THE UNIVERSITY
of EDINBURGH

Imaging genetic risk and episodic memory in psychosis

Holly Lee Redpath

Doctor of philosophy

The University of Edinburgh

2015

Table of contents

Declaration

I declare that this thesis has been composed solely by myself and that the work presented is my own, except where clearly indicated.

I certify that this work has not been submitted for any other degree or professional qualification.

Holly Lee Redpath

29/09/2015

Acknowledgements

First, I would like to thank all the participants that took part in this study for giving their time and effort, without which this study would not have been possible.

I would like to thank my principal supervisor, Professor Stephen Lawrie and my second supervisor Dr Heather Whalley for their help throughout this research project. I would also like to thank Professor Jeremy Hall who was initially one of my supervisors.

The Scottish Family Mental Health Study involved input from a large number of people and I would like to acknowledge that the results from this study are attributable to a wider team effort. I would like to thank all individuals who were involved in this study, in particular Barbara Duff who was involved in recruitment, cognitive testing and data organisation (and for her general support and help as a fellow PhD student) and Liana Romaniuk for her technical assistance.

I would also like to thank my family and friends for the on-going support and encouragement throughout my time as a PhD student, in particular my father for proof reading.

List of Figures and tables

Tables

Glossary of Abbreviations

ACC – anterior cingulate cortex

AC-PC – anterior commissure - posterior commissure

ANOVA – analysis of variance

BA – Brodmann area

BDNF - Brain-derived neurotrophic factor

BOLD – blood oxygen level dependent

CNV – copy number variant

COMT – catechol O-methyltransferase

CPZE – chlorpromazine equivalents

CT – computerised tomography

DISC1 – disrupted in schizophrenia 1

DLPFC – dorsolateral prefrontal cortex

DMN – default mode network

DSM-5 – diagnostic and statistical manual of mental disorders, 5th edition

DTI – diffusion tensor imaging

EPI – echo planar imaging

ERP – event related potential

FDR – false discovery rate

fMRI – functional magnetic resonance imaging

FOV – field of view

FWHM – full width half maximum

GAF – global assessment of functioning

GLM – general linear model

GWAS – genome-wide association study

HDRS – Hamilton depression rating scale

HRF – haemodynamic response function

LOD – log of the odds

MDD – major depressive disorder

MNI – Montreal Neurological Institute

MRI – magnetic resonance imaging

MTL – medial temporal lobe

NART – national adult reading test

NRG1 – neuregulin1

OPCRIT - Operational Criteria symptom checklist

PANSS – positive and negative symptom scale

PCC – posterior cingulate cortex

PCR – polymerase chain reaction

PET – positron emission tomography

PFC – prefrontal cortex

PRS – polygenic risk score

ROI – region of interest

SCID – structured clinical interview for DSM-IV axis I disorders

SFMHS – Scottish family mental health study

SNP – single nucleotide polymorphism

SPM – statistical parametric mapping

SPSS – statistical package for social sciences

SVC – small volume correction

TE – echo time

TI – inversion time

TR – repetition time

VLPFC – ventrolateral prefrontal cortex

WASI – Wechsler abbreviated scale of intelligence

YMRS – Young mania rating scale

Organisation of thesis

This thesis uses functional magnetic resonance imaging to examine brain activation patterns during episodic memory, in individuals at high genetic risk for psychosis with the disrupted in schizophrenia 1 (DISC1) t(1;11) translocation, and in patients with schizophrenia and patients with bipolar disorder. Overall this thesis spans two main areas of study 1) episodic memory in psychosis and 2) genetic imaging and DISC1. For this reason two introductory chapters (chapter one and two respectively) are included to cover these topics. A further chapter (chapter 3) links these two introductory chapters, provides justification for the current work and presents the hypotheses. As the same encoding and recognition task was used to study all participants, there is one methodology chapter (chapter 4) that covers recruitment, the groups studied, clinical and cognitive measures used, and the imaging protocol and analyses. There are two results chapters in this thesis investigating episodic memory function in individuals from a Scottish family with and without the DISC1 t(1;11) translocation (chapter 5), and healthy controls and patients with schizophrenia and bipolar disorder (chapter 6). Finally, chapter 7 provides an overall synthesis of the results presented in this thesis, with limitations and future research considerations.

The main aim of this study was to investigate the effect of the t(1;11) translocation by comparing functional activation during an encoding and recognition memory task in translocation carriers and non-carriers from a Scottish family. The impact of this translocation on brain imaging measures is largely unknown, however this family offers a unique opportunity to examine the effects of this translocation. Healthy controls and

patients with schizophrenia and bipolar disorder were recruited to compare the effects of the t(1;11) translocation to the effects of a having a psychiatric illness, while minimising key confounds. The analysis plan was therefore to examine the effects of the translocation in carriers and non-carriers, and then to relate any findings to controls versus patients with schizophrenia and bipolar disorder. A direct comparison between the translocation carriers and patients was not warranted given differences in degrees of relatedness and shared environmental effects between groups.

Data for this thesis was collected as part of a wider multimodal imaging study, the Scottish Family Mental Health Study (SFMHS), which is a major third wave follow-up of the original Scottish pedigree. This study aims to investigate what effect the t(1;11) translocation has on brain structure, chemistry and function by comparing individuals with and without the translocation. Data was collected from five groups of participants; healthy controls, family members (with and without the translocation), patients with schizophrenia and patients with bipolar disorder. My primary role in this study was to analyse functional imaging data for the encoding and recognition task. I was also involved in recruitment, arranging study appointments, collecting and documenting cognitive and functional imaging data.

Abstract

A key feature of many psychiatric disorders, including schizophrenia and bipolar disorder, are pervasive deficits in several domains of cognition. Episodic memory is one of the most consistently observed cognitive deficits exhibited by patients with schizophrenia, and can be a predictor of overall functional outcome. Several neuroimaging studies have assessed episodic memory in psychosis, however the neural mechanisms underlying this deficit remain somewhat unclear. Studying the impact of rare genetic variants of large effect can offer a powerful method to further our understanding of the pathophysiology of psychiatric disorders. One such gene, DISC1 (Disrupted in Schizophrenia 1) is a putative susceptibility gene for a spectrum of major psychiatric disorders such as schizophrenia, bipolar disorder and major depression. DISC1 was originally identified in a large Scottish pedigree, in which it is disrupted by a balanced translocation between chromosomes 1 and 11, and this translocation confers a dramatically increased risk of major psychiatric disorder. However, the impact of this translocation on brain imaging measures is largely unknown. The rarity of this variation results in small group numbers for analysis, however rare variants are likely to have large neural effects. This thesis offers a unique investigation into the effects of the t(1;11) translocation, by examining fMRI of members of the original Scottish pedigree.

Four groups of participants; 19 family members (8 with the translocation, 11 without), 30 patients with schizophrenia, 11 patients with bipolar disorder and 40 healthy controls underwent a functional MRI episodic memory encoding and recognition paradigm. Data processing and statistical analyses were performed using the standard approach in SPM8. The primary aim of this work was to investigate functional activation during episodic

memory in individuals with and without the translocation, to examine the impact of the t(1;11) translocation. Analyses were also performed to examine differences between controls and patients with schizophrenia and bipolar disorder, to compare the effects of the translocation to the effects of a having a psychotic illness.

During encoding of neutral scenes, translocation carriers showed greater activation of the left posterior cingulate, right fusiform gyrus and right superior frontal gyrus compared to non-carriers. During recognition, carriers showed greater activation in the right fusiform gyrus, left posterior cerebellum, right superior temporal gyrus, left anterior cingulate, right ventrolateral prefrontal cortex (VLPFC) and right dorsolateral prefrontal cortex (DLPFC). For both contrasts, no regions were found to be more active in family members without the translocation when compared to carriers. There were no significant differences between the groups in terms of their performance or reaction time on encoding and recognition conditions.

Compared to healthy controls, patients with schizophrenia demonstrated increased activation during encoding in the inferior parietal lobe bilaterally, and decreased activation during recognition in a region encompassing the caudate nucleus and anterior cingulate cortex. Patients with bipolar disorder showed no difference in activation compared to controls during encoding, and increased activation during recognition in a region encompassing the caudate and anterior cingulate, extending to the inferior frontal lobe and insula. There was also a significant difference between patients with schizophrenia and bipolar disorder during recognition, with patients with bipolar disorder again showing increased activation in the caudate extending to the anterior cingulate cortex. These

findings support previous research suggesting overactivation of fronto-limbic and striatal structures including the anterior cingulate and caudate in bipolar disorder, with a relative underactivation in schizophrenia.

This thesis presents the first evidence of functional alterations during episodic memory in association with the translocation, primarily in fronto-temporal regions. Brain regions that were over activated in translocation carriers have been shown to be involved in memory encoding and recognition, and are known to be affected in patients with major psychiatric disorders and unaffected relatives. Family members with the translocation demonstrated a more similar pattern of activation during recognition to patients with bipolar disorder compared to schizophrenia, perhaps due to the fact that most diagnoses in the carriers were of an affective disorder rather than a schizophrenia-related psychosis. Based on these findings it can be argued that the translocation has an influence on brain activations in areas associated with episodic memory processes. These findings begin to provide a better understanding of the neural effects of the t(1;11) translocation, and highlight the significance of rare but biologically informative genetic variants in understanding psychosis.

Lay Summary

Brain imaging is an important tool in trying to understand why some people develop mental health conditions whereas others do not. Functional magnetic resonance imaging can measure the way the brain functions during tasks that measure different aspects of cognition. Cognition is crucial for understanding and making sense of the world and includes thinking, learning and memory. Episodic memory, which is our ability to remember information about events in our lives, has been shown to be poorer in both patients with schizophrenia and with bipolar disorder. It has also been shown to negatively affect people's living status, occupation and overall quality of life.

This thesis is spilt into two parts. The first looked at members of a Scottish family, some who have a higher than usual risk of developing a mental health disorder, such as schizophrenia or bipolar disorder, because of a rare change in their genetic makeup. This work aimed to test whether this genetic change causes the brain to function differently during a task of episodic memory. It was found that this genetic variation was associated with greater activation in frontal and temporal parts of the brain. These brain regions have previously been shown to be linked to episodic memory and are known to be abnormal in patients with schizophrenia and bipolar disorder. However, it is important to note that all individuals with this rare genetic variant that took part had a diagnosis of an affective disorder, such as depression.

The second part of this thesis looked at patients with schizophrenia, patients with bipolar disorder and individuals with no background of mental illness, and compared how these groups performed during the same memory task. People with a mental illness showed

different patterns of brain activation compared to healthy individuals. There was also a difference between the patient groups; individuals with schizophrenia showed a pattern of underactivation in the caudate and anterior cingulate cortex, whereas patients with bipolar disorder showed overactivation in these regions. These findings highlight how functional imaging techniques can help us to understand the changes in how the brain works that underlie the development of different mental disorders.

Chapter 1: Episodic memory in psychosis

Chapter 1: Episodic memory in psychosis

This chapter introduces the different psychiatric disorders examined in this thesis, namely schizophrenia and bipolar disorder. It will also discuss the basic principles of the imaging technique used, that of functional magnetic resonance imaging (fMRI). It will then go on to discuss episodic memory in psychosis, providing a background on episodic memory deficits in psychosis and neuroimaging findings in these patient populations.

1.1 Introduction

1.1.1 Schizophrenia

Schizophrenia is a severe and debilitating psychiatric disorder with a lifetime prevalence of ~1% and is a major public health concern with a high cost for society. It is characterised by the presence of positive or psychotic symptoms, negative symptoms and cognitive dysfunction. Examples of psychotic symptoms include hallucinations and delusions, such as hearing or seeing things that are not there, or holding unusual beliefs that may seem irrational to others. Psychotic symptoms are characteristics of several psychiatric conditions including schizophrenia, schizoaffective disorder and bipolar disorder. Negative symptoms are a loss of normal functions such as lack of motivation, blunted affect and withdrawal from usual societal roles, and usually respond less well to medication (Murphy et al., 2006). Schizophrenia can be described as a polythetic disorder, in that no single characteristic is essential for a diagnosis and there are a wide range of heterogeneous symptoms that differ between individuals.

Schizophrenia

Diagnostic Criteria **295.90 (F20.9)**

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Figure 1.1: DSM-5 diagnostic criteria for schizophrenia

Source: Diagnostic and Statistical Manual (DSM-5), American Psychiatric Association

1.1.2 Epidemiology and aetiology of schizophrenia

The typical age of onset of schizophrenia is during adolescence or early adulthood, and occurs slightly earlier in males than females. There is also a higher rate of diagnosis in males with a male: female ratio of approximately 1.4:1 (Abel et al., 2010). Schizophrenia is a highly heritable disorder with heritability of around 80% (Sullivan et al., 2003) and therefore has a prominent genetic basis. The risk of developing schizophrenia increases exponentially with the degree of genetic relatedness to a relative suffering from it and is as

high as 50% for monozygotic twins (Sullivan et al., 2003). However, schizophrenia is a complex disorder caused by both genetic and environmental factors such as urbanicity, advanced paternal age, obstetric complications and substance abuse (Sorensen et al., 2014). The genetics of schizophrenia will be discussed in greater depth in the following chapter.

1.1.3 Neuroimaging findings in schizophrenia

1.1.3.1 Structural imaging

Abnormalities of brain structure and function are well established in schizophrenia. Research into structural abnormalities initially used Computerized tomography (CT) techniques, which demonstrated ventricular enlargement and an overall loss of brain tissue in patients compared to healthy controls (Johnstone et al., 1976, Lawrie et al., 2004, Raz and Raz, 1990). Structural magnetic resonance imaging has since replicated and furthered these findings showing additional volume reductions in the thalamus, hippocampus and anterior cingulate cortex (Konick and Friedman, 2001, Baiano et al., 2007, Nelson et al., 1998).

Investigations of brain structure, using diffusion tensor imaging (DTI) to map the diffusion of water molecules along white matter tracts, have also identified compromised white matter integrity in schizophrenia (Liu et al., 2013b). There is evidence of white matter volume or density reductions in a number of regions particularly in the frontal and temporal regions (Ellison-Wright and Bullmore, 2009, Samartzis et al., 2014). Deficits have also been identified in the anterior limb of the internal capsule (Shenton et al., 2001, Sussmann et al., 2009), left inferior longitudinal fasciculus and left inferior fronto-occipital fasciculus (Liu et al., 2013b).

1.1.3.2 Functional imaging

There has been a rapid increase over the past few decades in the use of fMRI to explore neural systems related to behavioural and cognitive deficits in patients with schizophrenia. Functional studies have reported abnormal activity in a wide range of tasks including memory, attention, word fluency and emotional processing (Gur and Gur, 2010), and during resting state (Argyelan et al., 2013).

1.1.3.3 Hypofrontality

Early functional imaging studies suggested that a primary deficit of schizophrenia was a failure to activate the prefrontal cortex (PFC) (Ingvar and Franzén, 1974). This emphasis on hypofrontality has since been revised and findings to support this hypothesis are less consistently reported when controlling for task performance. A complex pattern of hyper and hypoactivation has now been demonstrated and it is understood that underactivation in patients who have difficulty performing a cognitive task may reflect a deficit in the underlying systems related to that task or a lack of engagement (Gur et al., 2007, Lawrie et al., 2008).

1.1.3.4 Dysconnectivity

One possible synthesis of the literature is the dysconnectivity hypothesis of schizophrenia (Friston and Frith, 1995). This suggests that schizophrenia occurs as a result of abnormal connectivity between different parts of the brain, particularly between the PFC and other structures including the temporal lobe, thalamus, and striatum. Dysconnectivity between regions is also thought to underlie cognitive abnormalities in schizophrenia. Functional and structural dysconnectivity are among the most replicable findings associated with

schizophrenia (Schmitt et al., 2011), suggesting that brain dysconnectivity may be a plausible endophenotype for schizophrenia (White and Gottesman, 2012).

1.1.4 Bipolar disorder

Bipolar disorder is considered a primary disorder of mood, defined by episodes of mania and depression and characterized by recurring affective episodes. Symptoms of mania include racing thoughts, a decreased need for sleep, impulsivity and risky behaviour. These symptoms are accompanied by changes in activity levels and lead to marked disturbance of behaviour and function. There are different types of bipolar disorder depending on the duration and pattern of these affective symptoms. Elevated mood is more severe and sustained (mania) in bipolar I disorder and less severe with a lower level of disturbance (hypomania) in bipolar II disorder.

Affective symptoms are also accompanied by deficits in cognitive processes, with the greatest impairment in verbal learning, memory, attention and executive processing (Robinson et al., 2006, Torres et al., 2007, Balanzá-Martínez et al., 2008). Symptoms of psychosis are also common in patients with bipolar disorder, with studies reporting up to 68% of patients with the illness experiencing psychotic symptoms in their lifetime (Keck et al., 2003). There is substantial heterogeneity in the phenotype of bipolar disorder that complicates the attempts to understand the underlying pathophysiology of the illness.

Bipolar disorder diagnostic criteria DSM-5 (2014)
Bipolar I disorder - Current or recent major depressive episode - One or more previous manic episode or mixed episode - The mood symptoms are not due to the direct physiological effects of a substance (a drug of abuse, medication or other treatment) or a general medical condition - The mood episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified
Bipolar II disorder - Presence or history of one or more major depressive episodes - Current or history of at least one hypomanic episode - No history of manic episode or mixed episode - Mood symptoms not due to schizoaffective disorder or part of other disorders such as schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified - Symptoms cause significant distress as well as impairment in social occupational or other areas of functioning

Figure 1.2: Summary of DSM-5 diagnostic criteria for Bipolar disorder

1.1.5 Epidemiology and aetiology of bipolar disorder

Bipolar disorder is usually shown to have an overall lifetime prevalence of around 1 % in the general population (Bauer and Pfennig, 2005). A recent worldwide study found a median age of onset of about 25 years, with a lifetime prevalence of 0.6% for bipolar I disorder (more common in males) and 0.4% for bipolar II disorder (with a female predominance) (Merikangas et al., 2011).

Although the exact aetiology of bipolar disorder remains unknown, genetic epidemiological research (family and twin studies) supports a strong genetic component to

the illness, with heritability estimates as high as 89–93% (McGuffin et al., 2003). Genome wide association studies (GWAS) have also identified several common polymorphisms linked to bipolar disorder, including variants within CACNA1C, ODZ4, and NCAN, and robust evidence suggests there is a polygenic contribution to risk for the illness (Craddock and Sklar, 2013).

1.1.6 Neuroimaging findings in bipolar disorder

There are fewer imaging studies of bipolar disorder compared to schizophrenia, which has resulted in less consistency and somewhat contradictory findings. As bipolar disorder is classified as a disorder of mood, it has been proposed that the brain systems most likely to underline this illness involve regions that modulate emotional control (Mayberg, 1997). These networks include ventral prefrontal networks and limbic brain regions including the amygdala. Neuroimaging findings support dysfunction of the structure, function and connectivity of these networks (Strakowski et al., 2012).

1.1.6.1 White matter abnormalities in bipolar disorder

White matter abnormalities have been demonstrated in bipolar disorder, however they tend to be less severe and involve fewer brain regions compared to schizophrenia (Skudlarski et al., 2013, Lu et al., 2011). White matter density and volume reductions have mainly been found in prefrontal and limbic regions supporting the model that bipolar disorder involves dysconnectivity in regions supporting emotion regulation (Mahon et al., 2010). White matter integrity reductions have also been identified in unaffected relatives with bipolar disorder, suggesting this could be a potential endophenotype for this illness (Sprooten et al., 2011a). Several studies have also found abnormal connectivity within a fronto-limbic

pathway that may be an imaging marker in patients with bipolar disorder (Anand et al., 2009, Chepenik et al., 2010, Öngür et al., 2010, Chai et al., 2011).

1.1.6.2 Overactivation of medial temporal lobes and limbic regions

As bipolar disorder is classified as a disorder of mood, research has usually focused on paradigms involving emotional stimuli known to activate these regions, in which patients typically show overactivation of limbic and medial temporal lobe (MTL) structures compared to healthy controls (Hall et al., 2009, Malhi et al., 2004, Whalley et al., 2011). It has been suggested that this overactivation reflects an oversensitive system for determining the emotional importance of stimuli. This is consistent with reports that patients tend to identify stimuli as emotional rather than neutral, which may consequently may produce dysfunctional affective states as seen in this illness (Phillips et al., 2003). In comparison there is a reported underactivation in patients with schizophrenia, for example during facial affect processing (Delvecchio et al., 2013).

As previously mentioned, deficits in nonemotional, cognitive processes such as memory are also highly prevalent in this population. Comparatively few studies have examined the neural correlates of these deficits and whether limbic brain areas also show this pattern of abnormal overactivation during nonemotional, cognitive tasks. A recent study by Gruber et al. (2010) demonstrated hyperactivation of the amygdala in response to a non-emotional, working memory task (Gruber et al., 2010). However, due to the limited number of studies, overall findings are inconclusive demonstrating hyper and hypo-activations in prefrontal regions (including orbitofrontal cortex, medial prefrontal cortex including the anterior

cingulate region, and dorsolateral prefrontal cortex) as well as in the basal ganglia (Blumberg et al., 2003c, Strakowski et al., 2005, Gruber et al., 2004).

1.1.7 Overlap between schizophrenia and bipolar disorder

Bipolar disorder and schizophrenia are considered separate disorders, however convergent genetic, neuroimaging and clinical evidence indicate both overlap and discontinuity between them. Although affective symptoms (depression and mania) are more characteristic of bipolar disorder and psychotic symptoms are primary to schizophrenia, both types of symptoms can occur in individuals with either diagnosis. The extent to which common and distinct neural mechanisms underlie these symptoms and syndromes remains unclear, however functional brain imaging could offer a greater understanding of the biological basis of symptoms in these disorders.

Whalley et al. (2012) conducted a review of the fMRI literature to examine the evidence for diagnosis-specific patterns of brain activation in these two patient groups (Whalley et al., 2012b). Activation differences were found in the MTL and associated limbic regions, with additional limited evidence for the lateral PFC. These results suggest there are differences in the neurobiological substrates of schizophrenia and bipolar disorder, and functional neuroimaging may have utility as biomarkers to distinguish between disorders.

Hall et al. (2010) compared patients with schizophrenia and bipolar disorder during an encoding and retrieval face-name pair memory task and were able to distinguish between disorders at a group level using fMRI by differences in hippocampal and PFC activation (Hall et al., 2010). During encoding patients with schizophrenia showed decreased anterior

hippocampal activation and patients with bipolar disorder showed decreased dorsal PFC, relative to each other. These findings suggest a differential dysregulation of fronto-temporal neural systems in these disorders.

To generalise overall findings from the functional imaging literature in both disorders, it appears that there is an overactivation of MTL structures in bipolar disorder, and an underactivation of these structures in schizophrenia (Strakowski, 2012). However, there are a limited number of functional imaging studies reporting direct comparisons between the two disorders, and few studies directly comparing the neural correlates of episodic memory.

1.2 Functional neuroimaging – functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging is a methodological technique that allows images to be taken of the brain in vivo in order to measure brain activity by detecting changes in cerebral blood flow associated with neural activity. Over the past few decades fMRI has made substantial advances in the field of neuroscience, furthering our understanding of brain systems underlying specific behavioural deficits in schizophrenia. fMRI has become a dominant method in this field as it provides a non-invasive method with good spatial resolution, without the need for ionising radiation in contrast to other imaging techniques such as CT or positron emission tomography (PET).

1.2.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) can be used to create detailed images of tissues and structures in the brain, using a strong magnetic field and radio waves. Protons, present in water molecules within our bodies, align with the direction of the magnetic field in the scanner. When radio waves (RF pulse) are applied at the appropriate frequency, this changes the orientation of the spins as the protons absorb energy. When the RF pulse is stopped, the protons return to their original orientation and emit energy in the form of radio waves. This process causes a change in voltage and is detected using a coil placed around the head of the individual in the scanner.

Radio waves can be manipulated to change the contrast of the image acquired and can be T1 or T2 weighted. T1 is the longitudinal relaxation time and refers to the time it takes for the protons to realign with the magnetic field. T2 is the transverse relaxation time and is a measure of how long the protons remain in phase following a RF pulse. T2 decay is due to

magnetic interactions that occur between spinning protons and unlike T1 interactions, do not involve a transfer of energy but only a change in phase. As a result of these different relaxation measures, tissues appear different for example water appears bright in T1 weighted images but dark in T2 weighted images. fMRI uses acquisition techniques e.g. echo planar imaging (EPI) that are sensitive to changes in T2. EPI is capable of significantly shortening MRI acquisition time and reduces motion artefact, making it ideal for the application of fMRI.

1.2.2 Basic principles of fMRI

fMRI works by exploiting the fact that oxygenated and deoxygenated blood possess different magnetic properties (Pauling and Coryell, 1936). Haemoglobin is diamagnetic when oxygenated (oxyhaemoglobin) but paramagnetic when deoxygenated (deoxyhaemoglobin), and this leads to differences in the MR signal (areas with a greater concentration of oxyhaemoglobin will produce a higher signal and thus a brighter image). fMRI works on the principle that when a brain area is actively engaged the metabolic requirements of neurones increases, and this demand for energy causes vasodilation of local vessels resulting in increased cerebral blood flow to the region. There is also an increase in oxygen consumption, however the increase in oxygen supply exceeds the local demand for oxygen, resulting in an increased level of oxyhaemoglobin and a relative reduction of deoxyhaemoglobin (Fox and Raichle, 1986).

1.2.3 The BOLD signal and haemodynamic response function

There are different fMRI techniques that can detect a functional signal, however Blood oxygenation level-dependent (BOLD) fMRI, as discovered by Seiji Ogawa, is the most

widely applied method in fMRI research. The BOLD signal relies on the level of deoxyhaemoglobin in the blood. Deoxyhaemoglobin distorts the magnetic field in the scanner and causes changes in the MR decay parameter T2*, leading to image intensity changes in T2* weighted images (the presence of deoxyhaemoglobin shortens the T2* relaxation time).

BOLD signal changes are a dynamic process and are characterised by the haemodynamic response function (HRF) (see figure 1.4). There is typically an initial decrease in blood oxygenation immediately following exposure to stimuli known as the initial dip (Yacoub et al., 2001). This initial phase is hypothesised to originate from a rise in local deoxyhemoglobin due to an increase in metabolism as the neurons rapidly consume any available oxygen. This initial dip is not consistently reported and is more commonly observed at higher field strengths of >3T (Yacoub et al., 2001). This is followed by a dramatic increase in the supply of oxygenated blood, far more than is necessary, peaking at approximately 2s and lasting around 4s after stimulus onset. This is sustained for a short period of time before the blood oxygen concentration returns to pre-stimulus levels, which can take from 20s to up to 60s (Kwong et al., 1992). Some studies also report a post stimulus undershoot before levels return to baseline, which reflects an increase in local deoxyhaemoglobin that is hypothesized to be due to continued high metabolic demand of oxygen despite the return of cerebral blood flow to normal levels.

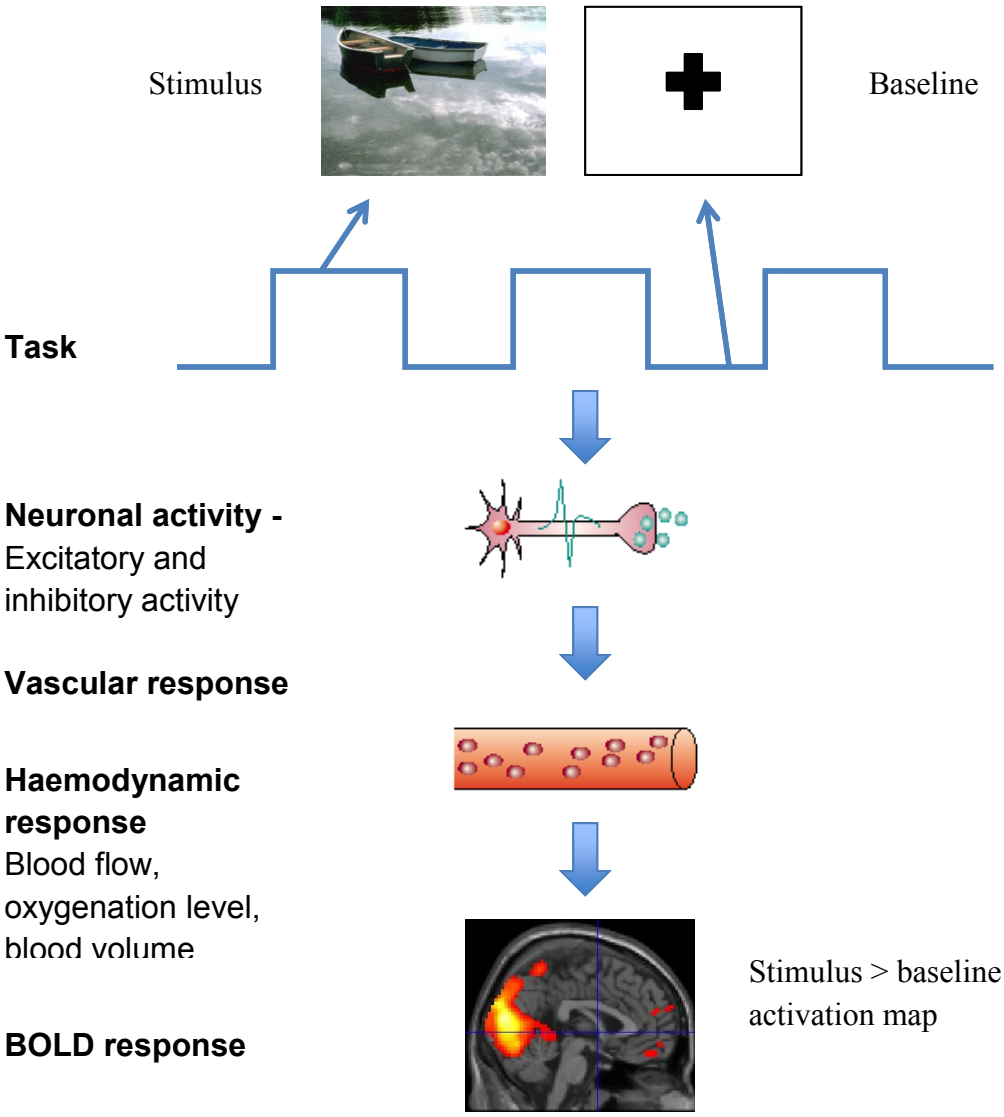


Figure 1.3: The haemodynamic response and BOLD signal

Illustration of the steps involved in an fMRI experiment based on the episodic memory encoding and recognition task used in this thesis.

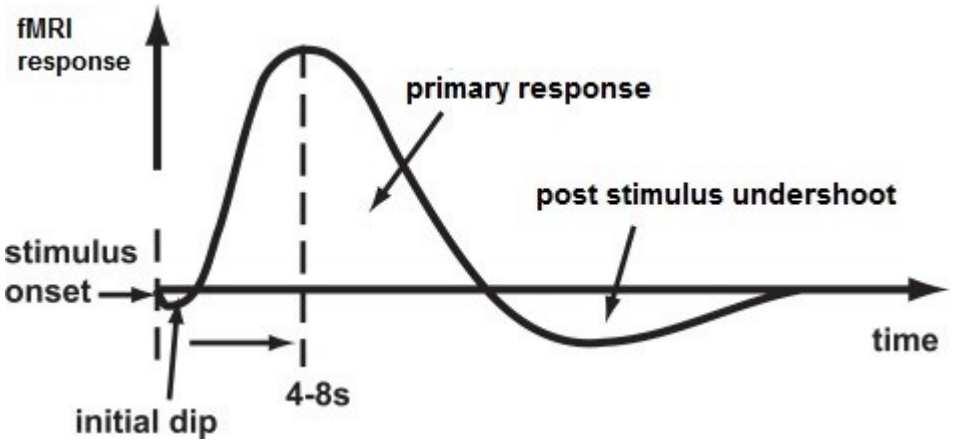


Figure 1.4: Illustration of the BOLD haemodynamic response function

1.2.4 Limitations of fMRI

These changes in blood oxygenation mean that the temporal resolution of fMRI is relatively poor (takes seconds) compared to the speed of neuronal activation (in milliseconds). Therefore, the BOLD signal is only an indirect measure of brain activity and understanding the underlying neurophysiology of fMRI is essential when interpreting data. There are further limitations of fMRI including movement, low signal to noise ratio, and due to the strong magnetic field individuals with metallic implants cannot be scanned. fMRI is also prone to signal loss in regions with large differences in magnetic susceptibility for example at air-tissue boundaries such as the frontal lobes which are adjacent to air filled sinuses. This can produce susceptibility artefacts (Lipschutz et al., 2001).

1.2.4.1 Movement

One of the main problems of fMRI research is subject movement in the scanner, and this can be particularly challenging when studying patient populations. Head movement in the scanner can result in a specific voxel within an image not corresponding to the same

location in the brain throughout the scan session. The standard realignment pre-processing stage in Statistical Parametric Mapping software (SPM) aims to realign all images in one session to a predefined scan, for example the first or mean volume in the series. Even after pre-processing excessive movement can still compromise the integrity of the data and can lead to exclusion of data from the analysis. Data loss due to this is especially problematic when working with rare patient groups such as the Scottish kindred in the research described in this thesis.

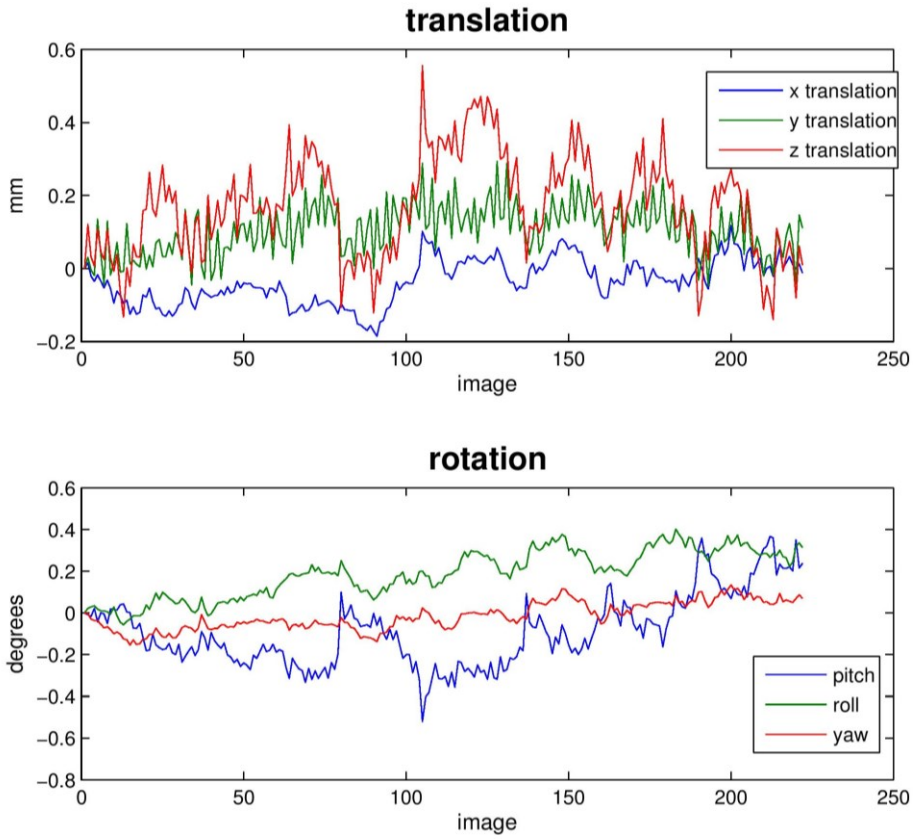


Figure 1.5: Within scanner movement for one subject

This figure demonstrates the movement from a subject scanned as part of the current study. The graphs represent the amount of movement (x, y, z) in translation and rotation.

1.3 Episodic memory

1.3.1 Cognitive function in psychosis

As previously mentioned, schizophrenia is a severe and debilitating psychiatric disorder usually characterised by the presence of psychotic symptoms, primarily hallucinations and delusions, and negative symptoms such as blunted affect and social withdrawal. However, it is now widely accepted that schizophrenia is also characterised by pervasive deficits in several domains of cognitive function including memory, attention, generalized intelligence, and executive functions (Wang et al., 2010). In recent years, there has been an increase in research on cognition in schizophrenia, partly due to the notion that cognitive function is a primary determinant of overall functional outcome in schizophrenia, perhaps more so than the presence of positive symptoms (Nuechterlein et al., 2011). Cognitive disturbance is also thought to be an enduring characteristic of schizophrenia that can predate illness onset and often persists beyond acute symptom expression (Heinrichs, 2005).

Schizophrenia is currently classified as a psychotic disorder with the emphasis on psychosis as the primary target for diagnosis and treatment. However, there has been a recent debate regarding the importance of cognitive underperformance in schizophrenia. It has been suggested that the emphasis on psychosis in schizophrenia has resulted in a lack of progress in understanding this illness, and defining and treating schizophrenia on the basis of psychotic features is too narrow (Kahn and Keefe, 2013). The domain of cognition now deserves greater attention to help aid diagnosis and potentially develop new treatments to help with cognitive impairment, both pharmacological and non-pharmacological.

The key symptoms seen in bipolar disorder are associated with states of depression such as low energy, low self-esteem and suicidal ideation, and states of mania including lessened need for sleep, impulsivity and risky behaviour. One of the more overlooked aspects of this illness is the degree of cognitive impairment that patients experience. Increasing evidence is emerging to disprove the Kraepelinian notion (Kraepelin, 1921) that bipolar disorder is not associated with cognitive decline. A wide range of neurocognitive deficits have been observed during episodes of depression and mania (Quraishi and Frangou, 2002). Functions including attention, processing speed, memory, and executive function have also been shown to be impaired in euthymic patients with bipolar disorder, reflecting trait features of the illness (Torres et al., 2007).

Cognitive deficits in both bipolar disorder and schizophrenia show similarities, however tend to be more severe in patients with schizophrenia (Hill et al., 2014). This overlap in cognitive impairment across both disorders is in line with the notion that patients do not solely fit into a diagnosis of schizophrenia or bipolar, based on classification systems such as DSM-5, but instead exist upon a continuum.

1.3.2 Episodic memory in schizophrenia

Memory is now regarded as one of the key areas of cognitive impairment in schizophrenia, with particularly pronounced deficits observed in episodic memory for both encoding and retrieval of newly acquired information (Talamini et al., 2010, Danion and Berna, 2007, Leavitt and Goldberg, 2009, Lepage et al., 2010). Recent reviews and meta-analyses indicate episodic memory tests have among the largest effect sizes in schizophrenia patients versus healthy control subjects (Mesholam-Gately et al., 2009, Fioravanti et al., 2005).

Research suggests that episodic memory deficits cannot be explained by demographic or clinical measures and cannot be entirely accounted for by impairments in other cognitive domains such as attention or executive functioning (Kopald et al., 2012).

1.3.3 Episodic memory in bipolar disorder

There is substantially less research on cognitive dysfunction in bipolar disorder compared to the literature on schizophrenia, and in the past cognition has been underestimated in this patient group. Episodic memory deficits are one of the most consistently reported findings in patients with bipolar disorder. There is increasing evidence that patients with bipolar disorder exhibit episodic memory impairments during both acute episodes (Quraishi and Frangou, 2002) and the euthymic state (Bourne et al., 2013, Bora et al., 2009, Torres et al., 2007, Robinson et al., 2006). A key finding in the literature, evident in neuroimaging as well as cognitive testing, is that abnormalities found in bipolar disorder are generally less severe than those seen in schizophrenia (Whalley et al., 2012b, Seidman et al., 2002, Reichenberg et al., 2009). Effect sizes for episodic memory deficits have been found to be large for patients with schizophrenia (range 1–1.27) and moderate to large for patients with bipolar disorder (range 0.59–0.85) (Skelley et al., 2008, Bora et al., 2009, Lefèbvre et al., 2010, Glahn et al., 2007a).

1.3.4 What is episodic memory?

The concept of episodic memory was introduced by Endel Tulving (Tulving, 1985) and can be defined as a form of declarative memory that consists of the ability to store and recall information about a seemingly endless series of episodes and events. Well-researched memory classification schemes have identified two types of long-term memory; declarative

memory and non-declarative memory. Declarative memory encompasses both episodic memory for events and semantic memory for general factual knowledge, whereas non-declarative memory is an implicit process that enables us to perform common tasks without conscious thought. Episodic memory can be distinguished from other forms of memory in terms of its ability to encode and store information about the spatial and temporal contexts of events i.e. what happened, in addition to where and when it happened. The ability to create accurate episodic memories of past events depends on the integration of different inputs of information about an event (Tulving, 1972).

1.3.4.1 Encoding strategy

The episodic memory system can be divided into three different stages; encoding, storage, and retrieval processes. There is substantial evidence to suggest that episodic memory dysfunction is primarily due to abnormalities at the encoding stage (Gold, 2004, Danion and Berna, 2007, Cirillo and Seidman, 2003, Talamini et al., 2005). For example, it has been proposed that individuals with schizophrenia fail to spontaneously engage in efficient elaborative processing during encoding and have an inability to spontaneously organize to-be-remembered information (Koh and Peterson, 1978). Patients with bipolar disorder also appear to rely less on organizational strategies during encoding and this may offer an explanation for episodic memory impairments in this patient group, rather than deficits in the retention of information (Deckersbach et al., 2004a).

Patients appear to process stimuli on a more superficial level and do not instinctively use semantic processing to assist encoding and retrieval (Ragland et al., 2001). However, research has demonstrated that patients are able to use elaborative strategies during

encoding when they are explicitly instructed to do so and show recognition memory improvements when encouraged to use specific encoding strategies (Bonner-Jackson et al., 2008). This suggests that episodic memory impairment can be somewhat alleviated and encoding strategies should perhaps be the focus of cognitive remediation therapies. Although most research supports a deficit at the encoding stage, evidence suggests that retrieval processing may not be entirely intact (Gold et al., 2000, Talamini et al., 2010).

1.3.4.2 Context memory deficit

Several theories have proposed there is a binding deficit in schizophrenia whereby contextual elements of an event are poorly linked during the encoding process (Waters et al., 2004). The context memory deficit theory suggests that patients encode and store certain information about what happened during an event relatively normally but have difficulty linking this with contextual components to form an intact memory representation (Rizzo et al., 1996, Ledoux et al., 2013). Therefore, patients are more likely to retrieve individual components of an event in isolation and have a more fragmented overall recollection of an experience.

Patients with schizophrenia have also been found to exhibit deficits in reality-monitoring tasks that involve distinguishing whether information is self-generated or the result of an external source. Some theories regarding auditory hallucinations in psychosis suggest that these symptoms may occur because patients fail to recognise thoughts and memories as internal cognitive functions (Bentall et al., 1991).

Contextual binding is associated with the function of medial temporal regions, including the hippocampus (Eichenbaum et al., 2007, Konkel and Cohen, 2009) and one of the most robust findings in schizophrenia is abnormal hippocampal structure and function (Weiss et al., 2005, Jessen et al., 2003). The hippocampus may reinforce newly encoded information by binding it with associations during encoding (Achim and Lepage, 2005).

1.3.4.3 Core cognitive deficit or distinct episodic memory deficit

A challenge researchers face in understanding the nature of episodic memory deficits in psychosis is whether such impairments are a distinct deficit with its own psychological and neural pathophysiology, or whether they share a common core mechanism with other cognitive domains such as working memory, language function, executive function, processing speed and attention (Barch and Ceaser, 2012). Many have argued that a common impairment in proactive control and the maintenance of goal representations contributes to a variety of cognitive deficits. At the neural level it has been suggested that abnormalities in the function and connectivity of the dorsolateral prefrontal cortex (DLPFC) and the influence of neurotransmitter systems, such as dopamine, GABA and glutamate (Lesh et al., 2011, Barch and Ceaser, 2012) contribute to a wide range of cognitive deficits.

For example, Raganath et al. (2003) found a substantial degree of overlap in the prefrontal regions (dorsolateral prefrontal, ventrolateral and middle frontal gyrus) activated during both working memory and episodic long-term memory, suggesting that the same PFC regions support different cognitive functions (Ranganath et al., 2003). Other researchers highlight the independence of episodic memory and other cognitive functions, both in

performance on various tasks and the brain regions supporting them (Cirillo and Seidman, 2003).

Schizophrenia is a complex psychiatric disorder and it would be an oversimplification to conclude that a single common mechanism could account for the wide range of cognitive impairments experienced by this patient population. Despite this, identifying a core mechanism that is central to at least a subset of deficits may act as a target for therapeutic interventions that could serve to broadly enhance cognitive function and overall outcome in these patients (Barch and Ceaser, 2012).

1.3.4.4 Inter-individual variability in episodic memory deficits

On the whole, the literature suggests that episodic memory is a cognitive domain that is robustly impaired in schizophrenia and bipolar disorder, however findings can be equivocal and a considerable degree of inter-individual variability exist (Leavitt and Goldberg, 2009). Methodological differences between studies may be partly responsible for this discrepancy, for example the use of verbal or nonverbal paradigms. Some studies report greater impairment in patients when using visual memory tasks (Heinrichs and Zakzanis, 1998), whereas others have found more reliable impairment using verbal memory stimuli (Cirillo and Seidman, 2003).

One study found differential episodic memory deficits depending on the task material used (Tracy et al., 2001). They found that deficits were primarily limited to encoding during the non-verbal task, whereas retrieval and encoding processes were disrupted during the verbal task, suggesting a material-specific deficit for retrieval. The majority of reports of episodic

memory impairments in schizophrenia have involved verbal measures such as words or narrative stories, whereas much less is known about the status of episodic memory for non-verbal material. The majority of research on episodic memory in bipolar disorder has also focused on the verbal domain, however patients with bipolar disorder have been shown to exhibit deficits in both verbal and non-verbal episodic memory (Deckersbach et al., 2004a, Deckersbach et al., 2004b). Episodic memories are often stored non-verbally as visual representations, therefore an exclusive use of verbal paradigms is not sufficient to examine the full picture of episodic memory impairment in psychosis (Conway, 2009).

1.3.4.5 Functional outcome

Episodic memory deficits can be observed in approximately 75-80% of patients with schizophrenia (Weickert et al., 2000, Holthausen et al., 2002) and are a significant predictor of poor outcome. Cognitive impairments often emerge prior to psychotic symptoms, are relatively consistent over time and are less responsive to antipsychotic medication (Mishara and Goldberg, 2004). Recent reviews of cognitive function in schizophrenia have consistently shown that episodic memory deficits are associated with poor functional outcome including work performance, social adaptation, and overall quality of life (Green et al., 2000). Therefore, it is important to further our understanding of episodic memory impairment in schizophrenia in order to develop treatments such as cognitive remediation or pharmacological interventions that are likely to improve cognition and functional outcome in patients (Nestor et al., 2007). It is likely that cognitive remediation of episodic memory would be most effective by encouraging patients to use efficient encoding strategies (Danion and Berna, 2007).

Cognitive deficits have also been shown to adversely affect functional outcomes in bipolar disorder. Cognitive factors contribute to psychosocial outcome in bipolar disorder and dysfunction is most evident in low-functioning patients, with verbal memory as the greatest predictor of functioning (Martinez-Aran et al., 2007). This highlights the importance of acknowledging cognition in terms of treatment and long-term management of bipolar disorder.

1.3.5 Confounding factors

Episodic memory and underlying brain activation can be affected by many confounding factors including but not limited to age, attention, medication, duration of illness and symptomatology. It is therefore important to consider these when designing, running and analysing fMRI results. This section will discuss several of these confounds and how the current study will aim to control for them.

1.3.5.1 Medication

When studying psychiatric populations, effects of medication are an important confound to consider. Antipsychotic medications have been shown to affect the BOLD signal during performance of a variety of cognitive paradigms. Antipsychotic drugs may affect the BOLD signal in several ways such as modification of neurons or cerebral blood flood, which further complicates the biological interpretation of the BOLD signal (Abbott et al., 2013). Specifically, studies have shown that antipsychotic medication effects are in general likely to have a normalising effect on brain function in patients across a range of cognitive tasks. However, this may depend on the type of antipsychotic medication for example if they are first or second generation antipsychotics (Ettinger et al., 2011).

A review by Ragland et al. (2009) examining functional imaging studies of episodic memory in schizophrenia reported that the majority of studies included patients who were receiving antipsychotic medication. However, when examining the few studies that only included unmedicated patients, similar patterns of activation in prefrontal, cingulate, thalamic and cerebellar regions were found to those studies of medicated patients. These results are reassuring, however it is still important to try and account for the effects of antipsychotic medication.

One-way to avoid the confounds of antipsychotic medication is to investigate unaffected relatives, who share some of the genetic risk without illness-related confounds. Several studies have investigated episodic memory in first-degree relatives and found similar activation patterns to that of patients with schizophrenia (Reichenberg and Harvey, 2007, Whyte et al., 2005).

Some of the patients in the current study were on a mood stabilizer (two individuals with schizophrenia and eight with bipolar disorder). Mood stabilizers, particularly lithium, have been shown to cause cognitive deficits primarily in tests of memory (Pachet and Wisniewski, 2003). A review examining medication effects in neuroimaging studies of bipolar disorder concluded that both antipsychotics and lithium either had no significant effect, or an ameliorative effect on abnormal functional neuroimaging measures, so that bipolar patients more closely resembled healthy controls (Phillips et al., 2008). A further study found that the effect of lithium was task, region and state-dependent. For example, there was no effect of lithium on working memory brain activation in both euthymic and depressed bipolar patients, however there was an effect during a word generation task but

only in euthymic patients (Silverstone et al., 2005).

1.3.5.2 Age

Episodic and working memory appear to be the forms of memory that are most affected by ageing. Behavioural studies have shown that deficits in episodic memory are evident at both the encoding and recognition stage. There is also evidence that healthy ageing is associated with impaired memory functioning using functional brain imaging techniques. Age related changes have been reported in the PFC and MTL regions. In general studies report an age-related reduction in lateralization in the PFC (specifically reduced left PFC activity), and a reduction of activity in the MTL during episodic memory (Daselaar et al., 2007). Therefore, it is important to try and match groups being studied as closely as possible in terms of age.

1.3.5.3 Duration of illness and symptomatology

There may be an effect of the duration of illness on episodic memory-related brain activation in patients. A longer period of illness has been linked with poorer performance on several cognitive tests including visual memory tasks in patients with schizophrenia (Cuesta et al., 1998). There is also evidence of an association of illness duration with structural brain changes, such as increased ventricles and decreased frontal lobe volume (Tomelleri et al., 2009). One study found sex-specific associations with illness duration and working memory activity for patients with schizophrenia, specifically illness duration correlated with reduced DLPFC activity in males and decreased activation of the cerebellum in females (Elsabagh et al., 2009). However, another study by Brandt et al. (2014) investigating functional activation patterns in schizophrenia and bipolar disorder

compared to healthy controls found that there was no effect of illness duration on large-scale brain networks associated with working memory (Brandt et al., 2014).

As previously discussed schizophrenia is characterised by the presence of positive and negative symptoms, which differ considerably between patients. These symptoms may have an impact on memory performance and beyond that, an effect on underlying brain function. A study by Zierhut et al. (2010) used a declarative memory fMRI task to investigate the role of hippocampal dysfunction and positive symptoms in schizophrenia. They found that reduced performance was correlated with positive symptoms as measured by the PANSS, which was in turn linked to increased hippocampal activation during successful encoding (Zierhut et al., 2010). The authors conclude that these results suggest that patients with greater positive symptomatology may need to recruit additional neuronal activity to compensate for dysfunctional memory encoding. On the other hand, negative symptoms were not found to be associated with behavioural performance or functional activation in this study. Other research has reported a relationship between negative symptoms and prefrontal lobe dysfunction during memory and other cognitive functions (Mattson et al., 1997, Menon et al., 2001a). In addition to positive and negative symptoms, depressive symptoms have been linked to dysfunctional memory processing in patients with schizophrenia (Brebion et al., 1997, Möser et al., 2006), and so in the current study a measure of depressive symptoms, the HDRS, was included in the clinical assessment battery, in addition to the PANSS to measure positive and negative symptoms of schizophrenia.

Bipolar disorder is considered a primary disorder of mood, defined by episodes of mania and depression. However, patients with bipolar disorder can be regarded as euthymic, which is defined as a relatively stable mood state, neither manic/hypomanic nor depressed. A wide range of neurocognitive deficits have been observed during episodes of both depression and mania (Quraishi and Frangou, 2002). However, there is increasing evidence that patients with bipolar disorder exhibit episodic memory impairments during the euthymic state, reflecting a trait feature of the illness (Bourne et al., 2013, Bora et al., 2009, Torres et al., 2007, Robinson et al., 2006). It has been proposed that bipolar disorder may arise from disruption in an anterior limbic network, and overactivation in this brain network leaves individuals at risk for mood and cognitive dysfunction, even during the euthymic state (Strakowski et al., 2004). Even though all bipolar patients in this study were euthymic at time of testing it is still important to consider symptoms of mania and depression by including relevant clinical measures.

1.3.5.4 Controlling for confounding variables

As discussed, these confounding factors can have a significant influence on overall memory performance and underlying brain activation, therefore it is important to try to control for these as much as possible. In the current study groups were matched as closely as possible on several demographic variables including age and gender. Premorbid and current IQ were measured to test whether there were significant differences between the groups being studied. Clinical assessments (the PANSS, HDRS, and YMRS) were performed on each participant to assess their level of symptomatology. An individual's level of attention to the task could interfere with task performance and brain activation. Ideally all participants should be scanned at a time of day when they are able to perform at their optimum. During

the quality assurance check, first level contrasts were visually examined for each subject to ensure there was significant activation, which provides an indication of whether participants were actively engaged with the task. During the task participants were also required to respond by pressing the corresponding trigger button, to encourage continuous attention to the task.

Where it was not possible to control for differences between the groups in terms of any of these variables, and there was a significant difference between the groups, this was taken into account and the variable was added as a covariate into the second level fMRI analysis. Due to the potential impact of symptomatology on brain function, the current study also aimed to investigate the relationship between clinical symptoms and brain activation during episodic memory. Correlation analyses were performed to test whether any differences between the groups were associated with psychopathology, by looking at the relationships between functional activation and symptom severity ratings using various clinical measures (PANSS, YMRS, HDRS and GAF).

With regards to medication effects, ideally drug free patients would have been recruited however these are rare, unrepresentative of the wider psychiatric population, and if unmedicated may not have been able to comply with experimental procedures, particularly the fMRI task. Therefore, antipsychotic medication status in the patient groups was recorded and was converted into chlorpromazine equivalents (CPZE). Medication effects could then be explored by performing correlations between antipsychotic medication and any significant results between patient groups and controls. Combining the antipsychotic doses as chlorpromazine equivalents is a useful way to examine different types of

medication together, however it should be noted that this might be an oversimplification of the heterogeneity of different antipsychotics. For example, it does not take into account that the receptor profiles of typical and atypical antipsychotics are different.

1.3.6 Neural correlates of episodic memory

Several neuroimaging studies have been carried out to assess episodic memory in psychosis, however the neural mechanisms underlying this deficit remain unclear, with studies demonstrating heterogeneous results with respect to hyper or hypoactivation of certain brain regions (Weiss and Heckers, 2001). Due to the complexity of the episodic memory system, it is assumed that the encoding, storage, and recognition of memories involve multiple brain regions (Leavitt and Goldberg, 2009). Patients with schizophrenia exhibit functional and structural abnormalities in brain structures that sub-serve episodic memory, most notably and consistently in the PFC and MTL including the hippocampus and parahippocampal gyrus (Stolz et al., 2012, Achim and Lepage, 2005, Ragland et al., 2009). The functional underpinnings of episodic memory deficits in bipolar disorder are still debatable, however abnormal patterns of activation are most commonly observed in frontal, occipital and limbic regions (Oertel-Knochel et al., 2014, Oertel-Knochel et al., 2015).

Achim et al. (2005) conducted a meta-analysis to identify the brain regions in which activity is most consistently affected during the performance of episodic memory tasks, using a quantitative meta-analytic method for combining results from different imaging studies (Achim and Lepage, 2005). Regions of consistent differential activation between individuals with schizophrenia and healthy controls were primarily observed in the

prefrontal cortex and in the temporal lobe, specifically in the left inferior prefrontal cortex, hippocampus, left cerebellum and medial temporal cortex bilaterally.

1.3.6.1 Prefrontal regions

The majority of research suggests that episodic memory deficits in schizophrenia are the result of MTL abnormalities, specifically in the hippocampus. However, the importance of prefrontal structures in the episodic memory network has become increasingly evident. One of the most convincing findings supporting a key role for prefrontal structures is that increased activation during encoding in frontal regions is highly predictive of subsequent memory performance (Wagner et al., 1998b). Further to this, lesion studies of PFC closely resemble episodic memory impairments similar to those experienced by individuals with schizophrenia.

During both encoding and retrieval, Achim et al. (2005) found that control groups demonstrated increased activation in the left inferior prefrontal cortex, and this region proved to be the most consistent in distinguishing controls from patients. The inferior prefrontal cortex in the ventrolateral prefrontal cortex (VLPFC) has been shown to be involved in in encoding of verbal and nonverbal information (Poldrack et al., 1999, Blumenfeld and Ranganath, 2007) and in the maintenance of successfully retrieved information (Simons and Spiers, 2003, Badre and Wagner, 2002). There is also evidence for involvement in the implementation of strategies during memory encoding. However, in contrast to these findings Heckers et al. (2000) found increased left prefrontal activation in patients during impaired recognition of previously seen stimuli (Heckers et al., 2000).

A more recent review by Ragland et al. (2009), using the same meta-analytic method but only examining whole-brain imaging studies, concluded that patients demonstrated less activation in the PFC during encoding in the frontopolar, dorsolateral and ventrolateral prefrontal cortex, and in the dorsolateral and ventrolateral prefrontal cortex during recognition (Ragland et al., 2009). However, when patients were encouraged to use explicit encoding strategies, only dorsolateral prefrontal cortex deficits remained, suggesting that ventral prefrontal regions are involved in the use of semantic elaboration strategies that promote subsequent memory.

1.3.6.2 Dorsolateral prefrontal cortex prefrontal cortex (DLPFC)

It has been suggested that abnormalities in the function and connectivity of the DLPFC may contribute to a wide range of cognitive deficits. There is recent evidence to suggest that the DLPFC may contribute specifically to relational memory, which refers to the ability to learn associations between items to encode, represent and bind individual memory traces (Murray and Ranganath, 2007, Blumenfeld et al., 2011). Increased DLPFC activation has been found in patients with schizophrenia and has been associated with lower levels of confidence during recognition, perhaps reflecting greater recruitment of resources to achieve a similar degree of accuracy during recognition (Buckner et al., 1998). Research suggests that DLPFC is more reliably activated during episodic recognition than encoding, and a similar pattern of activation can be seen during working memory.

A study investigating patients with bipolar disorder found that verbal episodic memory deficits were associated with abnormalities in brain regions involved in episodic memory including reduced activation in the DLPFC and increased MTL activity in the

hippocampus/parrahippocampus and fusiform gyrus (Deckersbach et al., 2006). Increasing evidence also supports DLPFC pathology in bipolar disorder (Cotter et al., 2002, Rajkowska et al., 2001).

Other prefrontal areas have shown involvement in episodic memory. The middle frontal gyrus has been shown to support post-retrieval monitoring, with activation usually in the right middle frontal gyrus for simplistic tasks and additional recruitment of the left hemisphere for more complex monitoring (Achim and Lepage, 2005). Increased activation in the left middle frontal gyrus during recognition in controls compared to patients has been reported, suggesting a specific impairment of more complex memory processing in schizophrenia. This is consistent with the finding that more complex memory tasks expose greater memory impairment (Danion et al., 1999). The anterior medial prefrontal cortex has also demonstrated increased activation during encoding and recognition, as this region is thought to be involved in the recognition of self-important information (Fossati et al., 2004, Simons and Spiers, 2003).

