An Investigation of In-vivo Neuroimaging in Schizophrenia, Using Various Modalities

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Personal Contribution Statement

I, Elvina May-Yin Chu confirm that this thesis is my own work. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I received technical assistance with MRI imaging from the departmental radiographers, assistance with OCT imaging from neurology colleagues and statistical advice were also sought. Where information was obtained from other sources, this has been clearly referenced in the thesis. Specific details are acknowledged as appropriate.

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Abstract

Schizophrenia is a devastating mental illness and a huge disease burden in terms of cost. The individual is typically affected in early adulthood, thus loosing the best years of their life. The stigma of mental illness and pattern of downward social drift also results in families and society being adversely affected.

With advances in neuroscience and neuroimaging, psychiatrists can advance their understanding of schizophrenia as a disease of the brain using biological models. This thesis investigates how volumetric magnetic resonance imaging (MRI), structural MRI techniques such as magnetisation transfer imaging (MTI), diffusion tensor imaging (DTI), and novel techniques such as optical coherence tomography (OCT) and visual function testing may be used to elucidate the neuropathology of schizophrenia in-vivo, in addition to explaining the cognitive deficits that are commonly observed.

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The following studies are included in this thesis:

1) A diffusion tensor imaging (DTI) study to explore white matter abnormalities in first episode psychosis and correlations with cognitive performance.
2) An exploratory study utilizing OCT to investigate whether retinal nerve fibre layer thickness varies between patients with schizophrenia and healthy controls.
3) A longitudinal study using MRI and MTI to examine structural brain changes following first episode psychosis and correlating these findings with cognitive performance.
4) An investigation of chromatic vision in schizophrenia spectrum disorders and correlations between hue discrimination ability and cognitive performance.
5) A cross-sectional comparison study of grey matter volume and associations with oculomotor function in first episode patients and healthy controls.

List of Abbreviations

Δ	time between two gradient pulses
δ	duration of gradient pulse
ω	angular precessional frequency of a proton
θ	angle
γ	gyromagnetic ratio
λ	eigenvalue
ε	eigenvector
5HT	5-Hydroxytryptamine
ADC	Apparent Diffusion Coefficient
B_0	Strength of MRI scanner's magnetic field
BADS	Behavioural Assessment of Dysexecutive Syndrome
BDNF	Brain Derived Neurotropic Factor
BET	Brain Extraction Tool
CANTAB	Cambridge Neuropscyhological Test Automated Battery
CBT	Cognitive Behavioural Therapy
CMHT	Community Mental Health Team
CRT	Cathode Ray Tube
CSF	Cerebrospinal Fluid
CT	Computerised axial tomography
D2	Dopamine 2 receptor
DA	Dopamine
DIP	Diagnostic Interview for Psychosis
DISC1	Disrupted in Schizophrenia 1
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IIIR	Diagnostic and Statistical Manual of Mental Disorders 3rd ed. revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revised
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
DT	Diffusion Tensor
DTI	Diffusion Tensor Imaging

EEG	Electroencephalogram
EPI	Echo Planar Imaging
FA	Fractional Anisotropy
FDR	False Discovery Rate
FE	First Episode
FEF	Frontal Eye Fields
FID	Free Induction Decay
FLIRT	FMRIB's Linear Image Registration Tool
FMRIB	Functional MRI of Brain
FSE	Fast Spin Echo
FSL	FMRIB Software Library
FWE	Family Wise Error
FWHM	Full Width Half Maximum
GABA	Gamma-Aminobutyric acid
GAD	Glutamate Decarboxylase
GLM	General Linear Model
GM	Grey Matter
H	Hydrogen
H_2O	Water Molecule
HamD	Hamilton Depression Rating Scale
ICD	International Classification of Mental & Behavioural Disorders
ICD-10	10^{th} International Classification of Mental & Behavioural Disorders
ILF	Inferior Longitudinal Fasciculus
ION	Institute of Neurology
IQ	Intelligence Quotient
LGN	Lateral Geniculate Nucleus
LSDI	Line Scan Diffusion Imaging
MD	Mean Diffusivity
MNI	Montréal Neurological Institute
Mo	Mean Signal Intensity (with signal on)
Ms	Mean Signal Intensity (with signal off)
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging

MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MT	Magnetisation Transfer
MTI	Magnetisation Transfer Imaging
MTR	Magnetisation Transference Ratio
NART	National Adult Reading Test
NMDA	N-Methyl-D-Aspartate
NMV	Net Magnetisation Vector
NRG	Neuregulin
OCT	Optical Coherence Tomography
OPCRIT	Operational Criteria Checklist for Psychosis
PD	Proton Density
PET	Positron Emission Tomography
PFG	Pulsed Field Gradient
PICo	Probabilistic Index of Connectivity
PT	Planum Temporale
PTR	Posterior Thalamic Radius
pu	Percentage Units
RA	Relative Anisotropy
RAVLT	Rey Auditory Verbal Learning Task
RF	Radio Frequency
RNFL	Retinal Nerve Fibre Layer
ROI	Region of Interest
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
SC	Superior Colliculus
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard Deviation
SEF	Supplementary Eye Fields
SNP	Single-Neucleotide Polymorphism
SPECT	Single-Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SPM5	Statistical Parametric Mapping 2005
STG	Superior Temporal Gyrus

TBSS	Tract Based Spatial Statistics
T	Tesla
T1	Spin Lattice Relaxation Time
T2	Spin-spin Relaxation Time
T2*	dephasing due to magnetic field inhomogeneities
TE	Echo Time
TR	Repetition Time
UF	Uncinate Fasciculus
UHR	Ultra high risk
VBM	Voxel-Based Morphometry
WAIS	Weschler Adult Intelligence Scale
WM	White Matter
WAIS	Wechsler Adult Intelligence Scale
WTAR	Wechsler Test of Adult Reading

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1. AN OVERVIEW OF SCHIZOPHRENIA

1.1 Introduction

Schizophrenia is a word derived from Greek which literally translates as “split mind”. As a diagnostic concept, “The Schizophrenias” were introduced by the Swiss psychiatrist Eugen Bleuler in 1911. This was supposed to describe the loss of coherent contact between different functions of the mind i.e. loosening of associations (Bleuler, 1911). Schizophrenia gradually replaced the Kraepelinian concept of Dementia Praecox, which described the symptoms of patients who had catatonic or paranoid presentations thought to be the result of a progressive brain disease with a poor prognosis (Kraepelin, 2009).

Today, schizophrenia remains a psychiatric disorder of major, global impact with 1% prevalence, affecting all ethnic groups in any of the various social strata. Contrary to popular belief, schizophrenia is equally common in men and women, although women typically have a later illness onset and often a less severe course of illness than men (Castle et al., 1998). One possible explanation for the difference in illness severity is due to the gender difference, with males and females being susceptible to what may be different subtypes of schizophrenia, which have different ages of onset (Murray et al., 1992).

Schizophrenia is a costly disease to both the affected individual and society as a whole. Symptom onset is usually in early adulthood at a period in the lifespan when humans are at their prime in terms of physical and intellectual development. In the Western world, direct expenditure for treatment and social care of patients with schizophrenia is estimated at 1 to 3% of the national healthcare budget (Knapp et al., 2004). In economic terms, schizophrenia cost an estimated total of £6.7 billion in the UK alone for 2004/5, with £2 billion spent on direct costs (i.e. treatment and social care) and the remainder accrued through indirect costs to society (Mangalore and Knapp, 2007). In the USA, the overall cost was estimated at $62.7 billion in 2002; with indirect costs estimated at $32.4 billion from days lost to

unemployment, reduced workplace productivity, premature death by suicide and family members providing care (Wu et al., 2005).

1.2 Clinical Diagnosis

A diagnosis of schizophrenia has historically been based on Schneider's First Rank Symptoms which describe a cluster of symptoms in four categories, including auditory hallucinations, thought broadcast, delusions of control and delusional perception (Schneider, 1959). Although a useful guideline, there is controversy as first rank symptoms are not specific for schizophrenia (Nordgaard et al., 2008), although they occur frequently in patients with schizophrenia (Thorup et al., 2007). First rank symptoms have historically contributed to the definition of schizophrenia in the two major classification systems for psychiatric disorders, the International Classification of Diseases (ICD) published by the World Health Organisation and the Diagnostic and Statistical Manual (DSM) published by the American Psychiatric Association. Both systems are under regular review and modification, and the suggestion that first rank symptoms should be de-emphasised in future editions as specificity for schizophrenia is poor (Nordgaard et al., 2008) has resulted in changes to the DSM-5 (American Psychiatric Association, 2013) criteria, which now states that it is characterized by delusions, hallucinations, disorganised speech and behaviour, and other symptoms that cause social or occupational dysfunction. For a diagnosis, at least two symptoms must have been present for six months. The ICD-10 (World Health Organisation, 1992) specifies at least 1 month duration of symptoms and also classifies different schizophrenia subtypes; instruments such as the Diagnostic Interview for Psychoses (Jablensky, 2000) and the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) have been developed from this. These instruments have been primarily used to identify symptom severity in those with an established diagnosis of schizophrenia but increasing research interest is focused on the schizophrenia prodrome and ways to identify the disease early.

Future aims include a more biologically based categorization of schizophrenia using endophenotypes, once these have been firmly

established (Tandon et al., 2009). As no medical test can confirm a diagnosis of schizophrenia, it remains difficult to ascertain an early diagnosis and predict disease progression or long-term prognosis. The search for biological phenotypes is underway but diagnosis is still determined by clinical observations. Schizophrenia remains an elusive illness as it encompasses a wide range of symptoms with no clear disease biomarker that can be readily measured or evaluated.

1.3 Epidemiological Findings

The incidence of schizophrenia is similar across different countries at a rate of 0.16 to 0.42 per 1000 population (Jablensky et al., 1992). Some ethnic groups are at increased risk of developing schizophrenia but reasons for this remain unclear. Second generation, black African-Caribbean immigrants in London are seven times more likely to develop schizophrenia than their Caucasian neighbours. Conversely, the Hutterites of Manitoba and South Dakota have low incidence rates compared to other white Caucasian, immigrant settlers (Nimgaonkar et al., 2000). Socio-demographic studies have found a particularly large cluster of schizophrenia cases in South London, suggesting an association with social deprivation and social isolation (Morgan et al., 2008).

Obstetric complications, poor social and occupational adjustment are all linked to early illness onset (Murray et al., 1992). An excess of schizophrenia patients are also found to have Winter-Spring births (Torrey et al., 1997).

Gender differences point to an effect of sex hormones and chronic oestrogen applications have been shown to significantly shorten episodes of dopamine-induced behaviour and reduce D_2 receptor sensitivity in the brain, at least in animal and post-mortem studies (Häfner et al., 1993). An X-linked susceptibility locus determining age of onset has also been postulated (DeLisi, 1992).

Perhaps the most controversial topic in schizophrenia research is the link between cannabis use and onset of psychosis. In a longitudinal study of

Swedish conscripts, it was found that those who smoked cannabis had double the risk of developing schizophrenia during a 15 year period of follow-up (Andréasson et al., 1987). Subsequent studies correlated the degree of exposure to cannabis with the risk of developing schizophrenia (van Os et al., 2002; Zammitt et al., 2002). A direct causal effect remains unfounded; however there are serious public health implications that call for the prevention of cannabis use (Macleod et al., 2006).

1.4 Chemical Neurotransmitters

Original treatments developed for schizophrenia were not based on scientific evidence and often resulted in more harm than good e.g. inducing malaria and insulin coma. While some have argued against the neurochemical model of mental illness (Moncrieff, 2007), others have challenged the medical model and concept of psychiatric illness itself (Laing, 1950).

In the 1950s, it was recognized that phenothiazines were useful antipsychotic agents. This was a serendipitous finding considering chemists at the time were attempting to develop an antihistamine. A similar tranquilizing effect was also seen in the butyrophenones (another chance finding). Carlsson and Lindquist demonstrated that both chlorpromazine and haloperidol increase monoamine turnover and postulated that they might act on dopamine (DA) receptors (Carlsson and Lindquist, 1963), thus providing a plausible explanation for their mechanism of action, which gave rise to explanatory theories of schizophrenia.

The dopamine hypothesis was subsequently born and confirmed by Positron Emission Tomography (PET) studies (Creese et al., 1976). PET scanning involves injecting a radio-active isotope which has been incorporated into a biologically active molecule e.g. fluorodeoxyglucose (FDG), which is then given time to accumulate in the tissue of interest. The scan is produced by measuring the concentration of radio-active tracer as it decays over time. In the case of antipsychotic drugs, it was shown that the degree of post-synaptic dopamine receptor blockade correlated with potency of the drug (Seeman et al., 1975). There are at least 5 dopamine receptor subtypes but

functional imaging studies have found evidence of an increase in brain D2 receptor density in schizophrenia (Laruelle, 1998). It is now understood that blockade of 60 to 70% of D2 receptors is required to optimize treatment of psychotic symptoms.

Glutamate, an excitatory neurotransmitter has also been implicated in schizophrenia. Blockade of NMDA glutamate receptors by agents such as amphetamines or cocaine closely mimic psychosis as seen in schizophrenia (Laruelle, 1998). Glutamate is also used to synthesise the inhibitory neurotransmitter GABA but regulation of GABA neurotransmission is partly due to its rate-limiting synthesizing enzyme glutamate decarboxylase (GAD). Thompson and colleagues found a widespread deficit in GAD_{67} mRNA expression throughout multiple areas of the brain in schizophrenia, with significant reductions in the anterior cingulated cortex, superior temporal gyrus, striatum and thalamus (Thompson et al., 2009).

Current developments are being made with LY404039 (a selective agonist for metabotropic glutamate 2 and glutamate 3 receptors), with a promising clinical trial using the oral pro-drug LY2140023. This treatment was safe and well-tolerated by patients who showed statistically significant improvements in both positive and negative symptoms of schizophrenia compared to a placebo after 4 weeks (Patil et al., 2007). It has subsequently been suggested that clinical antipsychotic action of a glutamate agonist may in fact depend on its ability to interfere with DA neurotransmission by its DA partial agonism (Seeman, 2009).

1.5 Neuropathology

For many decades, schizophrenia research produced no scientific breakthroughs and was described as the “graveyard of neuropathologists” (Plum, 1972) until 1976, when a seminal study by Eve Johnstone and colleagues reported increased ventricular size on the first in-vivo, controlled, comparison computerized tomography (CT) study of schizophrenia (Johnstone et al., 1976). Although earlier studies had reported an increased ventricular size in schizophrenia patients, they failed to attract much interest

as they used invasive techniques such as pneumo-encephalography or ventriculography on a small number of patients. Macroscopically, loss of brain tissue appeared to result in ventricular enlargement of the third and lateral ventricles, this is now a well-recognized feature of schizophrenia.

At a microscopic level, postmortem studies have suggested changes in the brain at a cellular level, which points to schizophrenia being a neurodevelopmental abnormality. An influential paper described abnormal cytoarchitecture and lamination of the entorhinal cortex, with prominent changes noted in lamina II of the entorhinal cortex (Jakob and Beckmann, 1986); however, a healthy control group was not used for comparison and material was sampled based on external landmarks, resulting in a possible sampling error (Harrison, 1999), hence the finding remains contentious. Reduction in the number of dendritic spines and dendritic length have been described in layer III of the dorsolateral prefrontal cortex (Glantz and Lewis, 2000), temporal and frontal association layers (Garey et al., 1998) and layer V of the pre-frontal cortex (Black et al., 2004). Volume loss in the brain is probably due to a reduction of neuropil (as proposed by the reduced neuropil hypothesis) rather than a reduction in the actual number of neurons, (Selemon and Goldman-Rakic, 1999). The main difficulty is in obtaining sufficient numbers of post-mortem samples and fresh brain tissue as the neuropathology studies quoted, each contained fewer than 25 brain tissue samples from schizophrenia patients.

Oligodendrocytes responsible for optimizing nerve conduction by myelination of the axons are also seen in reduced number (Uranova et al., 2004) and expression of six myelin-related genes have subsequently been found to have decreased expression in schizophrenia. The mouse model for dysmyelination (the MAG knockout mouse) has also been found to have changes in dendritic branching in layer III of the prefrontal cortex (Segal et al., 2007).

There is no firm evidence for schizophrenia being a progressive neurodegenerative disease (as initially postulated by Kraepelin himself).

Although gliosis was reported in one post mortem study of schizophrenia (Stevens, 1982) subsequent neuropathological investigations have revealed mixed results and a more likely explanation is that schizophrenia brains are more prone to cumulative damage resulting in gliosis (Harrison, 1999). Other neurodegenerative hallmarks such as cortical thinning have been reported in both post-mortem (Selemon et al., 1995) and in-vivo scanning studies (Nesvag et al., 2008) but concurrent increased neuronal density suggests the cortical thinning is probably due to a reduction in neuropil.

1.6 Models of schizophrenia

A neurodevelopmental explanation for schizophrenia seems plausible as evidence suggests an association of the schizophrenia diagnosis with obstetric complications such as prolonged labour or difficult births resulting in cerebral anoxia (Geddes and Lawrie, 1995). Furthermore, the earlier the age at onset of schizophrenia, the more likely the history of obstetric complications (Verdoux et al., 1997) and low birth weight (<2500 g) with the combination of low birth weight and short gestation (<37 weeks) more common among adults with schizophrenia (Jones et al., 1998). These suggest that schizophrenia may be an adverse outcome following perinatal and/or fetal insults.

White matter tracts relay information between different cortical areas of the brain and schizophrenia as a syndrome of disconnectivity has been postulated (Friston and Frith, 1995). Disordered connectivity as a result of disrupted white matter tract integrity has subsequently been evidenced by scanning studies using diffusion tensor imaging (DTI) (Kubicki et al., 2005a; Agartz et al., 2001). White matter tract integrity declines with chronicity of illness (Carpenter et al., 2008) which may explain why studies including patients at first episode of schizophrenia (Friedman et al., 2008) do not always appear to support this hypothesis.

The large degree of variation in clinical presentation of schizophrenia suggests that it is unlikely to be a single disease entity but ‘the schizophrenias’ may form part of a disease spectrum as there is some

symptom overlap between bipolar affective disorder and schizophrenia, with schizoaffective disorder sitting between these two diagnoses. From imaging studies, a generic association between genetic risk for both disorders and white matter volume reduction in the left frontal and tempo-parietal regions was consistent with left fronto-temporal disconnectivity as a genetically controlled, structural brain abnormality common to both disorders (McDonald et al., 2004). In another study comparing schizophrenia and bipolar disorder, both groups showed reduced white matter density in the anterior limb of the internal capsule (McIntosh et al., 2005). In a magnetic resonance spectroscopy (SPECT) study, a similar decrease in N-acetyl-aspartate (a breakdown product of the neurotransmitter acetylcholine) was found in the prefrontal region in both schizophrenia and bipolar disorder, compared to healthy controls (Molina et al., 2007). A meta-analysis of complete genome scans for schizophrenia and bipolar disorder also found some overlap between the two disorders, with the most promising regions for schizophrenia at 8p24, 13q32 and 22q11, and for bipolar disorder at 13q32 and 22q11 (Badner and Gershon 2002). These studies all suggest that the neuropathology of psychosis may arise from the same common root.

