based on systematic reviews, schizophrenia prevalence is estimated to be 0.5-1% (Saha et al., 2005), while incidence rates are 15 / 100000 and might vary according to gender, migration status, urbanicity and latitude (McGrath et al., 2008). A recent report from Denmark estimated the prevalence cumulative incidence to be 1.12% (Gottesman et al., 2010). The prevalence in Norway has been estimated to be 0.15% in Rogaland and 0.25% in Oslo in 1983 (Johannessen, 2002), and 0.4% in Oslo in a study from 2001 (Kringlen et al., 2001). The annual costs directly or indirectly related to schizophrenia in Norway have been estimated to 4 billion kroner in 1995 (Rund, 1995).

Clinical course, treatment and outcome

Illness debut is typically in adolescence or early adulthood, although earlier or later debut is not infrequent. The onset of illness occurs 5-7 years later in women than in men. Prior to onset, a premorbid phase with cognitive and motor abnormalities and a prodromal phase with emerging positive symptoms and declining function are often present. Illness debut is defined by the first psychotic episode. In addition to the symptoms that define the disorder, other psychopathological dimensions exist, such as cognitive, mood and motor symptoms (Tandon et al., 2009). Several psychotic episodes with variable duration typically occur with partial or total remission in between.

The disorder has predominantly been treated with antipsychotic medication during the last decades, supplemented by psychosocial therapy. Since the discovery that Chlorpromazine exerted antipsychotic effect through postsynaptic dopamine D2 blockade in the brain, a range of antipsychotic agents were developed acting on the same receptors (typical antipsychotics). Later, in the 1990s, a second generation of antipsychotic medication was developed, exerting more unspecific monoamine receptor effects, including the dopamine, serotonin and noradrenaline receptors (atypical antipsychotics). Although treatment with antipsychotics (AP) have improved outcome in schizophrenia, mainly positive symptoms are attenuated. Negative symptoms and cognitive impairments are only improved to a small or moderate degree (Woodward et al., 2005). In addition to treatment with antipsychotic medication, psychosocial treatment and cognitive remediation programs have been

developed. Both have shown promising effects on negative symptoms and cognitive functioning (McGurk et al., 2007;Pilling et al., 2002).

However, despite available treatment, the course of illness is heterogeneous, and both chronicity and recovery (6-17%) (Lauronen et al., 2005) may occur as the extreme outcomes of course progression. Statistically, patients with schizophrenia exhibit increased mortality (Brown, 1997), increased suicide risk (Barrett et al., 2010) and increased risk for co-morbid medical illnesses (Heiskanen et al., 2003) compared to the healthy population.

1.2 Bipolar spectrum disorders

Definition

The bipolar spectrum disorder group also consists of several subtypes (Appendix 1). For the present thesis bipolar disorder type 1 and 2 were included and based on the DSM-IV criteria (American Psychiatric Association, 1994). The DSM-IV criteria for a diagnosis of *bipolar disorder type 1* (BD I) include the occurrence of one or more manic episodes or mixed episodes, while for *bipolar disorder type 2* (BD II) these include the occurrence of one or more major depressive episodes accompanied by at least one hypomanic episode. A *major depressive episode* is defined by specifically described symptoms that have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Also, the symptoms cause distress or functional impairment, and are not better accounted for by bereavement. A *manic* or *hypomanic episode* is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week or 4 days respectively, accompanied by specifically described symptoms. In mania, the severity of symptoms cause marked impairment in functioning or necessitate hospitalization to prevent harm to self or others or, there are psychotic features. In hypomania the episode is associated with change in functioning, and together with symptoms, these disturbances are observable by others. Unlike mania, no marked functional decline or psychotic features are present. In order to fulfil the criteria for a bipolar disorder, none of the mood episodes must be caused or be better accounted for by physiological effects of substance abuse or a medical condition.

In the following bipolar disorder type 1 and 2 will collectively be referred to as "bipolar disorder".

Prevalence

The lifetime prevalence of bipolar disorder is 1% for BD I and 1-2% for BD II (Goodwin et al., 2007). The prevalence of BD is usually stated to be relatively consistent across cultures and regions. However, prevalence rates vary from 0.1 - 1.8% for BD I, and 0.3 - 3.0% for BD II (Angst, 1998;Sherazi et al., 2006;Weissman et al., 1996). In the Danish study by Gottesman *et al.* (2010) rates were estimated to be 0.63%. A Norwegian study reported life time prevalence to be 1.6% in Oslo (Kringlen et al., 2001).

Clinical course, treatment and outcome

Illness debut for bipolar disorder is typically in young adulthood (Goodwin et al., 2007;Larsson et al., 2010). During the course of illness, patients with bipolar disorder experience multiple affective episodes, the depressive episodes being longer than the manic episodes. Furthermore, there are sub-syndromal affective symptoms (Joffe et al., 2004) and cognitive impairment between episodes (Bora et al., 2009). But, as in schizophrenia, the individual illness course is variable with respect to frequency and duration of illness episodes (Salvatore et al., 2007). Symptoms are treated with mood-stabilizing medication, such as lithium, antiepileptics or atypical antipsychotics. Medication treatment is used for prevention of new episodes. However, 75% still relapse during the first five years (Gitlin et al., 1995). Adjuvant psychotherapy, such as psychoeducative treatment has proven helpful (Colom et al., 2003).

Bipolar patients may recover or as in schizophrenia exhibit a chronic course. Psychosocial functioning is often impaired even when full recovery is sustained (Coryell et al., 1993), and there is increased risk for co-morbid somatic disorders, suicide increased mortality rates (Khalsa et al., 2008) and shorter life span (McIntyre et al., 2007;Osby et al., 2001).

1.3 Neurocognitive functioning in schizophrenia and bipolar disorder

Neuropsychological tests are specifically designed tasks used to measure cognitive function in clinical groups. ***Neurocognitive*** *functioning* is a relatively new term used in research to describe cognitive functions presumably linked to the function of particular brain areas, neural pathways, or cortical networks in the brain. The terms cognitive and neurocognitive will be used interchangeably in the following.

Cognitive decline in schizophrenia was described by Kraepelin but defied by Bleuler. Bleuler proposed that cognitive symptoms were subordinate of other symptoms and

the absence of cognition in the current diagnostic disease criteria reflect these views. Later however, general intellectual deficits in chronic schizophrenia were demonstrated by Johnstone *et al.* (1978), who also suggested that the cognitive dysfunction was primary and not secondary to institutionalization or symptoms of the disease. Since then, a growing interest in the field and acknowledgment of its importance has emerged. Reviews and meta-analyses report neurocognitive dysfunction with large effect sizes in schizophrenia across neurocognitive domains (Dickinson et al., 2007;Heinrichs and Zakzanis, 1998), and neurocognitive dysfunction seems to represent an independent feature of the disease, although associations with negative symptoms have been shown (Nieuwenstein et al., 2001). In general, the pattern of neurocognitive dysfunction in bipolar disorder is similar to the neurocognitive profile of schizophrenia (Barch, 2009). Although impairment may be somewhat state dependent in bipolar disorder (Kurtz and Gerraty, 2009), a number of recent meta-analyses have reported neurocognitive dysfunction in bipolar disorder patients in the euthymic phase (Bora et al., 2009;Robinson et al., 2006). So far dysfunction is found to be more pervasive in schizophrenia than in bipolar disorder (Heinrichs, 2005;Krabbendam et al., 2005), but cognitive dysfunction has been related to functional outcome in both disorders (Green, 2006). The first-degree relatives of schizophrenia and bipolar disorder patients show similar cognitive dysfunction; although the abnormalities are less salient, this finding supports the heritability of cognitive dysfunction (Bora et al., 2009;Snitz et al., 2006). In general, neurocognitive dysfunction in all domains remain stable over the course of schizophrenia (Kurtz, 2005;Rund, 1998), whereas deficits in attention and executive function seem to be maintained over time in bipolar disorder (Burdick et al., 2006;Mur et al., 2008) and may even worsen as the disease progresses (Robinson and Ferrier, 2006). The effect of medication on neurocognition in schizophrenia and bipolar disorder is considered to be small to moderate (Balanza-Martinez et al., 2010;Mishara and Goldberg, 2004), but findings are inconclusive (Hill et al., 2010). In sum, neurocognitive dysfunction is consistently found in both schizophrenia and bipolar disorder and largely appears to be trait rather than state dependent. Furthermore, neurocognitive dysfunction is observed over the course of illness despite fluctuations in symptom severity and use of medication, and has been suggested to represent a core feature in both disorders.

1.4 Aetiology and neurobiology

The neurodevelopmental model has for several decades been posited and gained support as an explanatory model for schizophrenia. In this model, aberrations in

neurodevelopmental processes begin long before the onset of symptoms, and are caused by a combination of environmental and genetic factors (Murray and Lewis, 1987;Weinberger, 1987). Putative neurodevelopmental factors in bipolar disorder are less studied and hence, are more uncertain (Murray et al., 2004;Sanches et al., 2008). Despite great scientific effort, no single cause or determining factor has been discovered in either schizophrenia or bipolar disorder, but specific genetic and environmental risk factors, and gene-environmental interactions have been proposed as results from research.

1.4.1 Genetic risk factors

Twin-studies and epidemiological studies have estimated heritability to be 60-80% in schizophrenia and bipolar disorder (Cardno et al., 1999;Lichtenstein et al., 2009;Sullivan et al., 2003). Until recently, there was no evidence for the increased risk of one disorder among relatives of the other disorder (Berrettini, 2001), but the large-scale epidemiological study by Lichtenstein *et al.* (2009) involving 9 million Swedish subjects suggested shared and distinct genetic liability for the two disorders. Linkage studies have proposed shared genetic susceptibility loci for schizophrenia and bipolar disorder, but findings are inconclusive (Berrettini, 2001). Association studies have proposed candidate genes in both disorders, such as G72/G30 (Chumakov et al., 2002;Hattori et al., 2003;Maier et al., 2005), as has BDNF (Neves-Pereira et al., 2002;Rosa et al., 2006), and the so-called zinc-finger gene, ZNF804A (Williams et al., 2010). Similarly, the catechol-O-methyltransferase (COMT) gene which controls the breakdown of dopamine in the frontal cortex (Egan et al., 2001) has been reported to be weakly associated with schizophrenia (Kunugi et al., 1997;Shifman et al., 2002) and bipolar disorder (Shifman et al., 2004) and to modulate bipolar disorder, increasing the likelihood of rapid cycling (Kirov et al., 1998). Finally, rare copy number variants (CNVs) may account for some of the cases at least for schizophrenia (Stefansson et al., 2008).

1.4.2 Environmental risk factors

Both schizophrenia and bipolar disorder have been associated with various environmental factors; substance misuse (Henquet et al., 2005;Henquet et al., 2006), prenatal factors (Brown et al., 2000;Susser et al., 1996), negative life events and childhood trauma (van Os et al., 1998). Others may be more specific for schizophrenia, such as advanced paternal age (Dalman and Allebeck, 2002), specific infectious diseases, notably winter/spring birth and urbanicity (Mortensen et al., 2003).

On the background of shared genetic liability different clinical manifestations in schizophrenia and bipolar disorder might be due to different environmental influences on the same or a single genotype (Benes, 2007) or additional genes (for example, genes involved in neurodevelopment) may then act, or interact, upon this background.

1.4.3 Neurobiological findings

In addition to the clinical characteristics that define the diseases, both schizophrenia and bipolar disorder are characterized by neurobiological abnormalities. Neurobiological studies have revealed neurotransmittor abnormalities, neurophysiological abnormalities, neuropathological alterations and structural and functional imaging abnormalities. In the following, topics that are relevant to the studies of the present thesis will be presented with an emphasis on brain structure abnormalities.

Neurotransmittors

Both dopamine and glutamate disturbances have been implicated in the pathophysiology in schizophrenia and bipolar disorder (Keshavan et al., 2008;Stone and Pilowsky, 2006). Both disorders are treated with dopaminergic D2 antagonistic drugs, which ameliorate positive psychotic and manic symptoms, while dopamine agonists may induce psychotic symptoms. Also, manipulation of dopamine D1 receptors have been found to affect cognitive functions known to be impaired in schizophrenia and bipolar disorder, i.e., working memory (Abi-Dargham et al., 2002). It was recently proposed that schizophrenia was characterized by striatal hyperdopaminergic and prefrontal hypodopaminergic levels (Howes and Kapur, 2009). The dopamine mechanism in bipolar disorder has been less investigated, but region-specific increase in dopamine activity may account for some parts of the pathophysiology (Cousins et al., 2009).

Glutamate involvement is suggested based on the fact that NMDA receptor antagonists such as ketamine produce psychotic and cognitive symptoms resembling those found in schizophrenia (Moghaddam, 2003). Furthermore, genetic studies in both schizophrenia and bipolar disorder have implicated glutamate receptor genes (GRIN1, GRIN2A, GRIN2B and GRIK3), metabotropic glutamate receptor genes (such as GRM3), the G72/G30 locus and GABAergic genes (e.g. GAD1 and GABRB2) to varying degrees (Cherlyn et al., 2010). Research to develop glutamate-related antipsychotic medication has been initiated, but the results from this research have thus far not proven to be

effective.

In addition to dopamine and glutamate, other neurotransmitters, such as serotonin, acetylcholine and adrenaline have been implicated in severe mental diseases.

1.5 Neuroimaging

Neuroimaging methods include a variety of techniques that all image the structure or function of the brain in vivo. Imaging of brain *structure* was originally made available from x-ray images. These provided an image of the ventricular system of the brain, which had been directly or indirectly filled with air (pneumoencephalography) (Jacobi and Winkler, 1927). Computer Tomography (CT) was introduced in the 1970's and allowed for non-invasive detailed visualization of brain anatomy. This method involves potentially harmful amounts of ionizing radiation, while magnetism is currently believed to be safe for humans. Magnetic resonance imaging (MRI) became available in the 1980's and offered the advantages of allowing for excellent grey and white matter contrast resolution in cortical and subcortical regions, and it permitted imaging of structures not readily visible on CT, such as the cerebellum and certain temporal lobe structures, both of which are of interest in schizophrenia and bipolar disorder studies. Thus, MRI is the preferred neuroimaging technique for the study of brain grey and white matter abnormalities in severe mental diseases, as was the topic for this thesis.

1.5.1 Magnetic Resonance Imaging

The MRI method is based on the principle that different tissue types have different magnetic properties (Weishaupt et al., 2006). Some atomic nuclei, such as the hydrogen nucleus exhibit spin around their own axis. The hydrogen atom is abundant in body tissue as part of the water molecule (H_2O) and fat (carbon, oxygen and hydrogen atoms). The spin of its solitary proton gives a relatively large magnetic moment. In a normal environment, the magnetic moments of these protons point in random direction. When placed in a magnetic field, the protons line up with the magnetic field called alignment, either parallel with, or in the opposite direction of, the main field. Most are aligned in a parallel manner. Thus the net magnetization vector is parallel to the external field. In addition to the proton's spin around its own axis, the magnetic field causes a secondary spin, the recession, in a circular manner around the main field. The precession frequency or larmor (ω_0) is the rate at which spins wobble when placed in a magnetic field.

$\omega_0 = B_0 \times \lambda$

λ is constant and related to type of atomic nucleus. Thus the precession frequency is directly proportional to the strength of the magnetic field, B_0, which is measured in the unit Tesla (T). By applying radiofrequency (RF) pulse at the same frequency as the precession frequency of the MR active hydrogen nuclei, *resonance* occurs; the hydrogen nuclei absorb energy applied at 90^0 from the RF (excitation) causing the net magnetization vector to change direction compared to the external field, which is called a *flip angle*. The net magnetic vector in transverse plane induces a voltage in a receiver coil situated in this plane. When the RF pulse is removed, the voltage amplitude induced in the receiver coil decreases and is called free induction decay, which is a detectable signal. Through spatial encoding the signal is digitized and stored in K space. The 2-dimensional image consists of pixels which have each been allocated signal intensity. When slice thickness is considered, the 3-dimensional voxels are produced.

The resulting high and low signals result in different contrasts in the MR images, but can be controlled by extrinsic contrast parameters. Biological tissue features also contribute to signal intensity. Depending of which of these are emphasized in an MR sequence, the resulting images differ in their tissue-tissue contrast. On T1 weighted images, fatty tissue appears bright (high signal), whereas tissue containing a high proportion of water appear dark (low signal). T1 weighted images, which were used in the present studies, are best for depicting anatomy.

1.5.2 MRI and image processing

In order to obtain measures of brain structure from MRI scans (morphometry) different quantitative techniques are used. Most studies have used regions-of-interests (ROI) or computational morphometry approaches. In ROI analyses, discrete brain regions are obtained either by manual tracing on MRI scans or by semi-automated or automated processes. However, ROI methods are time-consuming and often limit the number of structures to be studied and, are subjected to bias. In computational morphometry, software programs automatically measure brain structure characteristics with a minimum of manual corrections, thus allowing for unbiased analyses of large datasets with high precision and whole-brain assessments. A widely used technique is voxel-based morphometry (VBM), which measures whole brain volumes on a voxel-by-voxel (commonly 1 mm^3) basis (Ashburner and Friston, 2000). More recently, Diffusion-Tensor-Imaging (DTI) techniques have been developed that measure macroscopic structural integrity of white matter bundles in the brain (Agartz

et al., 2001). Functional MRI (fMRI), in addition to electrophysiological studies, MR spectroscopy, and PET/SPECT are used to measure brain function (Malhi and Lagopoulos, 2008). In fact, the BOLD (Blood-Oxygen-Level dependent) - fMRI method is currently a more widely used method for investigating neural correlates of neurocognitive function than structural MRI measurements. However, given the variability in brain structure and neurocognitive functioning both in healthy individuals and in subjects with psychiatric disorders, and the interrelationship between functional and structural measurements on MRI (Lu et al., 2009), structural MRI complement the results from functional MRI studies in order to achieve a better understanding of the neurobiological foundation for disease-related cognitive changes (Fjell and Walhovd, 2010).

1.6 Brain structure

1.6.1 Development

During the first weeks of foetal life, the neural tube forms from the folding and fusion of the ectoderm (neurulation). The neural tube then folds into three primary brain vesicles, the most rostral part forms the telencephalon, which later forms into e.g. the cerebral cortex, hippocampus, amygdala, basal nuclei and lateral ventricles, and the diencephalon, which later forms into e.g. thalamus and the third ventricle. The most caudal part forms into the cerebellum and the brainstem (Brodal, 2007). Extensive neuronal proliferation begins on embryonal day 40 within the ventricular zone that lines the cerebral ventricles (Rakic, 1988). Depending on the neuroblasts position, they differentiate to either neuronal cell types or microglia, and then migrate out to form cortical laminae in an inside- and -out manner, meaning that deeper layers are formed before more superficial ones. Most neurons travel along radial glia cells that serve as paths to the final destination. By week 32, the developing cortex has a full adult complement of distinct vertical lamina. Some neurons originate and migrate from the basal ganglia. The neuronal migration continues until birth. Processes such as apoptosis (programmed cell death), synaptogenesis and myelination start before birth. Synaptogenesis ends by adolescence, while myelination ends in early adulthood. When the neurons have reached their final destination synapses (neuronal connections) start to form. The connections are under continuous refinement and modification forming later mature synaptic connections that are believed to underlie neural circuits. During childhood and adolescence, maturational pruning is observed as reduced synaptic density and reflect a selective elimination of weaker synaptic processes based on

experience and endogenic factors (Huttenlocher, 1979;McGlashan and Hoffman, 2000).

According to the "radial unit hypothesis" (Rakic, 1988), neurons originating within individual proliferative units in the ventricular zone, form ontogenetic columns within specific cytoarchitectonic areas. It is hypothesized that cortical surface area reflect the number of columns within a given region, and results from the number of proliferative units within the ventricular zone, whereas cortical thickness reflects the number of neurons within each cortical column and results from the number of cell-divisions within each unit. Thus, cortical thickness and surface area are products of two well-differentiated ontogenetic processes and the two parameters can therefore separately be affected by genetic defects or extrinsic factors (Rakic, 1988). One study on adolescent first-degree relatives of schizophrenia patients demonstrated reduction in surface area, along with only a slight increase in cortical thickness in a one-year follow-up study, suggesting different neurodevelopmental trajectories (Prasad et al., 2010). As such, demonstrations of separate abnormalities in cortical thickness and surface area measures could depict more detailed deviations than cortical volume, which is the product of the two, from normal brain development. Furthermore, it is believed that humans have experienced the increase in cortical surface size in evolutionary response to demands in the cognitive requirements (Rushton and Ankney, 2009), supported by consistent reports of positive correlations between whole-brain size and measures of intelligence (Witelson et al., 2006). Thus, if schizophrenia, and bipolar disorder to some extent, are neurodevelopmental disorders in which disruption of higher cognitive functioning is a core feature, abnormalities in normal cortical surface development may play a role in the pathophysiology of the diseases and, hence show disrupted relationships with neurocognitive performance.

1.6.2 Heritability

Heritability has been shown to be substantial for brain structure volumes (Peper et al., 2007;Wallace et al., 2006), with higher heritability scores for the deeper structures (ontogenetically earlier formed), and moderate heritability scores for the surface structures measured in volumes (Kaymaz and van Os, 2009). Heritability estimates for cortical thickness are significant but vary according to brain regions (Kremen et al., 2010;Rimol et al., 2010). Moreover, total and regional cortical thickness and surface area have been shown to be highly heritable in a twin study, but were essentially unrelated genetically (Panizzon et al., 2009), suggesting different genetic sources of influence. Interestingly, in a study of schizophrenia and bipolar probands and their

unaffected relatives (McIntosh et al., 2006), genetic liability to schizophrenia was related to brain structure abnormalities, which was not the case for bipolar disorder.

1.7 Brain structure abnormalities in schizophrenia and bipolar disorder

1.7.1 MRI studies

In view of the fact that anatomical MRI is the topic of the present thesis, the following neuroimaging overview is restricted to sMRI studies (based on search in Pubmed until March 2010).

Global brain volume and cortical regions

Global brain volume reduction has been estimated to 2-4% in schizophrenia (Steen et al., 2006;Wright et al., 2000), while results in bipolar disorder are more heterogeneous. One meta-analysis by Hoge *et al.* (1999) did not find whole brain volume loss in bipolar disorder supported by negative findings in a meta-analysis on first-episode subjects (Vita et al., 2009). However, a more recent meta-analysis reported a small, but significant whole-brain reduction in bipolar disorder (Arnone et al., 2009). In addition to reduced whole brain volumes, regional grey matter reductions have been demonstrated in both disorders (Arnone et al., 2009), but the reductions in schizophrenia appear more extensive both in pattern and magnitude compared with bipolar disorder. In schizophrenia, the most consistently reported volume reductions are in the superior temporal gyrus and the medial temporal regions (Honea et al., 2005), bilateral insula and anterior cingulate (Ellison-Wright et al., 2008;Fornito et al., 2009b), while for bipolar disorder left anterior cingulate and right insula reductions have been implicated across studies (Bora et al., 2010).

Although the meta-analyses suggest temporal lobe abnormalities to be specific to schizophrenia, studies that have made direct comparisons of cortical structure between schizophrenia and bipolar subjects have demonstrated similarities in temporal lobe volumes (Kasai et al., 2003b;Pearlson et al., 1997). However, these are few and limited by small sample sizes (Farrow et al., 2005;Lim et al., 1999), and have mainly investigated specific regions (Altshuler et al., 2000;Nakamura et al., 2007;Rossi et al., 1991). Two VBM studies have included both schizophrenia and bipolar disorder patients. McIntosh *et al.* (2004) found reduced middle frontal gyrus volume specifically in schizophrenia. However, this study did not directly compare between patient groups, but only reported comparisons with the healthy control group. A second study

(Morgan et al., 2007), compared cortical volumes in first-episode patients with schizophrenia and affective psychosis (including depressive psychosis) and found smaller bilateral anterior cingulate volumes in the affective psychosis group, compared with the schizophrenia group. However, the results in the affective psychosis group did not remain significant when antipsychotic medication was statistically controlled for. Thus, it remains elusive whether the observed brain volume abnormalities in schizophrenia and bipolar disorder are specific to either disorder.

Cortical thickness studies have demonstrated thinning in predominantly frontal and temporal regions in schizophrenia, although regional parietal and occipital thinning has also been found (Goldman et al., 2009;Kuperberg et al., 2003;Nesvag et al., 2008). Regional cortical surface area has been shown to be reduced in first-episode schizophrenia (FES) patients (Gutierrez-Galve et al., 2010) and in drug-naïve schizophrenia subjects (Crespo-Facorro et al., 2000), relative to healthy controls. The latter study demonstrated surface reduction without cortical volume differences, suggesting that surface based methods may be more sensitive to subtle cortical abnormalities than volumetric methods.

Only one study has explored whole-brain cortical thickness in bipolar disorder (Lyoo et al., 2006), and reported scattered regional thinning in frontal, temporal, parietal and occipital regions in bipolar disorder subjects, as compared with healthy controls. Other studies have examined cortical thickness in ROIs and reported cortical thinning in paracingulate regions (Fornito et al., 2008) and increased thickness in right anterior cingulate (Fornito et al., 2009c) in bipolar I disorder.

Subcortical regions

Ventricular enlargements are the most consistent findings common to both schizophrenia (Shenton et al., 2001), and bipolar disorder (Kempton et al., 2008;McDonald et al., 2004), with more extensive enlargements in schizophrenia. Enlarged striatal structures are also reported in both disorders (Brandt and Bonelli, 2008;Strakowski et al., 2005). However, the observed abnormalities may be confounded by use of antipsychotic medication (Navari and Dazzan, 2009). Reviews report hippocampal (Steen et al., 2006), amygdala (Shenton et al., 2001) and thalamic (Ellison-Wright and Bullmore, 2010) volume reductions to be consistent in schizophrenia, but not in bipolar disorder (Ellison-Wright and Bullmore, 2010), compared with healthy controls. One study that directly compared schizophrenia and

bipolar patients found smaller hippocampus in schizophrenia and larger amygdala in bipolar disorder (Altshuler et al., 2000). A specific focus on amygdala as an important brain structure in the neurobiology of bipolar disorder has not yielded consistent findings (Brambilla et al., 2008), which may be due to differences in age and lithium-use across studies (Usher et al., 2010a;Usher et al., 2010b).

There are reports of progressive ventricular enlargements (DeLisi et al., 2004;Kempton et al., 2010) and reductions in frontal (Zipparo et al., 2008) and temporal grey matter volumes (Hulshoff Pol and Kahn, 2008) in schizophrenia. Ventricular enlargement progression appears to continue in chronic stages (Kempton et al., 2010), while grey matter reductions may be more pronounced the first few years after disease onset (Kasai et al., 2003a;Yoshida et al., 2009). The study by Kasai *et al.*, found no progression in the early phases of affective disorder, and suggested progression to be specific to schizophrenia. However, progressive grey matter reductions in BD I patients have been demonstrated by others (Moorhead et al., 2007) and has been related to number of affective episodes (Strakowski et al., 2005).

1.7.2 Neuropathological post-mortem findings

The evidence from macroscopic post-mortem studies is largely consistent with *in vivo* MRI studies of patients with schizophrenia; reduced total brain volume, increased ventricular volumes and reduced size of temporal lobe and subcortical structure volumes have been found (Harrison, 1999), although not consistently. Of greater interest, however, are the microscopic findings that are undetectable with the current MRI scan resolution. Histological studies have not found overall neuron loss or gliosis (as signs of injury) in the brains of schizophrenia patients, in contrast with the findings in neurodegenerative disorders, and are consequently taken as support for the neurodevelopmental model of schizophrenia. Reductions in neuronal size and neuronal arborisation, and increased neuronal density in Brodmann areas 9 and 46 in the frontal lobe are reported, as well as trends for reduced cortical thickness (Selemon et al., 1995;Selemon et al., 1998). Interestingly, specific reductions of one layer (V) has been found, from which neuronal efferents project to subcortical structures (Brodal, 2007), possibly affecting communication with grey matter structures deeper within the brain. The observed cortical grey matter loss in schizophrenia has been proposed to be due to loss of neuropil, i.e., reduced glial cells and synaptic and dendritic arbors and reduced vascularization, as a result of exacerbated pruning during adolescence.

Similarly, reductions in neuronal size have been demonstrated in frontal brain regions in bipolar disorder. However, these findings are accompanied by a decrease in cortical density (Harrison, 2002), suggesting cytoarchitectural differences between schizophrenia and bipolar disorder (Rajkowska et al., 2001).

In summary, structural brain abnormalities are to a certain extent overlapping in schizophrenia and bipolar disorder, but appear more pronounced in schizophrenia than in bipolar disorder. However, compared to schizophrenia, structural brain abnormalities in bipolar disorder are less studied and the existing studies are possibly underpowered to detect the subtle abnormalities that may be present. Also, few direct comparisons have been made. Thus, larger studies that include both patient groups and directly compare between groups that are investigated with the same methodology are essential. The previous literature furthermore suggests that BD I patients may demonstrate similar abnormalities to schizophrenia patients, and that some brain abnormalities progress with age or illness duration. Therefore, separate analyses of within-spectrum subgroups, and individual differences in age and illness duration should be considered.

1.8 Brain structure relationships with neurocognitive functioning in schizophrenia and bipolar disorder

The idea that different brain functions are localized to discrete regions of the brain was originally described in 19th century by Gall and Spurzheim, who developed theories of phrenology (Gall and Spurzheim, 1808). Supporting the separation of brain functioning, Broca (1861) and Wernicke (1874) later discovered localized regions involved in language formation and comprehension through lesion studies on subjects with language difficulties, while around 1875, Hughlings Jackson proposed topographic representation of the cerebral cortex based on his studies on the complexity of epileptic seizures (Taylor, 1932). In contrast, Flourens did lesional work in animals, and found that any lesion anywhere produced altered behaviour consistent with the theory that general structure integrity or brain networks underlie cognitive function (Flourens, 1846). Today´s cortical regional classification is partly based on cytoarchitectonic differences, that is, regional differences in cellular organization first described by Brodmann (Brodmann, 1909). Later scientific work has shown that integrity of both general and specific brain structures is important for brain function.

1.8.1 Theoretical relationships

The notion that regional or localized structural deficits or abnormalities may relate to the cognitive dysfunction observed in schizophrenia and bipolar disorder may seem over-simplistic. However, specific relationships are hypothetically expected based on the following assumptions: 1) that brain tissue is altered in size in severe mental illness, 2) that neurocognitive functioning is impaired in severe mental illness and, 3) that neurocognitive functioning requires intact brain structures. The assumptions 1) and 2) were considered in the above sections and are present in schizophrenia and bipolar disorder. With regard to the third assumption, previous studies have demonstrated positive relationships between neurocognitive functions and regional brain structure as measured as cortical thickness in MRI-based studies of healthy adults (Dickerson et al., 2008;Fornito et al., 2004;Narr et al., 2007;Walhovd et al., 2006), as well as dysfunction in individuals with focal brain lesions (Stuss et al., 2001a;Stuss et al., 2001b). These findings suggest that regional brain structure integrity is important for cognitive performance, and that individual differences in regional brain structure measures, account for considerable variance in individual differences in neurocognitive functioning (Haier et al., 2004). Several theories have been introduced to explain how regional or discrete brain structures contribute to cognitive function in general, and how regionally constrained brain abnormalities, may lead to dysfunction in severe mental illnesses.

Separate brain regions are engaged in forming networks. Brain studies on animals have mapped structures that are anatomically connected to form parallel networks that underlie cognitive functioning (Goldman-Rakic, 1988). Furthermore, these networks form patterns of structural connections where specific regions or structures may function as nodes, or play a central role in specific cognitive functioning. The different nodes communicate through network activity, and may thus overlap with functional networks (Haier et al., 2004;Lu et al., 2009). It is not known whether these patterns or networks are stable or have high plasticity, but changes have been observed related to disease, ageing or experience, suggesting that communications may be altered.

In support of disrupted network communication in diseases, neuropathological studies have reported reduced neuronal arborization (Selemon and Goldman-Rakic, 1999), reduced synaptic function (McGlashan and Hoffman, 2000) and reduced connectivity

in distal dendritic processes (Kalus et al., 2000) in the presence of preserved neuron number in schizophrenia.

Similarly, Friston and Frith (1995) proposed that abnormal integration of physiological processes in diverse cortical regions lead to disrupted connectivity ("disconnectivity"), that in turn results in cognitive dysfunction in schizophrenia. Indeed, disrupted connectivity in schizophrenia and bipolar disorder has been demonstrated in fMRI studies (Wolf et al., 2007) or DTI studies (Ellison-Wright and Bullmore, 2009;Kyriakopoulos and Frangou, 2009;Mahon et al., 2010;White et al., 2007). Furthermore, one DTI study (Nestor et al., 2004) showed that neurocognitive functioning was correlated with impaired connectivity in schizophrenia patients, but not in healthy controls. Andreasen *et al.* (1998) extended the disconnectivity hypothesis to involve subcortical structures, and suggested that "Cognitive Dysmetria" or poor mental coordination resulted from disrupted connectivity between frontal lobe regions, thalamic nuclei and the cerebellum. Whereas Weinberger *et al.* (1992) proposed that fronto-temporolimbic (including the hippocampus) network dysfunction was related to cognitive dysfunction in schizophrenia. There is also evidence that other subcortical structures, such as the basal ganglia play a modulatory role in cognitive functioning (Graybiel, 2000;Simpson et al., 2010), and that "cognitive disorganization" in both mania and schizophrenia results from disruptions in prefronto-striato-pallido-thalamo-cortical loops.

Five separate loops or closed circuits appear to exist (Alexander et al., 1986), of which three involve non-motor cortical regions originating in the frontal cortical lobe, and all three are thought to be involved in cognitive processes.[1]

Although the loops are separate and organized in a parallel manner, there is a convergence of information at several levels. Hypothetically, structural deficits in any part of the circuits may affect cognition.

[1] 1) The dorsolateral prefrontal circuit originates from the cortical regions corresponding to Brodmann area 9 and 10. Neuronal connections project to caudatus nucleus, and then via substantia nigra to thalamus, then back to the originating cortical regions. The dorsolateral prefrontal circuit allows for organization of goal directed behaviour and has been linked with executive function. 2) The anterior cingulate circuit originates in the Brodmann area 24. Neurons project to caudate, putamen, nucleus accumbens and the olfactory tubercle, then via pallidum and substantia nigra, and then to thalamus, before projecting back to the anterior cingulate. The anterior cingulate circuit has been linked to apathetic behaviour. 3) The orbitofrontal circuit originates in the Brodmann regions 10, 11 and 47. Neurons projects to the caudate, via the pallidum and substantia nigra to thalamus and back to the same region. This circuit has been found to integrate limbic and emotional information into behaviour.

1.8.2 Empirical relationships

Kraepelin proposed that the observed cognitive dysfunction in dementia praecox was related to abnormal brain function, but at the time there were limited ways of investigating neural correlates of brain function. With the advent of neuroimaging in general, and MRI in particular, the possibility to investigate the relationship between brain structure and function was greatly facilitated. Johnstone *et al.* (1976;1978) demonstrated that enlarged ventricular size measured with CT was associated with intellectual impairment in chronic schizophrenia. Since the onset of MRI scanning in the 1980's and 90's, a large number of scientific studies have attempted to determine the relationships between brain structure and neurocognitive functioning in schizophrenia. Most studies have been ROI based and investigated regional volumes that were abnormal in schizophrenia as compared to healthy controls in order to investigate the clinical (or cognitive) significance of the structural abnormalities.