1.3.6.3 Anterior cingulate cortex (ACC)

The anterior cingulate cortex has also been implicated during memory retrieval. Retrieval associated activation of the ACC is a common finding in a variety of word recognition paradigms. It has been suggested that the ACC plays a role in cognitive control, and increased activity in this region may reflect the greater effort needed by patients to perform episodic memory tasks (Paus et al., 1998, MacDonald et al., 2000). Using a memory recognition task requiring the control of interfering information, Herrmann et al. (2001) found an anterior cingulate-prefrontal activation pattern, indicating that the control of

semantic interference in episodic memory recognition selectively engages specific PFC areas (Herrmann et al., 2001). Activity in the ACC has also been found to be positively correlated with the degree of task difficulty (Barch et al., 1997).

A recent study by Oertel-Knochel et al. (2014) examined episodic memory impairments in bipolar disorder during fMRI using a non-verbal memory task (Oertel-Knochel et al., 2014). Patients showed reduced activation during encoding in the ACC, precuneus and the left lingual gyrus, and during recognition showed higher activation in the left temporo-parietal junction. They also found structural abnormalities in the patient group including reduced gray matter volumes in the ACC, the precuneus/cuneus and the left temporo-parietal region. This is in contrast to other findings that show hyperactivity of limbic regions in this patient group (Chen et al., 2011).

1.3.6.4 Medial Temporal Lobes (MTL)

Functional neuroimaging studies in healthy controls have robustly implicated the MTL, which includes the hippocampus, in both memory encoding and recognition. Activation within and between the PFC and hippocampus is critical for different aspects of memory function including working memory and episodic memory. Anatomic and electrophysiological studies have shown that the PFC and hippocampus are mutually connected via both monosynaptic and polysynaptic pathways (Bertolino et al., 2006), and the PFC is believed to support control processes that facilitate the encoding and recognition of memory via the hippocampal formation.

The dysconnection hypothesis of schizophrenia suggests that the disorder occurs as the

result of abnormal connectivity between different parts of the brain, particularly between the PFC and other structures including the temporal lobes. For example, reduced connectivity has been found between the DLPFC and parrahippocampus (Wolf et al., 2007). Therefore, it has been proposed that a disruption in frontotemporal connectivity plays a key role in the memory deficits exhibited by individuals with schizophrenia.

In schizophrenia alterations in hippocampal volume, perfusion and activation have been consistently reported (Heckers, 2001), and the integrity of the hippocampus is necessary for declarative memory. The hippocampus is the key area implicated in the formation of associations and is responsible for the integration of different features of an event, to support the encoding of information in a meaningful way (Davachi and Wagner, 2002), and may be responsible for conscious recollection during retrieval (Yonelinas and Levy, 2002).

Research has found evidence of abnormal hippocampal neuronal activation in schizophrenia during episodic memory performance that may be affected by specific genetic variations (Goldberg et al., 2006, Hariri et al., 2003, Bertolino et al., 2006, Di Giorgio et al., 2008). Reduced hippocampal activation in patients relative to controls during encoding has been robustly reported (Heckers et al., 1998, Jessen et al., 2003, Achim and Lepage, 2005, Ledoux et al., 2013) and may reflect the less efficient use of encoding strategies in individuals with schizophrenia.

In contrast, a review by Ragland et al. (2009) did not find evidence to support a reduction in hippocampal activation in patients during both encoding and retrieval (Ragland et al., 2009). The only MTL activation difference identified was increased activity in the

parahippocampal gyrus in patients during both encoding and recognition. The parahippocampal gyrus has been shown to be involved in familiarity assessment (Yonelinas and Levy, 2002).

Research into hippocampal structure and function in bipolar disorder is less clear. There is some evidence of volume reduction in bipolar disorder (Blumberg et al., 2003a) and studies have shown evidence of increased hippocampal activation during affect processing tasks (Lawrence et al., 2004) and during verbal episodic memory (Deckersbach et al., 2006).

1.3.6.5 Other regions (cerebellum, thalamus)

Other regions have also been implicated in episodic memory, such as the thalamus and cerebellum. Achim et al. (2005) and Ragland et al. (2009) both identified abnormalities in these regions, providing support for disruptions to a frontocortical–thalamic cerebellar circuit in schizophrenia (Andreasen et al., 1996). The cerebellum has previously been implicated in episodic memory processes, for example cerebellar activity has frequently been found during recognition (Cabeza et al., 2002, Fliessbach et al., 2006, van der Veen et al., 2006). Evidence also supports a role of the cerebellum during memory encoding with visual stimuli (Weis, 2004, Fliessbach et al., 2007). Additionally, there is evidence for subtle episodic memory deficits in patients with cerebellar lesions (Gottwald et al., 2004).

Evidence suggests that a network between the PFC and cerebellum, linked through synapses in the thalamus, plays a crucial role in coordinating motor and cognitive functions. The thalamus is involved in attentional processing during the encoding of novel objects, and structural abnormalities of the thalamus have also been reported in schizophrenia

(Heckers et al., 2000). Heckers et al. (2000) used PET to investigate episodic object recognition in schizophrenia and found decreased right hemispheric thalamic activation during the recognition of novel visual stimuli. Other research has reported increased activation during retrieval in prefrontal regions, thalamus and insula in patients with schizophrenia compared to controls, and similar but milder abnormalities in first-degree relatives (Stolz et al., 2012).

1.3.6.6 Summary of neuroimaging findings

On review of the literature, it is evident that findings are not straightforward and are somewhat contradictory with respect to hyper or hypoactivation of certain brain regions. In patients with schizophrenia the key regions involved appear to be prefrontal and medial temporal regions. The main findings in bipolar disorder seem to be hypoactivity in frontal and hyperactivity in limbic brain regions involved in episodic memory processing (Brooks et al., 2009a, Deckersbach et al., 2006, Oertel-Knochel et al., 2014).

Findings depend on the experimental setting and design, for example whether verbal or visual stimuli, or strategic memory tasks are used. For example, incidental encoding has been associated with substantially fewer differences between controls and patients compared to intentional encoding. Bonner-Jackson et al. (2008) found that use of an incidental encoding strategy e.g. making living/non-living judgments improved retrieval in patients and resulted in a more similar pattern of activation to that of controls (Bonner-Jackson et al., 2008). Despite this, they did find increased activity in patients in bilateral inferior frontal gyrus, left inferior parietal lobe and the cerebellum, regions known to support episodic memory function.

Different memory tasks may also engage different regions of the PFC to enable successful memory performance. Memory can also be affected by many factors, therefore it is important to carefully address the confounding factors that are associated with memory performance such as age, overall intellectual ability, attention, medications and symptoms. Overall however the literature does point to episodic memory deficits in schizophrenia and bipolar disorder that are linked to several regions known to be involved in episodic memory in healthy controls.

1.3.7 Genetic component of episodic memory

Both the liability to developing a major psychiatric disorder, episodic memory itself, and several neuroimaging measures are highly heritable (Glahn et al., 2007b, Blokland et al., 2011). Schizophrenia and bipolar disorder are both highly heritable disorders with a heritability rate of around 80% for schizophrenia (Sullivan et al., 2003) and as high as 89% for bipolar disorder (McGuffin et al., 2003). Episodic memory can be defined as a genetically complex behavioural trait that shows substantial heritability, with values ranging from 30% to 60% (Papassotiropoulos and de Quervain, 2011). Episodic memory deficits are a putative endophenotype for schizophrenia, as milder deficits are evident in patients prior to the onset of psychotic symptoms, and in the unaffected relatives of individuals with schizophrenia (Reichenberg and Harvey, 2007, Whyte et al., 2005).

Unaffected relatives of patients with schizophrenia or bipolar disorder show episodic memory deficits of moderate effect size (range 0.44–0.65 for schizophrenia and 0.33–0.53 for bipolar disorder) (Christodoulou et al., 2012, Whyte et al., 2005, Snitz et al., 2006, Lefèbvre et al., 2010, Arts et al., 2008). Neuroanatomical findings of temporal lobe and

hippocampal volume reductions in unaffected relatives also suggest a genetic basis for deficits in episodic memory (Leavitt and Goldberg, 2009). This suggests that these impairments are at least in part heritable and are independent of psychotic symptoms (Cirillo and Seidman, 2003, Di Giorgio et al., 2013).

A twin study by Owens et al. (2011) investigated the heritability of visual and verbal episodic memory and its genetic relationship with schizophrenia (Owens et al., 2011). They found episodic memory was moderately heritable and shared substantial genetic overlap with schizophrenia, suggesting that episodic memory is a valid endophenotype. Therefore, episodic memory impairments appear to fit the criteria for the identification of endophenotypes set out by Gottesman and Gould (Gottesman and Gould, 2003). However, relatively little is known about the heritability of task-related BOLD signal phenotypes, as measured with fMRI during episodic memory related activation.

Employing a genetic approach may help to further our understanding of deficits in episodic memory in psychosis (Leavitt and Goldberg, 2009). Candidate genes for episodic memory dysfunction in schizophrenia have been selected on the basis of reported associations, including an allelic variation of the DISC1 gene. There is mounting evidence that the DISC1 gene contributes to sensitivity to schizophrenia and memory dysfunction (Hennah et al., 2006). Investigating endophenotypes, such as episodic memory, may help to bridge the gaps between genetic expression and clinical presentation (Hill et al., 2008). Genetic imaging approaches, with a focus on DISC1, will be discussed in the following chapter.

Chapter 2: Genetic Imaging

Chapter 2: Genetic imaging

This chapter will review the recent literature on genetic imaging in schizophrenia using DISC1 as an example of a risk genetic variant for psychosis. There is a focus on functional genetic imaging, specifically fMRI, because of its non-invasive ability to examine the effects of functional polymorphisms on information processing in multiple brain systems. The use of paradigms to examine complex cognitive processes and the relative ease with which large numbers of participants can be accumulated also makes fMRI the current functional method of choice for genetic imaging (Kempf and Meyer-Lindenberg, 2006). The potential challenges inherent in the field and implications for future research are also discussed in this chapter, including approaches to account for the complexity of epistatic effects, the study of rare structural variants, the importance of task selection, and the ethical, legal and social implications of the clinical application of genetic imaging are considered.

2.1 Genetic imaging approach

In recent years there has been a surge of interest in the application of imaging genetics to investigate the impact of genetic variation on the structure, function and connectivity of the human brain (Glahn et al., 2007b). Advances in neuroimaging techniques have resulted in a more comprehensive understanding of the structure and function of the brain in psychiatric disorders. For example, several imaging studies in patients with schizophrenia have found widespread structural and functional abnormalities in key brain regions, particularly in the frontal and temporal lobes (Lawrie and Abukmeil, 1998, Shenton et al., 2001, Frith et al., 1995). Further to this, major advances in molecular genetics research, primarily the Human Genome Project, have led to the ability to map the human genome sequence including particular risk genes (Lander et al., 2001). More recently, the advance

of genome-wide association studies (GWAS) has allowed researchers to examine the whole genome for either common or rare disease risk variants of small or large size, respectively. The role of rare genetic variants, including copy number variants (CNVs), have become a significant focus of genetic research in the aetiology of schizophrenia (Rodriguez-Murillo et al., 2012).

There has also been a complimentary increase in research integrating the fields of imaging and genetics to gain a more comprehensive understanding of the pathophysiology of complex psychiatric diseases such as schizophrenia. The emerging field of genetic imaging applies structural and functional neuroimaging to study individuals carrying susceptibility genes that relate to the disease of interest. Genetic imaging usually involves identifying a functional variant within a candidate gene that is thought to impact at the molecular and cellular level, searching for differences in the frequency of a particular allele in a specific population, and examining differences in neuroimaging results between genotype groups (Hariri and Weinberger, 2003).

Combining genetic and neuroimaging domains can help to further our understanding of the biological systems and neural mechanisms involved in mediating the effect of genetic variants on psychosis risk. In the future, this approach could have the potential to improve predictive testing of disorders in the at-risk population and may offer early intervention and novel targets for therapeutic interventions. For example, genetic imaging techniques could help to understand how individual genetic variation influences medication response, with the potential to offer more precisely tailored treatment plans for individual patients (Blasi and Bertolino, 2006).

2.1.1 Imaging genetics of psychosis

Schizophrenia is highly heritable, with multiple genetic components at work including both multiple common alleles and rare highly penetrant variants conferring susceptibility (Sawa and Snyder, 2002). A recent GWAS study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, using vast sample sizes, identified 108 schizophrenia associated genetic loci (Ripke et al., 2014). These findings were not randomly distributed across the genome but appeared to converge upon genes that are expressed in the brain, providing potential insight into the biology of schizophrenia. This study also found an overlap between genes affected by rare variants and more common loci identified by GWAS, supporting a complimentary mechanism involving both genetic components. Although the aetiology of schizophrenia remains uncertain, research consistently demonstrates that genetic factors play a fundamental role in the development and risk, and a number of candidate risk genes have been identified (Stefansson et al., 2008, Harrison and Owen, 2003), including DISC1.

Despite this clear genetic component and high heritability estimates of around 80% (Buchman and Illes, 2010), identifying psychosis susceptibility genes has been challenging and researchers are far from fully understanding the mechanisms by which genes increase the risk of schizophrenia (Blasi and Bertolino, 2006). Specific genetic variants are often inconsistently identified and difficult to replicate, and it is likely to be the combination of multiple genes in addition to a range of other factors including environmental, epigenetic and gene-environment interactions that results in the expression of the full clinical syndrome (Bearden et al., 2007). It is also probable however that a small number of cases

may be related to structural variants of large effect such as CNVs and the DISC1 translocation.

As with schizophrenia, there is a substantial genetic contribution to the aetiology of bipolar disorder with heritability estimates ranging from 89% (McGuffin et al., 2003) to as high as 93% (Kieseppä et al., 2014). Genome wide association studies and whole genome linkage scans have identified several chromosomal regions and susceptibility genes that are associated with increased risk of bipolar disorder (Alsabban et al., 2011). Individually these risk variants only account for a small proportion of the heritability, suggesting that risk for bipolar disorder is due to the cumulative effect of multiple loci each with modest effect (Craddock and Sklar, 2009).

There is evidence of an overlap in the genetic architecture of bipolar disorder and schizophrenia for example from genome wide linkage studies (Berrettini, 2003, Tsuang et al., 2004). A recent population-based study found evidence of a genetic association between these disorders, with 63% of comorbidity due to additive genetic effects common to both disorder (Lichtenstein et al., 2009). Genes implicated in schizophrenia have also been studied for their potential involvement in bipolar disorder, including DISC1, which has been associated with bipolar disorder in several studies (Hennah et al., 2009, Perlis et al., 2008, Hodgkinson et al., 2004). Variation at the DISC1 locus increases risk to a variety of psychiatric disorders, which merits further study of this gene in bipolar disorder. These findings support the idea that schizophrenia and bipolar disorder have partially overlapping genetic aetiology.

2.1.2 Endophenotypes

Direct associations between genes and clinical target variables have been difficult to determine, largely due to the subtle effects of genes on behaviour. Research suggests that the alleles that underlie the genetic risk to schizophrenia may largely exert their effects on endophenotypes such as brain function and structure (Meyer-Lindenberg and Weinberger, 2006, McIntosh et al., 2007). An endophenotype refers to a measurable component along the pathway between the disease syndrome itself and the underlying genotype and can be cognitive, neuroanatomical, neuropsychological, endocrinological or biochemical in nature (Gottesman and Gould, 2003). Gottesman and Gould (2003) set out criteria for the identification of endophenotypes including that they should be heritable, state-independent, co-segregate within families and occur in unaffected family members at a higher rate than in the general population. This approach is increasingly employed in psychiatric research, based on the hypothesis that endophenotypes are coded by a smaller number of genes compared to more complex clinical classification systems such as DSM-5, and may have a more straightforward inheritance pattern (Allen et al., 2009).

The penetrance of genetic effects is likely to be greater at the intermediate neural systems level than at the level of a more complex clinical disorder. Endophenotypes should therefore offer a powerful way to bridge the neurobiology of genes and behaviour (Kempf and Meyer-Lindenberg, 2006). Functional and structural brain imaging measures have been identified as attractive putative endophenotypes. For example, researchers have found more robust effects when comparing patients and controls using brain activation than with performance on a range of cognitive tasks (Weiss et al., 2003, Honey et al., 2002). This approach also allows for the study of smaller sample sizes than in conventional genetics.

Further to this, endophenotypes are usually more objectively measurable compared to the subjective behavioural and neuropsychological experience of these same processes (Hariri and Weinberger, 2003). Therefore, identifying an endophenotype through the use of imaging genetic techniques may one day provide a more accurate means for diagnosis compared to clinical assessments that are often affected by subjectivity and heterogeneity in symptoms (Hyde et al., 2011). However, it is important to note that neuroimaging measures are variable and prone to artefact due to experimental, statistical, or population stratification errors. Further to this, heritability has not been conclusively demonstrated for many functional imaging measures, including episodic memory, and research suggests that few candidate endophenotypes fulfill all the criteria outlined earlier.

Although the sensitivity of imaging genetics is markedly higher compared to studies focused solely on behavioural or clinical measures, comparatively large groups divided by genotype are required to find reliable differences, and the application of this technique at the individual level is not currently feasible. Further, due to the overlap between schizophrenia and other psychiatric disorders, imaging genetics is likely to predict a broader diagnostic range of diseases rather than specifically predicting schizophrenia.

2.1.3 Genome-wide Association Studies (GWAS)

There are a number of different techniques for identifying and mapping genetic variants that underlie complex traits and common diseases. GWAS examine the whole genome for genetic variants without prior assumptions regarding the genomic location of the causal variants. This approach has a number of advantages compared to traditional candidate gene studies that rely on prior information regarding gene function and location, and potentially

allows for the simultaneous detection of multiple susceptibility genes when sufficiently large sample sizes are assayed (Lee et al., 2012a).

Recently, the first common genetic variant associated with schizophrenia on a genome-wide level was discovered in the ZNF804A gene (rs1344706), encoding zinc-finger protein of undefined function (O'Donovan et al., 2008). Esslinger et al. (2009) demonstrated, using an imaging genetics approach, that healthy carriers of rs1344706 risk genotypes have marked alterations in functional coupling of the DLPFC across hemispheres and with the hippocampus during working memory (Esslinger et al., 2009). There is also further evidence that ZNF804A is of functional relevance to schizophrenia because this gene has been shown to influence the antipsychotic response of positive symptoms and may be a novel target for pharmacological treatment (Mössner et al., 2012).

2.1.3.1 Limitations of GWAS

Currently, there are several limitations of GWAS including the problem of multiple testing, the presence of variable extents of linkage disequilibrium, and the absence of biologically established causal variants (Porteous et al., 2006). Further to this, GWAS is neither powered nor designed for the detection of rare risk alleles and this is the case even for variants with high penetrance and impact. As a result, the full scientific potential of GWAS cannot be realised until sample sizes are sufficiently large enough and technological limitations are overcome. However, recent advances in next-generation sequencing technologies could facilitate progress in the identification of rare variants in individual samples.

Genes with strong biological validity have also been identified through other approaches, such as using linkage and the candidate gene approach, for example DISC1. However, there are currently no results demonstrating genome-wide levels of significance for these prominent candidate genes. Despite this, it must be acknowledged that the failure of a gene to achieve the genome-wide significance threshold (the standard is generally considered to be $p < 1 \times 10^{-8}$) should not necessarily be interpreted as rejection of a genetic hypothesis, as it may still be genuinely contributing to the aetiology of the disease (Lee et al., 2012a). DISC1 has strong independent evidence from other sources including convergent biological support for their involvement in schizophrenia (Chubb et al., 2008, Porteous et al., 2006), and is amongst the most strongly associated genes in schizophrenia as ranked on the Schizophrenia Research Forum (http://www.schizophreniaforum.org).

Ayalew et al. (2012) used a translational convergent functional genomics approach to integrate available evidence across multiple sources in the field, including GWAS data, gene expression studies, CNVs and animal model data, in order to identify genes potentially involved in schizophrenia (Ayalew et al., 2012). This approach prioritized genes, of which DISC1 was identified as the top candidate, with weaker GWAS data but with stronger evidence in terms of gene expression work and human or animal genetic studies. In comparison, some of the top genes identified in the GWAS data including ZNF804A, were assigned a lower prioritization score due to do fewer independent sources of evidence. Ultimately this highlights the fact that different genetic techniques can potentially identify different candidate genes for schizophrenia.

2.1.4 Polygenic risk

Research has demonstrated a significant polygenic contribution to major psychiatric disorders including schizophrenia, bipolar disorder and major depressive disorder (MDD), where risk is attributed to the cumulative effect of many common alleles of small effect (Purcell et al., 2009, Lubke et al., 2012). This is in line with the polygenic model of inheritance (Gottesman and Shields, 1967). Polygenic risk score (PRS) is a quantitative measure of the sum of trait-associated alleles across several genetic loci and can clinically be considered a genetic liability to disease risk. To obtain polygenic risk scores, a GWAS is conducted on an initial training sample to identify markers, which are then ranked by their evidence for an association with a particular disorder (usually by their p-value). PRS is then calculated in an independent replication sample by summing the trait-associated alleles within each subject, for a subset of top ranking markers (Dudbridge, 2013). This score can then be related to disease state or traits in the independent sample.

Research has found that PRS can discriminate between individuals with a diagnosis of schizophrenia from control subjects (Purcell et al., 2009). Data has also found overlapping genetic susceptibly between schizophrenia and bipolar disorder using PRS. Top markers identified from schizophrenia GWAS have been found to be associated with bipolar disorder and vice versa, and have been used to differentiate between different forms of bipolar disorder (Hamshere et al., 2011). These findings support the notion that psychiatric disorders have a substantial shared polygenic component.

Several studies have examined associations between PRS for different disorders and various neuroimaging measures. For example, Whalley et al. (2012) generated PRS for

bipolar disorder based on psychiatric GWAS consortium summary data. They found that increased PRS for bipolar disorder was associated with greater activation in limbic regions during a language based executive function task, as seen in patients with bipolar disorder (Whalley et al., 2012a). Another study investigated PRS for schizophrenia and working memory-related brain activation (Kauppi et al., 2014). They found that increased cumulative genetic risk for schizophrenia was associated with dysregulation of the frontal lobe, in both patients and controls. This approach to investigating imaging data using PRS may help to establish a link between additive genetic predisposition to psychiatric illness and neuroimaging markers of disease, to potentially inform models of risk.

A recent study investigated the neural effects of a cross-disorder PRS for a range of disorders during a language/executive task. They found an association between increased polygenic loading and increased frontal activation in healthy controls, again supporting shared genetic aetiology across the major psychiatric disorders (Whalley et al., 2015b).

2.2 Disrupted in Schizophrenia 1 (DISC1)

DISC1 is a putative susceptibility gene for a spectrum of major psychiatric disorders such as schizophrenia, bipolar disorder and major depression. It was originally identified in a large Scottish pedigree, in which it is disrupted by a balanced translocation between chromosomes 1 and 11 (Blackwood et al., 2001, St Clair et al., 1990). This translocation simultaneously disrupts two novel genes; DISC1, a conventional protein coding gene, and DISC2, a noncoding RNA gene antisense to DISC1 (Millar et al., 2000). Subsequently, several DISC1 single nucleotide polymorphisms (SNPs) and haplotypes have been related

to schizophrenia and other psychiatric conditions, albeit without consistently implicating any one SNP in particular.

2.2.1 The DISC1 translocation

DISC1 was first described as a risk factor for major psychotic disorders in a multiply affected Scottish pedigree (St Clair et al., 1990, Blackwood et al., 2001, Jacobs et al., 1970). This family was first discovered by Jacobs et al. (1970) who reported the translocation in an adolescent with conduct disorder (Jacobs et al., 1970). Years later it was found that the same chromosomal abnormality spanned four generations. The family has been regularly followed up as a consequence of this original finding by direct interview and review of medical case-notes. This revealed an increased incidence of major psychiatric disorders among relatives with the translocation but found no cases of these disorders in relatives with a normal karyotype (St Clair et al., 1990). However, it is important to note that penetrance of the translocation is incomplete and there are individuals with a normal karyotype with a psychiatric diagnosis, although none with major mental illness. Genetic and environmental interactions may partly explain this incomplete penetrance (Blackwood et al., 2001).

Figure 2.1: DISC1 Scottish kindred

DISC1 family tree diagram. Individuals scanned and included in current analysis are highlighted in red/blue. Image created in Haplopainter.

Carriers scanned

Non-carriers scanned

Y: t(1;11) carrier

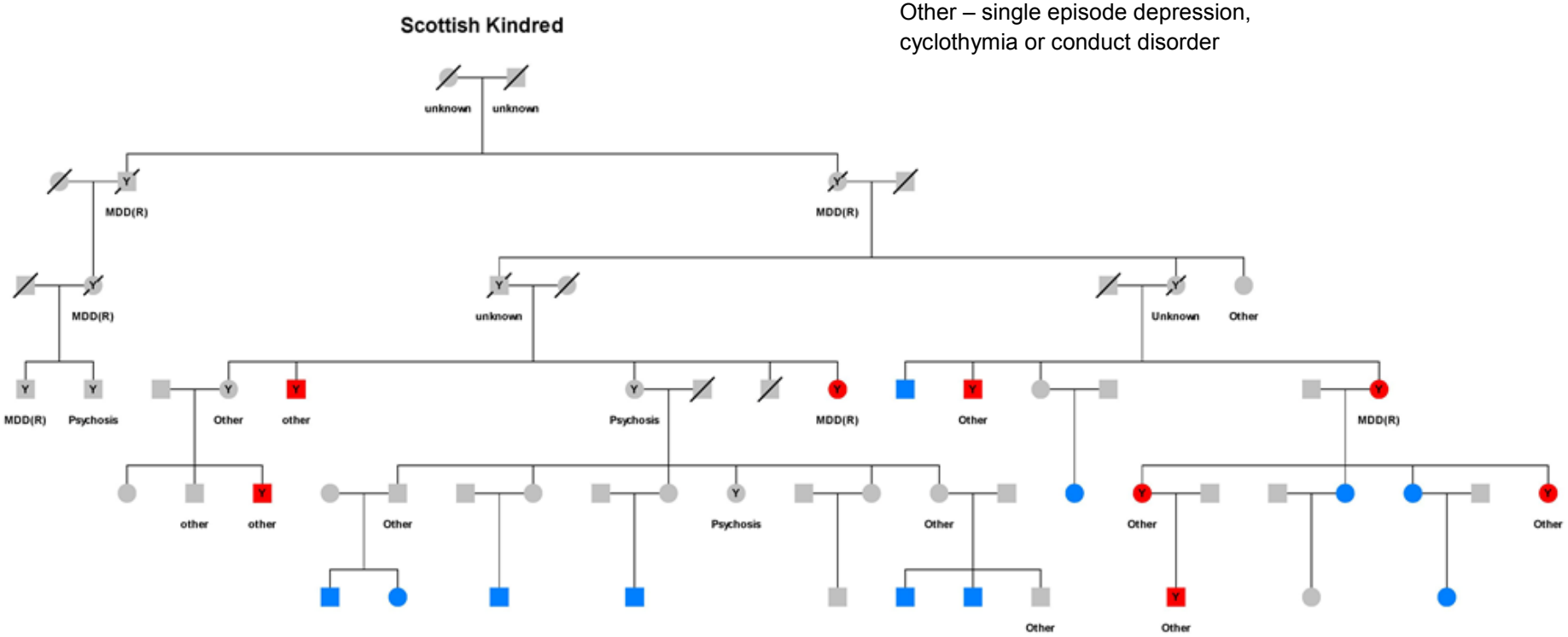
Diagnoses:

Unknown – unknown psychiatric status

Psychosis – schizophrenia, schizoaffective or psychotic bipolar disorder

MDD(R) – recurrent major depression

Other – single episode depression, cyclothymia or conduct disorder



An interesting feature of this family is the diversity of clinical diagnoses associated with the translocation including schizophrenia, recurrent major depression and bipolar disorder. Carriers of the translocation have a fifty-fold increased risk of developing a major psychiatric disorder, whereas relatives without the translocation face the same risk as in the general population (Blackwood and Muir, 2004). Linkage analysis yielded a log of the odds (LOD) score of 3.4 when the diagnosis was restricted to schizophrenia alone, and a LOD score of 7.1 when the phenotype was expanded to include recurrent major depression and bipolar disorder (Blackwood et al., 2001). Research has also provided independent evidence for the involvement of the DISC1 locus in psychiatric illness from linkage and association studies in other populations (Ekelund et al., 2000, Hovatta et al., 1999, Hwu et al., 2003).

The study of multiply affected families is important for the identification and investigation of variants that that are too rare to be detected by GWAS and have relatively large effects on illness risk. Insights from unique families have repeatedly served medical research well across the spectrum of conditions generally considered 'common and complex' (Blackwood et al., 2001). However, findings from family-based studies may be unique to one specific family, and as a result, not relevant to the disease itself. Additionally, because the translocation is rare, it is important to investigate possible phenotype differences between members of this family and unrelated individuals with psychosis.

2.2.2 Function of DISC1

Despite a wealth of research into the function of DISC1, the precise mechanisms by which variation in the DISC1 gene impacts upon risk for psychosis remain unknown. DISC1

encodes a multifunctional scaffold protein that impacts on many aspects of central nervous system function likely to be involved in the pathophysiology of schizophrenia (Bearden et al., 2007), and the translocation directly disrupts this protein sequence. For example, DISC1 is thought to be involved in mechanisms of neurodevelopment and synaptic plasticity including neuronal proliferation, differentiation and migration, through interaction with a number of proteins (Porteous et al., 2006, Mao et al., 2009, Brandon and Sawa, 2011, Porteous et al., 2011). This reflects the diversity of potential roles of DISC1 and its importance to overall brain function. Subsequent genetic association and linkage studies have replicated the original linkage findings and evidence now implicates DISC1 as one of the most potent risk genes for psychopathology (Chubb et al., 2008, Porteous et al., 2006). Certainly, the translocation in the original DISC1 family confers a dramatically increased risk of major psychiatric disorder.

Efforts to model DISC1 disease biology in transgenic mice, and more recently in drosophila and zebrafish, have been relatively successful (Sawamura et al., 2008, Wang et al., 2008, Drerup et al., 2009, Kellendonk et al., 2009). DISC1 mutant mice display behavioural abnormalities, information processing deficits and structural anomalies similar to those seen in patients with schizophrenia, bipolar disorder or major depression (Hikida et al., 2007, Shen et al., 2008).

2.2.3 Cognition in DISC1

Studies investigating cognitive function and genetic variation associated with DISC1 have reported significant findings across a range of cognitive domains (Burdick et al., 2005, Gasperoni et al., 2003, Paunio et al., 2004, Hennah et al., 2005, Cannon et al., 2005,

Thomson et al., 2005, Liu et al., 2006, Palo et al., 2007). Several human neuroimaging studies have used of a variety of genetic imaging techniques to investigate DISC1 and brain structure and function (Duff et al., 2013).

Blackwood et al. (2000) conducted a study on cognitive function in 12 relatives with the t(1;11) translocation and 8 relatives with a normal karyotype, and provided the first evidence that DISC1 variation might have subclinical effects (Blackwood, 2000). They found reduced event-related potential (ERP) P300 amplitude and increased latency, indicating deficits in the speed and efficiency of information processing. This amplitude abnormality was also independent of clinical symptoms because translocation carriers without symptoms also showed similar P300 abnormalities. These findings are similar to those found in other families with multiple members with schizophrenia, (Blackwood et al., 1991, Sham et al., 1994), are consistent with findings in patients with schizophrenia and their relatives (Schreiber et al., 1992, Blackwood, 2000) and also in families of patients with bipolar disorder (Pierson et al., 2000).

The impact of the t(1;11) translocation on brain imaging measures was largely unknown until the SFMHS, from which data in this thesis is part of. Research is emerging from this study providing greater insight into the impact of this translocation on several imaging measures including structural and functional MRI, spectroscopy and DTI. Whalley et al. (2015) found decreased white matter integrity using DTI in multiple neural pathways including callosal fibers and tracts connecting frontal regions, in carriers compared to non-carriers (Whalley et al., 2015a). White matter integrity in the corpus callosum was also significantly negatively correlated with positive symptoms on the positive and negative

symptom scale (PANSS), and was found in patients versus controls, indicating a potential role for DISC1 in the development of positive psychopathology.

2.2.4 DISC1 Single Nucleotide Polymorphisms (SNPs)

Studies examining the effects of common variants in DISC1 alleles in humans have suggested that variation at the DISC1 locus contributes to structural and functional changes across the brain (Duff et al., 2013). Research suggests that DISC1 is expressed at high levels within the hippocampus (Ma et al., 2002), and there is evidence to suggest that it is pivotal during hippocampal development (Callicott et al., 2005). However, DISC1 is also highly expressed in the developing brain and brain stem after birth (Schurov et al., 2004). The DISC1 locus contributes to structural and functional alterations in the PFC and hippocampus, and there is a relationship between DISC1 variation and several quantitative cognitive traits including altered working and episodic memory performance in schizophrenia patients and their relatives (Bearden et al., 2007). Prefrontal and hippocampal abnormalities are robust features of psychotic disorders and a risk gene would be expected to influence the structure and function of these brain regions.

2.2.4.1 Ser704Cys SNP

Callicott et al. (2005) explored the functional impact of the DISC1 polymorphism on phenotypes related to hippocampal formation (Callicott et al., 2005). They identified a common SNP within the DISC1 gene, resulting in a serine to cysteine substitution (Ser704Cys) that was associated with schizophrenia and also had a measurable impact on hippocampal structure and function as assayed with BOLD fMRI. They found that the common Ser allele was over-transmitted in schizophrenic patients, and in healthy subjects

this allele was associated with a significant reduction in hippocampal gray matter volume and altered engagement of the hippocampus during a range of cognitive tasks. Compared to Cys homozygotes, Ser subjects showed increased hippocampal activation during the *n*-back working memory task and abnormally decreased activation during an episodic memory task. These results lend support for findings in the wider clinical literature and are analogous to findings described in patients with schizophrenia (Hariri and Weinberger, 2003, Callicott et al., 2003, Hariri et al., 2003).

This study also implemented an extensive assessment battery to measure aspects of cognitive performance. DISC1 was found to have a greater impact on brain activation than on measures of cognition, which demonstrates the superior ability of neuroimaging to differentiate Ser and Cys subjects (Callicott et al., 2005). These findings support evidence that the penetrance of genetic variants is more robust at the level of brain information processing than at the level of behaviour (Egan et al., 2001). Despite the weaker association of Ser704Cys to measures of cognition, the Ser allele was associated with impaired logical memory performance in patients with schizophrenia. This suggests that additional genetic or environmental factors and epistatic interactions with other risk genes may be fundamental to produce measurable effects on these phenotypes. This study supports an association between variation in DISC1 and schizophrenia and suggests that the mechanism of this effect may involve neurodevelopmental abnormalities of the structure and function of the hippocampal formation.

DeRosse et al. (2007) investigated the association between Ser704Cys genotype and lifetime severity of positive symptoms in schizophrenia, detecting significantly higher

ratings of paranoid delusions in at-risk Ser carriers (DeRosse et al., 2007). However, in this sample the DISC1 haplotype was not significantly associated with a diagnosis of schizophrenia, therefore the authors suggest it is more likely that Ser704Cys acts as a modifier gene (Fanous and Kendler, 2005) that affects clinical features of schizophrenia rather than increasing overall risk for the illness itself.

A later study examined the association between the Ser704Cys polymorphism and the structure and function of the hippocampus (Di Giorgio et al., 2008). They found that healthy individuals homozygous for the Ser allele displayed greater engagement of the HF and greater hippocampal DLPFC functional coupling during encoding of recognition memory. These results suggest that the Ser704Cys polymorphism plays an important role in the modulation of functional connectivity between the hippocampus and DLPFC, and DISC1 genotype may affect functional coupling of these regions during information processing within the memory encoding neural network.

However, contrary to Callicott et al. (2005), this study found that the Ser allele was linked with increased gray matter volume in the hippocampus (Di Giorgio et al., 2008). Research has identified that the same DISC1 allele may display alternate risk or protection for schizophrenia, suggesting that the effect of a specific susceptibility gene is dependent not only on the existence of one risk variant on the gene, but also on the presence or absence of other risk variants within the same gene (Hennah et al., 2009). This demonstrates the complex nature of gene interactions and the need to take other genetic and environmental factors into consideration that might mediate the phenotypic consequence of DISC1 and risk for schizophrenia.

In addition to the hippocampal abnormalities addressed above, altered PFC activation has been consistently associated with psychosis and may contribute to many of the cognitive symptoms present in schizophrenia (Gur et al., 2007). For example, Prata et al. (2008) used fMRI during a verbal fluency task, a standard measure of prefrontal activation, to test the influence of DISC1 on prefrontal function in healthy volunteers (Prata et al., 2008). They found that Ser704 homozygotes demonstrated less efficient prefrontal activation, with greater function required to achieve the same behavioural outcome. This is consistent with the findings of Callicott et al. (2005) that there is an association between the Ser704 polymorphism and schizophrenia.

Prata et al. (2011) recently extended their research to examine the influence of the DISC1 polymorphism Ser704Cys on prefrontal activation in patients with schizophrenia and bipolar disorder (Prata et al., 2011). In contrast to their previous findings in healthy subjects, no significant effect of DISC1 variation was detected in the PFC or any other region in patients with schizophrenia. The authors interpret the absence of an observable effect in a patient sample as an indication of underlying interactions between DISC1 genotype and a multitude of other risk genes that have been implicated in schizophrenia together with potential interactions with unknown genetic factors.

Sprooten et al. (2011) reported an association between white matter integrity and variation in the DISC1 SNP (Ser704Cys) in healthy controls, as measured by DTI (Sprooten et al., 2011a). Individuals carrying the major Ser allele exhibited reduced white matter integrity in several regions. There is strong evidence of white matter abnormality in schizophrenia, and these findings support a role for DISC1 in white matter development. This suggests

that white matter integrity and density are potential endophenotypes for schizophrenia and other psychiatric disorders.

2.2.4.2 Leu607Phe SNP

Whalley et al. (2012) sought to examine the effects of another common SNP (Leu607Phe) on brain activation during a language task, in a group of subjects at high familial risk of schizophrenia (Whalley et al., 2012c). In comparison to the control group, there was no significant effect of the Phe risk variant on brain activation in the high risk subjects. This suggests that the effect of the Leu607Phe variant on brain activation differs in unaffected relatives at high familial risk versus healthy controls, presumably because relatives have a higher genetic loading and are more likely to reach a threshold of liability for schizophrenia.

Szesko et al. (2008) investigated the effect of the Leu607Phe polymorphism on cortical grey matter and positive symptoms in schizophrenia (Szeszko et al., 2008). They found that individuals (patients and healthy controls) with the risk allele had significantly reduced grey matter in the superior frontal gyrus and anterior cingulate gyrus. Further to this, patients with schizophrenia who had the risk variant (Phe carriers) had greater severity of positive symptoms compared to those who were leu/leu homozygotes.

2.2.4.3 DISC1 interactors

The influence of DISC1 is complicated, with allelic or haplotypic association reported over a large proportion of the DISC1 region (Hennah et al., 2006), and it appears to be the specific combination of DISC1 variants that results in increased susceptibility. This suggests that the DISC1 risk alleles identified thus far are not entirely causative, but might

be in disequilibrium with yet to be discovered gene variants (Mata et al., 2010). To gain a greater understanding of how variation within the putative DISC1 pathway affects brain function and increases risk for schizophrenia, further research must examine interactions with other candidate DISC1 polymorphisms, as well as with other potential DISC1-interacting partners.

DISC1 is a hub protein in a multidimensional risk pathway, and several interactors have been identified as independent genetic susceptibility factors for psychiatric illness (Chubb et al., 2008). Mutations within DISC1 affect multiple systems involved in central nervous system development and function, and are usually sufficient to substantially increase risk of developing major mental illness. Therefore, it is likely that DISC1 interactors and other genetic mechanisms that modulate the level of DISC1 expression can account for the growing evidence for this gene as a key risk factor for schizophrenia (Porteous et al., 2006).

Nicodemus et al. (2010) explored the potential interactions between 50 SNPs in DISC1 and five other potential interacting partners (Nicodemus et al., 2010a). They found evidence that SNPs in three genes in the DISC1 pathway, DISC1, CIT and NDEL1 act in epistasis to increase susceptibility to schizophrenia. Three significant interactions were then biologically validated using fMRI during a working memory task in a sample of controls. Carriers of the risk associated variants for both loci demonstrated a pattern of inefficient prefrontal cortical activity that has been linked to schizophrenia and is also seen in unaffected siblings (Callicott et al., 2003). This provides support to the notion that different genes interact to increase the risk for schizophrenia, however future research should

examine the many other networks and susceptibility gene variants linked to the DISC1 pathway.

2.2.5 Current challenges of genetic imaging

Recent advances in imaging genetics have made a substantial contribution to our understanding of major psychiatric disorders. This novel technique provides the tools necessary to explore the mechanisms through which the dynamic interplay of genes, brain and environment shapes individual differences in behaviour and risk for schizophrenia. Developments in genetic imaging represent a new era in predictive medicine, however there are difficulties interpreting the findings accurately and meaningfully. Therefore, it is important for researchers to understand and address the challenges to progress inherent in the field.

To date the potential of genetic imaging has been plagued by inconsistent attempts at replication of associations between specific genetic variants and psychosis (Viding et al., 2006). This inability to validate findings through independent replication may be due to methodological limitations such as insufficient power, or sample heterogeneity between different sites, for example the inclusion of different ethnic groups or gender. Alternatively, and arguably more importantly, inconsistency in the literature may reflect the stratification of genetic risk and the complexity of phenotypic association. This suggests that a new level of analysis is required to account for such complex functional interactions between larger sets of genes as they impact on imaging data (Hennah et al., 2009, Viding et al., 2006). For example, a novel approach is the use of genetic imaging to investigate the effects of multiple interacting risk variants using an overall genetic risk score for schizophrenia.

There are currently only a limited number of endophenotypes that are truly indicative of increased susceptibility for schizophrenia, and replication of these findings can be a formidable challenge. Functional neuroimaging offers a promising technique to further our understanding of the aetiology of schizophrenia, although notable problems remain, including both technical and statistical issues. Future research will benefit from collaboration and multi-centre imaging to obtain the substantially larger sample sizes that are required in imaging genetics research.

As larger numbers of genotype and phenotypes are becoming available for genetic imaging studies, there is an increasing concern over the possibility of spurious positive findings due to multiple comparisons. Meyer-Lindenberg et al. (2008) estimated the rate of false positives in imaging genetics by analysing a set of genetic variants without likely impact upon brain structure or function linked to schizophrenia (Meyer-Lindenberg et al., 2008). They observed low rates of positive findings, reflecting an empirical estimate of the expected rate of false positives. These findings provide encouraging evidence that the false positive association rate is well controlled by current commonly used multiple correction measures, however only in the context of adequately selected neuroimaging paradigms and specific analysis procedures. For example, permutation testing is currently considered the gold standard for accurate multiple testing correction, and may be a necessary step in bringing psychiatric genetic findings convincingly to the larger genetics community.

Further to this, Meyer-Lindenberg and Weinberger (2006) propose that a statistically significant result in neuroimaging is not sufficient to conclude that a given genetic variant is functional (Meyer-Lindenberg and Weinberger, 2006). Given the modest and equivocal

contribution of any single variant, it is essential to control for potential confounding variables. For example, when examining the influence of a specific genetic variant it is important to assess whether the studied groups, defined by genotype, differ in the distribution of other risk variants. A major issue to consider in genetic imaging research is that allele frequencies can be extremely rare and vary considerably within and across populations, for example between different ethnic groups or genders. Alleles that exist at relatively low frequencies can be a barrier to recruitment and can also be difficult to interpret during analysis (Casey et al., 2010)**.** Therefore, it is important to consider possible stratification effects that might mask or enhance the influence of a specified variant, in addition to demographic variables such as gender, age, ethnicity and IQ.

2.2.5.1 Pleiotropy

Convergent genetic, neuroimaging and clinical evidence indicate both overlap and discontinuity between schizophrenia and other psychiatric disorders. Pleiotropy, the influence of a single gene on multiple phenotypic traits, has been demonstrated in a variety of susceptibility genes. For example, research suggests that DISC1 is a genetic risk factor for a wide spectrum of psychiatric disorders including schizophrenia, bipolar disorder, major depression and autism spectrum disorders (Whalley et al., 2012c, Hennah et al., 2009, Millar et al., 2000). Research has also identified that genes such as DISC1, which act as a 'hub' or scaffold protein, are generally more complex in their regulation (Camargo et al., 2006), and are therefore associated with greater phenotypic diversity. Therefore, the presence or absence of a specific risk variant does not necessarily entail a vulnerability to schizophrenia, but potentially alters the risk for a range of psychiatric disorders.

2.2.5.2 Research on healthy controls

An important caveat in considering the literature is that the vast majority of imaging genomic research has been conducted on healthy controls with the assumption that patients will demonstrate similar effects. Therefore, it is difficult to infer a direct relationship between specific genetic variants and clinical phenotypes in schizophrenia. However, the existence of potential confounders related to illness and treatment in patients such as medication effects, may mask the effects of individual variants, potentially rendering them less detectable than in controls that carry the at-risk variant. Despite this, it is important for researchers to study patient samples as this allows for a more direct examination of genotype-disease interactions (Roffman et al., 2006).

A common practice in functional imaging research is to average data over groups of participants, and there is doubt as to whether such findings can accurately predict pathology at the individual level due to the heterogeneity of human structural, functional and chemical brain signatures (Buchman and Illes, 2010). Although the sensitivity and specificity of genetic imaging assessments is markedly higher than cognitive and behavioural measures, there will still be an inevitable number of diagnostic errors. Until it can be demonstrated that such errors are outweighed by true positives and negatives, it would be premature to rely on statistical parametric maps of brain activation linked to genetic risk variants as objective diagnostic measures (Hariri and Weinberger, 2003). However, it is questionable as to whether genetic imaging will ever be informative at the individual level. Rather, its purpose may be to biologically validate genetic variants using neuroimaging and identify imaging biomarkers that could be applied in a clinical setting to aid diagnosis or predict the onset of illness in individuals with a family history of schizophrenia.

A major challenge is to account for the complexity of gene-gene and gene-environmental interactions when understanding the effects of genetic variation on behaviour. The relatively small effect of any single polymorphism highlights the need for the examination of a broader network of genetic variation and its environmental influences, as progress is unlikely to come by focusing on a single variant, no matter how penetrant (Blakely and Veenstra-VanderWeele, 2011). Hyde et al. (2011) advocate an integrative strategy of imaging gene-environment interactions to help understand the mechanisms through which genetic variation, environmental factors and the brain interact to predict risk for schizophrenia (Hyde et al., 2011). Further to this, the true potential of genetic imaging is arguably only likely to be realised through its application within longitudinal developmental studies (Viding et al., 2006).

2.2.5.3 Rare structural or copy number variants

The majority of research supports the hypothesis that the genetic influence on schizophrenia is the result of a combination of common alleles, each contributing a small, additive effect. However, recent research has also identified certain genetic variants predisposing to schizophrenia that are highly penetrant but are individually rare (Walsh et al., 2008). This 'common disease; rare variant' hypothesis proposes that schizophrenia is a genetically heterogeneous disorder and many predisposing mutations are highly penetrant and individually rare, even specific to single cases or families (McClellan et al., 2007), of which the DISC1 translocation is a prime example.

Several case-control and family based studies have shown that the mutational burden of novel genomic deletions and duplications of genes is significantly greater in patients than

in healthy controls (Stone et al., 2008). These rare mutations appear to disrupt genes in neurodevelopmental pathways and confer substantial risk for psychiatric illness. The risk associated with some CNVs is substantially higher compared to frequent genetic variants such as SNPs, and in some cases can correspond to a tenfold increase in disease susceptibility (Meyer-Lindenberg and Weinberger, 2006). Evidence also indicates that rare structural variants are dispersed throughout the genome, involve many different genes and are likely to confer risk to a spectrum of other psychiatric disorders (Sebat et al., 2009). Further to this, mutations that are unique to single patients appear to demonstrate the strongest association with schizophrenia.

A major barrier to the investigation of rare variants is that large sample sizes are required due to the relatively low prevalence of these variants, even in clinical populations. For example, the presence of rare causal variants at any single locus is likely to be less than one in 500 patients (Sebat et al., 2009). However, a paramount aim of such research is to understand the penetrance of individually rare variants for a variety of clinical phenotypes. Grouping patients by specific CNV genotype could enhance the power of genetic imaging to investigate how rare variants influence the function of genes and neurobiological pathways, to increase susceptibility to schizophrenia. However, analysis of imaging data would need to be performed retrospectively on a small genetically pre-defined patient group.

2.2.5.4 Task selection

The interpretation of genetic effects depends largely on the validity of the neuroimaging paradigm used. Task selection must be carefully considered in order to identify the most

appropriate paradigms that maximize the sensitivity to be able to detect the relatively small effect of risk variants (Hariri and Weinberger, 2003).Whilst a wide range of fMRI tasks have been used in genetic imaging research, the majority of studies have focused on paradigms that activate PFC or pre-frontal interactions with other cortical regions, such as the n-back working memory paradigm (Egan et al., 2001, Weinberger et al., 2001, Callicott et al., 2005, Nicodemus et al., 2010b) and verbal fluency tasks such as the Hayling Sentence Completion Test (Whalley et al., 2012c, Hall et al., 2006, Krabbendam et al., 2005).

2.2.5.5 Limitations of current imaging paradigms

Further research is required to determine which imaging paradigms are the most conducive to genetic imaging studies. Future research should focus on the design and implementation of more effective stimulus paradigms specific to schizophrenia so that imaging genetics can be applied more efficiently in clinical settings (Demirci and Calhoun, 2009). For example, in comparison to the extensive work on working memory, the genetic impact on neural activation during social cognition has received limited attention. Walter et al. (2011) examined the effects of a genome-wide supported psychosis risk variant in the ZNF804A gene on brain activation during a theory of mind task (Walter et al., 2011). They found a significant risk allele dose effect in parts of the neural network supporting theory of mind functions therefore identifying dysfunction of this network as a potential endophenotype.

As previously mentioned, endophenotypes should be found in non-affected family members at a higher rate than in the general population, but heritability has not been conclusively demonstrated for the majority of functional parameters used. Imaging genetics paradigms must reach a higher threshold of heritability in order to be used as a putative

endophenotype, however there is currently limited data available to support endophenotypes outside of working memory.

2.2.6 Conclusion

Neuroimaging techniques offer a unique opportunity to explore the functional impact of brain-relevant genetic polymorphisms. It is expected that future research will increasingly focus on epistatic effects of multiple common variants of modest effect, account for the complexity of gene-environment interactions and characterize rare high risk structural variants. Further to this, the integration of research across disciplines, for example connecting human studies with animal models, will provide a more unified understanding of the biological and neural mechanisms that influence the aetiology and pathophysiology of schizophrenia (Casey et al., 2010).

It is estimated that 23% of variation in liability to schizophrenia is explained by common variants, providing support for an imaging genetic approach based on SNPs (Lee et al., 2012b). Given the polygenic nature of schizophrenia, summing the collective impact of multiple risk alleles to generate an overall genetic risk score is a novel and promising approach to identify individuals at risk of psychosis. Walton et al. (2012) derived a measure of cumulative genetic risk score, which combined the additive effects of 41 SNPs from 34 genes associated with schizophrenia, including DISC1 (Walton et al., 2012). Using genetic imaging, they investigated the effect of overall polygenic risk on functional activation during working memory. They found a relationship between genetic risk score and DLPFC inefficiency, which was not attributable to symptom severity. These findings suggest that genetic imaging of polygenic risk, using a widely accepted endophenotype, could be

advantageous compared to the study of single risk genes. With advances in computational modelling, future studies should aim to incorporate existing biological evidence and gene-gene interactions into this genetic risk score.

A promising development in the field of genetic imaging is the identification of novel genetic variants associated with pre-specified brain phenotypes of interest. This forward genetics strategy requires a combination of neuroimaging with genome-wide analysis, and requires relatively smaller sample sizes compared to using clinical phenotypes alone (Meyer-Lindenberg, 2010). For example, Potkin et al. (2009) discovered and verified the association of two novel genes, RSRC1 and ARHGAP18, not previously associated with schizophrenia (Potkin et al., 2009), using DLPFC activation as a phenotype. This approach should be further explored in post-mortem or animal studies in order to further evaluate the biological function of these novel variants, but has the potential to identify new molecular targets affecting brain systems linked to major psychiatric disorders.

Chapter 3: Aims and hypotheses

Chapter 3: Aims and hypotheses

The previous chapters introduced the two main areas of study in this thesis; episodic memory in psychosis, and genetic imaging and DISC1. This chapter aims to link the literature from these introductory chapters and provide justification for the current work. It will discuss the existing literature and knowledge about episodic memory and DISC1, and outline the overall aims and hypotheses of the current study.

3.1 The effects of genetic variation in DISC1

There are two main ways to examine the role of DISC1 in humans. First, genetic variation in DISC1 that occurs in the general population can be exploited to test whether common variants increase liability to develop psychiatric illness or have an impact on brain function. Second, the effect of rare variants such as the DISC1 t(1;11) translocation can be studied in depth, however this results in substantially smaller numbers of participants. The latter approach is the focus of the current work, however as the SFMHS is the first investigation into the effect of the translocation on several imaging modalities, we need to discuss the current knowledge gained from the first approach, looking into DISC1 SNPs.

3.2 Episodic memory and DISC1

There is currently limited research into the effect of DISC1 SNPs on episodic memory-related activation. A recent review by Duff et al. (2013) reviewed all human brain imaging studies of DISC1 in schizophrenia, bipolar disorder and depression, of which there were twenty-two at the time of publication. Of these, eight studies examined DISC1 variant effects on brain function using fMRI, and only two looked specifically at episodic memory, the remainder using tests of verbal fluency or working memory.

The two studies that investigated the effect of DISC1 variation of episodic memory, both looked at the Ser704Cys polymorphism, as previously outlined in chapter 2. Callicott et al. (2005) explored the impact of the Ser704Cys DISC1 polymorphism on declarative memory, using the same episodic memory task as the current work (Callicott et al., 2005). They found that healthy controls with the Ser allele (which was found to be over-transmitted in schizophrenic patients) showed decreased hippocampal activation during encoding and recognition, in comparison to Cyz homozygotes. Contrary to these findings, a further study by Di Giorgio et al. (2008) using the same task and investigating the same common variant, found that healthy controls with the Ser allele demonstrated increased activation of the hippocampus during encoding. Exploratory whole brain analyses also demonstrated increased activation in Ser subjects in temporal and frontal regions, including increased DLPFC activation and coupling with the hippocampus. So, whilst these studies begin to offer a clue about the effect of DISC1 on episodic memory function, further study is needed.

These studies only examined the effect of a single SNP. Studying a single common genetic variant may be problematic as little is known about the effect these small variations have on the complex biology of DISC1. The effect of one SNP may be relatively small, and may be interacting with many other unknown genetic variants. This may explain the contradictory results of the studies described above. Existing research into DISC1 and episodic memory has only investigated the Ser704Cys SNP, however there is no direct molecular evidence that this variant is functional and it may be a proxy for the actual causative loci in the gene (Callicott et al., 2005). Therefore, more robust effects may be found by examining other forms of variation within the DISC1 gene, such as the t(1;11)

translocation. Further to this, a recent meta-analysis found no evidence that common variants in DISC1, such as the Ser704Cys SNP, are markers for schizophrenia. However, evidence suggests that rare variants, such as the translocation, do show an association (Mathieson et al., 2012).

Previous research looking at DISC1 SNPs has done so in groups of healthy controls, patients with a range of psychiatric disorders, and those at high risk for illness. This is important to test whether effects of a single genetic variant vary depending on the presence or absence of other genetic and environmental effects. In a similar vein, it is also of interest to examine the effect of the translocation in carriers with a range of clinical diagnoses including schizophrenia, bipolar disorder, depression or no diagnosis, to determine if it is in fact the translocation that is causing an effect on brain activation, rather than the presence of a particular psychiatric condition. Therefore, this study aimed to recruit as many members of the family as possible to reflect the range of diagnoses present in this Scottish family. However, it is important to note that due to the rarity of this genetic alteration and the limited number of family members, this was somewhat out of the researcher's control.

Rare variants are likely to have larger neural effects and can offer a powerful method to further our understanding of the underlying neurobiology of psychiatric disorders. Specifically rare family-specific variants such as the translocation may play an important role due to the reduced genetic complexity present within families and the greater penetrance on endophenotypes. The endophenotype approach is further justification for why functional imaging was used in the current work. Research suggests that the penetrance of genetic effects is likely to be greater at the intermediate neural systems level

such as brain function, than at the level of behavioural performance on a cognitive task (Meyer-Lindenberg and Weinberger, 2006).

In conclusion, rare variants in DISC1 remain largely unexplored yet could provide valuable insight into DISC1 as a candidate gene for involvement in psychiatric conditions. The translocation has been shown to be associated with an increased risk of developing a major psychiatric disorder including schizophrenia, bipolar disorder and depression. Therefore, studying the translocation can help us to further understand the underlying biology of these conditions. The SFMHS aimed to expand on existing research into common DISC1 variants, to establish whether the translocation was associated with abnormalities in brain development and adult neuronal plasticity using structural and functional fMRI. As part of this same study, a group of healthy controls, patients with schizophrenia and patients with bipolar disorder were recruited, to compare the effects of the translocation to the effects of having a psychiatric illness, while minimising key confounds. Specifically the work in this thesis aimed to investigate the translocation in relation to episodic memory related brain activation using fMRI.

3.3 Why episodic memory?

Episodic memory was chosen as the cognitive function to investigate in the current work for several reasons, which will be discussed here. It should be noted that there are several other cognitive domains that would be of interest to investigate in relation to the DISC1 translocation. The wider SFMHS also investigated fMRI during a working memory task, however this data is not presented in the current thesis.

Previous research investigating the effect of DISC1 variation supports the idea that DISC1 increases risk for psychosis and that the mechanism of this effect may involve development and plasticity of the hippocampus (Callicott et al., 2005, Di Gorgio et al., 2008). Further to this, research suggests that DISC1 is expressed at high levels within the hippocampus (Ma et al., 2002), and there is evidence to suggest that it is pivotal during hippocampal development (Austin et al., 2004, Lee et al., 2015). Much remains to be investigated for DISC1, however the expression and function of DISC1 in the hippocampus, and evidence of hippocampal dysfunction in schizophrenia, gives the association between DISC1 and schizophrenia a biological appeal (Callicott et al., 2005). Therefore, it is of interest to investigate the effect of the DISC1 translocation, by measuring the impact on hippocampus-related intermediate phenotypes, and it was logical to select a task that is known to be dependent on the hippocampal formation, such as the episodic memory task used in this work.

The impact of DISC1 is not restricted to the hippocampus, as studies examining the effects of common variants in DISC1 suggest that variation at the DISC1 locus contributes to structural and functional changes across the brain, primarily in prefrontal and temporal regions (Duff et al., 2013). Patients with psychotic disorders exhibit functional and structural abnormalities in brain structures that sub-serve episodic memory, most notably and consistently in the prefrontal cortex and in the temporal lobe, which includes the hippocampus. Therefore, a risk gene for psychosis would be expected to influence the structure and function of these brain regions.