It is now evident that no single gene is responsible for causing schizophrenia. Although some candidate genes have aroused interest e.g. NRG1 (Neuregulin) on chromosome 8p22, there appears to be ethnic variation. Han Chinese schizophrenia populations were found to have at-risk haplotypes in different regions on the NRG1 gene from Icelandic or Scottish populations (Li et al., 2004). Studies on a large Scottish pedigree with schizophrenia have led to findings of a balanced translocation affecting two genes on chromosome 1, which have been named DISC (disrupted in schizophrenia) 1 and DISC2 but the mutation is probably unique to that pedigree alone (Millar et al., 2000). Molecular genetic studies in schizophrenia have rarely attempted to include environmental measures, assuming that if samples are sufficiently large enough and the number of molecular markers sufficiently numerous, genetic effects would be revealed even if underlying interaction with environmental factors were present (van Os and Murray, 2008).

1.7 Prodromal Schizophrenia

Before the first episode of psychosis, general decline in social and intellectual functioning is often noted in the proceeding weeks and months. In a review of the psychosis prodrome; Niendam and colleagues reported that individuals who are clinically at higher risk of developing schizophrenia but not reaching diagnostic criteria, had poorer psychosocial outcomes and worse cognitive ability (Niendam et al., 2009). In a study using the Structured Interview for Prodromal Syndromes, a large, multi-centred study found a 35% risk of conversion to psychosis over a 2½ year follow-up period for a cohort at clinically high risk of developing schizophrenia (Cannon et al., 2008). The advent of operational criteria to identify individuals at ultra-high risk (UHR) (Yung et al., 1998) has improved clinical ability for identifying those at high-risk of developing schizophrenia. To be classified UHR the individual is required to meet one of the following criteria: 1) Attenuated psychotic symptoms up to several times a week with change in mental state between 1 week and 5 years, 2) brief limited intermittent psychotic symptoms (BLIPS) of less than 1 week, 3) a first degree relative with psychotic disorder or an individual with schizotypal personality disorder and significantly decreased functioning between 1 and 12 months duration. Combined low dose risperidone and CBT in UHR individuals have been shown to reduce the rate of transition to psychosis (McGorry et al., 2002) and CBT alone may reduce or at least delay transition to psychosis in this group (Morrison et al., 2002).

In recent years, setting up early intervention and first episode psychosis services have been the vogue, yet clinical trials on prodromal psychosis have produced mixed results. While Olanzapine (an atypical, second generation antipsychotic) was useful in treating positive prodromal symptoms, it did not significantly reduce rate of conversion to psychosis when compared with a placebo (McGlashan et al., 2006). Other studies found that individuals with a schizophrenia prodrome and randomized to olanzapine, improved to a significantly greater degree over an 8-week period than patients randomized to placebo, when positive and negative syndrome rating scales were used (Woods et al., 2003).

Those suffering from first episode psychosis tend not to seek immediate medical attention and as a result, the duration of untreated psychosis (time from onset of psychotic symptoms to the start of treatment) can be variable. A large 2 year follow-up study, (Melle et al., 2008) found that first-episode patients from an area with “early detection of psychosis services” had a significantly lower duration of untreated psychosis, better clinical status, and milder negative symptoms at the start of treatment compared to a healthcare area without such a service. At 2-year follow-up, there was a significant difference in negative symptoms and cognitive function between groups. However; not all studies found a link between duration of untreated psychosis and illness course, outcome, symptom improvement, or cognitive level. Goldberg and colleagues found no association between longer duration of untreated psychosis and worse cognition at baseline or less improvement in cognitive function after 16 weeks of treatment with olanzapine or risperidone. They argued that early intervention for treatment of psychiatric symptoms may have little or no impact on cognitive function (Goldberg et al., 2009). A review of early intervention studies found little evidence of benefit in long term outcomes (Malla et al., 2005). With early intervention services, the diversion of precious clinical resources and the unnecessary treatment of false-positive patients are an issue of contention (Pelosi and Birchwood, 2003; Warner, 2005).

1.8 Treatment and Management

Apart from antipsychotic agents that primarily target dopamine receptors, no pharmacological agents are available that specifically target treatment of disabling negative symptoms, although new medications are currently in development (as described in section 1.4).

Psychological intervention has gained increasing attention in the treatment of schizophrenia. Randomized controlled trials have demonstrated the effectiveness of cognitive behavioural therapy (CBT) as an adjunct to “treatment as usual” in speeding recovery from acute symptoms in early schizophrenia (Lewis et al., 2002) and reducing levels of distress caused by auditory hallucinations in chronic, refractory illness (Wiersma et al., 2001).

Clinical studies have also reported success in areas of cognitive remediation training for improvement of social functioning (Combs et al., 2007) and emotion recognition (Wolwer et al., 2005).

Current social interventions focus on care in the community and re-integration into society, with Victorian asylums now institutions of a bygone era. Between 1988 and 2005, the UK lost 58,000 psychiatric beds coinciding with the growth of 'Home Treatment' and 'Assertive Outreach' mental health teams, emphasizing treatment within the community. In 2001, only 14 out of 130 psychiatric hospitals functioning in 1975 in England and Wales were still open (Leff, 2001). Sadly though, the stigma of mental illness means that in reality, many patients with schizophrenia remain marginalized by society and are shunned by fearful friends and family.

1.9 Oculomotor Movements and Visual Function

Abnormal smooth pursuit eye movements are known to occur in patients with schizophrenia, this is unlikely to be an effect of medication as this phenomenon has been observed in medication naïve, first episode patients (Holzman, 1974). Various types of oculomotor deficits have been reported in schizophrenia, including increased antisaccade latency (slower saccadic movement towards a mirror image location following stimulus presentation) and increased antisaccade error rate (erroneous saccades made towards a peripheral stimulus despite instructions to look at a mirror image location) (Turetsky et al., 2006). Abnormal eye movements are probably a trait rather than a state phenomenon as they are also present in first-degree relatives of patients with a level between that of healthy controls and schizophrenia patients (Clementz et al., 1994). Abnormal smooth pursuit eye movements are already present in children who have been diagnosed with schizophrenia, whereas typically developing children have eye movements similar to adults, suggesting development of this brain function is completed in early childhood (Ross et al., 1998). Antisaccade errors in patients with schizophrenia appear to be due to abnormal prefrontal cortical function and correlations have been found with poor spatial working memory performance (Hutton et al., 2004). Structural MRI studies have also demonstrated that smaller prefrontal lobe

volumes in patients with schizophrenia are associated with increased antisaccade latency (Schulze et al., 2006), while functional MRI data have shown lack of prefrontal cortex activation in patients with schizophrenia compared with healthy subjects performing an antisaccade task (McDowell et al., 2002). There is a large body of research on oculomotor-function in schizophrenia and it appears to be a promising genetic endophenotype but has not provided the diagnostic breakthroughs that were originally envisaged.

There is a growing body of evidence suggesting that early visual processing is impaired in schizophrenia. Butler et al. (2003) reported the effects of visual backward masking (VBM), where a target stimulus is quickly followed by another stimulus or “mask” that overlaps or surrounds the target stimulus resulting in delayed response to visual stimuli in patients with schizophrenia. Early visual processing impairment has also been demonstrated by electrophysiological measurement of visual evoked potentials, which are abnormal in patients with schizophrenia but unrelated to age, medication status or chronicity of illness (Yeap et al., 2008). Chromatic vision also appears to be adversely affected in schizophrenia and hue discrimination ability is worse compared to healthy controls (Shuwairi et al., 2002). Dopamine depletion is associated with deficits in blue-hue discrimination and as antipsychotics act to block dopamine receptors in ‘hyperdopaminergic’ schizophrenia patients this has been explored (Haug et al., 1997). Oculomotor function is further explored in chapter 9.

1.10 Cognitive Deficits

Cognitive function has been studied extensively in schizophrenia, the first major meta-analysis reported clear deficits across the entire range of neuropsychological tests (Heinrichs and Zakzanis, 1998) and it has been generally accepted that there is decline in attention and memory. Structural scanning has also shown a clear correlation between decreased white matter FA (a measure of WM tract integrity) and impaired cognitive function in patients with schizophrenia (Lim et al., 2006). It has now been suggested that different subgroups of schizophrenia patients may show different profiles of cognitive impairment. One study found that a high proportion of patients

(40%) displayed a decline in IQ from estimated premorbid levels, while a specific impairment of spatial working memory was present even in those with high/average IQ (Joyce et al., 2005). Most researchers have reported deficits in performance on executive tasks (which place demand on the frontal lobes) in addition to memory and learning (temporal lobe tasks), of these verbal memory seems disproportionately impaired in schizophrenia (Heinrichs and Zakzanis, 1998). While entire assessment batteries such as the Behavioural Assessment of Dysexecutive Syndrome (BADS) have been shown to be valid within a population with schizophrenia (Katz et al., 2007); a meta-analysis concluded that the digit symbol coding task (a subtest of the WAIS) is a reliable measure of processing speed in schizophrenia but has been overlooked by researchers (Dickinson et al., 2007). A description of the cognitive battery utilized for studies described in this thesis is given in chapter 4.

Subtle cognitive deficits are already present early on in the course of schizophrenia. In a comparison of chronic and first-episode schizophrenia patients, right-handed patients were noted to have better performance in verbal tests and male patients showed more cognitive deterioration than females (Bilder et al., 1992). A large proportion of children under 10 years of age who subsequently developed schizophrenia in adulthood, displayed poor social interaction and academic under-achievement compared to their healthy peers (Sobin et al., 2001). Healthy subjects who are at high risk of developing schizophrenia tend to perform at levels between those of schizophrenia patients and healthy individuals on cognitive tasks, as well as evidencing deficits in specific skills like visual memory. These cognitive deficits are present and appear to exist independently of any prodromal symptoms, supporting the hypothesis that a common pattern of cognitive deficits exist for individuals at genetic risk of developing psychosis (Bertisch et al., 2008).

1.11 Conclusions

Schizophrenia remains a complex disease to research and is probably an entity of illnesses rather than a single diagnosis and possibly even part of a

spectrum of psychiatric illness. Primarily, it is a syndrome identified by a range of characteristic symptoms that manifest adverse effects on social behaviour and cognitive function.

From epidemiological studies we know that certain factors such as birth trauma, maternal influenza, cannabis use, social deprivation and ethnicity are linked to an increased risk of developing schizophrenia. It seems likely that genetic loading can increase the risk of schizophrenia and gene-environment interactions may result in aberrant neurodevelopment. Schizophrenia clearly affects brain tissue as evidenced by imaging studies and postmortem neuropathology is demonstrated in the brains of affected adults. Schizophrenia also has adverse effects on cognitive function in at least a subgroup of patients but a decline in social and cognitive functioning is often seen in a prodromal phase of illness, which may be years before the first clinical episode of psychosis takes hold.

There now appears to be a range of possible schizophrenia endophenotypes but research findings for any sample of patients are likely to be “watered-down” by group heterogeneity. Perhaps the biggest hindrance is the absence of a biological disease marker that can be used to accurately identify schizophrenia and exclude those with other diagnoses who may also present with psychosis and schizophrenia-like symptoms. Additionally, the schizophrenia patient group is extremely difficult to follow-up as they often disengage from psychiatric services and may lack illness insight. This feature is unlike that of any other patient groups, for example in neurology, a longitudinal 20 year follow-up study in multiple sclerosis (MS) retained 107 of 140 patients i.e. 76% of those originally enrolled (Fisniku et al., 2008).

Despite all the drawbacks, advances in technology are now able to provide new means of exploring the brain that were unavailable just a few decades ago. Through these means it will eventually be possible to identify the biological mechanisms that lead to the development of schizophrenia and methods to slow, halt or possibly even reverse the disease process can then be developed.

My thesis presents a collection of experiments that were designed to test the neurodevelopmental and neurodegenerative models of schizophrenia that attempt to explain the biological basis for the development of schizophrenia. Hypotheses for each of my studies are described in further detail in chapter 4. Methods used included various neuroimaging modalities (see chapter 2) which enabled me to look for differences in brain tissue structure and neuropathological changes that develop over time in patients with psychosis compared with healthy, unaffected individuals. By designing studies using a first episode psychosis cohort, I was able to investigate a patient population to explore changes that may occur early in the course of illness when there has been minimal exposure to the confounding effects of medication and other treatment interventions.

2. AN INTRODUCTION TO THE PRINCIPLES OF MAGNETIC RESONANCE IMAGING

2.1 Introduction

Magnetic Resonance Imaging (MRI) was developed by British physicist Peter Mansfield and American chemist Paul Lauterbur in the 1970s. For their achievements in the field of MRI, both scientists were awarded the Nobel Prize for Medicine in 2003. With the advent of MRI scanning a non-invasive technique that could allow direct visualisation of the brain in-vivo had at last been found. Since then, advances in technology have led to improved resolution of images and better visualisation of different tissue subtypes. Without using harmful ionising radiation associated with other imaging techniques such as Computerised Tomography (CT), MRI is now a commonly performed medical investigation with scanners widely available in many hospitals in the UK.

This chapter describes the basic physics principles behind MRI and structural MRI methods of diffusion tensor imaging (DTI) and magnetisation transfer imaging (MTI). These techniques have been used in the studies described in subsequent chapters of my thesis and are described in further detail in the methods of the relevant chapters. Analyses of brain tissue volumes obtained from MRI data were made using Voxel Based Morphometry (VBM), while DTI data were analysed using Tract Based Spatial Statistics (TBSS) to measure white matter tract integrity (see section 2.7).

2.2 Basic principles of MRI

Magnetic resonance (MR) is based on the effect of a magnetic field on the positively charged proton found in the nucleus of hydrogen (H) atoms contained within a water molecule (H_2O). The human body is composed of approximately 60% water and with each water molecule containing 2 H atoms; there are many protons available from which to measure the MR signal.

Bloch's theory states that any charged particle i.e. an atomic nucleus with an odd number of neutrons plus protons produces an electromagnetic field. A hydrogen nucleus contains an unpaired proton and is therefore positively charged as the MR active nucleus is constantly spinning around its own axis. If a static, external, magnetic field ($B_{0)}$ is present, it aligns itself parallel or anti-parallel to this field and produces a secondary spin called "precession" which is best described by the Larmor equation.

Larmor Equation $\omega = B_0 \gamma$

Where: ω is the frequency of precession (Radians per second)

B_0 is the strength of external magnetic field (Tesla)

γ is the gyromagnetic ratio

B_0 is the magnetic field generated by the MRI scanner. Most protons will align themselves parallel to this i.e. in the same direction as the magnetic field because this is a low energy state. About 1 in a million protons will line up in the opposite direction and are in a high energy state and anti-parallel, thus producing a net magnetisation vector (NMV) resulting in macroscopic magnetisation.

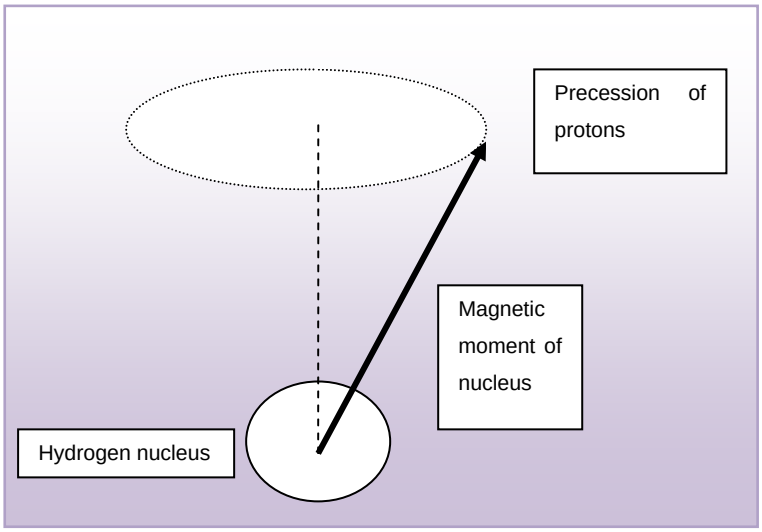


Figure 2.1 Precession of a proton about a hydrogen nucleus

The direction of spin can be manipulated by applying a radiofrequency (RF) pulse which causes all the protons to spin in alignment about a common axis. Spins correspond to the frequency of the RF pulse and nuclei return to

equilibrium and realign in the B_0 direction through two distinct relaxation patterns, when the RF pulse ends.
Signal can only be detected when there is net magnetisation in a comparative plane, hence the NMV must be flipped from the B_0 direction to a transverse plane by a RF pulse of magnitude given by the “flip angle”. The transverse NMV produced induces an MR signal and a coil in the MRI scanner detects the signal which is produced by a change in the frequency of spins. Degree of decay in the MR signal indicates how much free water is present.

Brain tissue is primarily compartmentalised into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The main component of CSF is free water, by contrast WM contains little free water, with the main constituent being phospholipid bi-layers and intracellular organelles. GM lies midway between these and contains more free water than WM but less free water than CSF so these different brain tissues are clearly identifiable by the difference in intensity with which they appear on an MRI scan.

T1 is the length of time required for 63% of the protons to achieve relaxation (i.e. the time taken to return to their state of equilibrium and recovery of longitudinal magnetisation to be achieved). 100% recovery is only achieved when T1 is lengthened fivefold. Repetition time (TR) is the interval between consecutive RF pulses. Fat has a short T1 compared with water because the degree of signal will vary between different tissue subtypes depending on their water content.

T2 is the length of time required for 63% of protons to loose their energy to neighbouring structures and recover transverse magnetisation. The rate of T2 decay is dependent on the extent of neighbouring macromolecules getting in the way.

Tissue	Approx T1 times (ms)	Approx T2 times (ms)
Cerebrospinal fluid	2000	300
Cerebral grey matter	520	100
Cerebral white matter	390	90

Table 2.1 Table Showing T1 and T2 Times of Different Brain Tissues

Adapted from the book MRI for Technologists (Woodward and Freimarck, 1995)

Tissues composed of large molecules with tightly bound proteins loose their energy quickly because the spins diphase at a rapid rate, thus T2 relaxation times are short. In comparison, tissues with high water content have more “free” hydrogen protons and a longer T2. Repetition time (TR) is the interval between consecutive RF pulses applied to the same slice. TR affects image contrast characteristics by determining how much the longitudinal magnetization can recover between pulses and is also a major factor in determining total scan time.

2.3 Image Processing

To collect 3 dimensional data, spatial information is gathered from 3 gradient coils each corresponding to the x, y or z axis in a three dimensional co-ordinates system.

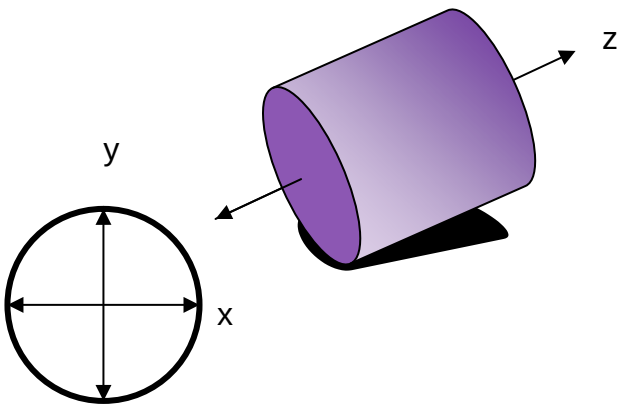


Figure 2.2 Diagram of the 3 Orthogonal Linear Magnetic Field Gradients

The magnitude of B_0 (external magnetic field) can be altered by the gradient coils, therefore magnetic field strength can be predicted along the gradient and precessional frequency of nuclei along the axis can be calculated. Collating the data in 3 dimensions (3D) gives rise to an MRI scan which is spatially encoded. Each pixel seen on a flat computer screen is in fact a representation of a voxel (a 3D area of brain tissue). Analysis of brain MRI data involves lengthy pre-processing steps so that individual variation in shape and size can be standardised to the same space before a voxel by voxel comparison can be made between different subjects. The three main pre-processing steps of registration, segmentation and smoothing are described below.