Cortical regions

Antonova *et al.* (2004) summarized the results from 35 ROI studies on schizophrenia published in the period from 1991 to 2005. This review reported regional frontal lobe volumes to be related to executive functioning, attention, verbal and visual memory in schizophrenia. Lateral regions of the temporal lobe were related to verbal abilities and executive functioning, while the medial temporal lobe structures were related to memory functions. There were some differences in relationship patterns between schizophrenia patients and healthy controls, which the authors in part related to gender differences. Among all studies in the review, only one study investigated posterior brain regions; Sullivan *et al.* (1996) included parietal and occipital lobe volumes when investigating relationships with several cognitive domains, and reported negative findings. Subsequent VBM studies have allowed for whole-brain analyses that are not restricted to predefined regions, and have reported highly localized relationships. VBM studies on schizophrenia patients have related larger precuneus volume to better verbal learning (Antonova et al., 2005), smaller orbitofrontal volume to poorer verbal learning (Matsui et al., 2008), smaller superior frontal (Bonilha et al., 2008), and dorsolateral prefrontal cortical and anterior cingulate volumes to poorer executive functioning (Rusch et al., 2007).

In bipolar disorder, frontal lobe volumes have been related to general cognitive dysfunction (Coffman et al., 1990) and attention (Sax et al., 1999) in two ROI studies, but in general, there has been a paucity of studies on structure/function in bipolar

disorder (Bearden et al., 2001). More recently, one VBM study related lateral and medial temporal lobe structures as measured with magnetization transfer imaging, to estimated IQ decline (Bruno et al., 2006), while in an ROI study (Zimmerman et al., 2006), relationships between anterior cingulate volumes and executive functioning in healthy controls subjects were found to be disrupted in bipolar disorder. A study that included both affective and schizophrenic first-episode psychosis patients (Minatogawa-Chang et al., 2009), found relationships between volumes of the left inferior frontal region and working memory in the schizophrenia group, but not in the affective psychosis group.

Subcortical regions

In schizophrenia, hippocampus and amygdala volumes (Goldberg et al., 1994;Gur et al., 2000;Killgore et al., 2009), and cerebellar volumes (Toulopoulou et al., 2004) have been related to performance on memory tasks. Striatal (Mamah et al., 2007;Stratta et al., 1997) and thalamic volumes (Crespo-Facorro et al., 2007b) have been related to executive functioning and attention. Caudate volumes have been related to motor speed (Hokama et al., 1995). Ventricular size has been related to impaired flexibility and attention (Antonova et al., 2004), and executive functioning, visuomotor speed and verbal IQ (Lawyer et al., 2006). Only a few studies have addressed such relationships in bipolar disorder patients; hippocampal volumes have been related to measures of attention (Sax et al., 1999), verbal fluency and verbal working memory (Ali et al., 2000), while others have reported negative findings (Haldane et al., 2008). In a direct comparison of patients with schizophrenia or bipolar disorder, Killgore *et al.* (2009) demonstrated opposite relationships between amygdala volumes and verbal memory performance between schizophrenia and bipolar disorder.

1.9 Synopsis and introduction to aims

To summarize the previous sections, the literature hitherto points to some similarities of brain structural abnormalities and of neurocognitive impairments across schizophrenia and bipolar disorder. However, there is also strong evidence for overall brain structural *differences* between the disorders as well as of greater neurocognitive impairment in schizophrenia than in bipolar disorder. Results from structure/function relationship studies have been inconsistent in schizophrenia. Based on findings in the previous literature, relationships between frontal lobe regions and executive functioning, and between medial temporal lobe regions and memory measures are expected in both schizophrenia and bipolar disorder. However, most studies have

focused on specific brain regions and associated these with performance on neurocognitive tests only from a limited number of domains within higher order cognitive functioning. Differences in methodology make it difficult to interpret the results, and the previous small sample sizes may not have had sufficient statistical power to detect the subtle relationships that are likely to be present. Given the proposed whole-brain networks underlying cognition, studies on brain structure and the relationships with neurocognition should include measurements encompassing the whole cortical mantle and most subcortical structures in order to adequately localize all relevant brain anatomical abnormalities, and be able to investigate the relative contribution of each structure to cognition dysfunction in schizophrenia and bipolar disorder. Also, methods that more closely reflect the cytoarchitectural properties of the cortex, such as cortical thickness or surface area may enhance our ability to investigate how structure and function are related/or disrupted in schizophrenia and bipolar disorder. Additionally, there is little knowledge about the possible specificity to either disorder. Results from direct comparisons of brain structure and the relationships with neurocognition in schizophrenia and bipolar disorder may aid in the efforts to better delineate the disease entities against each other and ultimately shed light on the pathophysiology of these diseases.

2. Aims

The aim of the present thesis was to 1) characterize brain structure and the relationships with neurocognitive performance in schizophrenia and bipolar disorder and healthy control subjects and, 2) to investigate these characteristics for differences and similarities between subject groups. To accomplish these goals, we conducted the following four studies:

Study I

The aim was to identify relationships between brain cortical thickness and neurocognitive performance, and investigate for differences in relationships between chronic schizophrenia patients and healthy controls.

Study II

The aim was to compare brain cortical thickness and subcortical volumes between schizophrenia and bipolar disorder patients to assess for differences and similarities in brain structure.

Study III

The aim was to characterize relationships between brain cortical thickness and surface area and neurocognitive functioning in schizophrenia and bipolar disorder and healthy controls and, investigate whether the relationships were similar or different between the groups.

Study IV

The aim was to characterize relationships between subcortical brain volumes and neurocognitive functioning in schizophrenia and bipolar disorder and healthy controls and, investigate for differences and similarities between the groups.

3. Methods

3.1 Subject material

The participants included in this thesis included patients with schizophrenia or bipolar spectrum disorders and healthy controls recruited at two separate sites:

Study I: Patients with schizophrenia spectrum disorder and healthy controls as part of the Human Brain Informatics (HUBIN) study, Stockholm, Sweden.

Study II-IV: Patients with schizophrenia or bipolar disorder spectrum disorders and healthy controls as part of the Thematically Organized Psychosis (TOP) research project, Oslo, Norway.

All studies were cross-sectional and conducted in a naturalistic setting. Group comparisons were performed. Subject description for the two cohorts is provided separately in the following, while an overview of demographics and clinical data is given in Appendix 2.

3.1.1 HUBIN

The HUBIN project is an ongoing project starting in 1995 with longitudinal clinical, neurocognitive, genetic and MRI assessments of adult schizophrenia spectrum patients and healthy controls.

For the present study, unrelated Caucasian subjects were included between 1999 and 2003. All healthy controls and patients within the schizophrenia spectrum (schizophrenia or schizoaffective disorder), who had undergone MRI scanning and clinical and neurocognitive assessments were included in the study (Appendix 2).

All patients were recruited from psychiatric outpatient clinics in the north-western part of Stockholm County in collaboration with Karolinska Institutet.

Control individuals had previously served as healthy comparison subjects in biological psychiatric research at Karolinska Institutet, or were recruited among hospital staff or their relatives, or were drawn from a representative sample of the population in Stockholm County.

Exclusion criteria for all subjects were a history of head trauma with loss of consciousness >5 minutes, current treatment for substance abuse, and/or somatic disorders affecting brain function.

Both patients and controls underwent a one and a half-hour neurocognitive assessment. The testing took place at different locations within Karolinska Institutet and was administered by psychologists in training, supervised by an experienced neuropsychologist.

Clinical assessments

All patients were assessed for DSM based lifetime diagnosis of schizophrenia using reviews of psychiatric records and unstructured interviews and/or with structured interviews (Spitzer and Williams, 1988) and parish register data. The interviews were performed by psychiatrists trained in Sweden. In this population, record reviews by using OCPRIT (McGuffin and Farmer, 1991) have been shown to be a reliable source for making DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) psychosis diagnosis. The ratings were performed by psychiatrists trained in the use of OCPRIT by the British developers of the instrument. Diagnostic reliability was ascertained by calculating the unadjusted agreement and Cohen's un-weighted nominal kappa among the research psychiatrists performing the clinical interviews. Addition of data emerging from structured interviews seldom altered a diagnosis based on record analysis alone (Ekholm et al., 2005;Vares et al., 2006). In contrast, using a structured interview as the only source for giving the diagnosis led to poor agreement with diagnosis based on multiple sources (Vares et al., 2006).

Controls were assessed for lifetime psychiatric diagnosis (DSM-III-R) using structured interviews (Spitzer and Williams, 1988). None of the control subjects were diagnosed with schizophrenia. All interviews and diagnostic formulations were performed by a psychiatrist trained in Sweden.

Age of onset of symptoms was defined as onset of psychotic symptoms according to reviews of hospital records and interviews. Abuse/dependence of alcohol, solvents or drugs according to DSM-III-R criteria was evaluated using all available sources. Data obtained on current medication were converted into equivalent doses of Haloperidol (Kane et al., 2003). Handedness was ascertained by means of asking the patients which hand they preferred when writing, using scissors and throwing/catching a ball.

3.1.2 TOP

The TOP study is an ongoing project starting in 2002 with longitudinal clinical, neurocognitive, genetic and structural and functional MRI assessments of adult

patients with mainly schizophrenia or bipolar spectrum disorders, and healthy controls.

For study II, III and IV, subjects were included between 2003 and 2009. All healthy controls and patients with schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder or schizophreniform disorder) or bipolar spectrum disorder (BD I or II) who had undergone MRI scanning (study II), and full neurocognitive assessment (studies III and IV) were included in the thesis (Appendix 2).

All patients were consecutively recruited from psychiatric in and outpatient clinics from four major hospitals in Oslo as part of the TOP study in collaboration with the University of Oslo.

The control subjects were randomly selected from statistical records from the same catchment area as the patient groups, and contacted by letter inviting them to participate. The healthy control subjects that responded to the letter inviting them to participate, received a phone call with questions concerning exclusion criteria, followed by a screening for psychiatric symptoms with PRIME-MD (Spitzer et al., 1994). Controls were asked and excluded from the study if they or any of their first-degree relatives, had a lifetime history of severe psychiatric disorder (schizophrenia spectrum disorders, bipolar disorder or major depression).

Exclusion criteria for all participants were: a history of moderate or severe head injury, neurological disorder, IQ < 65 points, and age outside the range of 18-65 years. In study III and IV, neurocognitive performance was included in the analyses, which required narrower inclusion criteria; all participants had to have IQ points > 70, and Norwegian as their first language, or had received their compulsory schooling in Norway, and had to score 15 or above in the forced recognition trial in the California Verbal Learning Test (CVLT)-II (Delis et al., 2004). Detailed criteria for inclusion and exclusion are presented in each paper.

All participants underwent a three-hour neuropsychological test battery in a standardized order. Clinical psychologists with training in standard neuropsychological testing administered the tests, under the supervision of an experienced clinical psychologist, specialized in neuropsychology. Reports from the clinical and neurocognitive assessments of the participating patients were sent to the treatment units after completion.

Clinical assessments

Different trained physicians and clinical psychologists performed clinical assessments under supervision of experienced psychiatrists specialized in diagnostic assessment. Lifetime diagnoses were based on Structured Clinical Interview for DSM-IV Axis I disorders (SCID I module A-E) (First, 2002), and examination of medical records. Close family members were contacted with the patient's approval, for additional information when needed. All investigators completed a training course in SCID I assessment, and frequent diagnostic consensus meetings were held to assure the best possible diagnostic inter-rater reliability. Diagnostic reliability was found satisfactory with overall agreement for DSM-IV diagnostic categories of 82% with $\kappa = 0.77$ (95% CI: 0.60-0.94) (Birkenaes et al., 2007). Current positive and negative symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning (GAF) scale, split version. Interrater reliability for PANSS positive and negative subscales (intraclass coefficients = 0.73) and the GAF scales (intraclass coefficient = 0.86) has been found to be satisfactory (Engh et al., 2010). Current depressive symptoms were rated using the Inventory of Depressive Symptomatology – Clinician rating (IDS-C) (Rush et al., 1996). Current manic symptoms were rated using the Young Mania Rating Scale (YMRS) (Young et al., 1978).

Age was defined as age at MRI scanning. Years of education were registered as years of schooling as reported by the subjects during interview. Age at onset (age at first contact with mental health care due to a primary symptom, i.e., psychotic symptoms for schizophrenia group; or psychotic or affective symptoms for the bipolar group) and current use of medication were derived from interviews and medical records. Dose of medication was converted to defined daily dose (DDD) according to the WHO guidelines (http://www.whocc.no/atcddd). Handedness was determined by hand preference when writing.

In order to obtain a clinically representative sample, all patients were included regardless of alcohol and illicit drug use, but abuse/dependency was diagnosed (SCID module E) if present.

3.2 Neurocognitive assessments

The tests in the neuropsychological test batteries used in the HUBIN and the TOP studies were selected for their extensive use in clinical settings, and for commercial

availability in the Swedish and Norwegian languages, respectively. Both neurocognitive test batteries were semi-computerized. One subtest within each test was selected in order to minimize the number of statistical tests. In order to make the results from the HUBIN and the TOP studies comparable in this thesis, subtests from the test batteries were assigned to the following six *specific neurocognitive domains* (although each test probably requires several and overlapping cognitive skills): ***Verbal learning, working memory, executive functioning/flexibility, verbal IQ, processing speed and motor speed***.

HUBIN

The administration of subtests and registration of data was guided by a computer program, which is useful for clinical use as well as in research settings. A total of 7 tests were administered to the participants. Five domains were used in study I:

Verbal learning: From the Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1995), the participant was presented a list of 15 words at a rate of one word per second, after which the subjects were required to reproduce as many words as they could recall. The same list was then repeated four more times with the subjects required to reproduce as many words as they could recall. The total number of words repeated immediately after 5 reading trials (total A 1-5) was used as a measure of verbal learning.

Working memory: During the Letter-Number-Sequencing test (LNS) (Wechsler, 1997), the subject was required to sort letters and numbers from a row of alternating letters and numbers that were presented verbally, and to separately recall the letters and numbers in successive order. The test ranges from two to seven items, with three trials at each level. The total number of series recalled was included as a measure of working memory.

Executive functioning: From a computerized version of the Wisconsin Card Sorting test (WCST) (Heaton et al., 1993), the subject was asked to sort 64 cards against a set of four stimulus cards according to a certain unknown rule: colour, shape or number of symbols on the cards. Once the subject had made a specified number of consecutive correct matches to the initial sorting principle, the sorting principle was changed without warning. The WCST proceeds in this manner through a number of shifts in

sorting principle among the three possible sorting categories. The subject is given immediate feedback from the computer if the choice is correct or incorrect. The computer program computes the test scores. The number of total errors was chosen as a measure of executive functioning.

Flexibility: On Trail Making Test B (TMT B) (Lezak, 1995), the participant was required to connect as quickly as possible randomly arranged numbers (from 1-13) and letters (from A to L) alternately in successive order on a sheet of paper with a pen. Time to complete was used as a measure of flexibility. The tests also measure aspects of psychomotor speed and executive functioning.

Verbal IQ: From the Vocabulary subtest in the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981), the subject was presented 70 words and was required to verbally explain the meaning of the presented words. The correct number of responses was used as a measure of Verbal IQ.

Higher scores equal better performance on all measures except for the TMT B and WCST tasks.

TOP

A semi-computerized test battery was administered to all participants. Test scoring was initially calibrated across investigators in order to assure a common scoring technique. Premorbid IQ was estimated using the National Adult Reading Test – Norwegian version (Sundet and Vaskinn, 2008). From a comprehensive test battery, seven tests in total were selected for study III and IV:

Verbal learning: From the California Verbal Learning Test, Second edition (CVLT-II) (Delis et al., 2004), a 16-word list was presented to the subject in a similar manner as the RAVLT. The total number of words repeated immediately after 5 reading trials (Total A 1-5) was used as a measure of verbal learning.

Working memory: From the Digit Span subtest in WAIS-III (Wechsler, 2003), the participant was presented an increasing number of digits. In the first part of the test, the subject was asked to repeat in forward order of presentation, and then in the second part backward order of presentation. The maximum number of recalled digits was recorded, and the total number of forward and backward recalls was used as a

measure of working memory. Notably, the score also demonstrates characteristics of attention.

Executive functioning: The interference control and set-shifting tasks are considered to measure aspects of executive functioning.

Interference control: From the third trial in the Color-Word Interference Test, which is part of the Delis-Kaplan Executive Function Scale (D-KEFS) (Delis et al., 2005), the time taken for the subject to name the colour of the ink on a list of written names of colours that are incongruent with the colour of the ink, was used as a measure of interference control.

Set shifting: From the Verbal Fluency test, which is part of the D-KEFS (Delis et al., 2005), the subject was asked to generate and alternate between words from different categories (fruits and furniture). The number of words generated within 60 seconds was used as a measure of semantic set-shift ability.

Verbal IQ was estimated with the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007a). The subject was presented 80 words and was required to verbally explain the meaning of the presented words. The correct number of responses was used as a measure of Verbal IQ.

Processing speed: In the Digit Symbol Test, part of the WAIS – III (Wechsler, 2003), certain digits and symbols are matched on top of a sheet of paper. The subject was asked to write the symbols matching the digits, which are played further down on the same sheet. The number of symbols written within 90 seconds was used as a measure of processing speed.

Motor speed: On the Grooved Pegboard Test (Klove, 1963), the subject must place 25 notched pegs into a board with 25 matching holes. Time to complete with the dominant hand was used as a measure of motor speed.

For raw scores, higher scores equal better performance on all measures, except for the Color-Word Interference Test and the Grooved Pegboard.

3.3 MRI assessments

3.3.1 MR image acquisition

HUBIN

All subjects were examined in a 1.5 Tesla General Electronics Signa system at the MR Research Center, Karolinska Hospital, Stockholm, Sweden. T1-weighted images were acquired using a three dimensional spoiled gradient recalled (SPGR) pulse sequence with the following parameters: 1.5 mm coronal slices, no gap, 35º flip angle, repetition time 24 ms, echo time 6.0 ms, number of excitations 2, field of view 24 cm, and acquisition matrix 256 x 192. From visual inspection, all scans were judged to be excellent without obvious motion artifacts.

TOP

All subjects were examined in a 1.5 Tesla Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil at Oslo University Hospital, Ullevål. After a conventional 3-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = 1.33 x 0.94 x 1 mm^3, number of partitions = 160).

3.3.2 MR Image processing

The FreeSurfer (FS) Software (http://surfer.nmr.mgh.harvard.edu) was used for processing of the image files from both sites. The HUBIN image files were processed in FS version 1.2, while the TOP image files were processed in FS version 3.0.2. The image files in DICOM format were transferred to a Linux workstation for morphometric analysis. Images were corrected for non-linear warping caused by gradient coil non-linearities, using tools developed through the Morphometry Biomedical Informatics Research Network (mBIRN) (Fennema-Notestine et al., 2007). From the HUBIN database *one* T1 weighted image was used, and from the TOP database *two* T1-weighted images were rigid body registered to each other (motion corrected), and subsequently averaged together to increase the signal to noise ratio. An overview of the methods used in each study is given in Table 1. FS was used to obtain measurements of cortical thickness by reconstructing representations of the grey/white matter boundary and the cortical surface, and then calculating the distance

between those surfaces at numerous points (vertices) across the cortical mantle (Dale et al., 1999;Dale and Sereno, 1993). Vertices were arranged in a triangular mesh with approximately 1 mm spacing, allowing for measures of cortical thickness at approximately 160 000 points in each hemisphere (Fig. 1).

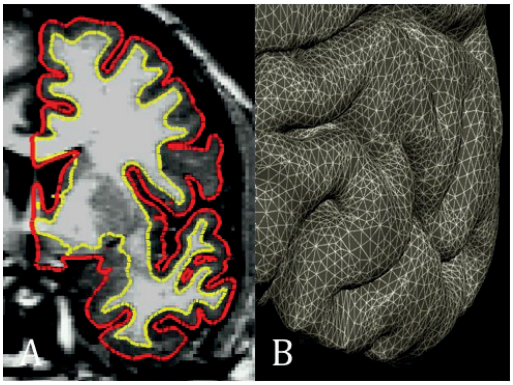


Fig. 1. Illustration of the methods used to obtain cortical measures. A) Coronal slice of MR image. Cortical thickness measurements are obtained by calculating the distance between the white/grey matter surface (yellow line) and the pial surface (red line) on numerous points across the cortex. B) A triangular mesh on the reconstructed surface. Cortical surface area measurements were obtained by summing the areas within each triangle within a given region of interest

Failures in FreeSurfer's initial Talairach alignments were identified by visual inspection of all images, and were rectified prior to reconstruction of the cortical surfaces. Surface maps were smoothed using a full-width-half-maximum Gaussian kernel of 25mm (study I) and 30 mm (study II) and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl et al., 1999) (Fig. 2). The method is fully described elsewhere (Dale et al., 1999;Fischl et al., 1999;Fischl et al., 2001).

The software also enables surface division into functionally relevant *parcellated regions* (study II and III) (regions-of-interest [ROI]) (Fischl et al., 2004), which are neuroanatomically labelled (Desikan et al., 2006) (Fig. 2). Average regional cortical thickness was calculated as the average distance between the grey/white boundary and the pial surface within each ROI (study II and III). Regional surface area was calculated as the sum of the areas of each triangle falling within a given ROI; this was done in each subject's native space (study III). Average cortical thickness measurements from parcellated regions were used in study II in addition to cortical thickness maps, in order to calculate mean differences and effect sizes in comparable regions across the subject groups. Average cortical thickness and total surface area within parcellated regions were used in study III in order to be able to directly

compare measurements of thickness and area within the same regions across the subject groups.

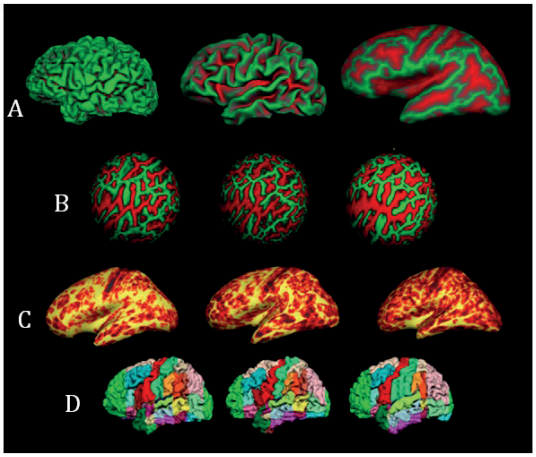


Fig. 2. Illustration of FreeSurfer methods for cortical analyses A) Visualization of structural anatomy, B) Intersubject registration, C) Cortical thickness statistical maps of point-by-point measurements and D) Parcellations into functionally regional relevant areas (Appendix 3) (By courtesy of A. Dale and B. Fischl).

Subcortical volumes (Fig. 3) were obtained from the automated procedure for volumetric measures of brain structures implemented in FreeSurfer (Fischl et al., 2002) as well as intracranial volume (ICV) estimates (Buckner et al., 2004). Topological defects in the automatically determined grey/white matter boundary and subcortical volume measurements were routinely manually corrected blinded to subject group identity. A total of 27 subcortical structure volumes (including the hippocampus and amygdala) were automatically segmented and included in the analyses in study II, while a selection of 18 structure volumes were included in study IV. The selection of structure volumes was in part based on previously shown group differences and in part made to limit the number of statistical tests. All parcellated regions and subcortical structure volumes are listed in appendix 3.

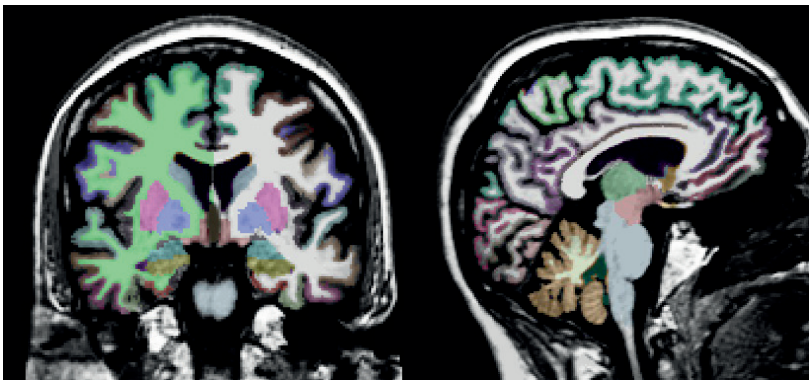


Fig. 3. Segmentation of subcortical structure volumes using the FreeSurfer software (Appendix 3). Left, coronal slice. Right, sagittal slice (image by L.M. Rimol).

3.4 Statistical analyses

The analyses were performed in the statistical software SPSS versions 14.0 and 16.0 (http://www.spss.com) and FreeSurfer software v. 3.0.2. All variables were checked for deviations from a normal distribution and logarithmic transformed if necessary, before being entered into the analyses. Demographic, clinical and neuropsychological test scores were compared across groups using Student's T-tests and chi-square analyses and analyses of variance (ANOVAs) followed by post-hoc tests. The main analyses in all articles were based on General Linear Models (GLMs) with the brain structure of interest as the dependent variable. Diagnostic group, age and the neurocognitive variables of interest were entered as independent variables. Sex and intracranial volume were corrected for, when appropriate. In studies (I and II), GLMs were estimated at each vertex across the cortical surface, with cortical thickness as the dependent variable, allowing for generation of thresholded statistical maps. Following the main analyses, subsequent analyses were performed to check for the effects of antipsychotic medication and illness duration, and to investigate categorical subtypes within each of the two patient groups separately.

Different approaches were employed to investigate group differences in structure/function relationships in Study I and Studies III/IV (Table 1). In Study I, brain cortical regions for which we detected a *common* effect of neurocognitive scores on cortical thickness, were selected for diagnostic interaction analyses. In Studies III/IV, brain regions for which we detected *groupwise* (separate) effects were selected for statistical comparisons between groups. We were especially interested in relationships in the separate patients groups and specifically aimed to identify

different relationships between the schizophrenia and bipolar groups. The relationships for the combined group in Study I and for the separate group analyses in Studies III and IV were identified at an uncorrected p level of 0.01 and chosen for further between-group analyses. By choosing this arbitrary p level, there is always a risk of running type I errors in hypothesis testing and thus one might present false positive findings as true findings. However, comparable previous studies have demonstrated low/moderate strengths in structure/function relationships and some researchers have, therefore, chosen to set a significance level at $p < 0.025$ (Antonova et al., 2005) in order to avoid type II errors. Our p level was set lower, and the final results were appropriately corrected with multiple comparison control. Application of conventional Bonferroni correction on all analyses would probably result in rejection of true positive results. Corrections for multiple comparisons were therefore done with a false discovery rate (FDR) of 0.05 on the cortical thickness maps, the Bonferroni-Holm step-down procedure on comparisons of discrete structures in Study II and Bonferroni correction in Studies III and IV. However, due to the high number of statistical tests performed some caution must be used when interpreting the results. The statistical procedures are described in more detail in the separate articles included in the thesis.

Table 1. Overview of brain measurements and statistical methods

Study	Brain structure	Measurement	Neurocognitive tests	Statistics
I	Cortical thickness	Vertex-by-vertex	5	Combined group
		Regions-of-interest		Interactions
II	Cortical thickness	Vertex-by-vertex Parcellated regions		Pairwise comparisons
	Subcortical volumes	Structure volumes		Omnibus test – pairwise comparisons
III	Cortical thickness and surface area	Parcellated regions	6	Combined group Separate analyses – pairwise comparisons
IV	Subcortical volumes	Structure volumes	7	Combined group Separate analyses – pairwise comparisons

3.5 Ethical considerations

The HUBIN project is conducted in accordance with the Declaration of Helsinki and approved by the local and regional committees for Research Ethics. All subjects have given their written consent to participate after a complete description of the study. The TOP study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. All subjects have given their written consent to participate, after a complete description of the study.

4. Summary of studies

Study I

"Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults".

Relationships between frontal and temporal cortical brain *volumes* and neurocognitive performance in schizophrenia have been reported in previous studies. However, the results have been inconsistent, which might be due to the methods used. The aim of this study was to perform an unbiased exploration of the relationships between cortical *thickness* and several neurocognitive domains across the whole cortical mantle, and for the first time, extend the cortical thickness method to schizophrenia patients, in order to identify possible localized and specific structure/function relationships in schizophrenia.

From the larger HUBIN cohort, 67 patients with chronic schizophrenia and 69 healthy controls underwent MR scanning and neurocognitive assessments at baseline. Cortical thickness measurements were obtained at over 160 000 points in each hemisphere for each subject.

In the combined sample of patients and controls, positive relationships were found between cortical thickness in frontal and temporal regions and verbal learning and executive functioning, and between cortical thickness in frontal, temporal and occipital regions and verbal IQ. There were diagnostic interactions for the relationships between verbal IQ and the left middle occipital region and the right temporo-occipital region.

In conclusion, we detected localized relationships between cortical thickness and specific neurocognitive test scores. Furthermore, the pattern of relationships appears similar in schizophrenia patients and healthy controls. There were, however, two cortical brain regions in which the relationships were disrupted in the patients with schizophrenia as compared to the healthy control subjects.

Study II

"Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder"

Regional cortical and subcortical brain structural abnormalities have consistently been demonstrated in schizophrenia. In bipolar disorder, which has been less studied, the most frequently shown abnormalities are enlargements of the cerebral ventricles and increased frequency of white matter hyperintensities. Although the symptomatology is overlapping and genetic studies have detected shared genetic liability between schizophrenia and bipolar disorder, few studies have directly compared schizophrenia patients with bipolar disorder patients using the exact same methodology in order to determine the similarities and differences in brain structural abnormalities.

From the TOP cohort, MR scans were obtained from 173 patients with schizophrenia, 139 patients with bipolar disorder (BD) and 207 healthy control subjects. Cortical thickness measurements and subcortical structure volumes were obtained for each subject.

The results presented as statistical cortical thickness maps, demonstrated frontal, temporal, parietal and occipital cortical thinning in schizophrenia compared with healthy controls, while there were no findings for the bipolar disorder group compared with the healthy control group, or between the schizophrenia and bipolar disorder group. The BD I subgroup displayed cortical thinning in frontal and temporal and parietal regions relative to healthy controls, which were partially overlapping with the abnormal regions found in schizophrenia, however the cortical thinning in the schizophrenia group was more extensive. In the subcortical brain, the schizophrenia and bipolar disorder group showed similar abnormalities compared to healthy controls; enlarged ventricles, reduced bilateral hippocampi, left thalamus, right nucleus accumbens and left cerebellar cortex volumes, and reduced volumes of the brainstem. Left amygdala volumes were reduced in schizophrenia relative to healthy controls, and right putamen volumes were enlarged in schizophrenia relative to bipolar disorder and healthy controls. In general, the effect sizes were larger for the schizophrenia group than for the bipolar disorder group, relative to the healthy control group. All results remained significant after corrections for duration of illness and use of antipsychotic medication.

In conclusion, there were similar brain structural abnormalities in schizophrenia and BD I in the cerebral cortex and between schizophrenia and the combined bipolar disorder group for subcortical structures. These findings are consistent with common underlying pathophysiology in schizophrenia and bipolar disorder. However, the schizophrenia group displayed more extensive brain structure abnormalities, both in pattern and magnitude.

Study III

"Brain cortical thickness and surface area correlates of neurocognitive performance between patients with schizophrenia, bipolar disorder and healthy control subjects"

Previous studies have demonstrated similar cortical brain abnormalities as well as neurocognitive dysfunction between schizophrenia and bipolar disorder. Studies that have investigated relationships between cortical characteristics and neurocognition in schizophrenia are inconsistent, and very few studies have been performed in bipolar disorder. In this study, we included both regional cortical *thickness* and *surface area* measurements, which together constitute cortical volume, and investigated for relationships with several neurocognitive domains across schizophrenia and bipolar disorder and healthy controls. We also aimed to clarify differences and similarities in cortical brain structure/function relationships between schizophrenia and bipolar disorder.

From the TOP cohort, 519 subjects had undergone MR scanning. From these, there were complete neurocognitive data available from 430 subjects, of which 117 were schizophrenia patients, 121 were bipolar disorder patients and 192 were healthy controls. Average cortical thickness and total surface area measurements were obtained from 14 selected parcellated cortical regions in each hemisphere for each subject and investigated for relationships with six neurocognitive tests.

For all subjects combined, one negative relationship was found between cortical thickness in the right anterior cingulate and working memory, and several positive relationships were found between cortical surface area in frontal and temporal regions and various neurocognitive tests. Three relationships were different between schizophrenia and bipolar disorder, of which the relationship between cortical thickness in the right temporal pole and working memory was specific to bipolar disorder, and the relationship between cortical thickness in the left transverse

temporal region and processing speed was specific to schizophrenia. Cortical thickness in several temporal regions related differently to processing speed in schizophrenia relative to healthy controls. The relationship between surface area in the left fusiform region and verbal learning in healthy controls was different from that in schizophrenia. In general, there were more relationship differences between schizophrenia and healthy controls, than between bipolar disorder and healthy controls.

In conclusion, we have demonstrated that relationships between cortical thickness and surface area, and neurocognition show both similarities and differences across schizophrenia and bipolar disorder and healthy control subjects. Some disease-specific relationships were found and suggest that the clinical significance of cortical brain abnormalities may in part be different in schizophrenia and bipolar disorder.

Study IV

"Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls"

Subcortical brain structures are anatomically connected with widespread cortical regions forming numerous networks, and are hypothesized to modulate motor and cognitive behaviour. Structural abnormalities in the subcortical brain have been demonstrated in schizophrenia, while bipolar disorder is less studied, and the findings are inconsistent. In a previous study (II) we demonstrated almost completely overlapping subcortical abnormalities across schizophrenia and bipolar disorder compared to healthy controls. The aim of this study was to complement the previous study (III) on cortical structures, and investigate the relationships between subcortical structure volumes and a range of neurocognitive tests, and to identify similarities and differences between schizophrenia and bipolar disorder.

MR scans and neurocognitive assessments were obtained for 117 schizophrenia patients, 121 bipolar disorder patients and 192 healthy controls. The subcortical structure volumes were automatically segmented and 9 volumes of interest from each hemisphere were chosen for the analyses and investigated for a relationship with seven neurocognitive tests.

For all subjects combined, larger volumes of the ventricles, hippocampus and putamen were related to poorer neurocognitive function. The relationships between ventricular volumes and motor speed and between putamen volumes and executive functions

were similar in schizophrenia and bipolar disorder, but different from healthy controls. The relationship between larger left putamen volume and poorer working memory was specific to schizophrenia.

In conclusion, on the background of overlapping subcortical abnormalities and neurocognitive dysfunction in schizophrenia and bipolar disorder, we have demonstrated both differences and similarities in subcortical structure/function relationships between schizophrenia and bipolar disorder. The findings suggest that putamen and ventricular volumes may reflect severity of neurocognitive functioning in both schizophrenia and bipolar disorder. Altered relationships may also be related to disruptions in the cortico-striatal-thalamico-cortical networks subserving or modulating neurocognitive functioning.

5. Discussion

First, the main findings are summarized, followed by interpretations of the findings (5.1). Then, methodological issues are discussed (5.2).

5.1 Findings and interpretations

To summarize, the main findings in the present thesis were:

- Brain cortical thinning in frontal, temporal and parietal regions is found in schizophrenia and bipolar disorder type 1, relative to healthy control subjects. The cortical thinning in schizophrenia was more extensive in pattern and magnitude compared with bipolar disorder.

- Subcortical volume abnormalities were found in both schizophrenia and bipolar spectrum disorders when compared to healthy controls, but with larger effect sizes in schizophrenia.

- In *chronic* schizophrenia patients and healthy controls, cortical thickness relationships with specific neurocognitive functional domains were positive and localized in frontal, temporal and occipital regions. The relationships were mainly similar in patients and controls.

- There were few cortical thickness relationships with neurocognitive performance in a replication study, which included both schizophrenia and bipolar disorder patients.