The current study aimed to investigate whether the DISC1 translocation influences brain activation primarily in prefrontal and temporal regions, which are key areas of episodic memory processing. The current task was chosen because it has been shown to activate regions including prefrontal (including DLPFC and VLPFC) and medial temporal regions, including the hippocampus.

Further to this, it is of interest to investigate episodic memory because it has been proposed to be a potential endophenotype. Episodic memory deficits are one of the most consistently reported findings in patients with schizophrenia and patients with bipolar disorder, and deficits are also evident in their unaffected relatives (Christodoulou et al., 2012). Episodic memory also appears to be a trait marker of illness and has shown to be linked to overall functional outcome (Nuechterlein et al., 2011, Green et al., 2000). Patients with schizophrenia and bipolar disorder show episodic memory related neural abnormalities in prefrontal and temporal regions (Ragland et al., 2009, Oertel-Knochel et al., 2014), which have also been demonstrated in unaffected relatives (Cannon et al., 2005) supporting a genetic basis for deficits in episodic memory function (Leavitt and Goldberg, 2009). Studying endophenotypes may help to bridge the gap between underlying genetic expression and clinical phenotypes, because the penetrance of genetic effects is likely to be greater at the intermediate systems level, such as brain function.

3.4 Why this episodic memory task?

The current task was chosen as it has been used in previous genetic imaging research (on DISC1 and other variants), and provides a point of reference between the current novel results and the wider literature. For example, it has been used to examine the effects of

DISC1 (Callicott et al., 2005), COMT (Bertolino et al., 2004, Di Giorgio et al., 2011), BDNF (Hariri et al., 2003, Baig et al., 2010) and NRG1 (Krug et al., 2010). Therefore, this task has previously been shown to be sensitive to effects of genetic variation.

This task has been used in previous studies examining episodic memory in a range of participant groups including healthy controls, patient groups, high risk groups, and has been shown to activate an extensive network of brain regions such as prefrontal (including DLPFC and VLPFC), cingulate, medial temporal and parietal regions (Hariri et al., 2003, Bertolino et al., 2006, Callicott et al., 2005, Stolz et al., 2012, Di Giorgio et al., 2008). This task has also consistently been shown to produce activation of the hippocampal formation (hippocampus and parahippocampal gyrus) during both encoding and recognition (Hariri et al., 2003). Further to this, this task requires a low cognitive demand, allowing it to be performed by participants with a wide range of abilities.

3.5 Overall aims and hypotheses

3.5.1 DISC1 t(1;11) translocation carriers and non-carriers

The aim of this study was to investigate the effect of the t(1;11) translocation by comparing functional activation during an encoding and recognition memory task in individuals with and without the translocation. The impact of this translocation on brain imaging measures is largely unknown, however this family offers a unique opportunity to examine the effects of this translocation.

It has previously been shown that there is a link between the t(1;11) translocation and several psychiatric disorders including schizophrenia and bipolar disorder, and this thesis

aimed to investigate the effect of the translocation on a putative endophenotype, episodic memory related activation. The analysis approach described in this chapter was chosen to simplify the reporting of results. No previous research has been carried out on this family to investigate functional brain activation, therefore the experiments reported in this thesis were exploratory and used a conservative whole brain approach.

It was hypothesised that episodic memory fMRI BOLD activation profiles would be abnormal in t(1;11) translocation carriers in contrast to related non-carriers. Given the known functions of DISC1 in vitro and in animal models, as well the heritability of certain brain regions and their involvement in psychosis, it was hypothesised that the translocation would have a measurable impact on brain activations in key areas associated with episodic memory. Research suggests that variation at the DISC1 locus contributes to structural and functional changes across the brain, primarily in prefrontal and temporal regions, specifically the hippocampus and PFC (Duff et al., 2013). Therefore, it was hypothesised that the translocation would impact upon hippocampal activation, based on expression of DISC1 in the hippocampus and evidence that allelic variation in this gene influences hippocampal function in humans (Callicott et al., 2005), and in the PFC. Prefrontal and hippocampal abnormalities are robust features of psychotic disorders and it is expected that a risk gene will influence the function of these brain regions.

3.5.2 Controls and Patients

As discussed in the literature review contained within chapter 1, the neuroimaging findings of episodic memory in patients are not straightforward and are somewhat contradictory with respect to hyper or hypoactivation of certain brain regions. Findings also depend on

the experimental setting and design, for example the task or stimuli used or patient population studied. However, for patients with schizophrenia the key regions involved in episodic memory appear to be prefrontal, including DLPFC, and medial temporal regions, specifically the hippocampus. The main findings in bipolar disorder seem to be hypoactivity in frontal regions, and more consistently hyperactivity in limbic brain regions involved in episodic memory processing. It was therefore hypothesised that in comparison to healthy controls, patients with schizophrenia would show abnormal activation in key regions associated with episodic memory including the hippocampus and prefrontal regions, specifically the DLPFC, whereas patients with bipolar disorder would show hyperactivity in limbic brain regions involved in episodic memory processing.

There are limited studies directly comparing episodic memory function between patients with schizophrenia and patients with bipolar disorder. However, based on the wider literature comparing these disorders, findings suggest an overactivation of MTL structures or limbic regions in bipolar disorder, and a relative underactivation of these structures in schizophrenia. It was therefore hypothesised that there would be a difference between these disorders at the functional level during episodic memory processing, specifically in MTL or limbic regions.

Chapter 4: Methodology

Chapter 4: Methodology

This chapter will detail the methodology for the two subsequent results chapters comparing (i) t(1;11) translocation carriers and non-carriers and (ii) patients and controls. The same assessments, fMRI task and data analysis were used in both experiments to compare different groups of participants, therefore methods for each of the results chapters have been combined. It will also outline recruitment, inclusion and exclusion criteria, and justification for inclusion of the different groups of participants.

4.1 Participants

Participants were recruited as part of a wider multimodal imaging study (SFMHS). The current study included three groups of participants;

1. Family members (with and without the t(1;11) translocation)
2. Patients (with schizophrenia or bipolar disorder)
3. Controls (with no history of serious mental disorder)

Participants who were aged 16 or over were eligible to take part, with no upper age restriction. This was the same across all groups of participants, in order to maximise the number of family members recruited. All participants were interviewed by an experienced psychiatrist and diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID) (First and Gibbon, 2004) and the Operational Criteria (OPCRIT) symptom check-list (McGuffin et al., 1991). All diagnoses were reviewed by a second psychiatrist. All participants received a detailed description of the study and provided written informed consent to participate in the trial. The study was approved by the Multicentre Research Ethics Committee for Scotland.

Exclusion criteria for each group were as follows:

Exclusion Criteria
For patients: - Impaired ability to provide informed consent to the study - MRI safety: potential participants could not take part if: o They had a cardiac pacemaker o Had metal fragments in or near their eyes o Had other magnetic metal implants - Current substance dependency - A history of major neurological disorders or serious brain injury
For controls: - As above for patients, with an additional criterion: o No history of psychosis, or diagnosed mental health problem based on the SCID or OPCRIT
For family members: - In order to maximise the number of family members recruited, the only exclusion criteria for this group were: o Impaired ability to provide informed consent to the study o MRI safety considerations (as described above)

Figure 4.1: Exclusion criteria

Participants excluded

A total of 132 subjects were recruited to the SFMHS. 17 subjects did not participate in the functional imaging protocol (for various reasons such as concerns about the scanner environment, unwillingness or unavailability), leaving 115 who completed the episodic memory paradigm. Of this number, 15 subjects were excluded, leaving 100 participants in the final analysis (see figure 4.2). Seven participants were excluded at the quality assurance stage due to poor scan quality. The reason for poor scan quality could have been due to several factors, for example poor positioning of the subject relative to the head coil, excessive motion causing significant image artefact, or incomplete scan data. Five scans

were excluded due to movement when examined in ArtRepair software, as they showed > 20% of volumes with excessive movement (further information provided in quality assurance section on page 122). Unfortunately these participants could not be rescanned due to time and financial restrictions.

Excluded participants (n = 15)
- **Carriers**: none excluded
- **Non-carriers**: 2 excluded due to; movement (n = 1) and incomplete scan data (n = 1)
- **Controls**: 2 excluded due to; movement (n = 1) and withdrawal of consent (n = 1)
- **Patients with schizophrenia**: 6 excluded due to; movement (n = 2), scan quality (n = 3), and invalid date due to participant being intoxicated during scanning session (n = 1)
- **Patients with bipolar disorder**: 5 excluded due to; movement (n = 1), scan quality (n = 4)

Figure 4.2: Excluded participants

It is of interest to test whether those who were excluded from the analysis differ from those who were included. From the 15 who were excluded, data is available for 14 participants (one individual withdrew consent and requested for their data to be destroyed). However, it should be noted that some of these participants did not complete certain clinical or cognitive assessments. There were no significant differences between the groups in terms of age, gender, premorbid IQ (NART), or manic symptoms (YMRS). The groups did differ on current IQ (WASI), with excluded individuals showing a lower IQ. They also differed on PANSS total score ($p = 0.027$), with excluded participants demonstrating higher scores, however they did not differ on the positive or negative subscale of the PANSS. There was

also a significant difference between groups on the HDRS with excluded participants demonstrating higher levels of depressive symptoms (p = 0.021). This group also had significantly lower GAF scores, reflecting lower overall functioning (p = 0.015). Therefore, it would appear that those participants who were excluded had worse symptomatology and this may explain why they were unable to provide usable fMRI data.

Table 1: Demographics, behavioural and clinical measures for included and excluded participants

	Included (n=100)	Excluded (n=14)	Between group comparison (T/U/X^2/F, p)
Demographic and Clinical Measures			
Mean age (years) (SD)	38.38 (14.54)	42.29 (14.88)	U = 595, 0.364*
Gender (M:F)	31:19	4:3	X^2 = 0.122, 0.727**
Mean NART score (SD)	109.77 (8.71)	106.2 (8.02)	T = 1.24, 0.219
Mean WASI score (SD)	107.68 (16.6)	95.8 (13.24)	**T = 2.25, 0.027**
Mean PANSS total score (SD)	40.72 (14.92)	55.92 (23.36)	**T = -2.56, 0.027**
Mean PANSS positive score (SD)	9.5 (4.06)	11.85 (6.2)	T = -1.65, 0.120
Mean PANSS negative score (SD)	9.35 (4.65)	12.42 (6.35)	T = -2.1, 0.054
Mean YMRS score (SD)	1.22 (2.94)	2.42 (4.12)	T = -1.27, 0.206
Mean HDRS score (SD)	4.17 (6.78)	8.86 (8.55)	**T = -2.34, 0.021**
Mean GAF score (SD)	72.12 (22.20)	55.61 (24.3)	**T = 2.47, 0.015**

**non parametric – Mann Whitney U ** Chi-square. Positive and negative symptom scale (PANSS), National adult reading test (NART), Young mania rating scale (YMRS), Hamilton depression rating scale (HDRS), Global assessment of functioning (GAF)*

Significant results highlighted in bold

It should be noted that no power calculation was performed to determine the appropriate sample size for the control and patient sample. For the family member comparison a power calculation was not appropriate due to the nature of the sample being studied, and therefore as many family members as possible were recruited. The limitations of not performing a power calculation are discussed later in chapter 7. However, it is reassuring that the current sample of controls (n = 40) and patients (n = 41) is larger than many previous studies using the same task. For example other studies have recruited group sizes of 12 vs. 16 (Callicot et al., 2005), 9 vs. 18 (Bertolino et al., 2006), 14 vs. 14 (Hariri et al., 2003), 22 vs. 16 vs. 28 (Stolz et al., 2012). Therefore, with a similar or greater sample size it was hoped that there would be a similar effect, without running an actual power analysis.

4.1.1 DISC1 t(1;11) translocation carriers and non-carriers

A large, previously reported Scottish kindred known to carry a unique genetic t(1;11) translocation (St Clair et al., 1990) were approached to participate. Researchers from the University of Edinburgh have been in contact with members of this family for several decades and through these original contacts, other family members were invited to participate in the current study. Due to the sensitive nature of the study for members of this family, a skilled research nurse was present at all study visits, with support from a psychologist if required. Inclusion criteria for this group was simply being a member of this unique family and ability to provide informed consent. The t(1;11) translocation status of each individual was then confirmed, dividing the group into those with and without the translocation. From the translocation carriers, all received a diagnosis of either recurrent major depression (n=2), single episode depression (n=2), cyclothymia (n=3) or conduct disorder (n=1). All non-carriers had no psychiatric diagnosis at time of testing.

Translocation status was tested on blood samples obtained from participants using polymerase chain reaction (PCR) based methods. This analysis was carried out by other members of the research team (please see appendix for further details).

A total of 30 members of this family took part in the study, 12 with the translocation, and 18 without. Of these, fMRI data was acquired during the episodic memory task for 8 translocation carriers, and 13 non-carriers. Two of the non-carriers were excluded (one due to movement artefacts and the other was unable to complete the scan thus leaving incomplete data) leaving 11 in total.

4.1.2 Patients (with schizophrenia or bipolar disorder)

A second group of participants consisted of patients with either schizophrenia or bipolar affective disorder. Inclusion criteria were having a diagnosis of either schizophrenia or bipolar disorder as determined by the SCID assessment, and being able to provide consent. This group was recruited from people who were in contact with secondary care mental health services Edinburgh. Consultant psychiatrists were approached to enquire whether people on their case load would be interested in taking part in the study. Once verbal consent was sought from the patient and their care team, the individual was approached by a researcher from the study team, who would provide further information about the study. It should be noted that all patients with bipolar disorder were euthymic at time of scanning, as determined by the SCID. This can also be reflected by the relatively low scores on the YMRS and HDRS in the bipolar group (see results section in chapter 6). Positive symptoms on the PANSS were also measured in all patients, including those with bipolar disorder, as a measure of psychotic symptoms.

In the patient group there was a mix of patients with schizophrenia and bipolar disorder, which reflects the range of conditions that the t(1;11) translocation was strongly associated with when the genetic association was first described, together with the evidence of overlapping genetic architecture between mood disorders and schizophrenia (Craddock and Owen, 2010). It is also in line with current approaches that look to investigate mental disorders not constrained by DSM diagnostic categories (Insel et al., 2010). Further to this, the recent revaluation of the extended family (Lawrie et al., In Press) found that linkage analysis yielded a log of the odds (LOD) score of 3.3 when the diagnosis was restricted to schizophrenia alone, a LOD score of 3.5 for only affective disorders (bipolar disorder and recurrent major depression), but a LOD score of 6.1 when including both cases of schizophrenia and bipolar disorder.

A total of 59 patients took part in the study, of which 52 were scanned during the episodic memory task. Of these, 11 scans were excluded; due to movement (n = 3), scan quality (n = 7), and one subject was excluded due to being intoxicated during the scan session. The final group therefore included 41 patients in the analysis, and consisted of 30 patients with schizophrenia and 11 patients with bipolar disorder. The recruitment of this group allows for the comparison of the effects of the t(1;11) translocation within the family to the effects of a having a psychotic illness, while minimising key confounds.

Medication status

From the subjects included in the analysis, twenty-seven patients with schizophrenia and four with bipolar disorder were treated with antipsychotic medication. Additional information regarding specific medication in the patient groups is provided in chapter 6.

All other patients, translocation carriers, non-carriers and healthy controls were un-medicated at the time of testing. The effect of antipsychotic medication was examined by converting different antipsychotic drug doses into chlorpromazine equivalents (CPZE) (Gardner et al., 2014).

4.1.3 Healthy controls

Healthy control subjects were recruited from the same geographical areas and social communities as both the patients and the t(1;11) kindred where possible. A primary source of recruitment was the Scottish Mental Health Research Register, which is a database of people who have previously agreed to be contacted about taking part in mental health research in Scotland. Other controls were recruited from the support network of patients who were involved in the study.

Research into how similar family members' brains are anatomically has suggested that certain areas are highly heritable (Glahn et al., 2007b). This means that direct comparisons between members of one family with a group of unrelated individuals would be significantly confounded by the shared heredity within the family. Therefore, direct comparisons between the t(1;11) kindred and patients or controls were not performed. The recruitment of the patient and control groups allows for the comparison of the effects of having a psychiatric disorder in general to the effects of the t(1;11) translocation within the family, without the need for direct comparisons between family members and patients. A total of 43 healthy controls took part in the study, 42 of which completed the episodic memory task. Two individuals were excluded (one withdrew consent, and one due to excessive movement in the scanner), leaving a total of 40 controls in the analysis.

4.2 Assessments

4.2.1 Clinical Measures

All participants were assessed using the Structured Clinical Interview for DSM-IV (SCID) and Positive and Negative Symptoms Scale (PANSS). The SCID is a structured clinical interview used to determine axis-1 psychiatric disorders, for example schizophrenia, bipolar disorder and MDD (First and Gibbon, 2004). The PANSS was developed by Kay, Fiszbein and Opler, (1987) to assess symptom severity in schizophrenia and other psychotic disorders (Kay et al., 1987). The PANSS is a 30 item, 7-point rating instrument that evaluates positive, negative and other general symptomatology on the basis of a formal semi-structured clinical interview and other informational sources. The positive and negative symptom subscales each consist of seven items (see figure 4.3). There is also a general subscale consisting of 16 items. This clinical interview was conducted by an experienced psychiatrist and took approximately 45 minutes to complete with each participant. Each item is rated on a 7-point rating scale, therefore the lowest possible total PANSS scores is 30. PANSS scores were obtained from all participants except 5 controls and 1 patient with bipolar disorder, who were unable to complete the assessment. When possible, symptom ratings took place within one week of the MRI scan.

PANSS subscales	
PANSS Positive items	**PANSS Negative items**
Delusions	Blunted affect
Conceptual disorganisation	Emotional withdrawal
Hallucinatory behaviour	Poor rapport
Excitement	Passive/apathetic social withdrawal
Grandiosity	Difficulty in abstract thinking
Suspiciousness/persecution	Lack of spontaneity and flow of conversation
Hostility	Stereotyped thinking

Figure 4.3: Positive and Negative Symptoms Scale subscale items

The Young mania rating scale (YMRS), Hamilton depression rating scale (HDRS) and global assessment of functioning (GAF) were also completed by a clinician for all participants. The YMRS (Young et al., 1978) consists of 11 items to measure the severity of manic symptoms and is based on the individuals' subjective report of their condition over the previous 48 hours and clinical observations during the interview. The HDRS, developed by Hamilton (1960), is a 17-item rating measure and is the most widely used depression assessment scale, assessing depressive symptoms over the past week (Hamilton, 1960). The GAF is a subjective clinician rating scale measuring an individual's overall level of functioning including social, occupational and psychological functioning. For example, it will consider how well or adaptively one is meeting various problems in life including work issues, interpersonal relationships, involvement in adequate activities, feelings of anxiety etc. This scale ranges from 0-100, with 100 representing superior functioning.

4.2.2 Cognitive Measures

Participants were administered two standardised neuropsychological measures to assess intelligence. The National Adult Reading Test (NART) (Blair and Spreen, 1989) measures pre-morbid intelligence and consists of 50 words that are irregular with respect to the common rules of pronunciation. It is administered by asking the participant to read each word out loud to the best of their ability. The total error score is obtained and then converted into a predicted full-scale IQ measure.

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1955) was administered to produce an estimate of general intelligence. The WASI consists of four subtests; 1) vocabulary (42 word items that the participant has to verbally define), 2) similarities (abstract verbal reasoning in which participants are required to assess how 26 sets of word pairs are alike), 3) block design (spatial perception in which a set of 13 geometric patterns have to be replicated using coloured cubes within a specific time limit), and 4) matrix reasoning (a measure of nonverbal abstract problem solving consisting of 35 incomplete grid patterns that the participant has to complete by selecting the correct response). Scores on these subtests are combined to create an overall measure of IQ, and take approximately 30 minutes in total to complete. WASI and NART data could not be collected for 4 individuals without the translocation, 2 healthy controls, 6 patients with schizophrenia, and 1 with bipolar disorder.

Clinical and cognitive measures were analysed using SPSS for windows (version 19.0, SPSS Inc., USA), using parametric tests when data met assumptions of normality (Shapiro-

Wilk test) and homogeneity of variance (Levene's test), or nonparametric tests when data did not meet these assumptions.

4.2.3 Polygenic risk score

Polygenic profile scores were generated from the whole genome sequencing data using the most recent Psychiatric Genomics Consortium summary GWAS reference data for schizophrenia (Ripke et al., 2011), bipolar disorder (Sklar et al., 2011) and MDD (Ripke et al., 2013). Polygenic scores were calculated according to the methods by Purcell et al. (2009) with the following adjustments. Polygenic profiling was performed using PLINK (an open-source whole genome association analysis toolset) (Chang et al., 2014) and as scoring was performed on a single family, no pruning for linkage disequilibrium was performed. As recommended by Dudbridge (2013), no p-value threshold was applied to the summary data, maximising the information retained. The author of this thesis did not carry out this analysis. Higher positive scores represent a higher polygenic risk of psychiatric illness. The number of variants scored in each individual was retained and used as a covariate in all analyses.

4.3 Functional magnetic resonance imaging protocol

Data for this thesis was collected as part of a wider multimodal imaging study (SFMHS) and included structural and functional MRI, spectroscopy, and diffusion tensor imaging measures. This thesis will present the results from fMRI episodic memory data.

4.3.1 Episodic memory paradigm

To test declarative memory, subjects performed an episodic memory task in the scanner that involved the encoding and subsequent recognition of novel, complex scenes. Prior to entering the scanner participants were given instructions by a research assistant to ensure they understood the task. They were told they would see a series of visual scenes and would be asked to judge whether each image represented an 'indoor' or 'outdoor' scene, by pressing the corresponding button to the instructions on screen. They were then told they would see a further set of scenes and would be asked whether they recalled the images by responding 'old' or 'new', again by pressing the corresponding trigger button. Participants were not explicitly instructed to memorize scenes during encoding for later recognition. They were also told that there would be a rest period between each set of scenes and to look at the cross displayed on screen during this time. They were informed that before each series of scenes there would be a brief instruction screen explaining what they had to do, to ensure continuous attention to the task.

This task has been used in previous studies examining episodic memory in a range of participant groups e.g. healthy controls, patient groups, high risk groups, and has been shown to activate an extensive network of brain regions such as prefrontal (including DLPFC and VLPFC), cingulate, medial temporal and parietal regions (Hariri et al., 2003, Bertolino et al., 2006, Callicott et al., 2005, Stolz et al., 2012, Di Giorgio et al., 2008). This task appears to activate a wide range of brain regions commonly associated with visuospatial information processing. Main effects of the task have also shown activation in the middle and medial frontal gyrus (BA 10), superior parietal lobule (BA 7), precuneus and the precentral gyrus (Stolz et al., 2012). This task has also consistently been shown to

produce activation of the hippocampal formation (hippocampus and parahippocampal gyrus) during both encoding and recognition (Hariri et al., 2003).

Variations of this task have been implemented using different stimuli for example verbal versions (Baig et al., 2010) and emotional stimuli or faces (Krug et al., 2010). Depending on the type of material to be encoded, other brain structures have been shown to be engaged including limbic regions, the amygdala, fusiform gyrus and parietal regions (Cabeza et al., 2002, Fernández and Tendolkar, 2001). This task has also been used to examine the effects of several genetic variants e.g. DISC1 (Callicott et al., 2005), COMT (Bertolino et al., 2004, Di Giorgio et al., 2011), BDNF (Hariri et al., 2003, Baig et al., 2010), NRG1 (Krug et al., 2010).

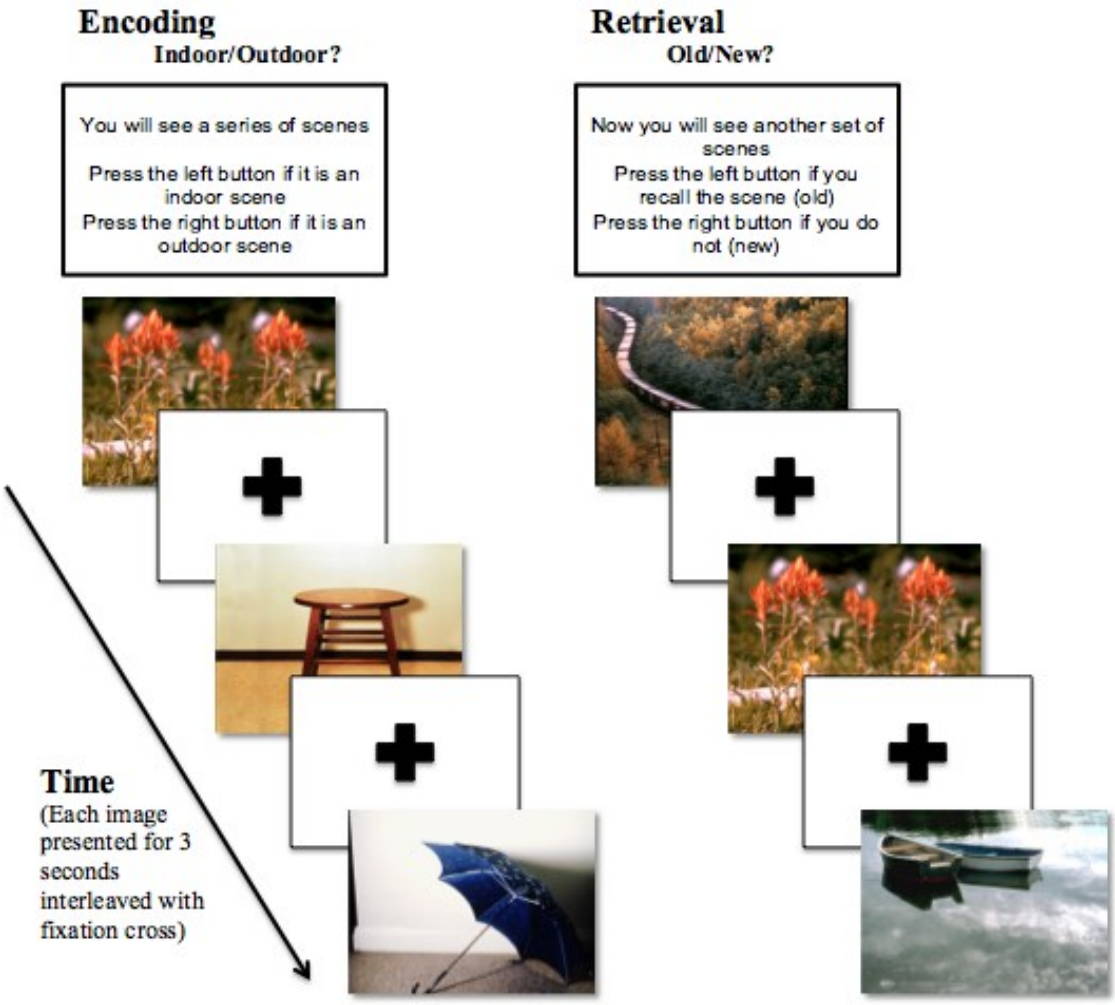


Figure 4.4: Encoding and recognition task design

Illustration of the encoding and recognition task described in this thesis. Images were interleaved with a baseline fixation cross. The task consisted of four blocks of encoding, followed by four blocks of recognition (see text for further details).

Stimuli were presented in a block design to maximize statistical power and sensitivity for BOLD signal change in this region. During encoding blocks participants were shown a series of visual scenes of neutral emotional valence, derived from the International Affective Picture System (Lang et al., 1997) and asked to judge whether each image represented an 'indoor' or 'outdoor' scene. During recognition blocks, subjects were presented with a further set of visual scenes and asked whether they recalled the images by

responding 'old' or 'new'; half of the images were 'old' (i.e. also presented during the encoding blocks) and the other half were 'new' (i.e. novel images) (figure 4.4). Prior to the start of each block, participants were shown a brief instruction asking them to respond by pressing the corresponding trigger button, which ensured continuous attention to the task and allowed for the determination of response accuracy and reaction time. The experimental paradigm was created and presented using Presentation software (https://www.neurobs.com) run on a Windows PC. The task was projected onto a screen, which subjects viewed using the goggles provided. The task was explained to participants prior to entering the scanner and an opportunity for questions was provided to ensure participants had a full understanding of the task.

The task consisted of four encoding blocks followed by four recognition blocks, interleaved with nine passive rest periods, during which participants were instructed to fixate on a centrally presented cross-hair. Each block lasted 20 sec and consisted of six images presented serially for three seconds each, resulting in a total of 48 images and 17 blocks, and a total scanning time of 5 minutes and 50 seconds. The images were presented in a random order throughout both the encoding and recognition conditions, and an equal number of 'indoor/outdoor' and 'old/new' scenes were shown in each block.

4.3.2 Behavioural data acquisition and processing

Behavioural performance and reaction time were recorded electronically with the Presentation programme. The dependent variable measuring performance on the episodic memory task was the percentage of correct responses. Percentage correct was calculated as the number of correct responses divided by the total possible correct responses, and was

determined for encoding and recognition conditions separately. Data was analysed using SPSS for windows (version 19.0, SPSS Inc., USA). Task performance was analysed using non-parametric tests (Kruskal–Wallis or Mann-Whitney U), as the data was not normally distributed. Mean reaction time in seconds across the whole experiment (encoding and recognition phases combined) was recorded for each participant and differences between groups were analysed using one-way ANOVA (in patients and controls) or independent samples t-test (t(1;11) carriers and non-carriers).

4.3.3 Scanning procedure

Functional imaging was carried out at the Clinical Research Imaging Centre for Scotland on a 3T Siemens Magnetom Verio Syngo MR scanner (Siemens, Erlangen, Germany). Structural images were acquired using T_1-weighted, magnetisation prepared rapid acquisition gradient echo (MP-RAGE) images prescribed parallel to the AC-PC line, providing 160 sagittal slices of 1.0mm thickness, field of view (FOV) 256mm x 256mm, matrix size 256 x 256. Further scan parameters were repetition time (TR) 2300ms, echo time (TE) 2.98ms, inversion time (TI) 900ms and a flip angle 9°. Functional data was acquired using an EPI sequence.

Functional data was acquired using a T_2* echo planar sequence sensitive to BOLD contrast, using the following parameters: axial orientation TR = 1560ms, TE = 26ms, matrix size 64 x 64, FOV 220mm x 220mm, 26 slices (slice thickness 4mm with a 1mm interslice gap) and voxel size 3.4 x 3.4 x 4.0mm. A total of 228 volumes were acquired, of which the first six volumes were discarded to avoid T1 saturation effects (to allow magnetisation to reach a steady state).

4.3.4 Image processing and Analysis

4.3.4.1 Pre-processing

Data processing and statistical analyses were performed using the standard SPM approach in SPM8 (Statistical Parametric Mapping: The Wellcome Department of Cognitive Neurology and collaborators, Institute of Neurology, London), running in Matlab version 7.13 (The MathWorks, Natick, MA). All functional volumes were spatially realigned to the mean volume in the series, normalised to MNI space (Montreal Neurological Institute template) and spatially smoothed with a 3-dimensional isotropic 8mm x 8mm x 8mhm full width half maximum (FWHM) Gaussian kernel. Functional data has a lower resolution and is not as detailed as the anatomical T1 image. Therefore, coregistration and segmentation steps were also performed using each individual's structural scan, to allow for better normalisation to the MNI template (see below for order of pre-processing stages).

Pre-processing stages:

- **Realignment:** for each participant the EPI volumes were realigned to the mean volume in the series, in order to correct for motion within each scan.
- **Coregistration:** each participant's anatomical scan was registered to their mean functional image.
- **Segmentation:** this stage separates the T1 image into CSF, white matter and grey matter, based on the MNI template. This information is required for normalisation.
- **Normalisation:** each participant's data was warped into MNI standard space in order to register images from different participants into roughly the same co-ordinate system. Normalisation of images from an individual scan is required before performing group comparisons.

- **Spatial smoothing:** this step averages the intensities of adjacent voxels to minimize residual inter-subject differences, and improves signal to noise ratio by removing high frequency information.

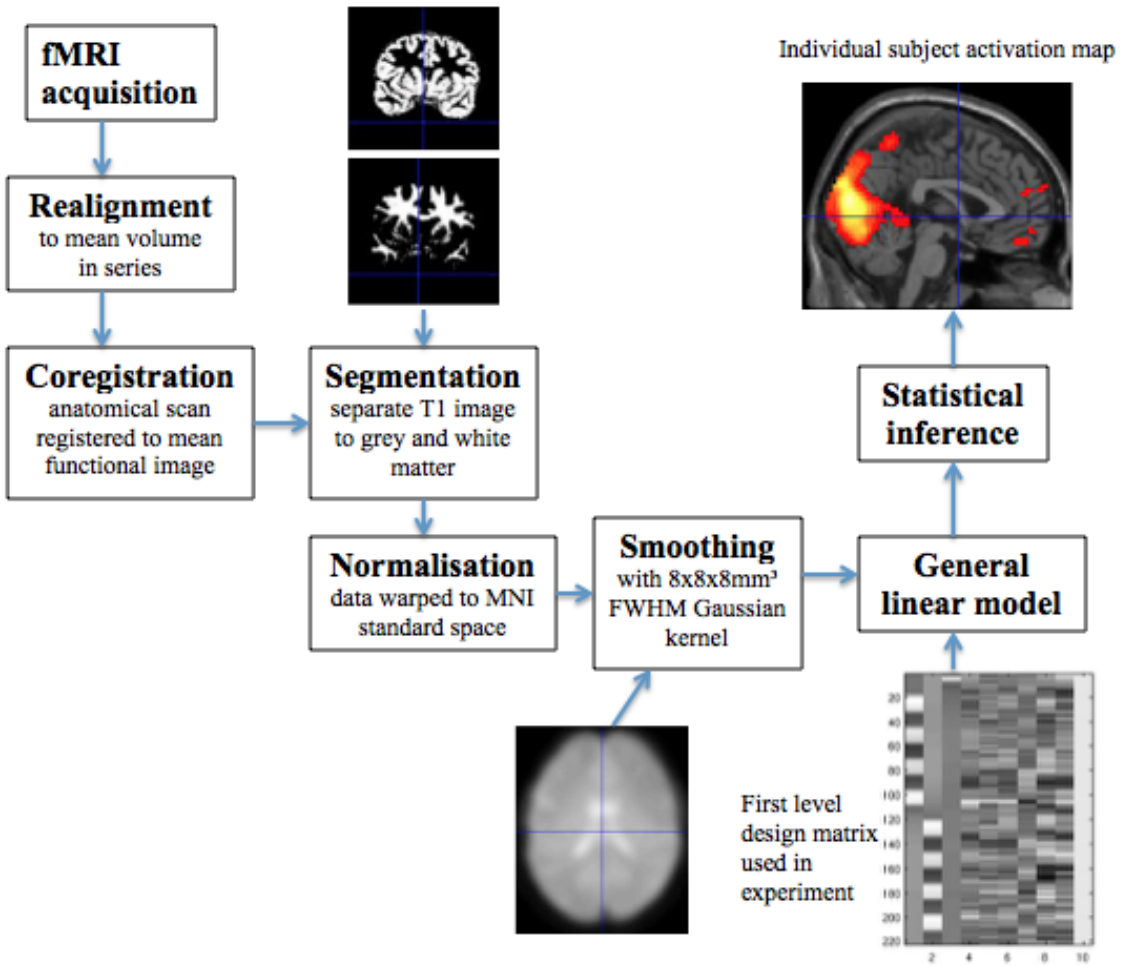


Figure 4.5: Pre-processing and first level analysis steps

4.3.4.2 Data quality and movement

To assess data quality, a quality assurance script was run in Matlab, after the pre-processing stage. This script produced a composite summary figure for each subject, to be visually inspected, to check image quality and to ensure that the image processing had been

successfully completed (see figure 4.6 for example). It displays motion parameter graphs, the raw functional and structural data before pre-processing, normalised data, and first level contrast (activation during baseline, to check subjects were engaged with the task). These were visually inspected for movement or any issues with the realignment or normalisation process, to identify if any subjects needed to be corrected for motion in ArtRepair or excluded. Seven subjects (three individuals with a diagnosis of schizophrenia and four with bipolar disorder) were excluded at this stage due to poor scan quality. The reason for poor scan quality was due to several factors, for example poor positioning of the subject relative to the head coil, excessive motion causing significant image artefact, or incomplete scan data. Unfortunately these participants could not be rescanned due to time and financial restrictions.

Subjects demonstrating excessive movement (>1.5mm motion per TR) at this stage were then examined further using ArtRepair software (Centre for Interdisciplinary Brain Sciences Research, Stanford University, Stanford, CA, USA). Volumes demonstrating >1.5mm of motion relative to the previous one were corrected by interpolating the immediately adjacent volumes (figure 4.7). These volumes were encoded as nuisances within the first-level general linear model (GLM). No more than 20% of the volumes were interpolated i.e. any subject with > 20% repaired volumes was excluded from the analysis. This is a standard threshold in the fMRI literature. Five scans were excluded due to this reason (one control subject, one non-carrier, two individuals with schizophrenia and one with bipolar disorder).

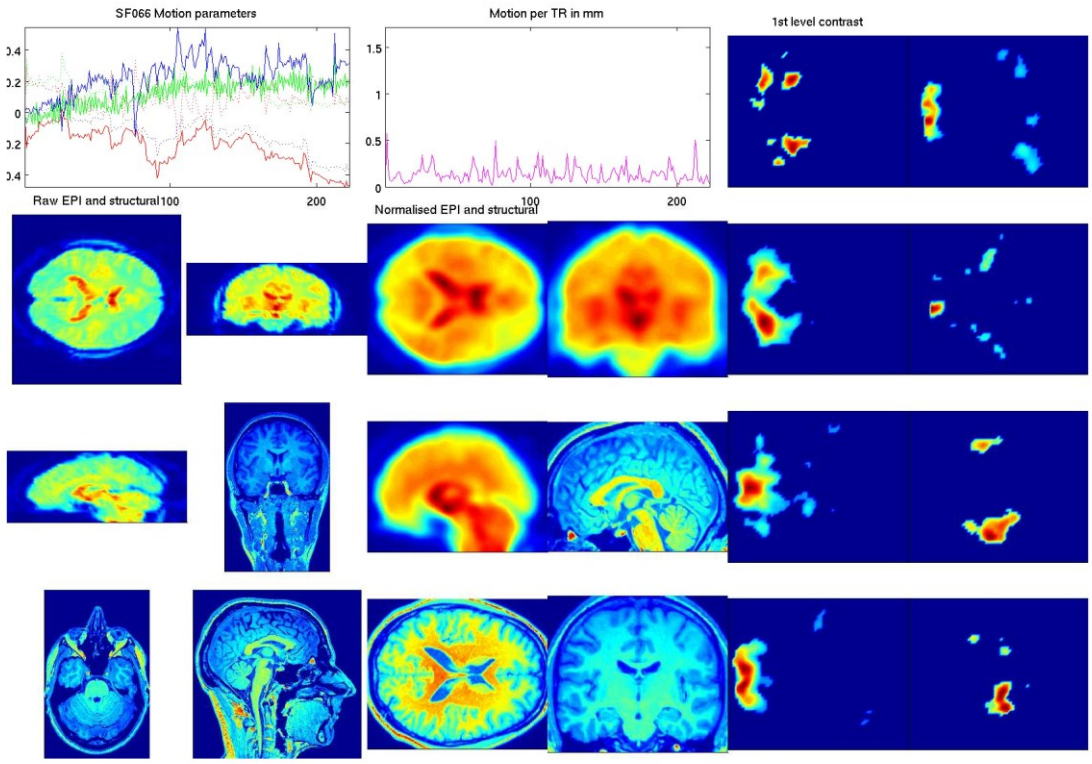


Figure 4.6: Subject output from quality assurance check

This output was created from the quality assurance script. It displays the raw functional and structural data before pre-processing (left), normalised data (centre), first level contrast (activation during baseline) (right), motion parameters (top left) and motion per TR (top centre) for one subject. With thanks to Liana Romaniuk for writing this script.

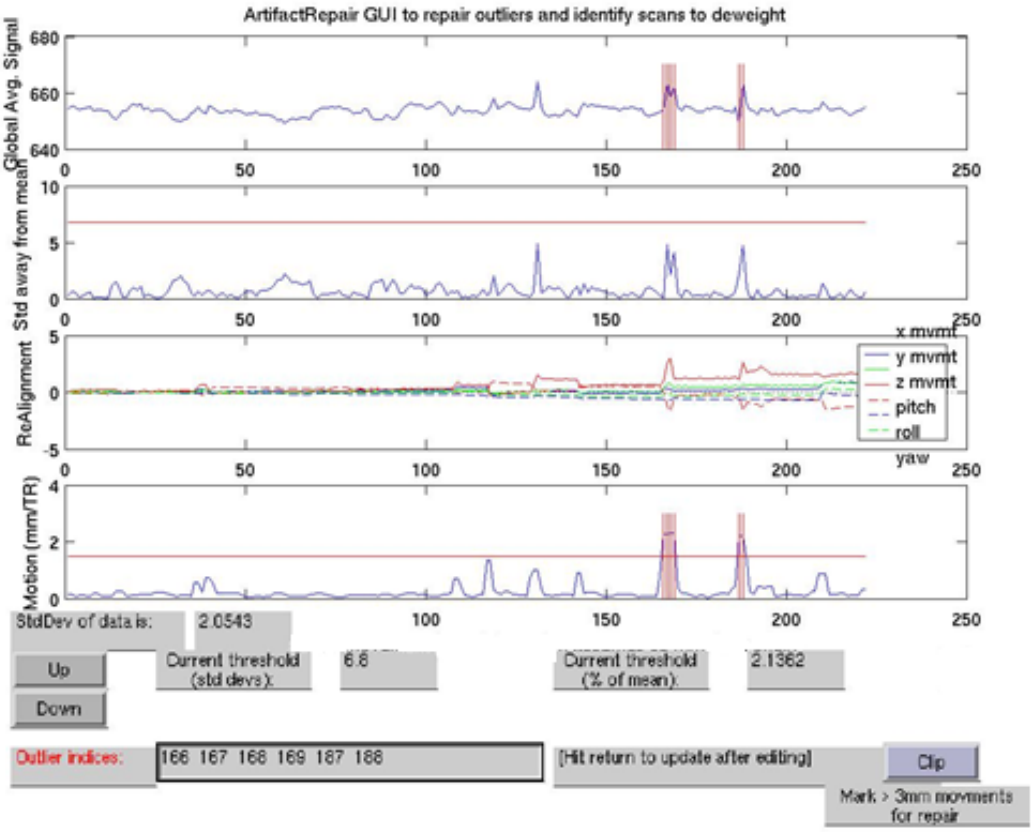


Figure 4.7: Subject output from ArtRepair

This output was generated using ArtRepair software. It identifies outlier volumes to be repaired for one subject ('outlier indices'). Volumes demonstrating >1.5mm of motion relative to the previous one were corrected by interpolating the immediately adjacent volumes.

4.3.4.3 First level analysis

Statistical analysis was performed using the general linear model approach as implemented in SPM8. Estimates of head movement from the realignment stage of pre-processing were included as additional regressors in the first level analysis. At the individual subject level the data were modelled with three conditions 'encoding', 'recognition' and 'baseline', each modelled by a boxcar convolved with a synthetic haemodynamic response function. Before fitting the model, the subject's data were filtered in the time domain using both a low-pass

(Gaussian kernel, 4 s FWHM) and a high-pass (400 s cut-off) filter. Due to the large number of participants that took part in this experiment, the pre-processing and 1st level analyses were performed using batch scripts. These scripts were pre-existing but tailored to the specific requirements of the current experiment.

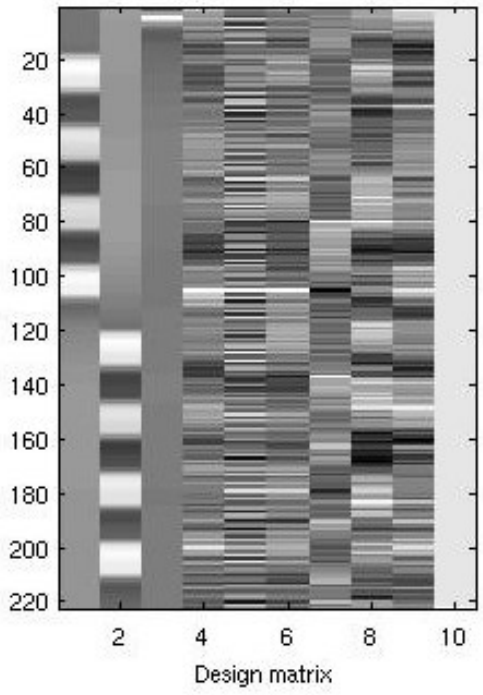


Figure 4.8: First level design matrix

The first 3 columns represent the 3 task conditions (encoding, recognition and baseline) and the remaining 6 represent the movement parameters (estimates of each subject's movement from the realignment stage of pre-processing – translations and rotations in x, y and z, were entered as covariates of no interest in the model). Numbers on y-axis represent images 1-220.

4.3.4.4 Second level analysis

All second level statistical analyses were conducted in SPM8. For each contrast of interest (encoding > baseline, recognition > baseline) one contrast image per subject was entered into a second-level random effects analysis to compare translocation carriers and non-

carriers, and to compare patients with healthy controls (two sample t-test). The encoding > baseline contrast examined activation during all scenes presented during the encoding phase versus baseline. The recognition > baseline contrast examined all scenes presented during the recognition phase (both old and new images) versus baseline.

Age was entered as a covariate in the second-level analysis when comparing individuals with and without the t(1;11) translocation, as this differed significantly between groups. Statistical maps were thresholded at a level of $p = 0.001$ uncorrected unless indicated (additional results are reported at a threshold of $p = 0.005$ uncorrected in the family analysis due to the small number of scans, and in the bipolar disorder analysis again due to small sample size). Regions were considered significant at $p < 0.05$ cluster level corrected for multiple comparisons across the whole brain volume. Cluster-extent based thresholding is considered to be the most common method for multiple comparison correction for whole brain analysis of statistical maps in fMRI studies. Cluster-level statistics take into account the spatial extent or width of the cluster (ke) when assessing significance, and accounts for the fact that voxel activations are not entirely independent of each other. In comparison, peak-level inference refers only to the height or intensity at one voxel. Therefore, the p-value is presented for the cluster rather than the peak voxel, and this was decided prior to analysis of the data. Based on prior reports regarding hippocampal involvement, small volume corrections (SVCs) were applied for region of interest (ROI) analyses in the hippocampus using the Wake Forest University (WFU) PickAtlas software. Co-ordinates are given using the MNI convention (http://www.mni.mcgill.ca). Brain regions were visualised using the MANGO software package (Multi-image Analysis GUI) (http://ric.uthscsa.edu/mango) and images from SPM are presented.

4.3.4.5 Correlation analyses

Whether any significant differences between the groups were associated with psychopathology (in all groups) or medication status (only in the patient and control analyses) was evaluated by looking at the relationship between functional activation and symptom severity ratings (PANSS total, positive and negative score, YMRS, HDRS and GAF) and antipsychotic medication dose (CPZE). Correlations between PRS score (for schizophrenia, bipolar disorder and major depressive disorder) and significant between group activations were also performed in the family (PRS data was only available in carriers and non-carriers). For these analyses, only areas that showed significant differences during the group comparison were investigated within each group. Activation data was extracted (for peak voxel of activation) from SPM for use in SPSS correlation analyses. Pearson correlations were carrier out in the control and patient samples as data met assumptions for parametric statistics, however Spearman's rank correlations were performed on the family member data as it did not meet the required assumptions. Correlation results are presented with and without correction for multiple comparisons, using false discovery rate (FDR) controlling procedures. FDR procedures have greater power than other methods of correcting for multiple comparisons such as Bonferroni. Bonferroni correction focuses on trying to reduce the familywise error rate, whereas FDR aims to reduce the rate of false discoveries. FDR correction ranks p-values in order of significance and applies a cut off p-value threshold, which is adjusted and reapplied for each significant result. For all correlations, p values were corrected using the Benjamini and Hochberg FDR procedure (1995), and considered significant when $p_{FDR} \leq .05$. This was conducted using SPSS syntax.

Chapter 5: Functional magnetic resonance imaging comparison of DISC1 t(1;11) translocation carriers and non-carriers

Chapter 5: Functional magnetic resonance imaging in the DISC1 t(1;11) translocation carriers and non-carriers

This chapter aims to describe the investigation of functional activation during an episodic memory paradigm in individuals with and without the DISC1 t(1;11) translocation, to examine the impact of this translocation.

5.1 Demographic details

Demographic and clinical data are summarized in table 2. The final fMRI sample comprised 19 members from the t(1;11) kindred, 8 with the translocation and 11 without the translocation. All translocation carriers received a diagnosis of either recurrent major depression (n = 2), single episode depression (n = 2), cyclothymia (n = 3) or conduct disorder (n = 1). Therefore individuals with the translocation appear to have diagnoses of an affective nature rather than schizophrenia-related psychosis. In the non-carrier group, none received a current or past mental health diagnosis. All carriers and non-carriers were un-medicated at the time of testing.

The mean age of the translocation carrier group was significantly higher than non-carriers ($p = 0.039$) and is therefore used as a covariate in the following analyses. There were no significant differences between the groups in terms of gender, current (WASI) and premorbid (NART) IQ, or on ratings of depression (HDRS). The groups did differ on PANSS total score ($p = 0.005$), which is expected due to the psychiatric diagnoses in the carrier group, however they did not differ on the positive or negative subscale of the PANSS. There was also a significant difference between groups on the YMRS with carriers demonstrating higher levels of manic symptoms ($p = 0.011$). The carriers also had

significantly lower GAF scores, reflecting lower overall functioning (p = 0.048). Symptom rating scales were obtained from all participants to determine whether any differences between the family members were related to an illness effect and/or a direct effect of the translocation.

Table 2: Demographics, behavioural and clinical measures in t(1;11) carriers and non-carriers

	Translocation carrier (n=8)	Non-carrier (n=11)	Between group comparison (T/U/X^2/F, p)
Demographic and Clinical Measures			
Mean age (years) (SD)	52.25 (16.82)	32.09 (18.68)	**U = 19, 0.039***
Gender (M:F)	1:1	6:5	X^2 = 0.038, 0.845**
Mean NART score (SD)	103.88 (4.29)	100.8 (4.09)	T = -1.28, 0.227
Mean WASI score (SD)	94.13 (13.13)	92.43 (11.46)	T = -0.265, 0.795
Mean PANSS total score (SD)	40.38 (9.81)	31.45 (3.24)	**U = 12.5, 0.005 ***
Mean PANSS positive score (SD)	8.5 (3.85)	7 (0)	U = 33, 0.088 *
Mean PANSS negative score (SD)	7.38 (1.06)	7 (0)	U = 38.5, 0.241*
Mean YMRS score (SD)	3.5 (6.89)	0 (0)	**U = 22, 0.011***
Mean HDRS score (SD)	3.75 (5.28)	1.27 (2.76)	U = 25, 0.087 *
Mean GAF score (SD)	80.63 (11.48)	89.5 (10.92)	**U = 18.5, 0.048***
Task Performance			
Mean encoding % correct (SD)	91.15 (13.82)	88.63 (6.88)	U = 26, 0.129 *
Mean recognition % correct (SD)	85.41 (21.60)	89 (15.62)	U = 34.5, 0.421 *
Mean reaction time (SD)	1.21 (0.28)	1.15 (0.26)	F = 0.2, 0.65

**non parametric – Mann Whitney U ** Chi-square. Positive and negative symptom scale (PANSS), National adult reading test (NART), Young mania rating scale (YMRS), Hamilton depression rating scale (HDRS), Global assessment of functioning (GAF)*

Significant results highlighted in bold

5.2 Episodic memory task performance

Episodic memory task performance data are shown in table 2 and figure 5.1. There were no significant differences between the groups in terms of their performance (% correct) on encoding ($p = 0.129$) and recognition conditions ($p = 0.421$). There was also no difference between groups on mean reaction time across the episodic memory paradigm ($p = 0.65$).

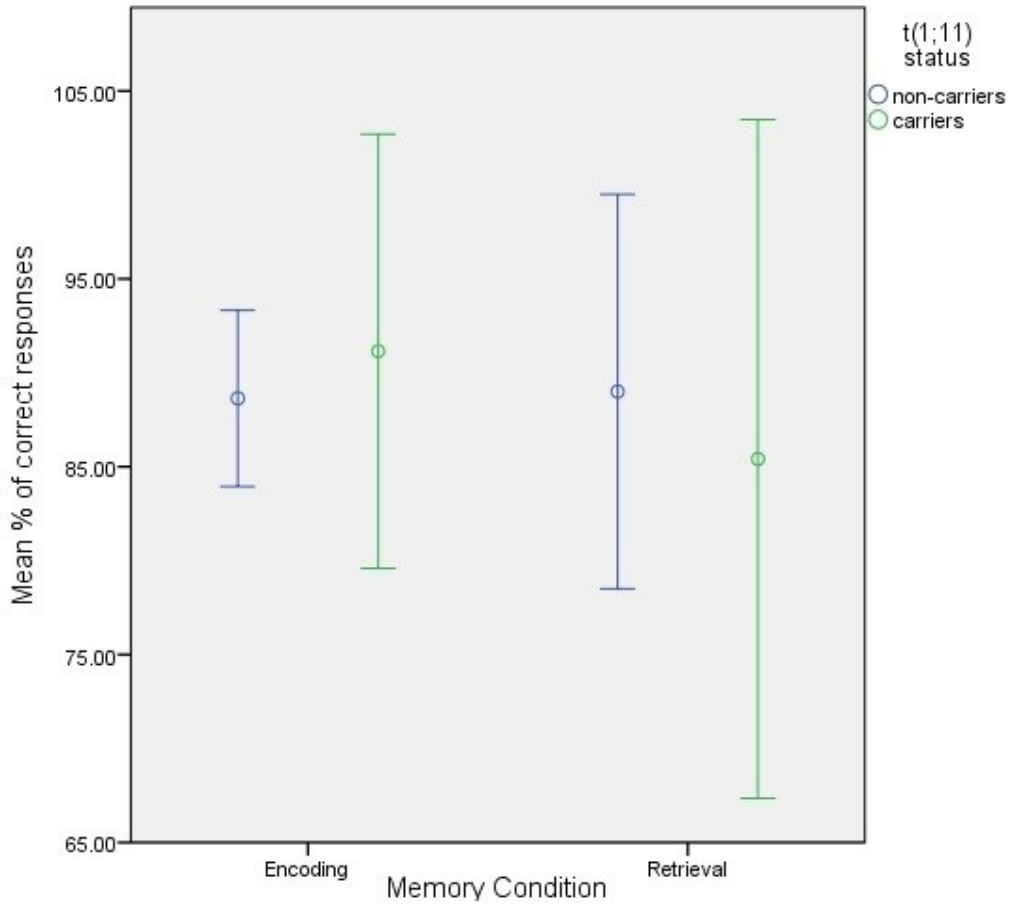


Figure 5.1: Episodic memory performance in t(1;11) carriers and non-carriers

Mean % of correct responses during encoding and recognition in individuals with and without the t(1;11) translocation (error bars: 95% CI).

fMRI results

For the imaging results, within group activations for encoding and recognition will be presented for each group in turn (carriers and non-carriers). Between group results will then be reported for encoding and recognition between groups. Statistical maps were thresholded at a level of $p = 0.001$ uncorrected (unless indicated at a level of $p = 0.005$ uncorrected due to small sample size) and regions were considered significant at $p < 0.05$ cluster level corrected for multiple comparisons across the whole brain volume. Brain regions were visualised using the MANGO software package and images from SPM are displayed. Mann-Whitney U nonparametric test revealed that there were no significant differences between the groups in terms of average motion per TR (mm) in the scanner ($p = 0.186$) (table 3).

Table 3: Mean motion per TR in t(1;11) carriers and non-carriers

	Translocation carrier (n=8)	Non-carrier (n=11)	Between group comparison (U, p)
Mean motion per TR (mm) (SD)	0.35 (0.17)	0.27 (0.21)	U = 28 0.186*

**non-parametric test used (Mann-Whitney U)*

5.3 Task-related activation - within group results

Tables 3 and 4 list the regions that were significantly activated during the encoding and recognition stages of the task within each group. Consistent with prior reports, significant activation of the hippocampal formation was found during both encoding and recognition in all subjects (using SVC for the hippocampus). For results of large clusters the threshold was set to $p < 0.0001$ to define more specific areas of activation.

5.3.1 Encoding

For the encoding > baseline contrast non-carriers showed clusters of activation in the inferior frontal lobe, cingulate gyrus and precentral gyrus. A large cluster with the peak voxel at the right parrahippocampus (30, -49, -11, $p < 0.001$) showed significant activation, encompassing the cerebellum, inferior parietal lobe and the cingulate gyrus. Significant activation was also found in a smaller cluster in the parrahippocampus when using a SVC. Translocation carriers showed bilateral inferior parietal gyrus, insula, inferior/middle frontal gyrus and precentral gyrus activation. Significant activation was found in a large cluster with the peak at the left middle occipital lobe (-15, -94, 16, $p < 0.001$), which covered multiple regions including the thalamus, fusiform gyrus and cingulate gyrus. Significant activation was also found in the bilateral hippocampus in carriers, when using a SVC (see table 4 and figure 5.2).

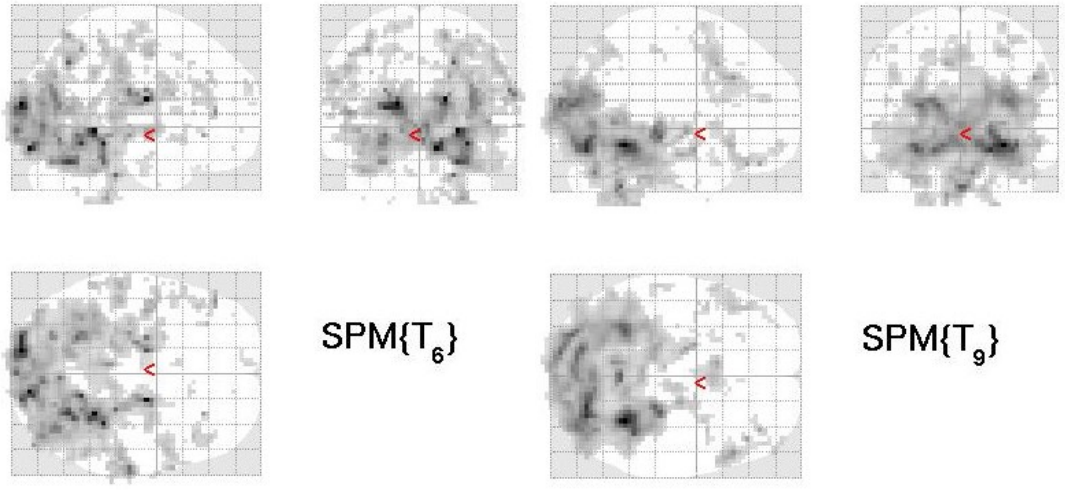
Table 4: Within group activations in t(1;11) translocation carriers and non-carriers during encoding

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann area
Encoding > Baseline				
Translocation carriers (n=8)				
<0.001	5486	5.19	-15, -94, 16	L middle occipital, 18
0.034	44	4.11	-42, -7, -2	L insula, 13
0.016	52	3.97	-48, -4, 49	L precentral gyrus, 4
<0.001	248	4.56	63, -19, 25	R inferior parietal gyrus, 40
<0.001	141	3.96	-60, -25, 31	L inferior parietal gyrus, 40
0.002	80	3.93	63, 11, 22	R inferior frontal gyrus, 9
0.014	54	3.75	42, 26, 16	R middle frontal gyrus, 46
0.004*	25	4.41	33, -37, -8	R hippocampus
0.049*	7	3.73	-27, -37, -5	L hippocampus

Table 4 continued

P value (cluster-level)	ke	Z	Peak height (x, y, z)	Peak voxel location, Brodmann area
Non-carriers (n=11)				
<0.001	6755	6.03	30, -49, -11	R parrahippocampus, 37
0.019*	17	4.37	-18, -28, -8	L parrahippocampus, 28
0.001	119	4.78	51, 26, 34	R precentral gyrus, 9
0.001	135	4.51	-9, 14, 43	L cingulate gyrus, 32
0.003	104	4.07	-45, 32, -20	L inferior frontal gyrus, 47

**thresholded at p=0.005 uncorrected*
Regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume



(a) Translocation carriers (b) non-carriers

Figure 5.2: Within group analysis in t(1;11) translocation carriers and non-carriers for encoding > baseline

Encoding versus baseline analysis within groups in (a) translocation carriers (n=8), (b) non-carriers (n = 11). Sagittal, axial and coronal sections displayed. Maps thresholded at p<0.001 uncorrected voxel level.