2.3.1 Registration

Because individuals each have heads of slightly different size and shape, they need to be scaled to the same space and images need to be in the same anatomical framework, so comparison of all component voxels can be made. This is done by transformation of the original source image to a reference or target image. Transforming the source to a reference image requires mapping of each voxel from the source image to the target image. Two different types of registration allow for different characteristics to be preserved during this mapping process, these are “rigid transformation” or “non-linear warping“. In rigid transformation, a single set of estimated transformation parameters in 3D are applied to all voxels in the image. There are six parameters – three translations and three rotations. Rigid *affine* transformation preserves ratios and distances between the source and reference image. In total there are twelve parameters in each of the three dimensions: 3 translations, 3 rotations, 3 shears and 3 scaling factors. Non-linear warping has the advantage of allowing for relative volume changes between tissues to be accounted for, (this may be of clinical interest), this model is used in the voxel-based morphometry (VBM) studies described in chapters 7 and 9.

2.3.2 Segmentation

In order to study each of the brain tissue compartments in more detail, it is necessary to separate out grey matter, white matter and CSF from the skull and from each other. Each voxel in an image is assigned a specific tissue class based on intensity value and likely spatial distribution, this classification is automated in SPM using Bayesian segmentation methods (Ashburner and Friston, 2000). Additional methods such as use of the Brain Extraction Tool (BET) www.fmrib.ox.ac.uk/fsl/bet2/index.html, allows for erosion of 1 or more pixels around the periphery of the brain volume so there is increased likelihood of sampling true cortical tissue and excluding any brain parenchymal tissue that could masquerade as grey matter.

2.3.3 Smoothing

Images that have been segmented require smoothing to address registration errors and inter-individual variance by increasing the signal to noise ratio. When a smoothing filter is applied, neighbouring voxels are averaged to make them more normally distributed. This is in keeping with the Central Limit Theorem which states that *the distribution of an average tends to be normal, even when the distribution from which the average is computed is not*. The Gaussian filter size can be chosen and variable kernel sizes of full-width-at half-maximum (FWHM) are available, for scanning studies of schizophrenia patient populations, the kernel smoothing size selected is usually between 6 and 12mm. Larger smoothing filters are used to detect diffuse effects but are unsuitable for observing smaller variations within small anatomical regions. The arbitrary choice of smoothing kernel size has been a subject of much debate, with one study demonstrating that MRI results from the same study population varied significantly depending on the kernel size chosen (Jones et al., 2005). A meta-analysis by Honea and colleagues found that studies using smaller smoothing kernels reported more volume reductions in small structures (Honea et al., 2005).

2.4 Voxel Based Morphometry: A method of comparing group differences in structural MRI

Voxel Based Morphometry (VBM) is an automated approach for detecting group differences in brain structure, it allows for analysis of the whole brain without observer bias and the precise location of differences between groups is automatically displayed. Statistical Parametric Mapping (SPM) is an internationally recognised method of VBM style processing. The software is freely available on-line (www.fil.ion.ucl.ac.uk/spm) and has been widely used by many research groups around the world. It is frequently revised by the authors and updated, although the basic pre-processing steps (which consist primarily of registration, segmentation and smoothing) have remained as described in the section above. MRI sequences can be taken either from an individual subject at different time points or from groups of subjects for a cross-sectional comparison. Images are initially segmented into three different tissue classes GM, WM or CSF. The next step involves normalisation of all MRI images to a template scan so they can be in the same stereotactic space. The Montréal National Institute (MNI) have produced several standard templates which are freely available and widely used, these templates were created by averaging a large number of scans from normal, healthy subjects; alternatively a custom template can be created by averaging scans from subjects within the study. Scan are said to be “normalised” once they have been registered to a template. The normalised images are then smoothed, so neighbouring voxels are averaged and the data will be more normally distributed thus increasing validity of parametric statistics. Smoothing is applied to segmented images, with data from an average value of neighbouring voxels, thus making it more normally distributed.

The “optimised VBM” protocol (Good et al., 2001b), contains two additional data processing concepts. Firstly, the normalised affine transformation is warped by Jacobian modulation, this local volumetric expansion or compression factor is stored in a three dimensional warping field so true amounts of each tissue volume can be retrieved. Analysis of modulated data tests for regional differences in GM volume, while analysis of unmodulated

data tests for differences in GM concentration per unit volume. Secondly, pre-processing steps are introduced to exclude non-brain voxels by segmenting images in native space and normalising the extracted segmented brain images. These normalisation parameters are then applied to original whole brain images and segmented again, this time in standard space.

Statistical tests are performed using a general linear model (GLM), which in effect allows linear regression to be performed on each voxel. Confounding effects of age, gender or diagnosis can be added to the GLM matrix for analysis. The outcome is a statistical parametric map (Friston, 1994), which shows statistical significance of group differences at a given position and assigns a p-value to the contrast.

Results of any experiment may contain a type I error (where a false positive result is accepted) or a type II error (where a false negative result is accepted). SPM analysis compares each voxel in all the slices that make up a complete scan from one individual. Correction for multiple comparisons is therefore applied to minimise the error rate. Taking into consideration that each voxel comparison is not an independent observation due to high correlation between neighbouring voxels, a family wise error (FWE) is considered appropriate to use (Worsley et al., 1992). The FWE rate is the probability of making one or more false discoveries of type I errors among all the hypotheses when performing multiple paired tests.

The Bonferroni correction is considered highly conservative and is only suitable for use in studies with small numbers of comparisons. Although able to control for any false positives, it also leads to very low statistical power, in other words reducing the ability of a statistical test to detect an effect where it really exists.

The false discovery rate (FDR), controls for an expected proportion of false positives among the suprathreshold voxels. Although a less conservative method for comparison with greater power than the FWE correction, there is an increased likelihood of obtaining type I errors.

2.5 Diffusion Tensor Imaging

Diffusion of free water is isotropic in-vitro, this means water diffuses equally in all directions. In-vivo, diffusion of water is anisotropic as it is hindered by cell walls and organelles hence the net movement of water will be greater in the direction with less restriction. Diffusion tensor imaging (DTI) is a quantitative MRI technique that allows diffusion of water to be measured in-vivo. Where there is no preferred direction for the diffusion of water molecules, the probability of displacement of a water molecule at any given time follows a Gaussian distribution. When diffusion of water molecules occur in-vivo, it is anisotropic and follows a multivariate Gaussian distribution. Mathematically this can be described by a diffusion-tensor matrix (D); a square 3x3 matrix composed of 9 elements about the three (x, y, z) axes. Only 6 of the 9 elements are independent as the matrix is symmetrical about the diagonal (Wheeler-Kingshott et al., 2003).

$$\mathbf{D} = \begin{bmatrix} d_{xx} & d_{xy} & d_{xz} \\ d_{yx} & d_{yy} & d_{yz} \\ d_{zx} & d_{zy} & d_{zz} \end{bmatrix}$$

Figure 2.3 The Diffusion Tensor Matrix

If a magnetic field gradient is applied, diffusion accumulates different phase shifts resulting in a loss of phase coherence and reduction in signal amplitude. A pulsed field gradient (PFG) allows a phase shift for all spins, with the second pulse reversing this shift and cancelling the phase shift for static spins. For spins that have changed location due to molecular diffusion during the time between first and second gradients, significant signal attenuation occurs with incomplete refocusing by the second PFG and reduced spin echo.

Signal change depends on the diffusion properties of a tissue and the magnetic field gradients applied. The larger the amplitude and duration of the magnetic field gradients, the stronger the diffusion weighting (b). If DT-MRI is

acquired without applying any diffusion weighting (b=0) and with diffusion gradient (b≠0) signal attenuation can be modeled as an exponential decay and the diffusion co-efficient calculated.

There are 3 main diagonal elements (λ_1 λ_2 λ_3) or eigenvalues representing the apparent diffusion co-efficient (ADC) values associated with the principal eigenvectors (ε_1 ε_2 ε_3), which represent the unique directions along which molecular displacements are uncorrelated. The combination of eigenvectors and eigenvalues is unique and indicates diffusion properties at each voxel. Fractional anisotropy (FA) is a quantifiable inter-voxel index of scalar value between 0 and 1, defined as a rotationally invariant parameter and can be defined for each voxel by the following formula:

$$\mathrm{FA} = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

In brain tissue, DTI reflects tissue microstructure and organization (Le Bihan, 2007), diffusion of free water molecules is restricted to longitudinal directions along white matter tracts and therefore FA is highest in the core of these tracts and nearest to 1 but lower in GM and approaching 0 in CSF. Changes in WM FA can be related to pathological processes, such as demyelination or axonal disruption (Kubicki et al., 2005b), FA may therefore be useful as a marker of neuropathology and could be used in tracking disease progression. Reduced WM FA can therefore be interpreted as impaired white matter integrity; which has been demonstrated in schizophrenia (Ardekani et al., 2003).

2.6 Tractography

DTI tractography enables investigation of white matter connectivity, an example of the image obtained by this technique is shown in fig 2.4. Each voxel has a principle eigenvector due to the net diffusion of water in one particular direction. This is most likely to follow the length of an axon because anisotropy occurs due to the cell walls restricting diffusion. Using this assumption, FA and the principle eigenvector associated with the largest

eigenvalue is utilized as the voxel of interest, FA of all the neighbouring pixels are identified and possible projections are traced by propagating a contiguous string of pixels along the estimated fibre orientations. Elimination of voxels where angulation of turn exceeds a set threshold and enters an area with FA lower than a certain threshold increases the likelihood that a true fibre tract is identified. There are a number of possible tractography algorithms that will allow fibre tract alignment to be estimated but the two main classes are deterministic (which follow the main fiber directions as revealed by the diffusion model and generate sequences of points that are considered as fibers) and probabilistic (by repeating the deterministic sequence and choosing the direction with highest probability of representing true connectivity to generate a tract). A study comparing 10 tractography methods found a high inter-method variability on visual comparison of the estimated tract positions (Fillard et al., 2011).

Although tractography is able to show the most likely position of fibre tracts, it is unable to calculate directionality hence the production of a colour map which is essentially a map of FA with added colour coding using the assumption that the principle eigenvector also indicates the dominant orientation of the fibres running through each pixel. The colour map is visualized using 3 colours; red, green and blue to represent the x,y and z axes.

For tract reconstruction, two or more regions of interest (ROIs) must be defined a-priori with a starting “seed point”. In addition a “through point” is selected which the tracts must all run through, this adds further constraint. This process creates three dimensional maps of white matter tracts based on the probability of connectivity between adjacent voxels running through the same ROIs. It is important to note that the lines creating the tracts do not represent individual axonal fibres because resolution is not yet good enough for this. Resolution of DTI acquisitions is usually between 3 mm^3 and 15 mm^3, while the diameter of bundles of axons considered in fibre tractography are in the order of 1mm and individual fibres are in the order of 1-30 µm (Mori and van Zijl, 2002).

Each pixel visualized on an MRI scan is 2 to 3 mm therefore specific connectivity of axons can not be identified. Where multiple fibre tracts cross one another e.g. the junction between the corpus callosum and corona radiata, caution must be taken. It is likely that in this area the pixels contain axonal tracts in multiple directions so anisotropy appears low and the area looks dark on a scan, when actually the area is rich in axons.

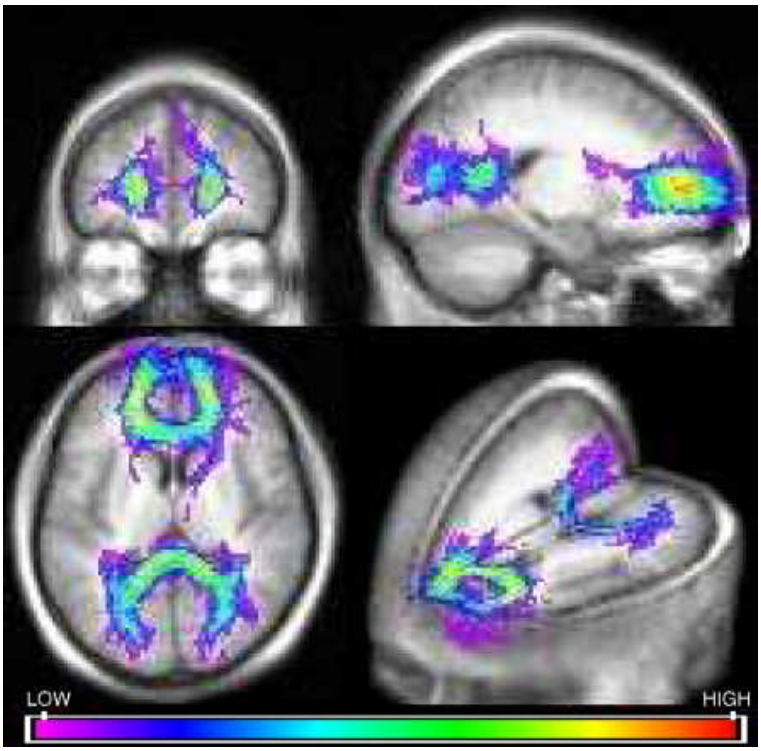


Figure 2.4 DTI Tractography of the Corpus Callosum
(Price et al., 2005)

2.7 Tract Based Spatial Statistics

Tract Based Spatial Statistics (TBSS) is used to examine white matter FA values. TBSS identifies contiguous voxels that form the core of all white matter tracts, where FA is likely to be higher than at the periphery and the probability of measuring FA in voxels which lie in white matter areas is much increased. Tract based Spatial Statistics (TBSS) is one method of DTI data analysis, which obviates some of the confounding variables by including the following processes:

1) Non-linear registration of all scans is to a “target” image. This means the FA map has been averaged from all subjects within the study cohort. This

corrects for misinterpretation of residual misalignment, which will be different for each group.

2) Smoothing is not required, so the hazards and complications of arbitrary selection of a variable smoothing kernel size is unnecessary.

3) A mean FA skeleton map of all white matter tracts is produced; to which each subject's scan can be compared, this allows comparison of all white matter tracts as opposed to using a pre-selected, hand drawn regions of interest.

2.8 Magnetisation transfer imaging

Magnetisation transfer imaging (MTI) allows measurement of the difference in energy levels of water molecules found in brain tissue. Water may be bound to large macromolecular structures, thought to be cell membrane proteins and phospholipids in grey matter and myelin in white matter; however, most water molecules exist in a free and unbound state.

In conventional MRI, the radio-frequency pulse must match the resonant frequency of water to excite protons and make the MRI signal measurable. An additional radio-frequency pulse can be used to saturate bound protons in the semi-solid pool without affecting the free water proton pool because restricted protons absorb energy at a frequency far from that of water. This causes a reduction in longitudinal magnetization from the free proton pool, reducing the apparent T1 relaxation time of water and decreasing signal intensity by 50 to 60%. The reduced signal is expressed as a ratio known as the magnetization transfer ratio (MTR) and is dependent on macromolecular density.

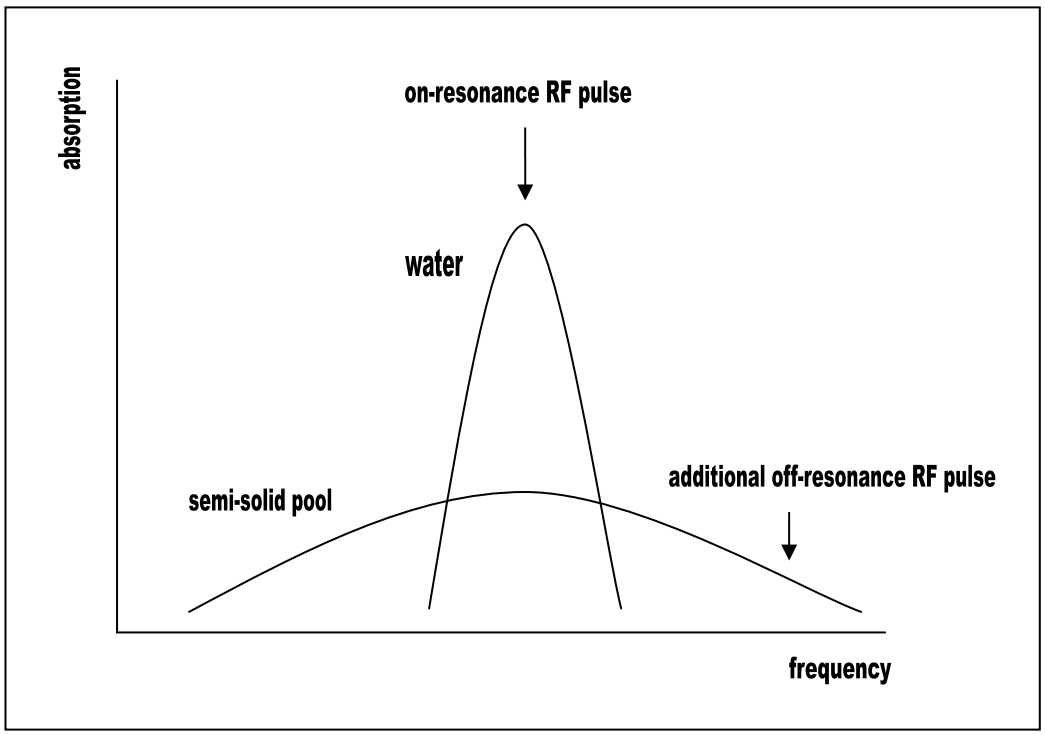


Figure 2.5 Water and Semi-solid Pool Absorption Rates Over a Range of Radio-frequencies

MTI was first described by (Wolff and Balaban, 1989), it shows a map of difference in saturation and is produced by a digital subtraction of saturated (MT weighted) from unsaturated (un-weighted) MT images. Amount of signal loss per voxel is therefore dependent on the degree of magnetization transfer, which reflects capacity of molecules in the tissue to exchange magnetization with surrounding free protons from water. In healthy brain tissue, the magnetization transfer ratio (MTR) is highest in white matter (30 to 50%) because of the high lipid content and a smaller free water pool, less in grey matter (20 to 40%) where there is a lower lipid content and lowest in CSF (~0%) as this is mainly composed of free water.

MTR can be calculated by the following formula, where Mo is mean signal intensity with signal on and Ms is mean signal intensity with signal off:

$$[M_o - M_s] / M_o \times 100 = \text{MTR in percentage units (pu)}$$

MTR measurements are highly reproducible in healthy subjects rescanned at various intervals (Barker et al., 1996). High intra and inter-rater reliability of

MTR measurements have been reported in healthy controls (Sormani et al., 2000). However; MTR varies according to pulse sequence and scanner used so results from different centers are not always readily comparable.

A reduction of MTR indicates pathological change in the tissue under investigation, presumably as more free water enters areas where the barrier to diffusion is no longer intact. Animal studies of neuroinflammation have shown that this can result in small MTR reductions (Stanisz et al., 2004). Reduction in myelin and axonal density results in reduced MTR (Schmierer et al., 2004), presumably because the semi-solid pool has a significant phospholipid content. There is some degree of change in MTR associated with the effects of ageing, particularly in white matter of the corpus callosum (Silver et al., 1997), although others have concluded there are no significant age-related variations (Rahul et al., 1995). Similarly, Hofman and colleagues reported higher mean MTR in males than females (Hofman et al., 1999), while others have reported no gender-related variation in MTR measures (Ge et al., 2002). Because of ambiguity over whether age and gender affect MT measures, they should always be incorporated as confounding factors in any MTI study model. MT images can be processed using SPM in the same way as for conventional volumetric MRI.