- Larger cortical surface area in frontal and temporal brain regions related to better neurocognitive performance across groups regardless of having a diagnosis of schizophrenia or bipolar disorder. However, one relationship in the left fusiform region appeared to be disrupted in schizophrenia, but not in bipolar disorder, compared to healthy controls.

- Larger volumes of the ventricular system, hippocampus and putamen were related to poorer neurocognition across schizophrenia, bipolar disorder and healthy controls.

- Group comparisons of specific structure/function relationships between schizophrenia and bipolar disorder demonstrated certain shared and specific relationships for both disorders.

5.1.1 Brain structure in schizophrenia and bipolar disorder

Cortical thinning

The present findings of cortical thinning in schizophrenia are consistent with regional thinning reported in studies of chronic (Kuperberg et al., 2003;Nesvag et al., 2008;Schultz et al., 2010a), first-episode (Crespo-Facorro et al., 2010;Narr et al., 2005;Schultz et al., 2010b) and in antipsychotic-naïve (Venkatasubramanian et al., 2008) schizophrenia patients. One study of subjects with high risk for psychosis found regional cortical thinning, but to a lesser extent than in schizophrenia subjects compared with healthy controls (Jung et al., 2009). Negative findings have been reported in first-episode patient studies with small sample sizes (Gutierrez-Galve et al., 2010;Wiegand et al., 2004) and in relatives of schizophrenia subjects (Goldman et al., 2009). Some of the previous studies report thinning to be limited to frontal and temporal regions (Nesvag et al., 2008), while several other studies also demonstrate parietal and occipital (Kuperberg et al., 2003;Schultz et al., 2010a) affection, supporting our findings. The present sample was comparably large to those used in previous studies enabling detection of subtle changes; the largest effect sizes in the current Study II were 3-4 % difference in thickness (equals app. 0.5 Cohen's d) in the lateral and medial frontal regions, and temporo-occipital regions. In comparison, reduction in cortical thinning has been reported to be 8-9 % at most in chronic patients (Nesvag et al., 2008) and about 4-7 % in FES patients (Schultz et al., 2010a), which suggests increasing thinning at later stages of the disease. The timing for progression is uncertain, although progression of grey matter loss in transition to psychosis (Pantelis et al., 2005) and at the initial stages of the disease has been proposed (Jung et al., 2009;Kasai et al., 2003a). Conflicting with the assumed progressive grey matter loss, we did not find an effect of illness duration on thinning in the present sample and, thus far, no longitudinal cortical thickness study on schizophrenia patients has been performed to confirm progressive thinning. Preliminary data from our Swedish chronic schizophrenia (HUBIN) cohort do not show any progression in cortical thinning or changes of subcortical structure volumes over a 5-year period, except from a slight increase of cerebral ventricular size as compared with healthy controls. The fact that abnormalities are present in subjects at high risk or in early parts of the illness and in AP naïve patients suggest that cortical thinning is related to the disorder itself and not mere effects of confounding factors, such as medication.

Similar patterns of thinning found in frontal and temporal regions in BD I (2-3 % difference relative to healthy controls) indicate that cortical thinning is a common feature of severe mental disease, at least in schizophrenia and bipolar disorder. We did not replicate the suggested cortical thinning scattered across several brain lobes in bipolar disorder patients as demonstrated by Lyoo *et al.* (2006). However, Lyoo *et al.* used a more lenient significance threshold ($p < 0.001$ uncorrected) and, furthermore, thickness of the left middle frontal cortex correlated negatively with duration of illness, which is consistent with progressive regional thinning in bipolar disorder, and the group of patients in the study by Lyoo *et al.* was characterized by longer duration of illness than the patients in the present study. In contrast, while they did not detect a difference between bipolar disorder type 1 and 2, the present Study II demonstrated significant frontal, temporal and parietal thinning in BD I, but not in BD II, compared with healthy controls. Substantiating the present findings, a just recently published cortical thickness study reported cortical thinning in frontal regions in BD I patients compared with healthy controls (Foland-Ross et al., 2011). The present BD I and II groups were similar on all demographic and clinical variables, except that the BD II patients as a group were more depressed (higher IDS score) and were higher functioning (higher GAF-F) than the BD I patients. Obviously, all BD I patients had experienced manic episodes, and 80 % had a history of psychosis. In the BD II group, 20 % had experienced a psychotic episode.

To date, only one study has directly compared cortical thickness between schizophrenia and bipolar disorder (Qiu et al., 2008), but the analyses were limited to the planum temporale region. Qiu *et al.* reported similar abnormalities in schizophrenia and bipolar disorder consistent with the findings of overlapping thinning in the temporo-parietal region in the present study. Although cortical thickness is not directly comparable to volume measures, the summarized findings from meta-analyses might be of interest for the interpretation of our results. Ellison-Wright *et al.* (2010) specifically aimed to review the VBM literature on schizophrenia and bipolar disorder, and reported grey matter reduction in bilateral insula and parts of the anterior cingulate in both disorders. In the present study, thickness of these regions was significantly reduced in schizophrenia, but not in bipolar disorder. However, the present effect sizes for the BD I group were intermediate between schizophrenia and healthy controls, implying that a larger subject sample of BD I patients may have detected the subtle changes that may be present. The present thinning in the lateral and medial frontal cortices found in BD I was circumscribed,

however still extensive, and these results find support from the frontal cortex volume reduction found in bipolar disorder patients as reported in a meta-analysis comparing volumetric MRI studies on schizophrenia and bipolar disorder by Arnone *et al.* (2009). Consistent with the present results, both meta-analyses conclude that regional frontal lobe reductions in schizophrenia and bipolar disorder are diagnostically unspecific (Arnone et al., 2009;Ellison-Wright and Bullmore, 2010).

Subcortical volumes

The subcortical abnormalities found in schizophrenia and bipolar disorder in the present study, were almost completely overlapping between the diseases. In schizophrenia, the findings are consistent with reports from previous studies of reduced volumes of the hippocampus (Honea et al., 2005), thalamus and amygdala (Ellison-Wright et al., 2008) and cerebellar regions (Honea et al., 2005). Putamen enlargement in chronic schizophrenia is consistently found, but has been related to treatment with mainly typical antipsychotic medication (Brandt and Bonelli, 2008). The present results for right putamen remained significant after correcting for medication use. The ventricular enlargements were substantial and consistent with the previous literature (Shenton et al., 2001). We expanded on previous findings, and reported abnormalities in nucleus accumbens and the brainstem, which neuroanatomy might be understudied in schizophrenia.

An important finding from the present studies is the unexpected extent of subcortical abnormalities found in bipolar disorder. The only consistently reported abnormalities in the previous literature of bipolar disorder have been ventricular enlargements and increased frequency of white matter hyperintensities (Kempton et al., 2008;McDonald et al., 2004). Similarly, a later study than ours, analyzed data from a large bipolar I sample (n = 321) recruited from different sites, and found increased right lateral ventricular size compared with healthy controls (Hallahan et al., 2011). In contrast, a study comparing between first-episode patients with schizophrenia and bipolar disorder, found larger ventricular volumes in schizophrenia patients, but not in bipolar disorder, compared with healthy controls (Rosa et al., 2010). However, the bipolar disorder group may have been too small to detect subtle abnormalities at illness onset, as ventricular enlargements are shown to be greater in multi-episode than in recent onset patients with bipolar disorder (Strakowski et al., 2002). The clinical significance of ventricular enlargements is not known, but the majority of longitudinal studies relate progression of ventricular volumes to poor outcome in schizophrenia (Ho et al.,

2003;Kempton et al., 2010). Enlarged amygdala volumes have been found in several bipolar disorder studies (Bora et al., 2010). However, this finding might be confounded by age, in terms of a positive correlation (Usher et al., 2010a) and use of lithium, which has been suggested to have psychotrophic effects (Hallahan et al., 2011;Usher et al., 2010b). The increased globus pallidum volume found in previous studies on bipolar disorder (Arnone et al., 2009) was not replicated in the present study; rather we found a trend for an increase in the schizophrenia group exclusively.

The effect sizes that we present are in accordance with those reported in previous meta-analyses (Arnone et al., 2009), although we report smaller effect sizes for amygdala volume in schizophrenia, and larger effects for hippocampus in both disorders relative to healthy controls, and larger ventricular size effects in bipolar disorder relative to healthy controls.

To sum up, a wide range of cortical and subcortical structures were found to be abnormal in schizophrenia and BD I patients. Subcortical volumes were also significantly different in the BD II patients, when compared to healthy controls. Thus, on a group level there are broad similarities between bipolar disorder and schizophrenia in terms of brain structural abnormalities. But overall, the abnormalities are more pronounced in schizophrenia.

Hypothetically, the present findings in schizophrenia and bipolar disorder could be due to 1) similar processes with different intensity or 2) different processes with similar outcome. Brain structure as a phenotype has been shown to be moderately to highly heritable, and since disturbances in brain development is suggested to be one of the explanations for schizophrenia, genes involved in brain development might overlap with causal genes or candidate genes for these disorders (Kaymaz and van Os, 2009). One example of the first hypothesis could be that there is a substantial polygenic component common to the risk of schizophrenia and bipolar disorder involving thousands of common alleles of very small effect, implicating partly shared genetic liability for the disorders (Purcell et al., 2009), but that other non-shared genes or interactions with other genes could account for the differences in brain structure. Also consistent with more extensive findings or a greater intensity in schizophrenia are the recent studies that find some of the disease specificity to schizophrenia to be associated with structural genomic variations, such as copy number variations (CNVs) (Grozeva et al., 2010;Sebat et al., 2009;Stefansson et al., 2008). Also, differences in exposure to biological environmental stressors such as viruses and obstetrical

complications could affect the common genes differently, leading to differences in degree of structural abnormalities.

The second hypothesis suggests differences in genetic factors and in the underlying pathophysiology. One neuropathological study showed cortical density changes (similar outcome) in both disorders, but the abnormalities were located in different cortical layers (Bouras et al., 2001). MRI cannot detect these microscopic findings with the currently employed magnetic fields, which limit the resolution. What appears to be common cortical thinning on MRI could reflect differences in cortical cellular pathology. Notably, neuropathological studies report conflicting results (Fornito et al., 2009a), and are confounded by long illness course and medication. In a study by Goldman *et al.* (2009), cortical thickness was shown to be heritable per se, but since first-degree relatives of schizophrenia patients did not demonstrate significant cortical thinning relative to healthy controls, the authors concluded that the observed thinning in schizophrenia was not related to the risk of developing schizophrenia, but rather to disease-related factors. Furthermore, a recent investigation of the present study sample by Bakken *et al.* (2011, Submitted), found specific genetic variants on chromosome 15 to be associated with the fronto-temporal cortical thinning found in schizophrenia, but not in bipolar disorder, nor was it associated with the risk for schizophrenia or bipolar disorder. The findings support the hypothesis of different aetiology with similar outcomes across schizophrenia and bipolar disorder.

5.1.2 Neurocognitive performance in schizophrenia and bipolar disorder

The neurocognitive case-control differences in the HUBIN study, and the TOP study respectively, have been addressed elsewhere (Ekerholm and Svala, 2008;Lawyer et al., 2006;Simonsen et al., 2011). However, a few aspects are relevant to discuss in the present thesis. In accordance with previous studies (Heinrichs and Zakzanis, 1998;Mesholam-Gately et al., 2009;Rund et al., 2006) we found neurocognitive dysfunction across all domains in schizophrenia, compared to healthy controls in both cohorts. The bipolar disorder group displayed significant impairment on selected domains, i.e., motor speed, processing speed, and set-shifting and interference control (executive functioning), compared with healthy controls. The findings for bipolar disorder are in line with those presented in meta-analyses (Bora et al., 2009). However, both the schizophrenia group and the bipolar disorder group in the TOP cohort were less severely impaired on verbal learning than expected from the meta-analyses.

Table 2. Overview of effect sizes for neurocognitive group comparisons.

Study		**I**		**III and IV**	
Subject group		**HC-SCH**		**HC-SCH**	**HC-BD**
Effect size		**d**		**d**	**d**
Verbal learning		1.25		0.71	0.13
Processing speed				1.10	0.62
Working memory		0.85		0.54	0.23
Verbal IQ		0.67		0.42	0.15
Executive Functioning	WCST	0.93	SSH	1.10	0.47
	TMT B	1.18	INT	0.80	0.53
Motor speed				0.87	0.79

HC, healthy controls; SCH, schizophrenia patients; BD, bipolar disorder patients; d, Cohen´s d; WCST, Wisconsin Card Sorting Test; TMT B, Trail Making Test B; SSH, Set-shifting; INT, Interference Control.

Overall, the effect sizes in Table 2 were larger in the HUBIN study and comparable to those in chronic schizophrenia studies (Heinrichs and Zakzanis, 1998), relative to the TOP findings, which were comparable to those found in first episode studies (Mesholam-Gately et al., 2009), underlining the differences in the two samples employed in our investigations. The differences may in part reflect cohort differences, i.e., that the HUBIN patients represented a more severely ill patient group.

5.1.3 Regional relationships between brain structure and neurocognition

Cortical thickness

To our knowledge, study I was the first study to explore relationships between cortical thickness throughout the cortical mantle, and neurocognition in schizophrenia. Previous studies on structure/function relationships have largely been performed using global or regional brain volume measurements, and reported relationships between frontal lobe regions and executive functioning (Bonilha et al., 2008;Rusch et al., 2007;Seidman et al., 1994;Szeszko et al., 2000) and memory functions (Baare et al., 1999;Premkumar et al., 2008;Seidman et al., 1994) in schizophrenia. Although more inconsistent, there are reports of relationships between the temporal lobe volumes and verbal memory (Gur et al., 2000;Nestor et al., 1993;Vita et al., 1995) and executive functioning (Nestor et al., 2007) in schizophrenia. Studies on healthy adults have found

widespread relationships between IQ scores and cortical volumes (Haier et al., 2004) and cortical thickness (Narr et al., 2007). In accordance with the previous literature, we found cortical thickness relationships with executive functioning, verbal memory and verbal IQ in the frontal and temporal lobe, and relationships with verbal IQ in the occipital lobe. In agreement with our expectations, the relationships were not strictly confined to pre-selected regions, but included relatively small clusters *within* regions, and in some instances, even surpassed adjacent regions that would normally be regarded as separate and thus be investigated separately, with the risk of not being detected. In all regions thicker cortex was associated with better performance on the cognitive tasks. Therefore, we postulated that these findings could represent nodes within cognitive networks, in which structural integrity is important for cognitive functioning. However, the relationships were for the most part similar in patients and controls, except in discrete temporo-occipital and occipital regions where a diagnostic interaction was found for the relationship with verbal IQ. Consequently, the observed fronto-temporal cortical thinning in patients with schizophrenia was neither related to nor predictive of the cognitive deficits observed in the patient group. Although neurodevelopmental damage to the cortical thickness in rats has been found to cause selective cognitive deficits (Flagstad et al., 2005), these findings were not replicated in the present study on adult chronic schizophrenia patients as measured *in vivo* with MRI. Subsequent to the publication of study I, several studies on cortical thickness/neurocognition in schizophrenia patients have been published; one study reported an inverse relationship between average cortical thickness in the global and parietal lobe with attention in FES patients (Crespo-Facorro et al., 2010), while two other FES studies failed to demonstrate any regional relationships (Gutierrez-Galve et al., 2010;Roiz-Santianez et al., 2010).

In study III, the research questions from study I were re-examined in a larger and younger study sample. In addition, bipolar disorder patients were included as a second clinical group, in order to address the issue of disease specificity. We found only one significant cortical thickness relationship in the combined group of subjects, and that was different from the ones in study I. The negative relationship between cortical thickness in the right rostral anterior cingulate (AC) and working memory in all patients and controls combined may partly be accounted for by the inclusion of the bipolar disorder group, who displayed the strongest relationship between AC cortical thickness and working memory performance. Functional MRI studies have frequently shown that working memory functions recruit the AC region (Hartley and Speer,

2000), and activity in the AC has been related to adjustment in performance (cognitive control), indirectly serving as a signal that engages in regulatory processes in the lateral prefrontal cortex, typically thought to be responsible for working memory (Ridderinkhof et al., 2004).

The failure to replicate the results in study I may be due to smaller effect sizes. The effect sizes for group differences in cortical thickness and neurocognitive performance were smaller in Study III than in those with chronic patients (Heinrichs and Zakzanis, 1998;Nesvag et al., 2008), which might have limited our ability to detect subtle relationships. Alternatively, taken together with the limited findings reported in cortical thickness studies of FES patients (Crespo-Facorro et al., 2010;Gutierrez-Galve et al., 2010;Roiz-Santianez et al., 2010), the limited findings for cortical thickness in Study III may reflect the effects of age (as discussed in section 5.1.4).

Cortical surface area

Cortical surface area reduction in certain frontal and temporal regions were found in schizophrenia relative to healthy subjects, and is consistent with the regional frontal area reductions found in adolescent-onset schizophrenia patients (Voets et al., 2008) and temporal area reductions in first-episode schizophrenia patients (Gutierrez-Galve et al., 2010). Equal or increased frontal and temporal surface area in bipolar disorder compared with schizophrenia patients and healthy controls, accord well with the preserved total brain size reported in bipolar disorder (Hoge et al., 1999). Gutierrez–Galve *et al.* (2010) reported weak, but significant relationships between regional frontal and temporal surface area and current IQ, and between regional frontal surface area and working memory in schizophrenia patients, but not healthy controls. By increasing the sample size, we were able to demonstrate that relationships between frontal and temporal surface area and verbal IQ and working memory are similar across schizophrenia, bipolar disorder and healthy controls. Interestingly, we found both cortical thickness and surface area in the anterior cingulate region to be related to working memory. Previous investigations have found *volume* of the anterior cingulate to be associated with working memory in bipolar disorder (Zimmerman et al., 2006), in schizophrenia patients (Szeszko et al., 2000) and in healthy controls (Minatogawa-Chang et al., 2009), however, with various directions of effect, which could be due to the separate contributions of cortical thickness and surface area to volume measurements.

Subcortical structures

The left inferior lateral ventricular volume was related to motor speed in all groups, but to a greater degree in both patient groups relative to healthy controls, implying that extent of ventricular enlargement is reflected in motor speed impairment, since both schizophrenia and bipolar patients were impaired on motor speed performance, compared with healthy controls. To our knowledge, this is the first demonstration of this specific relationship. However, ventricular volumes have been related to tests requiring motor speed, such as TMT B (Lawyer et al., 2006), and enlargement of the ventricular system has been demonstrated in diseases typically associated with motor symptoms, such as Parkinson´s disease (Dalaker et al., 2010). Surprisingly, enlarged ventricular size related significantly to poorer executive functioning only in bipolar disorder, which was unexpected since previous studies have demonstrated this relationship in schizophrenia (Lawyer et al., 2006;Toulopoulou et al., 2004), but could be of importance, since both ventricular enlargements and executive dysfunction are frequently implicated in bipolar disorder (Bora et al., 2009;Kempton et al., 2008).

Hippocampal volumes were related to working memory in all groups, which is in accordance with previous studies on bipolar disorder patients (Ali et al., 2000) and healthy controls (Cherbuin et al., 2009), while fMRI studies have shown activation in the hippocampus during working memory paradigms (Cabeza et al., 2002) in healthy subjects. From the literature one would expect the left hippocampus to be associated with verbal memory (Toulopoulou et al., 2004), whereas the right hippocampus has been shown to be important for spatial memory functioning (Antonova et al., 2004). Hippocampus volume relationships with various memory functions may hypothetically reflect participation in different networks connecting the hippocampus with various cortical regions and subcortical structures, or a common encoding/consolidation strategy across a variety of cognitive tasks. Alternatively, different subregions within the hippocampus could be associated with different neurocognitive tasks, as suggested by the specific CA3 subregion involvement in working memory (Kesner, 2007). Inconsistency across studies could also be due to methodological differences. For example, the FS segmentation of the hippocampus includes volumes of the whole hippocampal complex including the subiculum, fimbria and alveus (white matter) in addition to the CA regions and dentate gyrus (Cherbuin et al., 2009). Thus, it might not be comparable to manually traced hippocampi by other definitions.

The putamen volume relationship with verbal learning in all groups replicate the association found by Lawyer *et al.* (2006) in the HUBIN cohort. The strongest association was found in the schizophrenia group, suggesting that the normal negative relationship observed in healthy controls is exacerbated in schizophrenia.

The negative relationships in Study III and IV, i.e., that larger brain structure size was related to poorer neurocognitive performance, were unexpected in view of the findings from Study I of positive relationships only. One might speculate that the negative relationships indicate lack of functional pruning during development causing inefficient neurocognitive functioning, or a compensatory increase in size through synaptic formation in individuals with relatively poorer neurocognitive performance. It has been proposed that inverse relationships between hippocampus and neurocognition could reflect problems during neuronal migration, which may lead to abnormal proliferation of neurons and neuronal connections and, consequently, an increased size of the hippocampus. The resulting increased size may subsequently lead to inefficient information processing (Chantome et al., 1999). Alternatively, the inverse structure/function relationships in the younger TOP cohort may be due to age effects.

5.1.4 Effects of age

Normal ageing is characterized by overall brain tissue atrophy accompanied by ventricular enlargement. Cross-sectional studies on healthy subjects have demonstrated continuous decline in cortical thickness (Fjell et al., 2009a;Salat et al., 2004;Tamnes et al., 2010a) and subcortical volumes (Ostby et al., 2009;Raz et al., 2003;Walhovd et al., 2009) from late childhood into old age with considerable regional variability. Cortical thickness in prefrontal regions show the greatest age-related decline, while the medial temporal lobe is relatively spared (Lemaitre et al., 2010). The findings for surface area indicate a more homogeneous age decline across the cortex, and surface area is presumed to be less affected by normal ageing (Lemaitre et al., 2010).

Concurrent with the brain structure changes that occur during development, driven by pruning (elimination of excess neurons, synapses and dendrites) or myelination along the white matter/grey matter border, cognition continues to improve throughout childhood (Courchesne et al., 2000;Giedd and Rapoport, 2010;Sowell et al., 2001;Tamnes et al., 2010b). Cognitive decline begins in early adulthood for most neurocognitive measures, such as working and verbal memory and speed of processing. Vocabulary, which is an experience dependent measure, is stable until late

adulthood (Salthouse, 2010). However, the exact age for peak performance for each cognitive task remains poorly defined. Consequently, the normal relationships between brain structure measurements and cognitive performance change over time and, the results from scientific studies depend on the age range of the subject sample under investigation.

Earlier reports suggested accelerated age-related brain tissue loss in schizophrenia compared with healthy subjects (Hulshoff Pol et al., 2002). However, successive studies have found similar age effects on cortical thickness reduction in first-episode (Wiegand et al., 2004) and chronic (Kuperberg et al., 2003;Nesvag et al., 2008) schizophrenia, compared with healthy controls. With regard to structure/function relationships, similar effects of age have been found for schizophrenia patients and healthy controls (Premkumar et al., 2008), with stronger relationships in older subjects than in younger subjects. The different results for cortical structure/function relationships in the relatively older and younger cohorts in study I and study III, respectively, suggest that age effects are confounds that were not properly adjusted for by including age as a covariate.

Van Petten (2004) suggested three theories for structure/function relationships based on observations from studies on hippocampal volumes and memory functions in healthy subjects. The theories could also apply to other structure/function relationships and relationships in mental diseases. First, *the bigger is better* hypothesis simply suggests that larger brain structure size results in stronger or better function regardless of the underlying causative factors. Second, *the neuropsychological perspective* posits that any normal structure will support normal function, and that loss of tissue will lead to decline in function. However, taking into account normal ageing, with volume loss and cognitive decline, the timing for the onset of "ageing" needs to be defined for each brain structure, and for each neurocognitive domain. This theory predicts increasingly positive correlations between structure and function during ageing. Third, *the developmental perspective* emphasizes the concurrent grey matter tissue loss and cognitive improvement during childhood and adolescence. This theory predicts increasingly negative structure/function correlations from the onset of developmental tissue loss until the peak of cognitive performance. The two latter hypotheses may be combined.

The present findings of widespread positive cortical thickness relationships in the older cohort (Study I) and negative relationships in the younger cohort (Study III)

support the theory of increasingly positive relationships when brain tissue decrease related to ageing, consistent with *the neuropsychological perspective.* The main focus of the structure/function studies was that of diagnostic effects. Therefore, we did not specifically investigate the effects of age in the present studies. Investigations of age effects in a sample consisting of two patient groups and a healthy control group are highly complex, since different brain structure and cognition trajectories might hypothetically exist for all groups in the present sample.

5.1.5 Disease specific relationships

The relationships between brain structure and neurocognitive functioning demonstrated in the present studies were for the most part similar for all subject groups, but some relationships were specific to schizophrenia and/or bipolar disorder. These differences in relationships may provide valuable information about underlying pathophysiology and biological quantitative traits that may help to reduce the phenotypic heterogeneity of psychosis.

Most of the between-group differences for cortical relationships were near or within the temporal lobe. Different relationships between temporo-occipital cortical thickness and surface area and verbal abilities were found between schizophrenia patients and healthy controls. The temporo-occipital region is important for word recognition and is activated during word reading tasks in fMRI studies (Brem et al., 2006), with a left lateralization activation pattern. The present results suggest that these regions have been specifically excluded from the normal functioning network underlying word processing in schizophrenia. Also, there were diagnostic group interactions between schizophrenia and healthy controls for the relationships between cortical thickness and processing speed in several temporal brain regions. Processing speed performance, which has been proposed to represent a more generalized cognitive feature underlying other speed-dependent cognitive tasks (Dickinson et al., 2007), has previously been related to widespread brain regions (Sanfilipo et al., 2002). However, only the present relationship between *transverse temporal* cortical thickness and processing speed was found to be different from both bipolar disorder and healthy controls, and consequently, specific to schizophrenia. Interestingly, Kasai *et al*. (2003a) reported progressive grey matter reduction in the transverse temporal region in the early stages of disease specifically in schizophrenia, and not in affective psychoses. Moreover, the observed grey matter decline was associated with clinical scores of disorganization. In sum, these findings suggest that grey matter integrity in the

transverse temporal region may be important for clinical and cognitive functions known to be affected in schizophrenia.

To my knowledge, this is the first study (III) to demonstrate a specific relationship between size of temporal lobe cortex and working memory performance in bipolar disorder. Functional MRI studies have found abnormal activation in the temporal cortex during working memory tasks in bipolar disorder patients relative to healthy controls (Adler et al., 2004;Monks et al., 2004) and reduced fronto-temporal connectivity in pediatric bipolar disorder (Dickstein et al., 2010). The frontal lobe has consistently been implicated in working memory performance and, the present temporal pole abnormalities may be secondary to frontal lobe dysfunction.

We found specific relationships between left putamen volumes and working memory in schizophrenia and, common relationships between right putamen volumes and set-shifting in schizophrenia and bipolar disorder. Putamen, which is part of the dorsal striatum, is functionally and anatomically connected with other parts of the brain and participates in parallel loops, forming the so-called cortico-striatal-pallido-thalamo-cortical circuitries. Several of the loops include prefrontal and temporal non-motor areas (Alexander et al., 1986;Middleton and Strick, 2000). Although putamen is primarily connected with sensori-motor cortical regions, the loops have been shown to communicate with each other, enabling influence on other cortical regions known to be involved in higher order cognitive functioning. Thus, the differences in relationships between putamen and working memory and set-shifting in schizophrenia and bipolar disorder patients compared to healthy controls may be due not only to pathology directly related to putamen structure volumes, but also to any part of the several parallel loops involving the putamen.

Elevated striatal dopamine levels have consistently been shown in schizophrenia patients (Howes and Kapur, 2009) and there is evidence that striatal dopaminergic abnormalities are linked with cognitive dysfunction (Simpson et al., 2010) in the disease. Of pathophysiological relevance to the present findings, Kellendonk *et al.* (2006) performed a study on transgenic mice, that were overexpressing D2 receptors in the striatum, and showed that the mice exhibited selective deficits in working memory and flexibility compared with those with normal levels of dopamine, and that the deficits remained after the overexpression was switched off, thus suggesting that developmental changes caused the cognitive deficits. Furthermore, the striatal dopamine levels affected the level of prefrontal dopamine transmission; however, it is

not known whether the cognitive dysfunction is primary or secondary to striatal dysfunction.

The relationships between left lateral ventricular volumes and motor speed were also similar in schizophrenia and bipolar disorder, and significantly stronger than, but not opposite to the relationships found in healthy controls (see section 5.1.3).

According to the previously presented hypothesis (section 1.8.1), among the assumptions for specific relationships in schizophrenia and bipolar disorder were that the patient groups evidenced both brain structure reduction and cognitive dysfunction. In the present samples, the schizophrenia groups showed significant widespread brain structure abnormalities *and* neurocognitive dysfunction, although the effect sizes were greater in the HUBIN study (Study I) than in the TOP study (study III and IV), for both measures. The abnormalities in the bipolar group were less extensive for both brain structure and neurocognition, and some results were specific to the bipolar I disorder subgroup. Consequently, specific relationships in both groups were expected, but with a greater number of specific relationships in schizophrenia relative to bipolar disorder, which was true for the present studies. Larger inter-individual variability in brain structure and neurocognitive measures between schizophrenia patients compared to bipolar patients, and between bipolar patients compared to healthy controls could also account for the differences in number of relationships. Larger variability increases the probability to detect statistical relationships.

To summarize, the investigations of structure/function relationships in two independent samples demonstrated significant but *subtle* or weak relationships. This is in line with previous investigations in the field. Our comprehensive investigation of brain structures yielded relationships with neurocognition in both cortical and subcortical regions, consistent with the theories of brain networks as important for neurocognitive functioning. Certain specific relationships in schizophrenia and/or bipolar disorder were found and could reflect disturbances in specific regions within the networks underlying specific cognitive functions. One cannot automatically infer biological interaction from statistical interaction, but if our findings are replicated, they suggest that having a diagnosis of schizophrenia and bipolar disorder influence regional relationships between brain structure and neurocognition to some extent. If the demonstrated disrupted relationships are not replicated, and in consequence might not be true, the causes of structure abnormalities and cognitive impairment in

schizophrenia and bipolar disorder may be independent rather than interdependent, and these characteristics represent different, but co-occurring disease-related trajectories.

5.2 Methodological issues

5.2.1 Medication as confounding factor

Information on current medication was obtained during clinical interview, from the medical record, and by asking the patient's therapist if necessary. The description of types and dosages of medication used by the patient are considered to be quite accurate. However, we do not know to what extent the patients, chiefly the outpatients, were compliant to their treatment regimens. And even if fully compliant, individual differences in metabolism may have affected the biological significance of each medication. Both typical and atypical antipsychotics have been found to have an effect on cortical grey matter volumes, but findings are inconsistent (Smieskova et al., 2009). Studies on high-risk individuals (Fusar-Poli et al., 2010;Jung et al., 2009) and neuroleptic-naïve patients (Venkatasubramanian et al., 2008), which avoid the potentially confounding medication effects, show cortical abnormalities qualitatively similar to those found in medicated schizophrenia patients. Furthermore, some studies report that atypical antipsychotics even increase cortical volumes (Scherk and Falkai, 2006), implicating that findings of cortical brain reduction is, at least in part, related to having a psychotic disorder. For the basal ganglia, several reviews have reported that typical AP increase striatal volumes, while the atypical medication effects are inverse, or even reverse the enlargements exerted by typical AP medication (Brandt and Bonelli, 2008;Navari and Dazzan, 2009). We have found no significant effects of antipsychotic medication on the cortical or subcortical brain structure measures used in the present studies.

Only 14 % of the patients in the bipolar disorder group and 2 % of the patients in the schizophrenia group (study II) used lithium. Thus, due to the small numbers, there were limitations to the statistical analyses of a lithium effect on brain structure. Previous studies have found lithium use to be associated with increased grey matter volume in the anterior cingulate gyrus (Phillips et al., 2008), increased amygdala (Usher et al., 2010b) and hippocampus volumes (Hallahan et al., 2011). Differences in the proportion of patients using lithium between studies could explain some of the heterogeneity in the bipolar disorder literature. The mechanisms for medication effect

on brain structure have been proposed to be those of neurotoxicity or neuroprotection (Thompson et al., 2009). Neither lithium nor AP use were found to have a significant effect on the group differences in neurocognitive performance in a previous study on the TOP study sample (Simonsen et al., 2011).

In conclusion, due to the study design of a naturalistic study, the complete effects of medication are not known. And although we have statistically corrected for the potential effects of medication, we cannot completely exclude the possibility that the present brain structure abnormalities and relationships with neurocognition are partially related to medication use.

5.2.2 Other confounding factors

Potential demographic and clinical confounders were controlled for, unless considered to be illness related. However, in a naturalistic setting, there are variables that were not measured or are poorly defined or unknown and were consequently not corrected for, but which might affect the results. Brain structure and neurocognitive measurements may vary according to differences in sex, symptoms, smoking status, substance and alcohol abuse, stress, nutrition state, or other social factors (Weinberger and McClure, 2002).

Sex distributions were different between groups in all four studies and were consequently corrected for. Regional cortical thickness differences between men and women have been found by some (Luders et al., 2006;Sowell et al., 2007), but not all investigations (Fjell et al., 2009b) of healthy adults. We have found no effect of sex differences on regional cortical thickness in any of the present subject groups. The effect of sex on regional surface area appear to depend on whether the analyses are corrected for whole-brain volume or not and, whole-brain volumes and sex are highly correlated (Luders and Toga, 2010;Nopoulos et al., 2000). In the present study of cortical surface area (III), sex was a significant covariate and was therefore included in all analyses. In general, women perform better than men on neurocognitive tasks, but sex differences have not been found to affect the observed group differences in the TOP sample (Simonsen et al., 2011).

Symptom severity may relate to brain structure (Nesvag et al., 2009) and neurocognition. Negative symptoms in particular have been found to correlate with neurocognition (Dominguez et al., 2009;Nieuwenstein et al., 2001). In order for the patients to be included in the study in the first place, they had to complete a

comprehensive interview, blood tests, and MRI and neurocognitive assessments and accordingly had to be in a stable phase of the disease. Thus, symptom load is expected to demonstrate small effects on the present analyses.

The current subject sample included patients with *substance and alcohol abuse*. We performed the analyses without the subjects who had reported current cannabis abuse and found the same results. The effect of alcohol consumption has previously been investigated in the HUBIN sample, showing effects on white matter tissue volumes, but not grey matter tissue volumes (Nesvag et al., 2007). *Education* and current IQ were considered to be illness-related factors in all studies and the observed group differences were, therefore, not controlled for. A study representing an overlapping sample with the present, found no effect of differences in education and IQ on group differences in neurocognitive functioning between schizophrenia and bipolar disorder (Simonsen et al., 2011).

Last, in accordance with the notion that the neurons of the brain exhibit synaptic plasticity, as evident through formation and reformation or maintenance of dendrites and synapses, a number of MRI studies have investigated brain changes related to experience or cognitive and physical training. Grey matter changes have been found as a direct consequence of cognitive training in longitudinal studies (Draganski et al., 2004;Draganski et al., 2006;Engvig et al., 2010). Accordingly, lack of training or experience in mentally ill individuals who are unemployed or unable to sustain normal social and cognitive activity, could hypothetically account for parts of the smaller grey matter measures observed in mental illnesses, at least in those with advanced disease.