5.3.2 Recognition

For the recognition > baseline contrast non-carriers showed clusters of activation in the superior frontal gyrus and bilateral insula (right insula activation thresholded at p = 0.005 uncorrected). There was significant activation in a large cluster with peak voxel location at the right posterior cerebellum (21, -76, -14, p <0.001). This cluster covered several regions including the superior/inferior frontal gyrus, insula and precentral gyrus. Significant activation was also found in the bilateral parrahippocampus in non-carriers when using a SVC. Carriers showed bilateral activation in the lentiform nucleus, bilateral superior parietal gyrus, insula, superior frontal gyrus, bilateral precentral gyrus and middle frontal gyrus. Significant activation was also found in a smaller cluster in the right hippocampus when using a SVC (see table 5 and figure 5.3).

Table 5: Within group activations in t(1;11) carriers and non-carriers during recognition

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann area
Recognition > Baseline				
Translocation carriers (n=8)				
<0.001	297	5.85	21, 20, -7	R lentiform nucleus, sub-lobar
<0.001	210	4.11	-15, -7, -5	L lentiform nucleus, sub-lobar
<0.001	473	5.79	30, -61, 43	R superior parietal lobe, 7
<0.001	122	4.35	-36, -55, 55	L superior parietal lobe, 7
<0.001	111	4.54	36, 26, 4	R insula, 13
0.001	87	4.14	42, 44, 28	R superior frontal gyrus, 9
0.002	76	4.12	-48, -7, 46	L precentral gyrus, 4
0.013	53	4.03	30, -4, 55	R precentral gyrus, 6
0.001	80	4.01	42, 8, 31	R precentral gyrus, 0
0.028	45	3.91	36, 41, 10	R middle frontal gyrus, 10
0.043**	39	3.35	36, -25, -17	R hippocampus

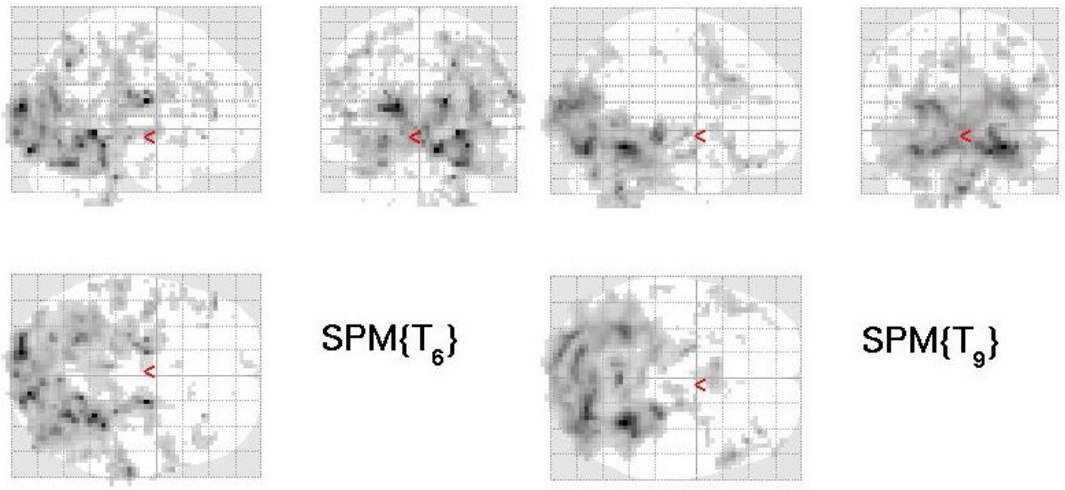
Table 5 continued

P value (cluster-level)	ke	Z	Peak height (x, y, z)	Peak voxel location, Brodmann area
Non-carriers (n=11)				
<0.001	5711	5.67	21, -76, -14	R posterior cerebellum
0.020	72	4.02	-30, 23, -2	L insula, 13
0.015	76	3.91	0, 14, 49	L superior frontal gyrus, 6
<0.001*	522	3.91	30, 26, 13	R insula, 13
0.002**	48	4.14	24, -28, -8	R parrahippocampus, 28
0.036**	11	3.67	-18, -28, -8	L parrahippocampus, 28

**thresholded at p = 0.005 uncorrected*

*** with SVC for hippocampus*

Regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume



(a) Translocation carriers (b) non-carriers

Figure 5.2: Within group analysis in t(1;11) translocation carriers and non-carriers for encoding > baseline

Encoding versus baseline analysis within groups in (a) translocation carriers (n=8), (b) non-carriers (n=11). Sagittal, axial and coronal sections displayed. Maps thresholded at p <0.001 uncorrected voxel level.

5.4 Between-group results

Between group comparisons for encoding and recognition contrasts are displayed in table 6. For both encoding and recognition contrasts, no regions were found to be more active in family members without the translocation compared to translocation carriers.

Table 6: Between group activations in t(1;11) translocation carriers and non-carriers during encoding and recognition

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann region
Encoding > Baseline				
Carriers > non-carriers				
0.001*	561	4.51	-15, -61, 16	L posterior cingulate, 30
0.02*	263	3.99	51, -37, -14	R fusiform gyrus, 37
0.022*	260	3.79	21, 59, 28	R superior frontal gyrus, 9
Recognition > Baseline				
Carriers > non-carriers				
0.012	108	4.92	57, -61, -17	R Fusiform gyrus, 37
0.001	164	4.46	-3, -85, -32	L posterior cerebellum,
0.007*	298	4.53	66, -10, 4	R superior temporal gyrus, 22
0.022*	237	4.29	-3, 50, -2	L anterior cingulate, 32
0.038*	209	4.22	30, 29, -11	R inferior frontal gyrus, 47 (VLPFC)
0.041*	206	3.83	39, 50, 28	R middle frontal gyrus, 9 (DLPFC)

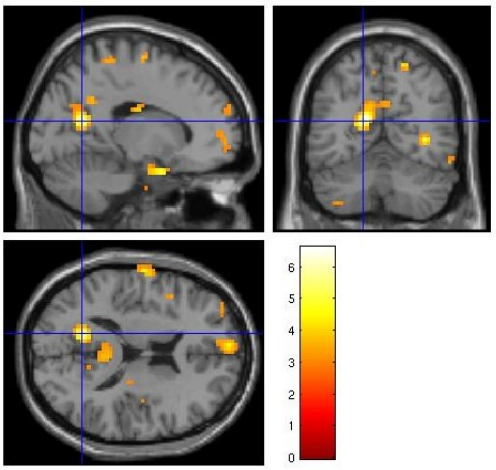
**thresholded at p = 0.005 uncorrected*

Reverse contrasts of non-carriers > carriers were not significant

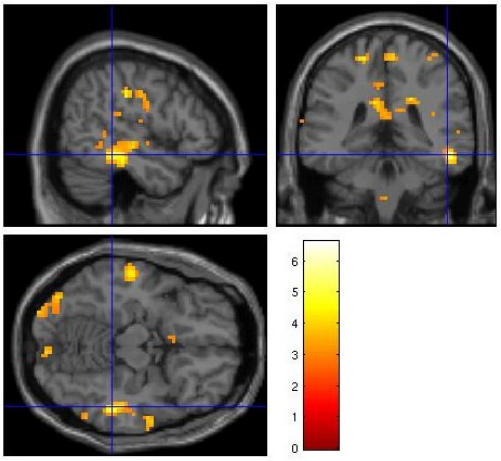
Regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume

5.4.1 Encoding

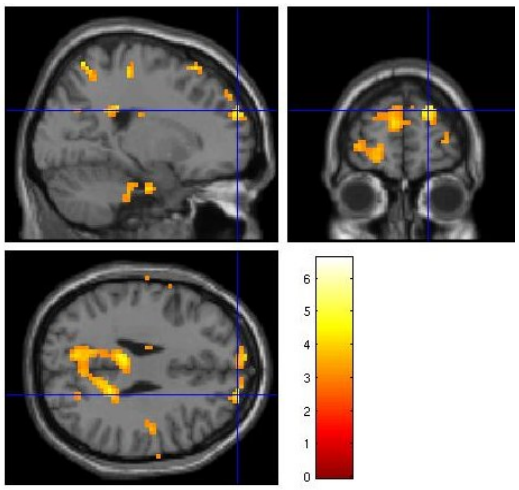
During encoding, translocation carriers showed greater activation in the left posterior cingulate, right fusiform gyrus, and right superior frontal gyrus (figure 5.4, 5.5 and 5.6).



(a) left posterior cingulate



(b) right fusiform gyrus



(c) right superior frontal gyrus

Figure 5.4: Between group results for encoding > baseline in t(1;11) translocation carriers > non-carriers

Effect of the t(1;11) translocation on fMRI activation during encoding. Encoding > baseline in carriers > non-carriers (p = 0.005) (a) left posterior cingulate (b) right fusiform gyrus (c) right superior frontal gyrus

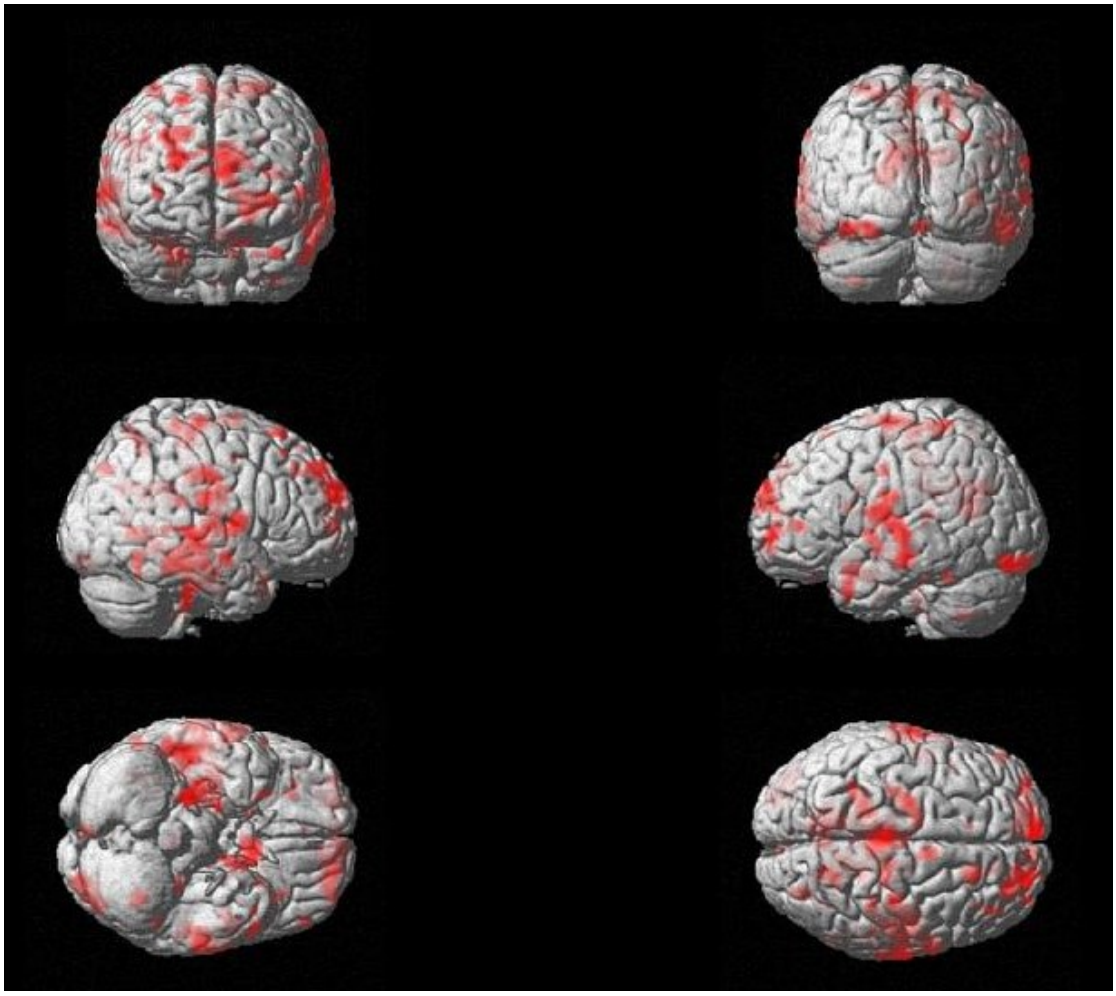


Figure: 5.5: Between group analysis for encoding > baseline in t(1;11) translocation carriers > non-carriers

Significant activations between groups (carriers > non-carriers) during encoding. Activations rendered on canonical brain T1 image

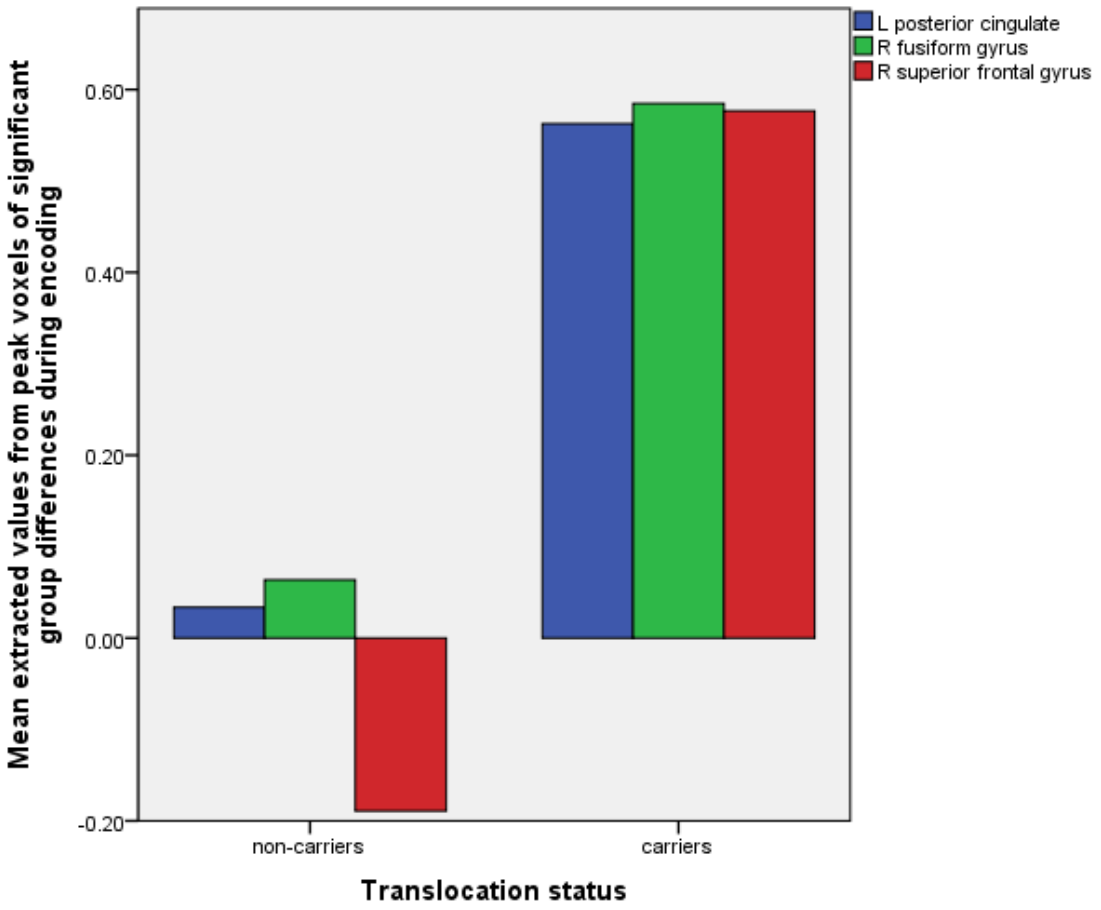
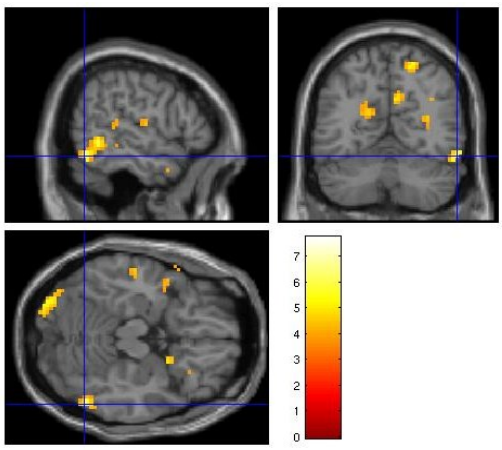


Figure 5.6: Extracted values from peak voxels of activation for between group differences during encoding

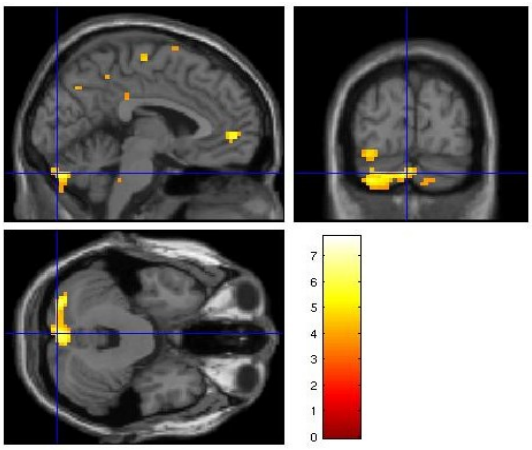
Extracted values from peak voxel in L posterior cingulate (-15, -61, 16), R fusiform gyrus (51, -37, -14) and R superior frontal gyrus (21, 59, 28) in non-carriers and carriers. Graph shows greater activation in carriers versus non-carriers

5.4.2 Recognition

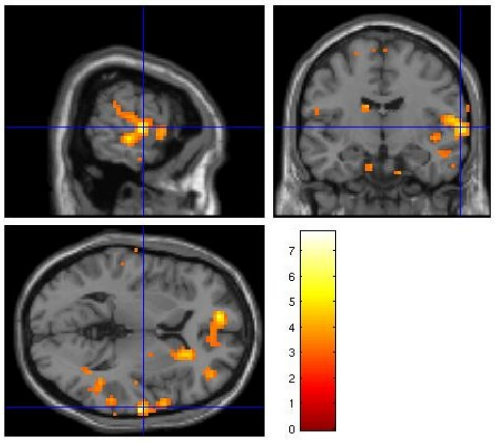
During recognition translocation carriers showed greater activation in six regions; the right fusiform, left posterior cerebellum, right superior temporal gyrus, left anterior cingulate, right inferior frontal gyrus and right middle frontal gyrus (figure 5.7, 5.8 and 5.9).



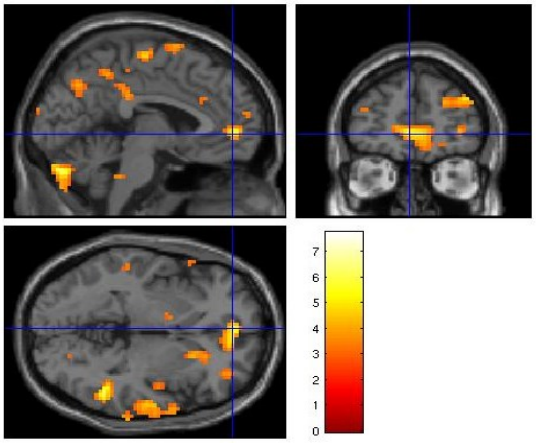
(a) right fusiform gyrus



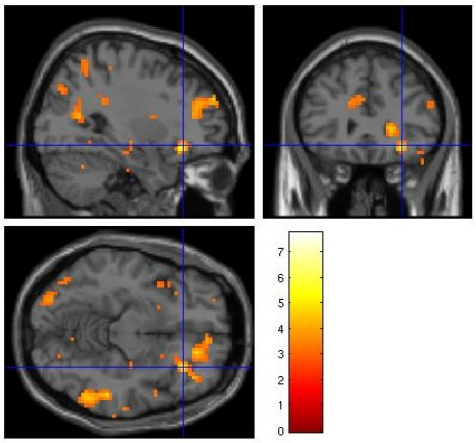
(b) left posterior cerebellum



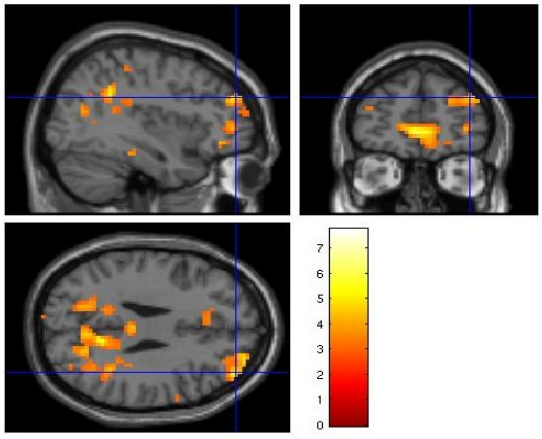
(c) right superior temporal gyrus



(d) left anterior cingulate cortex



(e) right inferior frontal gyrus



(f) right middle frontal gyrus

Figure 5.7: Between group results for recognition > baseline in t(1;11) translocation carriers > non-carriers

Effect of the t(1;11) translocation on fMRI activation during recognition. Recognition > baseline in carriers > non-carriers (p = 0.005)

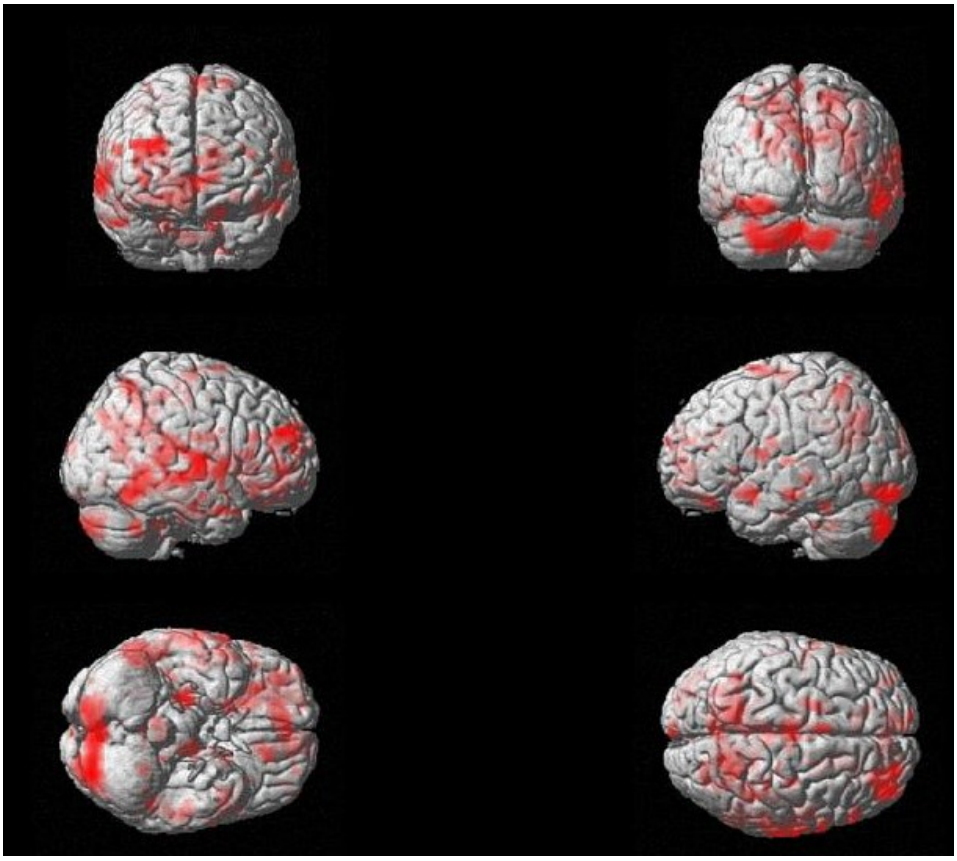


Figure 5.8: Between group analysis for recognition > baseline in t(1;11) translocation carriers > non-carriers

Significant activations between groups (carriers > non-carriers) during recognition. Activations rendered on canonical brain T1 image

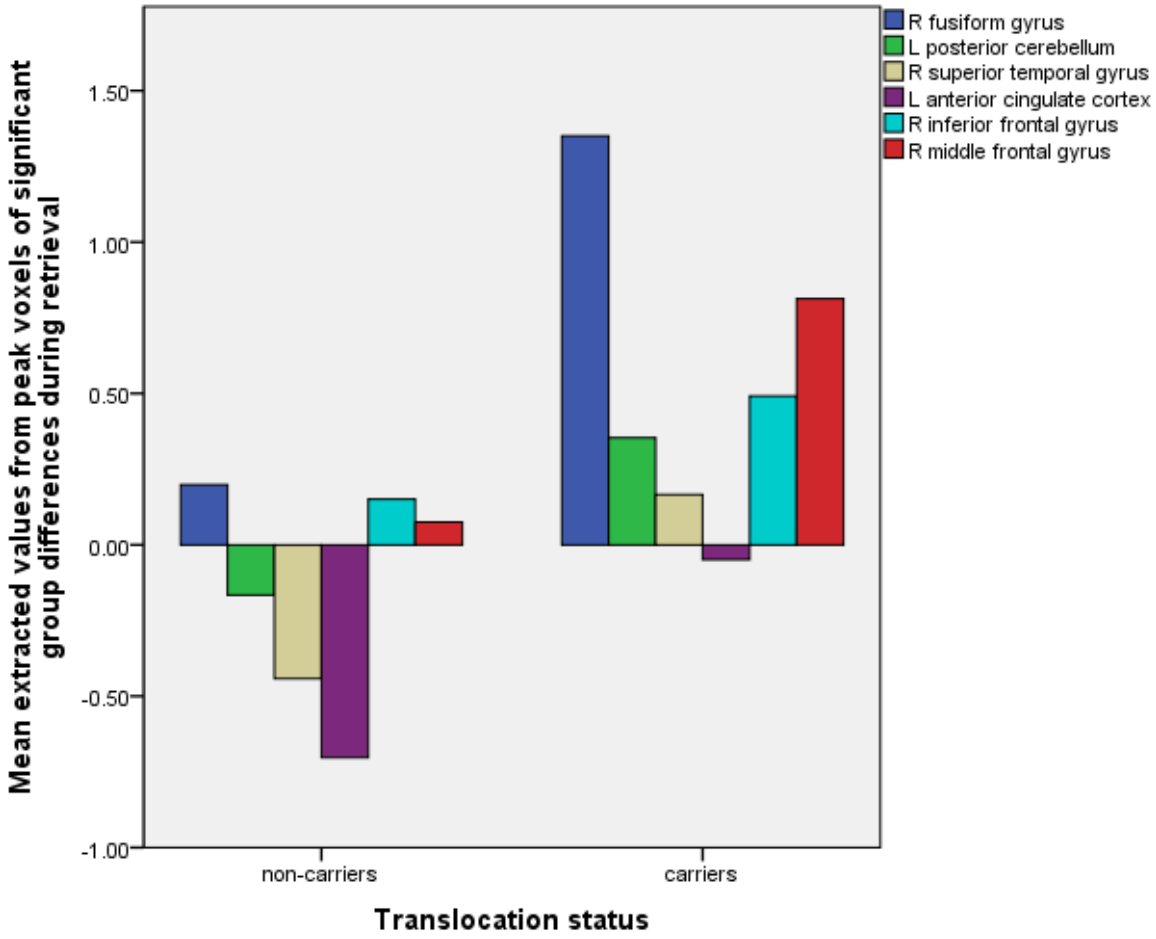


Figure 5.9: Extracted values from peak voxels of activation for between group differences during recognition

Extracted values from peak voxel in R fusiform gyrus (57, -61, -17), L posterior cerebellum (-3, -85, -32), R superior temporal gyrus (66, -10, 4), L anterior cingulate cortex (-3, 50, -2), R inferior frontal gyrus (30, 29, -11) and R middle frontal gyrus (39, 50, 28) in non-carriers and carriers. Graph shows greater activation in carriers versus non-carriers.

5.4.3 Post-hoc ROI analysis: hippocampus

Based on prior reports regarding hippocampal involvement in episodic memory, SVCs were applied for the hippocampus using the WFU PickAtlas software, however no significant hippocampal results were found.

5.4.4 Correlation analyses

Whether any differences between the groups were associated with psychopathology was evaluated by looking at the relationships between functional activation and symptom severity ratings using PANSS total score, PANSS positive, PANSS negative, YMRS, HDRS and GAF. For these analyses, activation data was extracted (for peak voxel of activation) from SPM for use in SPSS correlation analyses, in the areas that showed significant differences between groups (as shown in table 6). Spearman correlations were performed, as the data did not meet assumptions of normality. Exploratory correlations were examined for each group independently to avoid confounding the effects of group differences on correlation strengths. Correlation results are presented with and without correction for multiple comparisons (P-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq 0.05$).

5.4.4.1 Encoding

No correlations were significant during encoding in the carrier and non-carrier groups, between all imaging results (activation in the posterior cingulate, fusiform gyrus and superior frontal gyrus) and clinical measures (PANSS total score, PANSS positive, PANSS negative, YMRS, HDRS and GAF), all $p > 0.05$.

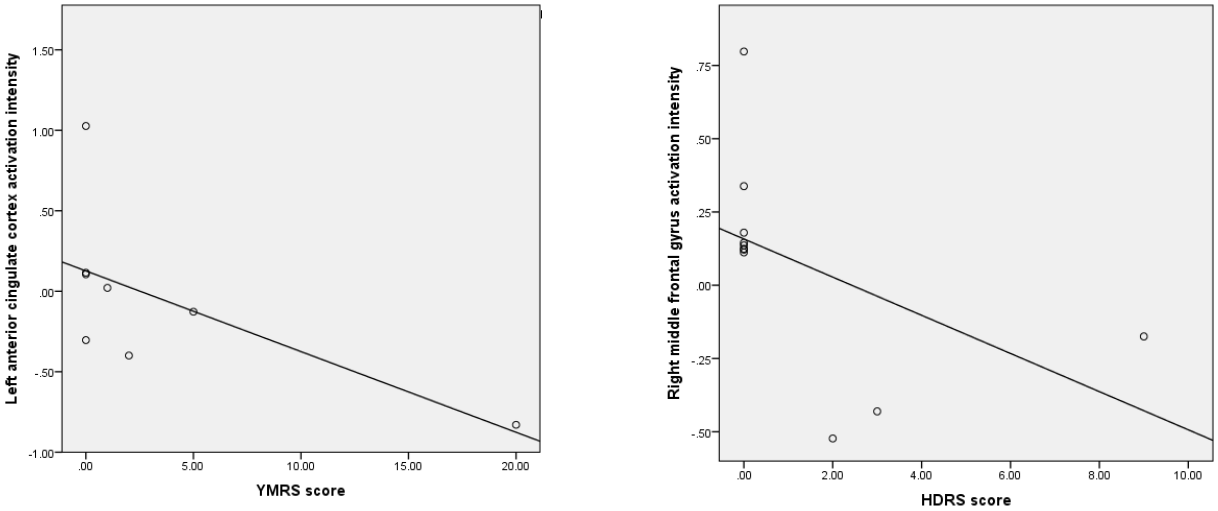
5.4.4.2 Recognition

In the carrier group, there was a significant negative correlation between activation in the left ACC and scores on the YMRS ($r_s(8) = -0.736$, p = 0.038), however this correlation did not survive FDR correction**.** In non-carriers, no correlation between activation in ACC and YMRS scores could be calculated because this clinical variable was constant across this group. In the non-carrier group there was a significant negative correlation between activation in the right middle frontal gyrus and scores on the HDRS ($r_s(11) = -0.740$, $p = 0.009$). This correlation survived FDR correction ($p_{FDR} = 0.009$), (see table 7 and figure 5.11). There was no significant correlation between carriers and activation in the right middle frontal gyrus (p = 0.740). No further correlations were significant between imaging data and other clinical measures during recognition (PANSS total, PANSS positive, PANSS negative and GAF, all p > 0.05).

Table 7: Correlations between clinical variables and significant between group activations during recognition

	L anterior cingulate cortex **Carrier group (n = 8)**	L anterior cingulate cortex **Non-carrier group (n = 11)**	R middle frontal gyrus **Carrier group (n = 8)**	R middle frontal gyrus **Non-carrier group (n = 11)**
PANSS total	p = .382, r_s = -.359	p = .509, r_s = -.224	p = .599, r_s = .117	p =.373, r_s = -.298
PANSS positive	p = .162, r_s = .546	n/a	p = .476, r_s = .296	n/a
PANSS negative	p = .861, r_s = .043	n/a	p = .310, r_s = .412	n/a
HDRS	p = .134, r_s = -.577	p = .196, r_s = -.422	p = .740, r_s = -.140	**pFDR = .009, r_s = -.740**
GAF	p = .379, r_s = -.361	p = .475, r_s = .325	p = .475, r_s = .385	p = 0.375, r_s = 0.315
YMRS	**p = .038, r_s = -.736 (pFDR not sig)**	n/a	p = .565, r_s = .241	n/a

r_s = Spearman rank-order correlation coefficient, ***significant results highlighted in bold***
n/a - correlations could not conducted because the clinical variable was constant



(a) carriers (b) non-carriers

Figure 5.11: Scatterplots showing correlations between extracted values and clinical measures during recognition in (a) carriers and (b) non-carriers

Graphs showing (a) significant negative correlation between YMRS total score and activation in the left anterior cingulate cortex (p = 0.038, r_s = -0.736) in carriers (n = 8) (b) significant positive correlation between HDRS score and activation in the right middle frontal gyrus (pFDR = 0.009, r_s = -0.740) in non-carriers (n = 11) during recognition. Result in carriers not FDR corrected.

5.4.5 Polygenic risk score

There was no difference between carriers and non-carriers in terms of their polygenic risk scores (PRS) for schizophrenia, bipolar disorder or major depressive disorder (all p > 0.05) (table 8). Partial correlations, controlling for the number of risk variants scored for each individual, were conducted to investigate the relationship between polygenic risk and imaging findings. There were no significant correlations between polygenic risk and imaging during encoding.

During recognition, when looking at the carrier group alone there were two significant correlations. There was a positive correlation between activation in the left ACC and PRS for bipolar disorder ($r_s(5) = 0.814$, $p = 0.026$), and between activation in the right superior

temporal gyrus and PRS for depression (r_s (5) = 0.775, p = 0.041) (table 9 and figure 5.12). However these correlations did not survive FDR correction procedures (p_{FDR} >0.05). There were no significant correlations in the non-carrier group (all p > 0.05).

Table 8: Polygenic risk scores for carriers and non-carriers

	Carriers (n=8)	Non-carrier (n=11)	Between group comparison (T/U, p)
Polygenic Risk Score			
PRS for Schizophrenia (SD)	0.0000024 (0.0000198)	0.0000111 (0.0000295)	t = 0.719, 0.482
PRS for Bipolar (SD)	0.00000424 (0.0000414)	0.000023 (0.0000439)	t = -0.943, 0.359
PRS for Depression (SD)	0.0000158 (0.0000242)	0.0000169 (0.000036)	U = 40.5, 0.772*

**non-parametric test used (Mann-Whitney U)*

Table 9: Correlations between polygenic risk scores and significant between group activations during recognition

	L anterior cingulate **Carrier group (n = 8)**	L anterior cingulate **Non carrier group (n = 11)**	R superior temporal gyrus **Carrier group (n = 8)**	R superior temporal gyrus **Non-carrier group (n=11)**
PRS schizophrenia	p = 0.760, r_s = 0.143	p = 0.463, r_s = -0.263	p = 0.835, r_s = -0.097	p = 0.483, r_s = 0.252
PRS bipolar disorder	**p = 0.026, r_s = 0.814 (pFDR not sig)**	p = 0.916, r_s = -0.039	p = 0.989, r_s = 0.006	p = 0.546, r_s = 0.217
PRS depression	p = 0.388, r_s = 0.390	p = 0.696, r_s = 0.142	**p = 0.041, r_s = 0.775 (pFDR not sig)**	p = 0.319, r_s = 0.352

r_s = *Spearman rank-order correlation coefficient, significant results highlighted in bold*

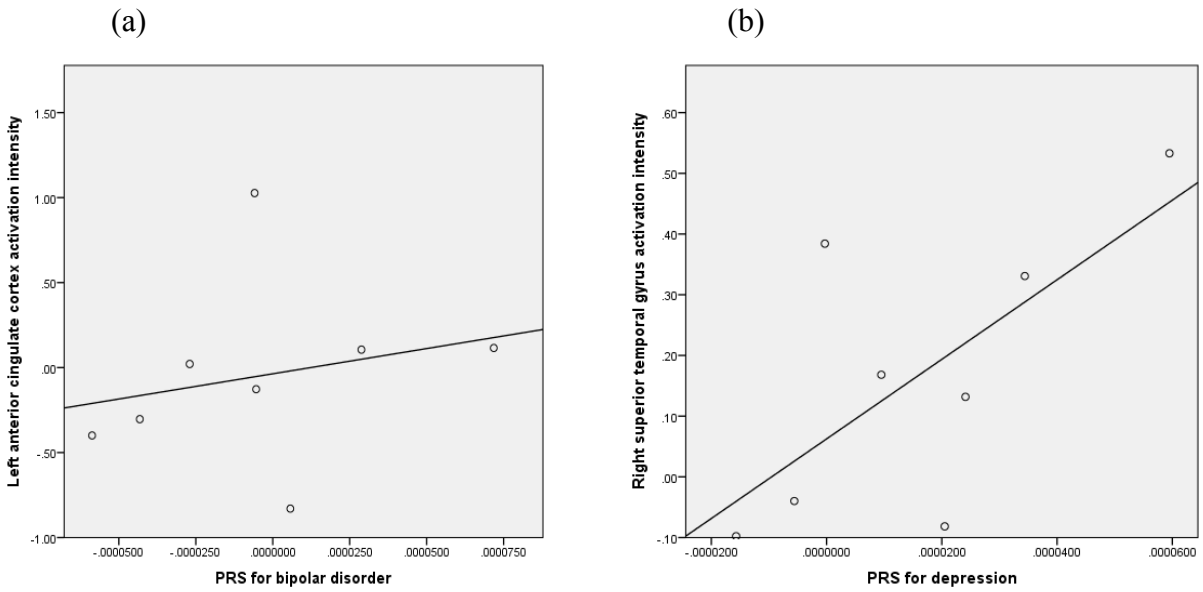


Figure 5.12: Scatterplots showing correlations between extracted values and PRS during recognition

Graphs showing significant positive correlation between (a) PRS for bipolar disorder and activation in the left anterior cingulate in carriers (n = 8) (b) PRS for depression and activation in the right superior temporal gyrus in carriers (n = 8). Results not FDR corrected.

5.5 Discussion

5.5.1 Summary of findings

This experiment used fMRI to investigate the BOLD response during an episodic encoding and recognition memory task in family members with and without the DISC1 t(1;11) translocation. During encoding of neutral scenes, carriers of the translocation showed greater activation of the left posterior cingulate, right fusiform gyrus and right superior frontal gyrus compared to non-carriers. During recognition, carriers showed greater activation in the right fusiform gyrus, left posterior cerebellum, right superior temporal gyrus, left anterior cingulate, right inferior frontal gyrus (VLPFC) and right middle frontal gyrus (DLPFC). For both contrasts, no regions were found to be more active in non-carriers than in translocation carriers. There were no significant differences between the groups in terms of their performance on encoding and recognition conditions. The mean age of the carriers was significantly higher than non-carriers and was therefore included as a covariate in the analysis.

Regions that were found to be over-active in carriers have been shown to be involved in memory encoding and recognition processing, and activation differences have been found in patients with schizophrenia and bipolar disorder, as will be discussed in this chapter. These findings begin to provide a better understanding of the neural effects of the t(1;11) translocation and support a role for the DISC1 translocation in episodic memory related brain activation.

This section will first discuss the sample of translocation carriers included in the analyses and justify why it is still relevant to discuss the current findings in relation to psychosis. It

will then discuss each significant between group result in carriers vs. non-carriers during encoding and recognition, focusing on the general function of each brain region, any evidence of an effect of DISC1 on the structure or function of each region, and finally its association with schizophrenia or bipolar disorder. It will then discuss limitations and strengths of the current experiment and future research considerations.

5.5.2 Translocation carriers

The current sample of family members with the translocation that took part all had a diagnosis of an affective nature ranging from MDD to cyclothymia, rather than a psychotic illness such as schizophrenia or bipolar disorder. This was not anticipated and is not representative of the wider family. From the recent re-evaluation of the family as part of the SFMHS, it can be noted that there has been a substantial increase in the proportion of translocation carriers with a diagnosis of schizophrenia since the original discovery of the family. Additional carriers that were recruited to the SFMHS had a diagnosis of either schizophrenia or bipolar disorder, however unfortunately they did not manage to complete the imaging section of the study. The sample of carriers who took part in the current study is discussed further as a limitation in chapter 7.

It was planned to compare the effect of the t(1;11) translocation to that of having a psychotic disorder, therefore the current results will still be discussed in relation to schizophrenia and bipolar disorder, despite the affective diagnoses in the carrier group. This is because the translocation is associated with a range of clinical outcomes in the family, but has been proposed to have a more homogeneous effect on imaging measures. Previous research has found an effect of the translocation on brain function similar to that of patients with

schizophrenia. Blackwood et al., (2001) found that translocation carriers (with a range of diagnoses including schizophrenia, depression or no diagnosis/symptoms) were similar to patients with schizophrenia on measures of P300 amplitude and latency, but differed significantly from non-carriers and controls. Further to this, they still found an effect of the translocation similar to that of schizophrenia, even when they only included carriers without a clinical diagnosis. Therefore, significant changes in the amplitude and the latency of P300 in translocation carriers appears not to be restricted to individuals with a psychiatric diagnosis, suggesting a trait marker of risk rather than state markers reflecting the presence of symptoms.

These findings, together with the results from the wider SFMHS, suggest that the presence of the translocation may result in disturbances of brain function in all individuals, even though it only leads to major psychotic illness in a subgroup, presumably due to other interacting genetic (including structural genetic variants and polygenic risk loads) and environmental factors. As will be discussed in chapter 7, results from the SFMHS suggest a greater genetic impact upon neurobiological measures than clinical phenotypes, which is consistent with the previous P300 event-related potential results by Blackwood et al. (2001). These findings support the interpretation that the brain imaging abnormalities evident in the t(1;11) carriers are primarily genetic in origin and confer risk across a range of phenotypes. Based on this approach, although the current affective diagnoses in the carrier group are acknowledged as a potential limitation, this may not be as problematic as first thought.

Further to this, there is substantial evidence in the literature to suggest that DISC1 is implicated in both schizophrenia and bipolar disorder (Ekelund et al., 2000, Hennah et al., 2003, Thomson et al., 2005), so it is still of interest to compare the effect of the translocation to that of having a psychotic disorder, regardless of carriers clinical diagnosis. A challenge now will be to determine why the outcomes of DISC1 dysfunction are so variable, and why some individuals with the translocation are protected (Thomson et al., 2013). Therefore, although it is important to acknowledge that none of the carriers included in this study had a diagnosis of schizophrenia or bipolar disorder, it is still relevant to compare the effect of the translocation to that of having a psychotic disorder.

However, it is still important to note that two explanations for the current findings are possible; the effect of the mental health disorders experienced by the carriers could be impacting brain function, or the translocation itself could be having the effect. The significant imaging findings were not correlated with psychotic or affective psychopathology in the carrier group, suggesting that the increased activation during episodic memory processing is due to the effects of the t(1;11) translocation, rather than the effects of having a disorder. This study is however unable to conclusively determine which explanation is correct and a more detailed evaluation of the family would be needed. However, the current results provide insight into the potential effect of the translocation.

5.5.3 Encoding

During encoding translocation carriers showed greater activation of the left posterior cingulate, right fusiform gyrus and right superior frontal gyrus compared to non-carriers.

5.5.3.1 Posterior cingulate cortex

The posterior cingulate cortex (PCC) has been shown to play an important role in cognition although there is no clear consensus regarding its function (Leech and Sharp, 2014). The PCC is a key part of the default mode network (DMN), which generally shows greater activation during periods of rest or internal thought, as well as deactivation during cognitive tasks requiring external attention (Buckner et al., 2008). This pattern of activation has been reported for a range of cognitive paradigms including a visual detection task (Singh and Fawcett, 2008). Episodic memory can be considered as internally directed cognition e.g. autobiographical memories, therefore increased activation in this network has been found during episodic memory recognition, specifically in posterior nodes (Sestieri et al., 2011, Spreng and Grady, 2010).

The DISC1 Ser704Cys polymorphism has been associated with reduced PCC volume. For example, one study found that healthy individuals carrying the Cys allele demonstrated gray matter reduction in this region, compared to Ser carriers (Hashimoto et al., 2006). Reductions in this region were found in addition to reduced bilateral ACC and cingulate gyrus grey matter volume. There are no current functional imaging results showing an effect of DISC1 on this region.

A failure to deactivate this network has been associated with cognitive impairment and is evident in many psychiatric disorders including schizophrenia (Kim et al., 2009, Pomarol-Clotet et al., 2008, Salgado-Pineda et al., 2011). A mixed pattern of findings in schizophrenia has been reported with studies either reporting greater deactivation of certain regions of the DMN compared to controls (Harrison et al., 2007), or a failure to deactivate

other regions, including the PCC (Garrity et al., 2007). Neuroimaging studies have found abnormalities of the structure of the PCC, primarily reduced gray matter volume (Pol et al., 2001, Koo et al., 2008), and its white matter connections in schizophrenia (Fujiwara et al., 2007).

5.5.3.2 Fusiform gyrus

Increased activation in translocation carriers was found during both the encoding and recognition of neutral scenes, in the right fusiform gyrus. The fusiform gyrus is part of the occipitotemporal lobe and is typically associated with facial recognition (Kanwisher et al., 1997, Cabeza and Nyberg, 2000). However, there have been reports of activation during the processing of visual stimuli including scenes (Stern et al., 1996, Gabrieli et al., 1997), and object recognition (Ishai et al., 1999, Chao et al., 1999). Co-activation of the fusiform gyrus and hippocampus has also been found during encoding of novel visual stimuli (Rand-Giovannetti et al., 2006, Golby et al., 2005), and a recent study by Smith et al. (2009) identified a pathway connecting the mid-fusiform and the amygdala/hippocampus that is important in object recognition (Smith et al., 2009). The fusiform gyrus may also be involved in novelty detection, (Tulving et al., 1996, Kirchhoff et al., 2000), which may support the current findings as novel visual scenes were presented during both encoding (all scenes) and recognition (of which half of the stimuli presented were 'new' scenes).

Previous research has found an effect of the DISC1 Ser704Cys polymorphism on grey matter volume in the fusiform gyrus (Di Giorgio et al., 2008). This study found a positive correlation between the number of Ser alleles and gray matter volume in bilateral fusiform gyrus in healthy individuals. An association between activation in this region has also been

found with other susceptibility genes for schizophrenia. For example, increased activation in the fusiform gyrus during episodic memory encoding has been associated with NRG1 genotype (Krug et al., 2010), which has been shown to interact with DISC1 (Mata et al., 2010).

Previous research has found activation in the fusiform gyrus during a novel picture encoding task in healthy controls (Stern et al., 1996), highlighting the importance of this region for visual object recognition. A further study using the same picture encoding task compared activation of patients with schizophrenia and controls using fMRI, and found decreased activation in the fusiform gyrus in their patient group (Zorrilla et al., 2003). Structural imaging studies have also revealed a reduction in grey matter volume in the fusiform gyrus in patients with schizophrenia compared to controls (Lee et al., 2002, Onitsuka et al., 2003).

5.5.3.3 Superior frontal gyrus

The superior frontal gyrus has been shown to play a role in higher cognitive functions including working memory (du Boisgueheneuc et al., 2006), however the nature of its exact involvement remains unclear. Several studies have shown an association between DISC1 polymorphisms and the structure and function of the superior frontal gyrus. Trost et al. (2013) found reduced grey matter volume in superior frontal regions was associated with the minor allele status for two DISC1 SNPs (Leu607Phe and Ser704Cys) (Trost et al., 2013). This is in line with other research that has demonstrated reduced superior frontal volumes in healthy subjects with the minor allele of the Ser704Cys polymorphism (Takahashi et al., 2009), and reduced grey matter in patients and controls with the

Leu607Phe risk allele (Szeszko et al., 2008). A further study Di Giorgio et al. (2008) has also provided evidence of an effect of DISC1 genotype in the Ser704Cys SNP on brain function in the superior frontal gyrus during the same memory encoding task used in the current experiment (Di Giorgio et al., 2008). This study found greater activation in this region in 'risk' Ser allele carriers using an exploratory whole-brain analysis.

Patients with schizophrenia have been found to have reduced cortical thickness compared to healthy controls in this region, which was unrelated to antipsychotic medication and duration of illness (Tully et al., 2014). This study also found that thinner cortex in this region was related to reduced cognitive control on a category fluency task and overall functional outcome. These results suggest that abnormalities in the superior frontal gyrus affect cognitive processing and have an influence upon real world functioning. Episodic memory deficits have also been associated with poor functional outcome (Green et al., 2000).

A recent meta-analysis of studies investigating individuals at high-risk for bipolar disorder concluded that increased activation in the superior and medial frontal gyrus was evident in those at high risk, regardless of the imaging task used (Fusar-Poli et al., 2012). These results, together with evidence of prefrontal hyperactivation in euthymic patients with bipolar disorder (Adler et al., 2004, Wessa et al., 2007), suggest that enhanced activation in prefrontal regions may be a trait marker of illness.

5.5.4 Recognition

During recognition, carriers showed greater activation in the right fusiform gyrus, left posterior cerebellum, right superior temporal gyrus, left anterior cingulate, right inferior frontal gyrus (VLPFC) and right middle frontal gyrus (DLPFC) compared to non-carriers.

5.5.4.1 Prefrontal cortex

The current results found that individuals with the t(1;11) translocation demonstrated increased activity compared to non-carriers during recognition in two prefrontal regions; the right VLPFC and DLPFC. The translocation appears to modulate PFC function during episodic memory, which is consistent with the critical role of this region in the pathophysiology of psychosis.

5.5.4.1.1 Inferior frontal gyrus (VLPFC)

The left inferior prefrontal cortex has been shown to be involved in the encoding of verbal and nonverbal information, the implementation of memory strategies (Simons and Spiers, 2003), and in the maintenance of successfully retrieved information (Badre and Wagner, 2002, Petrides, 2002). Whereas, the right inferior frontal gyrus has been shown to be involved in the effortful process of recognition, but not necessarily in successful memory recognition (Bremner et al., 2004). Further research has found evidence of a material-specific effect during episodic memory, reporting that activation in this region is left lateralized when verbal stimuli is used, whereas visuo-spatial stimuli is more likely to result in right VLPFC activity (Wagner et al., 1998a, Golby et al., 2001). This may support the current finding in the right VLPFC in translocation carriers during recognition, as the current task is simply measuring memory recognition processing (i.e. did not distinguish

between correct and incorrect responses), and was using non-verbal stimuli. There is also evidence that the VLPFC is involved in explicit encoding strategies as the use of such strategies has shown to engage this region and dramatically improve memory recognition (Ranganath et al., 2008).

5.5.4.1.2 Middle frontal gyrus (DLPFC)

Several lines of research suggest that the DLPFC is crucial for different memory processes including episodic and working memory. Research supports the idea that the DLPFC contributes to episodic long term memory formation through its role in working memory organization (Blumenfeld and Ranganath, 2006). Evidence suggests that there may be a hemispheric asymmetry of activation during episodic memory processes with greater involvement of the left DLPFC during encoding and greater activation in the right hemisphere during the recognition phase (Tulving, 1985), whereas other studies have reported bilateral activation of the DLPFC (Schmidt et al., 2002). Hemispheric activation may also depend on task complexity as activation is usually greater in the right middle frontal gyrus for more simple tasks, with additional recruitment of the left hemisphere for more complex designs (Achim and Lepage, 2005). These findings may provide support for the right lateralised DLPFC results during recognition in carriers, as the current task was relatively simple.

5.5.4.1.3 Effect of DISC1 on PFC function

Previous research has provided evidence to suggest that DISC1 has an influence on PFC functioning. Prata et al. (2008) used fMRI during a verbal fluency task, a standard measure of prefrontal activation, to test the influence of DISC1 on PFC function in healthy controls

(Prata et al., 2008). They found that Ser homozygotes demonstrated less efficient PFC activation, particularly in the middle and superior frontal gyri. In a later study the same authors examined the influence of this polymorphism in patients with schizophrenia and bipolar disorder, however found no effect on PFC activation. The authors interpret the absence of an observable effect in the patient sample as an indication of underlying interactions between DISC1 genotype and a multitude of other risk genes that have been implicated in schizophrenia together with potential interactions with unknown genetic factors. A study investigating the effect of the Ser704Cys polymorphism on brain morphology also found that Cys carriers have larger superior frontal volumes, but again only in health controls (Takahashi et al., 2009).

A recent study examined the effect of the same DISC1 polymorphism on PFC function, with Cys allele carriers considered at-risk (Opmeer et al., 2015). The Cys allele has previously been associated with affective disorders including depression (Hashimoto et al., 2006). This study used a visuospatial planning task in healthy controls and patients with an affective disorder, and found a differential effect of DISC1 on PFC activation depending on the presence of psychopathology. Controls with the risk Cys allele demonstrated lower activation in the DLPFC and ACC. This effect was reversed in patients with anxiety, whereas depressive patients showed no effect of genotype.

A recent study by Brauns et al. (2011) investigated the effects of another DISC1 SNP Leu607Phe, and found that neural activity in the DLPFC during a working memory task was increased in Phe allele carriers (Brauns et al., 2011). The Phe allele has been previously associated with schizophrenia (Cannon et al., 2005, Hodgkinson et al., 2004). The authors

interpreted this increased activity as cortical inefficiency, suggesting that risk carriers need to recruit additional neural resources to perform at the same level as those without the risk allele.

As discussed, previous research has investigated the effect of various DISC1 polymorphisms on brain structure and function. The literature is however mixed and shows different effects of DISC1 genotype depending on the sample studied e.g. controls or patients, the imaging paradigm used, or the genotype considered 'at-risk'. For example some studies consider the Ser allele the risk-variant as it has been shown to be over transmitted in patients (Callicott et al., 2005), whereas others suggest individuals homozygous for the Cys allele have increased susceptibility to schizophrenia (Qu et al., 2007).

Research has identified that the same DISC1 allele may display alternate risk or protection for schizophrenia, suggesting that the effect of a specific susceptibility gene is dependent not only on the existence of one risk variant on the gene, but also on the presence or absence of other risk variants within the same gene (Hennah et al., 2009). This demonstrates the complex nature of gene interactions and the need to take other genetic and environmental factors into consideration that might mediate the phenotypic consequence of DISC1 and risk for schizophrenia. However the effect of genotype variation in DISC1 SNPs on brain structure and function suggests that the DISC1 gene is at least partly involved in the neurobiology of schizophrenia (Takahashi et al., 2009). The effect of the DISC1 translocation on functional imaging measures has only recently been investigated as part of

the SFMHS. We therefore do not yet know the mechanism of this effect and it is also likely to be related to complex gene-gene and gene-environment interactions.

5.5.4.1.4 Prefrontal activation in patients

A recent quantitative meta-analysis of functional neuroimaging studies of episodic memory in schizophrenia found that deficits were most consistently associated with dysfunction in the PFC (Ragland et al., 2009). This review found that patients demonstrated significantly less prefrontal activation in dorsolateral and ventrolateral regions during both encoding and recognition. These findings are supported by another meta-analysis examining fMRI studies of executive function in schizophrenia showing disruption of a fronto-cingulate network including reduced activation in the bilateral DLPFC and right VLPFC (Minzenberg et al., 2009). There is further meta-analytic evidence that the VLPFC is a key region in distinguishing between patients and controls during episodic memory processing, however once again patients usually show reduced activation (Achim and Lepage, 2005). There are mixed findings of hyper and hypo-frontality during episodic memory tasks in patients with schizophrenia. It has been suggested that low task demand is associated with increased PFC activation in patients because the task is within their ability, however requires recruitment of more resources to achieve a similar level of accuracy to healthy controls (Manoach, 2003). The task used in this study appeared to be relatively easy and required low cognitive demand. All participants included in the analysis achieved a minimum of 75% accuracy during encoding and 70% during recognition. It may be the case that the increased PFC activation in the translocation carrier group in the current results reflects compensatory over-activation when viewing neutral scenes.

The neural underpinnings of episodic memory in bipolar disorder are still uncertain however several studies have found both dorsal and ventral PFC dysfunction across a range of tasks (Frangou et al., 2008). There are inconsistent findings regarding PFC activation in patients with bipolar disorder. Some studies show hypoactivation (Hamilton et al., 2009, Townsend et al., 2010), whereas others have found hyperactivation (Adler et al., 2004, Monks et al., 2004). A recent study examining working memory in euthymic patients showed an increase in activation in the right middle frontal gyrus compared to healthy controls (Dell'Osso et al., 2015).

Increased VLPFC activity has been reported in patients with bipolar disorder. Robinson et al. (2008) examined neural activity during an affective face-matching task in euthymic bipolar disorder (Robinson et al., 2008). They found that patients showed hyperactivation in inferior prefrontal regions compared to healthy controls. Another study also found increased activation in the right VLPFC in euthymic patients during an emotional stroop task (Blumberg et al., 2003b). Furthermore, there was a lateralization difference that related to mood state. Elevated mood was associated with right hemisphere lateralization whereas depression was linked to the left hemisphere. Results of these studies support a trait-related disruption of PFC activity in bipolar disorder.

5.5.4.2 Temporal regions

Translocation carriers showed increased activation in the superior temporal gyrus and fusiform gyrus during recognition. Studies have found an association between the superior temporal gyrus and DISC1 genotype. Ser homozygotes have been found to show an accelerated rate of cortical thinning in temporal regions including the superior temporal

gyrus (Raznahan et al., 2011). Reduced cortical thickness in this region has also been reported in relation to another DISC1 SNP (rs1322784) (Brauns et al., 2011). These findings suggest a relationship between DISC1 genotype and cortical development in the superior temporal gyrus.

Neuroimaging studies have found that patients with schizophrenia demonstrate greater activation in the superior temporal gyrus in response to visual working memory tasks, reflecting a failure to deactivate this region compared to controls (Walter et al., 2007). Abnormal fronto-temporal connectivity between the superior temporal and frontal cortex has also been implicated in schizophrenia (Lawrie et al., 2002). Further to these findings, first episode patients and individuals with an 'at risk mental state' for psychosis have also shown temporal lobe dysfunction and abnormal functional connectivity during working memory but to a lesser extent than patients (Crossley et al., 2009). These findings suggest that the superior temporal gyrus may be involved in the neurobiology of psychosis.