3. Structural Imaging Abnormalities in Schizophrenia: A Review of Magnetic Resonance Imaging, Diffusion Tensor Imaging and Magnetisation Transfer Imaging Studies

3.1 Structural MRI findings in longitudinal studies of schizophrenia

The first structural MRI study of schizophrenia (Smith et al., 1984) concluded that patients with chronic schizophrenia had enlarged ventricles. Although not a novel finding, this confirmed the results of earlier studies reporting ventricular enlargement using CT (Johnstone et al., 1976). The primary advantage of MRI was it's safety compared to other imaging techniques such as CT (associated with ionizing radiation exposure risks) and the now obsolete pneumo-encephalogram (with iatrogenically induced headache, tachycardia and other medical sequelae). MRI has since been used extensively to determine different brain tissue compartment volumes. Two major papers in this area were a review (Shenton et al., 2001b) and a meta-analysis (Wright et al., 2000) both concluded that differences in brain tissue volumes between patients with schizophrenia and healthy individuals are small, while ventricular volume differences are of a larger magnitude. In order to identify when these structural brain changes might be occurring, the importance of a longitudinal study design following the course of illness was recognised.

The neurodevelopmental hypothesis for schizophrenia suggests that brain abnormalities occur early in life and do not continue to progress throughout adulthood. Evidence to support this hypothesis include abnormalities of early motor and cognitive development that can be observed in those who subsequently develop schizophrenia (Weinberger, 1987). Fetal growth retardation and obstetric complications during pregnancy and delivery are all associated with increased risk of developing schizophrenia later on in life (Cannon et al., 2002); these are considered to be discreet mechanisms predisposing to schizophrenia rather than progressive brain insults. This

contrasts with the earliest proposals of Emil Kraepelin who after classifying this mental illness in 1887 suggested a neurodegenerative hypothesis for dementia praecox (Kraepelin, 2009). He believed destruction of neural tissue was associated with psychosis; however, there is an absence of neurodegenerative pathology in postmortem brain tissue from schizophrenia patients, with no evidence of gliosis, no loss of cortical neurons and no consistent evidence of neuronal degeneration (Harrison, 1999). The neurodegenerative versus neurodevelopmental hypothesis of schizophrenia has been fiercely debated in the past, as described in this extract taken from DeLisi (2008), "*In December of 1990, an all-day symposium conducted by L. E. DeLisi and J. A. Lieberman as an ACNP (American College of Neuropsychopharmacology) satellite brought together many of the investigators in this field to debate the facts on neurodevelopment vs neurodegeneration. The proceedings from this day were later published in a special issue of Schizophrenia Research in 1991. During the conference, Brian Woods (from McLean Hospital at that time) presented data showing an extreme case of a patient with schizophrenia who had obvious visible ventricular enlargement over time; but this was dismissed by many present as a case of a degenerative neurological disease of unknown origin with accompanying psychosis. Despite heated and at times emotional debate, no consensus was reached at this meeting because carefully collected case and control data were not yet available to confirm whether the structural brain findings were stable over time or progressed.*"

Longitudinal brain imaging studies have subsequently allowed investigators to track morphometric changes as the disease progresses. The first, major longitudinal imaging study (DeLisi et al., 1992) reported a two-year follow-up of 30 first-episode schizophrenia patients and controls. Lateral ventricular size at time of first-episode presentation generally correlated with outcome and the larger the ventricles, the poorer the outcome. Although there were no changes in mean ventricular or temporal lobe size over the two year follow-up, ventricular enlargement was inversely correlated with the number of hospitalizations and some patients showed individual changes greater than 20% in ventricular volume and 10% in temporal lobe volume.

A review of the earliest longitudinal imaging studies in schizophrenia containing a mixture of CT and MRI data, mostly showed an increase in ventricular volume over time in chronic schizophrenia patients but these changes were less clear in longitudinal studies of first episode patients (DeLisi, 1999). Since then, a large number of longitudinal MRI studies in schizophrenia have been published. Articles in English language journals listed on PubMed under the search terms “schizophrenia, MRI and longitudinal follow-up” published since 2000 were retrieved (table 3.1) and are discussed in further detail below (sections 3.1.1 to 3.1.6).

Table 3.1 Longitudinal Magnetic Resonance Imaging Studies in Schizophrenia

sz=schizophrenia, sa=schizoaffective disorder, sf=schizophreniform disorder, pt=patient, ctrl=control, FE=first episode, GM=grey matter, WM=white matter, CSF=cerebrospinal fluid, WB=whole brain, ICV=intra-cranial volume, ROI=region of interest

Study Reference (author and year of publication)	**Description of patient group(s)**	**Sample Size (Pt /**Ctrl)	**Method (field strength, time to follow-up, regions of analysis)**	**Summary of Main Findings**
(Gharaibeh et al., 2000)	First episode of non-affective acute psychosis	**55** / 22	1.5T, 33 to 64 months, 11 landmark configuration and shape analysis	Change in midline brain morphology in patients with schizophrenia during the subsequent 3–5 years consistent with either a neurodegenerative disease process or effect of treatment with psychiatric drugs.
(Saijo et al., 2001)	In-patients with schizophrenia	**15** / 12	0.2T, 4 and 10yrs, volume of lateral ventricles	Progressive ventricular enlargement in patients with schizophrenia continues even in the chronic stage of disease.
(Mathalon et al., 2001)	Male in-patients with schizophrenia	**24** / 25	1.5T, 4 years, ICV and ROIs lateral ventricles, 2 frontal and 2 temporal lobe regions	Patients exhibited accelerated fronto-temporal GM decline and cortical, sulcal and lateral ventricular expansion. Greater clinical severity associated with faster rates of fronto-temporal brain volume changes.
(Lieberman et al., 2001)	First episode psychosis	**107** / 20 baseline **51** / 13 follow-up	1T, 18 months, cortical regions and white matter, excluding subcortical structures	Poor outcome schizophrenia is associated with increased ventricular volume. No significant reductions in cortical and hippocampal volumes over time.

(Lang et al., 2001)	First episode sz treated with risperidone (30), pts chronically treated with typical antipsychotics (12)	**30** / **12** / 23 baseline - / 15 / 17 follow-up	1.5T, 12 months, basal ganglia volume (caudate, putamen and globus pallidus)	Pts chronically treated with typical antipsychotics had higher basal ganglia volumes. Baseline basal ganglia volumes were similar in FE and healthy ctrls. No significant changes in basal ganglia volume after 1 year of risperidone in FE pts.
(Puri et al., 2001)	First presentation to psychiatric services with schizophreniform illness	**24** / 12	1T, 8 months, ventricular volumes	No difference between pts and ctrls in ventricular volume mean change but pts had more variable increases and decreases in ventricular volume size than ctrls.
(Wood et al., 2001)	First episode in-pts (30) and chronic schizophrenia >18 mth continuous illness in rehabilitation unit (12)	**30** / **12** / 26	1.5T, hippocampus, 1.9yrs fu for fep 2.3yrs fu for sz 2.2yrs fu for ctrls WB, temporal lobe and ICV	Only WB volume loss in both pt groups, rate of volume loss similar in FE psychosis for chronic and first WH injury. Hippocampal and temporal lobes, no volume change reported.
(Tauscher-Wisniewski et al., 2002)	Schizophrenia (11) & schizoaffective (4) pts	**15** / 10	1.5T, 5yrs, caudate nuclei volume	Significant 9% age-related decline in caudate volume of pts and ctrls
(Cahn et al., 2002)	First episode schizophrenia (29) and schizoaffective (5)	**34** / 36 baseline **29** / 36 follow-up	1.5T, 1yr, total brain volume, cerebral GM and lateral ventricles	Decreased total brain volume and GM volume Lateral ventricle volume increase in pts Decrease in global GM volume correlated with outcome

(Kasai et al., 2003a)	First episode sz (13), first episode affective psychosis (15)	**13** / **15** / 14	1.5T, 1.5yrs, MRI volumes of GM in superior temporal gyrus and amygdalae-hippocampal complex	Progressive decrease in GM volume of left STG in schizophrenia
(Ho et al., 2003)	Recent onset schizophrenia	**73** / 23	1.5T, 3yrs, total brain volume, lateral ventricles, cortical CSF, tissue and CSF for frontal, temporal, parietal and cerebellar ROIs	Progressive reduction in frontal lobe WM with reciprocal increase in frontal lobe CSF volume occurred more rapidly in patients than controls. Poor outcome pts had greater lateral ventricle enlargement, frontal lobe changes associated with functional impairment.
(Milev et al., 2003)	Recent onset sz, sa and sf disorder	**123** / -	1.5T, 5yrs, cerebral volume, lateral ventricles, brain tissue and CSF volume of frontal and temporal lobes, cerebellar volume	Temporal lobe volume was predictive of outcome with smaller temporal GM volume associated with hallucinations.
(Kasai et al., 2003b)	First episode sz (13), first episode affective psychosis (15)	**13** / **15** / 22	1.5T, 1.5yrs, Heschl's gyrus and planum temporale volume	Significant decrease in GM volume of left Heschl's gyrus and planum temporale for pts with first-episode schizophrenia in contrast to first-episode affective psychosis or ctrls.
(DeLisi et al., 2004)	First episode sz	**50** / 20 baseline **26** / 10 follow-up	1.5T, 10yrs, ventricles and hemispheres	Significantly greater ventricular enlargement during the last 5 yrs in pts. Rate of ventricular change in first 5 yrs correlated with age at first hospitalisation, in yrs 5-10 correlated with time spent in hospital. Greater ventricular change correlated with better outcome.

(Bachmann et al., 2004)	First episode psychosis	**14** / 11	1.5T, 14mths, frontal and temporal lobes, cerebellum and CSF volumes	Significant volume reductions in pt group. Association of symptom severity with CSF volume and structural volume over time.
(Lieberman et al., 2005)	First episode psychosis (sz/sa/sf)	**263** / 58 baseline **161** / 58 follow-up	1.5T, 12, 24, 52 and 104 weeks, whole brain GM and lateral ventricle volume	No change in GM volume in ctrls but decreased GM in some patients. Haloperidol associated with GM loss but olanzapine was not.
(DeLisi and Hoff, 2005)	First hospitalisation for psychosis (sf/sz)	**27** / 10	1.5T, 5 and 10yrs, whole temporal lobe volume and STG volume	No change over time in these structures when pts were compared with ctrls.
(Garver et al., 2005)	Schizophrenia	**19** / 7	1.5T, 28 days, cerebral cortical GM	Volume increase of cerebral cortical GM with second generation antipsychotics but not with first generation haloperidol.
(Farrow et al., 2005)	First episode psychosis (schizophrenia 25 & bipolar 8)	**33** / 22	1.5T, 2yrs, whole brain GM and WM	Sz pts had GM deficits in lateral and medial frontal regions and bilateral posterior temporal lobe regions with losses over time in lateral fronto-temporal and left anterior cingulate gyrus. BPAD pts had GM deficit in bilateral inferior temporal gyri with loss over time in anterior cingulate cortex.

(Molina et al., 2005)	Schizophrenia (treatment naïve 17, treatment resistant 12)	**29** / 11	1.5T, 2yrs, GM and WM volumes in frontal, parietal, occipital and temporal lobes	Increase in GM and decrease in WM volume in parietal and occipital regions over time in pts. Diffuse cortical GM also increased in chronic grp after clozapine or risperidone treatment, most marked GM gain in occipital area.
(Molina et al., 2006)	First episode psychosis (sz 22, no clinical evidence for sz 15)	**37** / 44	1.5T, 2yrs, ROIs in DLPFC and STG	Less GM in right DLPFC and STG in sz than ctrls or non-sz psychosis.
(McCormick et al., 2005)	Schizophrenia neuroleptic naïve	**31** / 18	1.5T, 3yrs, anterior cingulate cortex	Increased ACC volume over time with increased typical neuroleptic exposure but increased atypical neuroleptic exposure correlated to decreased ACC volume over time.
(Whitworth et al., 2005)	First episode sz (21) and chronic multi-episode sz (30)	**21** / **30** / 32 baseline **-** / **17** / 20 follow-up	1.5T, 2 to 4yrs, ROIs ventricles, bilateral hippocampus, amygdala, hippocampus-amygdala complexes and hemispheres	Sz pts showed ventricular enlargement and volume reduction of hippocampus-amygdala complexes compared to ctrls at baseline and follow-up.

(Whitford et al., 2006)	First episode sz	**41** / 47 baseline **25** / 26 follow-up	1.5T, 2 to 3yrs, global GM volume	GM in frontal, parietal, temporal cortices and cerebellum reduced and occipital lobe GM increased compared to pts at baseline. Pts lost more GM over time than ctrls, especially in parietal and temporal cortices.
(Steen et al., 2006)	52 cross-sectional and 16 longitudinal studies	Systematic review and meta-analysis		No significant longitudinal change in WM or cerebellum but several studies reported decrease in brain volume, which may be limited to GM in schizophrenia.
(Price et al., 2006)	First episode sz	**16** / 12	1.5T, 3.7yrs, whole brain volume	WM volume loss in pt group adjacent to lateral ventricles in both temporal lobes, medial temporal gyrus and in/around right middle frontal gyrus.
(Khorram et al., 2006)	Chronic schizophrenia	**10** / 20	1.5T, 1yr, ICV and whole thalamus volumes	Gtr thalamic volumes in sz subjects at baseline. At follow-up no difference btw groups, +ve correlation with baseline thalamic volume and typical antipsychotic dose. Higher baseline doses correlated with larger reductions in volume.

(van Haren et al., 2007)	Schizophrenia	**159** / 158 baseline **96** / 113 follow-up	1.5T, 5yrs, whole brain, GM and WM volumes	Excessive decrease in GM were found in left superior frontal and temporal gyri, right caudate nucleus and thalamus in pts. Progression in left frontal density loss related to increased number of psychotic episodes.
(Salisbury et al., 2007)	Within 1yr of first hospitalization for psychosis, sz (20), BPAD (21)	**20** / **21** / 32 baseline **11** / **13** / 13 follow-up	1.5T, 1.5yrs, Heschl's gyrus GM volume and mismatch negativity	First-hospitalised sz subjects had reduced Heschl gyrus GM volume than ctrls and BPAD subjects. Progressive reduction in volume over time in sz but not BPAD or ctrls.
(Whitford et al., 2007a)	First episode schizophrenia	**19** / -	1.5T, 2-3yrs, GM volume and EEG recordings in lobar ROIs (frontal, temporal, parietal and occipital)	Pts lost a significant amount of GM volume in frontal, parietal, temporal and occipital lobes in first 2 to 3 years of schizophrenia onset.
(Panenka et al., 2007)	Chronic schizophrenia	**10** / 20	1.5T, 1yr, ROIs bilateral hippocampi, thalamus, caudate nucleus, putamen, globus pallidus, hippocampus	Pts had smaller hippocampi volume at baseline, left smaller than right. PANSS scores were negatively correlated with right hippocampal volume.

(Nakamura et al., 2007)	First episode psychosis in schizophrenia (29) & affective disorder (34)	**29** / **34** / 36 baseline **17** / **21** / 26 follow-up	1.5T, 1.5yrs, ROIs frontal, temporal and parieto-occipital	Smaller neocortical GM volume and enlarged sulcal CSF in both pt groups compared to ctrls at baseline. Progressive reduction of GM vol in sz (with bilateral enlargement of lateral ventricles and supratentorial SCSF enlargement). In affective psychosis pts had diffuse increase of GM volume.
(Whitford et al., 2007b)	Schizophrenia	**41** / 47 baseline **25** / 26 follow-up	1.5T, 2 to 3yrs, VBM at baseline and longitudinal tensor based morphometry	Volumetric deficits in WM of frontal and temporal lobes at baseline, with increased WM in fronto-parietal junction bilaterally. Pts lost more WM over time than ctrls in middle and inferior temporal cortices
(Théberge et al., 2007)	First episode sz, never- treated (2 females, 14 males)	**16** / 15 baseline **16** / 14 10mth fu **16** / 16 34mth fu	4T, 10 and 34mths fu, VBA of whole brain GM and spectroscopy for glutamatergic metabolites	At 10mths limited grey matter loss and widespread GM loss by 30mths. Parietal and temporal GM loss correlated with thalamic glutamine loss.
(Borgwardt et al., 2007)	Ultra high risk of sz	**35** / 22	1.5T, 2yrs, VBM whole brain	Hippocampal abnormalities in UHR group

(Wood et al., 2008)	A review of studies in subjects at ultra high risk for psychosis	Review article		Unclear cause for progressive changes but onset of psychosis associated with visuospatial and executive dysfunction that mirrors progressive changes identified on neuroimaging.
(McClure et al., 2008)	Chronic schizophrenia or schizoaffective disorder	**10** / -	1.5T, 12 weeks after re-starting atypical antipsychotic medication, ROIs caudate, GM, WM and sulcal CSF	No change in caudate or grey matter volume over time. No change in volume of frontal or temporal lobe GM or WM, or lateral, third or fourth ventricular CSF volume.
(Zipparo et al., 2008)	First episode schizophrenia	**52** / - baseline **20** / - follow-up	1.5T, 2-3yrs, VBA GM, frontal and temporal lobes	Progressive GM atrophy in whole brain and frontal lobes associated with mild improvement in overall cognitive functioning.
(Reig et al., 2009)	Adolescents with first episode psychosis (5 females, 16 males)	**23** / 34 baseline **21** / 34 follow-up	1.5T, 2yrs, VBA whole brain GM and CSF, ROIs frontal, parietal, temporal and occipital,	Frontal lobe GM volume loss higher in male pts than ctrls. Left frontal lobe CSF volume increased more than ctrls. Clinical changes not correlated with brain changes over time.
(Rais et al., 2008)	First episode psychosis (sz 39, sa 1, sf 9, nos 2) all meeting diagnosis of sz (51) at follow-up	**51** / 31	1.5T, 5yrs, ICV, total brain, GM, WM, lateral and third ventricle volumes	Sz patients had larger GM volume decrease over time and larger increases in lateral and third ventricles. More pronounced GM loss in pts using cannabis.
(Hulshoff Pol and Kahn, 2008)	Review of 11 longitudinal studies (9 MRI and 2 CT) in chronic schizophrenia	Review of studies **10 to 96pts** / 5 to 113 ctrls	1 to 10 yr follow-up	Continuous progressive brain tissue decreases and lateral ventricle volume increases in chronic sz pts continue for at least the first 20yrs of illness. Most prominent GM loss in fronto-temporal areas and associated with poor outcome and –ve symptoms.

(DeLisi, 2008)	Historical perspective on renewal of Kraeplinian concepts in brain imaging in schizophrenia	Review article		GM and WM structure change prior to illness and before medication, with active and widespread progression. Ventricular enlargement is a consequence of cortical change. Genetic and medication effects remain speculative.
(van Haren et al., 2008a)	Comparison of findings from Utrecht sz study group and other results of other studies	Review article		Schizophrenia is a progressive brain disease with different age-related trajectories of brain tissue loss. Genetic and environmental factors appear to play a role.
(Brandt and Bonelli, 2008)	MRI imaging studies of the basal ganglia in schizophrenia	Review article		Typical and atypical neuroleptics may produce different effects on brain morphology, these changes are dynamic and may be reversible.
(Koo et al., 2008)	First episode psychosis schizophrenia (39) affective disorder (41)	**39** / **41** / 40 baseline **17** / **18** / 18 follow-up	1.5T, 1.5yrs, Cingulate gyrus GM in 1 posterior and 3 anterior subregions (subgenual, affective and cognitive)	Progressive GM volume decrease in subgenual, affective, cognitive and posterior cingulate subregions in sz pts, also smaller left subgenual and right cingulate gyrus GM than ctrls.