5.2.3 Neurocognitive assessments

Neuropsychological functioning has been proposed to be well suited for investigations of structure/function relationships in schizophrenia and bipolar disorder, since dysfunction appear to be trait, rather than state dependent and is relatively stable after illness onset. Previously, there has been a lack of consensus on a standard way to separate cognitive functioning into key dimensions, or identify the cognitive process that is assessed with each cognitive test. The MATRICS (Measurement and Treatment Research to improve Cognition in Schizophrenia) initiative, for which one of the primary goals was to develop a cognitive battery for treatment evaluation, identified major separable cognitive domains in schizophrenia, based on statistical factor analyses (Nuechterlein et al., 2008). Of relevance to the present topic, these domains were also to serve as a basic structure to understand the underlying nature of

cognitive impairment in such disorders. The selected standardized neuropsychological tests used in the present thesis are not equal to, but accord well with those found in the MATRICS battery, with a few exceptions. We did not include measures of sustained attention or visual memory learning and memory. Especially measures of sustained attention have been related to grey matter measures in healthy subjects (Salgado-Pineda et al., 2003;Westlye et al., 2011). However, the selection of tasks was limited in order to restrict the number of statistical tests. For the current analyses we used single tests from each domain, and in this way we might have missed relationships with other relevant cognitive functions. For instance, the selected verbal learning tests only included measures of immediate learning from lists, while tests of delayed recall and story learning was not included. In the TOP sample immediate verbal learning was highly correlated with short delayed list recall and long delayed list recall (r = 0.83), while the correlation with story learning, as measured with the Wechsler Memory Scale (Wechsler, 2007b) was moderate (r = 0.30). By using single tests from widely used neuropsychological tests, instead of data-derived composite scores, direct replications of the current findings and comparisons across studies are facilitated.

The TOP sample is characterized by higher IQ scores than expected from the previous literature both in the patient and healthy control populations. The measure of current IQ was based on the WASI (Wechsler, 2007a). However, the WASI does not contain measures of processing speed or working memory. A previous thesis from the TOP study reported IQ to reduce from 106.5 to 100.6 in the schizophrenia group if the Digit Symbol and Digit Span tasks were included in accordance with WAIS III (Vaskinn, 2008). Still, higher than average IQ scores may reflect that high functioning individuals with academic interests have been more likely to participate in the TOP study. Alternatively, this may suggest that the current outpatients and non-acute inpatients are in fact better functioning than indicated by studies with different recruitment procedures than in TOP.

5.2.4 MRI measurements and processing

For both MR scanner sites, the acquisition parameters were optimized for increased grey/white matter image contrast. All MR images were evaluated for gross neuropathology by neuroradiologists. MR scanning of patients and controls were performed concurrently during the whole study periods thus securing that time did not confound the results and, there were no scanner upgrades during the study periods. The same magnetic field strength was used at both sites, but there were still

minor differences in MR data acquisition between the two sites that might impinge on a comparison of the results, such as number of acquisitions, different pulse sequences and manufacturers (Han et al., 2006).

Previous reviews have commented on the variability in how cortical brain regions and subcortical structure volumes are defined, leading to difficulties in the interpretation of findings across studies (Antonova et al., 2004;Crespo-Facorro et al., 2007a). The cortical region boundaries (parcellations) as defined by the FreeSurfer software are anatomically valid and parcel the brain regions into functionally relevant compartments. Furthermore, using a standardized method facilitates replications in independent samples. The methods used for the cortical measures in FreeSurfer have been validated by histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). For sub-cortical segmentation, reliable measurements have been shown for ventricle, hippocampus, caudate, putamen, pallidum and brainstem volumes (Fischl et al., 2002;Morey et al., 2009) and across multiple acquisitions within-scanners (Jovicich et al., 2009). The reliability of relationships between cortical thickness and cognitive performance has been tested across scanners and at different time points. The results were shown to be highly reliable in terms of both spatial localization and magnitude of absolute cortical thickness measurements (Dickerson et al., 2008). Hippocampus volumes that were automatically segmented by FreeSurfer and manually traced have been found to show essentially equal relationships with working memory performance (Cherbuin et al., 2009). No formal validity or reliability testing was performed for the processing of MR images. However, the automated procedures need only minimal manual intervention, which was performed without knowledge of the subjects' group identity. The data images from both data sets were processed by laboratory assistants. The assistants working on the TOP data were part of the FreeSurfer laboratory in San Diego. Laboratory assistants working at the Institute of Psychology in Oslo processed the HUBIN data set and, were closely supervised by senior researchers who have received their training from the FreeSurfer group at Harvard University.

5.2.5 Diagnostic categories

All diagnoses were made according to the DSM manual, in which schizophrenia and bipolar spectrum disorders are mutually exclusive. Yet difficulties in delineating the disorders and their subtypes against each other are common in clinical practice due to symptom overlap. In studies like the present, where patients are categorized according

to diagnosis, and subsequently compared with each other on a group level, great care must be used in the diagnostic assessments. For instance, the schizoaffective disorder group differs from the bipolar disorder group only by having psychotic symptoms in a certain period of time, without simultaneous affective symptoms. In the HUBIN study, diagnostic reliability between researchers performing clinical interviews was ascertained by calculating agreement and Cohen's un-weighted nominal kappa among the research psychiatrists performing the clinical interviews. Also, the psychiatrists who rated the record reviews using OPCRIT, which has been shown to be a reliable source for making DSM psychosis diagnosis (McGuffin and Farmer, 1991), had received their training by the British developers of the instrument. The diagnostic evaluations in the TOP study were discussed in frequent consensus meetings supervised by experienced psychiatrists specialized in diagnostic assessments. In order to optimize reliability, all interviewers in the TOP study participated in standardized training in all parts of the protocol (also for PANSS and GAF). Tests for inter-rater reliability were conducted for the SCID diagnoses with a kappa for concordance of diagnosis of 0.77 (Birkenaes et al., 2007). Last, about 1/3 of the patients in study II were followed as part of a longitudinal study, and information from follow-up visits was used to secure correct diagnoses, ensuring temporal stability.

5.2.6 Representativity

The HUBIN and TOP studies have recruited patients from the Swedish and Norwegian health care system respectively. Both systems are based on catchment area patient admittance systems, which provide public mental health care to all individuals with severe mental illness within a given catchment area, resulting in high degree of patient representativity. However, patients who for some reason were not treated at psychiatric units or were not able or willing to consent to participate in the studies were not eligible for examination. The control subjects were randomly selected from statistical records and were from the same catchment areas as the patients. Not all responded to the invitation to the study. Those who did participate are expected to be biased towards higher education, better social adjustment and to be more than average interested in research than in the general population.

5.2.7 Limitations

The cross-sectional design limits inferences about causality. In case causality has been implied by the use of terms like "predictor" in the regression models, I would like to emphasize that all relationships in the present thesis are mere *correlations* of

phenotypes. Also, this design limits our understanding of the course of brain structure alteration and cognitive decline; for example, the performance of an individual on neuropsychological tests might be perceived as within the normal range while the subject in question, in fact, had experienced decline from a high-performing level during the course of illness. Also, rate of change, not captured in a cross-sectional design, may be associated with cortical thickness changes (Murphy et al., 2010).

The statistical models used in the present studies were based on the assumption of linear relationships between structure and function; yet, non-linear relationships might better explain some of the relationships. Moreover, only correlational analyses were performed in the present studies. A different approach could be to compare brain structure measurements between patient groups based on degree of neurocognitive impairment (Rusch et al., 2007;Wexler et al., 2009). In general, dividing a sample into sub-samples lower the statistical power in the analyses. In order to do a meaningful comparison, one would have to compare those without impairment with those who are severely or clinically impaired. Clinically significant impairment is often defined as scores equal or below 1.5 SD below the mean of the controls. Simonsen *et al.* (2011) found 33% of the schizophrenia group and 23% of the bipolar disorder group in the TOP study sample to be impaired by this definition, rendering small groups to be compared. In addition, both the brain structure measurements and the neurocognitive score distributions, demonstrate great overlap between the groups with unimodal distributions. By using a longitudinal design, comparing brain structure between patients with significant cognitive decline over time with cognitively stable patients would be possible, which in turn could yield clinical meaningful information, enhancing our ability to predict outcome.

6. Conclusion

The studies in the present thesis have demonstrated widespread brain structure abnormalities that are similar in schizophrenia and bipolar disorder, which is consistent with common underlying pathophysiology. However, the findings from the current thesis do not show that cognitive dysfunction in schizophrenia and bipolar disorder have common brain structural correlates that are deviant from what is found in healthy controls. In fact, there were only two such relationships that were common to both patient groups. Brain structure abnormalities in schizophrenia are more pronounced compared to bipolar disorder and, there were more structure/function relationships that were specific to schizophrenia than to bipolar disorder, confirming the more extensive abnormalities in schizophrenia. Specific relationships between brain structure and neurocognition in schizophrenia and/or bipolar disorder could reflect disturbances in specific regions within the brain networks underlying specific cognitive functions.

Future research

The current findings suggest that age effects should be considered when conducting structure/function studies. In order to disentangle the effects of age and illness duration, and to investigate structure/function relationships in different stages, longitudinal studies of large samples are needed. Also, enhanced cognitive abilities concurrent with reductions in brain structures in childhood and adolescence may imply that refinement in connectivity, rather than or in addition to grey matter amount, is beneficial for cognitive performance. Thus, multimodal studies including fMRI and DTI measures to study connectivity and white matter integrity could elucidate some of the processes accompanying cognitive changes related to disease.

Suggestions for future studies

- *Replication.* Being the first comprehensive study to compare cortical thickness and the relationship with neurocognition across schizophrenia, bipolar disorder and healthy controls, our results need to be replicated in independent samples

- The *statistical analyses* in the present studies were limited to general linear models. There are reports of high specificity and sensitivity in diagnostic predictions, using advanced statistical models, such as Principal Component

Analysis (PCA) on brain structure measurements and neuropsychological test scores combined. The results from using other statistical clustering models remain largely unexplored. The ability to predict diagnosis can contribute to the clinical work and help defining phenotypes in psychiatric research.

- *Longitudinal study.* The currently used data are part of a longitudinal study. Results from longitudinal studies will aid in the understanding of individual brain structure and neurocognitive trajectories and how, and if, they are inter-related. Optimally, such a study should meet several criteria: (1) a large first episode sample; (2) a large healthy control sample; (3) a low attrition rate in both samples in order to ensure that they are representative; (4) surveillance over an adequate period of time to determine the pattern and degree of change; (5) sampling with multiple time points in order to determine the pattern of change and its relation to the time of onset.

- *White matter* integrity as measured with DTI and subcortical white matter volume relationships with neurocognition may complement the present findings.

- *Surface area* relationships with IQ. Results from previous studies indicate differential regional relationships between surface area and general neurocognitive measures such as IQ, between schizophrenia patients and healthy controls. However, no study has explored such relationships across the whole cortical mantle in a large subject sample such as the present. Unpublished work from our group demonstrates regional surface area abnormalities specifically in schizophrenia, compared with bipolar disorder and healthy controls. Further investigations of putative relationships with general cognitive functioning might add to the understanding of the functional relevance of these findings.

- *Genetic and environmental effects* on structure/function relationships. Mainly similar structure/function relationships in the patient and healthy populations were found in the present thesis. Genetic variation and environmental factors such as obstetrical complications, may modulate the relationships, and differentiate between patients groups and healthy controls.

7. Reference List

Abi-Dargham, A., Mawlawi, O., Lombardo, I. et al, 2002. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci. 22, 3708-3719.

Adler, C. M., Holland, S. K., Schmithorst, V. et al, 2004. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disord. 6, 540-549.

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

Alexander, G. E., DeLong, M. R. and Strick, P. L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 9, 357-381.

Ali, S. O., Denicoff, K. D., Altshuler, L. L. et al, 2000. A preliminary study of the relation of neuropsychological performance to neuroanatomic structures in bipolar disorder. Neuropsychiatry Neuropsychol Behav Neurol. 13, 20-28.

Altshuler, L. L., Bartzokis, G., Grieder, T. et al, 2000. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry. 48, 147-162.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders - Revised., 3rd edn. Washington DC.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders., 4th edn. Washington DC.

Andreasen, N. C., Paradiso, S. and O'Leary, D. S., 1998. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull. 24, 203-218.

Angst, J., 1998. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord. 50, 143-151.

Antonova, E., Kumari, V., Morris, R. et al, 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry. 58, 457-467.

Antonova, E., Sharma, T., Morris, R. et al, 2004. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res. 70, 117-145.

Arnone, D., Cavanagh, J., Gerber, D. et al, 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. Br J Psychiatry. 195, 194-201.

Ashburner, J. and Friston, K. J., 2000. Voxel-based morphometry--the methods. Neuroimage. 11, 805-821.

Baare, W. F., Hulshoff Pol, H. E., Hijman, R. et al, 1999. Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. Biol Psychiatry. 45, 1597-1605.

Bakken, T., Bloss, C. S., Cooper, R. et al, 2011. A common genetic variant on chromosome 15q12 associates with frontotemporal cortical thinning and executive function in schizophrenia. Submitted.

Balanza-Martinez, V., Selva, G., Martinez-Aran, A. et al, 2010. Neurocognition in bipolar disorders--a closer look at comorbidities and medications. Eur J Pharmacol. 626, 87-96.

Barch, D. M., 2009. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. Curr Psychiatry Rep. 11, 313-319.

Barrett, E. A., Sundet, K., Faerden, A. et al, 2010. Suicidality before and in the early phases of first episode psychosis. Schizophr Res. 119, 11-17.

Bearden, C. E., Hoffman, K. M. and Cannon, T. D., 2001. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disord. 3, 106-150.

Benes, F. M., 2007. Searching for unique endophenotypes for schizophrenia and bipolar disorder within neural circuits and their molecular regulatory mechanisms. Schizophr Bull. 33, 932-936.

Berrettini, W. H., 2001. Molecular linkage studies of bipolar disorders. Bipolar Disord. 3, 276-283.

Birkenaes, A. B., Opjordsmoen, S., Brunborg, C. et al, 2007. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 68, 917-923.

Bleuler, E., 1950. Dementia Praecox or the Group of Schizophrenias. International Universities Press, New York.

Bonilha, L., Molnar, C., Horner, M. D. et al, 2008. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. Schizophr Res. 101, 142-151.

Bora, E., Fornito, A., Yucel, M. et al, 2010. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol Psychiatry. 67, 1097-1105.

Bora, E., Yucel, M. and Pantelis, C., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord. 113, 1-20.

Bouras, C., Kovari, E., Hof, P. R. et al, 2001. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. Acta Neuropathol. 102, 373-379.

Brambilla, P., Hatch, J. P. and Soares, J. C., 2008. Limbic changes identified by imaging in bipolar patients. Curr Psychiatry Rep. 10, 505-509.

Brandt, G. N. and Bonelli, R. M., 2008. Structural neuroimaging of the basal ganglia in schizophrenic patients: a review. Wien Med Wochenschr. 158, 84-90.

Brem, S., Bucher, K., Halder, P. et al, 2006. Evidence for developmental changes in the visual word processing network beyond adolescence. Neuroimage. 29, 822-837.

Broca, P., 1861. Remarquès sur la siège de la faculté du langage articulé, suivés d'une observation d'aphémie (perte de la parole). Billions de la Société Anatomique de Paris, Paris, pp. 330-357.

Brodal, P., 2007. Sentralnervesystemet., 4th edn. Universitetsforlaget, Oslo.

Brodmann, K., 1909. Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipen dargestellt auf Grund des Zellenbaues. Barth, Leipzig.

Brown, A. S., van, O. J., Driessens, C. et al, 2000. Further evidence of relation between prenatal famine and major affective disorder. Am J Psychiatry. 157, 190-195.

Brown, S., 1997. Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry. 171, 502-508.

Bruno, S. D., Papadopoulou, K., Cercignani, M. et al, 2006. Structural brain correlates of IQ changes in bipolar disorder. Psychol Med. 36, 609-618.

Buckner, R. L., Head, D., Parker, J. et al, 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage. 23, 724-738.

Burdick, K. E., Goldberg, J. F., Harrow, M. et al, 2006. Neurocognition as a stable endophenotype in bipolar disorder and schizophrenia. J Nerv Ment Dis. 194, 255-260.

Cabeza, R., Dolcos, F., Graham, R. et al, 2002. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. Neuroimage. 16, 317-330.

Cardno, A. G., Marshall, E. J., Coid, B. et al, 1999. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry. 56, 162-168.

Chantome, M., Perruchet, P., Hasboun, D. et al, 1999. Is there a negative correlation between explicit memory and hippocampal volume? Neuroimage. 10, 589-595.

Cherbuin, N., Anstey, K. J., Reglade-Meslin, C. et al, 2009. In vivo hippocampal measurement and memory: a comparison of manual tracing and automated segmentation in a large community-based sample. PLoS One. 4, e5265.

Cherlyn, S. Y., Woon, P. S., Liu, J. J. et al, 2010. Genetic association studies of glutamate, GABA and related genes in schizophrenia and bipolar disorder: a decade of advance. Neurosci Biobehav Rev. 34, 958-977.

Chumakov, I., Blumenfeld, M., Guerassimenko, O. et al, 2002. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A. 99, 13675-13680.

Coffman, J. A., Bornstein, R. A., Olson, S. C. et al, 1990. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biol Psychiatry. 27, 1188-1196.

Colom, F., Vieta, E., Martinez-Aran, A. et al, 2003. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry. 60, 402-407.

Coryell, W., Scheftner, W., Keller, M. et al, 1993. The enduring psychosocial consequences of mania and depression. Am J Psychiatry. 150, 720-727.

Courchesne, E., Chisum, H. J., Townsend, J. et al, 2000. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology. 216, 672-682.

Cousins, D. A., Butts, K. and Young, A. H., 2009. The role of dopamine in bipolar disorder. Bipolar Disord. 11, 787-806.

Crespo-Facorro, B., Barbadillo, L., Pelayo-Teran, J. M. et al, 2007a. Neuropsychological functioning and brain structure in schizophrenia. Int Rev Psychiatry. 19, 325-336.

Crespo-Facorro, B., Kim, J., Andreasen, N. C. et al, 2000. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. Biol Psychiatry. 48, 110-119.

Crespo-Facorro, B., Roiz-Santianez, R., Pelayo-Teran, J. M. et al, 2007b. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. Neuroimage. 35, 1613-1623.

Crespo-Facorro, B., Roiz-Santianez, R., Perez-Iglesias, R. et al, 2010. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. Psychol Med. 1-12.

Dalaker, T. O., Zivadinov, R., Ramasamy, D. P. et al, 2010. Ventricular enlargement and mild cognitive impairment in early Parkinson's disease. Mov Disord. doi: 10.1002/mds.23443.

Dale, A. M., Fischl, B. and Sereno, M. I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 9, 179-194.

Dale, A. M. and Sereno, M. I., 1993. Improved Localization of Cortical Activity by Combining Eeg and Meg with Mri Cortical Surface Reconstruction - A Linear-Approach. Journal of Cognitive Neuroscience. 5, 162-176.

Dalman, C. and Allebeck, P., 2002. Paternal age and schizophrenia: further support for an association. Am J Psychiatry. 159, 1591-1592.

Delis, D., Kramer, J., Kaplan, E. et al, 2004. California Verbal Learning Test - Second edition (CVLT-II). Norwegian Manual Supplement Pearson Assessment, Stockhom.

Delis, DC., Kaplan, E. and Kramer, J., 2005. The Delis-Kaplan Executive Function System (D-KEFS). Norwegian Manual Supplement Pearson Assessment, Stockholm.

DeLisi, L. E., Sakuma, M., Maurizio, A. M. et al, 2004. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res. 130, 57-70.

Desikan, R. S., Segonne, F., Fischl, B. et al, 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 31, 968-980.

Dickerson, B. C., Fenstermacher, E., Salat, D. H. et al, 2008. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage. 39, 10-18.

Dickinson, D., Ramsey, M. E. and Gold, J. M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry. 64, 532-542.

Dickstein, D. P., Gorrostieta, C., Ombao, H. et al, 2010. Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. Biol Psychiatry. 68, 839-846.

Dominguez, M. G., Viechtbauer, W., Simons, C. J. et al, 2009. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. Psychol Bull. 135, 157-171.

Draganski, B., Gaser, C., Busch, V. et al, 2004. Neuroplasticity: changes in grey matter induced by training. Nature. 427, 311-312.

Draganski, B., Gaser, C., Kempermann, G. et al, 2006. Temporal and spatial dynamics of brain structure changes during extensive learning. J Neurosci. 26, 6314-6317.

Egan, M. F., Goldberg, T. E., Kolachana, B. S. et al, 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 98, 6917-6922.

Ekerholm, M. and Svala, F., 2008. Neurocognitive function in schizophrenia: A follow-up study. Stockholm University, Faculty of Social Sciences, Stockholm.

Ekholm, B., Ekholm, A., Adolfsson, R. et al, 2005. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. Nordic Journal of Psychiatry. 59, 457-464.

Ellison-Wright, I. and Bullmore, E., 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res. 108, 3-10.

Ellison-Wright, I. and Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 117, 1-12.

Ellison-Wright, I., Glahn, D. C., Laird, A. R. et al, 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am J Psychiatry. 165, 1015-1023.

Engh, J. A., Friis, S., Birkenaes, A. B. et al, 2010. Delusions are associated with poor cognitive insight in schizophrenia. Schizophr Bull. 36, 830-835.

Engvig, A., Fjell, A. M., Westlye, L. T. et al, 2010. Effects of memory training on cortical thickness in the elderly. Neuroimage. 52, 1667-1676.

Farrow, T. F., Whitford, T. J., Williams, L. M. et al, 2005. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biol Psychiatry. 58, 713-723.

Fennema-Notestine, C., Gamst, A. C., Quinn, B. T. et al, 2007. Feasibility of multi-site clinical structural neuroimaging studies of aging using legacy data. Neuroinformatics. 5, 235-245.

First, M. B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders.

Fischl, B., Liu, A. and Dale, A. M., 2001. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging. 20, 70-80.

Fischl, B., Salat, D. H., Busa, E. et al, 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 33, 341-355.

Fischl, B., Sereno, M. I. and Dale, A. M., 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9, 195-207.

Fischl, B., van der, K. A., Destrieux, C. et al, 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex. 14, 11-22.

Fjell, A. M. and Walhovd, K. B., 2010. Structural brain changes in aging: courses, causes and cognitive consequences. Rev Neurosci. 21, 187-221.

Fjell, A. M., Westlye, L. T., Amlien, I. et al, 2009a. High consistency of regional cortical thinning in aging across multiple samples. Cereb Cortex. 19, 2001-2012.

Fjell, A. M., Westlye, L. T., Amlien, I. et al, 2009b. Minute effects of sex on the aging brain: a multisample magnetic resonance imaging study of healthy aging and Alzheimer's disease. J Neurosci. 29, 8774-8783.

Flagstad, P., Glenthoj, B. Y. and Didriksen, M., 2005. Cognitive deficits caused by late gestational disruption of neurogenesis in rats: a preclinical model of schizophrenia. Neuropsychopharmacology. 30, 250-260.

Flourens, P., 1846. Phrenology examined Hogan and Thompson, Philadelphia.

Foland-Ross, L. C., Thompson, P. M., Sugar, C. A. et al, 2011. Investigation of Cortical Thickness Abnormalities in Lithium-Free Adults With Bipolar I Disorder Using Cortical Pattern Matching. Am J Psychiatry. doi: appi.ajp.2010.10060896 [pii];10.1176/appi.ajp.2010.10060896.

Fornito, A., Malhi, G. S., Lagopoulos, J. et al, 2008. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. Psychiatry Res. 162, 123-132.

Fornito, A., Yucel, M. and Pantelis, C., 2009a. Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder. Curr Opin Psychiatry. 22, 312-319.

Fornito, A., Yucel, M., Patti, J. et al, 2009b. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. Schizophr Res. 108, 104-113.

Fornito, A., Yucel, M., Wood, S. et al, 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. Cereb Cortex. 14, 424-431.

Fornito, A., Yucel, M., Wood, S. J. et al, 2009c. Anterior cingulate cortex abnormalities associated with a first psychotic episode in bipolar disorder. Br J Psychiatry. 194, 426-433.

Friston, K. J. and Frith, C. D., 1995. Schizophrenia: a disconnection syndrome? Clin Neurosci. 3, 89-97.

Fusar-Poli, P., Borgwardt, S., Crescini, A. et al, 2010. Neuroanatomy of vulnerability to psychosis: A voxel-based meta-analysis. Neurosci Biobehav Rev. doi: S0149-7634(10)00206-X [pii];10.1016/j.neubiorev.2010.12.005.

Gall, F. J. and Spurzheim, J. C., 1808. Recherches sur le système nerveux en général, et sur celui du cerveau en particulier. Memoirs, Paris.

Giedd, J. N. and Rapoport, J. L., 2010. Structural MRI of pediatric brain development: what have we learned and where are we going? Neuron. 67, 728-734.

Gitlin, M. J., Swendsen, J., Heller, T. L. et al, 1995. Relapse and impairment in bipolar disorder. Am J Psychiatry. 152, 1635-1640.

Goldberg, T. E., Torrey, E. F., Berman, K. F. et al, 1994. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. Psychiatry Res. 55, 51-61.

Goldman, A. L., Pezawas, L., Mattay, V. S. et al, 2009. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry. 66, 467-477.

Goldman-Rakic, P. S., 1988. Topography of cognition: parallel distributed networks in primate association cortex. Annu Rev Neurosci. 11, 137-156.

Goodwin, F. K., Ghaemi, S. N. and Jamison, K. R., 2007. Manic-depressive illness: bipolar disorders and recurrent depression. Oxford University Press.

Gottesman, I. I., Laursen, T. M., Bertelsen, A. et al, 2010. Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch Gen Psychiatry. 67, 252-257.

Graybiel, A. M., 2000. The basal ganglia. Curr Biol. 10, R509-R511.

Green, M. F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry. 67, Suppl-8.

Grozeva, D., Kirov, G., Ivanov, D. et al, 2010. Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. Arch Gen Psychiatry. 67, 318-327.

Gur, R. E., Turetsky, B. I., Cowell, P. E. et al, 2000. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 57, 769-775.

Gutierrez-Galve, L., Wheeler-Kingshott, C. A., Altmann, D. R. et al, 2010. Changes in the frontotemporal cortex and cognitive correlates in first-episode psychosis. Biol Psychiatry. 68, 51-60.

Haier, R. J., Jung, R. E., Yeo, R. A. et al, 2004. Structural brain variation and general intelligence. Neuroimage. 23, 425-433.

Haldane, M., Cunningham, G., Androutsos, C. et al, 2008. Structural brain correlates of response inhibition in Bipolar Disorder I. J Psychopharmacol. 22, 138-143.

Hallahan, B., Newell, J., Soares, J. C. et al, 2011. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 69, 326-335.

Han, X., Jovicich, J., Salat, D. et al, 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage. 32, 180-194.

Harrison, P. J., 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain. 122 (Pt 4), 593-624.

Harrison, P. J., 2002. The neuropathology of primary mood disorder. Brain. 125, 1428-1449.

Hartley, A. A. and Speer, N. K., 2000. Locating and fractionating working memory using functional neuroimaging: storage, maintenance, and executive functions. Microsc Res Tech. 51, 45-53.

Hattori, E., Liu, C., Badner, J. A. et al, 2003. Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. Am J Hum Genet. 72, 1131-1140.

Heaton, R. K., Chelune, G. J., Talley, J. L. et al, 1993. Wisconsin Card Sorting Test Manual, Revised and Expanded. Odessa.

Heinrichs, R. W., 2005. The primacy of cognition in schizophrenia. Am Psychol. 60, 229-242.

Heinrichs, R. W. and Zakzanis, K. K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 12, 426-445.

Heiskanen, T., Niskanen, L., Lyytikainen, R. et al, 2003. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry. 64, 575-579.

Henquet, C., Krabbendam, L., de, G. R. et al, 2006. Cannabis use and expression of mania in the general population. J Affect Disord. 95, 103-110.

Henquet, C., Murray, R., Linszen, D. et al, 2005. The environment and schizophrenia: the role of cannabis use. Schizophr Bull. 31, 608-612.

Hill, S. K., Bishop, J. R., Palumbo, D. et al, 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. Expert Rev Neurother. 10, 43-57.

Ho, B. C., Andreasen, N. C., Nopoulos, P. et al, 2003. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry. 60, 585-594.

Hoge, E. A., Friedman, L. and Schulz, S. C., 1999. Meta-analysis of brain size in bipolar disorder. Schizophr Res. 37, 177-181.

Hokama, H., Shenton, M. E., Nestor, P. G. et al, 1995. Caudate, putamen, and globus pallidus volume in schizophrenia: a quantitative MRI study. Psychiatry Res. 61, 209-229.

Honea, R., Crow, T. J., Passingham, D. et al, 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry. 162, 2233-2245.

Howes, O. D. and Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 35, 549-562.

Hulshoff Pol, H. E. and Kahn, R. S., 2008. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull. 34, 354-366.

Hulshoff Pol, H. E., Schnack, H. G., Bertens, M. G. et al, 2002. Volume changes in gray matter in patients with schizophrenia. Am J Psychiatry. 159, 244-250.

Huttenlocher, P. R., 1979. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res. 163, 195-205.

Jacobi, W. and Winkler, H., 1927. Encephalographische Studien an chronisch schizophrenen. Archiv für Psychiatrie und Nervenkrankheiten. 81, 299-332.

Joffe, R. T., MacQueen, G. M., Marriott, M. et al, 2004. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disord. 6, 62-66.

Johannessen, J. O., 2002. [Schizophrenia--incidence and significance]. Tidsskr Nor Laegeforen. 122, 2011-2014.

Johnstone, E. C., Crow, T. J., Frith, C. D. et al, 1976. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 2, 924-926.

Johnstone, E. C., Crow, T. J., Frith, C. D. et al, 1978. The dementia of dementia praecox. Acta Psychiatr Scand. 57, 305-324.

Jovicich, J., Czanner, S., Han, X. et al, 2009. MRI-derived measurements of human subcortical, ventricular and intracranial brain volumes: Reliability effects of scan sessions, acquisition sequences, data analyses, scanner upgrade, scanner vendors and field strengths. Neuroimage. 46, 177-192.

Jung, W. H., Kim, J. S., Jang, J. H. et al, 2009. Cortical Thickness Reduction in Individuals at Ultra-High-Risk for Psychosis. Schizophr Bull. doi: sbp151 [pii];10.1093/schbul/sbp151.

Kalus, P., Muller, T. J., Zuschratter, W. et al, 2000. The dendritic architecture of prefrontal pyramidal neurons in schizophrenic patients. Neuroreport. 11, 3621-3625.

Kane, J. M., Leucht, S., Carpenter, D. et al, 2003. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. J Clin Psychiatry. 64 Suppl 12, 5-19.

Kasai, K., Shenton, M. E., Salisbury, D. F. et al, 2003a. Progressive decrease of left Heschl gyrus and planum temporale gray matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry. 60, 766-775.

Kasai, K., Shenton, M. E., Salisbury, D. F. et al, 2003b. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch Gen Psychiatry. 60, 1069-1077.

Kay, S. R., Fiszbein, A. and Opler, L. A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 13, 261-276.

Kaymaz, N. and van Os, J., 2009. Heritability of structural brain traits an endophenotype approach to deconstruct schizophrenia. Int Rev Neurobiol. 89, 85-130.

Kellendonk, C., Simpson, E. H., Polan, H. J. et al, 2006. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron. 49, 603-615.

Kempton, M. J., Geddes, J. R., Ettinger, U. et al, 2008. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. Arch Gen Psychiatry. 65, 1017-1032.

Kempton, M. J., Stahl, D., Williams, S. C. et al, 2010. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. Schizophr Res. 120, 54-62.

Keshavan, M. S., Tandon, R., Boutros, N. N. et al, 2008. Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. Schizophr Res. 106, 89-107.

Kesner, R. P., 2007. Behavioral functions of the CA3 subregion of the hippocampus. Learn Mem. 14, 771-781.

Khalsa, H. M., Salvatore, P., Hennen, J. et al, 2008. Suicidal events and accidents in 216 first-episode bipolar I disorder patients: predictive factors. J Affect Disord. 106, 179-184.

Killgore, W. D., Rosso, I. M., Gruber, S. A. et al, 2009. Amygdala volume and verbal memory performance in schizophrenia and bipolar disorder. Cogn Behav Neurol. 22, 28-37.

Kirov, G., Murphy, K. C., Arranz, M. J. et al, 1998. Low activity allele of catechol-O-methyltransferase gene associated with rapid cycling bipolar disorder. Mol Psychiatry. 3, 342-345.

Klove, H., 1963. Clinical neuropsychology. In: F.M.Forster (Ed.), Saunders, New York, pp. 1647-1658.

Krabbendam, L., Arts, B., van, O. J. et al, 2005. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. Schizophr Res. 80, 137-149.

Kraepelin, E., 1917. Dementia Praecox and Paraphrenia Robert E. Krieger Publishing Co, New York.

Kremen, W. S., Prom-Wormley, E., Panizzon, M. S. et al, 2010. Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study. Neuroimage. 49, 1213-1223.

Kringlen, E., Torgersen, S. and Cramer, V., 2001. A Norwegian psychiatric epidemiological study. Am J Psychiatry. 158, 1091-1098.

Kunugi, H., Vallada, H. P., Sham, P. C. et al, 1997. Catechol-O-methyltransferase polymorphisms and schizophrenia: a transmission disequilibrium study in multiply affected families. Psychiatr Genet. 7, 97-101.

Kuperberg, G. R., Broome, M. R., McGuire, P. K. et al, 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry. 60, 878-888.

Kurtz, M. M., 2005. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophr Res. 74, 15-26.

Kurtz, M. M. and Gerraty, R. T., 2009. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology. 23, 551-562.

Kyriakopoulos, M. and Frangou, S., 2009. Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry. 22, 168-176.

Larsson, S., Lorentzen, S., Mork, E. et al, 2010. Age at onset of bipolar disorder in a Norwegian catchment area sample. J Affect Disord. 124, 174-177.

Lauronen, E., Koskinen, J., Veijola, J. et al, 2005. Recovery from schizophrenic psychoses within the northern Finland 1966 Birth Cohort. J Clin Psychiatry. 66, 375-383.

Lawyer, G., Nyman, H., Agartz, I. et al, 2006. Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression. BMC Psychiatry. 6, 31.

Lemaitre, H., Goldman, A. L., Sambataro, F. et al, 2010. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol Aging. doi: S0197-4580(10)00321-0 [pii];10.1016/j.neurobiolaging.2010.07.013.

Lezak, MD., 1995. Neuropsychological Assessment, 3 edn. Oxford Univ.Press, New York.

Lichtenstein, P., Yip, B. H., Bjork, C. et al, 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet. 373, 234-239.

Lim, K. O., Rosenbloom, M. J., Faustman, W. O. et al, 1999. Cortical gray matter deficit in patients with bipolar disorder. Schizophr Res. 40, 219-227.

Lopez, A. D. and Murray, C. C., 1998. The global burden of disease, 1990-2020. Nat Med. 4, 1241-1243.

Lu, L. H., Dapretto, M., O'Hare, E. D. et al, 2009. Relationships between brain activation and brain structure in normally developing children. Cereb Cortex. 19, 2595-2604.

Luders, E., Narr, K. L., Thompson, P. M. et al, 2006. Gender effects on cortical thickness and the influence of scaling. Hum Brain Mapp. 27, 314-324.

Luders, E. and Toga, A. W., 2010. Sex differences in brain anatomy. Prog Brain Res. 186, 3-12.

Lyoo, I. K., Sung, Y. H., Dager, S. R. et al, 2006. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord. 8, 65-74.

Mahon, K., Burdick, K. E. and Szeszko, P. R., 2010. A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev. 34, 533-554.

Maier, W., Hofgen, B., Zobel, A. et al, 2005. Genetic models of schizophrenia and bipolar disorder: overlapping inheritance or discrete genotypes? Eur Arch Psychiatry Clin Neurosci. 255, 159-166.

Malhi, G. S. and Lagopoulos, J., 2008. Making sense of neuroimaging in psychiatry. Acta Psychiatr Scand. 117, 100-117.