4.5.4.3 Anterior cingulate cortex

Activation in the anterior cingulate was also found to be increased in translocation carriers during recognition. Both groups showed a pattern of deactivation in this region, therefore the between-group finding reflects less deactivation in the carriers compared to non-carriers. Research suggests that the ACC plays a role in memory and cognitive control, and imaging studies indicate a prominent role for the ACC in episodic memory recognition (Paus et al., 1998, Lepage et al., 2000, Weis, 2004). Herrmann et al. (2001) found an anterior cingulate-prefrontal activation pattern during a memory retrieval task requiring the control of interfering information, indicating that the control of semantic interference in

episodic memory retrieval selectively engages specific frontal regions (Herrmann et al., 2001).

Several studies have reported effects of DISC1 genotype on the structure and function of the cingulate cortex, including the ACC. Hashimoto et al. (2006) studied healthy controls to investigate the impact of the Ser704Cys SNP, reporting decreased ACC grey matter volume in Cys homozygotes. The Cys allele has been associated with MDD, and decreased ACC volume has also been reported in patients and individuals with a family history of depression (Hashimoto et al., 2006). The Ser allele has also been associated with abnormal structure in this region, with a recent study reporting accelerated cortical thinning in the left ACC in healthy Ser carriers (Raznahan et al., 2011). The Leu607Phe SNP has also been implicated in the structure of the ACC. Szeszko et al. (2008) found an association between Phe carriers and reduced grey matter in the ACC, in both a sample of healthy controls and patients with schizophrenia (Szeszko et al., 2008). A recent study by Chakirova et al. (2011) found an effect of a different DISC1 risk variant (rs821633) on activation in the cingulate gyrus (Chakirova et al., 2011). Risk allele carriers showed reduced activation in this region from a sample of patients with bipolar disorder. These findings provide evidence that variation in the DISC1 gene may affect the structure and function of the ACC.

The ACC is important in the pathophysiology of both schizophrenia and bipolar disorder (Adams and David, 2007, Brooks et al., 2010). Several studies have reported underactivation of the ACC in patients with schizophrenia (Schlosser et al., 2008, Garrity et al., 2007, Whalley et al., 2006), whereas overactivation in these regions has been consistently demonstrated in patients with bipolar disorder (Cerullo et al., 2009). The

following chapter (chapter 6) will discuss the ACC in relation to schizophrenia and bipolar disorder in greater depth.

4.5.4.4 Cerebellum

The current results demonstrate increased activity in translocation carriers during recognition in the left posterior lobe of the cerebellum. The cerebellum has previously been implicated in episodic memory processes and cerebellar activity has frequently been found during recognition (Cabeza et al., 2002, Fliessbach et al., 2007, Weis, 2004).

DISC1 is widely expressed in the brain in several regions including the cerebellum (Chubb et al., 2008). Chakirova et al. (2011) found an interaction between genotype and group status in the left cerebellum, during a sentence completion task. In patients with schizophrenia, risk allele carriers showed greater activation in the cerebellum, whereas in the control group risk status was associated with decreased activation (Chakirova et al., 2011). These results illustrate the different effect SNPs can have depending on unknown underlying genetic and environmental factors. Carless et al. (2011) also found an effect of another DISC1 SNP (rs16854954) on left cerebellum volume in a large family based study in individuals without psychiatric illness (Carless et al., 2011).

Meta-analyses investigating episodic memory deficits in schizophrenia have also identified the cerebellum amongst the most extensive difference between patients and controls, with increased activation usually in controls (Achim and Lepage, 2005, Ragland et al., 2009). However, the specific functional mechanisms underlying the contribution to cognition and memory by the cerebellum remain to be resolved. Evidence suggests that a network

between the PFC and cerebellum, linked through synapses in the thalamus, plays a crucial role in coordinating motor and cognitive functions (Andreasen et al., 1998, Andreasen et al., 1999). Abnormalities in these regions provide support for disruption to a frontocortical–thalamic cerebellar circuit in schizophrenia. There is also recent evidence that the DISC1 Ser704Cys polymorphism influences the thalamic-prefrontal circuitry (Liu et al., 2013a). As highlighted in this discussion, there is evidence that components of this network are involved in cognitive functions that are key for episodic memory recognition, including the DLPFC, the ACC and the cerebellum. The current results also found significant group differences in these regions, however did not however find activation in the thalamus.

The cerebellum also appears to be implicated in the pathophysiology of bipolar disorder. Studies have reported structural deficits in posterior cerebellar regions (Kim et al., 2013). The cerebellum has also been shown to play a role in emotional processing and regulation, which is implicated in bipolar disorder (Hoppenbrouwers et al., 2008). However, a recent study comparing cerebellar volume in schizophrenia and bipolar disorder with and without psychotic features found that reduction in cerebellar cortical volume was specific to schizophrenia (Laidi et al., 2015).

5.5.5 Correlation analyses

Exploratory correlation analyses were also performed to investigate whether abnormalities involving episodic memory processing circuitry were associated with clinical symptoms. There was a significant negative correlation between YMRS score and activation in the left ACC in the carrier group during recognition. Relatively few imaging studies have focused on symptoms of mania in mood disorders. Studies have reported activation differences in

this region, however contrary to the current results, they tend to report increased activation of the ACC associated to manic symptoms (Blumberg et al., 2000, Goodwin et al., 1997, Whalley et al., 2009). However, it is important to note that manic symptoms in our current sample were relatively low in all subjects.

In the non-carriers there was a significant negative correlation between HDRS scores and activation in the right middle frontal gyrus during recognition. Findings from fMRI studies suggest that there is decreased DLPFC activation in patients with depression (Blumberg et al., 2003b). This finding is in line with previous studies. Whalley et al. (2009) investigated emotional memory during fMRI in patients with schizophrenia and bipolar disorder, and associations between activation levels and symptom severity across the disorders. This study found a negative correlation between depression scores on the HDRS and activation in the DLPFC, mainly driven by the bipolar group (Whalley et al., 2009).

Hypofrontality has been reported in depression during resting state activity, primarily in the DLPFC (Koenigs and Grafman, 2009, Galynker et al., 1998). Previous research on bipolar depression has been less consistent but has also reported decreased DLPFC activation, with some evidence of a negative relationship between activation and measures of depression (Brooks et al., 2009b). Further research has found that patients with depression tend to show greater activation of the DLPFC during tests of working memory and cognitive control when performance is matched to controls (Harvey et al., 2005). This is assumed to reflect the need for greater recruitment of resources in this region to maintain a similar level of performance. This may be the case in the current findings demonstrating increased activation of the DLPFC in the translocation carrier group.

The correlations conducted in the family must be interpreted with caution due to small group numbers and the presence of outliers, in particular one individual in the carrier group who scored substantially higher on all clinical measures. Outliers were not removed from the analysis due to small numbers and nonparametric statistics were performed to account for this where possible.

Overall, differences in activation were observed between carriers and non-carriers in several regions during encoding and recognition despite similar behavioural performance on an episodic memory task. Association with manic and depression scores within groups were also reported indicating different mood states may be associated with different pathophysiological processes.

5.5.6 Polygenic risk score

There was no significant difference between carriers and non-carriers in terms of their PRS for schizophrenia, bipolar disorder or MDD. This suggests that it is the translocation that is causing differences in activation between groups and not simply an increased polygenic liability to psychiatric illness. PRS data was not available for patients and controls in the current sample so it could not be investigated whether the family members (carriers and non-carriers) have an increased PRS compared to controls.

Partial correlations, controlling for the number of risk variants scored for each individual, were also performed to investigate the relationship between polygenic risk and imaging findings. There were no significant correlations between polygenic risk and imaging during encoding. When looking at the carrier group alone there was a significant positive

correlation between activation in the left ACC and PRS for bipolar disorder, and between activation in the right superior temporal gyrus and PRS for depression. There were no significant correlations in the non-carrier group.

There were only significant correlations when examining the carrier group alone. Therefore, it could be the effect of increased polygenic risk in addition to the presence of the translocation that is influencing the relationship between PRS and imaging findings. Previous research on polygenic risk has suggested that genetic risk factors not captured by PRS, for example the presence of rare variants, could influence the relationship between polygenic risk and brain function (Whalley et al., 2015b).

Previous research has used this polygenic approach and found increased activation of limbic regions to be associated with increased polygenic risk for bipolar disorder, for example in the ACC (Whalley et al., 2012a). The ACC has been implicated in bipolar disorder and as will be demonstrated in the following results chapter, it is a key region found to be over activated in patients with bipolar disorder during the current episodic memory task.

5.5.7 Strengths and limitations

There are several limitations to the current findings. Firstly, the sample size was small for both groups, which may have resulted in insufficient power to detect significant effects. Low statistical power also reduces the probability that a statistically significant finding actually mirrors a true effect (Button et al., 2013). The age of the translocation carrier group was significantly higher than the non-carrier group and was therefore entered as a covariate

in the second-level analysis, however it is still possible that the current findings are due to the effects of age. However, the low number and age of participants was unavoidable due to the nature of the family being studied, as cases occur infrequently and are often difficult to recruit. The unique nature of the family being studied and that no research has previously investigated the effect of the t(1;11) translocation on neuroimaging measures, arguably outweighs such methodological limitations. The current findings of this work are novel and provide evidence to suggest that the translocation does impact on neuroimaging measures, despite potential confounding factors.

Contrary to the hypothesis, and to previous studies investigating DISC1 allelic variation using the same memory task (Callicott et al., 2005, Di Giorgio et al., 2008), the current results did not find an influence of the translocation on hippocampal activation during episodic memory. This may have been due to several methodological limitations, or may reflect the true absence of an effect of the translocation in this region. Activation in the hippocampus was only found within groups during both encoding and recognition when a SVC in the hippocampus was applied. Therefore, it is possible that the amplitude of neural responses in the groups in the hippocampus may not have been sufficient to evoke detectable differences in hemodynamic response between groups (Sheth et al., 2004).

A lack of findings in the hippocampus has also been reported in other studies. Ragland et al. (2009) did not find consistent evidence for altered hippocampal activity in their quantitative meta-analysis of functional neuroimaging studies of episodic memory in schizophrenia (Ragland et al., 2009). A further study did not find an effect of the Ser704Cys polymorphism on hippocampal activation during episodic memory in healthy participants

(Opmeer et al., 2015). fMRI studies examining associations between DISC1 polymorphisms, including Ser704Cys and Leu607Phe, with hippocampal activation have provided inconsistent results (Duff et al., 2013). There are further limitations regarding the analysis and task used however these will be discussed in the final chapter.

5.5.8 Conclusion

In summary, this chapter presents the first evidence of functional alterations during encoding and recognition in association with the DISC1 t(1;11) translocation, in brain regions that are known to be affected in patients with major psychiatric disorders. Many of these brain regions have also been shown to be associated with genetic variation in DISC1 polymorphisms. Primarily, translocation carriers showed greater activation in fronto-temporal regions compared to non-carriers. This may reflect the need for carriers to recruit additional neural resources to perform at the same level as those without the translocation. Activation in these regions during recognition was also correlated to polygenic risk for bipolar disorder and depression, and to symptom measures of mania and depression. There were no correlations to psychosis related symptoms or PRS for schizophrenia. As will be discussed in the final synthesis chapter, patients with schizophrenia and bipolar disorder, and their unaffected relatives, show episodic memory related neural abnormalities in prefrontal and temporal regions. The current findings of this work are novel and provide insight into the potential effect of the translocation in episodic memory related brain activation. However as previously discussed, results must be considered in light of potential confounding factors in particular the age difference between groups and the affective diagnoses and symptoms present in the carrier group.

Chapter 6: Functional magnetic resonance imaging comparison of controls and patients with schizophrenia or bipolar disorder

Chapter 6: Functional magnetic resonance imaging comparison of controls and patients

This chapter will present the neuroimaging findings in healthy controls, patients with schizophrenia and patients with bipolar disorder, in order to look at differences in activation during encoding and recognition between groups. This sample of controls and patients was included to allow the comparison of having a psychiatric disorder to the effects of the t(1;11) translocation, without the need for direct comparisons between family members and patients, which would be confounded by relatedness within the family.

6.1 Demographic Details

Demographic and clinical data are summarized in table 10. The final fMRI sample comprised of 40 healthy controls and 41 patients (30 with schizophrenia, 11 with bipolar disorder). There were no significant differences between the groups in terms of age, gender or current (WASI) and premorbid (NART) IQ (all $p > 0.05$) however they did differ on PANSS total score, negative symptoms and positive symptoms as expected. PANSS measures were significantly higher in both patient groups compared to healthy controls (controls versus schizophrenia $U = 89$, $p < 0.001$, controls versus bipolar disorder $U = 60$, $p < 0.001$), however there was no significant difference between patients with schizophrenia and bipolar disorder. There were also significant differences between groups on the YMRS and HDRS ($p < 0.05$), again higher in both patient groups compared to healthy controls, however no significant difference between patient groups. GAF scores were significantly different between all groups with controls scoring highest, followed by patients with bipolar disorder, and patients with schizophrenia scored significantly lower

(controls versus schizophrenia U = 21, $p < 0.001$, controls versus bipolar disorder U = 14, $p < 0.001$, schizophrenia versus bipolar disorder U = 58.5, $p = 0.021$).

Table 10: Demographics and clinical measures in controls and patients

	Controls (n=40)	Schizophrenia (n=30)	Bipolar disorder (n=11)	Between group comparison (U/X^2, p)
Demographic and Clinical Measures				
Mean age (years) (SD)	38 (14.47)	35.83 (10.25)	42.91 (13.67)	$\chi^2 = 1.47, 0.480$*
Gender (M:F)	11:9	11:4	8:3	$\chi^2 = 2.91, 0.233$**
Mean NART (SD)	111.24 (7.47)	109.17 (10.86)	114.9 (6.33)	$\chi^2 = 2.18, 0.337$*
Mean WASI score (SD)	114.89 (11.91)	104.29 (17.85)	110.0 (15.74)	$\chi^2 = 5.72, 0.057$*
Mean PANSS total score (SD)	31.4 (3.99)	53.5 (16.95)	45.5 (15.71)	**$\chi^2 = 48.85, <0.001$***
Mean PANSS positive score (SD)	7.2 (0.72)	13.2 (5.48)	10.2 (2.57)	**$\chi^2 = 41.7, <0.001$***
Mean PANSS negative score (SD)	7.06 (0.24)	12.97 (5.75)	11.2 (6.48)	**$\chi^2 = 41.7, <0.001$***
Mean YMRS score (SD)	0.13 (0.79)	2.03 (3.17)	2.55 (2.54)	**$\chi^2 = 31.72, <0.001$***
Mean HDRS score (SD)	0.8 (2.93)	8.37 (8.29)	8.18 (8.36)	**$\chi^2 = 34.28, <0.001$***
Mean GAF score (SD)	87.58 (7.89)	48.48 (17.68)	62.89 (17.89)	**$\chi^2 = 45.12, <0.001$***
Antipsychotic medication (CPZE) (SD)	-	414.14 (335.08)	152.27 (152.27)	**U = 79, 0.011***

**non parametric test used (Mann Whitney U/Kruskal-Wallis) ** Chi square*

Positive and negative symptom scale (PANSS), National adult reading test (NART), Wechsler Abbreviated Scale of Intelligence (WASI), Young mania rating scale (YMRS), Hamilton depression rating scale (HDRS)

Significant results highlighted in bold

6.2 Medication Status

From the subjects included in the analysis, twenty-seven patients with schizophrenia and four patients with bipolar disorder were treated with antipsychotic medication, which was examined by converting different antipsychotic drug doses into chlorpromazine equivalents (CPZE). There was a significant difference between patients with schizophrenia and bipolar disorder in terms of CPZE ($p = 0.011$), with patients with schizophrenia taking greater levels of antipsychotic medication (table 10).

In the schizophrenia group, antipsychotic medication included olanzapine, clozapine, amisulpride, risperidone, depixol, clopixol, stelazine, chlorpromazine, aripiprazole and quetiapine. Three patients with schizophrenia were not on antipsychotic medication, however two of these individuals were on a mood stabilizer (carbamazepine) or anti-depressant (fluoxetine), and one was not taking any medication. In the bipolar group, eight were taking a mood stabilizer (valproate, lithium or lamotrigine), and four individuals were taking antipsychotic medication (three on olanzapine and one on modecate). One individual was also taking an anti-depressant in addition to a mood stabiliser and antipsychotic. Two patients with bipolar disorder were not taking any medication.

6.3 Episodic memory task performance

Episodic memory task performance data are shown in table 11 and figure 6.1. Kruskal-Wallis nonparametric tests revealed that there were no significant differences between the groups in terms of their performance (% correct) on encoding ($p = 0.659$) and recognition conditions ($p = 0.081$). Mean reaction time (seconds) across the whole experiment (encoding and recognition phases) was compared between the groups. A one-way ANOVA

found a significant difference between groups ($F(2,78) = 4.46$, $p = 0.015$) and post-hoc Bonferroni corrections revealed that this difference was between controls and patients with schizophrenia ($p = 0.012$), with patients taking longer to respond (figure 6.2).

Table 11: Episodic memory performance in controls and patients

	Controls (n=40)	Schizophrenia (n=30)	Bipolar disorder (n=11)	Between group comparison (X^2/F, p)
Task performance				
Mean encoding % correct (SD)	95.94 (4.27)	91.39 (14.05)	95.84 (3.71)	$\chi^2 = 0.833$, 0.659*
Mean recognition % correct (SD)	91.77 (9.9)	82.77 (18.53)	92.49 (8.74)	$\chi^2 = 5.035$, 0.081*
Mean reaction time (sec) (SD)	1.12 (0.18)	1.26 (0.22)	1.20 (0.24)	F = 4.46, 0.015 con vs. scz, 0.012

**non-parametric test used (Kruskal-Wallis)*

Controls (con), patients with schizophrenia (scz)

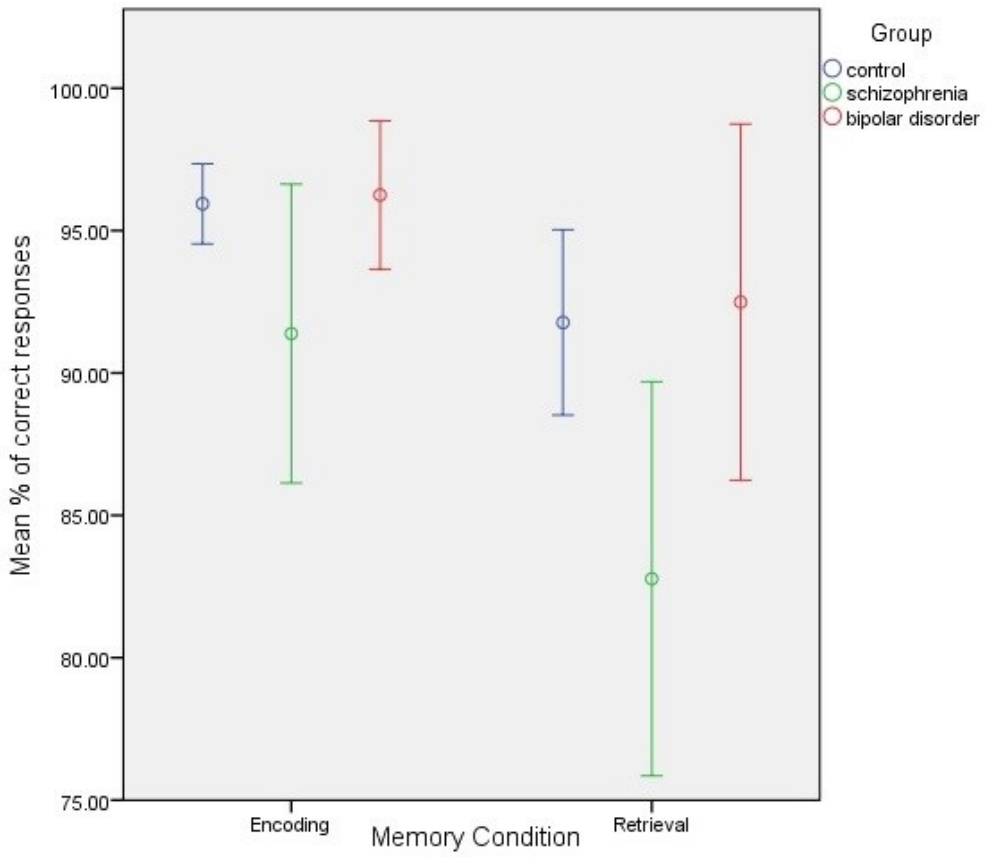


Figure 6.1: Episodic memory performance in controls and patients

Mean % of correct responses during encoding and recognition in healthy controls, patients with schizophrenia and bipolar disorder (error bars: 95% CI).

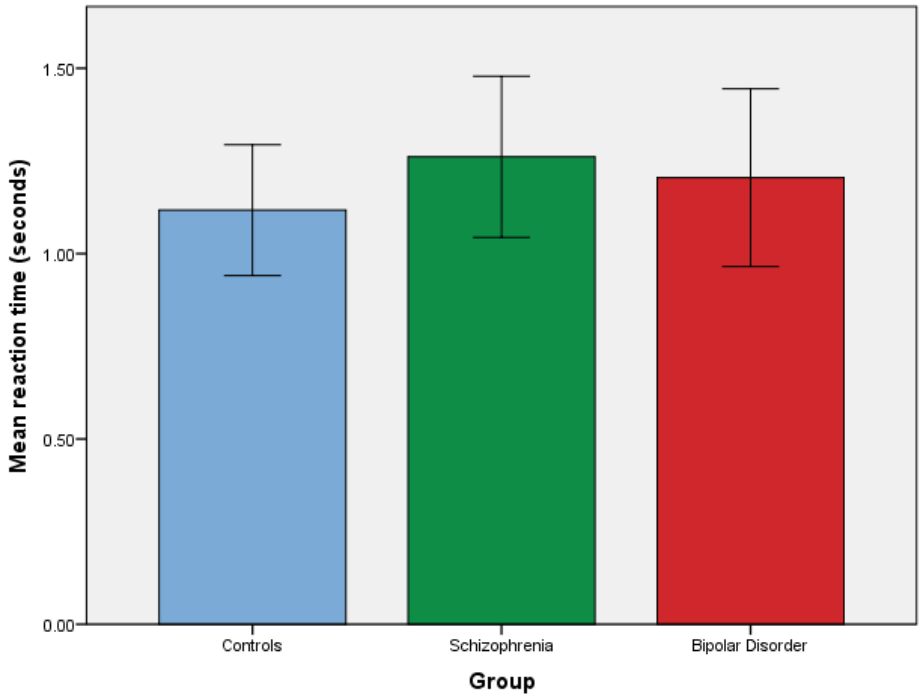


Figure 6.2: Reaction time in patients and controls

Mean reaction time (seconds) across the episodic memory paradigm (encoding and recognition phases) in controls and patients (error bars: +/- 1 SD).

fMRI results

For the imaging results, within group activations for encoding and recognition will be presented for each group in turn (controls, patients with schizophrenia and patients with bipolar disorder). Between group results will then be reported for encoding and recognition for the following group comparisons; controls vs. schizophrenia, controls vs. bipolar disorder, and schizophrenia vs. bipolar disorder. Statistical maps were thresholded at a level of $p = 0.001$ uncorrected (unless indicated at a level of $p = 0.005$) and regions were considered significant at $p < 0.05$ cluster level corrected for multiple comparisons across the whole brain volume. Brain regions were visualised using MANGO and images from SPM are displayed. Kruskal-Wallis nonparametric tests revealed that there were no

significant differences between the groups in terms of average motion per TR (mm) in the scanner (p = 0.11) (table 12).

Table 12: Mean motion per TR (mm) in patients and controls

	Controls (n=40)	Schizophrenia (n=30)	Bipolar disorder (n=11)	Between group comparison (X^2, p)
Mean motion per TR (mm) (SD)	0.195 (0.07)	0.260 (0.14)	0.264 (0.14)	χ^2 = 4.4, 0.11*

**non-parametric test used (Kruskal-Wallis)*

6.4 Task-related activation - within group results

Table 13 lists the regions that were significantly activated during the encoding stage of the task and table 14 lists the areas of activation during recognition, both within each group. Figures 6.3 and 6.4 illustrate within group activations during encoding and recognition, respectively. For results of large clusters the threshold was set to p < 0.0001 to define more specific areas of activation.

6.4.1 Encoding

6.4.1.1 Controls

During encoding controls showed significant activation compared to baseline in a large cluster with the peak at the left cerebellum (-18, -79, -8, p < 0.001). This result encompassed multiple regions including frontal cortices (including DLPFC and VLPFC), bilateral activation in the hippocampal formation (hippocampus and parrahippocampus), parietal cortices, and other structures including the cingulate gyrus, insula, thalamus, fusiform gyrus and cerebellum (see figure 6.3a). Several of these regions form a distributed network

that is crucial for visuospatial information processing (Di Giorgio et al., 2008, Bertolino et al., 2006).

6.4.1.2 Patients with schizophrenia

During encoding patients with schizophrenia showed significant activation compared to baseline in a large region with the peak at the right cuneus (9, -94, 10, $p < 0.001$). This cluster encompassed many regions including frontal lobes (middle, inferior, superior and medial), inferior/superior parietal, bilateral insula, caudate, thalamus, parrahippocampus and precuneus (see figure 6.3b).

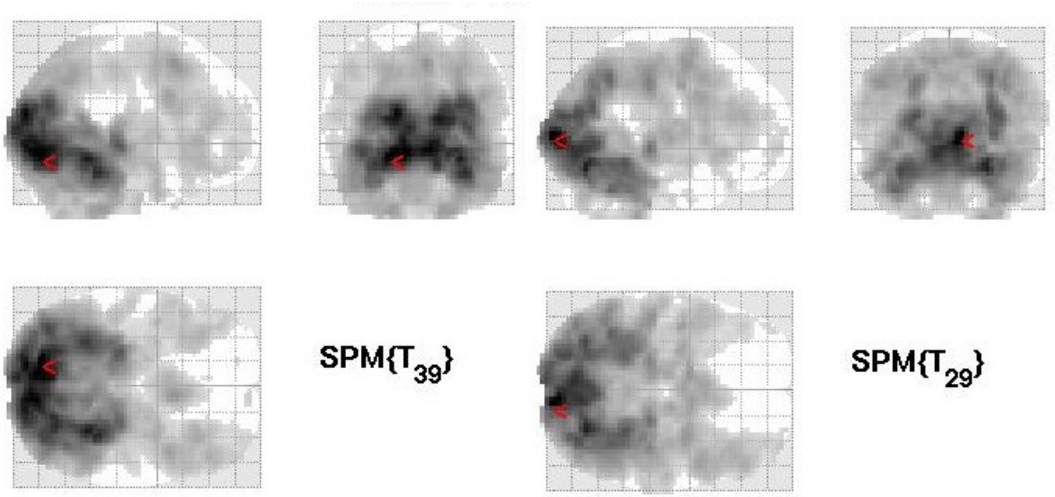
6.4.1.3 Patients with bipolar disorder

During encoding compared to baseline, patients with bipolar disorder showed significant activation in a large cluster with the peak at the right cerebellum (24, -52, -14, $p < 0.001$) (see figure 6.3c). This cluster encompassed many regions including bilateral hippocampus, thalamus, fusiform gyrus, posterior cingulate and insula. Other significant results included left inferior parietal, right middle frontal, right inferior frontal and cingulate gyrus (see table 13).

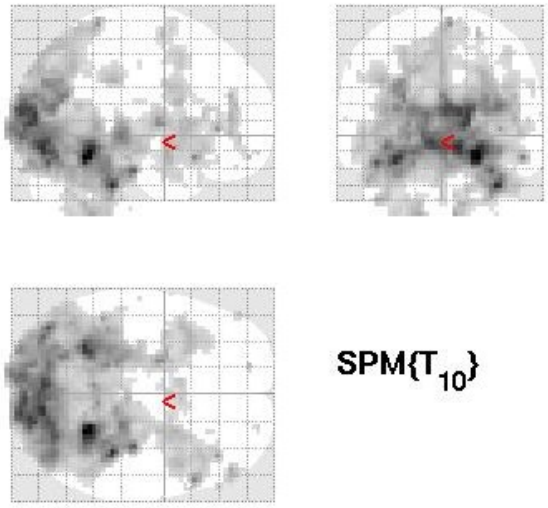
Table 13: Within group activations in patients and controls during encoding

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann area
Encoding > Baseline				
Controls (n=40)				
<0.001	26310	inf	-18, -79, -8	Peak L cerebellum
Schizophrenia (n=30)				
<0.001	26483	inf	9, -94, 10	Peak R cuneus, 17
Bipolar disorder (n=11)				
<0.001	11191	6.17	24, -52, -14	Peak R cerebellum, culmen
0.003	119	4.41	-39, -34, 34	L inferior parietal, 40
0.012	92	4.40	48, 44, 10	R middle frontal, 46
0.002	137	4.27	45, 11, 22	R inferior frontal. 9
0.029	75	3.88	-6, 11, 46	L cingulate, 24
<0.001*	473	4.20	24, -1, 64	R middle frontal, 6

**thresholded at p=0.005 uncorrected*
Regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume.



(a) controls (b) patients with schizophrenia



(c) patients with bipolar disorder

Figure 6.3: Within group analysis in controls and patients for encoding > baseline

Encoding > baseline analysis within groups in (a) controls (n = 40), (b) patients with schizophrenia (n = 30) and (c) patients with bipolar disorder (n = 11). Sagittal, axial and coronal sections displayed. Maps thresholded at $p < 0.001$ uncorrected voxel level.

6.4.2 Recognition

6.4.2.1 Controls

During recognition there was significant activation in a large cluster with a peak at the left middle occipital gyrus (-12, -91, 19, $p < 0.001$). This region of significant activation included frontal (medial, superior, inferior, middle gyrus, cingulate gyrus), temporal (bilateral thalamus, parahippocampus/hippocampus, fusiform), parietal (bilateral superior, inferior gyrus) precuneus and caudate, in contrast to baseline (see figure 6.4a).

6.4.2.2 Patients with schizophrenia

During recognition patients showed significant activation in a large cluster with the peak at the right lingual gyrus in the occipital lobe (3, -88, 4, $p < 0.001$). This result included several regions associated with the task including middle, medial and inferior frontal, inferior/superior parietal cortices, occipital lobe, parrahippocampus, cingulate gyrus, insula, thalamus, fusiform gyrus and precuneus. There was also another significant cluster at the left precentral gyrus (-39, 2, 31, $p < 0.001$) (see figure 6.4b).

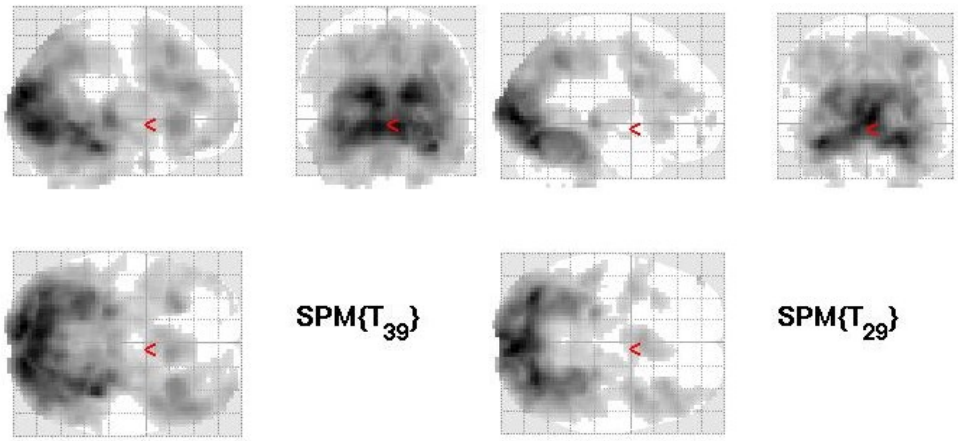
6.4.2.3 Patients with bipolar disorder

During recognition patients showed significant activation with a peak at the left cerebellum (-33, -52, -20, $p < 0.001$) encompassing superior/inferior frontal gyrus, insula and precentral gyrus (see figure 6.4c). Other significant results were in a large cluster with peak at the right middle frontal (51, 32, 25, $p < 0.001$), which included the left middle frontal, inferior parietal, left claustrum and right caudate (see table 14).

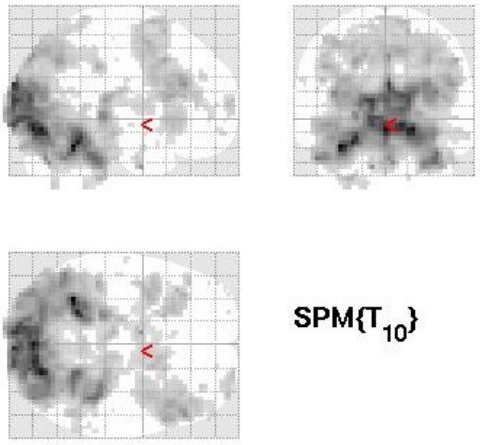
Table 14: Within group activations in patients and controls during recognition

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann area
Recognition > Baseline				
Controls (n=40)				
<0.001	25721	inf	-12, -91, 19	Peak L middle occipital gyrus, 18
Schizophrenia (n=30)				
<0.001	14563	inf	3, -88, 4	Peak R lingual gyrus, occipital lobe, 18
<0.001	331	5.23	-39, 2, 31	L precentral gyrus, frontal lobe, 6
Bipolar disorder (n=11)				
<0.001	8896	6.01	-33, -52, -20	L cerebellum, culmen
<0.001	1173	4.69	51, 32, 25	R middle frontal, 9
0.010	94	4.36	-45, -34, 37	L inferior parietal, 40
<0.001	535	4.20	-36, 5, 55	L middle frontal, 6
<0.001	176	4.09	-27, 23, -5	L Claustrum, sub-lobar
0.011	92	3.81	15, 11, 16	R caudate body, sub-lobar

Regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume.



(a) controls (b) patients with schizophrenia



(c) patients with bipolar disorder

Figure 6.4: Within group analysis in controls and patients for recognition > baseline

Recognition > baseline analysis within groups in (a) controls (n = 40), (b) patients with schizophrenia (n = 30) and (c) patients with bipolar disorder (n = 11). Sagittal, axial and coronal sections displayed. Maps thresholded at $p < 0.001$ uncorrected voxel level.

6.5 Between-group results

Table 15 shows the group comparisons between controls, patients with schizophrenia and patients with bipolar disorder, during memory encoding and recognition. This section will report encoding and recognition results in turn for the following group comparisons; controls vs. schizophrenia, controls vs. bipolar disorder, schizophrenia vs. bipolar disorder and the patient group as a whole vs. controls.

Table 15: Between group activations in patients and controls during encoding and recognition

p value (cluster-level)	ke	Z	Peak Height (x, y, z)	Peak voxel location, Brodmann area
Encoding > Baseline				
Schizophrenia > controls				
<0.001	567	4.89	39, -34, 52	R inferior parietal lobe, 40
<0.001	277	4.46	-57, -31, 34	L inferior parietal lobe, 40
All patients > controls				
<0.001	383	5.09	-57, -31, 34	L inferior parietal lobe, 40
<0.001	508	4.75	39, -34, 52	R inferior parietal lobe, 40
0.034	115	4.78	-54, -73, 7	L inferior temporal lobe, 37
Recognition > Baseline				
Control > schizophrenia				
0.006	206	4.44	6, 20, 10	R caudate, anterior cingulate, 33
Bipolar disorder > controls				
0.018*	324	4.53	-24, 29, 7	L caudate, anterior cingulate 33, insula 13, inferior frontal lobe 45/46
Bipolar disorder > schizophrenia				
0.012	108	4.92	15, 14, 16	R caudate, anterior cingulate, 33

**thresholded at p=0.005 uncorrected (regions were considered significant at p < 0.05 cluster level corrected for multiple comparisons across the whole brain volume)*

For the encoding > baseline contrast, there were no significant results when comparing controls and patients with bipolar disorder. For the recognition > baseline contrast, there were no significant results when comparing controls and all patients combined.

6.5.1 Controls vs. patients with schizophrenia

6.5.1.1 Encoding

During encoding, patients with schizophrenia demonstrated increased activation bilaterally in the inferior parietal lobe compared to healthy controls (39, -34, 52, $p < 0.001$ in right hemisphere, -57, -31, 34, $p < 0.001$ in left hemisphere). Patients did not show any regions with decreased BOLD responses compared to healthy controls.

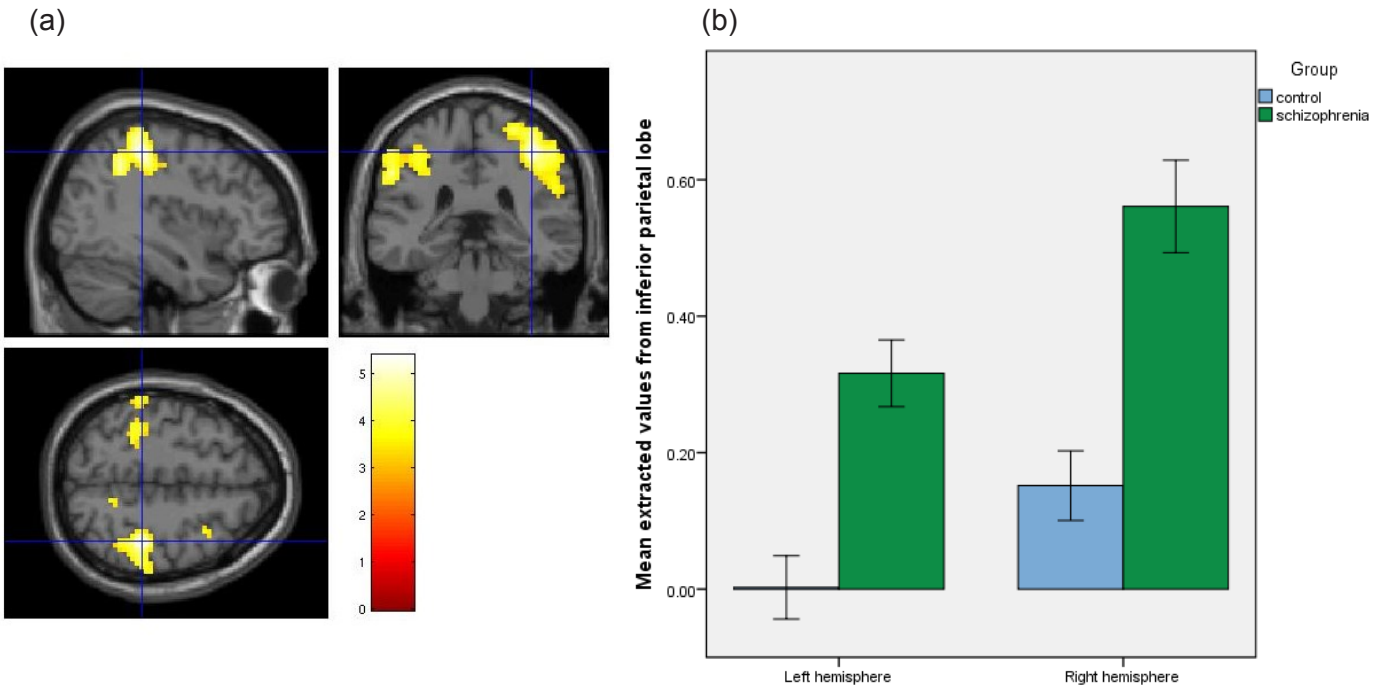


Figure 6.5: Between group result for encoding > baseline contrast in patients with schizophrenia > controls

(a) Result shows area of greater activation in patients with schizophrenia compared to controls in bilateral inferior parietal lobe ($p < 0.001$). Maps thresholded at $p = 0.001$ uncorrected. Crosshair position at right IPL, x = 39, y = -34, z = 52. Image from SPM
(b) Extracted values from peak voxel at inferior parietal lobe in left (-57, -31, 34) and right (39, -34, 52) hemisphere in controls and patients with schizophrenia (error bars: +/- 1 standard error)

6.5.1.2 Recognition

During recognition controls showed increased activation of a region including the right caudate and anterior cingulate compared to patients with schizophrenia (6, 20, 10, p = 0.006). Patients did not show any significant regions of increased activation.

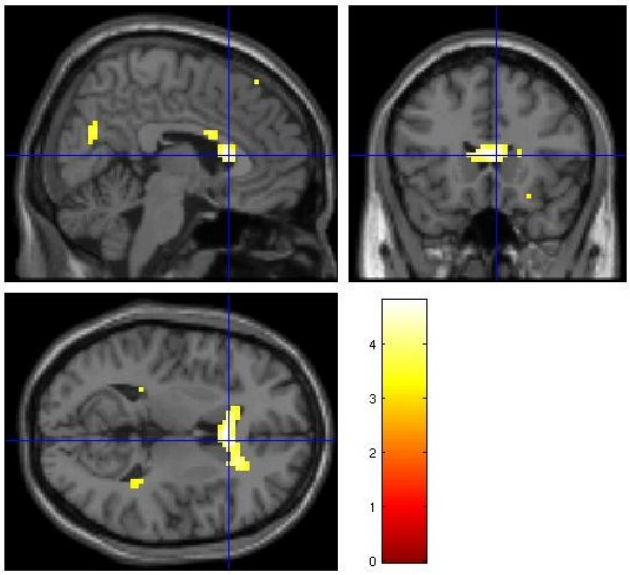


Figure 6.6: Between group result for recognition > baseline contrast in controls > patients with schizophrenia

Result shows greater activation in healthy controls in a region encompassing the caudate and anterior cingulate (p = 0.006), compared to patient with schizophrenia. Maps thresholded at p = 0.001 uncorrected. Crosshair position at right caudate: x= 6, y = 20, z =10.

6.5.2 Controls vs. patients with bipolar disorder

6.5.2.1 Encoding

Patients with bipolar disorder showed no significant differences in activation compared to healthy controls during the encoding phase of the task.

6.5.2.2 Recognition

During recognition patients demonstrated increased activation in a region encompassing the left caudate and anterior cingulate, extending to inferior frontal lobe and insula (-24, 29, 7, p = 0.018) (map thresholded at p = 0.005).

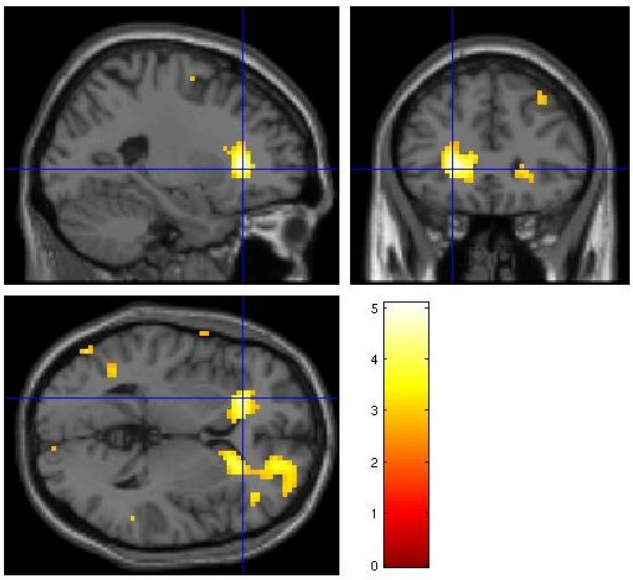


Figure 6.7: Between group result for recognition > baseline contrast in patients with bipolar disorder > controls

Result shows greater activation in patients with bipolar disorder in a region encompassing the caudate and anterior cingulate (p = 0.018), compared to healthy controls. Maps thresholded at p = 0.005 uncorrected. Crosshair position at left caudate: x = -24, y = 29, z = 7).

6.5.3 Schizophrenia vs. bipolar disorder

6.5.3.1 Encoding

When comparing the two patient groups, there were no significant differences during the encoding phase.

6.5.3.2 Recognition

During recognition there was a significant difference between patient groups, with patients with bipolar disorder showing increased activation in the right caudate extending to the anterior cingulate (15, 14, 16, p = 0.012).

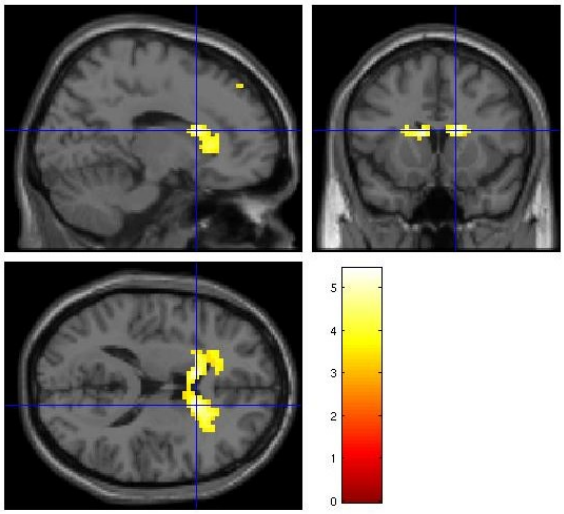


Figure 6.8: Between group result for recognition > baseline contrast in patients with bipolar disorder > patients with schizophrenia

Result shows greater activation in patients with bipolar disorder in a region encompassing the caudate and anterior cingulate (p = 0.012), compared to patients with schizophrenia. Maps thresholded at p = 0.001 uncorrected. Crosshair position, right caudate: x = 15, y = 14, z = 16).

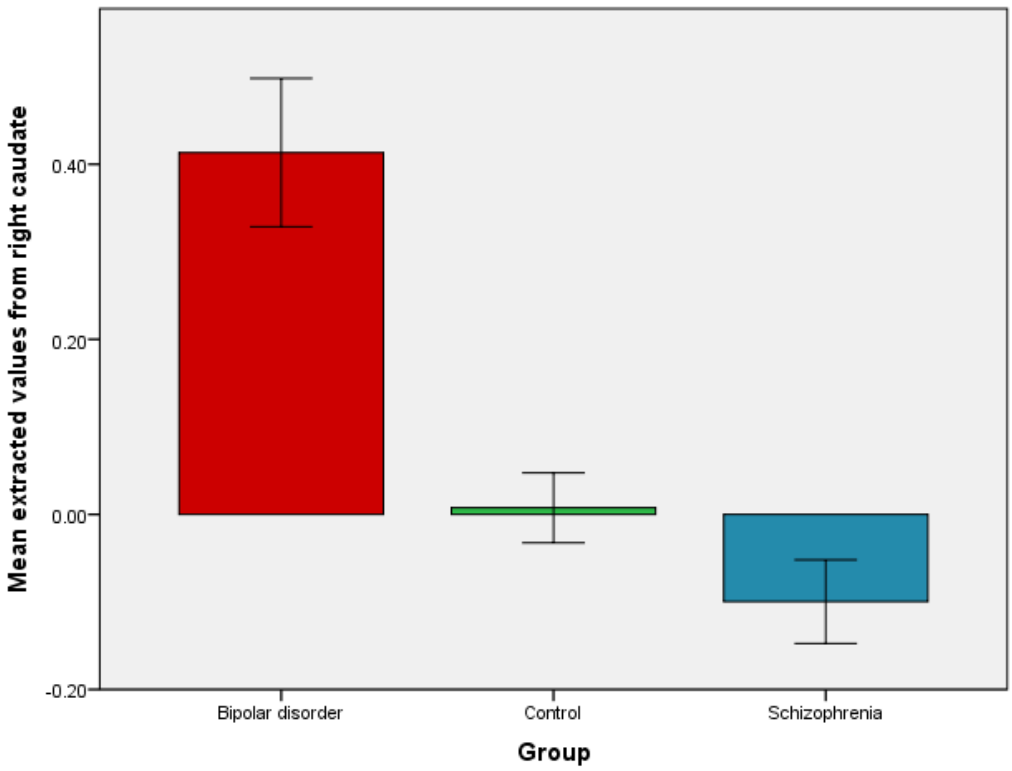


Figure 6.9: Extracted values from peak voxel of activation in the right caudate during recognition across groups

Extracted values from peak voxel in right caudate (15, 14, 16) in controls, patients with schizophrenia and patients with bipolar disorder (error bars: +/- 1 Standard Error)

6.5.4 Patient group as a whole vs. controls

To further investigate the between group results, differences between healthy controls and the patient groups combined (participants with schizophrenia and bipolar disorder) were examined to investigate overall effects of illness. There were no significant results during recognition, however during encoding the patient group showed an area of greater activation in bilateral inferior parietal lobe (this result seems to be driven by the patients with schizophrenia), and also in the left inferior temporal gyrus (-54, -73, 7, t = 4.78, z = 4.47, p = 0.034) (figure 6.10). This result was not correlated with any clinical measure or medication status.

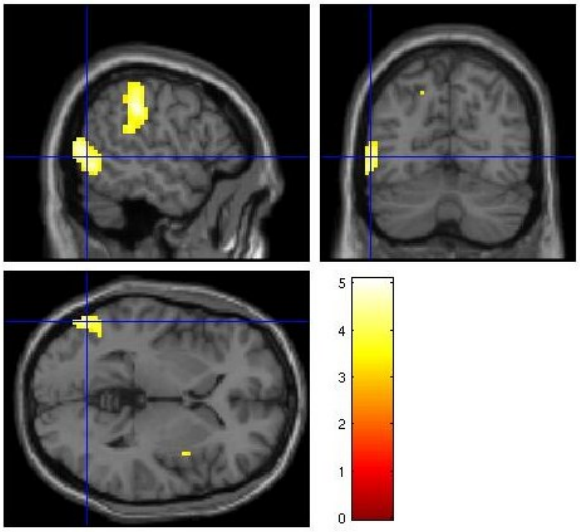


Figure 6.10: Between group result for encoding > baseline contrast in patient group as a whole > controls

Result shows greater activation in all patients (with schizophrenia and bipolar disorder) in the left inferior temporal gyrus (p = 0.034), compared to controls. Maps thresholded at p = 0.001 uncorrected. Crosshair position, right caudate: x = -54, y = -73, z = 7).

6.5.5 Post-hoc ROI analysis: hippocampus

Based on prior reports regarding hippocampal involvement in episodic memory, SVCs were applied for the hippocampus using the WFU PickAtlas software, however no significant hippocampal results were found.

6.5.6 Correlation analyses

Data was extracted from SPM for the peak voxel of activation for each significant between group result (as displayed in table 15) and then correlated against medication status and clinical measures using SPSS. Pearson correlations were performed as the data was normally distributed. All correlation analyses were computed for each subject group independently to avoid confounding the effects of group differences on correlation strengths. Correlation results are presented with and without correction for multiple comparisons (P-values were corrected using the FDR procedure and considered significant when $p_{FDR} \leq 0.05$).

6.5.6.1 Effects of antipsychotic medication

Any significant differences between patients and controls were investigated by relating functional activation to antipsychotic medication dose (chlorpromazine equivalents). During encoding, there was a significant positive association of moderate effect between CPZE and peak activation in the left inferior parietal lobe in the schizophrenia group ($r = 0.406$, $p = 0.026$, $n = 30$), however this did not survive FDR correction, $p_{FDR} > 0.05$. There were no statistically significant correlations between antipsychotic medication status and fMRI group results during recognition (all $p > 0.05$) (table 16).

6.5.6.2 Effects of psychopathology

Whether any differences between groups were associated with psychopathology was evaluated by looking at the relationships between functional activation and symptom severity ratings; PANSS total score, PANSS positive, PANSS negative, YMRS and HDRS.

Table 16: Correlations between clinical variables and significant between group activations during encoding and recognition

	Encoding – L inferior parietal lobe Schizophrenia group (n = 30)	Recognition – caudate Schizophrenia group (n = 30)	Recognition – caudate Bipolar disorder group (n = 11)
PANSS total	p = 0.071, r = -0.335	p = 0.151, r = -0.269,	p = 0.188, r = 0.453, n = 10
PANSS positive	p = 0.512, r = -0.125	p = 0.825, r = -0.042	**p = 0.034, r = 0.669, n = 10 (pFDR not sig)**
PANSS negative	p = 0.249, r = -0.271	**p = 0.035, r = -0.387 (pFDR not sig)**	p = 0.155, r = 0.486, n = 10
HDRS	**p = 0.020, r = -0.421 (pFDR not sig)**	p = 0.495, r = -0.130	p = 0.607, r = 0.175, n = 11
YMRS	p = 0.060, r = -0.347	p = 0.916, r = 0.020	p = 0.166, r = 0.449, n = 11
Medication status (CPZE)	**p = 0.026, r = 0.406 (pFDR not sig)**	p = 0.190, r = -0.246	p = 0.311, r = 0.337, n = 11

r = Pearson's r coefficient, significant results highlighted in bold

Encoding

During encoding there was a moderate negative correlation between activation in the left inferior parietal lobe and scores on the HDRS in the schizophrenia group ($r = -0.421$, $p = 0.020$, $n = 30$) i.e. those with greater depressive symptoms showed decreased activation of the inferior parietal lobe (figure 6.11). However, this result did not survive FDR correction, $p_{FDR} > 0.05$. This result was derived from the schizophrenia > controls contrast during encoding, so there is no corresponding result in the bipolar group.

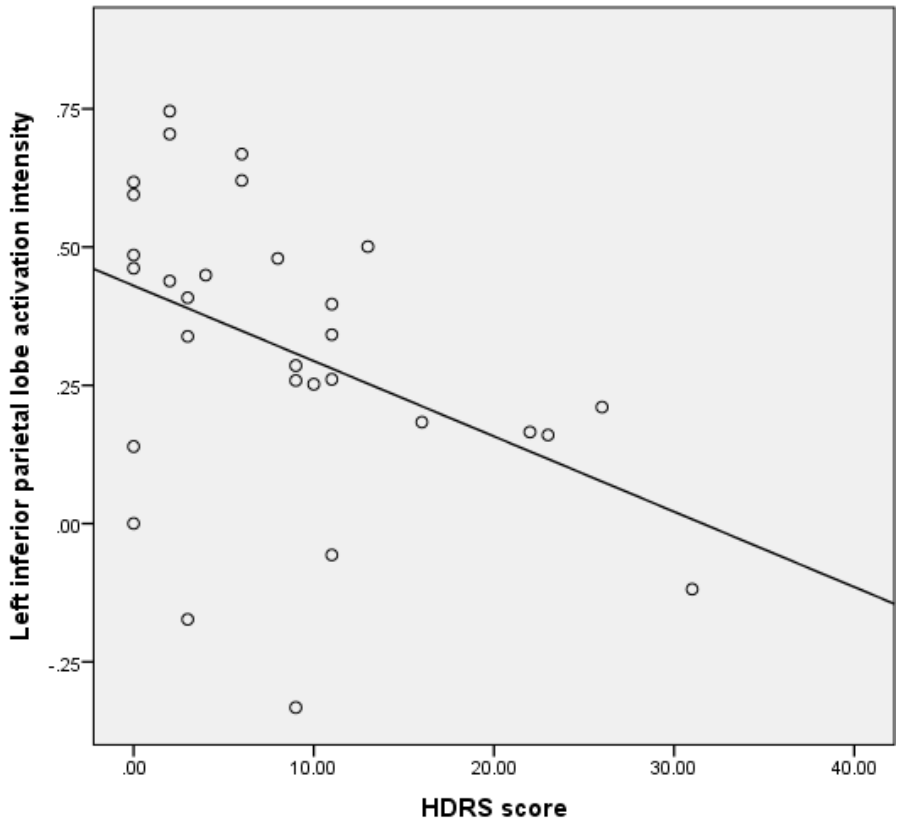


Figure 6.11: Scatterplot of activation in the left inferior parietal lobe and HDRS score during encoding for patients with schizophrenia

Significant negative correlation between Hamilton Depression Rating Scale scores and activation in the left inferior parietal lobe during the encoding versus baseline contrast in patients with schizophrenia (not FDR corrected).

Recognition

During recognition there were two significant correlations. There was a weak negative correlation between activation in the right caudate and PANSS negative scores in the schizophrenia group ($r = -0.387$, $p = 0.035$, $n = 30$). This correlation was not significant in the bipolar group ($p = 0.155$). A test of the interaction was also performed and was non-significant ($p = 0.249$) (figure 6.12).

In the bipolar group activation in the right caudate was strongly positively correlated with PANSS positive scores ($r = 0.669$, $p = 0.034$, $n = 10$), whereas this was not significant in the schizophrenia group ($p = 0.825$). A test of the interaction was also performed and was non-significant ($p = 0.321$) (figure 6.13).

All other correlations with symptom measures were non-significant (all $p > 0.05$). It should also be noted that neither of these correlations survived FDR correction, $p_{FDR} > 0.05$

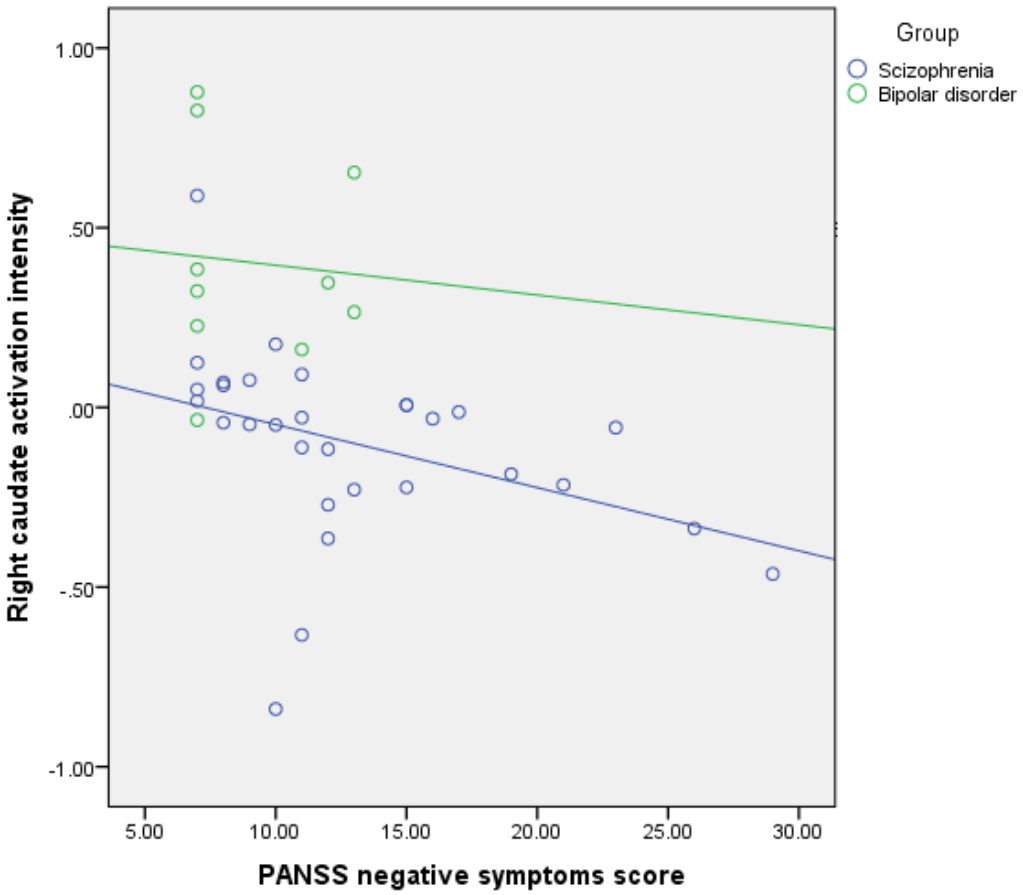


Figure 6.12: Scatterplot of activation intensity in the right caudate and PANSS negative symptoms score during recognition for patients with schizophrenia and bipolar disorder

Significant negative correlation between PANSS negative symptom scores and activation in the right caudate during the recognition versus baseline contrast in patients with schizophrenia (not FDR corrected). Patients with greater negative symptoms showed lower activation of this region.