(Fornito et al., 2008)	Ultra High Risk subjects (35 became psychotic, 35 did not)	**35** / **35** / 33	1.5T, 1 to 2 yrs, ROI anterior cingulate cortex (ACC)	UHR psychotic subjects have bilateral thinning of rostral paralimbic ACC region that was negatively correlated with –ve symptoms. UHR normal subjects had relative thickening of dorsal and rostral limbic areas.
(Borgwardt et al., 2008)	At Risk Mental State (10 became psychotic, 10 did not)	**20** / 20	1.5T, 3yrs, whole brain GM, VBM	Volume decrease in orbito-frontal, superior frontal, inferior temporal, medial and superior parietal cortices and cerebellum only in pts who developed psychosis.
(Sun et al., 2009b)	First episode schizophrenia (13 males, 3 females)	**16** / 14	1.5T, 2yrs, Cortical Pattern Matching and Structural Image Evaluation using Normalisation of Atrophy (SIENA)	Brain surface contraction in pts and ctrls showed similar anatomical patterns although exaggerated in magnitude across entire brain. Exaggerated, progressive changes seen in pts.
(Wang et al., 2008)	Schizophrenia (90 males, 49 females)	**139** / 136 baseline **56** / 62 follow-up	1.5T, 2yrs, Large Deformation High-Dimensional Brain Mapping of deep brain nuclei and hippocampal-amygdala formation	Pattern of progressive change in deep brain nuclei and hippocampal-amygdala formation variable. Thalamus, caudate, nucleus accumbens and hippocampus showed specific changes to sz but amygdala and putamen changes similar in pt and ctrls.
(Brans et al., 2008b)	Schizophrenia (12 males, 4 females), same gender siblings (14 males, 4 females)	**16** / **18** / 43	1.5T, 5yrs, ICV, total brain, GM and WM, cerebellum, lateral and third ventricle volumes	Whole brain and cerebral GM volumes decreased excessively in pts compared to their siblings and ctrls, suggesting brain tissue loss in schizophrenia may be related to the disease process.

(Brans et al., 2008a)	92 participants (9 monozygotic, 10 dizygotic twin pairs discordant for sz and 14 monozygotic, 13 dizygotic healthy ctrl twin pairs)	**18** / **20** / 28 / 26	1.5T, 5yrs, ICV, total brain, GM, WM, cerebellum, lateral and third ventricle volumes and lobar ROIs (frontal, parietal, temporal and occipital)	Decrease in whole brain, frontal and temporal lobe volumes in sz and their unaffected twin siblings compared to ctrl twins over time. Progressive volume loss is at least partly attributable to genetic factors related to schizophrenia.
(Cahn et al., 2009)	First episode psychosis patients sz(42), sa (5), sf(1)	**48** / -	1.5T, 5yrs, total brain, GM, WM, cerebellum, lateral and third ventricle volumes	Assocation between longer duration of psychosis and larger GM volume decrease with ventricular volume increase
(Sun et al., 2009a)	Ultra High Risk subjects (12 developed psychosis, 23 did not)	**35** / - baseline **12** / 23 / - follow-up	1.5T, 1yr, Cortical Pattern Matching	Significantly greater brain contraction in right prefrontal region in “converters” compared to UHR subjects who did not develop psychosis. Cortical volume loss is associated with psychosis onset.
(Takahashi et al., 2009a)	First episode sz (23), chronic sz (11)	**23** / **11** / 26	1.5T, 1 to 4yrs, whole brain and insular cortex volumes	FEP patients showed GM reduction of insular cortex over time compared to ctrls. This GM loss correlated with severity of +ve and –ve symptoms. No difference in rate of GM loss over time between chronic sz group and ctrls.

(Wobrock et al., 2009)	First episode sz Good outcome (12) and poor outcome (11) sz	**32** / - baseline **12** / **11** / - follow-up	1.5T, 1yr, ROIs hippocampus, lateral ventricle and anterior limb of internal capsule (ALIC)	Reduced maximal area of ALIC, associated with poor outcome in 1 year
(Navari and Dazzan, 2009)	Antipsychotics and brain structure in 23 longitudinal studies	Systematic review		Antipsychotics act regionally not globally on the brain, Volumetric changes are of greater magnitude in association with typicals increasing basal ganglia volume than atypicals.
(Takahashi et al., 2009b)	Neuroleptic naïve UHR (11 developed psychosis and 20 did not)	**31** / 20	1.5T, 1 to 4yrs, ROIs insular cortex	In pts who developed psychosis, greater reduction of insula cortex GM volume bilaterally than in ctrls or non-psychotic UHR subjects.
(Douaud et al., 2009)	Adult onset schizophrenia (35) and healthy ctrls (35) Adolescent onset schizophrenia (25) and healthy ctrls (25)	**35**/35 and **25**/25 follow-up scan **12**/12 adolescent group only	1.5T, 2.5yrs, whole brain GM volumes and TBSS of WM tracts	Reduction of GM density over time in healthy adolescents but increase of GM density in sz pts. Analysis of WM tracts showed FA was increasing in adolescent onset sz but roughly constant in healthy ctrls.

(Yoshida et al., 2009)	Chronic schizophrenia all subjects male	**16** / 20	1.5T, 3.1yrs for pts and 1.4yrs for ctrls Volumes of STG, amygdale and hippocampal complex	Smaller relative volumes in schizophrenia compared with ctrls in posterior STG and AHC. No statistically significant progression of volume reduction in either area. Volume change in left anterior AHC correlated with PANSS negative symptoms.
(Mitelman et al., 2009a)	Good outcome (23) and poor outcome (26) schizophrenia	**23** / **26** / 16	1.5T, 4yrs, Volumes of caudate nucleus and putamen	Poor outcome pts had gtr decline in volume of putamen than good outcome pts. Caudate volumes were lower at baseline and follow-up in pts compared to ctrls but showed no differential pattern of progression between groups.
(Deng et al., 2009)	Newly diagnosed and anti-psychotic naïve schizophrenia	**20** / 20	1.5T, 3 to 8 weeks, whole brain cortical GM volume	After 3 wks anti-psychotic treatment, GM volume increase in right caudate, superior and inferior frontal gyrus, precentral gyrus and left inferior parietal lobe. After 8 wks volume increase right thalamus and bilateral cerebellum. Meanwhile progressive left medial frontal gyrus GM reduction.

(Kasparek et al., 2009)	First episode schizophrenia	**23** / 18 all subjects male	1.5T, 1year, Volumes of superior temporal gyrus and amygdale hippocampal complex	FES subjects had smaller GM volume in left orbito-frontal and fronto-polar cortex. GM volume was reduced in left prefrontal cortex of pts with poor functioning at 1yr follow-up.
(Sun et al., 2009b)	First episode schizophrenia (16)	**16** / 14	1.5T, 2yrs, whole brain cortical surface mapping	Exaggerated progressive changes in sz but early changes correspond to that associated with normal development in ctrls.
(Mané et al., 2009)	First episode schizophrenia or schizophreniform disorder, all subjects neuroleptic naïve	**28** / 17 baseline **15** / 11 follow-up	1.5T, 4yrs, GM change whole brain VBM	GM decrease in patients compared to healthy individuals in the left superior temporal gyrus and right orbitofrontal gyrus, and increase in bilateral lingual gyrus and right cuneus. GM changes in patients in left lingual gyrus, right insula and cerebellum, inversely related to functional outcome.
(Smieskova et al., 2009)	6 cross-sectional and 24 longitudinal studies investigating effect of antipsychotics on brain volume	Systematic review		Sz pts tended to have reduced GM volume, particularly in frontal and temporal lobes. Typical antipsychotics led to increased GM volume in basal ganglia, while atypical antipsychotics reversed this effect after switching. Atypical antipsychotics seem to have no effect on basal ganglia structure.
(Mitelman et al., 2009b)	Chronic schizophrenia good outcome (23) and poor outcome (26)	**49** / 16 baseline **23** / **26** / 16 follow-up	1.5T, 4yrs Volume and FA of corpus callosum	Patients had more pronounced decline in absolute size of corpus callosum, with poor-out come patients displaying more pronounced decline in size and good outcome patients more decline in anisotropy.

(Hartz et al., 2010)	Schizophrenia (99) and schizoaffective disorder (11)	**110** / -	1.5T, 3yrs Frontal lobe volume	Frontal lobe volume loss related to G72 haplotype 1 and frontal lobe WM loss related to increased cerebral cortical WM.
(Takahashi et al., 2010)	First episode sz (18) Schizotypal disorder (13)	**18** / **13** / 20	1.5T, 2.7yrs Volume of STG and subregions (planum polare, Heschl's gyrus, planum temporale, rostral and caudal STG)	At baseline pts had smaller left planum temporale and caudal STG than controls. Significant GM volume reduction of STG over time in schizophrenia compared with schizotypal pts or controls.
(van Haren et al., 2010)	Sz smokers (54) and sz non-smokers (42) Control smokers (35) and ctrl non-smokers (78)	**96** / 113	1.5T, 5yr Volumes from total brain, GM, WM, cerebellum, third and lateral ventricles	Cigarette smoking did not explain GM volume decreases seen in patients and was not associated with brain volume change in controls.
(Eack et al., 2010)	Early course of sz (35) or sa (18) disorder, symptomatically stable but cognitively disabled out-pts	**53** /	3T, 2yrs Amygdala, caudate, cingulate gyrus, DLPFC, fusiform gyrus, hippocampus, parahippocampal gyrus, putamen and sup temporal gyrus GM	Pts receiving cognitive enhancement therapy demonstrated greater GM preservation in left hippocampus, parahippocampal gyrus and fusiform gyrus.
(Mitelman et al., 2010)	Chronic sz patients (49) with poor outcome (26) and good outcome (23)	**49** / 16	1.5T, 4yrs	Expansion of lateral ventricles appears to have stabilised by time of chronic phase of illness. Posterior cortical GM deficits and occipital horns of lateral ventricles expand in poor-outcome pts.
(Kempton et al., 2010)	13 longitudinal MRI studies on sz patients measuring lateral ventricles		Meta-analysis	Patients showed progressive ventricular enlargement after illness onset. Chronic sz patients also showed progressive ventricular enlargement.

(Bhojraj et al., 2011)	Young adult non-psychotic offspring of sz patients (56)	**56** / 36	1.5T, 1yr Auditory association areas in the STG	Left auditory association surface area showed decline and cortical thinning in the non-psychotic offspring of sz patients.
(Takahashi et al., 2011)	First episode psychosis (18) and schizotypal disorder (13)	**18** / **13** / 20	1.5T, 2.7yrs Pituitary volume	Pituitary volume larger in sz patients than ctrls at baseline. Over time both pt groups had significant pituitary volume increase than controls.
(Schaufelberger et al., 2011)	First episode psychosis patients who developed sz	**39** / 52	1.5T, 2ys Ventricle:brain ratios GM volume	No longitudinal difference in ventricle:brain ratios between pts and ctrls. Reversible GM vol changes in sup temporal cortex and hippocampus in pts.
(McIntosh et al., 2011)	High genetic risk of schizophrenia (146) of whom 17 developed sz	**146** / 36	1.5T, 2yr scan intervals for up to 10yrs WB volume, lobar volumes	Pts at high genetic risk of sz showed greater whole brain, left and right prefrontal and temporal lobe volume reductions over time than controls.
(Ho et al., 2011)	Schizophrenia (192) schizoaffective (19) presenting for treatment of first psychotic episode at baseline	**211** / -	1.5T, 3 scans in 7.2yrs Total cerebral tissue volume, total GM and WM, frontal, parietal, temporal lobes, caudate, putamen and cerebellum, CSF	Longer f/u correlated with smaller brain tissue and larger CSF volumes. Smaller GM volume associated with more antipsychotic medication and progressive WM volume decrement with more antipsychotic treatment

(Olabi et al., 2011)	27 studies 928 schizophrenia patients and 32 different brain ROIs	**928** / 867	Meta-analysis 1 to 10yrs f/u Volumes of WB, GM, frontal GM, frontal WM, parietal and temporal WM, lateral ventricles	In pts brain volume decreases over time in whole brain, whole brain GM, frontal grey and WM, parietal WM and temporal WM and lateral ventricles increase in volume.
(Prasad et al., 2011)	Fiest episode sz antipsychotic naive (26)	**26** / 38	1.5T, 1yr Brodmann's areas 8, 9, 32	GM loss in posterior cingulate gyrus in HSV1 seropositive sz subjects over time. No change in prefrontal GM volumes.
(Andreasen et al., 2011)	First episode sz	**202** / 125	1.5T, 2yrs then every 3 to 4 yrs for up to 15 yrs Whole brain	Decrease in GM and WM with corresponding CSF increase was most severe in early years after sz onset, occurring at severe levels only in a subset of patients.
(Takahashi et al., 2011)	First episode sz (18) and schizotypal disorder (13)	**18** / **13** / 20	1.5T, 2.7yrs GM volume of fusiform, middle temporal and inferior temporal gyri	Smaller fusiform gyri bilaterally in patients at both time points with significant reduction of fusiform gyrus volume in sz patients over time.
(Boonstra et al., 2011)	Schizophrenia (57)	**57** / 56	1.5T, 5yrs Brain volume change	No evidence for relationship between duration of untreated illness and brain volume change in sz.
(van Haren et al., 2011)	Schizophrenia (92) and schizoaffective (4)	**154** / 156 baseline **96** / 113 follow-up	1.5T, 5yrs Cortical thickness and change in cortical thickness	Widespread progressive cortical thinning over time in patients but higher cumulative intake of atypical antipsychotic medication was associated with less cortical thinning. Frontal and temporal cortices were thinner while parietal and occipital cortices were thicker in patients than controls at baseline.

(Asami et al., 2011)	First episode sz (33)	**33** / 36 baseline **21** / 23 follow-up	1.5T, 1.5yrs VBM analysis of whole brain GM with manual ROI comparison	GM volume reduction in left STG, frontal, parietal and limbic regions including the cingulate gyrus. Worse cognitive function was linked to volume reduction in frontal, temporal and parietal regions.
(Kong et al., 2012)	First-episode schizophrenia (20)	**20** / 20 baseline **20** / - follow-up	1.5T, 1yr GM changes	At follow-up patients had significantly decreased neurological soft signs. Localised changes in left frontal lobe, cerebellum and cingulate gyrus in those who improved while GM reductions of sub-lobar claustrum, cingulate gyrus, cerebellum, frontal lobe and middle frontal gyrus in those who worsened.
(Li et al., 2012)	First-episode drug naïve schizophrenia (66)	**66** / 23 baseline **42** / 23 follow-up	3T, 6 weeks Volume of putamen	Increased grey matter volume in right putamen of patients after 6 weeks treatment. Volume increase correlated with improved psychopathology (reduced positive symptoms)
(Collin et al., 2012)	Schizophrenia and related spectrum disorders (105)	**105** / 100	1.5T, 5yrs Global brain volume	Sz patients with higher levels of disorganization exhibit more progressive decrease of brain volume and have lower IQs.
(Roiz-Santiáñez et al., 2012)	First episode schizophrenia spectrum pts (59 males and 34 females)	**93** / 70	1.5T, 1 yr Straight gyrus morphometry	Straight gyrus volume change over 1 yr was similar to healthy controls and not associated with clinical variables.

(Takahashi et al., 2012)	Chronic sz (17) from in-pt and out-pt clinics with at least 3yrs illness duration	**17** / 17	1.5T, pituitary volume	No significant change in pituitary volume over time, patients had a larger pituitary volume than ctrls at both time points.
(Cobia et al., 2012)	Schizophrenia (20)	**20** / 20	1.5T, 2yrs Cortical GM thickness, volume and surface area	Cortical thinning of middle frontal, superior and middle temporal gyri in patients
(Treszniak et al., 2012)	FE psychosis patients with sz (62), mood disorders (46) and other psychosis (14) and ctrls (94)	**122** / 94 baseline **80** / 52 follow-up	1.5T, 13 months Length of adhesion interthalamica and cavum septum pellucidum	Significant reduction in AI length in sz FE patients at baseline. Cavum septum pellucidum length more prominent increase in the psychosis than controls over time.
(Nesvag et al., 2012)	Long-term treated schizophrenia (52) and healthy subjects (63)	**52** / 63	1.5T, 5yrs Cortical thickness and subcortical volumes	Regional differences in cortical thickness and volume between patients and controls are stable across 5 yrs. Right lateral ventricle volume increases more in patients. Some progression in subcortical structures may be present in pts with poor outcome.
(Mamah et al., 2012)	FE patients from 14 international centres receiving haloperidol or olanzapine	**134** / 51	104 weeks follow-up Hippocampal volume and shape metrics	No change in hippocampal volume over time but surface deformation was variable with olanzapine having less longitudinal effect on hippocampal surface deformation than haloperidol.
(Walter et al., 2012)	Antipsychotic naïve at- risk mental state patients (18) 8 transitioned to psychosis and 10 did not	**8** / 10	1.5T, 988 days hippocampal volume	Significant decrease in hippocampal volume over time seen in both groups and independent of clinical outcome.

(Vita et al., 2012)	19 studies comparing longitudinal GM changes in patients with sz and controls	Meta-analysis **813** / 718		Higher volume loss of total cortical GM in patients, especially in left hemisphere. FE patients showed more significant progressive loss.
(Welch et al., 2012)	Increased risk of sz Exposed to cannabis (23) and not exposed to cannabis (32)	**23** / **32**	3T, 2 yrs, GM volume, tensor based morphometry	Cannabis exposure was associated with significantly greater loss of right anterior hippocampal and left superior frontal lobe GM.

3.1.1 Discussion of Methods Used

Only two papers included a preliminary power calculation to ensure recruitment of sufficient numbers of subjects for an 80% or greater probability of detecting structural differences that were being sought between groups (Kanaan et al., 2009b). Insufficiently powered studies are likely to have increased error rates and some studies had so few subjects e.g. 10 patients (McClure et al., 2008) and 8 patients (Walter et al., 2012) it is questionable how much weight these findings can add to our current knowledge base.

Difficulty with recruitment and retention of patients is perhaps the most obvious problem faced by any clinical researcher, especially in longitudinal studies with high dropout rates. A longitudinal study by van Haren and colleagues (van Haren et al., 2007) only managed to scan 96 of 159 patients at 5 years follow-up with “refusal to participate” and “too unwell” being the most commonly cited reasons for a 40% drop out. A further 14 patient scans were not useable because of poor image quality probably due to movement artefacts. Lieberman and colleagues fared even worse with a dropout rate of over 50%, with only 51 out of 107 patients returning for a follow-up scan after 18 months (van Haren et al., 2007; Lieberman et al., 2001). Imaging studies often suffer additional sample attrition due to claustrophobia and discomfort from the noise produced by the MRI scanner leading to patients being unable to tolerate scanning.