Mamah, D., Wang, L., Barch, D. et al, 2007. Structural analysis of the basal ganglia in schizophrenia. Schizophr Res. 89, 59-71.

Matsui, M., Suzuki, M., Zhou, S. Y. et al, 2008. The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders. Prog Neuropsychopharmacol Biol Psychiatry. 32, 1854-1862.

McDonald, C., Zanelli, J., Rabe-Hesketh, S. et al, 2004. Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. Biol Psychiatry. 56, 411-417.

McGlashan, T. H. and Hoffman, R. E., 2000. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry. 57, 637-648.

McGrath, J., Saha, S., Chant, D. et al, 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 30, 67-76.

McGuffin, P. and Farmer, A. H. I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch Gen Psychiatry. 764-770.

McGurk, S. R., Twamley, E. W., Sitzer, D. I. et al, 2007. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry. 164, 1791-1802.

McIntosh, A. M., Job, D. E., Moorhead, T. W. et al, 2004. Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biol Psychiatry. 56, 544-552.

McIntosh, A. M., Job, D. E., Moorhead, W. J. et al, 2006. Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. Am J Med Genet B Neuropsychiatr Genet. 141B, 76-83.

McIntyre, R. S., Soczynska, J. K., Beyer, J. L. et al, 2007. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry. 20, 406-416.

Mesholam-Gately, R. I., Giuliano, A. J., Goff, K. P. et al, 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 23, 315-336.

Middleton, F. A. and Strick, P. L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev. 31, 236-250.

Minatogawa-Chang, T. M., Schaufelberger, M. S., Ayres, A. M. et al, 2009. Cognitive performance is related to cortical grey matter volumes in early stages of schizophrenia: a population-based study of first-episode psychosis. Schizophr Res. 113, 200-209.

Mishara, A. L. and Goldberg, T. E., 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biol Psychiatry. 55, 1013-1022.

Moghaddam, B., 2003. Bringing order to the glutamate chaos in schizophrenia. Neuron. 40, 881-884.

Monks, P. J., Thompson, J. M., Bullmore, E. T. et al, 2004. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. Bipolar Disord. 6, 550-564.

Moorhead, T. W., McKirdy, J., Sussmann, J. E. et al, 2007. Progressive gray matter loss in patients with bipolar disorder. Biol Psychiatry. 62, 894-900.

Morey, R. A., Petty, C. M., Xu, Y. et al, 2009. A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. Neuroimage. 45, 855-866.

Morgan, K. D., Dazzan, P., Orr, K. G. et al, 2007. Grey matter abnormalities in first-episode schizophrenia and affective psychosis. Br J Psychiatry Suppl. 51, s111-s116.

Mortensen, P. B., Pedersen, C. B., Melbye, M. et al, 2003. Individual and familial risk factors for bipolar affective disorders in Denmark. Arch Gen Psychiatry. 60, 1209-1215.

Mur, M., Portella, M. J., Martinez-Aran, A. et al, 2008. Neuropsychological profile in bipolar disorder: a preliminary study of monotherapy lithium-treated euthymic bipolar patients evaluated at a 2-year interval. Acta Psychiatr Scand. 118, 373-381.

Murphy, E. A., Holland, D., Donohue, M. et al, 2010. Six-month atrophy in MTL structures is associated with subsequent memory decline in elderly controls. Neuroimage. 53, 1310-1317.

Murray, R. M. and Lewis, S. W., 1987. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed). 295, 681-682.

Murray, R. M., Sham, P., van, O. J. et al, 2004. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. Schizophr Res. 71, 405-416.

Nakamura, M., Salisbury, D. F., Hirayasu, Y. et al, 2007. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol Psychiatry. 62, 773-783.

Narr, K. L., Toga, A. W., Szeszko, P. et al, 2005. Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry. 58, 32-40.

Narr, K. L., Woods, R. P., Thompson, P. M. et al, 2007. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex. 17, 2163-2171.

Navari, S. and Dazzan, P., 2009. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med. 39, 1763-1777.

Nestor, P. G., Kubicki, M., Gurrera, R. J. et al, 2004. Neuropsychological correlates of diffusion tensor imaging in schizophrenia. Neuropsychology. 18, 629-637.

Nestor, P. G., Onitsuka, T., Gurrera, R. J. et al, 2007. Dissociable contributions of MRI volume reductions of superior temporal and fusiform gyri to symptoms and neuropsychology in schizophrenia. Schizophr Res. 91, 103-106.

Nestor, P. G., Shenton, M. E., McCarley, R. W. et al, 1993. Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. Am J Psychiatry. 150, 1849-1855.

Nesvag, R., Frigessi, A., Jonsson, E. G. et al, 2007. Effects of alcohol consumption and antipsychotic medication on brain morphology in schizophrenia. Schizophr Res. 90, 52-61.

Nesvag, R., Lawyer, G., Varnas, K. et al, 2008. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res. 98, 16-28.

Nesvag, R., Saetre, P., Lawyer, G. et al, 2009. The relationship between symptom severity and regional cortical and grey matter volumes in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 33, 482-490.

Neves-Pereira, M., Mundo, E., Muglia, P. et al, 2002. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet. 71, 651-655.

Nieuwenstein, M. R., Aleman, A. and de Haan, E. H., 2001. Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. Wisconsin Card Sorting Test. Continuous Performance Test. J Psychiatr Res. 35, 119-125.

Nopoulos, P., Flaum, M., O'Leary, D. et al, 2000. Sexual dimorphism in the human brain: evaluation of tissue volume, tissue composition and surface anatomy using magnetic resonance imaging. Psychiatry Res. 98, 1-13.

Nuechterlein, K. H., Green, M. F., Kern, R. S. et al, 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatry. 165, 203-213.

Osby, U., Brandt, L., Correia, N. et al, 2001. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 58, 844-850.

Ostby, Y., Tamnes, C. K., Fjell, A. M. et al, 2009. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. J Neurosci. 29, 11772-11782.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T. et al, 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 19, 2728-2735.

Pantelis, C., Yucel, M., Wood, S. J. et al, 2005. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull. 31, 672-696.

Pearlson, G. D., Barta, P. E., Powers, R. E. et al, 1997. Ziskind-Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol Psychiatry. 41, 1-14.

Peper, J. S., Brouwer, R. M., Boomsma, D. I. et al, 2007. Genetic influences on human brain structure: a review of brain imaging studies in twins. Hum Brain Mapp. 28, 464-473.

Phillips, M. L., Travis, M. J., Fagiolini, A. et al, 2008. Medication effects in neuroimaging studies of bipolar disorder. Am J Psychiatry. 165, 313-320.

Pilling, S., Bebbington, P., Kuipers, E. et al, 2002. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. Psychol Med. 32, 763-782.

Prasad, K. M., Goradia, D., Eack, S. et al, 2010. Cortical surface characteristics among offspring of schizophrenia subjects. Schizophr Res. 116, 143-151.

Premkumar, P., Kumari, V., Corr, P. J. et al, 2008. Neuropsychological function-brain structure relationships and stage of illness: an investigation into chronic and first-episode schizophrenia. Psychiatry Res. 162, 195-204.

Purcell, S. M., Wray, N. R., Stone, J. L. et al, 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 460, 748-752.

Qiu, A., Vaillant, M., Barta, P. et al, 2008. Region-of-interest-based analysis with application of cortical thickness variation of left planum temporale in schizophrenia and psychotic bipolar disorder. Hum Brain Mapp. 29, 973-985.

Rajkowska, G., Halaris, A. and Selemon, L. D., 2001. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol Psychiatry. 49, 741-752.

Rakic, P., 1988. Specification of cerebral cortical areas. Science. 241, 170-176.

Raz, N., Rodrigue, K. M., Kennedy, K. M. et al, 2003. Differential aging of the human striatum: longitudinal evidence. AJNR Am J Neuroradiol. 24, 1849-1856.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A. et al, 2004. The role of the medial frontal cortex in cognitive control. Science. 306, 443-447.

Rimol, L. M., Panizzon, M. S., Fennema-Notestine, C. et al, 2010. Cortical thickness is influenced by regionally specific genetic factors. Biol Psychiatry. 67, 493-499.

Robinson, L. J. and Ferrier, I. N., 2006. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord. 8, 103-116.

Robinson, L. J., Thompson, J. M., Gallagher, P. et al, 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord. 93, 105-115.

Roiz-Santianez, R., Perez-Iglesias, R., Quintero, C. et al, 2010. Insular cortex thinning in first episode schizophrenia patients. Psychiatry Res. 182, 216-222.

Rosa, A., Cuesta, M. J., Fatjo-Vilas, M. et al, 2006. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: evidence from a family-based association study. Am J Med Genet B Neuropsychiatr Genet. 141B, 135-138.

Rosa, P. G., Schaufelberger, M. S., Uchida, R. R. et al, 2010. Lateral ventricle differences between first-episode schizophrenia and first-episode psychotic bipolar disorder: A population-based morphometric MRI study. World J Biol Psychiatry. 11, 873-887.

Rosas, H. D., Liu, A. K., Hersch, S. et al, 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology. 58, 695-701.

Rossi, A., Stratta, P., Di, M., V et al, 1991. Temporal lobe structure by magnetic resonance in bipolar affective disorders and schizophrenia. J Affect Disord. 21, 19-22.

Rund, B. R., 1995. [Schizophrenia--how much do we need for the cost of treatment and research?]. Tidsskr Nor Laegeforen. 115, 2682-2683.

Rund, B. R., 1998. A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull. 24, 425-435.

Rund, B. R., Sundet, K., Asbjornsen, A. et al, 2006. Neuropsychological test profiles in schizophrenia and non-psychotic depression. Acta Psychiatr Scand. 113, 350-359.

Rusch, N., Spoletini, I., Wilke, M. et al, 2007. Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. Schizophr Res. 93, 79-89.

Rush, A. J., Gullion, C. M., Basco, M. R. et al, 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 26, 477-486.

Rushton, J. P. and Ankney, C. D., 2009. Whole brain size and general mental ability: a review. Int J Neurosci. 119, 691-731.

Saha, S., Chant, D., Welham, J. et al, 2005. A systematic review of the prevalence of schizophrenia. PLoS Med. 2, e141.

Salat, D. H., Buckner, R. L., Snyder, A. Z. et al, 2004. Thinning of the cerebral cortex in aging. Cereb Cortex. 14, 721-730.

Salgado-Pineda, P., Baeza, I., Perez-Gomez, M. et al, 2003. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. Neuroimage. 19, 365-375.

Salthouse, T. A., 2010. Selective review of cognitive aging. J Int Neuropsychol Soc. 16, 754-760.

Salvatore, P., Tohen, M., Khalsa, H. M. et al, 2007. Longitudinal research on bipolar disorders. Epidemiol Psichiatr Soc. 16, 109-117.

Sanches, M., Keshavan, M. S., Brambilla, P. et al, 2008. Neurodevelopmental basis of bipolar disorder: a critical appraisal. Prog Neuropsychopharmacol Biol Psychiatry. 32, 1617-1627.

Sanfilipo, M., Lafargue, T., Rusinek, H. et al, 2002. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res. 116, 1-23.

Sax, K. W., Strakowski, S. M., Zimmerman, M. E. et al, 1999. Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry. 156, 139-141.

Scherk, H. and Falkai, P., 2006. Effects of antipsychotics on brain structure. Current Opinion in Psychiatry. 19, 145-150.

Schultz, C. C., Koch, K., Wagner, G. et al, 2010a. Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. Psychiatry Res. 182, 134-140.

Schultz, C. C., Koch, K., Wagner, G. et al, 2010b. Reduced cortical thickness in first episode schizophrenia. Schizophr Res. 116, 204-209.

Sebat, J., Levy, D. L. and McCarthy, S. E., 2009. Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders. Trends Genet. 25, 528-535.

Seidman, L. J., Yurgelun-Todd, D., Kremen, W. S. et al, 1994. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. Biol Psychiatry. 35, 235-246.

Selemon, L. D. and Goldman-Rakic, P. S., 1999. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry. 45, 17-25.

Selemon, L. D., Rajkowska, G. and Goldman-Rakic, P. S., 1995. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry. 52, 805-818.

Selemon, L. D., Rajkowska, G. and Goldman-Rakic, P. S., 1998. Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: application of a three-dimensional, stereologic counting method. J Comp Neurol. 392, 402-412.

Shenton, M. E., Dickey, C. C., Frumin, M. et al, 2001. A review of MRI findings in schizophrenia. Schizophr Res. 49, 1-52.

Sherazi, R., McKeon, P., McDonough, M. et al, 2006. What's new? The clinical epidemiology of bipolar I disorder. Harv Rev Psychiatry. 14, 273-284.

Shifman, S., Bronstein, M., Sternfeld, M. et al, 2004. COMT: a common susceptibility gene in bipolar disorder and schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 128B, 61-64.

Shifman, S., Bronstein, M., Sternfeld, M. et al, 2002. A highly significant association between a COMT haplotype and schizophrenia. Am J Hum Genet. 71, 1296-1302.

Simonsen, C., Sundet, K., Vaskinn, A. et al, 2011. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. Schizophr Bull. 37, 73-83.

Simpson, E. H., Kellendonk, C. and Kandel, E., 2010. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia. Neuron. 65, 585-596.

Smieskova, R., Fusar-Poli, P., Allen, P. et al, 2009. The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?--a systematic review. Curr Pharm Des. 15, 2535-2549.

Snitz, B. E., Macdonald, A. W., III and Carter, C. S., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull. 32, 179-194.

Sowell, E. R., Peterson, B. S., Kan, E. et al, 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex. 17, 1550-1560.

Sowell, E. R., Thompson, P. M., Tessner, K. D. et al, 2001. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. J Neurosci. 21, 8819-8829.

Spitzer, R. L. and Williams, J. B., 1988. Revised diagnostic criteria and a new structured interview for diagnosing anxiety disorders. J Psychiatr Res. 22 Suppl 1, 55-85.

Spitzer, R. L., Williams, J. B., Kroenke, K. et al, 1994. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA. 272, 1749-1756.

Steen, R. G., Mull, C., McClure, R. et al, 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry. 188, 510-518.

Stefansson, H., Rujescu, D., Cichon, S. et al, 2008. Large recurrent microdeletions associated with schizophrenia. Nature. 455, 232-236.

Stone, J. M. and Pilowsky, L. S., 2006. Antipsychotic drug action: targets for drug discovery with neurochemical imaging. Expert Rev Neurother. 6, 57-64.

Strakowski, S. M., DelBello, M. P. and Adler, C. M., 2005. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry. 10, 105-116.

Strakowski, S. M., DelBello, M. P., Zimmerman, M. E. et al, 2002. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry. 159, 1841-1847.

Stratta, P., Mancini, F., Mattei, P. et al, 1997. Association between striatal reduction and poor Wisconsin card sorting test performance in patients with schizophrenia. Biol Psychiatry. 42, 816-820.

Stuss, D. T., Bisschop, S. M., Alexander, M. P. et al, 2001a. The Trail Making Test: a study in focal lesion patients. Psychological assessment. 13, 230-239.

Stuss, D. T., Floden, D., Alexander, M. P. et al, 2001b. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia. 39, 771-786.

Sullivan, E. V., Shear, P. K., Lim, K. O. et al, 1996. Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. Biol Psychiatry. 39, 234-240.

Sullivan, P. F., Kendler, K. S. and Neale, M. C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 60, 1187-1192.

Sundet, K. and Vaskinn, A., 2008. Estimating premorbid IQ (in Norwegian with English abstract). Journal of the Norwegian Psychological Association. 45, 1108-1115.

Susser, E., Neugebauer, R., Hoek, H. W. et al, 1996. Schizophrenia after prenatal famine. Further evidence. Arch Gen Psychiatry. 53, 25-31.

Szeszko, P. R., Bilder, R. M., Lencz, T. et al, 2000. Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. Schizophr Res. 43, 97-108.

Tamnes, C. K., Ostby, Y., Fjell, A. M. et al, 2010a. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb Cortex. 20, 534-548.

Tamnes, C. K., Ostby, Y., Walhovd, K. B. et al, 2010b. Neuroanatomical correlates of executive functions in children and adolescents: a magnetic resonance imaging (MRI) study of cortical thickness. Neuropsychologia. 48, 2496-2508.

Tandon, R., Nasrallah, H. A. and Keshavan, M. S., 2009. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res. 110, 1-23.

Taylor, J., 1932. Selected Writings of John Hughlings Jackson. London.

Thompson, P. M., Bartzokis, G., Hayashi, K. M. et al, 2009. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cereb Cortex. 19, 1107-1123.

Toulopoulou, T., Grech, A., Morris, R. G. et al, 2004. The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. Biol Psychiatry. 56, 447-453.

Usher, J., Leucht, S., Falkai, P. et al, 2010a. Correlation between amygdala volume and age in bipolar disorder - a systematic review and meta-analysis of structural MRI studies. Psychiatry Res. 182, 1-8.

Usher, J., Menzel, P., Schneider-Axmann, T. et al, 2010b. Increased right amygdala volume in lithium-treated patients with bipolar I disorder. Acta Psychiatr Scand. 121, 119-124.

van Os, J., Jones, P., Sham, P. et al, 1998. Risk factors for onset and persistence of psychosis. Soc Psychiatry Psychiatr Epidemiol. 33, 596-605.

Van Petten, C., 2004. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia. 42, 1394-1413.

Vares, M., Ekholm, A., Sedvall, G. C. et al, 2006. Characterization of patients with schizophrenia and related psychoses: evaluation of different diagnostic procedures. Psychopathology. 39, 286-295.

Vaskinn, A., 2008. The link between neurocognition and social problem solving in normal IQ schizophrenia: An investigation of possible mediators. University of Oslo, Oslo.

Venkatasubramanian, G., Jayakumar, P. N., Gangadhar, B. N. et al, 2008. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naive schizophrenia. Acta Psychiatr Scand. 117, 420-431.

Vita, A., De, P. L. and Sacchetti, E., 2009. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord. 11, 807-814.

Vita, A., Dieci, M., Giobbio, G. M. et al, 1995. Language and thought disorder in schizophrenia: brain morphological correlates. Schizophr Res. 15, 243-251.

Voets, N. L., Hough, M. G., Douaud, G. et al, 2008. Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. Neuroimage. 43, 665-675.

Walhovd, K. B., Fjell, A. M., Dale, A. M. et al, 2006. Regional cortical thickness matters in recall after months more than minutes. Neuroimage. 31, 1343-1351.

Walhovd, K. B., Westlye, L. T., Amlien, I. et al, 2009. Consistent neuroanatomical age-related volume differences across multiple samples. Neurobiol Aging. doi: S0197-4580(09)00174-2 [pii];10.1016/j.neurobiolaging.2009.05.013.

Wallace, G. L., Eric, S. J., Lenroot, R. et al, 2006. A pediatric twin study of brain morphometry. J Child Psychol Psychiatry. 47, 987-993.

Wechsler, D., 2003. Wechsler Adult Intelligence Scale - Third edition (WAIS-III). Norwegian Manual. Pearson Assessment., Stockholm.

Wechsler, D., 2007a. Wechsler Abbreviated Scale of Intelligence (WASI). Norwegian Manual supplement. Pearson Assessment, Stockholm.

Wechsler, D., 1981. The Wechsler Adult Intelligence Scale-Revised. Psychological Corporation; New York.

Wechsler, D., 1997. The Wechsler Adult Intelligence Scale-III. Psychological Corporation; New York.

Wechsler, D., 2007b. Wechsler Memory Scale - third edition (WMS-III). Norwegian Manual. Pearson Assessment., Stockholm.

Weinberger, D. R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 44, 660-669.

Weinberger, D. R., Berman, K. F., Suddath, R. et al, 1992. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry. 149, 890-897.

Weinberger, D. R. and McClure, R. K., 2002. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? Arch Gen Psychiatry. 59, 553-558.

Weishaupt, D., Kochli, V. D. and Marincek, B., 2006. How does MRI work? An introduction to the physics and function of magnetic resonance imaging. Springer, Berlin.

Weissman, M. M., Bland, R. C., Canino, G. J. et al, 1996. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 276, 293-299.

Wernicke, C., 1874. Der aphasische Symptomenkomplex. Cohn and Weigert, Brieslau.

Westlye, L. T., Grydeland, H., Walhovd, K. B. et al, 2011. Associations between regional cortical thickness and attentional networks as measured by the attention network test. Cereb Cortex. 21, 345-356.

Wexler, B. E., Zhu, H., Bell, M. D. et al, 2009. Neuropsychological near normality and brain structure abnormality in schizophrenia. Am J Psychiatry. 166, 189-195.

White, T., Kendi, A. T., Lehericy, S. et al, 2007. Disruption of hippocampal connectivity in children and adolescents with schizophrenia--a voxel-based diffusion tensor imaging study. Schizophr Res. 90, 302-307.

Wiegand, L. C., Warfield, S. K., Levitt, J. J. et al, 2004. Prefrontal cortical thickness in first-episode psychosis: a magnetic resonance imaging study. Biol Psychiatry. 55, 131-140.

Williams, H. J., Norton, N., Dwyer, S. et al, 2010. Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry. doi: mp201036 [pii];10.1038/mp.2010.36.

Witelson, S. F., Beresh, H. and Kigar, D. L., 2006. Intelligence and brain size in 100 postmortem brains: sex, lateralization and age factors. Brain. 129, 386-398.

Wolf, D. H., Gur, R. C., Valdez, J. N. et al, 2007. Alterations of fronto-temporal connectivity during word encoding in schizophrenia. Psychiatry Res. 154, 221-232.

Woodward, N. D., Purdon, S. E., Meltzer, H. Y. et al, 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int J Neuropsychopharmacol. 8, 457-472.

World Health Organization, 1993. The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. WHO, Geneva.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W. et al, 2000. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry. 157, 16-25.

Yoshida, T., McCarley, R. W., Nakamura, M. et al, 2009. A prospective longitudinal volumetric MRI study of superior temporal gyrus gray matter and amygdala-hippocampal complex in chronic schizophrenia. Schizophr Res. 113, 84-94.

Young, R. C., Biggs, J. T., Ziegler, V. E. et al, 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 133, 429-435.

Zimmerman, M. E., DelBello, M. P., Getz, G. E. et al, 2006. Anterior cingulate subregion volumes and executive function in bipolar disorder. Bipolar Disord. 8, 281-288.

Zipparo, L., Whitford, T. J., Redoblado Hodge, M. A. et al, 2008. Investigating the neuropsychological and neuroanatomical changes that occur over the first 2-3 years of illness in patients with first-episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 32, 531-538.

Appendices

Appendix 1. Diagnostic subtypes

Schizophrenia spectrum (and other psychotic) disorders	Bipolar spectrum disorders
• Schizophrenia	• Bipolar I disorder
• Schizophreniform disorder	• Bipolar II disorder
• Schizoaffective disorder	• Cyclothymic disorder
• Delusional disorder	• Mood disorder due to a general medical condition
• Brief psychotic disorder	• Substance-induced mood disorder
• Shared psychotic disorder	• Bipolar disorder not otherwise specified (NOS)
• Psychotic disorder due to a general medical condition	
• Substance-induced psychotic disorder	
• Psychotic disorder not otherwise specified (NOS)	

Appendix 2. Demographics and clinical data

	HUBIN Study sample (I) n = 136						TOP Study sample (II – IV) n = 519								
Subject group	Schizophrenia n = 67			Healthy controls n = 69			Schizophrenia n = 173			Bipolar disorder n = 139			Healthy controls n = 207		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age (years)	41.9	(7.3)	25-55	43.2	(8.5)	20-56	32.3	(9.0)	18-63	35.4	(11.3)	19-65	36.2	(9.7)	18-59
Education (years)	12.3	(2.7)	8-19	14.0	(3.0)	9-22	13.4	(2.8)	8-21	14.2	(3.0)	9-23	14.1	(2.3)	9-20
Age of onset (years)	24.4	(5.6)	14-40				26.8	(8.1)	15-62	28.9	(11.0)	11-59			
Duration of illness (years)	17.3	(8.1)	0.4-33				5.4	(5.8)	0.1-30	6.5	(6.5)	0.5-38			
	Number	%		Number	%		Number	%		Number	%		Number	%	
Sex (M/F)	53/14	79/21		41/28	59/41		104/69	60/40		54/85	39/61		108/99	52/48	
Ethnicity (Caucasian/other)	100/0	100/0		100/0	100/0		141/32	82/18		128/11	92/8		205/2	99/1	
Handedness (Right/Left or Ambi)	59/8	88/12		58/11	84/16		136/16	90/10		98/15	87/13		190/17	92/8	
Medication (Atypical/Typical/none)	24/38/5	36/57/7					126/9/16	73/5/9		55/4/18	40/3/13				

Appendix 3. List of brain structure segmentations from FreeSurfer

Cortical regions (parcellations)	Subcortical regions
Banks superior temporal sulcus	Hippocampus
Caudal anterior cingulate	Amygdala
Caudal middle frontal	Thalamus
Corpus callosum	Lateral ventricle
Cuneus	Inferior lateral ventricle
Entorhinal	Third ventricle
Fusiform	Fourth ventricle
Inferior parietal	Nucleus accumbens
Inferior temporal	Ventral diencephalon
Isthmus cingulate	Cerebellar cortex
Lateral occipital	Cerebellar white matter
Lateral orbitofrontal	Caudate
Lingual	Putamen
Medial orbitofrontal	Pallidum
Middle temporal	Brainstem
Parahippocampal	
Paracentral	
Pars opercularis	
Pars orbitalis	
Pars triangularis	
Pericalcarine	
Postcentral	
Posterior cingulate	
Precentral	
Precuneus	
Rostral anterior cingulate	
Rostral middle frontal	
Superior frontal	
Superior parietal	
Superior temporal	
Supramarginal	
Frontal pole	
Temporal pole	
Transverse temporal	

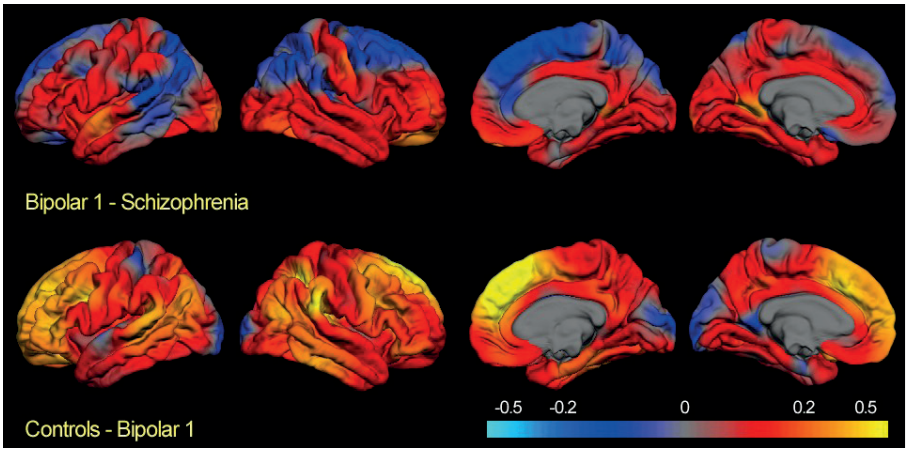
Errata

Study II:

Page 42, section Subjects, second paragraph and Table 1, line 10: "Positive and Negative Symptom Scale" should be "**Positive and Negative Syndrome Scale**".

Page 43, Table 1, line 10 in footnotes, "(http://www.whocc.no/atcdd)" should be "**(http://www.whocc.no/atcddd)**".

Page 45, Figure 2 B), the figure with effect sizes of Controls - Bipolar 1 (bottom row) has been replaced with Controls – Bipolar. The right figure should be:



Page 45, Figure 2, figure legend should read: ... (B) Upper row: bipolar disorder Type 1 versus schizophrenia, and bottom row: healthy control subjects versus bipolar disorder Type 1 (Schizophrenia = schizophrenia, schizophreniform disorder, and schizoaffective disorder).

I

II

III

Brain cortical thickness and surface area correlates of neurocognitive performance in patients with schizophrenia, bipolar disorder and healthy control subjects

C. B. Hartberg[1*], K. Sundet[2,6], L. M. Rimol[1], U. K. Haukvik[1,3], E. H. Lange[1,3], R. Nesvåg[1,3], A. M. Dale[4,5,6], I. Melle[1,6], O. A. Andreassen[1,6], I. Agartz[1,3,7]

[1] Institute of Clinical Medicine, Psychiatry Section, University of Oslo, Norway.

[2] Department of Psychology, University of Oslo, Norway.

[3] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.

[4] Department of Neurosciences, University of California San Diego, La Jolla, USA.

[5] Department of Radiology, University of California San Diego, La Jolla, USA.

[6] Division of Mental Health and Addiction, Psychosis Research Unit, Oslo University Hospital, Norway.

[7] Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden.

[*]Corresponding author: Cecilie Bhandari Hartberg,
P.O. Box 85 Vinderen, University of Oslo, N-0319 Oslo, Norway.
Phone +4722029856, Fax +4722495862, e-mail : c.b.hartberg@medisin.uio.no

Number of words
in abstract: 198
in manuscript: 4643
Tables: 4
Figures: 2
Supplemental tables: 2

Abstract:

Relationships between cortical brain structure and neurocognitive functioning have been reported in schizophrenia but findings are inconclusive, and only a few studies in bipolar disorder have addressed this issue. This is the first study to directly compare relationships between cortical thickness and surface area with neurocognitive functioning in patients with schizophrenia (n=171) and bipolar disorder (n=121) and healthy controls (n=192).

MRI scans were obtained, and regional cortical thickness and surface area measurements were analyzed for relationships with test scores from 6 neurocognitive domains.

In the combined sample, cortical *thickness* in the right rostral anterior cingulate was inversely related to working memory, and cortical *surface area* in four frontal and temporal regions were positively related to neurocognitive functioning. A positive relationship between left transverse temporal thickness and processing speed was specific to schizophrenia. A negative relationship between right temporal pole thickness and working memory was specific to bipolar disorder.

In conclusion, significant cortical structure/function relationships were found in a large sample of healthy controls and patients with schizophrenia or bipolar disorder. The differences that were found between schizophrenia and bipolar may indicate differential relationship patterns in the two disorders, which may be of relevance for understanding the underlying pathophysiology.

Keywords: MRI, neuropsychological tests, cerebral cortex, brain structure, cognition

1. Introduction

In schizophrenia, there is substantial evidence for widespread cortical structure abnormalities such as cortical volume reduction (Arnone et al., 2009;Ellison-Wright and Bullmore, 2010;Glahn et al., 2008) as well as frontotemporal cortical thinning (Nesvag et al., 2008) as measured with magnetic resonance imaging (MRI). Moreover, cortical surface area reductions have been demonstrated in adolescent-onset (Voets et al., 2008) and first-episode (Gutierrez-Galve et al., 2010) psychosis patients. For bipolar disorder, results have been more heterogeneous, but recent meta-analyses in bipolar patients have summarized that cortical grey matter reduction in the anterior cingulate and fronto-insular regions are characteristic features (Bora et al., 2010;Ellison-Wright and Bullmore, 2010). Schizophrenia and bipolar disorder are classified as separate disorders, but overlapping clinical and neurocognitive features (Barch, 2009) as well as commonalities in genetic disposition (Lichtenstein et al., 2009) suggest a shared pathophysiology. Our research group recently demonstrated that cortical thinning in the frontal lobe appear common to schizophrenia and bipolar type 1 disorder (Rimol et al., 2010).

Neurocognitive dysfunction has consistently been demonstrated in schizophrenia (Rund et al., 2006) and to some extent in bipolar disorder (Bora et al., 2009), and is recognized as a possible intermediate phenotype and predictor of functional outcome (Green, 2006). Comparisons of cognitive performance across schizophrenia and bipolar disorder suggest that the differences between the patient groups are quantitative rather than qualitative, since the neurocognitive profiles are largely similar between the disorders (Jabben et al., 2010) although the magnitude of change is greater in schizophrenia. The similarities in neurocognitive profiles may suggest common underlying brain pathology (Lewandowski et al., 2011).

Generally, specific cortical brain structures have been related with specific neurocognitive function in MRI-based studies with healthy adults (Dickerson et al., 2008;Fornito et al., 2004;Gur et al., 1998;Sanfilipo et al., 2002;Walhovd et al., 2006) as well as dysfunction in individuals with focal brain lesions (Stuss et al., 2001a;Stuss et al., 2001b). In schizophrenia patients, performance on specific neurocognitive tests has been related to regional brain cortical *volumes* (Antonova et al., 2005;Bonilha et al., 2008;Matsui et al., 2008;Minatogawa-Chang et al., 2009;Rusch et al., 2007;Wolf et al., 2008). The most consistent findings are positive relationships between frontal cortical volumes and executive functioning and with verbal memory. Only a few studies have investigated structure/function relationships in bipolar disorder (Bearden et al., 2001). In one study, subregional

volumes of the anterior cingulate were differently related to executive functioning in bipolar patients and healthy controls (Zimmerman et al., 2006b). Since volume is the product of thickness and surface area, the ability to separately study these two cortical characteristics enhances the opportunity of revealing even more specific relationships between cortical anatomy and cognitive abilities.

We have previously, in an independent sample of healthy subjects and chronic schizophrenia patients demonstrated that cortical thickness in localized frontal/temporal regions were positively related with verbal learning, verbal IQ and executive functioning (Hartberg et al., 2010). In this study, the relationships between temporal and occipital regions with verbal IQ appeared disrupted in schizophrenia. In a recent study, the investigators reported widespread cortical thinning in first-episode schizophrenia (FES) patients compared to healthy controls, but only a weak correlation between total and parietal cortical thickness and measures of attention (Crespo-Facorro et al., 2010). However, Crespo-Facorro et al only investigated relationships within the patient group and used only lobar measurements.

Regional cortical *surface area* has been related to general cognitive function (IQ) and working memory in another study of FES patients (Gutierrez-Galve et al., 2010). Finally, only a few studies have compared cortical structure/function relationships across schizophrenia and bipolar disorder patients in order to determine illness-specificity. Minatogawa-Chang et al (2009) found the middle frontal gyrus volume to be related with a composite cognitive test score specifically in a first-episode psychosis group, however, subdividing into schizophrenic and affective psychosis did not yield illness-specific relationships.

Taken together, although frontal and temporal brain cortical abnormalities are suggestive of cognitive dysfunction in both disorders, findings from studies addressing structure/function relationships in schizophrenia are inconsistent and there is a paucity of studies on cortical surface area, and in bipolar disorder. Thus, it is still unclear if and how cortical structure is related to neurocognition in schizophrenia and bipolar disorder.

The objective of the present study was to investigate how cortical thickness and surface area were related to cognitive performance in a large sample (n=430) of patients with schizophrenia or bipolar spectrum disorders, and healthy control subjects. The three diagnostic groups were

investigated combined for general relationships between brain structure and cognitive function as well as separately for specific relationships. We also aimed at clarifying differences in structure/function relationships between schizophrenia and bipolar disorder, which to our knowledge, has not been done using both cortical thickness and surface area before.

2. Materials and methods

Subjects

All participants were recruited between 2003 and 2009 as part of an ongoing study on psychotic disorders, the Thematically Organized Psychosis (TOP) Research Study (Rimol et al., 2010) in Norway. Patients were inpatients and outpatients and were referred from psychiatric units from four major hospitals in the greater Oslo area. In order to ensure a representative control group, the healthy controls were randomly selected from statistical records from the same catchment area as the patient groups, and contacted by letter inviting them to participate.

All participants gave informed consent to participation, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

All subjects from the larger TOP study who had undergone both MRI scanning and neuropsychological testing were included in the current study, but were excluded if they met the following criteria: a history of hospitalized head injury, neurological disorder, IQ < 70 points, and age outside the range of 18-65 years. To assure valid neurocognitive test performance, all participants had to have Norwegian as their first language or have received their compulsory schooling in Norway and had to score 15 or above in the forced recognition trial in the California Verbal Learning Test (CVLT)-II (Delis et al., 2004), which is a measure of adequate test effort. All MRI scans were evaluated by a neuroradiologist, and excluded if significant pathology was present.