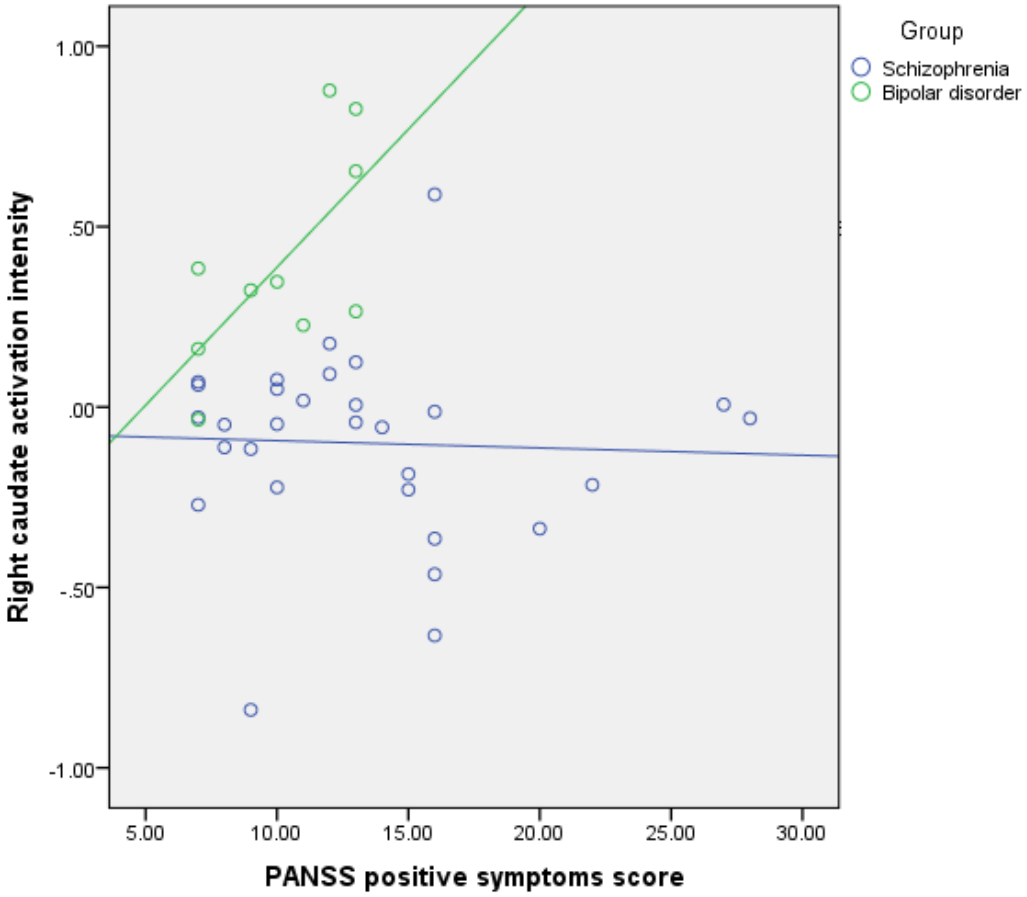


Figure 6.13: Scatterplot of activation intensity in the right caudate and PANSS positive symptoms score during recognition for patients with bipolar disorder and schizophrenia

Significant positive correlation between PANSS positive symptom score and activation in the right caudate during the recognition versus baseline contrast in patients with bipolar disorder (not FDR corrected). Patients with higher negative symptoms showed greater activation of this region.

6.6 Discussion

6.6.1 Summary of findings

This experiment used fMRI to investigate the BOLD response during an episodic encoding and recognition memory task in a sample of healthy controls and patients with schizophrenia and bipolar disorder. Compared to healthy controls, patients with schizophrenia demonstrated increased activation during encoding in the inferior parietal lobe bilaterally, and decreased activation of the anterior cingulate and caudate nucleus during recognition. Patients with bipolar disorder showed no differences compared to controls during encoding, and increased activation during recognition in a region encompassing the caudate and anterior cingulate, extending to inferior frontal lobe and insula. Patients with bipolar disorder also showed increased activation in the same region, encompassing the ACC and caudate, compared to patients with schizophrenia.

6.6.2 Encoding results

6.6.2.1 Inferior parietal lobe

Patients with schizophrenia showed greater activation than controls bilaterally in the inferior parietal lobe. Although the literature suggests that the most common regions activated during episodic memory are in prefrontal and medial temporal lobes, memory processing also involves several other brain regions including the parietal lobes (Wagner et al., 2005). The parietal cortex, the inferior parietal lobe in particular, is relevant in the neurobiology of schizophrenia with structural deficits reported in patients (primarily reductions in volume however results are inconsistent) (Torrey, 2007). Patterns of abnormal activation in this region have also been demonstrated during various cognitive processes, for example, hypoactivation of the parietal lobe during working memory has been found in

patients with schizophrenia and has been associated with poorer performance (Menon et al., 2001a).

The parietal lobe has been shown to support the frontal lobe in the storage and retrieval of information (Jonides et al., 1998), and forms connections with the frontal lobe (Seltzer and Pandya, 1984). There is also evidence to suggest that functional and structural abnormalities related to schizophrenia may begin in the parietal lobe and progress to frontal regions, suggesting that these alterations may occur early in the course of the illness (Yildiz et al., 2011). Prefrontal-parietal networks are also involved in several cognitive processes including working memory (Deserno et al., 2012) and episodic memory recognition (Weiss et al., 2009).

The parietal lobe has also been implicated in studies with individuals at high genetic risk of schizophrenia. Studies have shown altered activation of the parietal lobe in relation to several cognitive tasks such as increased activation during a verbal fluency task (Whalley et al., 2004), increased activation during working memory (Callicott et al., 2003) and decreased activation during spatial working memory in high risk individuals (Keshavan et al., 2002).

During encoding there was a significant negative correlation of moderate effect between activation in the left inferior parietal lobe and scores on the HDRS in the schizophrenia group i.e. patients with higher depressive scores showed lower activation in this region. This is in line with previous findings, for example Whalley et al. (2009) found a negative correlation between depression scores and activation in the same region during an

emotional memory task (Whalley et al., 2009).

Dysfunction of the left inferior parietal cortex has been found in patients with schizophrenia and depression (Müller et al., 2013). The inferior parietal lobe has also been shown to play a role in attentional processing, and patients with depressive symptoms exhibit greater activation in this region in response to negative stimuli (Canli et al., 2004), whereas the current task used non-emotive neutral stimuli. This finding suggests that there is an association between depressive symptoms and disrupted episodic memory encoding in patients with schizophrenia.

Any significant differences between patients and controls were investigated by relating significant between group activations to antipsychotic medication. There was no evidence of any effect of medication on brain activation in the regions of interest except for a moderate positive correlation between antipsychotic dose and left inferior parietal activation during encoding in the schizophrenia group ($p = 0.026$). This finding may represent an effect of antipsychotic medication rather than a true difference between groups. However, this association was only found in the left hemisphere and not in the significant result from the right hemisphere, and did not survive FDR correction procedures.

The current results provide support for an association between schizophrenia and altered activity in the inferior parietal lobe during episodic memory encoding. Despite research supporting an important role of this region in schizophrenia, the inferior parietal lobe has not received as much attention in the literature compared to other areas such as the PFC

and hippocampus, and perhaps deserves more investigation to establish the role it plays in this disorder.

6.6.2.2 Patient group as a whole

To further investigate the between group results, differences between healthy controls and the patient groups combined (participants with schizophrenia and bipolar disorder) were examined to investigate overall effects of illness. This was done in order to reflect the range of conditions that the t(1;11) translocation has been associated with (Craddock and Owen, 2010) and is in line with current approaches that look to investigate mental disorders not constrained by DSM diagnostic categories (Insel et al., 2010). During encoding the patient group showed an area of greater activation bilaterally in the inferior parietal lobe (this result seems to be driven by the patients with schizophrenia), and an additional result in the left inferior temporal gyrus.

Neuroimaging studies have found that the inferior temporal gyrus is involved in visual mental imagery (Cabeza et al., 2004) and selectively responds to task-relevant visual stimuli (Hamamé et al., 2012). Functional deficits in these cognitive processes have been reported in patients with schizophrenia (Tek et al., 2002), alongside evidence of grey matter volume reductions in bilateral inferior temporal gyrus in patients with chronic schizophrenia (Onitsuka et al., 2014). There is also limited evidence of decreased grey matter volume in this region in patients with bipolar disorder (Farrow et al., 2005). A further study found deficits in left inferior temporal grey matter that were related to an increased genetic liability to schizophrenia but not bipolar disorder (McIntosh et al., 2006).

These findings suggest that this region appears to play a role in the pathophysiology of schizophrenia.

6.6.3 Recognition results

6.6.3.1 Patients with schizophrenia

Compared to healthy controls and patients with bipolar disorder, patients with schizophrenia demonstrated decreased activation in a region encompassing the caudate nucleus and ACC during recognition. During recognition in the contrast examining bipolar disorder > schizophrenia, there was a negative correlation between PANSS negative symptom scores and right caudate activation in the schizophrenia group.

6.6.3.2 Anterior cingulate cortex

The ACC is implicated in the neurobiology of schizophrenia with structural deficits such as reduced volume reported in patients (Galderisi et al., 2008, Zetzsche et al., 2007, Narr et al., 2005, Haznedar et al., 2004). The ACC has been found to be differentially activated in response to a range of neuropsychological tasks (Haznedar et al., 1997, Dolan et al., 1995, Hofer et al., 2014) and studies have found both hyper and hypo activation of this region. In line with the current findings, several studies have reported underactivation of the ACC in patients with schizophrenia (Schlosser et al., 2008, Garrity et al., 2007, Whalley et al., 2006). A review of activation deficits during episodic memory in schizophrenia found that during recognition, reduced activation in the right ACC was amongst the most extensive differences between patients and controls (Ragland et al., 2009).

The ACC has been hypothesised to be involved in the recognition of newly learned information (Meunier et al., 1997) and has been proposed to play an important role in executive control (D'Esposito et al., 1995). The ACC has also been associated with several cognitive processes including amplification of task relevant stimuli (Egner and Hirsch, 2005), and resolving conflict during information processing (Van Veen and Carter, 2002). Therefore, failure to activate this region in the patient group could reflect an attentional deficit or executive functioning difficulties (Hofer et al., 2014).

The cingulate cortex has extensive connections between core limbic structures such as the amygdala and frontal regions such as the PFC, as part of a fronto-limbic system that is crucial for successful execution of internally generated, task-oriented actions (Szeszko et al., 2008). Fronto-limbic connectivity also plays a key role in the pathophysiology of schizophrenia (Bilder and Degreef, 1991). Using a verbal version of the current task, a recent study found decreased activation in the cingulate cortex during recognition in individuals at high genetic risk for schizophrenia due to the presence of the high risk variant of the BDNF val66met polymorphism (Baig et al., 2010).

A study by Hofer et al. (2014) investigated patterns of brain activity during episodic encoding and recognition of words in unmedicated patients during an acute episode of schizophrenia compared to healthy controls. During word recognition, reduced activation was found in the patient group in the DLPFC and limbic/paralimbic regions including the ACC and insula (Hofer et al., 2014). These results provide support for a difference between patients with schizophrenia and healthy controls during recognition even when patients are

not prescribed antipsychotic medication. The current findings in this region during recognition were not correlated with antipsychotic medication doses.

6.6.3.3 Caudate

Reduced activation was found during recognition in the caudate nucleus in patients with schizophrenia. The caudate, along with the putamen and nucleus accumbens, is part of the striatum, which is a component of the basal ganglia. The basal ganglia has increasingly been shown to be involved in several cognitive functions, with the caudate playing an important role in the planning and execution of strategies required for goal-directed behaviours (Grahn et al., 2008). The caudate also plays a role in learning and memory, specifically in stimulus-response associations, as evidence by lesion and neurobehavioural studies in animals, and neurodegenerative diseases and neuroimaging in humans (Packard and Knowlton, 2002). Research has also demonstrated deficits in basal ganglia activation in patients with schizophrenia during a motor sequencing task (Menon et al., 2001b).

Koch et al. (2008) examined working memory retrieval during fMRI and found that patients with schizophrenia revealed decreased activation in the caudate bilaterally and the ACC compared to controls, when matched for performance (Koch et al., 2008). The authors interpret the finding of hypoactivation in these regions as a result of impaired general cognitive rather than motor processes in patients, due to the fact that results were still detectable after matching for performance. The caudate and the ACC have both been linked with impaired cognitive control (Postuma and Dagher, 2006, Egner and Hirsch, 2005), and disturbances in the function of these regions have been reported in several psychiatric disorders including schizophrenia.

One study found that the basal ganglia and medial temporal lobe memory systems may compete with each other during declarative memory processing (Poldrack et al., 2001). This study found that activation in the caudate nucleus and medial temporal lobe was negatively correlated within subjects. Further to this, learning appeared to be dependent on MTL structures during the early stages of learning whereas individuals relied on the striatum with increased training.

Caudate volume reduction in patients with schizophrenia has been found, however it is not consistently reported (Ebdrup, 2010). Caudate reduction has also been demonstrated in the offspring of patients with schizophrenia, which may represent a measure of familial risk of psychosis (Rajarethinam et al., 2007). However, other studies have reported no difference in caudate volume in at risk individuals (Lawrie et al., 2001). Findings in the literature are inconsistent however appear to report that reduced caudate volume is likely to be associated with the pathophysiology of schizophrenia. However, enlarged caudate size is typically related to antipsychotic medication exposure, which may explain findings of increased volume size in chronically treated patients with schizophrenia (Lang et al., 2014). It is likely that medication can induce alterations in the striatum as medicated patients with a first episode of psychosis have shown greater reductions in caudate size compared to patients with chronic schizophrenia treated with antipsychotics (Ellison-Wright et al., 2008). The current finding of reduced activation in the caudate in patients during recognition was not correlated with medication dose, suggesting that this finding is not due to antipsychotic medication dose in the patient group. However, it cannot be entirely dismissed that the caudate hypoactivation is a result of the antipsychotic medication that patients received.

A recent study was able to categorize individuals into schizophrenia and control groups using a measure of hemispheric specialization (altered brain asymmetry) of the caudate nucleus with an accuracy rate of 74% (Mueller et al., 2015). The authors highlight the importance of caudate connectivity and asymmetry, and suggest that this could serve as a potential endophenotype of schizophrenia.

The current results found that patients with schizophrenia with greater negative symptoms on the PANSS demonstrated lower activation of the right caudate. Previous research has found an association between the caudate and negative symptoms. Young et al. (1991) found that patients with marked negative symptoms had a bilateral reduction in the caudate nucleus (Young et al., 1991). On the other hand, increased caudate volume has been associated with greater severity of negative symptoms in patients treated with antipsychotic medication (Gur et al., 1998). Another study investigating medication-naïve patients found that all items on the negative subscale of the PANSS were negatively correlated with regional blood flow in several regions including the basal ganglia and cingulate (Sabri et al., 1997).

The current finding in the right caudate extended to the ACC. The ACC has been shown to be involved in the development of negative symptoms in patients (Cascella et al., 2010). A recent review by Bersani et al. (2014) suggested that hypoactivity of the cingulate cortex, in particular the ACC, is related to negative symptoms such as social withdrawal in patients with schizophrenia (Bersani et al., 2014). Volume reduction in the ACC has also been shown to be more pronounced in patients with greater negative symptoms (Preuss et al., 2010).

6.6.3.4 Fronto-striatal network

Disruption of a fronto-striatal network, including both the caudate and ACC, appears to contribute towards negative symptoms such as apathy and lack of motivation (Cummings, 1993). Altered function of fronto-striatal circuitry is a key finding in schizophrenia, with reports of increased (Salvador et al., 2010) and decreased fronto-striatal connectivity (Welsh et al., 2010). fMRI studies have demonstrated altered fronto-striatal activity in patients undergoing various cognitive tasks, for example during working memory performance (Quidé et al., 2013). Fronto-striatal dysfunction has also been found in the unaffected siblings of individuals with schizophrenia during reward processing (de Leeuw et al., 2015). This study found reduced activation in this circuit in siblings compared to controls, which correlated with the degree of sub-clinical negative symptoms including lack of motivation and apathy. These findings support a genetic vulnerability for fronto-striatal functioning in schizophrenia

The results found that patients with schizophrenia showed decreased activation in a region including the caudate and ACC during recognition, and those with increased negative symptoms showed an even greater reduction in this region. Therefore negative symptoms in schizophrenia may be associated with reduced activity in the caudate and ACC.

6.6.3.5 Patients with bipolar disorder

The current results demonstrated overactivation of a region including the caudate nucleus and ACC, extending to inferior frontal (VLPFC) and insula in patients with bipolar disorder compared to healthy controls during recognition. Patients with bipolar disorder also showed increased activation in the caudate and ACC compared to patients with schizophrenia.

During recognition in the contrast examining bipolar disorder > schizophrenia, there was a positive correlation between PANSS positive symptom scores and right caudate activation in the bipolar group.

6.6.3.6 Anterior limbic network

It has been proposed that bipolar disorder arises from disruption in an anterior limbic network consisting of VLPFC areas with connections to limbic regions including the amygdala, insula and ACC (Strakowski, 2012, Strakowski et al., 2004). A pattern of overactivation in these regions has been consistently demonstrated in patients with bipolar disorder (Cerullo et al., 2009) and the current findings are in line with previous research. These regions are involved in emotion regulation and a dysfunction of this network results in a susceptibility to mood disruptions as evident in patients with bipolar disorder (Whalley et al., 2011). This hypothesis proposes that the overactivation in this brain network is persistent and leaves individuals at risk for mood and cognitive dysfunction, even during the euthymic state (Strakowski et al., 2004).

Overactivation of emotion-processing regions including the ACC, thalamus and insula has also been found in individuals at high genetic risk for bipolar disorder (Whalley et al., 2015c). This suggests that these abnormalities are not confounded by long-term illness or medication. In addition to functional deficits, structural abnormalities of the ACC have also been demonstrated, including increased size of this region in patients with bipolar disorder (Javadapour et al., 2007).

The majority of existing research has employed emotional tasks in order to investigate emotional brain circuitry in bipolar disorder, however overactivation in such regions has been demonstrated using neutral stimuli (Strakowski et al., 2004, Gruber et al., 2010). The task used in the current experiment was a non-emotional paradigm and patients still demonstrated this pattern of overactivation, suggesting that patients may attach greater emotional valence to neutral stimuli, in comparison to healthy controls or patients with schizophrenia.

Most studies investigating episodic memory in bipolar disorder have focused on verbal tasks however episodic memories are often stored as visual images (Conway, 2009), therefore the current experiment specifically targeted non-verbal encoding and recognition. In line with the current results, a recent study by Oertel-Knochel et al. (2014) found a disruption of primarily left fronto-temporal-parietal brain regions including ACC in patients with bipolar disorder during a non-verbal episodic memory task (Oertel-Knochel et al., 2014).

6.6.3.7 Caudate

The current findings also showed increased activation during recognition in the caudate nucleus in patients with bipolar disorder. Increasing evidence suggests that the neurobiology of bipolar disorder is associated with structural and functional abnormalities in the caudate (Shahana et al., 2011). Structural imaging studies generally show increased caudate volume in patients compared to controls (DelBello et al., 2004), however findings in the literature are contradictory. A recent study found that right caudate volume was reduced in bipolar subjects compared to healthy controls (Beyer et al., 2004), whereas

patients with schizophrenia only show a modest volume reduction (Tayebani et al., 2014). There is also evidence of increased caudate volume in individuals at high risk for bipolar disorder, with these individuals showing comparable caudate size to patients (Hajek et al., 2009). Another study of monozygotic twins found that the caudate was larger in both affected and unaffected twins of bipolar disorder compared to healthy comparison twins (Noga et al., 2001).

Functional abnormalities in the caudate of patients with bipolar disorder have also been reported. In line with the current findings, previous research has found increased activity in the left caudate, associated with mania in bipolar disorder (Blumberg et al., 2000). Further functional imaging studies have also found increased caudate activity in patients during affective tasks (Chang et al., 2004, Wessa et al., 2007).

The caudate receives projections from other structures including the ACC, amygdala and prefrontal regions including the DLPFC (Blumberg et al., 2000). The known structural connectivity between these regions suggests that increased activity occurs within the context of a prefrontal-striatal-thalamic network that is modulated by limbic structures and is central to emotional processing (Ong et al., 2012). Overall, the current results support the hypothesis that patients with bipolar disorder demonstrate dysfunction of the anterior limbic network that includes the ACC and caudate.

The current findings showed that patients with bipolar disorder who had higher positive symptom scores on the PANSS demonstrated greater activation of the right caudate. Previous research in patients with bipolar disorder has found an association between

increased caudate and ACC activation in bipolar mania (Blumberg et al., 2000, Whalley et al., 2009). A significant correlation in this region with mania scores on the YMRS was not found as might have been expected. It could be argued however that many of the positive items on the PANSS e.g. conceptual disorganization (loose associations, disorganized thinking), excitement (hyperactivity reflected in accelerated motor behaviour) and hostility, appear to overlap with measures of mania on the YMRS e.g. language/thought disorder (tangentiality), increased motor activity and irritability/disruptive behaviour, however this is only speculative.

The current finding in the right caudate extended to the ACC. Positive symptoms have been associated with increased activation of the ACC (Assaf et al., 2006, Lahti et al., 2006) and significant activation in the ACC has been observed during auditory hallucinations (Silbersweig et al., 1995, Cleghorn et al., 1990). Decreased ACC volume has also been observed in patients and this has been correlated with positive symptom severity (Choi et al., 2005). Around 50% of patients with bipolar disorder experience psychotic symptoms at some point (Keck et al., 2003) and research has begun to explore the neurocognitive profiles of nonpsychotic and psychotic bipolar disorder. A recent study was able to distinguish between nonpsychotic and psychotic bipolar disorder by examining ventral ACC connectivity, concluding that patients with bipolar disorder with psychosis showed a more similar pattern of connectivity to patients with schizophrenia (Anticevic et al., 2014).

The current findings suggest that patients with bipolar disorder show increased activation in a region encompassing the caudate and ACC during recognition, and those with psychotic symptoms show even greater activation in this region. Therefore psychotic

symptoms in bipolar disorder may be associated with heightened activity in these regions.

6.6.4 Limitations

There are several limitations of the current findings. Unavoidably, the majority of patients were on medication at the time of scanning. As discussed in chapter 1, antipsychotic medications have been shown to affect the BOLD signal during performance of a variety of cognitive paradigms. Ideally drug free patients would have been recruited however these are rare, unrepresentative of the wider psychiatric population, and if unmedicated may not have been able to comply with experimental procedures, particularly the fMRI task. Therefore, antipsychotic medication status in the patient groups was noted and was converted into chlorpromazine equivalents, to compare different types of medication together. Medication effects were then explored by performing correlations between antipsychotic medication and any significant results between patients and controls. No significant medication effects were seen to impact on the main findings, however this cannot be entirely ruled out. Further to this, duration of illness was not recorded for the patients included in this study, and as discussed previously, this may have influenced the current results.

Contrary to the hypothesis, the current results did not find between group differences in medial temporal lobe structures such as the hippocampus. Previous studies have shown the hippocampus is central to memory function and have reported differences in activation between patients with schizophrenia and bipolar disorder (Hall et al., 2010). The task used in the current study had a relatively low cognitive demand and may not have elicited a substantial neural response in this region to evoke differences in hemodynamic response.

The hippocampus is involved in several aspects of memory processing including relational binding (Stolz et al., 2012) and shows greater activation when individuals are required to encode multiple items and bind them to form a representative memory (Davachi and Wagner, 2002). The current task only involved one single visual input and did not require individuals to use relational binding, which may explain the lack of results in the hippocampal region. There are further limitations regarding the analysis and task used however these will be discussed in the final chapter of this thesis.

6.6.5 Conclusion

In conclusion, the episodic memory paradigm produced activation differences between patients with schizophrenia and bipolar disorder in the ACC and caudate during recognition that were evident despite similar behavioural performance. Correlations between positive and negative symptoms on the PANSS and activation in this region were also found. These findings add to previous research suggesting that there may be distinct neurobiological substrates associated with each disorder.

Furthering the understanding of common and distinct pathophysiologies associated with schizophrenia and bipolar disorder may help to biologically classify psychiatric illness in the future, rather than relying on current diagnostic classification systems based on clinical characteristics such as DSM-5. Further to this, enhancing our understanding of the underlying biological causes of cognitive deficits in psychosis may also aid the development of treatment options including pharmacological agents or cognitive remediation.

Chapter 7: Synthesis

Chapter 7: Synthesis

This chapter will provide an overall summary and discussion of the key results presented in this work. It will also discuss the implications of these findings, limitations and strengths of the experiment and analyses performed, and considerations for future research.

7.1 Overall summary of findings

The primary aim of the study described in this thesis was to investigate functional activation during an episodic memory paradigm in individuals with and without the DISC1 t(1;11) translocation, to examine the impact of this translocation. A parallel study was also performed to examine differences between controls and patients with schizophrenia or bipolar disorder. The recruitment of the patient and healthy control groups allowed the comparison of the effects of the t(1;11) translocation to the effects of a having a psychotic illness, while minimising key confounds. Four groups of participants, 19 family members (8 with the translocation, 11 without), 30 patients with schizophrenia, 11 patients with bipolar disorder and 40 healthy controls underwent a functional MRI encoding and recognition paradigm and provided useable data.

During encoding of neutral scenes, family members with the translocation showed greater activation of the left posterior cingulate, right fusiform gyrus and right superior frontal gyrus compared to non-carriers. During recognition, carriers showed greater activation in prefrontal regions (DLPFC and VLPFC), the anterior cingulate, and temporal regions (fusiform gyrus, and superior temporal gyrus). For both contrasts, no regions were found to be more active in unaffected family members than in translocation carriers. There were

no significant differences between the groups in terms of their performance on encoding and recognition conditions.

Compared to healthy controls, patients with schizophrenia demonstrated increased activation during encoding in the inferior parietal lobe bilaterally, and decreased activation in a region encompassing the caudate nucleus and ACC during recognition. Patients with bipolar disorder showed no difference in activation compared to controls during encoding, and increased activation during recognition in a region encompassing the caudate and anterior cingulate, extending to the inferior frontal lobe and insula. There was also a significant difference between patients with schizophrenia and bipolar disorder during recognition, with bipolar disorder again showing increased activation in the caudate extending to the ACC. There were no differences between groups in terms of their episodic memory performance.

7.2 Family studies and rare variants

The segregation of the t(1;11) translocation with schizophrenia, bipolar disorder and MDD (St Clair et al., 1990) suggests that disruption of the DISC1 gene is likely to be a risk factor for major psychiatric illness. Studying the effects of this translocation can help to identify the disease pathways that are affected by DISC1 and inform how DISC1 mediates its effects on psychopathology through endophenotypes such as brain function.

Single-family studies with multiply affected individuals are important for the study of genetically complex and common disorders such as schizophrenia and bipolar disorder, as they allow for the investigation of rare variants. DISC1 is a prime example of the ‘common

disease; rare variant' hypothesis. Rare variants have a large effect on underlying biology compared to common variants that have relatively weak impact but result in illness due to their cumulative presence. It is also plausible that variants with the largest effect sizes will be those that have important functional consequences (Cirulli and Goldstein, 2010). Rare, family-specific genetic variants may also have a particularly important role in elucidating the neurobiology of major psychiatric disorders, due to reduced genetic complexity within families and greater penetrance on endophenotypes such as brain function (Whalley et al., 2015a). Recent findings from the Schizophrenia Working Group of the Psychiatric Genomics Consortium large scale GWAS found an overlap between genes affected by rare variants and more common loci (Ripke et al., 2014). These findings suggest that studies of rare genetic variants, even though specific to small groups, will be informative for illness more widely.

A disadvantage of studying family-specific mutations is that findings may be specific to one family and thus lack generalisability to the disease itself. However, insights from rare cases and family studies have provided invaluable insights into other complex disorders such as Alzheimer's disease (Bertram et al., 2010). A major incentive for studying risk factors for major mental illness is hopefully to identify and develop more effective treatment options. Studying rare variants such as DISC1 may help to identify disease pathways that may be viable drug targets to help alleviate the symptoms of psychiatric disorders.

7.3 Evidence against DISC1

Despite the evidence discussed for an association between DISC1 and schizophrenia, the role of this gene has recently been challenged (Sullivan, 2013, Farrell et al., 2015). There is conflicting evidence regarding the association of common variants in DISC1 with schizophrenia. For example, a recent meta-analysis using data collected from 10 candidate gene studies and three GWAS found no evidence that common variants at the DISC1 locus were associated with schizophrenia (Mathieson et al., 2012). SNPs in the DISC1 gene were also not highlighted in the latest psychiatric genomics consortium study (Ripke et al., 2014). There are currently no results demonstrating genome-wide levels of significance for DISC1 and recent GWAS data has failed to find evidence of DISC1 for any major psychiatric disorder (Ripke et al., 2011, Sklar et al., 2011). GWAS help to identify susceptibility loci that are common in the general population, but exert only small risk effects. Individually these risk variants only account for a small proportion of the heritability of psychiatric disorders, with the remaining heritability likely to be accounted for by other genetic factors including rare variants. The GWAS approach is neither powered nor designed for the detection of rare risk alleles and this is the case even for variants with high penetrance and impact (Bertram et al., 2010). The failure of a gene to achieve the genome-wide significance threshold should not necessarily be interpreted as rejection of a genetic hypothesis, as it may still be genuinely contributing to the aetiology of the disease (Lee et al., 2012a). DISC1 has strong independent evidence from other sources including convergent biological support for its involvement in major psychiatric disorders (Chubb et al., 2008, Porteous et al., 2006), and is amongst the most strongly associated genes in schizophrenia and bipolar disorder. Studies have also highlighted the importance of DISC1 at different stages of neurogenesis such as neuronal proliferation, differentiation and

migration (Porteous et al., 2006, Mao et al., 2009, Brandon and Sawa, 2011, Porteous et al., 2011), reflecting the diversity of potential roles of DISC1 and its importance to overall brain function.

7.4 SFMHS multimodal imaging results

Recent yet-to-be published work by colleagues using data from the SFMHS have found differences between carriers and non-carriers using multimodal imaging. These findings include reduced left superior temporal sulcus cortical thickness and reduced right superior frontal gyrification index in carriers. Carriers also demonstrated reductions in glutamate concentrations in the right DLPFC. fMRI results from an *n*-back working memory task have found increased activation in the caudate nucleus in carriers (Lawrie et al., In Press). As with the current results, no differences have been found on measures of cognition, suggesting that the translocation may have a more measurable impact upon the intermediate neural systems level, supporting the endophenotype approach.

The current results also found differences in the aforementioned regions, including increased activation in carriers the right DLPFC and right superior frontal gyrus. Findings in the current patient sample also reported abnormal activity in the caudate nucleus, as reported in carriers during the working memory task. It is reassuring that there is an overlap between the current fMRI results and the wider imaging findings from the SFMHS. Combined, these findings suggest that the t(1;11) translocation is associated with a range of clinical outcomes in the family, but may have a more homogeneous effect on imaging measures. However, the current fMRI results from this thesis only included carriers with affective psychopathology, whereas participants included in the wider SFMHS included

carriers with a range of diagnoses. Therefore, a logical inference based on the different imaging modalities is not straightforward and warrants further investigation.

7.5 Translocation carriers vs. patient sample

In the current results, patients with bipolar disorder showed a pattern of overactivation in a region including the ACC and VLPFC during recognition when compared to healthy controls. Overactivation in these structures was also observed during recognition in translocation carriers. These findings are in line with previous research suggesting that bipolar disorder arises from disruption in a fronto-limbic network consisting of VLPFC areas with connections to limbic regions including the amygdala, insula and ACC (Strakowski, 2012, Strakowski et al., 2004). A pattern of overactivation in these regions was found in the current patient sample and has been consistently demonstrated in patients with bipolar disorder (Cerullo et al., 2009, Wessa et al., 2007, Chang et al., 2004). Several studies have also found abnormal connectivity within a fronto-limbic pathway that may be an imaging marker in patients with bipolar disorder (Anand et al., 2009, Chepenik et al., 2010, Öngür et al., 2010, Chai et al., 2011). There is also evidence of hyperactivation of the VLPFC in bipolar disorder (Robinson et al., 2008, Blumberg et al., 2003b). It has been proposed that the overactivation in this brain network is persistent and leaves individuals at risk for mood and cognitive dysfunction, even during the euthymic state (Strakowski et al., 2004).

In the current results, patients with schizophrenia showed reduced activation during memory recognition in a region encompassing the ACC and caudate, compared to both controls and patients with bipolar disorder. The current findings support previous studies

suggesting overactivation of fronto-limbic and striatal structures including the ACC and caudate in bipolar disorder (Wessa et al., 2007), and a relative underactivation in schizophrenia (Koch et al., 2008). Therefore, family members with the translocation appeared to demonstrate a more similar pattern of overactivation during recognition to patients with bipolar disorder, compared to schizophrenia. This may reflect the fact that most diagnoses in the carriers were of an affective disorder rather than a schizophrenia-related psychosis, and may be due to the presence of symptoms in the carriers rather than a direct effect of the translocation. Compared to recognition, there was no overlap in findings between family members and patients during the encoding phase of the task. It would also be of interest to understand the results in relation to depression, which was diagnosed in 4 of the carriers (2 with recurrent and 2 with single episode depression), and in hindsight a comparison group of patients with depression would have been of interest to include.

7.6 Overlap between schizophrenia and bipolar disorder

Bipolar disorder and schizophrenia are historically considered two distinct disorders but convergent genetic, neuroimaging and clinical evidence indicates both overlap and discontinuity between them. Diagnostic classifications based on clinical presentation of symptoms, such as the DSM, enable reliable diagnosis but do not neatly align with neuroimaging and genetic evidence. Therefore, current diagnostic categories may not reflect the underlying pathophysiology of psychiatric disorders, and this may limit their ability to deliver novel therapeutic approaches (Insel et al., 2010). Functional neuroimaging offers a tool to explore the underlying neurobiological processes of these disorders in order to establish if there are illness-specific features, ultimately to inform diagnosis and treatment options.

The neuroimaging literature that compares schizophrenia and bipolar disorder is extensive. Recent reviews of studies directly comparing both disorders using fMRI conclude that in tasks involving emotion, reward and memory, overactivation is generally seen in MTL structures or limbic regions in bipolar disorder compared to schizophrenia (Whalley et al., 2012b, Strakowski, 2012). The current results in the patient groups are in line with these findings and suggest that there is evidence for differences between these disorders at the functional level during episodic memory recognition. Activation in a region including the caudate and ACC may distinguish between patients with schizophrenia and bipolar disorder, with lower activity seen in schizophrenia and enhanced activation in bipolar disorder. The ability to distinguish between schizophrenia and bipolar disorder using non-invasive imaging techniques suggests that there are at least partly distinct mechanisms underlying the disorders, which ultimately may facilitate efforts to develop a neuroscience-based approach to the classification of mental disorders (Hall et al., 2010).

7.7 Episodic memory as an endophenotype

Episodic memory deficits are evident in both schizophrenia and bipolar disorder, have been found in unaffected relatives of patients and individuals at high genetic risk (Christodoulou et al., 2012, Hill et al., 2008), and have been found to be moderately heritable and share substantial genetic overlap with schizophrenia (Owens et al., 2011). Therefore, episodic memory deficits have been suggested as a potential endophenotype for psychosis (Leavitt and Goldberg, 2009).

Patients with schizophrenia and bipolar disorder show episodic memory related neural abnormalities in prefrontal and temporal regions (Ragland et al., 2009, Oertel-Knochel et

al., 2014), which have also been demonstrated in unaffected relatives (Cannon et al., 2005), supporting a genetic basis for deficits in episodic memory (Leavitt and Goldberg, 2009). Studies examining the effects of common variants in DISC1 alleles suggest that variation at the DISC1 locus contributes to structural and functional changes across the brain, particularly in prefrontal and temporal regions (Duff et al., 2013, Callicott et al., 2005, Cannon et al., 2005, Thomson et al., 2013). Genetic studies have also shown that variation in DISC1 has an effect on the neural correlates of episodic memory in healthy subjects (Callicott et al., 2005, Di Giorgio et al., 2008). The current findings provide evidence to support a potential role for the DISC1 translocation on brain activations in prefrontal and temporal regions.

Previous research suggests that episodic memory impairments may share a common mechanism with other cognitive domains such as working memory, language function, executive function, processing speed and attention (Barch and Ceaser, 2012). Research has found common neural activity during episodic memory recognition and working memory tasks, particularly in the DLPFC (Cabeza et al., 2002, Ranganath et al., 2003). The current results found an impact of the translocation on activation in the DLPFC during episodic memory recognition. Previous research has also found evidence of an effect of DISC1 genotype on activity in the DLPFC during a working memory task, interpreting increased activity in risk allele carriers as cortical inefficiency (Brauns et al., 2011). These findings suggest that the function of a specific brain region should not be over specified. DISC1 may impact upon DLPFC inefficiency, which may underlie several cognitive deficits including episodic memory and working memory, which are also reported in patients with both schizophrenia and bipolar disorder.

7.8 Limitations

7.8.1 Family members

The current findings suggest that the DISC1 translocation has a measurable impact upon episodic memory-related activation. However, this finding should be considered with caution, as there are several confounding factors that may interfere with the interpretation of results.

As outlined in chapter one, there is evidence that ageing is associated with impaired memory functioning using functional brain imaging techniques. The age of the translocation carrier group (mean age of 52) was significantly higher than the non-carrier group (mean age of 32) and was therefore entered as a covariate in the second-level analyses. It was originally planned to run an additional post-hoc analysis based on a subgroup of participants, if there was a significant difference in terms of age between the groups. This would be done by removing a group of significantly younger individuals in the non-carrier group (seven individuals aged 17-23), as has been performed in other studies examining this family (Whalley et al., 2015). However, the non-carrier group who successfully completed the fMRI task was not large enough, and this would have left only four individuals in the analysis. Therefore, although age was controlled for in this analysis, it is still possible that the current findings are confounded by the effects of age. For the comparison of patients versus controls, the groups were not significantly different in terms of age.

A major limitation of the family member results, and perhaps the most important to highlight, is the sample of carriers who were recruited. All the translocation carriers that

took part had a psychiatric diagnosis of an affective nature ranging from MDD to cyclothymia, rather than a psychotic illness such as schizophrenia or bipolar disorder. In total 12 family members with the translocation took part in the wider SFMHS, however four did not complete the fMRI section of the study for various reasons. It is unfortunate that the carriers who did not manage to complete the fMRI task all had a diagnosis of either schizophrenia or bipolar disorder. It is possible that these four individuals had worse symptomatology that interfered with their ability to take part in the fMRI part of the study. However, from a comparison of the carriers who took part vs. those who did not (results not reported in thesis), there was no significant difference in age, gender, IQ or any clinical measures (all $p > 0.05$).

It was originally planned to recruit and compare individuals with and without psychosis within in the carrier group, to compare the effect of having a psychotic disorder in addition to the translocation. However, this was not possible due to the sample of carriers that took part. Instead imaging findings were correlated to clinical measures including positive symptoms on the PANSS. There was no association between psychotic symptoms and peak activation in any region during encoding or recognition in the carrier group. Further to this, there were no significant correlations between measures of depression on the HDRS, in the carriers. This supports the idea that the results are due to the effect of the translocation, rather than having psychotic or depressive symptoms. However, these correlations should be interpreted with caution due to small group numbers and the presence of outliers, in particular one individual in the carrier group who scored substantially higher on all clinical measures. Outliers were not removed from the analysis due to small numbers and nonparametric statistics were performed to account for this where possible. Therefore,

although symptomatology has been taken into consideration, it is still possible that the current between group imaging findings are due to the presence of symptoms or affective diagnoses in the carrier group, rather than a direct effect of the translocation.

The clinical status and age of the carrier group, in addition to the low number recruited, was unavoidable due to the nature of the family being studied, as cases occur infrequently and are often difficult to recruit. The unique nature of the family being studied and that no research (until recently as part of the SFMHS) has previously investigated the effect of the t(1;11) translocation on neuroimaging measures, arguably outweighs such methodological limitations. The current findings of this work are novel and provide evidence to suggest that the translocation does impact on neuroimaging measures, however it is imperative to interpret the results in light of these potential confounding factors.

7.8.2 Patients and controls

The patient groups recruited to the current study included individuals with schizophrenia and bipolar disorder, however it is noted that all family members with the translocation had diagnoses of major depressive disorder, as well as other psychiatric disorders including cyclothymia and conduct disorder. Therefore, the patient groups recruited might not have been the best mix of psychiatric diagnoses. In hindsight it would have been beneficial to include a sample of patients with major depressive disorder in addition to schizophrenia and bipolar disorder.

In the past, the majority of research into DISC1 has focused on schizophrenia. After the initial identification of the DISC1 gene in 2000, subsequent genetic linkage and association

studies provided evidence to suggest that DISC1 may be implicated in both schizophrenia and bipolar disorder (Ekelund et al., 2000, Hennah et al., 2003, Thomson et al., 2005). However, there was limited research to examine the association between the DISC1 gene and major depression, despite there being more patients with depression than those with schizophrenia in the original Scottish family (Hashimoto et al., 2006). Therefore, there is substantially more evidence to support a link between DISC1 and schizophrenia, which explains the reason for the focus on patients with schizophrenia in the current study. However, more recently there has been increasing evidence to support an association between MDD and variation in the DISC1 locus, for example the Ser704Cys SNP (Hashimoto et al., 2006), suggesting DISC1 is also implicated in the biology of major depression.

DISC1 research has been criticized by some, suggesting that linkage analyses are more consistent with a mood disorder phenotype (Sullivan et al., 2013), and ultimately suggesting that naming this gene 'disrupted in schizophrenia' is prone to misinterpretation. Some researchers have also highlighted that the spectrum of psychiatric disorders and clinical heterogeneity seen in the wider family is of concern and makes results interpretable. However, this is what is key to this unique family. Clinically all members of the family with the translocation that took part in the wider SFMHS have a mental health diagnosis that ranged from chronic schizophrenia to cyclothymia. This phenotypic pleiotropy of DISC1 is evident in the wider DISC1 family (St Clair et al., 1990). The spectrum of diagnoses seen in this family reflects the genetic and biological overlap between different DSM-defined disorders and is consistent with accumulating GWAS evidence for shared genetic liability (Smoller et al., 2013). The presence of different diagnoses in the family is

also consistent with estimates of co-heritability from GWAS research, for example schizophrenia and bipolar disorder (0.68), or schizophrenia and MDD (0.43) (Lee et al., 2013). Further, many neuroimaging abnormalities in specific brain regions and during various cognitive tasks have been found not only in one particular disorder such as schizophrenia but also in a wide range of diagnoses including bipolar disorder, depression and even autism. Therefore, studying DISC1 may help to inform us not only about a single disorder such as schizophrenia but also a wider range of potentially overlapping psychiatric conditions. Ultimately, DISC1 may not be a specific genetic risk factor for disorders that are based on DSM classifications, but instead may confer a risk at the endophenotype level that underlies several major psychiatric disorders. The wide spectrum of diagnoses in the family may be due to additional genetic or non-genetic factors, such as shared environmental influences, which are currently under investigation.

7.8.3 Other limitations

Retrospectively it is acknowledged that a power calculation should have been performed to determine the appropriate sample size for the control and patient sample. For the family member comparison a power calculation was not appropriate due to the nature of the sample being studied, and therefore as many family members as possible were recruited. It is highly recommended to perform a power calculation when designing a research study as they allow researchers to calculate the minimum number of subjects required to obtain the desired statistical power, which is usually 80% or more. Power calculations allow researchers to optimise the cost of an fMRI experiment. They prevent wasting time and money on studies that are underpowered to detect a true effect, and avoid recruiting too

many participants when sufficient power would have been available with a lower number (Durnez et al., 2016).

It is relatively simple to perform a power computation for a single, univariate response, however it is substantially more complex to determine power for an fMRI study, as several parameters must be specified including between and within subject variance, 1st and 2nd level design and the size of the hypothesized effect (Durnez et al., 2016). Many of the parameters required for power computation need to be estimated based on pilot data, however many research studies do not have the funds or resources to generate data for a power calculation. Therefore, many published fMRI studies do not present power calculations and it is argued by some that much neuroscience research suffers from low power as a result.

7.8.4 Strengths and limitations of the task

The fMRI paradigm used to measure episodic memory has several limitations. For example it was a blocked design, which does not allow for the distinction between neural activity for correct and incorrect responses during the recognition phase. Examination using a more temporally sensitive measure, such as an event related design, would allow for this. However, the current block design task was chosen to improve power with our anticipated small sample size in the family member groups. This task was also selected as it has been used previously to investigate the effect of genetic variation on functional activation and has shown to be a reliable activator of the hippocampus, upon which the translocation was hypothesised to have an impact.

A further limitation of this task is that the interpretation of the recognition phase is particularly complex because it included a mixture of both encoding (new scenes) and recognition (old scenes) processes, likely to engage encoding-related activity in addition to recognition mechanisms. Passive rest was used as a control condition in the current task, which may not offer an optimal baseline condition as previous research has found elevated activity of the hippocampus during rest (Di Giorgio et al., 2008). This also may have contributed to the lack of findings in the hippocampus.

The memory task used was relatively easy and required low cognitive demand as evident by the high performance accuracy seen in all participants, and therefore may not elicit BOLD response differences sufficient enough to reach our statistical threshold. Previous studies have demonstrated that the effect of genetic variants on functional activation is more evident at the highest cognitive load in parametric tasks (Bertolino et al., 2004, Blasi and Bertolino, 2006, Egan et al., 2001). These factors together may have significantly contributed to the subtlety of some of the differences between the groups. However, the relative ease of the current task ensured that all subjects could perform the task adequately to be included in analysis. A further strength is that task performance was balanced across groups, therefore between group differences in activation are unlikely to be attributed to differences in performance.

Furthermore the paradigm used in this study was an incidental memory task, as participants were not explicitly instructed to memorize each scene for later recognition. Incidental encoding has been associated with substantially fewer differences between controls and patients, compared to intentional encoding. Bonner-Jackson et al. (2008) found that use of

an incidental encoding strategy e.g. making living/non-living judgments, improved recognition in patients and resulted in a more similar pattern of activation to that of controls (Bonner-Jackson et al., 2008). However, use of an incidental memory task hopefully represents a more realistic and ecologically valid representation of everyday memory function.

7.9 Future analysis

Polygenic risk scores had not been calculated for the sample of healthy controls and patients included within this thesis at the time of writing, and therefore could not be investigated. Future analysis is planned to examine PRS within these groups to investigate the effect of cumulative genetic risk on episodic memory-related activation in controls and patients with schizophrenia and bipolar disorder.

Future analysis could also examine a measure of cross-disorder polygenic risk, based on the additive effects of genetic susceptibility to a range of psychiatric disorders. This is in order to reflect the range of diagnoses present in the translocation carriers. A cross-disorder measure of polygenic risk is likely to account for a greater proportion of overall risk compared to PRS for individual disorders (Smoller et al., 2013). A recent study by Whalley et al. (2015) used this technique to investigate the impact of cumulative genetic risk for five major psychiatric disorders on brain activation during a language-based executive task (Whalley et al., 2015b). This study found that increased cross-disorder PRS was associated with increased frontal activation in individuals without a family history of psychiatric illness.

7.9.1 Connectivity of brain networks

The current findings in the family demonstrate a more distributed network of brain regions during recognition than during encoding. Translocation carriers showed increased activation in frontal, limbic, temporal and cerebellar regions during recognition of scenes. In future analyses it would be of interest to investigate the effect of the translocation on functional or effective connectivity of brain networks, and compare findings to networks disrupted in psychiatric disorders.

Functional connectivity is used to examine statistical patterns in fMRI data whereas effective connectivity uses a causal model to investigate how regions interact (Goldenberg and Galván, 2015). There are several different methods to explore connectivity using fMRI data including psychophysiological interactions, independent component analysis, and dynamic causal modelling (DCM). Specifically, DCM offers a tool to explore effective connectivity by creating a neuronal model of interacting cortical regions by treating the brain as a nonlinear dynamic system (Friston et al., 2003). DCM is not however an exploratory method and requires specific priori hypotheses. This analysis would be of interest for future study.

Additional future analyses could include a multimodal approach to examine the current fMRI results with structural and functional data from the SFMHS, in order to investigate whether there is an overlap between different imaging modalities. For example, relating the current fMRI findings to magnetic resonance spectroscopy data, to investigate glutamate concentrations in regions of interest e.g. the DLPFC (results from the SFMHS show that carriers have a reduction in glutamate concentrations in the right DLPFC). This may offer

a potential neurochemical explanation of the current results. Glutamatergic disruption has been implicated in schizophrenia and mood disorders, and research has suggested that genetic risk associated with alterations in glutamatergic function may be implicated in the pathophysiological pathways of major psychiatric disorders (Coyle, 2006, Yüksel and Öngür, 2010, Hall et al., 2009).

7.9.2 Connectivity and DISC1

Few studies have investigated the effect of DISC1 on functional connectivity. The effects of DISC1 on brain connectivity, in networks that have been shown to be implicated in different psychiatric disorders, are therefore largely unknown. A recent study by Lui et al. (2013) used resting-state fMRI data to examine the effect of the DISC1 Ser704Cys polymorphism on functional connectivity of brain networks (Liu et al., 2013a). They found an effect of DISC1 on the thalamic-prefrontal network, specifically that Cys carriers showed increased functional connectivity and significantly decreased thalamic-prefrontal anatomical connectivity.

Another study found evidence of an association between six DISC1 SNPs and connectivity between the right precuneus and inferior frontal gyrus, during resting state activity (Gong et al., 2014). As previously discussed DISC1 interacts with other genetic variants, and evidence has found an effect of DISC1 and interacting SNPs on connectivity. Callicott et al. (2013) found that individuals homozygous for risk alleles in both DISC1 and SLC12A2 resulted in reduced connectivity between the hippocampus and VLPFC during an encoding memory paradigm (Callicott et al., 2013).

Non-human studies have also investigated connectivity, for example transgenic mice expressing a truncated DISC1 gene demonstrated altered connectivity in hippocampal-PFC and thalamus-PFC connectivity, both of which have been reported in psychiatric illness (Dawson et al., 2015). Using functional connectivity may help to provide greater insight into the neural effects of variation in the DISC1 gene and the link to psychiatric disorders.

A recent study using DTI data from the SFMHS found structural connectivity differences in prefrontal association fibers in translocation carriers, including those connecting the frontal cortex with temporal and limbic regions. These findings were also replicated in a comparison between patients with psychosis and healthy controls and are consistent with evidence of abnormal fronto-temporal connectivity in schizophrenia, bipolar disorder and unaffected relatives (Sprooten et al., 2011b, Lawrie et al., 2002, Maniega et al., 2008). Disconnection between these regions has been hypothesised to underlie cognitive impairments in psychosis. Studies examining the effects of common variants in DISC1 alleles suggest that variation at the DISC1 locus contributes to structural and functional changes across the brain, particularly in prefrontal and temporal regions (Callicott et al., 2005, Cannon et al., 2005, Duff et al., 2013). The current results in this work found an effect of the translocation in prefrontal and temporal regions during both encoding and recognition, supporting evidence that DISC1 impacts upon these regions.

7.10 Conclusion

Studying the impact of rare genetic variants offers a powerful method to advance our understanding of the pathophysiology of psychiatric disorders. The current findings are novel and provide insight into the potential effect of the DISC1 t(1;11) translocation in

episodic memory related brain activation. Brain regions that were over activated in translocation carriers have been shown to be involved in memory encoding and recognition, and are known to be affected in patients with major psychiatric disorders, such as schizophrenia and bipolar disorder, and their unaffected relatives. Family members with the translocation demonstrated a more similar pattern of activation during recognition to patients with bipolar disorder compared to schizophrenia, perhaps due to the fact that most diagnoses in the carriers were of an affective nature rather than a schizophrenia-related psychosis. Based on these findings it can be argued that the translocation has an influence on brain activations in areas associated with episodic memory processes, however these results must be considered in light of potential confounding factors as discussed throughout. Nonetheless, these findings begin to provide a better understanding of the neural effects of the t(1;11) translocation, and highlight the significance of rare but biologically informative genetic variants in understanding psychosis.

Publications

Literature review contained within this thesis (chapter 2):

REDPATH, H. L., LAWRIE, S. M., SPROOTEN, E. S., WHALLEY, H. C., MCINTOSH, A. M. & HALL, J. 2013. Progress in imaging the effects of psychosis susceptibility gene variants. *Expert Review of Neurotherapeutics,* 13, 37-47.

REDPATH, H. L., COOPER, D. & LAWRIE, S. L. 2013. Imaging symptoms and syndromes: similarities and differences between schizophrenia and bipolar disorder. *Biological psychiatry*, 73, 495–96.

THOMSON, P. A., DUFF, B., BLACKWOOD, D. H. R., ROMANIUK, L., WATSON, A., WHALLEY, H. C., LI, X., DAUVERMANN, M. R., MOORHEAD, T. W. J., BOIS, C., RYAN, N. M., **REDPATH, H. L.**, HALL, L., MORRIS, S. W., VAN BEEK, E. J. R., ROBERTS, N., PORTEOUS, D. J., ST. CLAIR, D., WHITCHER, B., DUNLOP, J., BRANDON, N. J., HUGHES, Z. A., HALL, J., MCINTOSH, A., LAWRIE, S. M. 2016. Balanced translocation linked to psychiatric disorder, glutamate, and cortical structure/function. *Npj Schizophrenia,* 2, 16024.

References

ABBOTT, C., JARAMILLO, A., E WILCOX, C. & A HAMILTON, D. 2013. Antipsychotic drug effects in schizophrenia: a review of longitudinal FMRI investigations and neural interpretations. *Current medicinal chemistry,* 20**,** 428-437.

ABEL, K. M., DRAKE, R. & GOLDSTEIN, J. M. 2010. Sex differences in schizophrenia. *International Review of Psychiatry,* 22**,** 417-428.

ACHIM, A. M. & LEPAGE, M. 2005. Episodic memory-related activation in schizophrenia: meta-analysis. *Br J Psychiatry,* 187**,** 500-9.

ADAMS, R. & DAVID, A. S. 2007. Patterns of anterior cingulate activation in schizophrenia: a selective review. *Neuropsychiatric disease and treatment,* 3**,** 87.

ADLER, C. M., HOLLAND, S. K., SCHMITHORST, V., TUCHFARBER, M. J. & M STRAKOWSKI, S. 2004. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disorders,* 6**,** 540-549.

ALLEN, A. J., GRISS, M. E., FOLLEY, B. S., HAWKINS, K. A. & PEARLSON, G. D. 2009. Endophenotypes in schizophrenia: a selective review. *Schizophr Res,* 109**,** 24-37.

ALSABBAN, S., RIVERA, M. & MCGUFFIN, P. 2011. Genome-wide searches for bipolar disorder genes. *Current psychiatry reports,* 13**,** 522-527.

ANAND, A., LI, Y., WANG, Y., LOWE, M. J. & DZEMIDZIC, M. 2009. Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research: Neuroimaging,* 171**,** 189-198.

ANDREASEN, N. C., NOPOULOS, P., O'LEARY, D. S., MILLER, D. D., WASSINK, T. & FLAUM, M. 1999. Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. *Biological psychiatry,* 46**,** 908-920.

ANDREASEN, N. C., O'LEARY, D. S., CIZADLO, T., ARNDT, S., REZAI, K., PONTO, L., WATKINS, G. L. & HICHWA, R. D. 1996. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proceedings of the National Academy of Sciences,* 93**,** 9985-9990.

ANDREASEN, N. C., PARADISO, S. & O'LEARY, D. S. 1998. " Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophrenia Bulletin,* 24**,** 203.

ANTICEVIC, A., SAVIC, A., REPOVS, G., YANG, G., MCKAY, D. R., SPROOTEN, E., KNOWLES, E. E., KRYSTAL, J. H., PEARLSON, G. D. & GLAHN, D. C. 2014. Ventral anterior cingulate connectivity distinguished nonpsychotic bipolar illness from psychotic bipolar disorder and schizophrenia. *Schizophrenia bulletin***,** sbu051.

ARGYELAN, M., IKUTA, T., DEROSSE, P., BRAGA, R. J., BURDICK, K. E., JOHN, M., KINGSLEY, P. B., MALHOTRA, A. K. & SZESZKO, P. R. 2013. Resting-

state FMRI connectivity impairment in schizophrenia and bipolar disorder. *Schizophrenia bulletin***,** sbt092.

ARTS, B., JABBEN, N., KRABBENDAM, L. & VAN OS, J. 2008. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological medicine,* 38**,** 771-785.

ASSAF, M., RIVKIN, P. R., KUZU, C. H., CALHOUN, V. D., KRAUT, M. A., GROTH, K. M., YASSA, M. A., HART, J. & PEARLSON, G. D. 2006. Abnormal object recall and anterior cingulate overactivation correlate with formal thought disorder in schizophrenia. *Biological psychiatry,* 59**,** 452-459.

AUSTIN, C., KY, B., MA, L., MORRIS, J. & SHUGHRUE, P. 2004. Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. *Neuroscience,* 124**,** 3-10.

AYALEW, M., LE-NICULESCU, H., LEVEY, D., JAIN, N., CHANGALA, B., PATEL, S., WINIGER, E., BREIER, A., SHEKHAR, A. & AMDUR, R. 2012. Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. *Mol Psychiatry*.

BADRE, D. & WAGNER, A. D. 2002. Semantic retrieval, mnemonic control, and prefrontal cortex. *Behavioral and Cognitive Neuroscience Reviews,* 1**,** 206-218.

BAIANO, M., DAVID, A., VERSACE, A., CHURCHILL, R., BALESTRIERI, M. & BRAMBILLA, P. 2007. Anterior cingulate volumes in schizophrenia: a systematic review and a meta-analysis of MRI studies. *Schizophrenia research,* 93**,** 1-12.

BAIG, B. J., WHALLEY, H. C., HALL, J., MCINTOSH, A. M., JOB, D. E., CUNNINGHAM-OWENS, D. G., JOHNSTONE, E. C. & LAWRIE, S. M. 2010. Functional magnetic resonance imaging of BDNF val66met polymorphism in unmedicated subjects at high genetic risk of schizophrenia performing a verbal memory task. *Psychiatry Res,* 183**,** 195-201.

BALANZÁ-MARTÍNEZ, V., RUBIO, C., SELVA-VERA, G., MARTINEZ-ARAN, A., SANCHEZ-MORENO, J., SALAZAR-FRAILE, J., VIETA, E. & TABARES-SEISDEDOS, R. 2008. Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. *Neuroscience & Biobehavioral Reviews,* 32**,** 1426-1438.

BARCH, D. M., BRAVER, T. S., NYSTROM, L. E., FORMAN, S. D., NOLL, D. C. & COHEN, J. D. 1997. Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia,* 35**,** 1373-1380.

BARCH, D. M. & CEASER, A. 2012. Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn Sci,* 16**,** 27-34.

BAUER, M. & PFENNIG, A. 2005. Epidemiology of bipolar disorders. *Epilepsia,* 46**,** 8-13.

BEARDEN, C. E., VAN ERP, T. G., THOMPSON, P. M., TOGA, A. W. & CANNON, T. D. 2007. Cortical mapping of genotype-phenotype relationships in schizophrenia. *Hum Brain Mapp,* 28**,** 519-32.