Duration of follow-up is also problematic, with most studies following patients for intervals between 18 months to 3 years, usually commencing from an early stage of illness. Range and duration of follow-up was highly variable between studies, this variation in length of follow-up makes comparisons between studies difficult, one paper reported a 2 to 4 year follow-up interval (Whitworth et al., 2005) while another reported a range of 33 to 64 months follow-up interval (Gharaibeh et al., 2000). The longest follow-up study appeared to span 10 years, (DeLisi et al., 2004) but there were so few 10 year follow-up studies published, valid comparisons could not be made.

DeLisi and colleagues reported that ventricular enlargement during the latter 5 years in schizophrenia patients correlated with time spent in hospital (DeLisi et al., 2004); while another 10 year follow-up study reported that lateral ventricular volume continues to increase even in chronic stages of disease between 4 and 10 years after schizophrenia has been initially diagnosed (Saijo et al., 2001); this study used a 0.2T MRI scanner but almost all other studies used 1.5T or 3T scanners, hence limitations of low resolution may have affected results. The ability to maintain scanner stability over a 10 year period is also questionable. With the above limitations in mind, a review of 11 longitudinal schizophrenia imaging studies (Hulshoff Pol and Kahn, 2008) concluded that there is progressive loss of cortical grey matter in fronto-temporal areas, with volume increase in the lateral ventricles.

When comparing imaging studies, techniques for MRI data analysis are variable; although automated voxel based morphometry (VBM) is commonly used. VBM is useful in studies looking at whole brain measures and different tissue volumes i.e. grey, white and CSF with comparisons made between subjects of interest and controls. Where a strong apriori hypothesis exists, a region of interest analysis may be more appropriate, for example a study specifically investigating volumes of Heschl's gyrus and planum temporale in schizophrenia patients with auditory hallucinations (Kasai et al., 2003b), as both these structures form part of the auditory cortex. One continuing criticism of ROI studies has been the accuracy of hand-drawn areas, which

are both time consuming and open to operator error. Other groups have used cortical surface mapping (Sun et al., 2009a) and further combined this with other techniques to compare the rate of cortical surface contraction between patients and controls (Sun et al., 2009b) utilizing programmes such as “Structural Image Evaluation, using Normalisation of Atrophy” (SIENA).

3.1.2 First Episode Studies

Many studies have recruited patients at their first episode of psychosis, with the rationale of recruiting patients at illness onset in an attempt to visualise the earliest structural changes in schizophrenia and avoid chronicity related confounders such as medication or institutionalisation. The definition of this group; however, has clear overlap with studies recruiting “recent onset schizophrenia patients” (Ho et al., 2003; Milev et al., 2003) which encompassed a wide time range for untreated psychosis. Similarly, some patient groups were described as being “at first hospitalization for psychosis” (Deng et al., 2009; Dickey et al., 2004; Salisbury et al., 2007) within this group some patients were acutely unwell in their first episode of psychosis while others had been chronically unwell in the community prior to their first admission. If we are to truly understand the effect of schizophrenia on various brain structures, we need to carry out imaging at time of disease onset; internationally recognised and standardised terminology would enable this to happen through improved study design.

3.1.3 Ultra High Risk Studies

By the time of onset of first episode psychosis, pre-morbid decline in social and cognitive function has typically occurred. In recent years, research interest has turned to Ultra High Risk (UHR) subjects, who are not formally diagnosed with a schizophrenia spectrum disorder but are at high risk through one or more of the following: 1) attenuated psychotic symptoms; 2) brief, limited intermittent psychotic symptoms with spontaneous resolution; 3) family history of psychosis accompanied by a decline in general functioning over the previous 12 months. Fornito and colleagues (2008) reported that UHR subjects who subsequently converted to frank psychosis had bilateral

thinning of rostral paralimbic ACC regions (an effect mainly driven by those who developed a schizophrenia spectrum psychosis). Hippocampal abnormalities in UHR subjects have also been reported (Phillips et al., 2002) and those who converted to frank psychosis after 1 year were found to have loss of right, prefrontal cortex compared to those who remained non-psychotic (Sun et al., 2009a), suggesting that significant changes to brain structure occur around the time of first episode psychosis.

3.1.4 Childhood Onset Schizophrenia

In children and adolescents the course of schizophrenia appears to be different to that of adults. A different neuropathological course of disease has been described in adolescent onset schizophrenia, which typically manifests with severe psychotic symptoms. A greater grey matter involvement is seen compared to adult onset schizophrenia, including Heschl's gyrus, parietal operculum, sensory, primary and supplementary motor areas (Douaud et al., 2007). In healthy adolescence, synaptic pruning usually results in grey matter volume loss but this process appears to "fail to occur" in those with schizophrenia (Douaud et al., 2009). Rates of subsequent brain volume reduction were significantly higher for patients with childhood-onset schizophrenia than for healthy comparison subjects. In childhood-onset schizophrenia, the rate of grey matter volume reduction was related to baseline severity of clinical symptoms and premorbid impairment in cognitive and social development but not to gender, ethnicity, or age at onset (Sporn et al., 2003).

3.1.5 Medication Effects

Medication effects may account for at least some of the structural changes observed in longitudinal imaging studies and the potential confounding effects of medication have been considered in detail. This medication effect was initially described by Lang et al. (2001), who found larger basal ganglia volumes in patients treated with typical antipsychotics but no significant volume changes after using the atypical antipsychotic risperidone. In studies measuring whole brain GM volume the picture has been variable; a large

study with 161 patients who completed 2 years follow-up by Lieberman and colleagues (2005), found that the typical antipsychotic haloperidol was associated with whole brain GM loss but the atypical antipsychotic olanzapine was not. Conversely, Garver et al. (2005) described cortical GM volume increase with atypical antipsychotics risperidone and ziprasidone but not with the typical antipsychotic haloperidol; however, this study only sampled 19 patients who were scanned after a very short 28 day interval. Diffuse, cortical GM increase has also been described in parietal and occipital regions after treatment with risperidone or clozapine (Molina et al., 2005) and in the anterior cingulate cortex following exposure to typical antipsychotics (McCormick et al., 2005).

Khorram et al. (2006) described thalamic volume decrease in patients who were switched from typical antipsychotics to the atypical olanzapine. Within 1 year, patients had thalamic volumes similar to the control group. The authors argued that following a medication switch, reversal of brain abnormalities can occur, even in patients with chronic schizophrenia.

Antipsychotic naïve patients recruited in one study (Deng et al., 2009) were scanned at 3 and 8 weeks after starting antipsychotic medication. GM volume was found to have increased in some areas (right caudate, frontal gyrus, precentral gyrus and left inferior parietal lobe) during this short follow-up period, but decreased in other areas (left medial frontal gyrus). This finding suggests that medication effects on GM volume are already apparent within a short period of time. In another study, decreased hippocampal volume was seen in the hippocampi of medication naïve first episode psychosis patients regardless of whether or not they transitioned to develop schizophrenia (Walter et al., 2012). The authors concluded that it was not possible to determine whether hippocampal volume reduction was due to psychosis as antipsychotic medication might mask this effect by protecting against further volume loss. In a large longitudinal study, Ho et al. (2011) described widespread GM volume reduction associated with the use of antipsychotic medications. Elsewhere it is reported that there may be

differences in action between typical and atypical antipsychotics on GM volume (Borgwardt et al., 2008). A literature review concluded that while typical antipsychotics increased GM volume of the basal ganglia, atypical antipsychotics reversed this effect after a medication switch and had no effect on basal ganglia structure (Smieskova et al., 2009).

The prescription of cannabinoid drugs has been controversial in the medical profession and an association between use of cannabis and development of psychotic illness has been hotly debated in recent years (Arsenault et al., 2004). Whether cannabis is a causal factor for schizophrenia remains unanswered but there is good evidence that the risk of developing psychotic illness is increased by frequency of exposure to cannabis (Moore et al., 2007). Rate of GM loss is also influenced by cannabis, with one longitudinal imaging study showing more pronounced GM loss after five years in schizophrenia patients using cannabis regularly compared to patients not using cannabis (Rais et al., 2008). Another study of cannabis exposure described hippocampal volume loss, regardless of whether a first episode patient transitioned to schizophrenia or not (Walter et al., 2012).

Two reviews concluded that schizophrenia patients tend to have reduced GM volume but while typical antipsychotic medication led to increased basal ganglia volume, atypical antipsychotics had no effect on basal ganglia volume. Atypicals did however appear to reduce basal ganglia volumes down to normal again following a medication switch (Smieskova et al., 2009; Navari and Dazzan, 2009).

3.1.6 Region of Interest Studies

Many studies examine specific regions of interest (ROIs) in schizophrenia but one of the continuing criticisms of ROI studies is the lack of a uniform, standardised methodology. Regions are usually hand drawn, hence time consuming and studies often contain small subject numbers, therefore they lack statistical power and reproducibility of results is limited.

The superior temporal gyrus (STG) has been investigated in several longitudinal schizophrenia studies. Abnormalities of this structure are already well-documented in cross-sectional imaging studies of schizophrenia, as described by Honea (Honea et al., 2005) and Shenton (Shenton et al., 2001b). The STG contains primary and secondary auditory and language-related areas. There appears to be convincing evidence that STG cortical volume is already reduced in patients at first episode of schizophrenia compared to healthy controls but it continues to decrease with disease progression (Milev et al., 2003; Kasai et al., 2003a; Molina et al., 2006). In chronic schizophrenia, the picture has been more confusing, Yoshida et al. (2009) did not find progressive reduction in STG volume in patients with chronic schizophrenia at 3 year follow-up but van Haren et al. (2007) found STG volume loss at 5 year follow-up in a large patient cohort. This suggests that volume loss in the STG may occur more rapidly early on in the course of illness or it may evolve differently, depending on age at illness onset. More specific regions of interest within the STG have been Heschl's gyrus and the planum temporale, where significant volume reductions over time have been described (Kasai et al., 2003b).

3.2 Cortical and deep grey matter

Cortical GM loss has been described in numerous studies comparing brains of healthy individuals with those of adult onset schizophrenia, with the fronto-temporal regions being particularly affected (Ho et al., 2003; Mathalon et al., 2001; Smieskova et al., 2009), although more widespread GM loss has been documented by others (Whitford et al., 2007a; Théberge et al., 2007). In a study comparing schizophrenia patients and their unaffected siblings with a healthy control group Brandt and Bonelli (2008) found that whole brain and cerebral GM volumes of patients decreased excessively compared to their siblings and healthy controls, suggesting that brain tissue loss in schizophrenia is related to the disease and is not a genetically pre-determined trait. Zipparo (2008) described an association between progressive GM atrophy and mild improvement in overall cognitive functioning. One possible reason for this surprising finding would be that

patients at follow-up were no longer psychotic and therefore found it easier to complete the cognitive tests while an alternative explanation is due to practice effects. Other studies have found GM loss to be associated with poor outcome and negative symptoms (Hulshoff Pol and Kahn, 2008).

Some studies additionally identified deep GM structures changing in volume in response to trials of antipsychotic medications (Smieskova et al., 2009). These include use of typical antipsychotics leading to increased GM volume in the basal ganglia, an effect that was reversible by an atypical antipsychotic medication switch. Similarly caudate and putamen volumes were lower in patients than controls or poor outcome patients; who would have been on larger doses of antipsychotic medications compared with good outcome patients (Mitelman et al., 2009a).

Surface area and cortical thickness measures have seen a recent surge of interest in schizophrenia as foci of investigations (Bhoraj et al., 2011; Cobia et al., 2012; Nesvag et al., 2012; van Haren et al., 2011). Findings demonstrate that cortical morphology is clearly different from that of healthy controls and include cortical thinning and misfolding. These suggest an abnormality in the columnar microstructure of cortical cell layers and support a neurodevelopmental explanation for schizophrenia.

3.3 CSF and the Ventricles

Most studies concluded that ventricular enlargement was occurring regardless of whether the patient was at first episode of psychosis (Cahn et al., 2002); or suffering from chronic schizophrenia (Saijo et al., 2001). Only one study reported no difference in ventricular volume change between patients and controls but the mean time to follow-up was only 8 months and patients were noted to have more variable increases and decreases in ventricular volume than controls (Puri et al., 2001). A Dutch study showed an association of ventricular enlargement with cannabis use (Rais et al., 2008), suggesting that specific environmental factors may increase the rate of ventricular enlargement. Changes to adjacent white matter may also

influence rate of ventricular enlargement (Christensen et al., 2004). An earlier study from my research group (Price et al., 2006) reported volume loss in white matter areas adjacent to the lateral ventricles in the right and left temporal lobes of patients, a finding which has subsequently been reported by others as well (Hulshoff Pol and Kahn, 2008).

3.4 Diffusion Tensor Imaging Studies in schizophrenia

Since 1998, an increasing number of publications have emerged in schizophrenia research reporting findings from diffusion tensor imaging (DTI) studies. DTI is useful in structural imaging of white matter tracts, as a tool for pre-operative planning in neurosurgery and has been extensively used to study brain injury.

Literature searches for studies in schizophrenia on Psych Info and Ovid Medline databases were used to identify the publications listed in table 3.2. This is not intended as an exhaustive list of all published DTI literature available, but summarizes articles published in English language journals describing DTI findings in schizophrenia, the cohort(s) used, the methodology and main findings. From the studies reviewed, it is observed that methods have continued to be refined in order to improve the quality of results obtained. Cardiac gating and methods of dealing with image artefacts were not mentioned in any literature predating 2005, yet personal experience shows that approximately 10% of DTI data obtained is unsuitable for inclusion to studies, most commonly due to movement artefacts. Head stabilization is not included as part of the methodology in a number of studies, which is surprising given that movements are a common extrapyramidal side-effect of anti-psychotic medication.

Table 3.2 Diffusion Tensor Imaging Studies in Schizophrenia

ROI = Region of interest, ROI-T = Region of interest with tractography, LSDI = Line scan diffusion imaging, EPI = Echo planar imaging

Author and Year	Patient group	Sample Size (Pt / Ctrl)	Method (field strength, sequence, analysis type, slice no. and thickness)	Results (patients compared to controls)
(Buchsbaum et al., 1998)	Schizophrenia out-pt and in-pt sample	5 / 6	1.5T, LSDI, WB Unspecified slice number, 1.8mm thick	Lower average anisotropy in white matter of PFC, internal capsule and temporal lobes
(Lim et al., 1999)	Schizophrenia, armed forces veterans	10 / 10	1.5T, EPI, ROI 18 axial oblique slices, 5mm thick	Widespread decrease in FA from frontal to occipital regions
(Foong et al., 2000b)	Chronic in-pt schizophrenia	20 / 20	1.5T, EPI, ROI 12 axial slices, 5mm thick	Increased MD and decreased FA in splenium but not genu of the CC
(Agartz et al., 2001)	Chronic schizophrenia	20 / 24	1.5T, EPI, WB 22 axial oblique slices, 4mm thick	Decreased FA in splenium of CC and occipital WM (forceps major) bilaterally
(Steel et al., 2001)	Chronic schizophrenia	10 / 10	2T, EPI, ROI 10 axial slices, 6mm thick	No difference in diffusion anisotropy in pre-frontal white matter ROI
(Foong et al., 2002)	Chronic schizophrenia	14 / 19	1.5T, EPI, WB 12 axial slices, 5mm thick	No difference in whole brain VBM analysis
(Kubicki et al., 2002)	Schizophrenia, out-pt, in-pt, day treatment and foster care	15 / 18	1.5T, LSDI, ROI 31 to 35 coronal slices, 4mm thick	FA similar in both groups but patients lacked asymmetry seen in controls (L>R)

(Hoptman et al., 2002)	Schizophrenia COMT genotype	14 / -	1.5T, EPI, ROI 21 axial slices, 2.5mm thick	No control group but lower FA in inferior frontal WM associated with impulsivity and aggression in patients
(Kubicki et al., 2003)	Schizophrenia, Out-pt, in-pt, day treatment and foster care	16 / 18	1.5T, LSDI, ROI 31 to 35 coronal slices, 4mm thick	Decreased FA and smaller area in cingulum bundle
(Sun et al., 2003)	Schizophrenia	30 / 19	1.5T, EPI, ROI unspecified slice number, 5mm thick	Decreased FA in anterior cingulum only
(Minami et al., 2003)	Schizophrenia	12 / 11	1.5T, EPI, ROI 4 axial slices, 6mm thick	FA decreased in all regions of WM bilaterally
(Burns and Job, 2003)	Schizophrenia	30 / 30	1.5T, EPI, ROI 31 axial slices, 5mm thick	Decreased FA in left uncinate and arcuate fasciculi
(Wang et al., 2003)	Schizophrenia	29 / 30	1.5T, EPI, ROI 12 slices, 3mm thick	No FA difference in superior or middle cerebellar peduncles
(Wolkin et al., 2003)	Schizophrenia in and out pt	10 / -	1.5T, EPI, ROI 5 axial slices, 5mm thick	Decreased FA in inferior frontal WM, which is correlated with severity of negative symptoms
(Begre et al., 2003)	First episode schizophrenia	7 / 7	1.5T, EPI, ROI 12 axial slices, 5mm thick	No difference in hippocampal FA

(Ardekani et al., 2003)	Schizophrenia (7) and schizoaffective (7) disorder	14 / 14	1.5T, EPI, WB 20 axial slices, 5mm thick	Reduced FA in the corpus callosum, left STG, MTG, IPG, parahippocampal gyri, medial occipital lobe and deep frontal perigenual region
(Wang et al., 2004)	Schizophrenia	21 / 20	1.5T, EPI, ROI 12 axial slices, 3mm thick	Reduced FA both sides of anterior cingulum bundle and less L>R FA asymmetry
(Kalus et al., 2004)	Schizophrenia paranoid subtype	15 / 15	1.5T, EPI, ROI 13 slices parallel to long hippocampal axis, 2.5mm thick	Decreased intervoxel coherence in posterior hippocampus and reversed coherence asymmetry with anterior hippocampus in schizophrenia
(Okugawa et al., 2004)	Schizophrenia, paranoid (15), disorganized (8) and catatonic (2)	25 / 21	1.5T, EPI, ROI unspecified slice number, 6mm thick	Reduced FA in middle cerebellar peduncles
(Kumra et al., 2004)	Young people with Early Onset Schizophrenia	12 / 9	1.5T, EPI, ROI 18 slices, 5mm thick	Reduced FA in frontal WM bilaterally and right occipital WM
(Hubl et al., 2004)	Acute Schizophrenia with auditory hallucinations (13) & without (13)	13 / 13 / 13	1.5T, LSDI, WB 12 axial slices, 5mm thick	Reduced FA in all brain WM regions Increased FA in parts of arcuate fasciculus and corpus callosum
(Kalus et al., 2004)	Schizophrenia	14 / 14	1.5T, EPI, ROI 13 slices, 2.5mm thick	Inter-voxel coherence reduced bilaterally in the hippocampus