Included in the statistical analyses were patients with schizophrenia (n = 117) or bipolar spectrum disorders (n = 121), and healthy controls (n = 192). The schizophrenia spectrum included patients with schizophrenia (n = 94), schizophreniform disorder (n = 7) and schizoaffective disorder (n = 16), the bipolar disorder group included both bipolar type 1 disorder (n = 76) and bipolar type 2 disorder (n = 45). In the following we will refer to schizophrenia spectrum as “schizophrenia” and

bipolar type 1 and 2 disorder as "bipolar disorder". Age was defined as age at MRI scanning. Years of education were registered as years of schooling as reported by the subjects during the interview.

The healthy control sample was evaluated by an interview of severe mental disorder symptoms and the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994). Controls were excluded if they had a diagnosis of drug abuse/dependency the last three months or had used drugs within the last 2 weeks, if they or any of their first-degree relatives had a life time history of a severe psychiatric disorder, or if they had a history of medical problems thought to interfere with brain function.

Clinical assessment

Clinical assessment was carried out by trained physicians and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First, 2002). Diagnostic interrater reliability was found satisfactory, with overall agreement for DSM-IV diagnostic categories of 82 % with $\kappa = 0.77$ (95% CI: 0.60-0.94) (Birkenaes et al., 2007). Current positive and negative symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning (GAF) scale, split version. Interrater reliability for PANSS and GAF has been found to be satisfactory (Engh et al., 2010). Data on current medication were derived from interviews and medical records and for standardization purposes converted into Defined Daily Doses according to the WHO guidelines (http://www.whocc.no/atcdd).

In order to obtain a clinically representative sample, all patients were included regardless of illicit drug use, but substance abuse/dependency was diagnosed (SCID module E) if present. Nine of the patients with schizophrenia spectrum and five of the patients with bipolar disorder had either a current diagnosis of cannabis abuse or were in early partial remission.
Demographic and clinical data are displayed in table 1.

Neurocognitive assessment

Psychologists who were trained in standardized neuropsychological testing carried out the neurocognitive assessments. A comprehensive test battery was administered in a fixed order. Handedness was determined by hand preference when writing. Premorbid IQ was estimated using the National Adult Reading Test – Norwegian version (Sundet and Vaskinn, 2008). For the present study, neurocognitive tests were included from the full test-battery if 1) they or near identical tests

had previously shown a relationship with brain cortical thickness in an independent study of chronic schizophrenia (Hartberg et al., 2010), or 2) had previously been found to differ between schizophrenia and bipolar disorder patients (Simonsen et al., 2011). In the Simonsen et al study, we used a subject sample that overlapped with the present, but all calculations were independently performed in the current sample, and previous test results were used only to guide the selection of tests.

In total, six measures were selected (see table 2): ***Verbal learning*** was tested with the Total recall trial score (list A1 – A5) from the California Verbal Learning Test, Second edition (CVLT-II) (Delis et al., 2004). ***Processing speed*** was assessed with the Digit Symbol subtest from the Wechsler Adult Intelligence Scale, Third edition (WAIS-III) (Wechsler, 2003). ***Working memory*** was assessed with the Digit Span subtest (sum of forward and backward trials) from the WAIS-III (Wechsler, 2003). ***Interference control*** was tested with the Inhibition subtest from the Color-Word Interference Test (Delis-Kaplan Executive Function Scale, D-KEFS) (Delis et al., 2005). ***Set shifting*** was measured with the Category Switching subtest (correct scores) from the Verbal Fluency Test (D-KEFS) (Delis et al., 2005). Both interference control and set-shifting are considered to be aspects of executive functioning. ***Verbal IQ*** was estimated with the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007).

Manual-based age and gender (when indicated) adjusted scaled scores [(T-scores: 50±10) or (S-scores: 10 ±30)] are reported. For raw scores, higher scores equal better performance on all measures except for the Color-Word Interference Test.

Brain imaging

MR image acquisition

All participants underwent MRI scanning on a 1.5T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional 3-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = 1.33 x 0.94 x 1 mm^3, number of partitions = 160). Acquisition parameters were optimized for increased grey/white matter image contrast. There was no scanner upgrade during the study period.

MR image processing

The image files in DICOM format were transferred to a Linux workstation for morphometric analysis. Images were corrected for non-linear warping caused by gradient coil non-linearities, using tools developed through the Morphometry Biomedical Informatics Research Network (mBIRN), and the two T1-weighted images were rigid body registered to each other (motion corrected) and subsequently averaged together to increase the signal to noise ratio. In order to measure surface area and thickness the FreeSurfer software was used for cortical surface reconstruction followed by a procedure to obtain a representation of the grey/white matter boundary and the cortical (pial) surface (Dale et al., 1999;Fischl and Dale, 2000). Next, manual corrections of topological defects were performed blinded to diagnostic group identity. The software enables surface division into 34 parcellated [regions-of-interest (ROI)] regions in each hemisphere which are neuroanatomically labeled (Desikan et al., 2006;Fischl et al., 2004). Cortical thickness was calculated as the average distance between the grey/white boundary and the pial surface within each ROI. Surface area was calculated as the sum of the areas of each tessellation falling within a given ROI; this was done in each subjects' native space. ICV estimates were obtained from the automated procedure for volumetric measurements of brain structures implemented in Freesurfer (Buckner et al., 2004).

Selection of brain regions to be used in the analysis

For the current study, we selected 28 predefined cortical regions (Fig. 1) within all brain lobes, but predominantly from the frontal and temporal lobes. These regions have shown to be abnormal in schizophrenia or bipolar disorder in previous MRI studies (Arnone et al., 2009;Lyoo et al., 2006;Nesvag et al., 2008) and were also comparable with those used in the similar study on cortical thickness/area and cognition in FES patients (Gutierrez-Galve et al., 2010).

Statistical analyses

All analyses were performed in the statistical software SPSS 16.0.

Group differences in demographic, clinical, neurocognitive and brain structure measurements

Demographic and clinical, and standardized neuropsychological variables were compared across groups using Student's t-tests, chi-square analyses and analyses of variance (ANOVAs) followed by Tukey's post-hoc tests. Neuropsychological test comparisons for a subject sample partly overlapping with the present have been published earlier (Simonsen et al., 2011), but were repeated for this particular sample with standardized test scores. Group comparisons of average

cortical thickness and surface area measurements from each of the predefined brain regions were analyzed using ANCOVAs.

Structure/function relationships by regression analysis

The main analyses of relationships between cortical measurements and neurocognitive function were conducted as follows. First, multiple stepwise linear regression analyses were performed for the combined sample and separately for each of the three subject groups (groupwise analyses). Each cortical measure was entered as the dependent variable. Age, sex (and diagnosis for the combined group analyses) and all six neurocognitive test scores (raw scores) were entered as independent variables. Separate analyses were performed for the left and right hemisphere and for thickness and area. Due to demographic differences between the diagnostic groups, all analyses were corrected for age and sex differences.

Group differences in correlations between cortical thickness/area and neurocognition

Next, in order to test for differences in relationships, partial correlation coefficients from the group-wise regression analyses, selected at alpha = 0.01, were contrasted with the corresponding correlation coefficients from the other groups in a pairwise manner using Fisher z transformations. Sixteen regions in total were selected from the separate group analyses for pairwise between-group contrasts of correlation coefficients based on this criterion. This alpha level was chosen in order to identify putative structure/function relationships. To correct for multiple comparisons, a conservative Bonferroni correction was applied to both the main analyses and to the pairwise contrast analyses.

Medication and duration of illness

Possible confounding factors were investigated with duration of illness and antipsychotic DDD (both logarithmic transformed) as covariates for the two patient groups. Only those patients who were prescribed medication were included.

Subgroup analysis

All analyses were repeated with bipolar type 1 separately, and for the narrow schizophrenia group (including schizophrenia and schizophreniform disorder, and excluding schizoaffective disorder), and excluding patients with current cannabis abuse. All analyses were two-tailed.

3. Results

Demographic and clinical characteristics

The three diagnostic groups differed on demographic variables with regard to age, sex and ethnicity (table 1). The schizophrenia group had lower mean age and more males than the two other groups. The groups also differed on clinical variables as expected from diagnostic categories. There were no group differences in handedness, education, premorbid IQ or intracranial volume. The two patient groups did not differ with regard to age at onset of illness or duration of illness.

Group differences in neurocognitive performance

The groups differed overall on all neuropsychological measures (Table 2). The highest effect sizes were observed for tasks in processing speed and attention demanding set-shifting. The schizophrenia group performed worse than the bipolar group and the healthy controls on all test scores, while the bipolar group performed worse than healthy controls on the processing speed, interference control and set-shifting tasks.

Group differences in cortical thickness and area

Comparisons of cortical thickness and surface area of the 28 predefined cortex regions conducted across the three diagnostic subject groups are presented in supplemental tables (S1 and S2, respectively). The cortical thickness results parallel those reported by Rimol et al (2010). Thickness reduction was found in 11 frontal and temporal regions in both schizophrenia and bipolar disorder compared with healthy controls, and in two regions in schizophrenia compared with bipolar disorder. Cortical surface area was smaller in four regions in schizophrenia relative to bipolar disorder and healthy controls. Surface area was larger in the left superior frontal region and the right temporal pole in bipolar disorder relative to healthy controls and schizophrenia patients.

Relationships between cortical thickness/area and neurocognition

In the combined group, there was one significant cortical thickness relationship and four significant surface area relationships with neurocognitive performance (Fig.2). There were no overlapping relationships between area and thickness. Increased cortical *thickness* in the right rostral anterior cingulate was related to poorer working memory performance. A larger *surface area* was related to better neurocognitive performance for the relationships between left rostral anterior cingulate and right rostral middle frontal regions with working memory performance, between left caudal middle frontal region and processing speed, and between left fusiform region and verbal IQ.

The results ($p < 0.01$) for the groupwise analyses are displayed in Table 3. In the schizophrenia group, larger cortical *thickness* in the left transverse temporal region was significantly related to better processing speed performance. In the bipolar disorder group, larger cortical *surface area* in the left inferior temporal region was significantly related to better processing speed performance, whereas in the healthy control group, larger cortical *surface area* in the right caudal middle frontal and left fusiform regions was significantly related to poorer verbal learning (Table 3).

Group differences in correlations between cortical thickness/area and neurocognition

Results for the group comparisons between partial correlation coefficients (derived from the groupwise regression analyses), are displayed in Table 4. After correction for multiple testing, *8* of the contrasts remained statistically significant. There were three significantly different correlations between schizophrenia and bipolar disorder; between cortical thickness in the left pars opercularis and working memory, between the left transverse temporal region and processing speed and between the right temporal pole and working memory. The latter correlation also differentiated the bipolar disorder patients from the healthy control group. The schizophrenia group displayed positive correlations in all three regions, while the bipolar group correlations were negative. There were four significantly different correlations between schizophrenia and healthy controls in temporal lobe regions; between cortical thickness in the left middle and transverse temporal regions and the left temporal pole and processing speed, and between surface area in the left fusiform region and verbal learning. All four correlations were positive in the schizophrenia group, while they were all negative in the healthy control group.

Medication, duration of illness and subgroup analyses

The patterns of relationships in the narrow schizophrenia (excluding schizoaffective disorder) and in the bipolar disorder type 1 groups were essentially the same as in the schizophrenia and bipolar spectrum groups respectively. Overall, the strength of relationships in Table 3 remained essentially the same after controlling for duration of illness and antipsychotic medication, and when excluding patients with current cannabis abuse.

4. Discussion

This is the first study to investigate relationships between regional cortical thickness/area and neurocognitive performance and directly compare between patients with schizophrenia and bipolar disorder investigated with the same MRI scanner, post-processing methodology and neurocognitive test battery. We detected a limited number of significant cortical structure/function relationships;

five relationships were significant in the combined group of participants i.e. were found to be the same in all three groups, and one relationship was significant in each of the separate groups. Additionally, there were significant group differences in relationships; three specific relationships between regional cortical *thickness*/function were different in schizophrenia compared with bipolar disorder, of which the negative relationship between cortical thickness in the right temporal pole and working memory was specific to bipolar disorder, and the positive relationship between cortical thickness in the left transverse temporal region and processing speed was specific to schizophrenia. Cortical thickness in several temporal regions was differently related to processing speed in schizophrenia relative to healthy controls. One cortical *surface area*/function relationship in healthy controls was different from that in schizophrenia, but not from bipolar disorder patients.

Common significant relationships between all three groups suggest that there are general relationships that are not disrupted by having a diagnosis of either schizophrenia or bipolar disorder. For the relationship between cortical thickness in the right rostral anterior cingulate (AC) and working memory, the correlation was strongest in the bipolar disorder group, which is in accordance with the negative, but non-significant correlation between rostral AC grey matter volumes and measures of working memory that was previously demonstrated in bipolar disorder patients and healthy controls (Zimmerman et al., 2006b). The rostral AC has been related to emotional processes (Devinsky et al., 1995) known to be of importance in bipolar disorder, as well as implicated in circuitries disrupted in schizophrenia (Benes, 2010). The present results suggest that structural integrity in this region is related to working memory, regardless of group status. The results for frontal surface area relationships in the combined group are supported by the previous findings in FES patients (Gutierrez-Galve et al., 2010), however in Gutierrez-Galve et al study, there were significant relationships in the patient group only and not in controls.

Although the present correlations between regional cortical thickness and working memory and processing speed are of small/medium effect sizes (Cohen, 1988), they are, as shown in the pair wise contrast analyses, in opposite directions in the schizophrenia and bipolar disorder patients, which suggest different patterns of relationships. Consistent with this, post-mortem studies demonstrate cellular differences in some, but not all regions of the frontal lobe between schizophrenia and bipolar patient groups (Selemon and Rajkowska, 2003).

Interestingly, several frontal and temporal brain regions showed diagnostic group interactions between schizophrenia and healthy controls for the relationship between cortical thickness and processing speed. Processing speed, which has been proposed to represent a more generalized cognitive feature underlying other speed-dependent cognitive tasks (Dickinson et al., 2007), has previously been related to widespread brain regions (Sanfilipo et al., 2002).

We have previously demonstrated that a positive relationship between cortical thickness in the right fusiform (temporo-occipital) region and Verbal IQ in healthy controls were disrupted in chronic schizophrenia (Hartberg et al., 2010) which suggested that this region might be of special importance in the disorder. However, in the present study cortical *area* in the left fusiform region was significantly correlated with verbal learning in the healthy control group and, as shown in the pairwise contrast analysis, differentiated between healthy control group and the schizophrenia patients.

How *altered* brain structure as found in the severe psychotic diseases such as schizophrenia or bipolar disorder relate to the impaired cognition is not known, but abnormal regional neuronal organization or density (Fornito et al., 2009;Selemon, 2001) has been proposed as factors. Cortical thickness and surface area have been shown to be genetically unrelated (Panizzon et al., 2009) and may represent different underlying cellular organization (Rakic, 1988) and hence relate differently to neurocognitive test scores. This assumption finds support in the present study, where regions of significant relationships between neurocognition and area and neurocognition and thickness did not overlap. Furthermore, there were more differences in relationships between subject groups for thickness than for area. Cortical thickness demonstrate variable regional heritability (Kremen et al., 2010) and may be sensitive to environmental influences such as drug use (Habets et al., 2010), and illness-related factors (Goldman et al., 2009). We therefore corrected for cannabis abuse, illness duration and medication use in the analyses and our interpretation is that the present differences in cortical thickness relationships between subject groups reflect pathophysiological processes inherent to the disorders and not environmental. Although environmental effects on cortical surface area development cannot be excluded (White et al., 2002), surface area is mainly determined during embryonic and neonatal life without undergoing major subsequent changes (Rakic, 1988), and as such represents a window for investigating early neurodevelopmental disturbances. Reduced regional surface area (Table S2) and the disrupted relationship with verbal learning in

schizophrenia, but not in bipolar disorder, support theories of more severe neurodevelopmental disturbances in schizophrenia than in bipolar disorder.

From our previous report on cortical thickness relationships with cognitive performance in chronic schizophrenia (Hartberg et al., 2010), we expected more widespread cortical thickness relationships in the present study. The patients who participated in the present study had been ill for a relatively short period of time (Table 1) as compared to other chronic patient cohorts, and in this regard were similar to the subjects in two studies on FES patients (Crespo-Facorro et al., 2010;Gutierrez-Galve et al., 2010). Both FES studies reported sparse results for relationships between cortical structure and specific neurocognitive domains. Also, the effect sizes for group differences in cortical thickness and neurocognitive performance were smaller in the present study (Table S1, Table 2) than in those with chronic patients (Heinrichs and Zakzanis, 1998;Nesvag et al., 2008), which might have limited our ability to detect subtle relationships. Furthermore, direct comparisons of younger with older (above approximately 40 years) adults have revealed stronger and positive relationships in the older subjects (Zimmerman et al., 2006a) regardless of having a schizophrenia diagnosis or not (Premkumar et al., 2008), suggesting that structure/function relationships generally become more pronounced with higher age. Also, there may be non-linear effects of age or a dynamic age-dependent interplay between structure and function, which makes the relationships change over time and difficult to detect in cross-sectional studies. An example of this would be the demonstrated progression of grey matter loss concurrent with neurocognitive improvements in the first years after illness onset in schizophrenia (Zipparo et al., 2008).

There were a few limitations to this study. The group differences in age and sex may have affected the results although they were statistically corrected for in all statistical analyses. In order to give an account of the pattern of relationships in each group, separate group analyses were conducted which resulted in a large number of statistical tests. Because of this, the results must be interpreted with some caution. However, the threshold for selection of groupwise relationships for further group comparisons are in accordance with the threshold used by other researchers in the field, and furthermore, a conservative multiple comparison control (Bonferroni) was applied to the final results. Lastly, it has been reported that use of medication can affect cortical structure (Navari and Dazzan, 2009). In our analyses, we corrected for the current dose of antipsychotic medication, which was found not to affect the results. Only a few subjects (n=17) were prescribed Lithium, and thus the effect of Lithium on cortical structure could not be investigated.

In conclusion, in the present sample of healthy controls and patients with schizophrenia or bipolar disorder, we find significant relationships between regional cortical thickness or surface area and neurocognitive test scores, of which some are common to all groups and other are unique to schizophrenia or bipolar disorder. Different patterns of structure/function relationships between schizophrenia and bipolar disorder suggest differences in underlying pathophysiology, but whether these patterns are consistent should be tested in independent samples. Future longitudinal studies are needed to determine how structure and function interrelate over time.

Acknowledgments

We thank patients and controls for their participation in the study. We also wish to thank Merete Øibakken, Martin Furan, Petr S. Bjerkan, Thomas Bjella and Eivind Bakken, for technical and administrative assistance, Oslo University Hospital and the University of Oslo to support the Thematically Organized Psychosis (TOP) Research Study group.

The study was supported by grants from the Research Council of Norway (grant number 190311/V50); Eastern and Western Norway Health Authority (grant number 2004-123) and South-Eastern Norway Regional Health Authority (grant numbers 2008-011, 2009-037, 2009-038).

Financial disclosures

IM has received Speaker's honorarium from Janssen, AstraZeneca and Lundbeck. RN has received Speaker's honorarium from Janssen and AstraZeneca. AMD is a founder and holds equity in CorTechs Labs, and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. OAA has received Speaker's honorarium from
AstraZeneca, Janssen, BMS and GSK. All other authors report no conflict of interest.

Reference list

Antonova, E., Kumari, V., Morris, R. et al, 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry. 58, 457-467.

Arnone, D., Cavanagh, J., Gerber, D. et al, 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. Br J Psychiatry. 195, 194-201.

Barch, D. M., 2009. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. Curr Psychiatry Rep. 11, 313-319.

Bearden, C. E., Hoffman, K. M. and Cannon, T. D., 2001. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disord. 3, 106-150.

Benes, F. M., 2010. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. Neuropsychopharmacology. 35, 239-257.

Birkenaes, A. B., Opjordsmoen, S., Brunborg, C. et al, 2007. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 68, 917-923.

Bonilha, L., Molnar, C., Horner, M. D. et al, 2008. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. Schizophr Res. 101, 142-151.

Bora, E., Fornito, A., Yucel, M. et al, 2010. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol Psychiatry. 67, 1097-1105.

Bora, E., Yucel, M. and Pantelis, C., 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord. 113, 1-20.

Buckner, R. L., Head, D., Parker, J. et al, 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage. 23, 724-738.

Cohen, J., 1988. Statistical power analysis for the behavioral sciences Erlbaum, Hillsdale, NJ.

Crespo-Facorro, B., Roiz-Santianez, R., Perez-Iglesias, R. et al, 2010. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. Psychol Med. 1-12.

Dale, A. M., Fischl, B. and Sereno, M. I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 9, 179-194.

Delis, D., Kramer, J., Kaplan, E. et al, 2004. California Verbal Learning Test - Second edition (CVLT-II). Norwegian Manual supplement.

Delis, DC., Kaplan, E. and Kramer, J., 2005. The Delis-Kaplan Executive Function System (D-KEFS). Norwegian Manual.

Desikan, R. S., Segonne, F., Fischl, B. et al, 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 31, 968-980.

Devinsky, O., Morrell, M. J. and Vogt, B. A., 1995. Contributions of anterior cingulate cortex to behaviour. Brain. 118 (Pt 1), 279-306.

Dickerson, B. C., Fenstermacher, E., Salat, D. H. et al, 2008. Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. Neuroimage. 39, 10-18.

Dickinson, D., Ramsey, M. E. and Gold, J. M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry. 64, 532-542.

Ellison-Wright, I. and Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 117, 1-12.

Engh, J. A., Friis, S., Birkenaes, A. B. et al, 2010. Delusions are associated with poor cognitive insight in schizophrenia. Schizophr Bull. 36, 830-835.

First, M. B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders.

Fischl, B. and Dale, A. M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 97, 11050-11055.

Fischl, B., van der, K. A., Destrieux, C. et al, 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex. 14, 11-22.

Fornito, A., Yucel, M. and Pantelis, C., 2009. Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder. Curr Opin Psychiatry. 22, 312-319.

Fornito, A., Yucel, M., Wood, S. et al, 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. Cereb Cortex. 14, 424-431.

Glahn, D. C., Laird, A. R., Ellison-Wright, I. et al, 2008. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biol Psychiatry. 64, 774-781.

Goldman, A. L., Pezawas, L., Mattay, V. S. et al, 2009. Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry. 66, 467-477.

Green, M. F., 2006. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry. 67, Suppl-8.

Gur, R. E., Cowell, P., Turetsky, B. I. et al, 1998. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry. 55, 145-152.

Gutierrez-Galve, L., Wheeler-Kingshott, C. A., Altmann, D. R. et al, 2010. Changes in the frontotemporal cortex and cognitive correlates in first-episode psychosis. Biol Psychiatry. 68, 51-60.

Habets, P., Marcelis, M., Gronenschild, E. et al, 2010. Reduced Cortical Thickness as an Outcome of Differential Sensitivity to Environmental Risks in Schizophrenia. Biol Psychiatry. doi: S0006-3223(10)00844-9 [pii];10.1016/j.biopsych.2010.08.010.

Hartberg, C. B., Lawyer, G., Nyman, H. et al, 2010. Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. Psychiatry Res. 182, 123-133.

Heinrichs, R. W. and Zakzanis, K. K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 12, 426-445.

Jabben, N., Arts, B., van, O. J. et al, 2010. Neurocognitive functioning as intermediary phenotype and predictor of psychosocial functioning across the psychosis continuum: studies in schizophrenia and bipolar disorder. J Clin Psychiatry. 71, 764-774.

Kay, S. R., Fiszbein, A. and Opler, L. A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 13, 261-276.

Kremen, W. S., Prom-Wormley, E., Panizzon, M. S. et al, 2010. Genetic and environmental influences on the size of specific brain regions in midlife: the VETSA MRI study. Neuroimage. 49, 1213-1223.

Lewandowski, K. E., Cohen, B. M. and Ongur, D., 2011. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med. 41, 225-241.

Lichtenstein, P., Yip, B. H., Bjork, C. et al, 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet. 373, 234-239.

Lyoo, I. K., Sung, Y. H., Dager, S. R. et al, 2006. Regional cerebral cortical thinning in bipolar disorder. Bipolar Disord. 8, 65-74.

Matsui, M., Suzuki, M., Zhou, S. Y. et al, 2008. The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders. Prog Neuropsychopharmacol Biol Psychiatry. 32, 1854-1862.

Minatogawa-Chang, T. M., Schaufelberger, M. S., Ayres, A. M. et al, 2009. Cognitive performance is related to cortical grey matter volumes in early stages of schizophrenia: a population-based study of first-episode psychosis. Schizophr Res. 113, 200-209.

Navari, S. and Dazzan, P., 2009. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med. 39, 1763-1777.

Nesvag, R., Lawyer, G., Varnas, K. et al, 2008. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res. 98, 16-28.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T. et al, 2009. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 19, 2728-2735.

Premkumar, P., Kumari, V., Corr, P. J. et al, 2008. Neuropsychological function-brain structure relationships and stage of illness: an investigation into chronic and first-episode schizophrenia. Psychiatry Res. 162, 195-204.

Rakic, P., 1988. Specification of cerebral cortical areas. Science. 241, 170-176.

Rimol, L. M., Hartberg, C. B., Nesvag, R. et al, 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 68, 41-50.

Rund, B. R., Sundet, K., Asbjornsen, A. et al, 2006. Neuropsychological test profiles in schizophrenia and non-psychotic depression. Acta Psychiatr Scand. 113, 350-359.

Rusch, N., Spoletini, I., Wilke, M. et al, 2007. Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. Schizophr Res. 93, 79-89.

Sanfilipo, M., Lafargue, T., Rusinek, H. et al, 2002. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res. 116, 1-23.

Selemon, L. D., 2001. Regionally diverse cortical pathology in schizophrenia: clues to the etiology of the disease. Schizophr Bull. 27, 349-377.

Selemon, L. D. and Rajkowska, G., 2003. Cellular pathology in the dorsolateral prefrontal cortex distinguishes schizophrenia from bipolar disorder. Curr Mol Med. 3, 427-436.

Simonsen, C., Sundet, K., Vaskinn, A. et al, 2011. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. Schizophr Bull. 37, 73-83.

Spitzer, R. L., Williams, J. B., Kroenke, K. et al, 1994. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA. 272, 1749-1756.

Stuss, D. T., Bisschop, S. M., Alexander, M. P. et al, 2001a. The Trail Making Test: a study in focal lesion patients. Psychological assessment. 13, 230-239.

Stuss, D. T., Floden, D., Alexander, M. P. et al, 2001b. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia. 39, 771-786.

Sundet, K. and Vaskinn, A., 2008. Estimating premorbid IQ (in Norwegian with English abstract). Journal of the Norwegian Psychological Association. 45, 1108-1115.

Voets, N. L., Hough, M. G., Douaud, G. et al, 2008. Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. Neuroimage. 43, 665-675.

Walhovd, K. B., Fjell, A. M., Dale, A. M. et al, 2006. Regional cortical thickness matters in recall after months more than minutes. Neuroimage. 31, 1343-1351.

Wechsler, D., 2003. Wechsler Adult Intelligence Scale - Third edition (WAIS-III). Norwegian Manual Pearson Assessment., Stockholm.

Wechsler, D., 2007. Wechsler Abbreviated Scale of Intelligence (WASI). Norwegian Manual supplement. Pearson Assessment, Stockholm.

White, T., Andreasen, N. C. and Nopoulos, P., 2002. Brain volumes and surface morphology in monozygotic twins. Cereb Cortex. 12, 486-493.

Wolf, R. C., Hose, A., Frasch, K. et al, 2008. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. European psychiatry. 23, 541-548.

Zimmerman, M. E., Brickman, A. M., Paul, R. H. et al, 2006a. The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. Am J Geriatr Psychiatry. 14, 823-833.

Zimmerman, M. E., DelBello, M. P., Getz, G. E. et al, 2006b. Anterior cingulate subregion volumes and executive function in bipolar disorder. Bipolar Disord. 8, 281-288.

Zipparo, L., Whitford, T. J., Redoblado Hodge, M. A. et al, 2008. Investigating the neuropsychological and neuroanatomical changes that occur over the first 2-3 years of illness in patients with first-episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 32, 531-538.

Table 1. Demograhics and clinical data

	1. Schizophrenia	**2. Bipolar disorder**	**3. Healthy controls**	**ANOVA / Chi square analysis / t – tests**		
	N = 117	N = 121	N = 192	$F_{2,427}$/ χ^2/t	p	Post hoc[a]
Demographics						
Age, years	31.7 (7.9)	34.7 (11.4)	36.1 (9.6)	F = 7.5	p = ***0.001***	1 < 2, 3
Sex *n* (% males)	68 (58.1)	49 (40.5)	98 (51.0)	χ^2 = 7.5	p = ***0.023***	1 > 2, 3
Handedness *n* (% right)	98 (87.5)	91 (85.8)	176 (91.7)	χ^2 = 4.5	p = 0.338	
Ethnicity *n* (% Caucasian)	102 (87.2)	114 (94.2)	190 (99.0)	χ^2 = 26.4	p = ***0.003***	1 < 2 < 3
Education, years	13.6 (2.8)	14.2 (2.8)	14.2 (2.3)	F = 2.2	p = 0.111	
NART IQ	105.9 (4.5)	106.2 (4.1)	106.9 (4.0)	F = 2.6	p = 0.078	
Intracranial volume (ml)	1564.2 (174.7)	1552.7 (163.6)	1580.1 (180.8)	F = 1.1	P = 0.343	
Clinical data						
Age at onset of illness, years[b]	26.3 (6.8)	28.3 (11.3)		t = 1.6	p = 0.107	
Duration of illness, years[b]	5.3 (5.2)	6.3 (6.6)		t = 1.3	p = 0.187	
Symptom ratings						
PANSS positive score	14.7 (5.8)	10.1 (3.6)		t = 7.5	p = ***< 0.001***	
PANSS negative score	14.7 (6.9)	10.4 (3.8)		t = 5.8	p = ***< 0.001***	
GAF symptom score	42.5 (11.1)	56.9 (11.1)		t =10.0	p = ***< 0.001***	

GAF function score	43.8 (10.7)		54.6 (12.4)		t = 7.3	p = ***< 0.001***
Medication	***N (%)***	***DDD***	***N (%)***	***DDD***		
Antipsychotic [c]	99 (85)	1.6 (1.3)	52 (43)	1.0 (0.7)		
Lithium	1 (1)	0.5	16 (13)	1.0 (0.3)		
Antiepileptic	12 (10)	0.9 (0.3)	43 (36)	0.6 (0.4)		
Antidepressive	31 (26)	1.7 (1.3)	39 (32)	1.5 (0.8)		
Sedative	15 (13)	0.5 (0.4)	12 (10)	0.9 (1.1)		

ANOVA, univariate analysis of variance; NART, National Adult Reading Test – Norwegian version; IQ, Intelligent Quotient; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; DDD, Defined Daily Doses, in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd).

Means and SDs are reported unless otherwise specified.

[a] Tukey post hoc tests

[b] Age at onset was defined as age at first contact with the mental health service due to a primary symptom. Duration of illness was defined as number of years between age at onset and age at MRI scanning. Median (Interquartil range)age at onset: schizophrenia: 25.5 (9.0), bipolar disorder: 26.0 (16.8), Median (Interquartil range) illness duration: schizophrenia: 2.7 (7.8), bipolar disorder: 4.0 (7.8).

[c] Eight (7%) patients with schizophrenia and 4 (3%) patients with bipolar disorder received typical antipsychotic medication and 84 (72%) patients with schizophrenia and 46 (38%) patients with bipolar disorder received atypical antipsychotic medication, while 7 (6%) patients with schizophrenia and 1 (1%) patient with bipolar disorder received both. Thirteen (11%) patients with schizophrenia and 18 (15%) patients with bipolar disorder received no psychopharmacological medication.

Number of missing data: Handedness; schizophrenia: 5, bipolar disorder: 15; education; schizophrenia: 1; NART IQ; schizophrenia: 11, bipolar disorder: 2; age of onset and illness duration; schizophrenia: 1, bipolar disorder: 6.

Table 2. Results of neurocognitive comparisons

	1.Schizophrenia	**2. Bipolar disorder**	**3. Healthy controls**	**ANCOVA**			
	N = 117	N = 121	N = 192	$F_{(2, 427)}$	p	η^{2a}	Post hoc [b]
Verbal learning							
CVLT-II: List A, Total trials[c]	49.2 (11.4)	55.8 (11.4)	57.2 (10.1)	F = 21.1	p < ***0.001***	0.09	1 < 2,3
Processing speed							
Digit Symbol (WAIS-III)[d]	7.5 (2.4)	8.9 (2.4)	10.4 (2.5)	F = 51.0	p < ***0.001***	0.19	1 < 2 < 3
Working memory							
Digit Span (WAIS-III)[d]	8.2 (2.0)	8.9 (2.5)	9.6 (2.5)	F = 11.8	p < ***0.001***	0.05	1 < 2,3
Interference control							
Color-Word Inhibition (D-KEFS)[d]	8.0 (3.6)	9.5 (3.1)	10.9 (2.5)	F = 34.4	p < ***0.001***	0.14	1 < 2 < 3
Set shifting							
Category Switching (D-KEFS)[d]	8.0 (2.9)	10.1 (3.3)	11.4 (3.2)	F = 42.3	p < ***0.001***	0.17	1 < 2 < 3
Verbal IQ							
Vocabulary (WASI)[c]	52.9 (9.3)	55.7 (8.6)	56.1 (7.0)	F = 5.9	p = ***0.003***	0.03	1 < 2,3

Mean and SD are reported. Standardized scores are shown and used in the analyses. Abbreviations: ANOVA, analysis of variance; CVLT-II, California Verbal Learning Test––Revised; WAIS-III, Wechsler Adult Intelligence Scale III Revision; D-KEFS, Delis-Kaplan Executive Functioning System; WASI, Wechsler Abbreviated Scale of Intelligence. [a]Eta square effect size. [b]Tukey's post-hoc test. [c]T-scores. [d]S-scores

Table 3. Relationships between cortical thickness and surface area and neurocognitive test scores.

		Schizophrenia (n = 117)		Bipolar disorder (n = 121)		Healthy controls (n = 192)	
Cortical regions	Side	Thickness	Area	Thickness	Area	Thickness	Area
Frontal regions							
caudal ant cingulate	L						
	R					Digit Symbol (-.20)	
caudal middle frontal	L						
	R						***CVLT (-.22)****
pars opercularis	L	Digit Span (.24)					
	R						
rostral ant cingulate	L						
	R			Digit Span (-.26)			
rostral middle frontal	L						
	R						
superior frontal	L						CVLT (-.20)
	R						
Temporal regions							
fusiform	L						***CVLT (-.27)**,* Vocabulary (.19)
	R	C-W Interference (-.25)					
inferior temporal	L				***Digit Symbol (.27)****		
	R						
middle temporal	L					Digit Symbol (-.19)	
	R						
superior temporal	L						
	R						
temporal pole	L	Digit Symbol (.27)					
	R			Digit Span (-.24)			
transverse temporal	L	***Digit symbol (.28)**,** C-W Interference (-.24)					
	R						
Parietal regions							
superior parietal	L				CVLT (-.24)	Digit Span (.19)	
	R						
Occipital regions							
lateral occipital	L						
	R						

Note. Digit Span, Working memory; Digit Symbol, Processing speed; C-W Interference, Interference control; CVLT, California Verbal Learning test, Verbal learning; Vocabulary, Verbal IQ.