BENTALL, R. P., BAKER, G. A. & HAVERS, S. 1991. Reality monitoring and psychotic hallucinations. *British Journal of Clinical Psychology,* 30**,** 213-222.

BERRETTINI, W. Evidence for shared susceptibility in bipolar disorder and schizophrenia. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 2003. Wiley Online Library, 59-64.

BERSANI, F. S., MINICHINO, A., FOJANESI, M., GALLO, M., MAGLIO, G., VALERIANI, G., BIONDI, M. & FITZGERALD, P. 2014. Cingulate Cortex in Schizophrenia: its relation with negative symptoms and psychotic onset. A review study. *European review for medical and pharmacological sciences*.

BERTOLINO, A., CAFORIO, G., BLASI, G., DE CANDIA, M., LATORRE, V., PETRUZZELLA, V., ALTAMURA, M., NAPPI, G., PAPA, S. & CALLICOTT, J. H. 2004. Interaction of COMT Val108/158 Met genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *American Journal of Psychiatry,* 161**,** 1798-1805.

BERTOLINO, A., RUBINO, V., SAMBATARO, F., BLASI, G., LATORRE, V., FAZIO, L., CAFORIO, G., PETRUZZELLA, V., KOLACHANA, B., HARIRI, A., MEYER-LINDENBERG, A., NARDINI, M., WEINBERGER, D. R. & SCARABINO, T. 2006. Prefrontal-hippocampal coupling during memory processing is modulated by COMT val158met genotype. *Biol Psychiatry,* 60**,** 1250-8.

BERTRAM, L., LILL, C. M. & TANZI, R. E. 2010. The genetics of Alzheimer disease: back to the future. *Neuron,* 68**,** 270-281.

BEYER, J. L., KUCHIBHATLA, M., PAYNE, M., MOO-YOUNG, M., CASSIDY, F., MACFALL, J., KRISHNAN, R. & RANGA, K. 2004. Caudate volume measurement in older adults with bipolar disorder. *International journal of geriatric psychiatry,* 19**,** 109-114.

BILDER, R. M. & DEGREEF, G. 1991. Morphologic markers of neurodevelopmental paths to schizophrenia. *Developmental neuropathology of schizophrenia.* Springer.

BLACKWOOD, D. 2000. P300, a state and a trait marker in schizophrenia. *Lancet,* 355**,** 771-2.

BLACKWOOD, D., FORDYCE, A., WALKER, M., ST CLAIR, D., PORTEOUS, D. & MUIR, W. 2001. Schizophrenia and affective disorders - cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *The American Journal of Human Genetics,* 69**,** 428-433.

BLACKWOOD, D. & MUIR, W. 2004. Clinical phenotypes associated with DISC1, a candidate gene for schizophrenia. *Neurotoxicity research,* 6**,** 35-41.

BLACKWOOD, D., ST CLAIR, D. & MUIR, W. 1991. DNA markers and biological vulnerability markers in families multiply affected with schizophrenia. *European archives of psychiatry and clinical neuroscience,* 240**,** 191-6.

BLAIR, J. R. & SPREEN, O. 1989. Predicting premorbid IQ: a revision of the National Adult Reading Test. *The Clinical Neuropsychologist,* 3**,** 129-136.

BLAKELY, R. D. & VEENSTRA-VANDERWEELE, J. 2011. Genetic Indeterminism, the 5-HTTLPR, and the Paths Forward in Neuropsychiatric Genetics. *Arch Gen Psychiatry,* 68**,** 457-458.

BLASI, G. & BERTOLINO, A. 2006. Imaging genomics and response to treatment with antipsychotics in schizophrenia. *NeuroRx,* 3**,** 117-30.

BLOKLAND, G. A., MCMAHON, K. L., THOMPSON, P. M., MARTIN, N. G., DE ZUBICARAY, G. I. & WRIGHT, M. J. 2011. Heritability of working memory brain activation. *J Neurosci,* 31**,** 10882-90.

BLUMBERG, H. P., KAUFMAN, J., MARTIN, A., WHITEMAN, R., ZHANG, J. H., GORE, J. C., CHARNEY, D. S., KRYSTAL, J. H. & PETERSON, B. S. 2003a. Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder. *Archives of general psychiatry,* 60**,** 1201-1208.

BLUMBERG, H. P., LEUNG, H.-C., SKUDLARSKI, P., LACADIE, C. M., FREDERICKS, C. A., HARRIS, B. C., CHARNEY, D. S., GORE, J. C., KRYSTAL, J. H. & PETERSON, B. S. 2003b. A functional magnetic resonance imaging study of bipolar disorder: state-and trait-related dysfunction in ventral prefrontal cortices. *Archives of General Psychiatry,* 60**,** 601-609.

BLUMBERG, H. P., MARTIN, A., KAUFMAN, J., LEUNG, H.-C., SKUDLARSKI, P., LACADIE, C., FULBRIGHT, R. K., GORE, J. C., CHARNEY, D. S. & KRYSTAL, J. H. 2003c. Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. *American Journal of Psychiatry,* 160**,** 1345-1347.

BLUMBERG, H. P., STERN, E., MARTINEZ, D., RICKETTS, S., DE ASIS, J., WHITE, T., EPSTEIN, J., MCBRIDE, P. A., EIDELBERG, D. & KOCSIS, J. H. 2000. Increased anterior cingulate and caudate activity in bipolar mania. *Biological psychiatry,* 48**,** 1045-1052.

BLUMENFELD, R. S., PARKS, C. M., YONELINAS, A. P. & RANGANATH, C. 2011. Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. *Journal of cognitive neuroscience,* 23**,** 257-265.

BLUMENFELD, R. S. & RANGANATH, C. 2006. Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *The Journal of Neuroscience,* 26**,** 916-925.

BLUMENFELD, R. S. & RANGANATH, C. 2007. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. *The Neuroscientist,* 13**,** 280-291.

BONNER-JACKSON, A., YODKOVIK, N., CSERNANSKY, J. G. & BARCH, D. M. 2008. Episodic memory in schizophrenia: the influence of strategy use on behavior and brain activation. *Psychiatry Res,* 164**,** 1-15.

BORA, E., YUCEL, M. & PANTELIS, C. 2009. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of affective disorders,* 113**,** 1-20.

BOURNE, C., AYDEMIR, O., BALANZA-MARTINEZ, V., BORA, E., BRISSOS, S., CAVANAGH, J. T., CLARK, L., CUBUKCUOGLU, Z., DIAS, V. V.,

DITTMANN, S., FERRIER, I. N., FLECK, D. E., FRANGOU, S., GALLAGHER, P., JONES, L., KIESEPPA, T., MARTINEZ-ARAN, A., MELLE, I., MOORE, P. B., MUR, M., PFENNIG, A., RAUST, A., SENTURK, V., SIMONSEN, C., SMITH, D. J., BIO, D. S., SOEIRO-DE-SOUZA, M. G., STODDART, S. D., SUNDET, K., SZOKE, A., THOMPSON, J. M., TORRENT, C., ZALLA, T., CRADDOCK, N., ANDREASSEN, O. A., LEBOYER, M., VIETA, E., BAUER, M., WORHUNSKY, P. D., TZAGARAKIS, C., ROGERS, R. D., GEDDES, J. R. & GOODWIN, G. M. 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand,* 128**,** 149-62.

BRANDON, N. J. & SAWA, A. 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nature Reviews Neuroscience,* 12**,** 707-722.

BRANDT, C. L., EICHELE, T., MELLE, I., SUNDET, K., SERVER, A., AGARTZ, I., HUGDAHL, K., JENSEN, J. & ANDREASSEN, O. A. 2014. Working memory networks and activation patterns in schizophrenia and bipolar disorder: comparison with healthy controls. *The British Journal of Psychiatry***,** bjp. bp. 113.129254.

BRAUNS, S., GOLLUB, R. L., ROFFMAN, J. L., YENDIKI, A., HO, B.-C., WASSINK, T. H., HEINZ, A. & EHRLICH, S. 2011. DISC1 is associated with cortical thickness and neural efficiency. *Neuroimage,* 57**,** 1591-1600.

BREBION, G., AMADOR, X., SMITH, M. & GORMAN, J. 1997. Mechanisms underlying memory impairment in schizophrenia. *Psychological medicine,* 27**,** 383-393.

BREMNER, J. D., VYTHILINGAM, M., VERMETTEN, E., VACCARINO, V. & CHARNEY, D. S. 2004. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *American Journal of Psychiatry,* 161**,** 637-645.

BROOKS, J. O., HOBLYN, J. C. & KETTER, T. A. 2010. Metabolic evidence of corticolimbic dysregulation in bipolar mania. *Psychiatry Research: Neuroimaging,* 181**,** 136-140.

BROOKS, J. O., ROSEN, A. C., HOBLYN, J. C., WOODARD, S. A., KRASNYKH, O. & KETTER, T. A. 2009a. Resting prefrontal hypometabolism and paralimbic hypermetabolism related to verbal recall deficits in euthymic older adults with bipolar disorder. *The American Journal of Geriatric Psychiatry,* 17**,** 1022-1029.

BROOKS, J. O., WANG, P. W., BONNER, J. C., ROSEN, A. C., HOBLYN, J. C., HILL, S. J. & KETTER, T. A. 2009b. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. *Journal of psychiatric research,* 43**,** 181-188.

BUCHMAN, D. Z. & ILLES, J. 2010. Neuroscience: Imaging Genetics for Our Neurogenetic Future. *Minn. JL Sci. & Tech.,* 11**,** 79-901.

BUCKNER, R. L., ANDREWS-HANNA, J. R. & SCHACTER, D. L. 2008. The brain's default network. *Annals of the New York Academy of Sciences,* 1124**,** 1-38.

BUCKNER, R. L., KOUTSTAAL, W., SCHACTER, D. L., WAGNER, A. D. & ROSEN, B. R. 1998. Functional–anatomic study of episodic retrieval using fMRI: I. Retrieval effort versus retrieval success. *Neuroimage,* 7**,** 151-162.

BURDICK, K. E., HODGKINSON, C. A., SZESZKO, P. R., LENCZ, T., EKHOLM, J. M., KANE, J. M., GOLDMAN, D. & MALHOTRA, A. K. 2005. DISC1 and neurocognitive function in schizophrenia. *Neuroreport,* 16**,** 1399.

BUTTON, K. S., IOANNIDIS, J. P., MOKRYSZ, C., NOSEK, B. A., FLINT, J., ROBINSON, E. S. & MUNAFO, M. R. 2013. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci,* 14**,** 365-76.

CABEZA, R., DASELAAR, S. M., DOLCOS, F., PRINCE, S. E., BUDDE, M. & NYBERG, L. 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral cortex,* 14**,** 364-375.

CABEZA, R., DOLCOS, F., GRAHAM, R. & NYBERG, L. 2002. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage,* 16**,** 317-330.

CABEZA, R. & NYBERG, L. 2000. Neural bases of learning and memory: functional neuroimaging evidence. *Current opinion in neurology,* 13**,** 415-421.

CALLICOTT, J. H., EGAN, M. F., MATTAY, V. S., BERTOLINO, A., BONE, A. D., VERCHINKSI, B. & WEINBERGER, D. R. 2003. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *American Journal of Psychiatry,* 160**,** 709-719.

CALLICOTT, J. H., FEIGHERY, E. L., MATTAY, V. S., WHITE, M. G., CHEN, Q., BARANGER, D. A., BERMAN, K. F., LU, B., SONG, H. & MING, G.-L. 2013. DISC1 and SLC12A2 interaction affects human hippocampal function and connectivity. *The Journal of clinical investigation,* 123**,** 2961.

CALLICOTT, J. H., STRAUB, R. E., PEZAWAS, L., EGAN, M. F., MATTAY, V. S., HARIRI, A. R., VERCHINSKI, B. A., MEYER-LINDENBERG, A., BALKISSOON, R., KOLACHANA, B., GOLDBERG, T. E. & WEINBERGER, D. R. 2005. Variation in DISC1 affects hippocampal structure and function and increases risk for schizophrenia. *Proc Natl Acad Sci U S A,* 102**,** 8627-32.

CAMARGO, L., COLLURA, V., RAIN, J., MIZUGUCHI, K., HERMJAKOB, H., KERRIEN, S., BONNERT, T., WHITING, P. & BRANDON, N. 2006. Disrupted in Schizophrenia 1 Interactome: evidence for the close connectivity of risk genes and a potential synaptic basis for schizophrenia. *Mol Psychiatry,* 12**,** 74-86.

CANLI, T., SIVERS, H., THOMASON, M. E., WHITFIELD-GABRIELI, S., GABRIELI, J. D. & GOTLIB, I. H. 2004. Brain activation to emotional words in depressed vs healthy subjects. *Neuroreport,* 15**,** 2585-2588.

CANNON, T. D., HENNAH, W., VAN ERP, T. G., THOMPSON, P. M., LONNQVIST, J., HUTTUNEN, M., GASPERONI, T., TUULIO-HENRIKSSON, A., PIRKOLA, T. & TOGA, A. W. 2005. Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short-and long-term memory. *Archives of general psychiatry,* 62**,** 1205-1213.

CARLESS, M., GLAHN, D., JOHNSON, M., CURRAN, J., BOZAOGLU, K., DYER, T., WINKLER, A., COLE, S., ALMASY, L. & MACCLUER, J. 2011. Impact of

DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Molecular psychiatry,* 16**,** 1096-1104.

CASCELLA, N. G., FIELDSTONE, S. C., RAO, V. A., PEARLSON, G. D., SAWA, A. & SCHRETLEN, D. J. 2010. Gray-matter abnormalities in deficit schizophrenia. *Schizophrenia Research,* 120**,** 63-70.

CASEY, B. J., SOLIMAN, F., BATH, K. G. & GLATT, C. E. 2010. Imaging genetics and development: challenges and promises. *Hum Brain Mapp,* 31**,** 838-51.

CERULLO, M. A., ADLER, C. M., DELBELLO, M. P. & STRAKOWSKI, S. M. 2009. The functional neuroanatomy of bipolar disorder. *Int Rev Psychiatry,* 21**,** 314-22.

CHAI, X. J., WHITFIELD-GABRIELI, S., SHINN, A. K., GABRIELI, J. D., CASTAÑÓN, A. N., MCCARTHY, J. M., COHEN, B. M. & ÖNGÜR, D. 2011. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. *Neuropsychopharmacology,* 36**,** 2009-2017.

CHAKIROVA, G., WHALLEY, H. C., THOMSON, P. A., HENNAH, W., MOORHEAD, T. W., WELCH, K. A., GILES, S., HALL, J., JOHNSTONE, E. C., LAWRIE, S. M., PORTEOUS, D. J., BROWN, V. J. & MCINTOSH, A. M. 2011. The effects of DISC1 risk variants on brain activation in controls, patients with bipolar disorder and patients with schizophrenia. *Psychiatry Res,* 192**,** 20-8.

CHANG, C. C., CHOW, C. C., TELLIER, L. C., VATTIKUTI, S., PURCELL, S. M. & LEE, J. J. 2014. Second-generation PLINK: rising to the challenge of larger and richer datasets. *ArXiv e-prints*.

CHANG, K., ADLEMAN, N. E., DIENES, K., SIMEONOVA, D. I., MENON, V. & REISS, A. 2004. Anomalous Prefrontal-Subcortical Activation in Familial Pediatric BipolarDisorder: A Functional Magnetic Resonance Imaging Investigation. *Archives of General Psychiatry,* 61**,** 781-792.

CHAO, L. L., HAXBY, J. V. & MARTIN, A. 1999. Attribute-based neural substrates in temporal cortex for perceiving and knowing about objects. *Nature neuroscience,* 2**,** 913-919.

CHEN, C. H., SUCKLING, J., LENNOX, B. R., OOI, C. & BULLMORE, E. T. 2011. A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar disorders,* 13**,** 1-15.

CHEPENIK, L. G., RAFFO, M., HAMPSON, M., LACADIE, C., WANG, F., JONES, M. M., PITTMAN, B., SKUDLARSKI, P. & BLUMBERG, H. P. 2010. Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Research: Neuroimaging,* 182**,** 207-210.

CHOI, J.-S., KANG, D.-H., KIM, J.-J., HA, T.-H., ROH, K. S., YOUN, T. & KWON, J. S. 2005. Decreased caudal anterior cingulate gyrus volume and positive symptoms in schizophrenia. *Psychiatry Research: Neuroimaging,* 139**,** 239-247.

CHRISTODOULOU, T., MESSINIS, L., PAPATHANASOPOULOS, P. & FRANGOU, S. 2012. The impact of familial risk for schizophrenia or bipolar disorder on cognitive control during episodic memory retrieval. *Psychiatry Res,* 197**,** 212-6.

CHUBB, J. E., BRADSHAW, N. J., SOARES, D. C., PORTEOUS, D. J. & MILLAR, J. K. 2008. The DISC locus in psychiatric illness. *Mol Psychiatry,* 13**,** 36-64.

CIRILLO, M. A. & SEIDMAN, L. J. 2003. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychology review,* 13**,** 43-77.

CIRULLI, E. T. & GOLDSTEIN, D. B. 2010. Uncovering the roles of rare variants in common disease through whole-genome sequencing. *Nature Reviews Genetics,* 11**,** 415-425.

CLEGHORN, J., GARNETT, E., NAHMIAS, C., BROWN, G., KAPLAN, R., SZECHTMAN, H., SZECHTMAN, B., FRANCO, S., DERMER, S. & COOK, P. 1990. Regional brain metabolism during auditory hallucinations in chronic schizophrenia. *The British Journal of Psychiatry,* 157**,** 562-570.

CONWAY, M. A. 2009. Episodic memories. *Neuropsychologia,* 47**,** 2305-2313.

COTTER, D., MACKAY, D., CHANA, G., BEASLEY, C., LANDAU, S. & EVERALL, I. P. 2002. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cerebral cortex,* 12**,** 386-394.

COYLE, J. T. 2006. Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cellular and molecular neurobiology,* 26**,** 363-382.

CRADDOCK, N. & OWEN, M. J. 2010. The Kraepelinian dichotomy–going, going... but still not gone. *The British Journal of Psychiatry,* 196**,** 92-95.

CRADDOCK, N. & SKLAR, P. 2009. Genetics of bipolar disorder: successful start to a long journey. *Trends in Genetics,* 25**,** 99-105.

CRADDOCK, N. & SKLAR, P. 2013. Genetics of bipolar disorder. *The Lancet,* 381**,** 1654-1662.

CROSSLEY, N. A., MECHELLI, A., FUSAR-POLI, P., BROOME, M. R., MATTHIASSON, P., JOHNS, L. C., BRAMON, E., VALMAGGIA, L., WILLIAMS, S. C. & MCGUIRE, P. K. 2009. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Human brain mapping,* 30**,** 4129-4137.

CUESTA, M., PERALTA, V. & ZARZUELA, A. 1998. Illness duration and neuropsychological impairments in schizophrenia. *Schizophrenia Research,* 33**,** 141-150.

CUMMINGS, J. L. 1993. Frontal-subcortical circuits and human behavior. *Archives of neurology,* 50**,** 873-880.

D'ESPOSITO, M., DETRE, J. A., ALSOP, D. C., SHIN, R. K., ATLAS, S. & GROSSMAN, M. 1995. The neural basis of the central executive system of working memory. *Nature,* 378**,** 279-281.

DANION, J.-M. & BERNA, F. 2007. Functional mechanisms of episodic memory impairment in schizophrenia. *Canadian Journal of Psychiatry,* 52**,** 693.

DANION, J.-M., RIZZO, L. & BRUANT, A. 1999. Functional mechanisms underlying impaired recognition memory and conscious awareness in patients with schizophrenia. *Archives of General Psychiatry,* 56**,** 639-644.

DASELAAR, S., DENNIS, N. & CABEZA, R. 2007. Ageing: Age-related changes in episodic and working memory. *Clinical applications of functional brain MRI***,** 115-148.

DAVACHI, L. & WAGNER, A. D. 2002. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. *Journal of Neurophysiology,* 88**,** 982-990.

DAWSON, N., KURIHARA, M., THOMSON, D., WINCHESTER, C., MCVIE, A., HEDDE, J., RANDALL, A., SHEN, S., SEYMOUR, P. & HUGHES, Z. 2015. Altered functional brain network connectivity and glutamate system function in transgenic mice expressing truncated Disrupted-in-Schizophrenia 1. *Translational psychiatry,* 5**,** e569.

DE LEEUW, M., KAHN, R. S. & VINK, M. 2015. Fronto-striatal dysfunction during reward processing in unaffected siblings of schizophrenia patients. *Schizophrenia bulletin,* 41**,** 94-103.

DECKERSBACH, T., DOUGHERTY, D. D., SAVAGE, C., MCMURRICH, S., FISCHMAN, A. J., NIERENBERG, A., SACHS, G. & RAUCH, S. L. 2006. Impaired recruitment of the dorsolateral prefrontal cortex and hippocampus during encoding in bipolar disorder. *Biol Psychiatry,* 59**,** 138-46.

DECKERSBACH, T., MCMURRICH, S., OGUTHA, J., SAVAGE, C. R., SACHS, G. & RAUCH, S. L. 2004a. Characteristics of non-verbal memory impairment in bipolar disorder: the role of encoding strategies. *Psychological Medicine,* 34**,** 823-832.

DECKERSBACH, T., SAVAGE, C. R., REILLY-HARRINGTON, N., CLARK, L., SACHS, G. & RAUCH, S. L. 2004b. Episodic memory impairment in bipolar disorder and obsessive–compulsive disorder: the role of memory strategies. *Bipolar Disorders,* 6**,** 233-244.

DELBELLO, M. P., ZIMMERMAN, M. E., MILLS, N. P., GETZ, G. E. & STRAKOWSKI, S. M. 2004. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar disorders,* 6**,** 43-52.

DELL'OSSO, B., CINNANTE, C., DI GIORGIO, A., CREMASCHI, L., PALAZZO, M. C., CRISTOFFANINI, M., FAZIO, L., DOBREA, C., AVIGNONE, S. & TRIULZI, F. 2015. Altered prefrontal cortex activity during working memory task in bipolar disorder: A functional magnetic resonance imaging study in euthymic bipolar I and II patients. *Journal of Affective Disorders*.

DELVECCHIO, G., SUGRANYES, G. & FRANGOU, S. 2013. Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies. *Psychol Med,* 43**,** 553-69.

DEMIRCI, O. & CALHOUN, V. D. 2009. Functional Magnetic Resonance Imagingâ€“Implications for Detection of Schizophrenia. *European neurological review,* 4**,** 103.

DEROSSE, P., HODGKINSON, C. A., LENCZ, T., BURDICK, K. E., KANE, J. M., GOLDMAN, D. & MALHOTRA, A. K. 2007. Disrupted in schizophrenia 1 genotype and positive symptoms in schizophrenia. *Biol Psychiatry,* 61**,** 1208-10.

DESERNO, L., STERZER, P., WÜSTENBERG, T., HEINZ, A. & SCHLAGENHAUF, F. 2012. Reduced prefrontal-parietal effective connectivity and working memory deficits in schizophrenia. *The Journal of Neuroscience,* 32**,** 12-20.

DI GIORGIO, A., BLASI, G., SAMBATARO, F., RAMPINO, A., PAPAZACHARIAS, A., GAMBI, F., ROMANO, R., CAFORIO, G., RIZZO, M., LATORRE, V., POPOLIZIO, T., KOLACHANA, B., CALLICOTT, J. H., NARDINI, M., WEINBERGER, D. R. & BERTOLINO, A. 2008. Association of the SerCys DISC1 polymorphism with human hippocampal formation gray matter and function during memory encoding. *Eur J Neurosci,* 28**,** 2129-36.

DI GIORGIO, A., CAFORIO, G., BLASI, G., TAURISANO, P., FAZIO, L., ROMANO, R., URSINI, G., GELAO, B., BIANCO, L. L., PAPAZACHARIAS, A., SINIBALDI, L., POPOLIZIO, T., BELLOMO, A. & BERTOLINO, A. 2011. Catechol-O-methyltransferase Val(158)Met association with parahippocampal physiology during memory encoding in schizophrenia. *Psychol Med,* 41**,** 1721-31.

DI GIORGIO, A., GELAO, B., CAFORIO, G., ROMANO, R., ANDRIOLA, I., D'AMBROSIO, E., PAPAZACHARIAS, A., ELIFANI, F., BIANCO, L. L., TAURISANO, P., FAZIO, L., POPOLIZIO, T., BLASI, G. & BERTOLINO, A. 2013. Evidence that hippocampal-parahippocampal dysfunction is related to genetic risk for schizophrenia. *Psychol Med,* 43**,** 1661-71.

DOLAN, R., FLETCHER, P., FRITH, C., FRISTON, K., FRACKOWIAK, R. & GRASBY, P. 1995. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia.

DRERUP, C. M., WIORA, H. M., TOPCZEWSKI, J. & MORRIS, J. A. 2009. Disc1 regulates foxd3 and sox10 expression, affecting neural crest migration and differentiation. *Development,* 136**,** 2623-2632.

DU BOISGUEHENEUC, F., LEVY, R., VOLLE, E., SEASSAU, M., DUFFAU, H., KINKINGNEHUN, S., SAMSON, Y., ZHANG, S. & DUBOIS, B. 2006. Functions of the left superior frontal gyrus in humans: a lesion study. *Brain,* 129**,** 3315-3328.

DUDBRIDGE, F. 2013. Power and predictive accuracy of polygenic risk scores. *PLoS Genet,* 9**,** e1003348.

DUFF, B. J., MACRITCHIE, K. A., MOORHEAD, T. W., LAWRIE, S. M. & BLACKWOOD, D. H. 2013. Human brain imaging studies of DISC1 in schizophrenia, bipolar disorder and depression: a systematic review. *Schizophrenia Research,* 147**,** 1-13.

DURNEZ, J., DEGRYSE, J., MOERKERKE, B., SEURINCK, R., SOCHAT, V., POLDRACK, R. & NICHOLS, T. 2016. Power and sample size calculations for fMRI studies based on the prevalence of active peaks. *bioRxiv***,** 049429.

EBDRUP, B. 2010. Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *Journal of Psychiatry and Neuroscience,* 35**,** 95-104.

EGAN, M. F., GOLDBERG, T. E., KOLACHANA, B. S., CALLICOTT, J. H., MAZZANTI, C. M., STRAUB, R. E., GOLDMAN, D. & WEINBERGER, D. R. 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A,* 98**,** 6917-22.

EGNER, T. & HIRSCH, J. 2005. Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature neuroscience,* 8**,** 1784-1790.

EICHENBAUM, H., YONELINAS, A. & RANGANATH, C. 2007. The medial temporal lobe and recognition memory. *Annual review of neuroscience,* 30**,** 123.

EKELUND, J., LICHTERMANN, D., HOVATTA, I., ELLONEN, P., SUVISAARI, J., TERWILLIGER, J. D., JUVONEN, H., VARILO, T., ARAJÄRVI, R. & KOKKO-SAHIN, M.-L. 2000. Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. *Human Molecular Genetics,* 9**,** 1049-1057.

ELLISON-WRIGHT, I. & BULLMORE, E. 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia research,* 108**,** 3-10.

ELLISON-WRIGHT, I., GLAHN, D. C., LAIRD, A. R., THELEN, S. M. & BULLMORE, E. 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *The American journal of psychiatry,* 165**,** 1015-1023.

ELSABAGH, S., PREMKUMAR, P., ANILKUMAR, A. P. & KUMARI, V. 2009. A longer duration of schizophrenic illness has sex-specific associations within the working memory neural network in schizophrenia. *Behavioural brain research,* 201**,** 41-47.

ESSLINGER, C., WALTER, H., KIRSCH, P., ERK, S., SCHNELL, K., ARNOLD, C., HADDAD, L., MIER, D., VON BOBERFELD, C. O. & RAAB, K. 2009. Neural mechanisms of a genome-wide supported psychosis variant. *Science,* 324**,** 605-605.

FANOUS, A. & KENDLER, K. 2005. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. *Mol Psychiatry,* 10**,** 6-13.

FARRELL, M., WERGE, T., SKLAR, P., OWEN, M., OPHOFF, R., O'DONOVAN, M., CORVIN, A., CICHON, S. & SULLIVAN, P. 2015. Evaluating historical candidate genes for schizophrenia. *Molecular psychiatry,* 20**,** 555-562.

FARROW, T. F., WHITFORD, T. J., WILLIAMS, L. M., GOMES, L. & HARRIS, A. W. 2005. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. *Biological psychiatry,* 58**,** 713-723.

FERNÁNDEZ, G. & TENDOLKAR, I. 2001. Integrated brain activity in medial temporal and prefrontal areas predicts subsequent memory performance: human declarative memory formation at the system level. *Brain research bulletin,* 55**,** 1-9.

FIORAVANTI, M., CARLONE, O., VITALE, B., CINTI, M. E. & CLARE, L. 2005. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology review,* 15**,** 73-95.

FIRST, M. B. & GIBBON, M. 2004. *The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)*, John Wiley & Sons Inc.

FLIESSBACH, K., TRAUTNER, P., QUESADA, C. M., ELGER, C. E. & WEBER, B. 2007. Cerebellar contributions to episodic memory encoding as revealed by fMRI. *Neuroimage,* 35**,** 1330-7.

FLIESSBACH, K., WEIS, S., KLAVER, P., ELGER, C. E. & WEBER, B. 2006. The effect of word concreteness on recognition memory. *Neuroimage,* 32**,** 1413-1421.

FOSSATI, P., HEVENOR, S. J., LEPAGE, M., GRAHAM, S. J., GRADY, C., KEIGHTLEY, M. L., CRAIK, F. & MAYBERG, H. 2004. Distributed self in episodic memory: neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage,* 22**,** 1596-1604.

FOX, P. T. & RAICHLE, M. E. 1986. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences,* 83**,** 1140-1144.

FRANGOU, S., KINGTON, J., RAYMONT, V. & SHERGILL, S. S. 2008. Examining ventral and dorsal prefrontal function in bipolar disorder: a functional magnetic resonance imaging study. *European Psychiatry,* 23**,** 300-308.

FRISTON, K. J. & FRITH, C. D. 1995. Schizophrenia: a disconnection syndrome. *Clin Neurosci,* 3**,** 89-97.

FRISTON, K. J., HARRISON, L. & PENNY, W. 2003. Dynamic causal modelling. *Neuroimage,* 19**,** 1273-1302.

FRITH, C., FRISTON, K., HEROLD, S., SILBERSWEIG, D., FLETCHER, P., CAHILL, C., DOLAN, R., FRACKOWIAK, R. & LIDDLE, P. 1995. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *The British Journal of Psychiatry,* 167**,** 343-349.

FUJIWARA, H., NAMIKI, C., HIRAO, K., MIYATA, J., SHIMIZU, M., FUKUYAMA, H., SAWAMOTO, N., HAYASHI, T. & MURAI, T. 2007. Anterior and posterior cingulum abnormalities and their association with psychopathology in schizophrenia: a diffusion tensor imaging study. *Schizophrenia research,* 95**,** 215-222.

FUSAR-POLI, P., HOWES, O., BECHDOLF, A. & BORGWARDT, S. 2012. Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies. *Journal of psychiatry & neuroscience: JPN,* 37**,** 170.

GABRIELI, J. D., BREWER, J. B., DESMOND, J. E. & GLOVER, G. H. 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science,* 276**,** 264-266.

GALDERISI, S., QUARANTELLI, M., VOLPE, U., MUCCI, A., CASSANO, G. B., INVERNIZZI, G., ROSSI, A., VITA, A., PINI, S. & CASSANO, P. 2008. Patterns

of structural MRI abnormalities in deficit and nondeficit schizophrenia. *Schizophrenia bulletin,* 34**,** 393-401.

GALYNKER, I. I., CAI, J., ONGSENG, F., FINESTONE, H., DUTTA, E. & SERSENI, D. 1998. Hypofrontality and negative symptoms in major depressive disorder. *Journal of Nuclear Medicine,* 39**,** 608-612.

GARDNER, D. M., MURPHY, A. L., O'DONNELL, H., CENTORRINO, F. & BALDESSARINI, R. J. 2014. International consensus study of antipsychotic dosing. *FOCUS*.

GARRITY, A. G., PEARLSON, G. D., MCKIERNAN, K., LLOYD, D., KIEHL, K. A. & CALHOUN, V. D. 2007. Aberrant "default mode" functional connectivity in schizophrenia. *American journal of psychiatry,* 164**,** 450-457.

GASPERONI, T. L., EKELUND, J., HUTTUNEN, M., PALMER, C. G., TUULIO-HENRIKSSON, A., LÖNNQVIST, J., KAPRIO, J., PELTONEN, L. & CANNON, T. D. 2003. Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics,* 116**,** 8-16.

GLAHN, D. C., BEARDEN, C. E., BARGUIL, M., BARRETT, J., REICHENBERG, A., BOWDEN, C. L., SOARES, J. C. & VELLIGAN, D. I. 2007a. The neurocognitive signature of psychotic bipolar disorder. *Biol Psychiatry,* 62**,** 910-6.

GLAHN, D. C., PAUS, T. & THOMPSON, P. M. 2007b. Imaging genomics: mapping the influence of genetics on brain structure and function. *Hum Brain Mapp,* 28**,** 461-3.

GOLBY, A., SILVERBERG, G., RACE, E., GABRIELI, S., O'SHEA, J., KNIERIM, K., STEBBINS, G. & GABRIELI, J. 2005. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain,* 128**,** 773-787.

GOLBY, A. J., POLDRACK, R. A., BREWER, J. B., SPENCER, D., DESMOND, J. E., ARON, A. P. & GABRIELI, J. D. 2001. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. *Brain,* 124**,** 1841-1854.

GOLD, J. M. 2004. Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia research,* 72**,** 21-28.

GOLD, J. M., REHKEMPER, G., BINKS III, S. W., CARPENTER, C. J., FLEMING, K., GOLDBERG, T. E. & WEINBERGER, D. R. 2000. Learning and forgetting in schizophrenia. *Journal of Abnormal Psychology,* 109**,** 534.

GOLDBERG, T. E., STRAUB, R. E., CALLICOTT, J. H., HARIRI, A., MATTAY, V. S., BIGELOW, L., COPPOLA, R., EGAN, M. F. & WEINBERGER, D. R. 2006. The G72/G30 gene complex and cognitive abnormalities in schizophrenia. *Neuropsychopharmacology,* 31**,** 2022-32.

GOLDENBERG, D. & GALVÁN, A. 2015. The use of functional and effective connectivity techniques to understand the developing brain. *Developmental cognitive neuroscience,* 12**,** 155-164.

GONG, X., LU, W., KENDRICK, K. M., PU, W., WANG, C., JIN, L., LU, G., LIU, Z., LIU, H. & FENG, J. 2014. A Brain-wide association study of DISC1 genetic

variants reveals a relationship with the structure and functional connectivity of the precuneus in schizophrenia. *Human brain mapping,* 35**,** 5414-5430.

GOODWIN, G. M., CAVANAGH, J., GLABUS, M. F., KEHOE, R. F., O'CARROLL, R. & EBMEIER, K. 1997. Uptake of 99mTc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients: associations with mania. *The British Journal of Psychiatry,* 170**,** 426-430.

GOTTESMAN, II & GOULD, T. D. 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry,* 160**,** 636-645.

GOTTESMAN, I. I. & SHIELDS, J. 1967. A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America,* 58**,** 199.

GOTTWALD, B., WILDE, B., MIHAJLOVIC, Z. & MEHDORN, H. 2004. Evidence for distinct cognitive deficits after focal cerebellar lesions. *Journal of Neurology, Neurosurgery & Psychiatry,* 75**,** 1524-1531.

GRAHN, J. A., PARKINSON, J. A. & OWEN, A. M. 2008. The cognitive functions of the caudate nucleus. *Prog Neurobiol,* 86**,** 141-55.

GREEN, M. F., KERN, R. S., BRAFF, D. L. & MINTZ, J. 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the" right stuff"? *Schizophrenia bulletin,* 26**,** 119.

GRUBER, O., TOST, H., HENSELER, I., SCHMAEL, C., SCHERK, H., ENDE, G., RUF, M., FALKAI, P. & RIETSCHEL, M. 2010. Pathological amygdala activation during working memory performance: Evidence for a pathophysiological trait marker in bipolar affective disorder. *Hum Brain Mapp,* 31**,** 115-25.

GRUBER, S. A., ROGOWSKA, J. & YURGELUN-TODD, D. A. 2004. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. *Journal of affective disorders,* 82**,** 191-201.

GUR, R. E. & GUR, R. C. 2010. Functional magnetic resonance imaging in schizophrenia. *Dialogues in clinical neuroscience,* 12**,** 333.

GUR, R. E., KESHAVAN, M. S. & LAWRIE, S. M. 2007. Deconstructing psychosis with human brain imaging. *Schizophr Bull,* 33**,** 921-931.

GUR, R. E., MAANY, V., MOZLEY, P. D., SWANSON, C., BILKER, W. & GUR, R. C. 1998. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia.

HAJEK, T., GUNDE, E., SLANEY, C., PROPPER, L., MACQUEEN, G., DUFFY, A. & ALDA, M. 2009. Striatal volumes in affected and unaffected relatives of bipolar patients–high-risk study. *Journal of psychiatric research,* 43**,** 724-729.

HALL, J., ROMANIUK, L., MCINTOSH, A. M., STEELE, J. D., JOHNSTONE, E. C. & LAWRIE, S. M. 2009. Associative learning and the genetics of schizophrenia. *Trends in neurosciences,* 32**,** 359-365.

HALL, J., WHALLEY, H. C., JOB, D. E., BAIG, B. J., MCINTOSH, A. M., EVANS, K. L., THOMSON, P. A., PORTEOUS, D. J., CUNNINGHAM-OWENS, D. G.,

JOHNSTONE, E. C. & LAWRIE, S. M. 2006. A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. *Nat Neurosci,* 9**,** 1477-8.

HALL, J., WHALLEY, H. C., MARWICK, K., MCKIRDY, J., SUSSMANN, J., ROMANIUK, L., JOHNSTONE, E. C., WAN, H. I., MCINTOSH, A. M. & LAWRIE, S. M. 2010. Hippocampal function in schizophrenia and bipolar disorder. *Psychol Med,* 40**,** 761-70.

HAMAMÉ, C. M., VIDAL, J. R., OSSANDÓN, T., JERBI, K., DALAL, S. S., MINOTTI, L., BERTRAND, O., KAHANE, P. & LACHAUX, J.-P. 2012. Reading the mind's eye: online detection of visuo-spatial working memory and visual imagery in the inferior temporal lobe. *Neuroimage,* 59**,** 872-879.

HAMILTON, L. S., ALTSHULER, L. L., TOWNSEND, J., BOOKHEIMER, S. Y., PHILLIPS, O. R., FISCHER, J., WOODS, R. P., MAZZIOTTA, J. C., TOGA, A. W. & NUECHTERLEIN, K. H. 2009. Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task. *Human brain mapping,* 30**,** 3958-3969.

HAMILTON, M. 1960. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry,* 23**,** 56.

HAMSHERE, M. L., O'DONOVAN, M. C., JONES, I. R., JONES, L., KIROV, G., GREEN, E. K., MOSKVINA, V., GROZEVA, D., BASS, N. & MCQUILLIN, A. 2011. Polygenic dissection of the bipolar phenotype. *The British Journal of Psychiatry,* 198**,** 284-288.

HARIRI, A. R., GOLDBERG, T. E., MATTAY, V. S., KOLACHANA, B. S., CALLICOTT, J. H., EGAN, M. F. & WEINBERGER, D. R. 2003. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *The Journal of neuroscience,* 23**,** 6690-6694.

HARIRI, A. R. & WEINBERGER, D. R. 2003. Imaging genomics. *British medical bulletin,* 65**,** 259-270.

HARRISON, B. J., YÜCEL, M., PUJOL, J. & PANTELIS, C. 2007. Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI. *Schizophrenia research,* 91**,** 82-86.

HARRISON, P. J. & OWEN, M. J. 2003. Genes for schizophrenia? Recent findings and their pathophysiological implications. *The Lancet,* 361**,** 417-419.

HARVEY, P.-O., FOSSATI, P., POCHON, J.-B., LEVY, R., LEBASTARD, G., LEHÉRICY, S., ALLILAIRE, J.-F. & DUBOIS, B. 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage,* 26**,** 860-869.

HASHIMOTO, R., NUMAKAWA, T., OHNISHI, T., KUMAMARU, E., YAGASAKI, Y., ISHIMOTO, T., MORI, T., NEMOTO, K., ADACHI, N. & IZUMI, A. 2006. Impact of the DISC1 Ser704Cys polymorphism on risk for major depression, brain morphology and ERK signaling. *Human molecular genetics,* 15**,** 3024-3033.

HAZNEDAR, M. M., BUCHSBAUM, M. S., HAZLETT, E. A., SHIHABUDDIN, L., NEW, A. & SIEVER, L. J. 2004. Cingulate gyrus volume and metabolism in the schizophrenia spectrum. *Schizophrenia research,* 71**,** 249-262.

HAZNEDAR, M. M., BUCHSBAUM, M. S., LUU, C., HAZLETT, E. A., SIEGEL, B. V., LOHR, J., WU, J., HAIER, R. J. & BUNNEY, W. E. 1997. Decreased anterior cingulate gyrus metabolic rate in schizophrenia. *American Journal of Psychiatry,* 154**,** 682-684.

HECKERS, S. 2001. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus,* 11**,** 520-528.

HECKERS, S., CURRAN, T., GOFF, D., RAUCH, S. L., FISCHMAN, A. J., ALPERT, N. M. & SCHACTER, D. L. 2000. Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. *Biological psychiatry,* 48**,** 651-657.

HECKERS, S., RAUCH, S., GOFF, D., SAVAGE, C., SCHACTER, D., FISCHMAN, A. & ALPERT, N. 1998. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature neuroscience,* 1**,** 318-323.

HEINRICHS, R. W. 2005. The primacy of cognition in schizophrenia. *American Psychologist,* 60**,** 229.

HEINRICHS, R. W. & ZAKZANIS, K. K. 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology,* 12**,** 426.

HENNAH, W., THOMSON, P., MCQUILLIN, A., BASS, N., LOUKOLA, A., ANJORIN, A., BLACKWOOD, D., CURTIS, D., DEARY, I. J., HARRIS, S. E., ISOMETSA, E. T., LAWRENCE, J., LONNQVIST, J., MUIR, W., PALOTIE, A., PARTONEN, T., PAUNIO, T., PYLKKO, E., ROBINSON, M., SORONEN, P., SUOMINEN, K., SUVISAARI, J., THIRUMALAI, S., ST CLAIR, D., GURLING, H., PELTONEN, L. & PORTEOUS, D. 2009. DISC1 association, heterogeneity and interplay in schizophrenia and bipolar disorder. *Mol Psychiatry,* 14**,** 865-73.

HENNAH, W., THOMSON, P., PELTONEN, L. & PORTEOUS, D. 2006. Genes and schizophrenia: beyond schizophrenia: the role of DISC1 in major mental illness. *Schizophr Bull,* 32**,** 409-416.

HENNAH, W., TUULIO-HENRIKSSON, A., PAUNIO, T., EKELUND, J., VARILO, T., PARTONEN, T., CANNON, T. D., LONNQVIST, J. & PELTONEN, L. 2005. A haplotype within the DISC1 gene is associated with visual memory functions in families with a high density of schizophrenia. *Mol Psychiatry,* 10**,** 1097-103.

HERRMANN, M., ROTTE, M., GRUBICH, C., EBERT, A. D., SCHILTZ, K., MÜNTE, T. F. & HEINZE, H. J. 2001. Control of semantic interference in episodic memory retrieval is associated with an anterior cingulate-prefrontal activation pattern. *Human brain mapping,* 13**,** 94-103.

HIKIDA, T., JAARO-PELED, H., SESHADRI, S., OISHI, K., HOOKWAY, C., KONG, S., WU, D., XUE, R., ANDRADÉ, M. & TANKOU, S. 2007. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. *Proceedings of the National Academy of Sciences,* 104**,** 14501-14506.

HILL, S. K., HARRIS, M. S., HERBENER, E. S., PAVULURI, M. & SWEENEY, J. A. 2008. Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. *Schizophrenia bulletin,* 34**,** 743-759.

HILL, S. K., REILLY, J. L., KEEFE, R. S., GOLD, J. M., BISHOP, J. R., GERSHON, E. S., TAMMINGA, C. A., PEARLSON, G. D., KESHAVAN, M. S. & SWEENEY, J. A. 2014. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *American Journal of Psychiatry*.

HODGKINSON, C. A., GOLDMAN, D., JAEGER, J., PERSAUD, S., KANE, J. M., LIPSKY, R. H. & MALHOTRA, A. K. 2004. Disrupted in schizophrenia 1 (DISC1): association with schizophrenia, schizoaffective disorder, and bipolar disorder. *The American Journal of Human Genetics,* 75**,** 862-872.

HOFER, A., WEISS, E. M., GOLASZEWSKI, S. M., SIEDENTOPF, C. M., BRINKHOFF, C., KREMSER, C., FELBER, S. & FLEISCHHACKER, W. W. 2014. Neural correlates of episodic encoding and recognition of words in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. *American Journal of Psychiatry*.

HOLTHAUSEN, E. A., WIERSMA, D., SITSKOORN, M. M., HIJMAN, R., DINGEMANS, P. M., SCHENE, A. H. & VAN DEN BOSCH, R. J. 2002. Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive compensation? *Psychiatry research,* 112**,** 1-11.

HONEY, G. D., BULLMORE, E. T. & SHARMA, T. 2002. De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. *Schizophr Res,* 53**,** 45-56.

HOPPENBROUWERS, S. S., SCHUTTER, D. J., FITZGERALD, P. B., CHEN, R. & DASKALAKIS, Z. J. 2008. The role of the cerebellum in the pathophysiology and treatment of neuropsychiatric disorders: a review. *Brain research reviews,* 59**,** 185-200.

HOVATTA, I., VARILO, T., SUVISAARI, J., TERWILLIGER, J. D., OLLIKAINEN, V., ARAJÄRVI, R., JUVONEN, H., KOKKO-SAHIN, M.-L., VÄISÄNEN, L. & MANNILA, H. 1999. A genomewide screen for schizophrenia genes in an isolated Finnish subpopulation, suggesting multiple susceptibility loci. *The American Journal of Human Genetics,* 65**,** 1114-1124.

HWU, H., LIU, C., FANN, C. S., OU-YANG, W. & LEE, S. F. 2003. Linkage of schizophrenia with chromosome 1q loci in Taiwanese families. *Molecular psychiatry,* 8**,** 445-452.

HYDE, L. W., BOGDAN, R. & HARIRI, A. R. 2011. Understanding risk for psychopathology through imaging gene-environment interactions. *Trends Cogn Sci,* 15**,** 417-27.

INGVAR, D. & FRANZÉN, G. 1974. Distribution of cerebral activity in chronic schizophrenia. *The Lancet,* 304**,** 1484-1486.

INSEL, T., CUTHBERT, B., GARVEY, M., HEINSSEN, R., PINE, D. S., QUINN, K., SANISLOW, C. & WANG, P. 2010. Research domain criteria (RDoC): toward a

new classification framework for research on mental disorders. *American Journal of Psychiatry,* 167**,** 748-751.

ISHAI, A., UNGERLEIDER, L. G., MARTIN, A., SCHOUTEN, J. L. & HAXBY, J. V. 1999. Distributed representation of objects in the human ventral visual pathway. *Proceedings of the National Academy of Sciences,* 96**,** 9379-9384.

JACOBS, P. A., BRUNTON, M., FRACKIEWICZ, A., NEWTON, M., COOK, P. J. & ROBSON, E. B. 1970. Studies on a family with three cytogenetic markers. *Annals of Human Genetics,* 33**,** 325-336.

JAVADAPOUR, A., MALHI, G. S., IVANOVSKI, B., CHEN, X., WEN, W. & SACHDEV, P. 2007. Increased anterior cingulate cortex volume in bipolar I disorder. *Australian and New Zealand Journal of Psychiatry,* 41**,** 910-916.

JESSEN, F., SCHEEF, L., GERMESHAUSEN, L., TAWO, Y., KOCKLER, M., KUHN, K.-U., MAIER, W., SCHILD, H. H. & HEUN, R. 2003. Reduced hippocampal activation during encoding and recognition of words in schizophrenia patients. *American Journal of Psychiatry*.

JOHNSTONE, E. C., FRITH, C., CROW, T., HUSBAND, J. & KREEL, L. 1976. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *The Lancet,* 308**,** 924-926.

JONIDES, J., SCHUMACHER, E. H., SMITH, E. E., KOEPPE, R. A., AWH, E., REUTER-LORENZ, P. A., MARSHUETZ, C. & WILLIS, C. R. 1998. The role of parietal cortex in verbal working memory. *The Journal of Neuroscience,* 18**,** 5026-5034.

KAHN, R. S. & KEEFE, R. S. 2013. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA psychiatry,* 70**,** 1107-1112.

KANWISHER, N., MCDERMOTT, J. & CHUN, M. M. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *The Journal of Neuroscience,* 17**,** 4302-4311.

KAUPPI, K., WESTLYE, L. T., TESLI, M., BETTELLA, F., BRANDT, C. L., MATTINGSDAL, M., UELAND, T., ESPESETH, T., AGARTZ, I. & MELLE, I. 2014. Polygenic Risk for Schizophrenia Associated With Working Memory-related Prefrontal Brain Activation in Patients With Schizophrenia and Healthy Controls. *Schizophrenia bulletin***,** sbu152.

KAY, S. R., FLSZBEIN, A. & OPFER, L. A. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin,* 13**,** 261.

KECK, P. E., MCELROY, S. L., HAVENS, J. R., ALTSHULER, L. L., NOLEN, W. A., FRYE, M. A., SUPPES, T., DENICOFF, K. D., KUPKA, R. & LEVERICH, G. S. 2003. Psychosis in bipolar disorder: phenomenology and impact on morbidity and course of illness. *Comprehensive psychiatry,* 44**,** 263-269.

KELLENDONK, C., SIMPSON, E. H. & KANDEL, E. R. 2009. Modeling cognitive endophenotypes of schizophrenia in mice. *Trends in neurosciences,* 32**,** 347-358.

KEMPF, L. & MEYER-LINDENBERG, A. 2006. Imaging genetics and psychiatry. *Focus,* 4**,** 327.

KESHAVAN, M. S., DIWADKAR, V. A., SPENCER, S. M., HARENSKI, K. A., LUNA, B. & SWEENEY, J. A. 2002. A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. *Progress in Neuro-psychopharmacology and biological psychiatry,* 26**,** 1143-1149.

KIESEPPÄ, T., PARTONEN, T., HAUKKA, J., KAPRIO, J. & LÖNNQVIST, J. 2014. High concordance of bipolar I disorder in a nationwide sample of twins. *American Journal of Psychiatry*.

KIM, D., CHO, H. B., DAGER, S. R., YURGELUN-TODD, D. A., YOON, S., LEE, J. H., LEE, S. H., LEE, S., RENSHAW, P. F. & LYOO, I. K. 2013. Posterior cerebellar vermal deficits in bipolar disorder. *Journal of affective disorders,* 150**,** 499-506.

KIM, D. I., MANOACH, D. S., MATHALON, D. H., TURNER, J. A., MANNELL, M., BROWN, G. G., FORD, J. M., GOLLUB, R. L., WHITE, T. & WIBLE, C. 2009. Dysregulation of working memory and default-mode networks in schizophrenia using independent component analysis, an fBIRN and MCIC study. *Human brain mapping,* 30**,** 3795-3811.

KIRCHHOFF, B. A., WAGNER, A. D., MARIL, A. & STERN, C. E. 2000. Prefrontal–temporal circuitry for episodic encoding and subsequent memory. *The Journal of Neuroscience,* 20**,** 6173-6180.

KOCH, K., WAGNER, G., NENADIC, I., SCHACHTZABEL, C., SCHULTZ, C., ROEBEL, M., REICHENBACH, J., SAUER, H. & SCHLÖSSER, R. 2008. Fronto-striatal hypoactivation during correct information retrieval in patients with schizophrenia: an fMRI study. *Neuroscience,* 153**,** 54-62.

KOENIGS, M. & GRAFMAN, J. 2009. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural brain research,* 201**,** 239-243.

KOH, S. D. & PETERSON, R. A. 1978. Encoding orientation and the remembering of schizophrenic young adults. *Journal of Abnormal Psychology,* 87**,** 303.

KONICK, L. C. & FRIEDMAN, L. 2001. Meta-analysis of thalamic size in schizophrenia. *Biological psychiatry,* 49**,** 28-38.

KONKEL, A. & COHEN, N. J. 2009. Relational memory and the hippocampus: representations and methods. *Frontiers in Neuroscience,* 3**,** 166.

KOO, M.-S., LEVITT, J. J., SALISBURY, D. F., NAKAMURA, M., SHENTON, M. E. & MCCARLEY, R. W. 2008. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. *Archives of General Psychiatry,* 65**,** 746-760.

KOPALD, B. E., MIRRA, K. M., EGAN, M. F., WEINBERGER, D. R. & GOLDBERG, T. E. 2012. Magnitude of impact of executive functioning and IQ on episodic memory in Schizophrenia. *Biol Psychiatry,* 71**,** 545-51.

KRABBENDAM, L., ARTS, B., VAN OS, J. & ALEMAN, A. 2005. Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. *Schizophr Res,* 80**,** 137-149.

KRAEPELIN, E. 1921. Dementia Praecox and Paraphrenia. *The Journal of Nervous and Mental Disease,* 54**,** 384.

KRUG, A., MARKOV, V., KRACH, S., JANSEN, A., ZERRES, K., EGGERMANN, T., STOCKER, T., SHAH, N. J., NOTHEN, M. M., TREUTLEIN, J., RIETSCHEL, M. & KIRCHER, T. 2010. The effect of Neuregulin 1 on neural correlates of episodic memory encoding and retrieval. *Neuroimage,* 53**,** 985-91.

KWONG, K. K., BELLIVEAU, J. W., CHESLER, D. A., GOLDBERG, I. E., WEISSKOFF, R. M., PONCELET, B. P., KENNEDY, D. N., HOPPEL, B. E., COHEN, M. S. & TURNER, R. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences,* 89**,** 5675-5679.

LAHTI, A. C., WEILER, M. A., HOLCOMB, H. H., TAMMINGA, C. A., CARPENTER, W. T. & MCMAHON, R. 2006. Correlations between rCBF and symptoms in two independent cohorts of drug-free patients with schizophrenia. *Neuropsychopharmacology,* 31**,** 221-230.

LAIDI, C., D'ALBIS, M. A., WESSA, M., LINKE, J., PHILLIPS, M., DELAVEST, M., BELLIVIER, F., VERSACE, A., ALMEIDA, J. & SARRAZIN, S. 2015. Cerebellar volume in schizophrenia and bipolar I disorder with and without psychotic features. *Acta Psychiatrica Scandinavica,* 131**,** 223-233.

LANDER, E. S., LINTON, L. M., BIRREN, B., NUSBAUM, C., ZODY, M. C., BALDWIN, J., DEVON, K., DEWAR, K., DOYLE, M. & FITZHUGH, W. 2001. Initial sequencing and analysis of the human genome. *Nature,* 409**,** 860-921.

LANG, D. J., KOPALA, L. C., VANDORPE, R. A., RUI, Q., SMITH, G. N., GOGHARI, V. M. & HONER, W. G. 2014. An MRI study of basal ganglia volumes in first-episode schizophrenia patients treated with risperidone. *American Journal of Psychiatry*.

LANG, P. J., BRADLEY, M. M. & CUTHBERT, B. N. 1997. International affective picture system (IAPS): Technical manual and affective ratings. *NIMH Center for the Study of Emotion and Attention***,** 39-58.

LAWRENCE, N. S., WILLIAMS, A. M., SURGULADZE, S., GIAMPIETRO, V., BRAMMER, M. J., ANDREW, C., FRANGOU, S., ECKER, C. & PHILLIPS, M. L. 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biological psychiatry,* 55**,** 578-587.

LAWRIE, S. M. & ABUKMEIL, S. S. 1998. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *The British Journal of Psychiatry,* 172**,** 110-120.

LAWRIE, S. M., BUECHEL, C., WHALLEY, H. C., FRITH, C. D., FRISTON, K. J. & JOHNSTONE, E. C. 2002. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological psychiatry,* 51**,** 1008-1011.

LAWRIE, S. M., MCINTOSH, A. M., HALL, J., OWENS, D. G. & JOHNSTONE, E. C. 2008. Brain structure and function changes during the development of

schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophr Bull,* 34**,** 330-40.

LAWRIE, S. M., WEINBERGER, D. R. & JOHNSTONE, E. C. 2004. *Schizophrenia: From neuroimaging to neuroscience*, Oxford University Press.

LAWRIE, S. M., WHALLEY, H. C., ABUKMEIL, S. S., KESTELMAN, J. N., DONNELLY, L., MILLER, P., BEST, J. J. K., OWENS, D. G. C. & JOHNSTONE, E. C. 2001. Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biol Psychiatry,* 49**,** 811-823.

LEAVITT, V. M. & GOLDBERG, T. E. 2009. Episodic memory in schizophrenia. *Neuropsychol Rev,* 19**,** 312-23.

LEDOUX, A. A., PHILLIPS, J. L., LABELLE, A., SMITH, A., BOHBOT, V. D. & BOYER, P. 2013. Decreased fMRI activity in the hippocampus of patients with schizophrenia compared to healthy control participants, tested on a wayfinding task in a virtual town. *Psychiatry Res,* 211**,** 47-56.

LEE, C. U., SHENTON, M. E., SALISBURY, D. F., KASAI, K., ONITSUKA, T., DICKEY, C. C., YURGELUN-TODD, D., KIKINIS, R., JOLESZ, F. A. & MCCARLEY, R. W. 2002. Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. *Archives of General Psychiatry,* 59**,** 775-781.

LEE, H., KANG, E., GOODSMITH, D., YOON, D. Y., SONG, H., KNIERIM, J. J., MING, G.-L. & CHRISTIAN, K. M. 2015. DISC1-mediated dysregulation of adult hippocampal neurogenesis in rats. *Frontiers in systems neuroscience,* 9.

LEE, K. W., WOON, P. S., TEO, Y. Y. & SIM, K. 2012a. Genome wide association studies (GWAS) and copy number variation (CNV) studies of the major psychoses: What have we learnt? *Neuroscience & Biobehavioral Reviews*.

LEE, S. H., DECANDIA, T. R., RIPKE, S., YANG, J., SULLIVAN, P. F., GODDARD, M. E., KELLER, M. C., VISSCHER, P. M. & WRAY, N. R. 2012b. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nature Genetics,* 44**,** 247-250.

LEECH, R. & SHARP, D. J. 2014. The role of the posterior cingulate cortex in cognition and disease. *Brain,* 137**,** 12-32.

LEFÈBVRE, A.-A., CELLARD, C., TREMBLAY, S., ACHIM, A., ROULEAU, N., MAZIADE, M. & ROY, M.-A. 2010. Familiarity and recollection processes in patients with recent-onset schizophrenia and their unaffected parents. *Psychiatry research,* 175**,** 15-21.

LEPAGE, M., GHAFFAR, O., NYBERG, L. & TULVING, E. 2000. Prefrontal cortex and episodic memory retrieval mode. *Proceedings of the National Academy of Sciences,* 97**,** 506-511.

LEPAGE, M., PELLETIER, M., ACHIM, A., MONTOYA, A., MENEAR, M. & LAL, S. 2010. Parietal cortex and episodic memory retrieval in schizophrenia. *Psychiatry Res,* 182**,** 191-9.