(Hoptman et al., 2004)	Schizophrenia or schizoaffective disorder	25 / -	1.5T, EPI, WB 20 axial slices, 5mm thick	Negative correlations between FA and impulsivity in inferior frontal WM, anterior cingulate, caudate, insula and inferior parietal lobe
(Hoptman et al., 2004)	Schizophrenia or schizoaffective disorder	25 / -	1.5T, EPI, WB 20 axial slices, 5mm thick	Negative correlations between FA and impulsivity in inferior frontal WM, anterior cingulate, caudate, insula and inferior parietal lobe
(Park et al., 2004)	Schizophrenia out-pt, in-pt, day treatment and foster care	23 / 32	1.5T, LSDI, WB 31 to 35 coronal slices, 4mm thick	FA asymmetry lower in cingulum and anterior CC, absent in anterior limb of internal capsule, uncinate fasciculus and superior cerebellar peduncle
(Nestor et al., 2004)	Schizophrenia	41 / 46	1.5T, LSDI, ROI 31 to 35 coronal slices, 4mm thick	Lower levels of declarative-episodic verbal memory correlated with reduced left uncinate and executive function errors link to left cingulum
(Price et al., 2005)	First episode schizophrenia	20 / 29	1.5T, EPI, ROI 21 axial slices, 5mm thick	No differences in FA or diffusivity in the splenium or genu of the corpus callosum
(Kitamura et al., 2005)	Schizophrenia	6 / 6	3T, EPI, ROI 5 axial slices, 5mm thick	Frontal FA reduced
(Kalus et al., 2005)	Paranoid schizophrenia	14 / 14	1.5T, EPI, ROI 13 slices, 2.5mm thick	Decreased inter-voxel coherence in the amygdala

(Szeszko et al., 2005)	First episode schizophrenia and schizoaffective disorder	10 / 10	1.5T, EPI, WB 18 axial slices, 5mm thick	Reduced FA in left internal capsule, left middle frontal gyrus and posterior superior temporal gyrus
(Kubicki et al., 2005a)	Schizophrenia out-pt, in-pt, day treatment and foster care	21 / 26	1.5T, LSDI, WB 31-35 coronal slices, 4mm thick	Decreased diffusion anisotropy in the fornix, corpus callosum and bilaterally in the cingulum bundle, superior occipito-frontal fasciculus, internal capsule, right inferior occipito-frontal fasciculuc and left arcuate fasciculus
(Okugawa et al., 2005)	Schizophrenia, paranoid (15), disorganized (8) & catatonic (2)	25 / 21	1.5T, EPI, ROI axial slices parallel to AC-PC line, 6mm thick	Reduced FA in middle cerebellar peduncle in patients with schizophrenia
(Kumra et al., 2005)	Schizophrenia (17), schizoaffective (8) schizophreniform (1)	26 / 34	1.5T, EPI, WB 23 slices, thickness unspecified	Reduced FA in the left anterior cingulate
(Jones et al., 2006)	Schizophrenia in-pt and out-pt	14 / 14	1.5T, EPI, ROI Unspecified slice number or thickness	FA lower in patients in the superior longitudinal fasciculus but this may be due to correlation with age
(Kuroki et al., 2006)	Schizophrenia out-pt, in-pt, day treatment and foster care	24 / 31	1.5T, LSDI, ROI 31-35 coronal slices, 4mm thick	Reduced FA in fornix and mean diffusivity increase seen in bilateral hippocampi
(Kanaan et al., 2006)	Schizophrenia in remission	39 / 43	Field strength unspecified, EPI, ROI >60 near-axial slices, 2.5mm thick	No difference in FA in genu of corpus callosum using conventional ROI method but reduced FA when tractographic ROI method used

(Shin et al., 2006)	Schizophrenia in-pt and out-pt	19 / 21	1.5T, EPI, WB 40 axial slices, 4mm thick	Increased apparent diffusion co-efficient in bilateral fronto-temporal areas.
(Okugawa et al., 2006)	Schizophrenia (14 paranoid, 4 disorganised, 3 catatonic)	21 / 21	1.5T, EPI, ROI Unspecified slice number, 6mm thick	Lower FA in superior cerebellar peduncles
(Mitleman et al., 2006)	Schizophrenia, in-pt and out-pt	104 / 41	1.5T, EPI, WB 14 axial slices, 7.5mm thick	Lower FA in widespread temporoparietal and prefrontal white matter regions and associated with lower regional GM volumes
(Rose et al., 2006)	Schizophrenia	12 / 12	1.5T, EPI, WB 45 axial slices, 2.5mm thick	Increased mean diffusivity in temporal, parietal and prefrontal cortical regions, also thalamus (dorsal medial and anterior nucleus) including caudate
(Federspiel et al., 2006)	Schizophrenia	12 / 12	1.5T, EPI, WB 12 axial slices, 5mm thick	Intervoxel coherence higher in 3 clusters and lower in 11 clusters
(Buchsbaum et al., 2006a)	Schizophrenia, in-pt, out-pt, day treatment and vocational rehab	63 / 55	3T, EPI, WB 28 slices, 3mm thick	Reduced FA in the frontal white matter, corpus callosum, cingulate gyrus and superior longitudinal fasciculus

(Buchsbaum et al., 2006b)	Schizophrenia, in-pt, out-pt, day treatment and vocational rehab	103 / 41	T not mentioned, EPI, ROI 14 axial slices, 7.5mm thick	Manual tractography found that anterior thalamic radiations from internal capsule to prefrontal WM was shorter in length and FA lower
(Caan et al., 2006)	Recent onset schizophrenia or related DSM IV disorder	34 / 24	1.5T, EPI, WB Unspecified slice number and thickness	Decreased FA in genu of corpus callosum and increased FA in posterior limb of internal capsule and uncinate fasciculus
(DeLisi et al., 2006)	High risk of schizophrenia	15 / 25	1.5T, EPI, WB 19 slices, 5mm thick	ADC was reduced in four regions of the left brain: parahippocampal gyrus, lingual gyrus, superior frontal gyrus and middle frontal gyrus
(Lim et al., 2006)	Schizophrenia or schizoaffective disorder	25 / -	1.5T, EPI, WB 20 slices, 5mm thick	Better performance in verbal memory, attention and executive function correlates with higher FA in task relevant WM regions.
(Butler et al., 2006a)	Schizophrenia (15) and schizoaffective (2)	17 / 21	1.5T, EPI, ROI 20 slices, 5mm thick	Optic radiations show reduced FA bilaterally
(Schlösser et al., 2006)	Schizophrenia	18 / 18	1.5T, EPI, WB 19 axial slices, 3mm thick	Reduced FA in right medial temporal lobe and right frontal lobe

(White et al., 2007)	Children and adolescents with schizophrenia (14) and schizoaffective disorder (1)	15 / 15	3T, EPI, WB Unspecified slice number, 2mm thick	Decreased FA in left posterior hippocampus and posterior limbic regions with concurrent increase in average diffusivity
(Nestor et al., 2007b)	Chronic schizophrenia	18 / 30	1.5T, LSDI, ROI Coronal oblique unspecified number, 4mm thick	Left cingulum bundle FA correlated with orienting of attention
(Mori et al., 2007)	Chronic schizophrenia	42 / 42	1.5T, EPI, WB and ROI 20 axial slices, 5mm thick	Reduced FA in bilateral frontal and temporal lobes, uncinate fascicule, cingulum bundles and corpus callosum, age related reduction in FA more prominent in patients
(Mitelman et al., 2007)	Schizophrenia poor outcome (53) & good outcome (51)	104 / 41	1.5T, EPI, ROI 14 axial slices, 7.5mm thick	Reduced FA in left cingulum, anterior thalamic radiation, fronto-occipital and inferior longitudinal fasciculus, corpus callosum, internal capsule, superior longitudinal fasciculus, optic radiation and fronto-temporal extra-fascicular white matter.
(Nestor et al., 2007a)	Schizophrenia	21 / 25	1.5T, LSDI, ROI Coronal oblique unspecified number, 4mm thick	Reduced FA of fornix correlated with reduced executive functioning

(Leitman et al., 2007)	Schizophrenia (17) schizoaffective disorder (2)	19 / 19	1.5T, EPI, WB 20 slices, 5mm thick	Lower FA correlates with impaired voice emotion identificationin auditory pathways, orbitofrontal cortex, corpus callosum and peri-amygdala white matter
(Seok et al., 2007)	Schizophrenia, hallucinating (15) and non-hallucinating (15)	15 / 15 / 22	1.5T, EPI, ROI About 45 axial slices, 2mm thick	FA significantly decreased in the left superior longitudinal fasciculus and increased in the left inferior longitudinal fasciculus
(Shergill et al., 2007)	Schizophrenia, from hospital wards and out-pt clinics (33)	33 / 40	1.5T, EPI, WB Over 60 near-axial slices, 2.5mm thick	Reduced FA in superior longitudinal fascicule bilaterally and genu of corpus callosum
(Miyata et al., 2007)	Schizophrenia, out-pt (42) and in-pt (3)	40 / 36	3T, EPI, ROI 40 axial slices, 3mm thick	Smaller anterior/total corpus callosum area and length
(Karlsgodt et al., 2007)	Schizophrenia, young adults with adolescent onset	12 / 17	1.5T, EPI, ROI 75 AC-PC aligned slices, 2mm thick	Lower FA in superior longitudinal fasciculus bilaterally, correlations with performance on verbal working memory in left but not right SLF
(Andreone et al., 2007)	Schizophrenia	68 / 64	1.5T, EPI, ROI 20 axial slices, 5mm thick	Greater apparent diffusion co-efficient in frontal, temporal and occipital white matter
(Fujiwara et al., 2007)	Schizophrenia	42 / 24	3T, EPI, ROI 40 axial slices, 3mm thick	Reduced FA in anterior and posterior cingulum bundles

(Manoach et al., 2007a)	Chronic schizophrenia out-pt	17 / 19	3T, EPI, ROI 64 axial oblique slices, 2mm thick	Reduced FA in right cingulate
(Tang et al., 2007)	Schizophrenia in-pt, out-pt, day treatment and vocational rehab	42 / 40	3T, EPI, ROI 28 slices, 3mm thick	Reduced FA in bilateral medial temporal lobes
(Kyriakopoulos et al., 2008)	Early onset schizophrenia	19 / 20	1.5T, EPI, WB 60 slices, 2.5mm thick	Lower FA in parietal association cortex bilaterally and in left middle cerebellar pedcuncle
(Szeszko et al., 2008)	Recent onset schizophrenia	33 / 30	1.5T, EPI, WB 23 axial slices, 5mm thick	Lower FA in the temporal lobe white matter, uncinate fasciculus , left inferior fronto-occipital fasciculus and left superior longitudinal fasciculus
(Maniega et al., 2008)	Schizophrenia (31), high risk of schizophrenia (22) and controls	31 / 22 / 51	1.5T, EPI, ROI 48 axial slices, 2.8mm thick	FA reduced in left arcuate fasciculus, bilateral uncinate fascicule and anterior limb of internal capsules. High risk subjects had reduced FA in anterior limb of internal capsules only.

(Peters et al., 2008)	Schizophrenia (10), ultra-high risk of psychosis (10)	10 / 10 / 10	3T, EPI, ROI Para-transversal, tilted to coronal	No difference in corpus callosum FA between healthy controls and either patient groups
(McIntosh et al., 2008b)	No patients, healthy control subjects genotyped for NRG1 polymorphism (risk allele for schizophrenia)	- / 43	1.5T, EPI, ROI 48 axial slices, 2.8mm thick	FA at anterior limb of internal capsule was lowest in homozygous TT, highest in homozygous CC and midway for heterozygous CT
(Carpenter et al., 2008)	Schizophrenia in-pt, out-pt, day treatment and vocational rehab	76 / 77	3T, EPI, ROI 28 slices, 3mm thick	Lower FA in genu but not splenium of corpus callosum. Correlation of lower FA with increasing age and duration of illness
(Mandl et al., 2008)	Schizophrenia	40 / 40	1.5T, EPI, ROI 60 slices, 2.5mm thick	Decreased FA in left uncinate fasciculus significantly correlated with age in patients but not controls
(Rowland et al., 2008)	Deficit schizophrenia with primary enduring –ve symptoms (10), non-deficit schizophrenia (10)	10 / 10 / 11	3T, EPI, ROI 60 slices, slice thickness unspecified	Reduced FA in right SLF and frontal white matter in deficit patients
(Kunimatsu et al., 2008)	Schizophrenia	19 / 20	1.5T, EPI, ROI 30 slices, 5mm thick	FA lower and ADC higher in superior occipito-frontal fasciculus
(Kubicki et al., 2008)	Chronic schizophrenia	32 / 42	1.5T, LSDI, ROI 5 sagittal oblique slices, 4mm thick	FA decreased in corpus callosal fibres connecting frontal regions
(McIntosh et al., 2008a)	Schizophrenia (25), bipolar (40) and controls	25 / 40 / 49	1.5T, EPI, ROI 48 axial slices, 2.8mm thick	FA reduced in uncinate and anterior thalamic radiations bilaterally in both groups

(Hoptman et al., 2008)	Schizophrenia (23), high genetic risk of sz (22) and controls	23 / 22 / 37	1.5T, EPI, WB Unspecified slice number, 5mm thick	High genetic risk group had reduced FA in the cingulate and angular gyri bilaterally.
(Narr et al., 2009)	Adult onset schizophrenia (26), unaffected first degree relatives (36), controls (20) and control relatives (32)	26 / 36 / 20 / 32	1.5T, EPI, WB 50 axial slices, 3mm thick	Mean diffusivity increases in bilateral temporal regions in schizophrenia compared with unrelated control probands
(Fitzsimmons et al., 2009)	Chronic schizophrenia	36 / 35	1.5T, LSDI, ROI Coronal oblique slices aligned to AC-PC line, 4mm thick	FA decreased in fornix bilaterally and higher fornix FA correlated with combined visual memory, verbal memory, recall and recognition in controls only.
(Kawashima et al., 2009)	Psychosis in-pts with schizophrenia (15) & affective psychosis (15)	15 / 15 / 15	1.5T, LSDI, ROI 31-35 coronal slices, 4mm thick	FA reduced bilaterally in uncinate fasciculus in schizophrenia, affective psychosis FA intermediate between between sz and ctrl groups
(Lee et al., 2009)	Schizophrenia	22/ 22	1.5T, LSDI, WB Coronal slices, 4mm thick	Mean diffusivity increased but no differences in FA
(Ellison-Wright and Bullmore, 2009)	Meta-analysis of 15 DTI studies in schizophrenia	407 / 383	Meta-analysis	FA reductions seen in left frontal and temporal deep white matter with no FA increases seen
(Kubicki et al., 2009)	Schizophrenia in-pt, out-pt, day treatment, foster care	18 / 18	1.5T, EPI, ROI 32-35 coronal oblique slices, 4mm thick	Decreased FA in bilateral cingulum bundles which correlated with reaction times and Stroop effect in pt group only.

(Kanaan et al., 2009b)	Schizophrenia in-pt and out-pt	33 / 33	1.5T, EPI, ROI 60 slices, 2.5mm thick	FA lower in WM tracts of the cerebellum but no difference in mean diffusivity
(Hao et al., 2009)	Schizophrenia pts (34) and healthy siblings (34)	34 / 34 / 32	1.5T, EPI, WB 30 axial slices, 4mm thick	FA values in prefrontal cortex, hippocampus and anterior cingulate cortex, lower in pts. Similar decreased FA in prefrontal cortex and hippocampus in siblings.
(Kyriakopoulos et al., 2009)	Adolescent onset schizophrenia (17) and adult onset schizophrenia (17)	17 / 17	1.5T, EPI, WB 60 slices, 2.5mm thick	Adolescent onset sz showed decreased FA in parietal areas but adult onset sz showed decreased FA in frontal, temporal and cerebellar areas.
(Bai et al., 2009)	Schizophrenia with tardive dyskinesia (TD), schizophrenia without TD and controls	20 / 20 / 20	1.5T, EPI, WB 70 axial slices, 2.2mm thick	Patients with TD had more widespread decreased FA than patients without TD, especially cortico-basal ganglion circuit.

(Wang et al., 2009)	Schizophrenia	31 / 36	1.5T, EPI, WB Unspecified slice number, 3mm thick	FA reduced in anterior cingulum with group by genotype interaction lowest in homozygous TT, highest in homozygous CC and midway for heterozygous CT
(Gasparotti et al., 2009)	Schizophrenia, first contact, drug-naïve (21)	21 / 21	1.5T, EPI, ROI 29 slices, 5mm thick	Lower FA in splenium but not genu of corpus callosum.
(Phillips et al., 2009)	Schizophrenia	23 / 22	1.5T, EPI, ROI 55 slices oblique to AC-PC line, 2.5mm thick	Reduced FA in arcuate fasciculi and inferior longitudinal fasciculi
(Camchong et al., 2009)	Study 1: Healthy monozygotic twins (18 pairs) Study2: First degree relatives of schizophrenia pts (22)	Study 1: 36 / - Study 2: 22 / 30	3T, EPI, ROI 55 axial slices, 2.5mm thick	Study 1: FA values more strongly correlated between MZ twins than randomly generated pairs in genu of corpus callosum, anterior cingulum and forceps minor. Study 2: Lower FA in right genu of corpus callosum in relatives
(Sussmann et al., 2009)	Familial schizophrenia (28), familial bipolar disorder (42) and controls	28 / 42 / 38	1.5T, EPI, ROI 48 axial slices, 2.8mm thick	Reduced FA in anterior limb of internal capsule, anterior thalamic radiation and uncinate fasciculus

(Cheung, 2009)	Never medicated first episode schizophrenia	25 / 24	-	FA reduced in the right posterior limb of internal capsule and substantia nigra, left middle temporal gyrus, cerebral peduncle and splenium of corpus callosum
(Peters et al., 2009)	Ultra high risk for psychosis (10) and recent onset schizophrenia (8) or schizoaffective disorder (2) and controls	10 / 10 / 10	3T, EPI, WB 48 slices, 2.2mm thick	FA reduced in the UHR group in right superior frontal lobe and left middle frontal lobe In sz group FA reduced in parietal lobes, left frontal and superior temporal lobe, right temporal lobe and insula
(Voineskos et al., 2009)	Schizophrenia	10 / 10	1.5T, EPI, ROI 57-62 axial slices, 2.6mm thick	Between group FA differences not calculated in this physics methods paper
(Kanaan et al., 2009a)	Schizophrenia in-pt and out-pt	76 / 76	1.5T, EPI, WB Over 60 near-axial slices, 2.5mm thick	Lower whole brain FA with widespread FA decreases throughout multiple WM structures
(Bai et al., 2009)	Schizophrenia with tardive dyskinesia (TD), schizophrenia without TD and controls	20 / 20 / 20	1.5T, EPI, WB 70 axial slices, 2.2mm thick	Patients with TD had more widespread decreased FA than patients without TD, especially cortico-basal ganglion circuit.

(Herbsman and Ziad, 2010)	Schizophrenia	13 / 16	3T, EPI, WB 30 slices, 3mm thick	Decreased diffusivity in right prefrontal cortex, left superior longitudinal fasciculus, cerebellum and increased FA in occipital projections of the corpus callosum
(Moriya et al., 2010)	Early stage of first episode schizophrenia	19 / 19	3T, EPI, WB Unspecified slice number, 4mm thick	Increased mean diffusivity in left parahippocampal gyrus, left insula and right anterior cingulate gyrus
(Nestor et al., 2010)	Schizophrenia	16 / 12	1.5T, LSDI, ROI 31 to 35 coronal slices, 4mm thick	Right cingulum bundle FA positively correlated with IQ
(Pérez-Iglesias et al., 2010)	First episode schizophrenia	62 / 54	1.5T, EPI, WB 27 axial slices, 5mm thick	Mean FA values lower in frontal and temporal poles and corpus callosum

The first study to investigate schizophrenia using DTI was published in 1998 (Buchsbaum et al., 1998). Subsequent findings have varied, although there has been a trend for studies to find lower fractional anisoptropy (FA) in patients with schizophrenia compared to healthy controls, despite variation in methodology. Kubicki's research group used line scan diffusion imaging (LSDI) which collects scan data in coronal slices and is supposedly prone to less movement artefacts but most studies used conventional echo planar imaging (EPI), which collects data in axial slices. Although high field MRI scanners are available, they are not suitable for clinical use and most of the published data reported findings from 1.5T scanners. Analysis of data used either of two main methods; whole brain voxel-wise analysis or tract specific comparison between groups. Although VBM is useful where no apriori hypothesis exists and a global search is required, there is more room for type I errors due to multiple comparisons on a larger scale than for a tract specific analysis. Registration has also been raised as a potential problem but using technology such as Spatial Parametric Mapping (SPM), processing can be automated, hence more accurate than calculating FA in a hand drawn ROI.