Partial correlation coefficients are shown for p values < 0.01.

* Significant after Bonferroni correction for multiple comparisons.

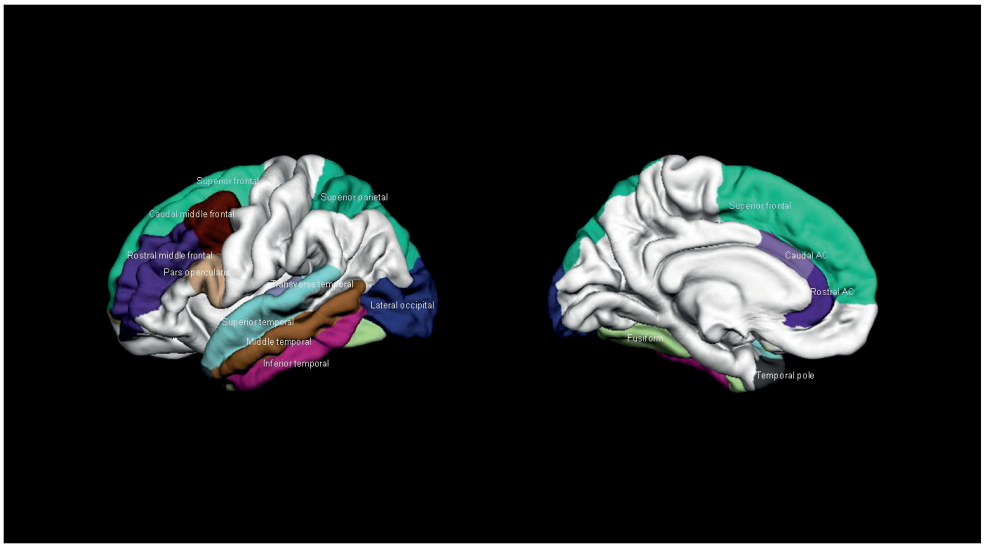
Table 4. Pairwise contrasts of correlations ($p < 0.01$) between cortical thickness or area and neurocognitive tests.

	Group relationships			Pairwise contrasts					
	SCH	BD	CTR	CTR – SCH		CTR – BD		SCH - BD	
		r		z	p	z	p	z	p
Regional thickness / test									
Caudal ant cingulate rh /dsy	0.06	-0.16	-0.20*	-2.2	0.027	-0.4	0.704	1.7	0.099
Pars opercularis lh /dsp	0.24*	-0.15	-0.01	-2.1	0.033	1.2	0.234	3.0	**0.003**
Rostral ant cingulate rh /dsp	-0.10	-0.26*	-0.16	-0.5	0.610	0.9	0.347	1.3	0.194
Fusiform rh /int	-0.25*	-0.01	0.00	2.1	0.033	0.1	0.920	-1.8	0.067
Middle temporal lh / dsy	0.18	-0.07	-0.19*	-3.1	**0.002**	-1.0	0.317	1.9	0.524
Temporal pole lh / dsy	0.27*	-0.04	-0.09	-3.1	**0.002**	-0.4	0.682	2.4	0.017
Temporal pole rh / dsp	0.23	-0.24*	0.06	-1.4	0.153	2.6	**0.009**	3.6	**<0.0005**
Transverse temp lh /dsy	0.28*	-0.04	-0.07	-3.0	**0.003**	-0.2	0.842	2.5	**0.011**
Transverse temp lh / int	-0.24*	-0.04	-0.04	1.8	0.072	0.0	0.992	-1.6	0.107
Superior parietal lh /dsp	0.14	-0.06	0.19*	0.4	0.660	2.2	0.030	1.5	0.124
Regional area / test									
Caud middle frontal rh /cvlt	0.00	-0.09	-0.22*	-1.9	0.054	-1.2	0.242	0.7	0.490
Superior frontal lh / cvlt	0.04	-0.03	-0.20*	-2.0	0.047	-1.5	0.142	0.5	0.631
Fusiform lh /cvlt	0.03	-0.13	-0.27*	-2.6	**0.009**	-1.3	0.208	1.2	0.223
Fusiform lh /voca	0.16	0.02	0.19*	0.3	0.780	1.5	0.134	1.1	0.276
Inferior temporal lh /dsy	0.14	0.27*	0.04	-0.9	0.384	-2.1	0.038	-1.1	0.285
Superior parietal lh /cvlt	-0.08	-0.24*	-0.14	-0.5	0.617	0.9	0.374	1.3	0.211

* Groupwise correlations significant at alpha level = 0.01. Bold indicates significant group differences (Bonferroni corrected).

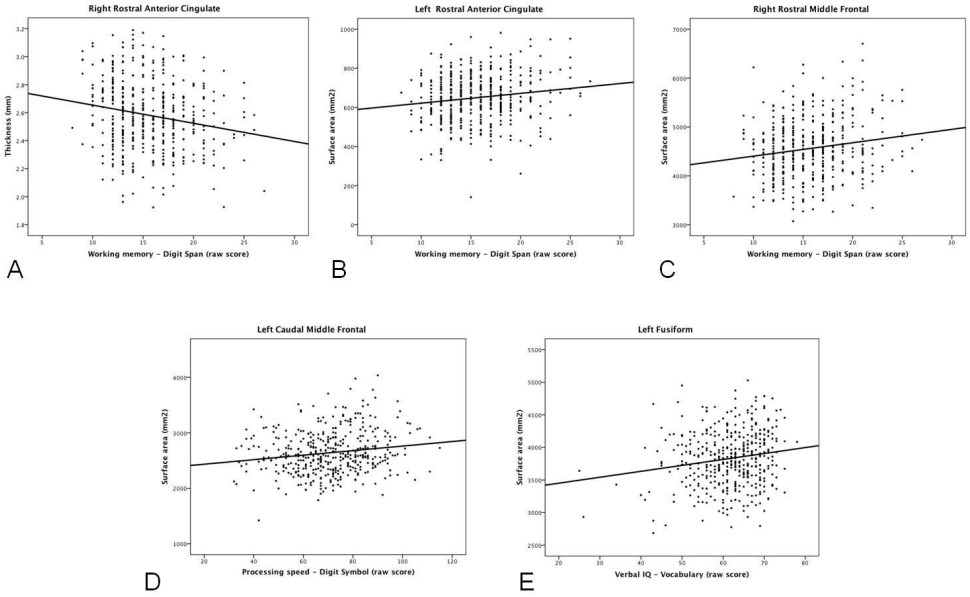
Abbreviations: CTR, Healthy control subjects; SCH, Schizophrenia; BD, Bipolar disorder; r, partial correlation coefficient; Z, Fisher's z value; ant, anterior; caud, caudal; lh, left hemisphere; rh, right hemisphere; dsp, Digit Span Total (working memory); dsy, Digit Symbol Test (Processing speed); int, Color-Word interference test (Interference control); cvlt, California Verbal Learning test (Verbal learning); voca; Vocabulary (Verbal IQ).

Figure 1.



Lateral and midsagittal views of the selected parcellations. AC, Anterior cingulate.

Figure 2. Relationships in the combined sample



Scatter plots showing significant relationships between cortical thickness (mm) and cortical surface area (mm^2) with neurocognitive performance, adjusted for age and sex in the combined sample. A) Larger cortical thickness in the right rostral anterior cingulate related to poorer working memory performance (B = 0.17, p = 0.0004), B) larger cortical surface area in the left rostral anterior cingulate related to better working memory performance (B = 0.14 , p = 0.003), C) larger cortical surface area in the right rostral middle frontal region related to better working memory performance (B = 0.14, p = 0.001) D) larger cortical surface area in the left caudal middle frontal region related to better processing speed performance (B = 0.15, p = 0.003), E) larger cortical surface area in the left fusiform region related to better verbal IQ (B = 0.14, p = 0.002)

Table S1. Comparisons of regional thickness across groups

	1. Schizophrenia		**2. Bipolar disorder**		**3. Healthy controls**		**ANCOVA**		
Region-of-interest, L/R	N = 117		N = 121		N = 192		$F_{(2, 425)}$	p	Pairwise comparisons[a]
Frontal regions									
Caudal anterior cingulate	2.48	(0.029)	2.57	(0.029)	2.59	(0.023)	4.66	***0.011***	1 < 2,3
	2.48	(0.021)	2.50	(0.021)	2.52	(0.017)	0.85	0.429	
Caudal middle frontal	2.24	(0.014)	2.25	(0.014)	2.31	(0.011)	8.99	***<0.001***	1,2 < 3
	2.23	(0.015)	2.23	(0.014)	2.28	(0.011)	5.14	***0.006***	1,2 < 3
Pars opercularis	2.21	(0.014)	2.23	(0.014)	2.28	(0.011)	7.72	***0.001***	1,2 < 3
	2.22	(0.015)	2.25	(0.015)	2.30	(0.012)	8.48	***<0.001***	1,2 < 3
Rostral anterior cingulate	2.62	(0.022)	2.63	(0.022)	2.67	(0.017)	2.30	0.101	
	2.55	(0.024)	2.52	(0.023)	2.57	(0.018)	1.86	0.157	
Rostral middle frontal	2.04	(0.012)	2.06	(0.011)	2.11	(0.009)	11.52	***<0.001***	1,2 < 3
	1.99	(0.011)	2.01	(0.011)	2.05	(0.009)	9.01	***<0.001***	1,2 < 3
Superior frontal	2.49	(0.013)	2.50	(0.013)	2.56	(0.010)	12.60	***<0.001***	1,2 < 3
	2.48	(0.012)	2.47	(0.012)	2.53	(0.009)	9.63	***<0.001***	1,2 < 3
Temporal regions									
Fusiform	2.39	(0.012)	2.42	(0.012)	2.43	(0.010)	3.27	0.039	
	2.46	(0.012)	2.48	(0.012)	2.52	(0.009)	8.94	***<0.001***	1,2 < 3
Inferior temporal	2.51	(0.016)	2.54	(0.016)	2.56	(0.012)	2.52	0.082	
	2.58	(0.013)	2.61	(0.013)	2.66	(0.010)	12.46	***<0.001***	1,2 < 3

Middle temporal	2.56	(0.015)	2.58	(0.015)	2.61	(0.012)	3.95	0.020	
	2.63	(0.015)	2.68	(0.015)	2.72	(0.012)	10.67	***<0.001***	1 < 2 < 3
Superior temporal	2.53	(0.015)	2.57	(0.015)	2.59	(0.012)	5.64	***0.004***	1 < 3
	2.60	(0.015)	2.62	(0.015)	2.66	(0.012)	5.04	***0.007***	1,2 < 3
Temporal pole	3.49	(0.028)	3.54	(0.027)	3.55	(0.021)	1.40	0.247	
	3.62	(0.027)	3.65	(0.026)	3.69	(0.021)	2.02	0.133	
Transverse temporal	2.03	(0.020)	2.07	(0.019)	2.04	(0.015)	0.96	0.384	
	2.07	(0.024)	2.06	(0.023)	2.09	(0.019)	0.92	0.401	
Parietal regions									
Superior parietal	1.86	(0.010)	1.85	(0.010)	1.87	(0.008)	1.32	0.270	
	1.84	(0.011)	1.84	(0.011)	1.87	(0.008)	3.71	0.025	
Occipital regions									
Lateral occipital	1.93	(0.011)	1.95	(0.010)	1.97	(0.008)	4.43	***0.013***	1 < 3
	1.95	(0.011)	1.95	(0.011)	1.97	(0.009)	2.08	0.127	

Adjusted means and SE are reported. Age (age = 34.5 years) and sex were included as covariates. Abbreviations: L/R, Left/Right; ANCOVA, univariate analysis of covariance. Pairwise comparisons are based on adjusted marginal means.

Bold; overall group differences (Bonferroni corrected).

[a] Post-hoc pairwise comparisons for schizophrenia vs. controls demonstrated cortical thickness reduction in schizophrenia in widespread regions in the frontal, temporal and occipital regions, for bipolar disorder vs. controls demonstrated cortical thickness reduction in bipolar disorder in several bilateral frontal regions and the right temporal regions. Schizophrenia patients displayed cortical thickness reduction in the left caudal anterior cingulate and right middle temporal regions as compared with bipolar disorder.

Table S2. Comparisons of regional area across groups

	1.Schizophrenia		**2. Bipolar disorder**		**3. Healthy controls**		**ANCOVA**		
Regions-of-interest L/R	N = 117		N = 121		N = 192		$F_{(2, 425)}$	p	Pairwise comparisons[a]
Frontal regions									
Caudal anterior cingulate	531.3	(11.9)	539.1	(11.6)	549.8	(9.2)	0.8	0.456	
	595.1	(9.9)	589.1	(9.6)	600.3	(7.6)	0.4	0.662	
Caudal middle frontal	2608.9	(36.4)	2698.1	(35.5)	2671.8	(28.2)	1.6	0.199	
	2399.1	(37.2)	2568.2	(36.2)	2524.3	(28.8)	5.7	***0.004***	1 < 2,3
Pars Opercularis	1847.2	(26.4)	1905.0	(25.7)	1911.2	(20.4)	2.0	0.140	
	4960.3	(51.1)	5102.1	(49.8)	5100.1	(39.6)	2.7	0.067	
Rostral anterior cingulate	643.3	(11.5)	662.8	(11.2)	654.2	(8.9)	0.7	0.483	
	554.2	(12.9)	544.2	(12.6)	530.9	(10.0)	1.1	0.350	
Rostral middle frontal	3722.8	(49.9)	3876.1	(48.6)	3794.3	(38.6)	2.4	0.091	
	4422.2	(57.0)	4665.7	(55.6)	4580.0	(44.1)	4.8	***0.009***	1 < 2,3
Superior frontal	8264.1	(81.5)	8589.3	(79.4)	8381.2	(63.1)	4.2	***0.015***	1,3 < 2
	7788.4	(77.2)	8057.0	(75.2)	7943.0	(59.8)	3.1	0.046	
Temporal regions									
Fusiform	3721.3	(40.4)	3863.1	(39.4)	3820.8	(31.3)	3.3	0.037	
	3982.0	(40.5)	4202.6	(39.5)	4111.5	(31.4)	7.6	***0.001***	1 < 2,3
Inferior temporal	3191.2	(40.8)	3330.3	(39.7)	3276.7	(31.5)	3.0	0.050	
	3282.2	(43.5)	3393.6	(42.4)	3365.3	(33.7)	1.8	0.163	

Middle temporal	3424.8	(39.0)	3569.4	(38.0)	3560.5	(30.2)	4.6	***0.011***	1 < 2,3
	3544.4	(37.0)	3665.2	(36.0)	3661.7	(28.6)	3.7	0.025	
Superior temporal	4152.5	(41.7)	4249.3	(40.6)	4172.7	(32.3)	1.6	0.202	
	3764.5	(37.2)	3900.3	(36.2)	3794.4	(28.8)	3.9	0.020	
Temporal pole	546.8	(6.7)	564.5	(6.5)	556.3	(5.2)	1.8	0.174	
	499.5	(5.8)	521.6	(5.7)	499.3	(4.5)	5.5	***0.004***	1,3 < 2
Transverse temporal	489.8	(7.3)	505.8	(7.1)	498.4	(5.7)	1.2	0.297	
	357.7	(5.5)	367.4	(5.3)	360.3	(4.2)	0.9	0.412	
Parietal regions									
Superior parietal	4899.9	(51.4)	5025.7	(50.1)	4933.7	(39.8)	1.7	0.185	
	1520.6	(24.5)	1560.4	(23.9)	1546.8	(19.0)	0.7	0.502	
Occipital regions									
Lateral occipital	4762.7	(51.0)	4901.4	(49.7)	4882.8	(39.5)	2.3	0.103	
	4098.0	(49.8)	4267.0	(48.5)	4212.9	(38.5)	3.1	0.048	

Adjusted means and SE are reported. Age (age = 34.5 years) and sex were included as covariates. Abbreviations: L/R, Left/Right; ANCOVA, univariate analysis of covariance;
Pairwise comparisons are based on adjusted marginal means

Bold; overall group differences (Bonferroni corrected).

[a] Post-hoc pairwise comparisons for schizophrenia vs. controls demonstrated cortical area reduction in schizophrenia in the right middle frontal regions, the right fusiform and left middle temporal regions, for bipolar disorder vs. schizophrenia demonstrated larger cortical area in bipolar disorder in several frontal and temporal regions. Bipolar disorder patients displayed cortical area increase in the left superior frontal and right temporal pole regions as compared with healthy controls.

IV

Subcortical brain volumes relate to neurocognition in schizophrenia and bipolar disorder and healthy controls

Cecilie B. Hartberg[a]*, Kjetil Sundet[b,d], Lars M. Rimol[a], Unn K. Haukvik[a,c], Elisabeth H. Lange[a,c], Ragnar Nesvåg[a,c], Ingrid Melle[a,d], Ole A. Andreassen[a,d], Ingrid Agartz[a,e]

[a] Institute of Clinical Medicine, Psychiatry Section, University of Oslo, Norway.

[b] Department of Psychology, University of Oslo, Norway.

[c] Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway.

[d] Division of Mental Health and Addiction, Psychosis Research Unit, Oslo University Hospital, Norway.

[e] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.

*Corresponding author: Cecilie Bhandari Hartberg,
Institute of Clinical Medicine,
P.O. Box 85 Vinderen, University of Oslo, N-0319 Oslo, Norway.
Phone +47 22 02 98 56, Fax +47 22 49 58 62, e-mail : c.b.hartberg@medisin.uio.no

Number of words
in abstract: 249
in manuscript: 4396

Tables: 3
Figures: 2
Supplemental tables: 2

Abstract:

Background: Similar patterns of subcortical brain abnormalities as well as neurocognitive dysfunction profiles have been demonstrated in schizophrenia and bipolar disorder, with more extensive findings in schizophrenia. It is not known whether relationships between subcortical brain volumes and neurocognitive performance are similar in these diseases or if there are illness-specific differences in schizophrenia as compared with bipolar disorder and healthy controls.

Methods: Magnetic Resonance Imaging scans and neuropsychological test performance were obtained from patients with schizophrenia (n = 117) or bipolar spectrum disorder (n = 121) and healthy control subjects (n = 192). Using the FreeSurfer software, volumes of 18 selected subcortical structures were automatically segmented and analyzed for relationships with 7 neurocognitive test scores for all subjects combined, and in separate groupwise analyses. Relationships from the separate group analyses were compared across groups.

Results: In the combined group, larger left inferior lateral ventricle volumes were related to poorer motor speed performance, larger right hippocampus volumes were related to poorer working memory, and larger bilateral putamen volumes were related to poorer verbal learning. The negative relationship between right putamen volume and set-shifting found in schizophrenia and bipolar disorder was found to be reversed in healthy controls. A negative relationship between left putamen with working memory was specific to schizophrenia.

Conclusion: The present findings suggest that there are similarities as well as differences in subcortical structure/function relationships between patients with schizophrenia or bipolar disorder and healthy individuals. More specifically, putamen may be of importance to neurocognitive dysfunction in these disorders.

Keywords: MRI, putamen, working memory, hippocampus, ventricles

Abbreviations

AP, Antipsychotic

ANOVA, Analysis of variance

ANCOVA, Analysis of covariance

CVLT, California Verbal Learning test

DDD, Defined Daily Doses

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders

D-KEFS, Delis-Kaplan Executive Function System

GAF, Global Assessment of Functioning

ICV, Intracranial volume

MRI, magnetic resonance imaging

PANSS, Positive and Negative Syndrome Scale

PRIME-MD, Primary Care Evaluation of Mental Disorders

SCID, Structured Clinical Interview for DSM-IV

TOP, Thematically Organized Psychosis Study

WAIS, Wechsler Adult Intelligence Scale

WASI, Wechsler Abbreviated Scale of Intelligence (WASI)

1. Introduction

Cognitive functioning has traditionally been related to the neocortical parts of the brain. Brain lesion studies have demonstrated that there are, to some extent, associations between localized cortical lesions and cognitive dysfunction such as impairment of attention and executive functioning (Stuss et al., 2000;Stuss et al., 2001). Magnetic Resonance Imaging (MRI) based investigations have demonstrated relationships between cortical volumes (Gur et al., 2000a;Sanfilipo et al., 2002) and cortical thickness (Hartberg et al., 2010;Tamnes et al., 2010;Walhovd et al., 2006), and specific neurocognitive test scores in healthy subjects.

Current views in neuroscience support the notion that cognitive functioning rely on neural distributed networks (Middleton and Strick, 2000b), which include subcortical structures, that work in parallel circuits. The prefrontal and temporal cortical areas are anatomically linked directly or indirectly, via the thalamic nuclei, with the basal ganglia structures (putamen and caudate nuclei and globus pallidum) (Groenewegen et al., 1997;Middleton and Strick, 2000b), the cerebellar cortices (Strick et al., 2009), and the hippocampus and amygdala (Groenewegen et al., 1997). It is increasingly recognized that the basal ganglia and the cerebellum influence or modulate cognitive behavior (Casey, 2005;Koziol and Budding, 2009) in addition to motor behavior. Neuronal circuits underlying cognitive control may be disturbed in neurodevelopmental diseases (Casey, 2005), such as schizophrenia (Rapoport et al., 2005) and possibly also in bipolar disorder (Sanches et al., 2008). In these diseases, projections between the cortex and the subcortical structures might undergo abnormal changes such as enhancement of some projections while others are eliminated through childhood and adolescent neurodevelopment, thus result in disrupted connectivity between crucial networks (Kyriakopoulos and Frangou, 2009;White et al., 2007). Hypothetically, these changes could be reflected in altered subcortical volumes and, consequently, result in abnormal subcortical/cognitive function relationships.

Previous scientific research on schizophrenia and bipolar patients has demonstrated subcortical structural abnormalities that co-occur with widespread cortical volume reduction (Arnone et al., 2009). The most consistent findings are enlarged lateral ventricles (Arnone et al., 2009) and reduced hippocampal and amygdala volumes in both disorders (Blumberg et al., 2003;Honea et al., 2005), and smaller thalamic volumes as well as enlarged striatal structure volumes in schizophrenia (Ellison-Wright and Bullmore, 2010). It is under debate whether the striatal

enlargements are related to illness duration, antipsychotic (AP) medication or to other illness-related factors (Brandt and Bonelli, 2008;Navari and Dazzan, 2009). Also, widespread age-related subcortical volume changes have been demonstrated in healthy subjects (Walhovd et al., 2009), thus individual differences in age should be corrected for.

We recently demonstrated similar subcortical abnormalities across schizophrenia and bipolar disorder as compared to healthy controls (Rimol et al., 2010); enlarged lateral and inferior ventricles, reduced bilateral hippocampi, cerebellar cortices and left thalamus, albeit larger differences (effect sizes) were detected in schizophrenia than in bipolar disorder as compared to healthy controls. Right putamen was significantly larger in schizophrenia than in bipolar disorder, and there were trends for larger left putamen and bilateral pallidum volumes as well. Current AP medication or illness duration did not significantly affect the results. Likewise, neurocognitive dysfunction is present in both schizophrenia and bipolar disorder. Comparisons across patient groups result in similar neurocognitive profiles, but the degree of cognitive impairment is worse in schizophrenia compared with bipolar disorder (Barch, 2009).

In schizophrenia, subcortical structure/function relationships have been demonstrated between hippocampal, amygdala (Goldberg et al., 1994;Gur et al., 2000b;Killgore et al., 2009) and cerebellar volumes (Toulopoulou et al., 2004), and memory measures. Striatal (Mamah et al., 2007;Stratta et al., 1997) and thalamic (Crespo-Facorro et al., 2007b) volumes have been related to executive functioning and attention. Caudate volumes have been related to motor speed (Hokama et al., 1995), while putamen volume has been related to verbal learning (Lawyer et al., 2006). Ventricular size has been related to executive functioning and visuomotor speed and verbal IQ (Lawyer et al., 2006). Some investigators have reported no findings (Antonova et al., 2005;Crespo-Facorro et al., 2007a;DeLisi et al., 1991). Only a few studies have addressed such relationships in bipolar disorder patients; hippocampal volume has been related to measures of attention (Sax et al., 1999), verbal fluency and verbal working memory (Ali et al., 2000), while others have found no relationships (Haldane et al., 2008). The majority of such studies have focused on single or few subcortical structures, and none of them made direct comparisons with other patient groups.

To our knowledge, only one study has directly compared subcortical structure/function relationships in schizophrenia with those in bipolar disorder. Killgore et.al (2009) demonstrated opposite relationships between amygdala volumes and memory performance in schizophrenia and

bipolar disorder. However, they limited their analyses to the hippocampus and amygdala and measures of verbal memory, and used a relatively small subject sample (n=30).

Thus, how an extensive range of subcortical structure volumes relate to neurocognitive function across schizophrenia and bipolar disorder and healthy controls remain unanswered. We used the Freesurfer software which performs automatic segmentation of subcortical brain structures, in contrast with manual delineation, allowing for measurement of a large range of subcortical structure volumes, of which we selected 18 of interest, in a large subject sample (n=430), comprising patients with schizophrenia or bipolar disorder, and healthy controls. Neuropsychological tests from seven domains were investigated in relation to the subcortical volumes and the relationships were directly compared across the three groups. Given the effect that antipsychotic medication may have on striatal structures, confounding effects of medication in our analyses were given special attention.

2. Materials and methods

2.1 Participants

All participants were recruited between 2003 and 2009 as part of an ongoing study on psychotic disorders Thematically Organized Psychosis (TOP) Research Study (Rimol et al., 2010) in Norway. Patients were inpatients and outpatients and were referred from psychiatric units from four major hospitals in the greater Oslo area. In order to ensure a representative control group, the controls were randomly selected from statistical records from the same catchment area as the patient groups, and contacted by letter inviting them to participate. All participants gave informed consent to participation, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

All subjects from the larger TOP study who had undergone both MRI scanning and neuropsychological testing were included in the current study, but were excluded if they met the following criteria: a history of hospitalized head injury, neurological disorder, IQ < 70 points, and age outside the range of 18-65 years. To assure valid neurocognitive test performance, all participants had to have Norwegian as their first language or have received their compulsory schooling in Norway, and had to score 15 or above on the forced recognition trial of the California Verbal Learning Test (CVLT)-II (Delis et al., 2004), which is a measure of adequate test effort. All MRI scans were evaluated by a neuroradiologist, and excluded if significant pathology was present.

Included in the statistical analyses were 117 patients with schizophrenia spectrum disorders, 121 patients with bipolar spectrum disorders, and 192 healthy control subjects. The schizophrenia spectrum included patients with schizophrenia (n = 94), schizophreniform disorder (n = 7) and schizoaffective disorder (n = 16), the bipolar disorder group included both bipolar type 1 disorder (n = 76) and bipolar type 2 disorder (n = 45). In the following we will refer to schizophrenia spectrum as "schizophrenia" and bipolar type 1 and 2 disorder as "bipolar disorder". Age was defined as age at MRI scanning. Years of education were registered as years of schooling as reported by the subjects during interview.

The healthy control sample was evaluated by a clinical interview of severe mental disorder symptoms and the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994). Controls were excluded if they had a diagnosis of drug abuse/dependency the last three months or had used drugs within the last 2 weeks, if they or any of their first-degree relatives had a lifetime history of a severe psychiatric disorder (schizophrenia spectrum disorders, bipolar disorder or major depression), or if they had a history of medical problems thought to interfere with brain function (uncontrolled hypertension, inadequately treated hypothyroidism or diabetes).

Trained physicians and clinical psychologists performed the clinical assessments. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First, 2002). Diagnostic interrater reliability was found satisfactory, with overall agreement for DSM-IV diagnostic categories of 82 % with $\kappa = 0.77$ (95% CI: 0.60-0.94) (Birkenaes et al., 2007). Current positive and negative symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning (GAF) scale, split version. Interrater reliability for PANSS and GAF has been found to be satisfactory (Engh et al., 2010). Data on current medication were derived from interviews and medical records. In order to obtain a clinically representative sample, all patients were included regardless of drug use, but abuse/dependency was diagnosed (SCID module E) if present. Nine of the patients with schizophrenia spectrum and five of the patients with bipolar disorder had either a current diagnosis of cannabis abuse or were in early partial remission. Demographic and clinical data are displayed in Table 1.

2.2 Neurocognitive assessment

Psychologists trained in standardized neuropsychological testing performed the neurocognitive assessments. A comprehensive test battery was administered in a fixed order. Handedness was determined by hand preference when writing. Premorbid IQ was estimated using the National Adult Reading Test – Norwegian version (Sundet and Vaskinn, 2008). For the present study, neurocognitive tests were included from the full test-battery if 1) they or near identical tests had previously shown a relationship with brain cortical thickness in an independent study of chronic schizophrenia (Hartberg et al., 2010), or 2) had previously been found to differ between schizophrenia and bipolar disorder patients in an overlapping sample with the present (Simonsen et al., 2011). In addition, given the relationship between basal ganglia and motor control, a measure of motor speed was included. In total, 7 neurocognitive function measures were selected: ***Verbal learning*** was tested with the Total recall trial score (list A1 – A5) from the California Verbal Learning Test, Second edition (CVLT-II) (Delis et al., 2004). ***Motor speed*** was measured with the dominant hand scores from the Grooved Pegboard Test (Klove, 1963). ***Processing speed*** was assessed with the Digit Symbol subtest from the Wechsler Adult Intelligence Scale, Third edition (WAIS-III) (Wechsler, 2003). ***Working memory*** was assessed with the Digit Span subtest (sum of forward and backward trials) from the WAIS-III (Wechsler, 2003). ***Interference control*** was tested with the Inhibition subtest from the Color-Word Interference Test (Delis-Kaplan Executive Function Scale, D-KEFS) (Delis et al., 2005). ***Set-shifting*** was measured with the Category Switching subtest (correct scores) from the Verbal Fluency Test (D-KEFS) (Delis et al., 2005). Both interference control and set-shifting are considered to be aspects of executive functioning. ***Verbal IQ*** was estimated with the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007). Raw scores were used in the main analyses, for which higher scores equal better performance on all measures except for the Color-Word Interference Test and the Grooved Pegboard Test for which higher scores equal poorer performance.

2.3 Brain imaging

2.3.1 MR image acquisition

All participants underwent MRI scanning on a 1.5T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional 3-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (TE = 3.93 ms, TR = 2730 ms, TI = 1000 ms, flip angle = 7°; FOV = 24 cm, voxel size = 1.33 x 0.94 x 1 mm^3, number of partitions =

160). Acquisition parameters were optimized for increased grey/white matter image contrast. There was no scanner upgrade during the study period.

2.3.2 MR image processing

The image files in DICOM format were transferred to a Linux workstation for morphometric analysis. Images were corrected for non-linear warping caused by gradient coil non-linearities, using tools developed through the Morphometry Biomedical Informatics Research Network (mBIRN) (Fennema-Notestine et al., 2007), and the two T1-weighted images were rigid body registered to each other (motion corrected) and subsequently averaged together to increase the signal to noise ratio. Subcortical volumes were obtained from the automated procedure for volumetric measures of brain structures implemented in Freesurfer (Fischl et al., 2002) as well as intracranial volume (ICV) estimates (Buckner et al., 2004). Next, manual corrections of topological defects were performed blinded to diagnostic group identity. In addition to ICV, nine measures from each hemisphere (18 in total) were chosen for the investigations; the lateral ventricles, the inferior lateral ventricles, hippocampus, amygdala, thalamus, pallidum, putamen, caudate, and the cerebellar cortex (Fig. 1).

2.4 Statistical analyses

All analyses were performed with the statistical software program SPSS 16.0.

2.4.1 Group differences in demographic, clinical, neurocognitive and subcortical volume variables

Demographic and clinical as well as age and sex-adjusted neuropsychological variables (standardized scores) were compared across groups using Student's t-tests, chi-square analyses and analyses of variance (ANOVAs) followed by Tukey's post-hoc tests. Group comparisons of subcortical volumes were done using ANCOVAs with age and ICV as covariates. Group comparisons of subcortical volumes have been published earlier by our research group for a larger, but completely overlapping subject sample (Rimol et al., 2010).

2.4.2 Regression analysis

The main analyses of relationships between subcortical volumes and neurocognitive function were conducted as follows. First, stepwise linear regression analyses were performed for the combined sample, then within each subject group (groupwise analysis). The subcortical measures in the left and right hemisphere, respectively, were entered as dependent variables. Age and ICV (and diagnosis for the combined group analyses) and all seven neurocognitive test scores were entered as independent variables, and were checked for collinearity. Preliminary analyses with sex as a

covariate were conducted but sex differences did not affect the results, and was therefore not included in the main analyses.

2.4.3 Group differences in correlations between subcortical volumes and neurocognition

Next, in order to test for differences in relationships, partial correlation coefficients from the group-wise regression analyses selected at alpha = 0.01, were tested for difference with the corresponding correlation coefficients from the other groups in a pairwise manner using Fisher z transformations. Thirteen subcortical structure volumes in total were selected from the separate group analyses for pairwise between-group contrasts. Bonferroni corrections were applied to the main analyses and to the pairwise contrasts.

2.4.4 Medication and duration of illness

Subsequent to the main analyses, the results in the patient groups were investigated for the potential effects of confounding factors; all analyses were repeated with logarithmic transformed duration of illness and antipsychotic DDD (Table 1), and estimated total lifetime exposure of AP medication (current antipsychotic DDD x illness duration) as covariates. Only subjects who were prescribed AP medication (Table 1) were included in the medication analyses. Medication as confounding factor was also explored by including only those who were using atypical AP medication in the analyses. The patients who were medication free or only used typical APs (Table 1) were too few to be investigated as separate groups.

2.4.5 Subgroup analysis

All analyses were repeated for bipolar disorder type 1 separately, and for the narrow schizophrenia group (schizophrenia and schizophreniform but excluding schizoaffective disorder), and finally excluding patients with current cannabis abuse. All analyses were two-tailed.

3. Results

3.1 Demographics and clinical characteristics

The groups differed on demographic variables with regard to age, sex and ethnicity, and on clinical variables as expected from diagnostic categories (Table 1). The schizophrenia group had lower mean age and more males than the two other groups. There were no overall group differences in handedness, education or premorbid IQ; or in age at onset of illness and duration of illness between the patient groups.

3.2 Group differences in neurocognition and subcortical volumes

The groups differed overall on all neuropsychological measures (Table S1). The highest effect sizes were observed for processing speed and set-shifting. The schizophrenia group performed worse than the bipolar group and the healthy controls on all tests, except for motor speed, on which both patient groups performed worse than the healthy control group. The bipolar group performed worse than healthy controls on the processing speed, interference control and set-shifting tasks.

Intracranial volumes did not significantly differ across groups (Table S2). The results from the subcortical group comparisons parallel those from a previous publication of mainly overlapping sample (Rimol et al., 2010); schizophrenia and bipolar patients exhibited larger ventricles, smaller bilateral hippocampi and left thalamus than the healthy controls, whereas the right putamen was larger in schizophrenia patients than in bipolar disorder patients and healthy controls, and the left cerebellar cortex was smaller in bipolar patients compared to healthy controls (Table S2).

3.3 Relationships between subcortical volumes and neurocognition

In the combined sample, four significant relationships were found (Fig. 2); a larger left inferior lateral ventricle was related to poorer motor speed performance; bilateral larger putamen volumes were related to poorer verbal learning performance, and a larger right hippocampus was related to poorer working memory performance. A trend-level relationship in the same direction was also observed for left hippocampus volume and working memory ($p = 0.01$).

The results from the groupwise analyses ($p < 0.01$) are presented in Table 2. Significant relationships in the schizophrenia group were found between larger left inferior lateral ventricles and poorer motor speed performance, and between larger bilateral putamen volumes and poorer performance on verbal learning, working memory and set-shifting, and between larger left putamen volume and poorer interference control. In the bipolar disorder group, larger left lateral and inferior lateral ventricle volumes were significantly related to poorer motor speed performance, and larger inferior lateral ventricle was related to poorer interference control. No relationships were found in the healthy control group or for any of the other structures.