LESH, T. A., NIENDAM, T. A., MINZENBERG, M. J. & CARTER, C. S. 2011. Cognitive control deficits in schizophrenia: mechanisms and meaning. *Neuropsychopharmacology,* 36**,** 316-338.

LICHTENSTEIN, P., YIP, B. H., BJÖRK, C., PAWITAN, Y., CANNON, T. D., SULLIVAN, P. F. & HULTMAN, C. M. 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet,* 373**,** 234-239.

LIPSCHUTZ, B., FRISTON, K. J., ASHBURNER, J., TURNER, R. & PRICE, C. J. 2001. Assessing study-specific regional variations in fMRI signal. *Neuroimage,* 13**,** 392-398.

LIU, B., FAN, L., CUI, Y., ZHANG, X., HOU, B., LI, Y., QIN, W., WANG, D., YU, C. & JIANG, T. 2013a. DISC1 Ser704Cys impacts thalamic-prefrontal connectivity. *Brain Structure and Function,* 220**,** 91-100.

LIU, X., LAI, Y., WANG, X., HAO, C., CHEN, L., ZHOU, Z., YU, X. & HONG, N. 2013b. Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: a diffusion tensor study using TBSS. *Behavioural brain research,* 252**,** 157-163.

LIU, Y.-L., FANN, C. S.-J., LIU, C.-M., CHEN, W. J., WU, J.-Y., HUNG, S.-I., CHEN, C.-H., JOU, Y.-S., LIU, S.-K. & HWANG, T.-J. 2006. A single nucleotide polymorphism fine mapping study of chromosome 1q42. 1 reveals the vulnerability genes for schizophrenia, GNPAT and DISC1: association with impairment of sustained attention. *Biological psychiatry,* 60**,** 554-562.

LU, L. H., ZHOU, X. J., KEEDY, S. K., REILLY, J. L. & SWEENEY, J. A. 2011. White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar disorders,* 13**,** 604-613.

LUBKE, G. H., HOTTENGA, J. J., WALTERS, R., LAURIN, C., DE GEUS, E. J., WILLEMSEN, G., SMIT, J. H., MIDDELDORP, C. M., PENNINX, B. W. & VINK, J. M. 2012. Estimating the genetic variance of major depressive disorder due to all single nucleotide polymorphisms. *Biological psychiatry,* 72**,** 707-709.

MA, L., LIU, Y., KY, B., SHUGHRUE, P. J., AUSTIN, C. P. & MORRIS, J. A. 2002. Cloning and characterization of Disc1, the mouse ortholog of DISC1 (Disrupted-in-Schizophrenia 1). *Genomics,* 80**,** 662-672.

MACDONALD, A. W., COHEN, J. D., STENGER, V. A. & CARTER, C. S. 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science,* 288**,** 1835-1838.

MAHON, K., BURDICK, K. E. & SZESZKO, P. R. 2010. A role for white matter abnormalities in the pathophysiology of bipolar disorder. *Neuroscience & Biobehavioral Reviews,* 34**,** 533-554.

MALHI, G. S., LAGOPOULOS, J., WARD, P. B., KUMARI, V., MITCHELL, P. B., PARKER, G. B., IVANOVSKI, B. & SACHDEV, P. 2004. Cognitive generation of affect in bipolar depression: an fMRI study. *European Journal of Neuroscience,* 19**,** 741-754.

MANIEGA, S. M., LYMER, G., BASTIN, M., MARJORAM, D., JOB, D., MOORHEAD, T., OWENS, D., JOHNSTONE, E., MCINTOSH, A. & LAWRIE, S. 2008. A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. *Schizophrenia research,* 106**,** 132-139.

MANOACH, D. S. 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophrenia research,* 60**,** 285-298.

MAO, Y., GE, X., FRANK, C. L., MADISON, J. M., KOEHLER, A. N., DOUD, M. K., TASSA, C., BERRY, E. M., SODA, T. & SINGH, K. K. 2009. Disrupted in Schizophrenia 1 Regulates Neuronal Progenitor Proliferation via Modulation of GSK3 [beta]/[beta]-Catenin Signaling. *Cell,* 136**,** 1017-1031.

MARTINEZ-ARAN, A., VIETA, E., TORRENT, C., SANCHEZ-MORENO, J., GOIKOLEA, J., SALAMERO, M., MALHI, G., GONZALEZ-PINTO, A., DABAN, C. & ALVAREZ-GRANDI, S. 2007. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar disorders,* 9**,** 103-113.

MATA, I., PEREZ-IGLESIAS, R., ROIZ-SANTIANEZ, R., TORDESILLAS-GUTIERREZ, D., GONZALEZ-MANDLY, A., BERJA, A., VAZQUEZ-BARQUERO, J. L. & CRESPO-FACORRO, B. 2010. Additive effect of NRG1 and DISC1 genes on lateral ventricle enlargement in first episode schizophrenia. *Neuroimage,* 53**,** 1016-22.

MATHIESON, I., MUNAFÒ, M. R. & FLINT, J. 2012. Meta-analysis indicates that common variants at the DISC1 locus are not associated with schizophrenia. *Molecular psychiatry,* 17**,** 634-641.

MATTSON, D. T., BERK, M. & LUCAS, M. D. 1997. A neuropsychological study of prefrontal lobe function in the positive and negative subtypes of schizophrenia. *The Journal of genetic psychology,* 158**,** 487-494.

MAYBERG, H. S. 1997. Limbic-cortical dysregulation: a proposed model of depression. *The Journal of neuropsychiatry and clinical neurosciences*.

MCCLELLAN, J. M., SUSSER, E. & KING, M.-C. 2007. Schizophrenia: a common disease caused by multiple rare alleles. *The British Journal of Psychiatry,* 190**,** 194-199.

MCGUFFIN, P., FARMER, A. & HARVEY, I. 1991. A polydiagnostic application of operational criteria in studies of psychotic illness: development and reliability of the OPCRIT system. *Archives of general psychiatry,* 48**,** 764-770.

MCGUFFIN, P., RIJSDIJK, F., ANDREW, M., SHAM, P., KATZ, R. & CARDNO, A. 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of general psychiatry,* 60**,** 497-502.

MCINTOSH, A. M., BAIG, B. J., HALL, J., JOB, D., WHALLEY, H. C., LYMER, G. K., MOORHEAD, T. W., OWENS, D. G., MILLER, P., PORTEOUS, D., LAWRIE, S. M. & JOHNSTONE, E. C. 2007. Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. *Biological Psychiatry,* 61**,** 1127-34.

MCINTOSH, A. M., JOB, D. E., MOORHEAD, W. J., HARRISON, L. K., WHALLEY, H. C., JOHNSTONE, E. C. & LAWRIE, S. M. 2006. Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. *Am J Med Genet B Neuropsychiatr Genet,* 141B**,** 76-83.

MENON, V., ANAGNOSON, R., MATHALON, D., GLOVER, G. & PFEFFERBAUM, A. 2001a. Functional neuroanatomy of auditory working memory in schizophrenia: relation to positive and negative symptoms. *Neuroimage,* 13**,** 433-446.

MENON, V., ANAGNOSON, R. T., GLOVER, G. H. & PFEFFERBAUM, A. 2001b. Functional magnetic resonance imaging evidence for disrupted basal ganglia function in schizophrenia. *American Journal of Psychiatry,* 158**,** 646-649.

MERIKANGAS, K. R., JIN, R., HE, J.-P., KESSLER, R. C., LEE, S., SAMPSON, N. A., VIANA, M. C., ANDRADE, L. H., HU, C. & KARAM, E. G. 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of general psychiatry,* 68**,** 241-251.

MESHOLAM-GATELY, R. I., GIULIANO, A. J., GOFF, K. P., FARAONE, S. V. & SEIDMAN, L. J. 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology,* 23**,** 315.

MEUNIER, M., BACHEVALIER, J. & MISHKIN, M. 1997. Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. *Neuropsychologia,* 35**,** 999-1015.

MEYER-LINDENBERG, A. 2010. Imaging genetics of schizophrenia. *Dialogues Clin. Neurosci,* 12**,** 449-456.

MEYER-LINDENBERG, A., NICODEMUS, K. K., EGAN, M. F., CALLICOTT, J. H., MATTAY, V. & WEINBERGER, D. R. 2008. False positives in imaging genetics. *Neuroimage,* 40**,** 655-61.

MEYER-LINDENBERG, A. & WEINBERGER, D. R. 2006. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Reviews Neuroscience,* 7**,** 818-827.

MILLAR, J. K., WILSON-ANNAN, J. C., ANDERSON, S., CHRISTIE, S., TAYLOR, M. S., SEMPLE, C. A., DEVON, R. S., ST CLAIR, D. M., MUIR, W. J. & BLACKWOOD, D. H. 2000. Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Human molecular genetics,* 9**,** 1415-1423.

MINZENBERG, M. J., LAIRD, A. R., THELEN, S., CARTER, C. S. & GLAHN, D. C. 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of general psychiatry,* 66**,** 811-822.

MISHARA, A. L. & 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. *Biological psychiatry,* 55**,** 1013-1022.

MONKS, P. J., THOMPSON, J. M., BULLMORE, E. T., SUCKLING, J., BRAMMER, M. J., WILLIAMS, S. C., SIMMONS, A., GILES, N., LLOYD, A. J. & LOUISE HARRISON, C. 2004. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. *Bipolar Disorders,* 6**,** 550-564.

MÖSER, C., KRIEG, J. C., ZIHL, J. & LAUTENBACHER, S. 2006. Attention and memory deficits in schizophrenia: the role of symptoms of depression. *Cognitive and behavioral neurology,* 19**,** 150-156.

MÖSSNER, R., SCHUHMACHER, A., WAGNER, M., LENNERTZ, L., STEINBRECHER, A., QUEDNOW, B. B., RUJESCU, D., RIETSCHEL, M. & MAIER, W. 2012. The schizophrenia risk gene ZNF804A influences the antipsychotic response of positive schizophrenia symptoms. *European Archives of Psychiatry and Clinical Neuroscience***,** 1-5.

MUELLER, S., WANG, D., PAN, R., HOLT, D. J. & LIU, H. 2015. Abnormalities in Hemispheric Specialization of Caudate Nucleus Connectivity in Schizophrenia. *JAMA psychiatry*.

MÜLLER, V. I., CIESLIK, E. C., LAIRD, A. R., FOX, P. T. & EICKHOFF, S. B. 2013. Dysregulated left inferior parietal activity in schizophrenia and depression: functional connectivity and characterization. *Frontiers in human neuroscience,* 7.

MURPHY, B. P., CHUNG, Y. C., PARK, T. W. & MCGORRY, P. D. 2006. Pharmacological treatment of primary negative symptoms in schizophrenia: a systematic review. *Schizophr Res,* 88**,** 5-25.

MURRAY, L. J. & RANGANATH, C. 2007. The dorsolateral prefrontal cortex contributes to successful relational memory encoding. *The Journal of neuroscience,* 27**,** 5515-5522.

NARR, K. L., BILDER, R. M., TOGA, A. W., WOODS, R. P., REX, D. E., SZESZKO, P. R., ROBINSON, D., SEVY, S., GUNDUZ-BRUCE, H. & WANG, Y.-P. 2005. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. *Cerebral cortex,* 15**,** 708-719.

NELSON, M. D., SAYKIN, A. J., FLASHMAN, L. A. & RIORDAN, H. J. 1998. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. *Archives of general psychiatry,* 55**,** 433-440.

NESTOR, P. G., KUBICKI, M., KUROKI, N., GURRERA, R. J., NIZNIKIEWICZ, M., SHENTON, M. E. & MCCARLEY, R. W. 2007. Episodic memory and neuroimaging of hippocampus and fornix in chronic schizophrenia. *Psychiatry Res,* 155**,** 21-8.

NICODEMUS, K. K., CALLICOTT, J. H., HIGIER, R. G., LUNA, A., NIXON, D. C., LIPSKA, B. K., VAKKALANKA, R., GIEGLING, I., RUJESCU, D., ST CLAIR, D., MUGLIA, P., SHUGART, Y. Y. & WEINBERGER, D. R. 2010a. Evidence of statistical epistasis between DISC1, CIT and NDEL1 impacting risk for schizophrenia: biological validation with functional neuroimaging. *Hum Genet,* 127**,** 441-52.

NICODEMUS, K. K., LAW, A. J., RADULESCU, E., LUNA, A., KOLACHANA, B., VAKKALANKA, R., RUJESCU, D., GIEGLING, I., STRAUB, R. E. & MCGEE, K. 2010b. Biological validation of increased schizophrenia risk with NRG1, ERBB4, and AKT1 epistasis via functional neuroimaging in healthy controls. *Archives of general psychiatry,* 67**,** 991.

NOGA, J. T., VLADAR, K. & TORREY, E. F. 2001. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. *Psychiatry Research: Neuroimaging,* 106**,** 25-34.

NUECHTERLEIN, K. H., SUBOTNIK, K. L., GREEN, M. F., VENTURA, J., ASARNOW, R. F., GITLIN, M. J., YEE, C. M., GRETCHEN-DOORLY, D. & MINTZ, J. 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia bulletin,* 37**,** S33-S40.

O'DONOVAN, M. C., CRADDOCK, N., NORTON, N., WILLIAMS, H., PEIRCE, T., MOSKVINA, V., NIKOLOV, I., HAMSHERE, M., CARROLL, L. & GEORGIEVA, L. 2008. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nature genetics,* 40**,** 1053-1055.

OERTEL-KNOCHEL, V., REINKE, B., FEDDERN, R., KNAKE, A., KNOCHEL, C., PRVULOVIC, D., PANTEL, J. & LINDEN, D. E. 2014. Episodic memory impairments in bipolar disorder are associated with functional and structural brain changes. *Bipolar Disord,* 16**,** 830-45.

OERTEL-KNOCHEL, V., REINKE, B., MATURA, S., PRVULOVIC, D., LINDEN, D. E. & VAN DE VEN, V. 2015. Functional connectivity pattern during rest within the episodic memory network in association with episodic memory performance in bipolar disorder. *Psychiatry Res,* 231**,** 141-50.

ONG, D., WALTERFANG, M., MALHI, G. S., STYNER, M., VELAKOULIS, D. & PANTELIS, C. 2012. Size and shape of the caudate nucleus in individuals with bipolar affective disorder. *Aust N Z J Psychiatry,* 46**,** 340-51.

ÖNGÜR, D., LUNDY, M., GREENHOUSE, I., SHINN, A. K., MENON, V., COHEN, B. M. & RENSHAW, P. F. 2010. Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research: Neuroimaging,* 183**,** 59-68.

ONITSUKA, T., SHENTON, M. E., KASAI, K., NESTOR, P. G., TONER, S. K., KIKINIS, R., JOLESZ, F. A. & MCCARLEY, R. W. 2003. Fusiform gyrus volume reduction and facial recognition in chronic schizophrenia. *Archives of general psychiatry,* 60**,** 349-355.

ONITSUKA, T., SHENTON, M. E., SALISBURY, D. F., DICKEY, C. C., KASAI, K., TONER, S. K., FRUMIN, M., KIKINIS, R., JOLESZ, F. A. & MCCARLEY, R. W. 2014. Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *American Journal of Psychiatry*.

OPMEER, E. M., VAN TOL, M.-J., KORTEKAAS, R., VAN DER WEE, N. J., WOUDSTRA, S., VAN BUCHEM, M. A., PENNINX, B. W., VELTMAN, D. J. & ALEMAN, A. 2015. DISC1 gene and affective psychopathology: A combined structural and functional MRI study. *Journal of psychiatric research,* 61**,** 150-157.

OWENS, S. F., PICCHIONI, M. M., RIJSDIJK, F. V., STAHL, D., VASSOS, E., RODGER, A. K., COLLIER, D. A., MURRAY, R. M. & TOULOPOULOU, T. 2011. Genetic overlap between episodic memory deficits and schizophrenia: results from the Maudsley Twin Study. *Psychol Med,* 41**,** 521-32.

PACHET, A. K. & WISNIEWSKI, A. M. 2003. The effects of lithium on cognition: an updated review. *Psychopharmacology,* 170**,** 225-234.

PACKARD, M. G. & KNOWLTON, B. J. 2002. Learning and memory functions of the basal ganglia. *Annual review of neuroscience,* 25**,** 563-593.

PALO, O. M., ANTILA, M., SILANDER, K., HENNAH, W., KILPINEN, H., SORONEN, P., TUULIO-HENRIKSSON, A., KIESEPPÄ, T., PARTONEN, T. & LÖNNQVIST, J. 2007. Association of distinct allelic haplotypes of DISC1 with psychotic and bipolar spectrum disorders and with underlying cognitive impairments. *Human Molecular Genetics,* 16**,** 2517-2528.

PAPASSOTIROPOULOS, A. & DE QUERVAIN, D. J. 2011. Genetics of human episodic memory: dealing with complexity. *Trends Cogn Sci,* 15**,** 381-7.

PAULING, L. & CORYELL, C. D. 1936. The magnetic properties and structure of the hemochromogens and related substances. *Proceedings of the National Academy of Sciences of the United States of America,* 22**,** 159.

PAUNIO, T., TUULIO-HENRIKSSON, A., HIEKKALINNA, T., PEROLA, M., VARILO, T., PARTONEN, T., CANNON, T. D., LÖNNQVIST, J. & PELTONEN, L. 2004. Search for cognitive trait components of schizophrenia reveals a locus for verbal learning and memory on 4q and for visual working memory on 2q. *Human Molecular Genetics,* 13**,** 1693-1702.

PAUS, T., KOSKI, L., CARAMANOS, Z. & WESTBURY, C. 1998. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. *Neuroreport,* 9**,** R37-R47.

PERLIS, R. H., PURCELL, S., FAGERNESS, J., KIRBY, A., PETRYSHEN, T. L., FAN, J. & SKLAR, P. 2008. Family-based association study of lithium-related and other candidate genes in bipolar disorder. *Archives of general psychiatry,* 65**,** 53-61.

PETRIDES, M. 2002. The mid-ventrolateral prefrontal cortex and active mnemonic retrieval. *Neurobiology of learning and memory,* 78**,** 528-538.

PHILLIPS, M. L., DREVETS, W. C., RAUCH, S. L. & LANE, R. 2003. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biological psychiatry,* 54**,** 515-528.

PHILLIPS, M. L., TRAVIS, M. J., FAGIOLINI, A. & KUPFER, D. J. 2008. Medication effects in neuroimaging studies of bipolar disorder. *American Journal of Psychiatry,* 165**,** 313-320.

PIERSON, A., JOUVENT, R., QUINTIN, P., PEREZ-DIAZ, F. & LEBOYER, M. 2000. Information processing deficits in relatives of manic depressive patients. *Psychological medicine,* 30**,** 545-555.

POL, H. E. H., SCHNACK, H. G., MANDL, R. C., VAN HAREN, N. E., KONING, H., COLLINS, D. L., EVANS, A. C. & KAHN, R. S. 2001. Focal gray matter density changes in schizophrenia. *Archives of General Psychiatry,* 58**,** 1118-1125.

POLDRACK, R. A., CLARK, J., PARE-BLAGOEV, E., SHOHAMY, D., MOYANO, J. C., MYERS, C. & GLUCK, M. 2001. Interactive memory systems in the human brain. *Nature,* 414**,** 546-550.

POLDRACK, R. A., WAGNER, A. D., PRULL, M. W., DESMOND, J. E., GLOVER, G. H. & GABRIELI, J. D. 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage,* 10**,** 15-35.

POMAROL-CLOTET, E., SALVADOR, R., SARRO, S., GOMAR, J., VILA, F., MARTINEZ, A., GUERRERO, A., ORTIZ-GIL, J., SANS-SANSA, B. & CAPDEVILA, A. 2008. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychological medicine,* 38**,** 1185-1193.

PORTEOUS, D. J., MILLAR, J. K., BRANDON, N. J. & SAWA, A. 2011. DISC1 at 10: connecting psychiatric genetics and neuroscience. *Trends in molecular medicine*.

PORTEOUS, D. J., THOMSON, P., BRANDON, N. J. & MILLAR, J. K. 2006. The genetics and biology of DISC1--an emerging role in psychosis and cognition. *Biol Psychiatry,* 60**,** 123-31.

POSTUMA, R. B. & DAGHER, A. 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cerebral cortex,* 16**,** 1508-1521.

POTKIN, S. G., TURNER, J. A., FALLON, J. A., LAKATOS, A., KEATOR, D. B., GUFFANTI, G. & MACCIARDI, F. 2009. Gene discovery through imaging genetics: identification of two novel genes associated with schizophrenia. *Mol Psychiatry,* 14**,** 416-28.

PRATA, D. P., MECHELLI, A., FU, C. H., PICCHIONI, M., KANE, F., KALIDINDI, S., MCDONALD, C., KRAVARITI, E., TOULOPOULOU, T., MIORELLI, A., MURRAY, R., COLLIER, D. A. & MCGUIRE, P. K. 2008. Effect of disrupted-in-schizophrenia-1 on pre-frontal cortical function. *Mol Psychiatry,* 13**,** 915-7, 909.

PRATA, D. P., MECHELLI, A., PICCHIONI, M., FU, C. H., KANE, F., KALIDINDI, S., MCDONALD, C., KRAVARITI, E., TOULOPOULOU, T., BRAMON, E., WALSHE, M., MURRAY, R., COLLIER, D. A. & MCGUIRE, P. K. 2011. No association of Disrupted-in-Schizophrenia-1 variation with prefrontal function in patients with schizophrenia and bipolar disorder. *Genes Brain Behav,* 10**,** 276-85.

PREUSS, U. W., ZETZSCHE, T., POGARELL, O., MULERT, C., FRODL, T., MÜLLER, D., SCHMIDT, G., BORN, C., REISER, M. & MÖLLER, H.-J. 2010. Anterior cingulum volumetry, auditory P300 in schizophrenia with negative symptoms. *Psychiatry Research: Neuroimaging,* 183**,** 133-139.

PURCELL, S. M., WRAY, N. R., STONE, J. L., VISSCHER, P. M., O'DONOVAN, M. C., SULLIVAN, P. F., SKLAR, P., RUDERFER, D. M., MCQUILLIN, A. & MORRIS, D. W. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature,* 460**,** 748-752.

QU, M., TANG, F., YUE, W., RUAN, Y., LU, T., LIU, Z., ZHANG, H., HAN, Y., ZHANG, D. & WANG, F. 2007. Positive association of the Disrupted-in-Schizophrenia-1 gene (DISC1) with schizophrenia in the Chinese han population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics,* 144**,** 266-270.

QUIDÉ, Y., MORRIS, R. W., SHEPHERD, A. M., ROWLAND, J. E. & GREEN, M. J. 2013. Task-related fronto-striatal functional connectivity during working memory performance in schizophrenia. *Schizophrenia research,* 150**,** 468-475.

QURAISHI, S. & FRANGOU, S. 2002. Neuropsychology of bipolar disorder: a review. *Journal of affective disorders,* 72**,** 209-226.

RAGLAND, J. D., GUR, R. C., RAZ, J., SCHROEDER, L., KOHLER, C. G., SMITH, R. J., ALAVI, A. & GUR, R. E. 2001. Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. *American Journal of Psychiatry*.

RAGLAND, J. D., LAIRD, A. R., RANGANATH, C., BLUMENFELD, R. S., GONZALES, S. M. & GLAHN, D. C. 2009. Prefrontal activation deficits during episodic memory in schizophrenia. *Am J Psychiatry,* 166**,** 863-74.

RAJARETHINAM, R., UPADHYAYA, A., TSOU, P., UPADHYAYA, M. & KESHAVAN, M. S. 2007. Caudate volume in offspring of patients with schizophrenia. *The British Journal of Psychiatry,* 191**,** 258-259.

RAJKOWSKA, G., HALARIS, A. & SELEMON, L. D. 2001. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biological psychiatry,* 49**,** 741-752.

RAND-GIOVANNETTI, E., CHUA, E. F., DRISCOLL, A. E., SCHACTER, D. L., ALBERT, M. S. & SPERLING, R. A. 2006. Hippocampal and neocortical activation during repetitive encoding in older persons. *Neurobiology of aging,* 27**,** 173-182.

RANGANATH, C., JOHNSON, M. K. & D'ESPOSITO, M. 2003. Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia,* 41**,** 378-389.

RANGANATH, C., MINZENBERG, M. J. & RAGLAND, J. D. 2008. The cognitive neuroscience of memory function and dysfunction in schizophrenia. *Biological psychiatry,* 64**,** 18-25.

RAZ, S. & RAZ, N. 1990. Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerized imaging. *Psychological Bulletin,* 108**,** 93.

RAZNAHAN, A., LEE, Y., LONG, R., GREENSTEIN, D., CLASEN, L., ADDINGTON, A., RAPOPORT, J. & GIEDD, J. 2011. Common functional polymorphisms of DISC1 and cortical maturation in typically developing children and adolescents. *Molecular psychiatry,* 16**,** 917-926.

REICHENBERG, A. & HARVEY, P. D. 2007. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological bulletin,* 133**,** 833.

REICHENBERG, A., HARVEY, P. D., BOWIE, C. R., MOJTABAI, R., RABINOWITZ, J., HEATON, R. K. & BROMET, E. 2009. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia Bulletin,* 35**,** 1022-1029.

RIPKE, S., NEALE, B. M., CORVIN, A., WALTERS, J. T., FARH, K.-H., HOLMANS, P. A., LEE, P., BULIK-SULLIVAN, B., COLLIER, D. A. & HUANG, H. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature,* 511**,** 421-427.

RIPKE, S., SANDERS, A. R., KENDLER, K. S., LEVINSON, D. F., SKLAR, P., HOLMANS, P. A., LIN, D.-Y., DUAN, J., OPHOFF, R. A. & ANDREASSEN, O. A. 2011. Genome-wide association study identifies five new schizophrenia loci. *Nature genetics*.

RIPKE, S., WRAY, N. R., LEWIS, C. M., HAMILTON, S. P., WEISSMAN, M. M., BREEN, G., BYRNE, E. M., BLACKWOOD, D. H., BOOMSMA, D. I. & CICHON, S. 2013. A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular psychiatry,* 18**,** 497-511.

RIZZO, L., DANION, J.-M., VAN DER LINDEN, M., GRANGÉ, D. & ROHMER, J.-G. 1996. Impairment of memory for spatial context in schizophrenia. *Neuropsychology,* 10**,** 376.

ROBINSON, J. L., MONKUL, E. S., TORDESILLAS-GUTIÉRREZ, D., FRANKLIN, C., BEARDEN, C. E., FOX, P. T. & GLAHN, D. C. 2008. Fronto-limbic circuitry in euthymic bipolar disorder: evidence for prefrontal hyperactivation. *Psychiatry Research: Neuroimaging,* 164**,** 106-113.

ROBINSON, L. J., THOMPSON, J. M., GALLAGHER, P., GOSWAMI, U., YOUNG, A. H., FERRIER, I. N. & MOORE, P. B. 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of affective disorders,* 93**,** 105-115.

RODRIGUEZ-MURILLO, L., GOGOS, J. A. & KARAYIORGOU, M. 2012. The genetic architecture of schizophrenia: new mutations and emerging paradigms. *Annual review of medicine,* 63**,** 63-80.

ROFFMAN, J. L., WEISS, A. P., GOFF, D. C., RAUCH, S. L. & WEINBERGER, D. R. 2006. Neuroimaging-genetic paradigms: a new approach to investigate the pathophysiology and treatment of cognitive deficits in schizophrenia. *Harv Rev Psychiatry,* 14**,** 78-91.

SABRI, O., ERKWOH, R., SCHRECKENBERGER, M., CREMERIUS, U., SCHULZ, G., DICKMANN, C., KAISER, H. J., STEINMEYER, E. M., SASS, H. & BUELL, U. 1997. Regional cerebral blood flow and negative/positive symptoms in 24 drug-naive schizophrenics. *J Nucl Med,* 38**,** 181-8.

SALGADO-PINEDA, P., FAKRA, E., DELAVEAU, P., MCKENNA, P., POMAROL-CLOTET, E. & BLIN, O. 2011. Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophrenia research,* 125**,** 101-109.

SALVADOR, R., SARRO, S., GOMAR, J. J., ORTIZ-GIL, J., VILA, F., CAPDEVILA, A., BULLMORE, E., MCKENNA, P. J. & POMAROL-CLOTET, E. 2010. Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. *Human brain mapping,* 31**,** 2003-2014.

SAMARTZIS, L., DIMA, D., FUSAR-POLI, P. & KYRIAKOPOULOS, M. 2014. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *Journal of Neuroimaging,* 24**,** 101-110.

SAWA, A. & SNYDER, S. H. 2002. Schizophrenia: diverse approaches to a complex disease. *Science's STKE,* 296**,** 692.

SAWAMURA, N., ANDO, T., MARUYAMA, Y., FUJIMURO, M., MOCHIZUKI, H., HONJO, K., SHIMODA, M., TODA, H., SAWAMURA-YAMAMOTO, T. & MAKUCH, L. A. 2008. Nuclear DISC1 regulates CRE-mediated gene transcription and sleep homeostasis in the fruit fly. *Molecular psychiatry,* 13**,** 1138-1148.

SCHLOSSER, R. G., KOCH, K., WAGNER, G., NENADIC, I., ROEBEL, M., SCHACHTZABEL, C., AXER, M., SCHULTZ, C., REICHENBACH, J. R. & SAUER, H. 2008. Inefficient executive cognitive control in schizophrenia is preceded by altered functional activation during information encoding: an fMRI study. *Neuropsychologia,* 46**,** 336-47.

SCHMIDT, D., KRAUSE, B., MOTTAGHY, F., HALSBAND, U., HERZOG, H., TELLMANN, L. & MÜLLER-GÄRTNER, H.-W. 2002. Brain systems engaged in encoding and retrieval of word-pair associates independent of their imagery content or presentation modalities. *Neuropsychologia,* 40**,** 457-470.

SCHMITT, A., HASAN, A., GRUBER, O. & FALKAI, P. 2011. Schizophrenia as a disorder of disconnectivity. *Eur Arch Psychiatry Clin Neurosci,* 261 Suppl 2**,** S150-4.

SCHREIBER, H., STOLZ-BORN, G., KORNHUBER, H. H. & BORN, J. 1992. Event-related potential correlates of impaired selective attention in children at high risk for schizophrenia. *Biological psychiatry,* 32**,** 634-651.

SCHUROV, I., HANDFORD, E., BRANDON, N. & WHITING, P. 2004. Expression of disrupted in schizophrenia 1 (DISC1) protein in the adult and developing mouse brain indicates its role in neurodevelopment. *Mol Psychiatry,* 9**,** 1100-1110.

SEBAT, J., LEVY, D. L. & MCCARTHY, S. E. 2009. Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders. *Trends Genet,* 25**,** 528-35.

SEIDMAN, L. J., KREMEN, W. S., KOREN, D., FARAONE, S. V., GOLDSTEIN, J. M. & TSUANG, M. T. 2002. A comparative profile analysis of neuropsychological functioning in patients with schizophrenia and bipolar psychoses. *Schizophrenia research,* 53**,** 31-44.

SELTZER, B. & PANDYA, D. 1984. Further observations on parieto-temporal connections in the rhesus monkey. *Experimental Brain Research,* 55**,** 301-312.

SESTIERI, C., CORBETTA, M., ROMANI, G. L. & SHULMAN, G. L. 2011. Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *The Journal of Neuroscience,* 31**,** 4407-4420.

SHAHANA, N., DELBELLO, M., CHU, W. J., JARVIS, K., FLECK, D., WELGE, J., STRAKOWSKI, S. & ADLER, C. 2011. Neurochemical alteration in the caudate: implications for the pathophysiology of bipolar disorder. *Psychiatry Res,* 193**,** 107-12.

SHAM, P. C., MORTON, N. E., MUIR, W. J., WALKER, M., COLLINS, A., SHIELDS, D. C., ST CLAIR, D. M. & BLACKWOOD, D. H. 1994. Segregation analysis of complex phenotypes: an application to schizophrenia and auditory P300 latency. *Psychiatric Genetics,* 4**,** 29-38.

SHEN, S., LANG, B., NAKAMOTO, C., ZHANG, F., PU, J., KUAN, S.-L., CHATZI, C., HE, S., MACKIE, I. & BRANDON, N. J. 2008. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. *The Journal of Neuroscience,* 28**,** 10893-10904.

SHENTON, M. E., DICKEY, C. C., FRUMIN, M. & MCCARLEY, R. W. 2001. A review of MRI findings in schizophrenia. *Schizophr Res,* 49**,** 1-52.

SHETH, S. A., NEMOTO, M., GUIOU, M., WALKER, M., POURATIAN, N. & TOGA, A. W. 2004. Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic responses. *Neuron,* 42**,** 347-355.

SILBERSWEIG, D., STERN, E., FRITH, C., CAHILL, C., HOLMES, A., GROOTOONK, S., SEAWARD, J., MCKENNA, P., CHUA, S. E. & SCHNORR, L. 1995. A functional neuroanatomy of hallucinations in schizophrenia.

SILVERSTONE, P. H., BELL, E. C., WILLSON, M. C., DAVE, S. & WILMAN, A. H. 2005. Lithium alters brain activation in bipolar disorder in a task-and state-dependent manner: an fMRI study. *Annals of General Psychiatry,* 4**,** 1.

SIMONS, J. S. & SPIERS, H. J. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. *Nature Reviews Neuroscience,* 4**,** 637-648.

SINGH, K. D. & FAWCETT, I. 2008. Transient and linearly graded deactivation of the human default-mode network by a visual detection task. *Neuroimage,* 41**,** 100-112.

SKELLEY, S. L., GOLDBERG, T. E., EGAN, M. F., WEINBERGER, D. R. & GOLD, J. M. 2008. Verbal and visual memory: characterizing the clinical and intermediate phenotype in schizophrenia. *Schizophrenia research,* 105**,** 78-85.

SKLAR, P., RIPKE, S., SCOTT, L. J., ANDREASSEN, O. A., CICHON, S., CRADDOCK, N., EDENBERG, H. J., NURNBERGER, J. I., RIETSCHEL, M. & BLACKWOOD, D. 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature genetics,* 43**,** 977.

SKUDLARSKI, P., SCHRETLEN, D. J., THAKER, G. K., STEVENS, M. C., KESHAVAN, M. S., SWEENEY, J. A., TAMMINGA, C. A., CLEMENTZ, B. A., O'NEIL, K. & PEARLSON, G. D. 2013. Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives. *American Journal of Psychiatry*.

SMITH, C. D., LORI, N. F., AKBUDAK, E., SORAR, E., GULTEPE, E., SHIMONY, J. S., MCKINSTRY, R. C. & CONTURO, T. E. 2009. MRI diffusion tensor tracking of a new amygdalo-fusiform and hippocampo-fusiform pathway system in humans. *Journal of Magnetic Resonance Imaging,* 29**,** 1248-1261.

SMOLLER, J., CRADDOCK, N., KENDLER, K., LEE, P., NEALE, B., NURNBERGER, J., RIPKE, S., SANTANGELO, S. & SULLIVAN, P. 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet,* 381**,** 1371-1379.

SNITZ, B. E., MACDONALD, A. W. & CARTER, C. S. 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia bulletin,* 32**,** 179-194.

SORENSEN, H. J., NIELSEN, P. R., PEDERSEN, C. B., BENROS, M. E., NORDENTOFT, M. & MORTENSEN, P. B. 2014. Population impact of familial and environmental risk factors for schizophrenia: a nationwide study. *Schizophr Res,* 153**,** 214-9.

SPRENG, R. N. & GRADY, C. L. 2010. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of cognitive neuroscience,* 22**,** 1112-1123.

SPROOTEN, E., SUSSMANN, J., MOORHEAD, T. & WHALLEY, H. 2011a. Association of white matter integrity with genetic variation in an exonic DISC1 SNP. *Mol Psychiatry,* 16**,** 688-689.

SPROOTEN, E., SUSSMANN, J. E., CLUGSTON, A., PEEL, A., MCKIRDY, J., MOORHEAD, T. W. J., ANDERSON, S., SHAND, A. J., GILES, S. & BASTIN, M. E. 2011b. White matter integrity in individuals at high genetic risk of bipolar disorder. *Biological psychiatry,* 70**,** 350-356.

ST CLAIR, D., BLACKWOOD, D., MUIR, W., WALKER, M., CAROTHERS, A., SPOWART, G., GOSDEN, C. & EVANS, H. 1990. Association within a family of a balanced autosomal translocation with major mental illness. *The Lancet,* 336**,** 13-16.

STEFANSSON, H., RUJESCU, D., CICHON, S., PIETILÃ¤INEN, O. P. H., INGASON, A., STEINBERG, S., FOSSDAL, R., SIGURDSSON, E., SIGMUNDSSON, T. & BUIZER-VOSKAMP, J. E. 2008. Large recurrent microdeletions associated with schizophrenia. *Nature,* 455**,** 232-236.

STERN, C. E., CORKIN, S., GONZALEZ, R. G., GUIMARAES, A. R., BAKER, J. R., JENNINGS, P. J., CARR, C. A., SUGIURA, R. M., VEDANTHAM, V. & ROSEN, B. R. 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences,* 93**,** 8660-8665.

STOLZ, E., PANCHOLI, K. M., GORADIA, D. D., PAUL, S., KESHAVAN, M. S., NIMGAONKAR, V. L. & PRASAD, K. M. 2012. Brain activation patterns during visual episodic memory processing among first-degree relatives of schizophrenia subjects. *Neuroimage,* 63**,** 1154-61.

STONE, J. L., OÂ€™DONOVAN, M. C., GURLING, H., KIROV, G. K., BLACKWOOD, D. H. R., CORVIN, A., CRADDOCK, N. J., GILL, M., HULTMAN, C. M. & LICHTENSTEIN, P. 2008. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature,* 455**,** 237-241.

STRAKOWSKI, S. 2012. *The bipolar brain: integrating neuroimaging and genetics*, Oxford University Press.

STRAKOWSKI, S. M., ADLER, C. M., ALMEIDA, J., ALTSHULER, L. L., BLUMBERG, H. P., CHANG, K. D., DELBELLO, M. P., FRANGOU, S., MCINTOSH, A., PHILLIPS, M. L., SUSSMAN, J. E. & TOWNSEND, J. D. 2012.

The functional neuroanatomy of bipolar disorder: a consensus model. *Bipolar Disord,* 14**,** 313-25.

STRAKOWSKI, S. M., ADLER, C. M., HOLLAND, S. K., MILLS, N. & DELBELLO, M. P. 2004. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology,* 29**,** 1734-40.

STRAKOWSKI, S. M., ADLER, C. M., HOLLAND, S. K., MILLS, N. P., DELBELLO, M. P. & ELIASSEN, J. C. 2005. Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. *American Journal of Psychiatry*.

SULLIVAN, P. F. 2013. Questions about DISC1 as a genetic risk factor for schizophrenia. *Mol Psychiatry,* 18**,** 1050-2.

SULLIVAN, P. F., KENDLER, K. S. & NEALE, M. C. 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry,* 60**,** 1187-1192.

SUSSMANN, J. E., LYMER, G. K. S., MCKIRDY, J., MOORHEAD, T. W. J., MANIEGA, S. M., JOB, D., HALL, J., BASTIN, M. E., JOHNSTONE, E. C. & LAWRIE, S. M. 2009. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar disorders,* 11**,** 11-18.

SZESZKO, P. R., HODGKINSON, C. A., ROBINSON, D. G., DEROSSE, P., BILDER, R. M., LENCZ, T., BURDICK, K. E., NAPOLITANO, B., BETENSKY, J. D., KANE, J. M., GOLDMAN, D. & MALHOTRA, A. K. 2008. DISC1 is associated with prefrontal cortical gray matter and positive symptoms in schizophrenia. *Biol Psychol,* 79**,** 103-10.

TAKAHASHI, T., SUZUKI, M., TSUNODA, M., MAENO, N., KAWASAKI, Y., ZHOU, S. Y., HAGINO, H., NIU, L., TSUNEKI, H., KOBAYASHI, S., SASAOKA, T., SETO, H., KURACHI, M. & OZAKI, N. 2009. The Disrupted-in-Schizophrenia-1 Ser704Cys polymorphism and brain morphology in schizophrenia. *Psychiatry Res,* 172**,** 128-35.

TALAMINI, L. M., DE HAAN, L., NIEMAN, D. H., LINSZEN, D. H. & MEETER, M. 2010. Reduced context effects on retrieval in first-episode schizophrenia. *PloS one,* 5**,** e10356.

TALAMINI, L. M., MEETER, M., ELVEVÅG, B., MURRE, J. M. & GOLDBERG, T. E. 2005. Reduced parahippocampal connectivity produces schizophrenia-like memory deficits in simulated neural circuits with reduced parahippocampal connectivity. *Archives of general psychiatry,* 62**,** 485-493.

TAYEBANI, M., GADO, O., ABDELAAL, M. & ELGAMAL, M. 2014. Caudate nucleus volume in schizophrenia, bipolar, and depressive psychosis. *Egyptian Journal of Psychiatry,* 35**,** 1.

TEK, C., GOLD, J., BLAXTON, T., WILK, C., MCMAHON, R. P. & BUCHANAN, R. W. 2002. Visual perceptual and working memory impairments in schizophrenia. *Archives of general psychiatry,* 59**,** 146-153.

THOMSON, P. A., HARRIS, S. E., STARR, J. M., WHALLEY, L. J., PORTEOUS, D. J. & DEARY, I. J. 2005. Association between genotype at an exonic SNP in DISC1 and normal cognitive aging. *Neurosci Lett,* 389**,** 41-5.

THOMSON, P. A., MALAVASI, E. L., GRUNEWALD, E., SOARES, D. C., BORKOWSKA, M. & MILLAR, J. K. 2013. DISC1 genetics, biology and psychiatric illness. *Front Biol (Beijing),* 8**,** 1-31.

TOMELLERI, L., JOGIA, J., PERLINI, C., BELLANI, M., FERRO, A., RAMBALDELLI, G., TANSELLA, M., FRANGOU, S., BRAMBILLA, P. & INITIATIVE, N. N. O. T. E. N. 2009. Brain structural changes associated with chronicity and antipsychotic treatment in schizophrenia. *European Neuropsychopharmacology,* 19**,** 835-840.

TORRES, I., BOUDREAU, V. & YATHAM, L. 2007. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatrica Scandinavica,* 116**,** 17-26.

TORREY, E. F. 2007. Schizophrenia and the inferior parietal lobule. *Schizophr Res,* 97**,** 215-25.

TOWNSEND, J., BOOKHEIMER, S. Y., FOLAND–ROSS, L. C., SUGAR, C. A. & ALTSHULER, L. L. 2010. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Research: Neuroimaging,* 182**,** 22-29.

TRACY, J. I., MATTSON, R., KING, C., BUNDICK, T., CELENZA, M. A. & GLOSSER, G. 2001. A comparison of memory for verbal and non-verbal material in schizophrenia. *Schizophrenia research,* 50**,** 199-211.

TROST, S., PLATZ, B., USHER, J., SCHERK, H., WOBROCK, T., EKAWARDHANI, S., MEYER, J., REITH, W., FALKAI, P. & GRUBER, O. 2013. DISC1 (disrupted-in-schizophrenia 1) is associated with cortical grey matter volumes in the human brain: a voxel-based morphometry (VBM) study. *Journal of psychiatric research,* 47**,** 188-196.

TSUANG, M. T., TAYLOR, L. & FARAONE, S. V. 2004. An overview of the genetics of psychotic mood disorders. *Journal of psychiatric research,* 38**,** 3-15.

TULLY, L. M., LINCOLN, S. H., LIYANAGE-DON, N. & HOOKER, C. I. 2014. Impaired cognitive control mediates the relationship between cortical thickness of the superior frontal gyrus and role functioning in schizophrenia. *Schizophrenia research,* 152**,** 358-364.

TULVING, E. 1972. Episodic and semantic memory 1. *Organization of Memory. London: Academic,* 381**,** 4.

TULVING, E. 1985. *Elements of Episodic Memory*, OUP Oxford.

TULVING, E., MARKOWITSCH, H. J., CRAIK, F. I., HABIB, R. & HOULE, S. 1996. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex,* 6**,** 71-79.

VAN DER VEEN, F. M., NIJHUIS, F. A., TISSERAND, D. J., BACKES, W. H. & JOLLES, J. 2006. Effects of aging on recognition of intentionally and incidentally stored words: an fMRI study. *Neuropsychologia,* 44**,** 2477-2486.

VAN VEEN, V. & CARTER, C. S. 2002. The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology & behavior,* 77**,** 477-482.

VIDING, E., WILLIAMSON, D. E. & HARIRI, A. R. 2006. Developmental imaging genetics: challenges and promises for translational research. *Development and psychopathology,* 18**,** 877-892.

WAGNER, A. D., POLDRACK, R. A., ELDRIDGE, L. L., DESMOND, J. E., GLOVER, G. H. & GABRIELI, J. D. 1998a. Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport,* 9**,** 3711-3717.

WAGNER, A. D., SCHACTER, D. L., ROTTE, M., KOUTSTAAL, W., MARIL, A., DALE, A. M., ROSEN, B. R. & BUCKNER, R. L. 1998b. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science,* 281**,** 1188-1191.

WAGNER, A. D., SHANNON, B. J., KAHN, I. & BUCKNER, R. L. 2005. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci,* 9**,** 445-53.

WALSH, T., MCCLELLAN, J. M., MCCARTHY, S. E., ADDINGTON, A. M., PIERCE, S. B., COOPER, G. M., NORD, A. S., KUSENDA, M., MALHOTRA, D., BHANDARI, A., STRAY, S. M., RIPPEY, C. F., ROCCANOVA, P., MAKAROV, V., LAKSHMI, B., FINDLING, R. L., SIKICH, L., STROMBERG, T., MERRIMAN, B., GOGTAY, N., BUTLER, P., ECKSTRAND, K., NOORY, L., GOCHMAN, P., LONG, R., CHEN, Z., DAVIS, S., BAKER, C., EICHLER, E. E., MELTZER, P. S., NELSON, S. F., SINGLETON, A. B., LEE, M. K., RAPOPORT, J. L., KING, M. C. & SEBAT, J. 2008. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science,* 320**,** 539-43.

WALTER, H., SCHNELL, K., ERK, S., ARNOLD, C., KIRSCH, P., ESSLINGER, C., MIER, D., SCHMITGEN, M., RIETSCHEL, M. & WITT, S. 2011. Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task. *Mol Psychiatry,* 16**,** 462-470.

WALTER, H., VASIC, N., HÖSE, A., SPITZER, M. & WOLF, R. C. 2007. Working memory dysfunction in schizophrenia compared to healthy controls and patients with depression: evidence from event-related fMRI. *Neuroimage,* 35**,** 1551-1561.

WALTON, E., TURNER, J., GOLLUB, R. L., MANOACH, D. S., YENDIKI, A., HO, B. C., SPONHEIM, S. R., CALHOUN, V. D. & EHRLICH, S. 2012. Cumulative Genetic Risk and Prefrontal Activity in Patients With Schizophrenia. *Schizophrenia Bulletin*.

WANG, L., METZAK, P. D., HONER, W. G. & WOODWARD, T. S. 2010. Impaired efficiency of functional networks underlying episodic memory-for-context in schizophrenia. *J Neurosci,* 30**,** 13171-9.

WANG, Q., JAARO-PELED, H., SAWA, A. & BRANDON, N. J. 2008. How has DISC1 enabled drug discovery? *Molecular and Cellular Neuroscience,* 37**,** 187-195.

WATERS, F. A., MAYBERY, M. T., BADCOCK, J. C. & MICHIE, P. T. 2004. Context memory and binding in schizophrenia. *Schizophrenia research,* 68**,** 119-125.

WECHSLER, D. 1955. Manual for the Wechsler Adult Intelligence Scale.

WEICKERT, T. W., GOLDBERG, T. E., GOLD, J. M., BIGELOW, L. B., EGAN, M. F. & WEINBERGER, D. R. 2000. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Archives of General Psychiatry,* 57**,** 907-913.

WEINBERGER, D. R., EGAN, M. F., BERTOLINO, A., CALLICOTT, J. H., MATTAY, V. S., LIPSKA, B. K., BERMAN, K. F. & GOLDBERG, T. E. 2001. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry,* 50**,** 825-844.

WEIS, S. 2004. Temporal and Cerebellar Brain Regions that Support both Declarative Memory Formation and Retrieval. *Cerebral Cortex,* 14**,** 256-267.

WEISS, A. & HECKERS, S. 2001. Neuroimaging of declarative memory in schizophrenia. *Scandinavian journal of psychology,* 42**,** 239-250.

WEISS, A. P., DEWITT, I., GOFF, D., DITMAN, T. & HECKERS, S. 2005. Anterior and posterior hippocampal volumes in schizophrenia. *Schizophrenia research,* 73**,** 103-112.

WEISS, A. P., ELLIS, C. B., ROFFMAN, J. L., STUFFLEBEAM, S., HAMALAINEN, M. S., DUFF, M., GOFF, D. C. & SCHACTER, D. L. 2009. Aberrant frontoparietal function during recognition memory in schizophrenia: a multimodal neuroimaging investigation. *The Journal of Neuroscience,* 29**,** 11347-11359.

WEISS, A. P., SCHACTER, D. L., C GOFF, D., RAUCH, S. L., ALPERT, N. M., FISCHMAN, A. J. & HECKERS, S. 2003. Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Biol Psychiatry,* 53**,** 48-55.

WELSH, R. C., CHEN, A. C. & TAYLOR, S. F. 2010. Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in schizophrenia. *Schizophrenia bulletin,* 36**,** 713-722.

WESSA, M., HOUENOU, J., PAILLÈRE-MARTINOT, M.-L., BERTHOZ, S., ARTIGES, E., LEBOYER, M. & MARTINOT, J.-L. 2007. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *The American journal of psychiatry,* 164**,** 638-646.

WHALLEY, H., PAPMEYER, M., SPROOTEN, E., ROMANIUK, L., BLACKWOOD, D., GLAHN, D., HALL, J., LAWRIE, S., SUSSMANN, J. & MCINTOSH, A. 2012a. The influence of polygenic risk for bipolar disorder on neural activation assessed using fMRI. *Translational psychiatry,* 2**,** e130.

WHALLEY, H. C., DIMITROVA, R., SPROOTEN, E., DAUVERMANN, M. R., ROMANIUK, L., DUFF, B., WATSON, A. R., MOORHEAD, B., BASTIN, M. & SEMPLE, S. I. 2015a. Effects of a Balanced Translocation between Chromosomes 1 and 11 Disrupting the DISC1 Locus on White Matter Integrity. *PloS one,* 10**,** e0130900.

WHALLEY, H. C., HALL, L., ROMANIUK, L., MACDONALD, A., LAWRIE, S. M., SUSSMANN, J. E. & MCINTOSH, A. M. 2015b. Impact of cross-disorder polygenic risk on frontal brain activation with specific effect of schizophrenia risk. *Schizophrenia research,* 161**,** 484-489.

WHALLEY, H. C., MCKIRDY, J., ROMANIUK, L., SUSSMANN, J., JOHNSTONE, E. C., WAN, H. I., MCINTOSH, A. M., LAWRIE, S. M. & HALL, J. 2009. Functional imaging of emotional memory in bipolar disorder and schizophrenia. *Bipolar disorders,* 11**,** 840-856.

WHALLEY, H. C., PAPMEYER, M., SPROOTEN, E., LAWRIE, S. M., SUSSMANN, J. E. & MCINTOSH, A. M. 2012b. Review of functional magnetic resonance imaging studies comparing bipolar disorder and schizophrenia. *Bipolar disorders,* 14**,** 411-431.

WHALLEY, H. C., SIMONOTTO, E., FLETT, S., MARSHALL, I., EBMEIER, K., OWENS, D., GODDARD, N., JOHNSTONE, E. & LAWRIE, S. 2004. fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. *Brain,* 127**,** 478-490.

WHALLEY, H. C., SIMONOTTO, E., MOORHEAD, W., MCINTOSH, A., MARSHALL, I., EBMEIER, K. P., OWENS, D. G., GODDARD, N. H., JOHNSTONE, E. C. & LAWRIE, S. M. 2006. Functional imaging as a predictor of schizophrenia. *Biological Psychiatry,* 60**,** 454-62.

WHALLEY, H. C., SUSSMANN, J. E., CHAKIROVA, G., MUKERJEE, P., PEEL, A., MCKIRDY, J., HALL, J., JOHNSTONE, E. C., LAWRIE, S. M. & MCINTOSH, A. M. 2011. The neural basis of familial risk and temperamental variation in individuals at high risk of bipolar disorder. *Biological Psychiatry,* 70**,** 343-349.

WHALLEY, H. C., SUSSMANN, J. E., JOHNSTONE, M., ROMANIUK, L., REDPATH, H., CHAKIROVA, G., MUKHERJEE, P., HALL, J., JOHNSTONE, E. C., LAWRIE, S. M. & MCINTOSH, A. M. 2012c. Effects of a mis-sense DISC1 variant on brain activation in two cohorts at high risk of bipolar disorder or schizophrenia. *Am J Med Genet B Neuropsychiatr Genet,* 159B**,** 343-53.

WHALLEY, H. C., SUSSMANN, J. E., ROMANIUK, L., STEWART, T., KIELTY, S., LAWRIE, S. M., HALL, J. & MCINTOSH, A. M. 2015c. Dysfunction of emotional brain systems in individuals at high risk of mood disorder with depression and predictive features prior to illness. *Psychol Med,* 45**,** 1207-18.

WHITE, T. & GOTTESMAN, I. 2012. Brain connectivity and gyrification as endophenotypes for schizophrenia: weight of the evidence. *Current topics in medicinal chemistry,* 12**,** 2393-2403.

WHYTE, M. C., MCINTOSH, A. M., JOHNSTONE, E. C. & LAWRIE, S. M. 2005. Declarative memory in unaffected adult relatives of patients with schizophrenia: a systematic review and meta-analysis. *Schizophr Res,* 78**,** 13-26.

WOLF, D. H., GUR, R. C., VALDEZ, J. N., LOUGHEAD, J., ELLIOTT, M. A., GUR, R. E. & RAGLAND, J. D. 2007. Alterations of fronto-temporal connectivity during word encoding in schizophrenia. *Psychiatry Res,* 154**,** 221-32.

YACOUB, E., SHMUEL, A., PFEUFFER, J., VAN DE MOORTELE, P.-F., ADRIANY, G., UGURBIL, K. & HU, X. 2001. Investigation of the initial dip in fMRI at 7 Tesla. *NMR in Biomedicine,* 14**,** 408-412.

YILDIZ, M., BORGWARDT, S. J. & BERGER, G. E. 2011. Parietal lobes in schizophrenia: do they matter? *Schizophr Res Treatment,* 2011**,** 581686.

YONELINAS, A. P. & LEVY, B. J. 2002. Dissociating familiarity from recollection in human recognition memory: different rates of forgetting over short retention intervals. *Psychonomic Bulletin & Review,* 9**,** 575-582.

YOUNG, A., BLACKWOOD, D., ROXBOROUGH, H., MCQUEEN, J., MARTIN, M. & KEAN, D. 1991. A magnetic resonance imaging study of schizophrenia: brain structure and clinical symptoms. *The British Journal of Psychiatry,* 158**,** 158-164.

YOUNG, R., BIGGS, J., ZIEGLER, V. & MEYER, D. 1978. A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry,* 133**,** 429-435.

YÜKSEL, C. & ÖNGÜR, D. 2010. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biological psychiatry,* 68**,** 785-794.

ZETZSCHE, T., PREUSS, U., FRODL, T., WATZ, D., SCHMITT, G., KOUTSOULERIS, N., BORN, C., REISER, M., MÖLLER, H.-J. & MEISENZAHL, E. M. 2007. In-vivo topography of structural alterations of the anterior cingulate in patients with schizophrenia: new findings and comparison with the literature. *Schizophrenia research,* 96**,** 34-45.

ZIERHUT, K., BOGERTS, B., SCHOTT, B., FENKER, D., WALTER, M., ALBRECHT, D., STEINER, J., SCHÜTZE, H., NORTHOFF, G. & DÜZEL, E. 2010. The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia. *Psychiatry Research: Neuroimaging,* 183**,** 187-194.

ZORRILLA, L. T. E., JESTE, D. V., PAULUS, M. & BROWN, G. G. 2003. Functional abnormalities of medial temporal cortex during novel picture learning among patients with chronic schizophrenia. *Schizophrenia research,* 59**,** 187-198.

Appendices

Appendix I: Genotyping methods

Genotypes of common nonsynonymous variants in DISC1 were extracted from whole genome sequencing data. Whole genome sequencing was performed by W. Richard McCombie at the The Stanley Institute for Cognitive Genomics, Cold Spring Harbor Genomics Centre under an NIH grant awarded to W. Richard McCombie and David J. Porteous (CGE, IGMM, University of Edinburgh; NIH award R01MH102088).

Briefly, whole genome sequencing of whole blood-derived DNA, or lymphoblastoid cell line-derived DNA, was performed on an Illumina HiSeq 2000 at an average read depth of >30x. Sequence reads from the Illumina HiSeq 2000 runs were aligned to human genome assembly hg19 using the BWA aligner (Li et al., 2009), allowing 2 mismatches in the 30-base seed. Alignments were then paired, imported to binary (bam) format, sorted and indexed using SAMtools. Picard was then used to fix any mate pair information altered by the sorting. Bamtools (Barnett et al., 2011) was used to filter alignments to retain only properly paired reads (reads aligned with appropriate insert size and orientation). PCR duplicates were removed using Picard. Bamtools was then used to select alignments with a minimum mapping quality score of 20. Target coverage for each NimbleGen exome capture was assessed using Picard's HSmetrics utility, and both depth and breadth of coverage were reviewed for each sample. The Genome Analysis Toolkit (Depristo et al., 2011) GATK was used for local read realignment around indels, and for base quality score recalibration using corrections for base position within the Illumina read, for sequence context, and for platform-reported quality. Variants were filtered for a minimum confidence score of 30, and minimum mapping quality of 40. Additional filters were applied for base quality score, strand bias and homopolymer stretches. SNP clusters (>3 SNPs per 10 bp window) were excluded. SNPs falling within called indel regions were also masked.

Genotypes were checked using Merlin (Abecassis et al., 2002) to identify errors in Mendelian segregation. Pedigree relationships were verified between samples by calculation of identity by state matrices between all individuals using a linkage disequilibrium pruned dataset of >100,000 variants in PLINK (Chang et al., 2015).

References

ABECASIS, G., R., CHERNY, S., S., COOKSON, W., O. and CARDON, L., R. 2002. Merlin-rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet*, 30, 97-101.

BARNETT, D., W., GARRISON, E., K., QUINLAN, A., R., STROMBERG, M., P., MARTH, G., T. 2011. BamTools: a C++ API and toolkit for analyzing and managing BAM files. *Bioinformatics*. 27(12), 1691–1692.

CHANG, C., C., CHOW, C., C., TELLIER, L., C., A., M., VATTIKUTI, S., PURCELL, S., M., and LEE, J., J. (2015) Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience*, 4.

DEPRISTO, M., A., BANKS, E., POPLIN, R., GARIMELLA, K., V., MAGUIRE, J., R., HARTL, C. 2011. et al. A framework for variation discovery and genotyping using next-generation DNA sequencing data. *Nat Genet*, 43(5), 491–498.

LI, H., DURBIN, R. 2009. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics*, 25(14),1754–1760.

Appendix II: Published literature review

Literature review contained within this thesis (chapter 2). Permission to include this article has been sought by the co-authors.