3.4 Group differences in correlations between subcortical volumes and neurocognition

The results from the group comparisons are displayed in Table 3. After correction for multiple testing, 9 of the contrasts were statistically significant. The correlations between the left inferior lateral ventricle volume and motor speed performance, and between putamen volumes (significant

for the right, trend for the left) and set-shifting, were similar in schizophrenia and bipolar disorder and significantly different from healthy controls. The correlations between bilateral putamen volumes and working memory were significantly different in schizophrenia patients as compared to healthy controls. The negative correlation between left putamen and working memory also differentiated the schizophrenia patients from the bipolar disorder patients, who displayed a positive correlation, and thus appears specific to schizophrenia. The same pattern of relationships were observed for the right putamen, albeit not significantly. The relationship between the left inferior lateral ventricle and interference control in the bipolar disorder group was different from that in healthy controls, but not from that in the schizophrenia group, thus no relationship was specific to the bipolar disorder group.

3.5 Medication and duration of illness

Co-varying for illness duration, current and lifetime exposure of antipsychotic medication, and investigating those patients using atypical medication separately, did not affect the results shown in Table 2. When controlling for medication effects there was one exception; left lateral ventricular size and processing speed in the bipolar disorder patient group was no longer related. However, all the other relationships in the bipolar group displayed in Table 2, resulted in higher correlation coefficients ($r = 0.33 – 0.47$) when medication, but not illness duration, was corrected for.

3.6 Subgroup analyses

The bipolar disorder type 1 and the narrow schizophrenia groups displayed similar results as the whole bipolar and schizophrenia groups, respectively. The exclusion of current cannabis abusers in the analyses did not affect the results.

4. Discussion

This is the first comprehensive study of relationships between subcortical structure volumes and neurocognitive functioning in schizophrenia, bipolar disorder and healthy controls. In addition, the relationships were directly compared across the three groups. We demonstrate four significant subcortical structure/function relationships in the combined sample, one additional relationship that was exclusive to schizophrenia and bipolar disorder, and another that was specific to schizophrenia. In the combined sample, larger left inferior lateral ventricle volumes were related to poorer motor speed performance, larger right hippocampus volumes were related to poorer working memory performance and larger left and right side putamen volumes were both related to poorer verbal learning. In schizophrenia and bipolar disorder, larger right putamen volumes were

related to poorer set-shifting performance, while the inverse relationship was found in healthy controls. The relationship between larger left putamen volume and poorer working memory performance was specific to schizophrenia.

The findings were essentially unchanged when co-varying for AP medication or illness duration. However, one interesting result emerged from the follow-up analyses in the bipolar disorder group; co-varying for AP medication effect, but not illness duration, resulted in stronger correlations between inferior lateral and lateral ventricular sizes and motor speed, indicating that use of medication in this group affected the relationship magnitudes between the ventricles and motor speed. This effect was not specific to the bipolar disorder type 1 subgroup, but may be mediated by more severe symptomatology or occurrence of psychotic episodes in those who were prescribed antipsychotic medication across the bipolar disorder spectrum.

To our knowledge, this is the first time ventricular volume size has been associated with motor speed performance. The relationships were the same in all groups but significantly stronger in both patients groups compared to the healthy control group. The inferior lateral ventricle, which is the temporal horn of the lateral ventricular system, borders with temporal lobe structures known to be smaller in schizophrenia and bipolar disorder (Blumberg et al., 2003;Honea et al., 2005;Rimol et al., 2010), and with parts of the caudate nucleus, which volume has been related to motor speed. (Hokama et al., 1995). However, surrounding gray matter reductions cannot completely explain the extensive ventricular enlargements in severe mental diseases. Whether white matter abnormalities can explain the ventricular enlargement remains to be determined.

The negative relationship between right hippocampus and *working memory* in the combined group is substantiated by previously reported findings in bipolar disorder (Ali et al., 2000) as well as in schizophrenia (Spoletini et al., 2011). Furthermore, functional MRI studies have shown hippocampal activity during working memory tasks in healthy individuals (Cabeza et al., 2002), suggesting hippocampal involvement in short-term memory networks as well as in long-term memory networks. The bilateral putamen volume relationships with verbal learning across all groups are in accordance with the findings by Lawyer et al. (Lawyer et al., 2006). We did not replicate the opposite relationships between amygdala volume and verbal memory in the patient groups that were shown by Killgore et al (2009).

Considering that the working memory task, and the interference control and set-shifting tasks selected for the present study measure aspects of attention and executive functioning, respectively, the present relationships with putamen in schizophrenia are supported by results from other studies in schizophrenia patients (Lawyer et al., 2006;Mamah et al., 2007;Stratta et al., 1997). However, by increasing the sample size and making direct comparisons between schizophrenia and bipolar disorder, we can show that the relationship with working memory was specific to schizophrenia; whereas the relationship with set-shifting performance was similar in the schizophrenia and bipolar disorder groups. Notably, in the present study, the bipolar patients were impaired on set-shifting performance, but not on working memory performance, while the schizophrenia patients were impaired on both tasks, compared to healthy controls. Larger putamen volumes have also been related to increased severity of positive symptoms in neuroleptic-naïve patients (Gur et al., 1998), and considering the present relationship with poorer neurocognitive functioning, putamen size may directly reflect the severity of clinical and neurocognitive dysfunctions observed in schizophrenia and bipolar disorder.

Putamen, which is part of the dorsal striatum, is functionally and anatomically connected with other parts of the brain and participates in parallel loops, forming the so-called cortico-striatal-pallido-thalamo-cortical circuitries. Several of the loops include prefrontal and temporal non-motor areas (Alexander et al., 1986;Middleton and Strick, 2000a). Thus, the differences in relationships between putamen and working memory and set-shifting in schizophrenia and bipolar disorder patients compared to healthy controls may be due not only to pathology directly related to putamen structure volumes, but also to any part of the several parallel loops involving the putamen.

Elevated striatal dopamine levels have consistently been shown in schizophrenia patients (Howes and Kapur, 2009) and there is evidence that striatal dopaminergic abnormalities are linked with cognitive dysfunction (Simpson et al., 2010) in the disease. Of pathophysiological relevance to the present findings, Kellendonk et al (2006) performed a study on transgenic mice, that were overexpressing D2 receptors in the striatum, and showed that the mice exhibited selective deficits in working memory and flexibility compared with those with normal levels of dopamine, and that the deficits remained after the overexpression was switched off, thus suggesting that developmental changes caused the cognitive deficits. Furthermore, the striatal dopamine levels affected the level of prefrontal dopamine transmission; however, it is not known whether the cognitive dysfunction is primary or secondary to striatal dysfunction.

Limitations

A limitation in this study is the possible confounding effect of antipsychotic medication. Several reviews have summarized the possible effects of APs on brain structure (Brandt and Bonelli, 2008;Navari and Dazzan, 2009;Scherk and Falkai, 2006). In sum, they report that use of typical but not atypical APs is associated with basal ganglia enlargement, and that the effects are dynamic and reversible (Chakos et al., 1995;Lang et al., 2004). Due to the small number of drug free participants or patients using typical AP in the present study, separate analyses for these particular groups were not possible. However, current and total dose of APs, and only those with atypical APs were included in separate analyses, none of which changed the main results. Also, the similarity of relationships between putamen volumes and verbal learning across groups may indicate that our findings are not merely medication-related effects. Therefore, we suggest that the relationships between putamen and working memory, interference control and set-shifting are illness-related rather than consequences of AP treatment. However, replications in independent samples, preferably of drug naïve patients or from longitudinal studies are needed.

Conclusion

In addition to demonstrating several structure/function relationships that are similar between schizophrenia, bipolar disorder and healthy controls in the subcortical brain, the present study also shows that disrupted relationships specifically occur between putamen and neurocognitive performance in schizophrenia, and to some extent also in bipolar disorder as compared with healthy controls, indicating that putamen volumes are of importance to neurocognitive dysfunction in these disorders.

Funding

IM has received Speaker's honorarium from Janssen, AstraZeneca and Lundbeck. RN has received Speaker's honorarium from Janssen and AstraZeneca. OAA has received Speaker's honorarium from AstraZeneca, Janssen, BMS and GSK. All other authors report no conflict of interest. This work was supported by grants from the Research Council of Norway [grant number 167153/V50, 190311/V50]; South-Eastern Norway Regional Health Authority [grant numbers 2004-123, 2006-258, 2008-011, 2009-037, 2009-038]. The funding source had no involvement in study design; in the collection, analysis or interpretation of data; in writing the report; or in the decision to submit the paper for publication.

Acknowledgments

We thank patients and controls for their participation in the study. We also wish to thank Ørjan Bergmann, Merete Øibakken, Martin Furan, Petr S. Bjerkan, Thomas Bjella and Eivind Bakken, for technical and administrative assistance and the Oslo University Hospital and the University of Oslo to support the Thematically Organized Psychosis (TOP) Research Study group.

Reference list

Alexander, G. E., DeLong, M. R. and Strick, P. L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 9, 357-381.

Ali, S. O., Denicoff, K. D., Altshuler, L. L. et al, 2000. A preliminary study of the relation of neuropsychological performance to neuroanatomic structures in bipolar disorder. Neuropsychiatry Neuropsychol Behav Neurol. 13, 20-28.

Antonova, E., Kumari, V., Morris, R. et al, 2005. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry. 58, 457-467.

Arnone, D., Cavanagh, J., Gerber, D. et al, 2009. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. Br J Psychiatry. 195, 194-201.

Barch, D. M., 2009. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. Curr Psychiatry Rep. 11, 313-319.

Birkenaes, A. B., Opjordsmoen, S., Brunborg, C. et al, 2007. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. J Clin Psychiatry. 68, 917-923.

Blumberg, H. P., Kaufman, J., Martin, A. et al, 2003. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. Arch Gen Psychiatry. 60, 1201-1208.

Brandt, G. N. and Bonelli, R. M., 2008. Structural neuroimaging of the basal ganglia in schizophrenic patients: a review. Wien Med Wochenschr. 158, 84-90.

Buckner, R. L., Head, D., Parker, J. et al, 2004. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage. 23, 724-738.

Cabeza, R., Dolcos, F., Graham, R. et al, 2002. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. Neuroimage. 16, 317-330.

Casey, B. J., 2005. Frontostriatal and Frontocerebellar Circuitry underlying Cognitive Control. In: Mayr U.E., Awh E.E. and Keele S.W.E. (Eds.), Developing individuality in the human brain: A tribute to Michael I. Posner, Decade of behavior, American Psychological Association, Washington DC, pp. 141-166.

Chakos, M. H., Lieberman, J. A., Alvir, J. et al, 1995. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. Lancet. 345, 456-457.

Crespo-Facorro, B., Roiz-Santianez, R., Pelayo-Teran, J. M. et al, 2007a. Caudate nucleus volume and its clinical and cognitive correlations in first episode schizophrenia. Schizophr Res. 91, 87-96.

Crespo-Facorro, B., Roiz-Santianez, R., Pelayo-Teran, J. M. et al, 2007b. Reduced thalamic volume in first-episode non-affective psychosis: correlations with clinical variables, symptomatology and cognitive functioning. Neuroimage. 35, 1613-1623.

Delis, D., Kramer, J., Kaplan, E. et al, 2004. California Verbal Learning Test - Second edition (CVLT-II). Norwegian Manual Supplement Pearson Assessment, Stockhom.

Delis, DC., Kaplan, E. and Kramer, J., 2005. The Delis-Kaplan Executive Function System (D-KEFS). Norwegian Manual Supplement Pearson Assessment, Stockholm.

DeLisi, L. E., Hoff, A. L., Schwartz, J. E. et al, 1991. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol Psychiatry. 29, 159-175.

Ellison-Wright, I. and Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res. 117, 1-12.

Engh, J. A., Friis, S., Birkenaes, A. B. et al, 2010. Delusions are associated with poor cognitive insight in schizophrenia. Schizophr Bull. 36, 830-835.

Fennema-Notestine, C., Gamst, A. C., Quinn, B. T. et al, 2007. Feasibility of multi-site clinical structural neuroimaging studies of aging using legacy data. Neuroinformatics. 5, 235-245.

First, M. B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders.

Fischl, B., Salat, D. H., Busa, E. et al, 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 33, 341-355.

Goldberg, T. E., Torrey, E. F., Berman, K. F. et al, 1994. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. Psychiatry Res. 55, 51-61.

Groenewegen, H. J., Wright, C. I. and Uylings, H. B., 1997. The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. J Psychopharmacol. 11, 99-106.

Gur, R. E., Cowell, P. E., Latshaw, A. et al, 2000a. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry. 57, 761-768.

Gur, R. E., Maany, V., Mozley, P. D. et al, 1998. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. Am J Psychiatry. 155, 1711-1717.

Gur, R. E., Turetsky, B. I., Cowell, P. E. et al, 2000b. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry. 57, 769-775.

Haldane, M., Cunningham, G., Androutsos, C. et al, 2008. Structural brain correlates of response inhibition in Bipolar Disorder I. J Psychopharmacol. 22, 138-143.

Hartberg, C. B., Lawyer, G., Nyman, H. et al, 2010. Investigating relationships between cortical thickness and cognitive performance in patients with schizophrenia and healthy adults. Psychiatry Res. 182, 123-133.

Hokama, H., Shenton, M. E., Nestor, P. G. et al, 1995. Caudate, putamen, and globus pallidus volume in schizophrenia: a quantitative MRI study. Psychiatry Res. 61, 209-229.

Honea, R., Crow, T. J., Passingham, D. et al, 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry. 162, 2233-2245.

Howes, O. D. and Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 35, 549-562.

Kay, S. R., Fiszbein, A. and Opler, L. A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 13, 261-276.

Kellendonk, C., Simpson, E. H., Polan, H. J. et al, 2006. Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron. 49, 603-615.

Killgore, W. D., Rosso, I. M., Gruber, S. A. et al, 2009. Amygdala volume and verbal memory performance in schizophrenia and bipolar disorder. Cogn Behav Neurol. 22, 28-37.

Klove, H., 1963. Clinical neuropsychology. In: F.M.Forster (Ed.), Saunders, New York, pp. 1647-1658.

Koziol, L. F. and Budding, D. E., 2009. Subcortical structures and cognition. Implications for neuropsychological assessment. Springer Science+Business Media, New York.

Kyriakopoulos, M. and Frangou, S., 2009. Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry. 22, 168-176.

Lang, D. J., Kopala, L. C., Vandorpe, R. A. et al, 2004. Reduced basal ganglia volumes after switching to olanzapine in chronically treated patients with schizophrenia. Am J Psychiatry. 161, 1829-1836.

Lawyer, G., Nyman, H., Agartz, I. et al, 2006. Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression. BMC Psychiatry. 6, 31.

Mamah, D., Wang, L., Barch, D. et al, 2007. Structural analysis of the basal ganglia in schizophrenia. Schizophr Res. 89, 59-71.

Middleton, F. A. and Strick, P. L., 2000a. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev. 31, 236-250.

Middleton, F. A. and Strick, P. L., 2000b. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn. 42, 183-200.

Navari, S. and Dazzan, P., 2009. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med. 39, 1763-1777.

Rapoport, J. L., Addington, A. M., Frangou, S. et al, 2005. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 10, 434-449.

Rimol, L. M., Hartberg, C. B., Nesvag, R. et al, 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 68, 41-50.

Sanches, M., Keshavan, M. S., Brambilla, P. et al, 2008. Neurodevelopmental basis of bipolar disorder: a critical appraisal. Prog Neuropsychopharmacol Biol Psychiatry. 32, 1617-1627.

Sanfilipo, M., Lafargue, T., Rusinek, H. et al, 2002. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res. 116, 1-23.

Sax, K. W., Strakowski, S. M., Zimmerman, M. E. et al, 1999. Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry. 156, 139-141.

Scherk, H. and Falkai, P., 2006. Effects of antipsychotics on brain structure. Current Opinion in Psychiatry. 19, 145-150.

Simonsen, C., Sundet, K., Vaskinn, A. et al, 2011. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. Schizophr Bull. 37, 73-83.

Simpson, E. H., Kellendonk, C. and Kandel, E., 2010. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia. Neuron. 65, 585-596.

Spitzer, R. L., Williams, J. B., Kroenke, K. et al, 1994. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA. 272, 1749-1756.

Spoletini, I., Cherubini, A., Banfi, G. et al, 2011. Hippocampi, thalami, and accumbens microstructural damage in schizophrenia: a volumetry, diffusivity, and neuropsychological study. Schizophr Bull. 37, 118-130.

Stratta, P., Mancini, F., Mattei, P. et al, 1997. Association between striatal reduction and poor Wisconsin card sorting test performance in patients with schizophrenia. Biol Psychiatry. 42, 816-820.

Strick, P. L., Dum, R. P. and Fiez, J. A., 2009. Cerebellum and nonmotor function. Annu Rev Neurosci. 32, 413-434.

Stuss, D. T., Floden, D., Alexander, M. P. et al, 2001. Stroop performance in focal lesion patients: dissociation of processes and frontal lobe lesion location. Neuropsychologia. 39, 771-786.

Stuss, D. T., Levine, B., Alexander, M. P. et al, 2000. Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. Neuropsychologia. 38, 388-402.

Sundet, K. and Vaskinn, A., 2008. Estimating premorbid IQ (in Norwegian with English abstract). Journal of the Norwegian Psychological Association. 45, 1108-1115.

Tamnes, C. K., Ostby, Y., Walhovd, K. B. et al, 2010. Neuroanatomical correlates of executive functions in children and adolescents: a magnetic resonance imaging (MRI) study of cortical thickness. Neuropsychologia. 48, 2496-2508.

Toulopoulou, T., Grech, A., Morris, R. G. et al, 2004. The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. Biol Psychiatry. 56, 447-453.

Walhovd, K. B., Fjell, A. M., Dale, A. M. et al, 2006. Regional cortical thickness matters in recall after months more than minutes. Neuroimage. 31, 1343-1351.

Walhovd, K. B., Westlye, L. T., Amlien, I. et al, 2009. Consistent neuroanatomical age-related volume differences across multiple samples. Neurobiol Aging. doi: S0197-4580(09)00174-2 [pii];10.1016/j.neurobiolaging.2009.05.013.

Wechsler, D., 2003. Wechsler Adult Intelligence Scale - Third edition (WAIS-III). Norwegian Manual. Pearson Assessment., Stockholm.

Wechsler, D., 2007. Wechsler Abbreviated Scale of Intelligence (WASI). Norwegian Manual supplement. Pearson Assessment, Stockholm.

White, T., Kendi, A. T., Lehericy, S. et al, 2007. Disruption of hippocampal connectivity in children and adolescents with schizophrenia--a voxel-based diffusion tensor imaging study. Schizophr Res. 90, 302-307.

Table 1. Demograhics and clinical data

	1. Schizophrenia	**2. Bipolar disorder**	**3. Healthy controls**	**ANOVA / Chi square analysis / t – tests**		
	N = 117	N = 121	N = 192	$F_{2,427}$/ χ^2/t	p	Post hoc[a]
Demographics						
Age, years	31.7 (7.9)	34.7 (11.4)	36.1 (9.6)	F = 7.5	p = ***0.001***	1 < 2, 3
Sex *n* (% males)	68 (58.1)	49 (40.5)	98 (51.0)	χ^2 = 7.5	p = ***0.023***	1 > 2, 3
Handedness *n* (% right)	98 (87.5)	91 (85.8)	176 (91.7)	χ^2 = 4.5	p = 0.338	
Ethnicity *n* (% European)	102 (87.2)	114 (94.2)	190 (99.0)	χ^2 = 26.4	p = ***0.003***	1 < 2 < 3
Education, years	13.6 (2.8)	14.2 (2.8)	14.2 (2.3)	F = 2.2	p = 0.111	
NART IQ	105.9 (4.5)	106.2 (4.1)	106.9 (4.0)	F = 2.6	p = 0.078	
Clinical data						
Age at onset of illness, years[b]	26.3 (6.8)	28.3 (11.3)		t = 1.6	p = 0.107	
Duration of illness, years[b]	5.3 (5.2)	6.3 (6.6)		t = 1.3	p = 0.187	
Symptom ratings						
PANSS positive score	14.7 (5.8)	10.1 (3.6)		t = 7.5	p = ***< 0.001***	
PANSS negative score	14.7 (6.9)	10.4 (3.8)		t = 5.8	p = ***< 0.001***	
GAF symptom score	42.5 (11.1)	56.9 (11.1)		t =10.0	p = ***< 0.001***	
GAF function score	43.8 (10.7)	54.6 (12.4)		t = 7.3	p = ***< 0.001***	

Medication	*N (%)*	*DDD*	*N (%)*	*DDD*
Antipsychotic [c]	99 (85)	1.6 (1.3)	52 (43)	1.0 (0.7)
Lithium	1 (1)	0.5	16 (13)	1.0 (0.3)
Antiepileptic	12 (10)	0.9 (0.3)	43 (36)	0.6 (0.4)
Antidepressive	31 (26)	1.7 (1.3)	39 (32)	1.5 (0.8)
Sedative	15 (13)	0.5 (0.4)	12 (10)	0.9 (1.1)

ANOVA, univariate analysis of variance; NART, National Adult Reading Test – Norwegian version; IQ, Intelligent Quotient; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; DDD, Defined Daily Doses, in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcddd).

Means and SDs are reported unless otherwise specified.

[a] Tukey post hoc tests

[b] Age at onset was defined as age at first contact with the mental health service due to a primary symptom. Duration of illness was defined as number of years between age at onset and age at MRI scanning.

[c] Eight (7%) patients with schizophrenia and 4 (3%) patients with bipolar disorder received typical antipsychotic medication and 84 (72%) patients with schizophrenia and 46 (38%) patients with bipolar disorder received atypical antipsychotic medication, while 7 (6%) patients with schizophrenia and 1 (1%) patient with bipolar disorder received both. Thirteen (11%) patients with schizophrenia and 18 (15%) patients with bipolar disorder received no psychopharmacological medication.

Number of missing data:

Handedness; schizophrenia: 5, bipolar disorder: 15; education; schizophrenia: 1; NART IQ; schizophrenia: 11, bipolar disorder: 2; age of onset and illness duration; schizophrenia: 1, bipolar disorder: 6.

Table 2. Relationships between subcortical volumes and neurocognitive functions.

Volumes	1. Schizophrenia (n = 117)	2. Bipolar disorder (n = 121)	3. Healthy controls (n = 192)
Lateral ventricle		**gpd (.30)*,** dsy (-.24)	
Inf. Lat. ventricle	***gpd (.31)****	**gpd (.29)*, int (.26)***	
Hippocampus			
Amygdala			
Pallidum			
Putamen	**cvlt (-.26)*, *dsp (-.28)*, int (.30*), ssh (-.31)****		
	cvlt (-.28)*, dsp (-.27)*, int (.25), **ssh (-.27)***		
Caudate			
Thalamus			
Cerebellar cortex	gpd (.24)		

Abbreviations: Inf. Lat. Ventricle, Inferior Lateral Ventricle; dsp, Digit Span Total; dsy, Digit Symbol Test; int, Color-Word interference test; cvlt, California Verbal Learning test; ssh, Set Shifting Test; gpd, Grooved Pegboard.

Partial correlation coefficients are shown for p values < 0.01, *significant after Bonferroni correction for multiple comparisons. Higher scores equal better performance on all measures except for the Color-Word Interference Test (int) and Grooved Pegboard (gpd).

Grey; left hemisphere, white; right hemisphere.

Table 3. Pairwise contrasts of correlations ($p < 0.01$) between subcortical volumes and neurocognitive tests.

	Group relationships			Pairwise contrasts					
	SCH	BD	CTR	CTR – SCH		CTR – BD		SCH - BD	
		r		z	p	z	p	z	p
Subcortical volume / test									
Lat ventricle L /gpd	0.02	0.30*	0.06	0.3	0.741	-2.2	0.029	-2.2	0.025
Lat ventricle L / dsy	0.06	-0.24*	0.03	-0.3	0.803	2.4	0.017	2.4	0.018
Inf lat ventricle L /gpd	0.31*	0.29*	0.02	-2.6	**0.011**	-2.4	**0.016**	0.2	0.873
Inf lat ventricle L / int	-0.01	0.26*	-0.03	-0.2	0.865	-2.5	**0.011**	-2.1	0.034
Cerebellar cortex L / gpd	0.24*	0.03	0.10	-1.2	0.234	0.7	0.497	1.7	0.093
Putamen L / cvlt	-0.26*	-0.16	-0.05	1.8	0.072	1.0	0.342	-0.8	0.441
Putamen R / cvlt	-0.28*	-0.15	-0.06	1.9	0.062	0.7	0.465	-1.0	0.303
Putamen L / dsp	-0.28*	0.08	0.05	3.2	**0.001**	-0.3	0.795	-2.8	**0.006**
Putamen R / dsp	-0.27*	-0.02	0.03	2.6	**0.009**	0.4	0.697	-2.0	0.043
Putamen L / int	0.30*	0.00	0.08	-1.9	0.054	0.7	0.509	2.3	0.020
Putamen R / int	0.25*	0.03	0.04	-1.8	0.066	0.1	0.928	1.7	0.082
Putamen L / ssh	-0.31*	-0.20	0.08	3.4	**0.001**	2.4	0.017	-0.9	0.363
Putamen R / ssh	-0.27*	-0.21	0.11	3.3	**0.001**	2.8	**0.005**	-0.5	0.624

* Only correlations significant at alpha level = 0.01 (as shown in Table 2) were selected for further pairwise comparisons. Bold indicates significant group differences in correlation coefficients after Bonferroni correction.

Abbreviations: CTR, Healthy control subjects; SCH, Schizophrenia; BD, Bipolar disorder; r, partial correlation coefficient; z, Fisher's z value; L, left hemisphere; R, right hemisphere; dsp, Digit Span Total; dsy, Digit Symbol Test; int, Color-Word interference test; cvlt, California Verbal Learning test; ssh, Set Shifting Test; gpd, Grooved Pegboard.

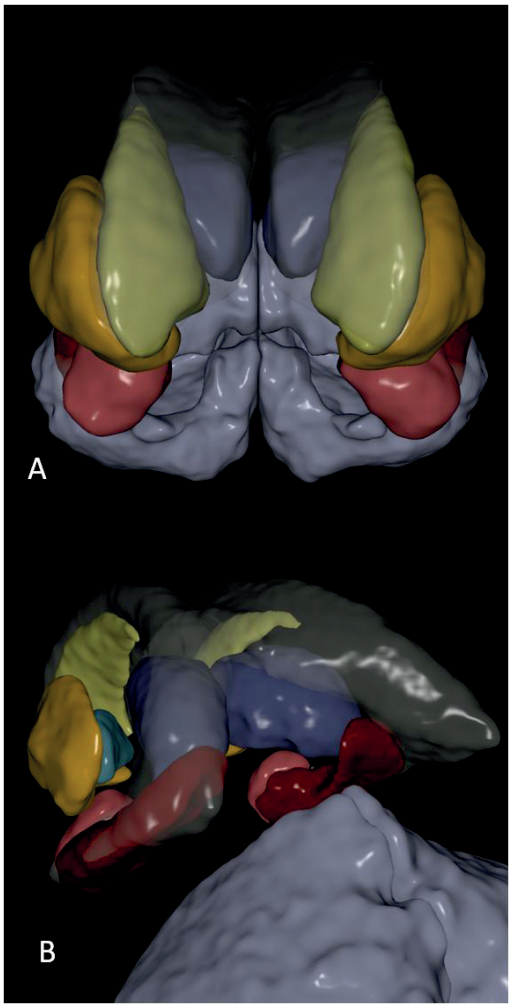


Figure 1

Subcortical brain volumes segmentation.

The figure shows the FreeSurfer segmentation results from the average brain template provided by the software (fsaverage). The three-dimensional representation illustrates the shape, extension, and relative position within the brain of the different neuroanatomical structures in the present study. A. Anterior view. B. Posterior angle view. Cerebellar cortex, grey; hippocampus, red; amygdala, pink; putamen, orange; globus pallidum, blue; thalamus, purple; caudate, yellow; the lateral and inferior lateral ventricles, transparent grey.

Figure 2

Relationships in the combined sample.

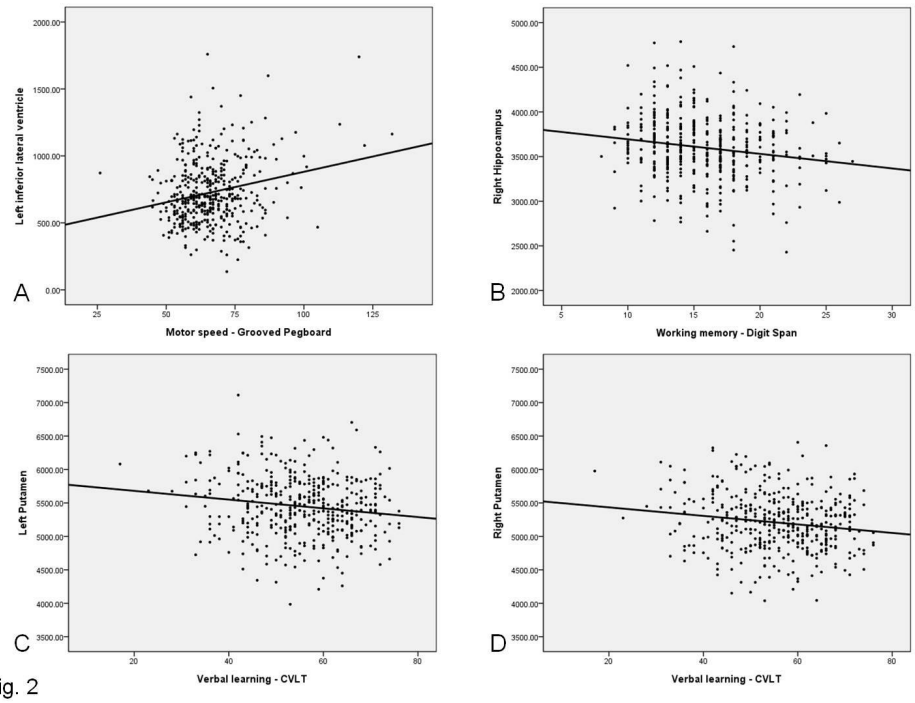


Fig. 2

Scatter plots showing significant relationships between subcortical volumes (µl) and neurocognitive performance, adjusted for age and ICV, in the combined sample. A) Larger left inferior lateral ventricle related to poorer motor speed performance (B = 0.21, p = 0.00003), B) larger right hippocampus related to poorer working memory performance (B = -0.13, p = 0.0009), C) and D) left (B = -0.11, p = 0.004) and right putamen (r = -0.11, p = 0.002) related to poorer verbal learning. CVLT; California Verbal Learning Test.

Table S1. Results of neurocognitive comparisons

	1.Schizophrenia	**2. Bipolar disorder**	**3. Healthy controls**	**ANOVA**			
	N = 117	N = 121	N = 192	$F_{(2, 427)}$	p	η^{2a}	Post hoc [b]
Verbal learning							
CVLT-II: List A, Total trials[c]	49.2 (11.4)	55.8 (11.4)	57.2 (10.1)	F = 21.1	p < ***0.001***	0.09	1 < 2,3
Motor speed							
Grooved Pegboard[c]	40.3 (12.0)	41.6 (10.8)	50.4 (10.7)	F = 39.0	p < ***0.001***	0.16	1,2 < 3
Processing speed							
Digit Symbol (WAIS-III)[d]	7.5 (2.4)	8.9 (2.4)	10.4 (2.5)	F = 51.0	p < ***0.001***	0.19	1 < 2 < 3
Working memory							
Digit Span (WAIS-III)[d]	8.2 (2.0)	8.9 (2.5)	9.6 (2.5)	F = 11.8	p < ***0.001***	0.05	1 < 2,3
Interference control							
Color-Word Inhibition (D-KEFS)[d]	8.0 (3.6)	9.5 (3.1)	10.9 (2.5)	F = 34.4	p < ***0.001***	0.14	1 < 2 < 3
Set shifting							
Category Switching (D-KEFS)[d]	8.0 (2.9)	10.1 (3.3)	11.4 (3.2)	F = 42.3	p < ***0.001***	0.17	1 < 2 < 3
Verbal IQ							
Vocabulary (WASI)[c]	52.9 (9.3)	55.7 (8.6)	56.1 (7.0)	F = 5.9	p = ***0.003***	0.03	1 < 2,3

Mean and SD are reported. Standardized scores are shown and used in the analyses. Abbreviations: ANOVA, analysis of variance; CVLT-II, California Verbal Learning Test––Revised; WAIS-III, Wechsler Adult Intelligence Scale III Revision; D-KEFS, Delis-Kaplan Executive Functioning System; WASI, Wechsler Abbreviated Scale of Intelligence. [a]Eta square effect size. [b]Tukey's post-hoc test. [c]T-scores. [d]S-scores

Table S2. Comparisons of subcortical volumes across groups

		1. Schizophrenia		**2. Bipolar disorder**		**3. Healthy controls**		**ANCOVA**		
Volumes	Side	N = 117		N = 121		N = 192		$F_{(2, 425)}$	p	Pairwise comparisons[a]
ICV[b]		1563	(15.9)	1559	(15.4)	1575	(12.3)	0.4	.685	
Lat ventricle	Left	10.321	(0.445)	10.373	(0.433)	8.468	(0.346)	8.1	**< .001**	1,2 > 3
	Right	9.572	(0.397)	9.572	(0.386)	7.871	(0.308)	8.3	**< .001**	1,2 > 3
Inf lat ventricle	Left	0.831	(0.022)	0.836	(0.021)	0.703	(0.017)	15.6	**< .001**	1,2 > 3
	Right	0.841	(0.020)	0.803	(0.020)	0.711	(0.016)	13.5	**< .001**	1,2 > 3
Hippocampus	Left	3.871	(0.030)	3.926	(0.029)	4.065	(0.023)	14.3	**< .001**	1,2 < 3
	Right	4.085	(0.032)	4.154	(0.032)	4.313	(0.025)	16.4	**< .001**	1,2 < 3
Amygdala	Left	1.745	(0.018)	1.768	(0.018)	1.816	(0.014)	5.1	.007	
	Right	1.739	(0.017)	1.765	(0.016)	1.793	(0.013)	3.1	.047	
Pallidum	Left	1.887	(0.015)	1.840	(0.015)	1.841	(0.012)	3.2	.041	
	Right	1.835	(0.015)	1.764	(0.015)	1.780	(0.012)	5.9	.003	
Putamen	Left	5.585	(0.042)	5.395	(0.041)	5.432	(0.032)	5.9	.003	
	Right	5.384	(0.039)	5.176	(0.038)	5.191	(0.030)	9.3	**< .001**	1 > 2,3
Caudate	Left	3.737	(0.035)	3.680	(0.034)	3.660	(0.027)	1.4	.240	
	Right	3.899	(0.035)	3.841	(0.034)	3.812	(0.027)	1.8	.168	
Thalamus	Left	6.891	(0.046)	6.924	(0.045)	7.100	(0.036)	7.8	**< .001**	1,2 < 3
	Right	6.882	(0.041)	6.918	(0.040)	7.009	(0.032)	3.3	.038	
Cerebellar cortex	Left	53.940	(0.408)	52.922	(0.396)	54.761	(0.316)	6.6	**.002**	2 < 3
	Right	54.634	(0.417)	53.696	(0.405)	55.418	(0.324)	5.5	.004	

Adjusted means and S.E. are reported. Volumes in mm. Age and ICV were included as covariates in the analyses. Bold; Significant after Bonferroni corrections for multiple tests. [a] Post-hoc comparisons. [b] Age-adjusted.