Despite differences in methodology the commonest reported finding appears to be lower FA in patients than controls (although some studies report no difference in FA between the groups). The only study to report higher FA in patients than controls (Hubl et al., 2004) was specifically testing the hypothesis that schizophrenia patients with auditory hallucinations might have increased FA in the middle and superior temporal gyri. The rationale for this hypothesis being that the auditory processing pathway extends through these brain regions and may be "over-developed" hence predisposed to hyperactivity and give rise to auditory hallucinations.

Many DTI studies have reported decreased FA in the corpus callosum but the specific regions have been variable; being the largest white matter tract in the brain, the margins of this structure are clearly visible on MRI. In a ROI study, Foong et al. (2000b) found decreased FA in the splenium of the corpus callosum of patients but no difference in FA of the corpus callosum in

a subsequent study using a whole brain voxel-based analysis (Foong et al., 2002), which suggests that whole brain voxel-based studies may be less sensitive to discrete FA changes. Two later studies by Caan et al. (2006) and Carpenter et al. (2008) reported decreased FA in the genu but not the splenium of the corpus callosum using a voxel based analysis. One explanation for this may be that patients were clinically worse affected by schizophrenia; conversely, FA of first episode schizophrenia patients was similar to healthy controls in ROIs of the genu and splenium of the corpus callosum (Price et al., 2005).

It has been suggested that white matter changes are progressive and may vary with illness duration but in some first episode psychosis studies (Foong et al., 2000b; Pérez-Iglesias et al., 2010), patients already had reduced WM FA compared to healthy controls, suggesting onset of WM microstructural changes have already started by the time of symptom onset. This finding has also been replicated in medication naïve subjects, suggesting FA variation is unlikely to be due to any effects of medication (Cheung, 2009). Some first episode studies reported no difference in WM FA compared to healthy controls (Price et al., 2005; Begre et al., 2003) but this apparent inconsistency may be due to the limited effect size as any group differences are likely to be very subtle.

A review of 18 DTI studies by Kubicki et al. (2007) concluded that the evidence for FA differences between schizophrenia patients and healthy controls were controversial. The authors pointed out that low spatial resolution and high signal to noise ratio probably contributed to the discrepancies found between studies. A more comprehensive review (Konrad and Winterer, 2008) including structural MRI, DTI, magnetic resonance spectroscopy (MRS) and post-mortem schizophrenia studies concluded that there is increasing evidence from multiple imaging modalities that structural connectivity might be pathologically altered in schizophrenia, giving rise to two models of WM disconnectivity for schizophrenia; global and macro-circuit. Global theory suggests that WM reductions occur uniformly

throughout the brain, possibly as a result of genetic abnormalities in the protein pathways controlling myelination; macro-circuit theory proposes that specific WM tracts connecting GM regions are disrupted either as a cause or a consequence of schizophrenia.

A subsequent meta-analysis of 15 DTI studies (Ellison-Wright and Bullmore, 2009); concluded that most studies enrolled chronic schizophrenia patients where white matter FA reduction is probably more widespread. Overall FA was significantly reduced in two regions, the left frontal and left temporal deep white matter. *"The first region, in the left frontal lobe, is traversed by white matter tracts interconnecting the frontal lobe, thalamus and cingulate gyrus. The second region, in the temporal lobe, is traversed by white matter tracts interconnecting the frontal lobe, insula, hippocampus–amygdala, temporal and occipital lobe. This suggests that two networks of white matter tracts may be affected in schizophrenia, with the potential for 'disconnection' of the grey matter regions which they link".*

Most DTI studies support the notion that white matter integrity is impaired in schizophrenia but findings need to be interpreted with caution for several reasons. FA measures are believed to reflect directionality and position of the white matter tract; however, anisotropy is highly variable in different white matter regions depending on the degree of coherence of fibre tract directions. In regions where WM tracts branch and axons cross, the fibre pattern is less coherent so diffusion anisotropy is significantly reduced (Pierpaoli and Basser, 1996). A further difficulty lies with sampling of patients, illness severity does not necessarily correlate with duration of illness and while some studies recruited chronic out-patients, others recruited from in-patient wards where patients would be more acutely unwell. Chronic patients are also likely to be older than first episode patients and there are clear age-related differences in brain maturation (Jones et al., 2006). Future studies should aim to improve methodology by introducing more stringent recruitment criteria, better correction of movement artefacts and increase uniformity in MRI processing.

3.4.1 Tractography Studies of Schizophrenia

In recent years there have been an increasing number of studies published investigating the integrity of WM tracts in schizophrenia (table 3.3). The WM tracts reconstructed using tractography can give an idea of the overall position and directionality of WM tracts in-vivo; hence the degree of connectivity between different brain regions can be estimated using quantitative measures of anisotropy or diffusivity obtained by this type of analysis of diffusion tensor imaging (DTI) data.

Table 3.3 summarizes DTI studies of schizophrenia found on literature search using PubMed that have been published in English language journals. While earlier studies tended to look at the number of seed tracts passing between two ROIs to determine strength of connectivity between two areas (Jones et al., 2006) there has been much variation in subsequent methodology. Where diffuse regions of change are sought, multiple regions of interest can be used; for example to demonstrate decreased FA in multiple projections of the DLPFC in schizophrenia (Oh et al., 2009) or in multiple cerebellar tracts (Kanaan et al., 2009b). Other studies have used novel techniques for analyzing DTI data, for example “Guided Tensor Restore Anatomical Connectivity Tractography” (Magnotta and Cheng, 2005) which is a two pass approach generating an approximation to the fibre tracts followed by guided tracking in regions of low FA or large curvature, which simulates the natural branching of fibre bundles. With the majority of studies using ROI rather than a whole brain analysis approach, tractography findings have been diverse; although FA is generally lower in patients with schizophrenia and FA changes are already apparent at first episode of psychosis (Gasparotti et al., 2009; Luck et al., 2010; Price et al., 2007; Price et al., 2008).

Table 3.3 Tractography Studies in Schizophrenia

Sz = schizophrenia, FA = fractional anisotropy, ILF = inferior longitudinal fasciculus, MD = mean diffusivity, UF = uncinate fasciculus, CB = cingulate bundle, DLPFC = dorsolateral prefrontal cortex, MROI = multiple regions of interest, PICo = probabilistic index of connectivity, ROI = Region of interest, WM = white matter

Author and Year	Patient group	Sample Size (Pt/Ctrl)	Field strength and methodology	Results (patients compared to controls)
(Jones et al., 2006)	Right-handed males with sz	14 / 14	1.5T Fibres between 2 ROIs sought using algorithm of 0.5mm tracking step and FA threshold 0.15	Youngest pts had lower diffusion anisotropy than age-matched ctrls but difference diminished with increasing age. This may be due to age related differences in brain maturation.
(Price et al., 2007)	FE sz spectrum disorders	18 / 21	1.5T Probabilistic index of connectivity (PICo) tractography algorithm with seed regions in genu and splenium	FA was reduced in tracts crossing the genu and splenium in pts but tract volumes were similar to controls.
(Ashtari et al., 2007)	Adolescents 11–18yrs sz/sa	23 / 21	1.5T Fibre assignment by continuous tracking (FACT), threshold FA 0.2 and turning angle < 41º to extract ILF.	Reduced FA in L inferior temporal and occipital regions. Reduced FA and increased radial diffusivity in left ILF of pts.
(Miyata et al., 2007)	Sz	40 / 36	3T Continuous tracking method between 2 ROIs with termination criteria FA < 0.2 of turning angle > 50º	Pts showed small anterior/total corpus callosum length and area suggesting interfrontal hypoconnectivity in sz. Lower FA and higher MD anteriorly.

(Price et al., 2008)	FE psychosis	19 / 23	1.5T Probabilistic tractography algorithm used to map uncinate fasciculus	Number of voxels with high FA values reduced in the core of the left UF suggesting changes in fibre alignment and tract coherence in pts.
(Zhou et al., 2008)	Paranoid sz in-pts	17 / 14	1.5T Fibre assignment by continuous tracking (FACT) used with FA threshold of 0.15 and angle > 10º performed in conjunction with fMRI.	Mean FA in the fornix was reduced in pts
(Nestor et al., 2008)	Sz	25 / 28	1.5T Fibre tractography from reconstructed entire WM fibre bundles (cingulate and uncinate) using stopping criteria FA 0.15 and angle 20º per 1mm.	Bilateral reductions of UF correlated with deficits in memory while bilateral reductions of CB correlated with deficits in executive functioning.
(Kim et al., 2008)	Sz	30 / 22	1.5T Probabilistic thalamocortical pathways were calculated from the thalamus to 4 parceled cortical masks with 5000 iterations per thalamic seed voxel	Decreased anisotropy and increased longitudinal and transverse diffusivity in pts within pathways from mediodorsal nucleus and pulvinar to orbitofrontal and parietal-occipital-temporal lobes.
(Rosenberger et al., 2008)	Sz	27 / 34	Reconstruction of cingulum, uncinate and inf occipito-frontal fasciculi using whole brain fiber tractography threshold FA < 0.15 & angle of curvature > 20º per 1mm. 2 ROIs per tract were selected for purposes of tractography.	Significant decline in FA with age in cingulum and uncinate of pts but not inf occipito-frontal fasciculi.

(Takei et al., 2008)	Sz	31 / 32	1.5T Seed point with 0.66 mm fixed steps along the principal axis. The diffusion tensor at the next location was determined from adjacent voxels by trilinear filtering, and its principal axis was subsequently estimated. Tracking lines were automatically traced in this way and were propagated in the anterograde and retrograde threshold FA > 0.2.	Reduced FA and increased MD in fornix of pts. Increased MD in left fornix correlated with lower verbal learning while increased MD in right fornix showed association with poorer semantic memory in patients.
(Magnotta et al., 2008)	Sz male pts	12 / 10	1.5T Novel fibre tracking algorithm "Guided Tensor Restore Anatomical Connectivity Tractography" tracking threshold 0.26, curvature 45º	Reduced FA in pts between cerebellar WM and thalamus connections with reduced anisotropy in the region of the sup cerebellar peduncles projecting towards red nucleus.
(Carpenter et al., 2008)	Age range 18-78 sz 18-82 ctrls	76 / 77	3T multiple region brute-force fibre tracking method threshold for FA 0.1 & angle change 45º	Decline in FA correlated with duration of illness in genu & splenium of corpus callosum but not the pyramidal tracts. Progressive loss of WM integrity in pts beyond that accounted for by ageing.
(Kubicki et al., 2008)	Chronic sz	32 / 42	1.5T Novel method for computation of probabilistic subdivision of the corpus callosum into 4 segments	Decreased FA within parts of corpus callosum interconnecting frontal regions in sz. No sig changes for callosal fibres interconnecting parietal and temporo-occipital regions.
(McIntosh et al., 2008)	Sz, bp and ctrl groups with 2 or more affected family members	25 / 40 / 49	1.5T Probabilistic tractography for segmentation of tract of interest. TBSS used to create reference tracts typifying general trajectory of fasciculus.	Reduced FA in the uncinate fasciculus and ant thalamic radiation of sz and bp as a feature common to both disorders

(Kunimatsu et al., 2008)	Male pts with sz	19 / 20	1.5T Knowledge-based , 2 ROI method Threshold of line-tracking at FA > 0.18	Mean FA reduced & apparent diffusion coefficient increased in sup occipitofrontal fasciculus of pts
(Phillips et al., 2009)	Sz	22 / 23	1.5T Fibre Assignment by Continuous Tracking algorithm used for MROI approach. 3D tract reconstruction with FA threshold of 0.2 and turning angle threshold of 41º	Reduced FA in arcuate fascicule and inf longitudinal fasciculi in pts
(Fitzsimmons et al., 2009)	Male pts with chronic sz	36 / 35	1.5T Multiple ROI method used with 5 ROIs identified	Bilateral decrease in fornix FA in sz. Higher fornix FA correlated with visual memory, verbal memory, recall and recognition in controls.
(Gasparotti et al., 2009)	First contact, antipsychotic drug-naïve sz	21 / 21	1.5T ROIs placed on splenium (40mm³) and genu (30mm$^{3)}$ on unregistered directionally encoded colour maps.	FA lower in splenium but not in genu of pts more pronounced in males
(Voineskos et al., 2009)	Sz	10 / 10	1.5T Whole brain tractography using deterministic (streamline) approach with comparison of clustering and MROI approaches.	Excellent interrater reliability of clustering and MROI methods, quantitatively and spatially.

(Kito, Jung & Kobayashi, 2009)	Sz	20 / 20	1.5T Streamlines Tracking Technique used with step width 0.5mm, fiber trajectories terminated when FA < 0.25 or angle > 45º	Pts showed reduction in cross-sectional area of L ant thalamic peduncle, no differences for mean FA but increased standard deviation of FA.
(Takei, Yamasue & Osamu, 2009)	Sz in-pts and out-pts	31 / 31	1.5T A “seed” was defined as the location for the initiation of tracking algorithm, which moved 0.66 mm along the principal axis. The diffusion tensor at the next location was determined from adjacent voxels by trilinear filtering, and its principal axis was subsequently estimated. Tracking lines were automatically traced in this way and were propagated in the antegrade and retrograde directions until FA fell below 0.18.	Bilaterally decreased FA in the pregenual CB and dorsal CB, and a bilaterally increased MD in the dorsal CB of pts, which showed significant correlations with a longer color–word incongruent and neutral reaction time in the Stroop task in patients
(Oh et al. 2009)	Chronic sz	18 / 21	1.5T LSDI Whole brain seeding tractography followed by multiple ROI selection technique	Decreased FA and increased MD in the DLPFC projections, decreased FA & unchanged MD in ACC projections, increased MD & unchanged FA frontal pole, orbitofrontal, inferior-prefrontal projections
(Kanaan, R.A. et al., 2009)	Sz pts	33 / 33	1.5T Tractography to dissect 4 WM cerebellar tracts & measure FA and mean diffusivity in these ROIs	FA was lower in sz group compared with controls. MD did not differ between groups.

(Savadjiev, P. et al., 2010)	Sz pts	23 / 20	3T Novel indices of computed WM dispersion and curving, a proof of concept paper	SZ group having higher index values in the UF, and lower values in the corona radiate
(Voineskos et al., 2010)	Younger sz pts < 56yrs & older sz pts > 55yrs (both grps matched with ctrls)	25 / 25 / 25 / 25	1.5T Whole brain deterministic tractography (Runge-Kutta order 2 tractography 0.5mm fixed steps) with manual extraction of specific tracts of interest	L uncinate fasciculus and R cingulum bundle are disrupted in younger chronic patients with sz. Older groups did not differ
(Luck, 2010)	FE sz	32 / 25	1.5T, reconstruction of fornices by Fiber Assistance by Continuous Tracking (FACT) Seeding voxels with FA>0.15, constraining angle <45º	Significant FA reduction in the fornix of patients
(Whitford, 2010)	Sz	19 / 19	3T, automated fiber clustering parcelled into 6 segments, FA & mode calculated for each segment	Corpus callosum showed a variety of diffusion abnormalities related to psychotic symptoms
(Pomarol-Clotet et al., 2010)	Sz	32 / 32	1.5T, 4 ROIs as seed regions for optimized tractography algorithm (Tractography was one of three imaging techniques used in this study)	WM abnormalities predominated in the anterior corpus callosum, implicating fibres projecting to the medial frontal cortex with convergent abnormality in the DLPFC.

There are still no standardized criteria for tractography studies and although there is a wide degree of variation in methodology amongst the studies reviewed in this chapter, the principal approaches are to measure FA in a specific region or to measure mean FA along a continuous WM tract. FA in a specific WM region can be measured by one of two approaches; entire WM fibre bundles are parcellated out and the FA of WM fibre tracts passing through at specific points is calculated or a specified ROI is drawn on a whole brain volume and FA is measured at this site. Tractography is an extension of the above technique and measures the degree of anisotropy between

neighbouring voxels in order to predict position of a tract. This technique relies on automated stepwise progression algorithms calculated by the degree of angulation between neighbouring voxels and strength of anisotropy. If there is a sharp turning angle or FA drops below a certain threshold, it is anatomically unlikely that fibres would continue in that particular direction and tracking is terminated but the threshold for turning angles varied between studies, from 50º (Miyata et al., 2007) to 10º (Zhou et al., 2008). Furthermore, consecutive fixed steps for track extension varied between 1mm (Nestor et al., 2008) and 0.5mm (Voineskos et al., 2010), with FA threshold varying between 0.26 (Magnotta et al., 2008) and 0.1 (Carpenter et al., 2008). Limitations of tractography arise when there are areas of crossing fibres or a high degree of branching, which cannot be effectively modelled using current techniques, leading to reduced confidence in the results obtained.

3.4.2 Tract Based Spatial Statistics Studies in Schizophrenia

Tract Based Spatial Statistics (TBSS) builds on the concept of tractography by comparing FA within a WM skeleton of the whole brain. The skeleton is formed of the core of WM tracts, where there is much higher probability of WM being present. There have been fewer studies using TBSS to investigate schizophrenia as this method of investigating FA in WM tracts has only been available since 2006 and was originally developed as a method of improved registration to avoid distortion by better alignment of FA images from multiple subjects (Smith et al., 2006).

The first TBSS study to be published in schizophrenia (Seal et al., 2007) reported lower FA in the external capsule, internal capsule and thalamus of patients with established schizophrenia compared to healthy controls. This was accompanied by higher radial diffusivity in the external capsule with no change in axial diffusivity. These components of diffusion can indicate pathology, with increased radial diffusivity suggesting increased movement of water in the horizontal direction as a result of more porous cell walls. There

was however, no indication of the chronicity or severity of illness in patients recruited to this study and subject numbers were small, with only 14 in each group.

Karlsgodt and colleagues published two studies (2008, 2009) using TBSS in a ROI study by using a mask for parcellating out the superior longitudinal fasciculus (SLF) for further analysis after processing of the whole brain WM skeleton was completed. In the first study, FA differences in 12 patients with schizophrenia and 17 healthy controls were investigated and FA of the left SLF correlated with verbal working memory as measured by the Modified Sternberg Item Recognition Task (Karlsgodt et al., 2008). In the second study, six ROIs had been defined apriori and these were parcellated out after analysis was run on the whole brain WM skeleton of each subject. The patient group consisted of 36 Ultra-High Risk for Psychosis (UHR) individuals who were clinically followed up at 6 and 15 months compared with 25 healthy controls. Main findings were a lower baseline FA in the UHR group in the SLF, an increased hippocampal FA with age in healthy subjects and at 15 month follow-up, lower FA in the hippocampus and inferior longitudinal fasciculus predicted decline in social function and a decrease in hippocampal volume in the UHR group (Karlsgodt et al., 2009).

Miyata et al. (2009) combined a whole brain FA analysis using TBSS with whole brain VBM analysis of grey matter, in a study which demonstrated direct association between two regional areas of FA reduction and multiple cortical and subcortical reductions in schizophrenia. However; it was difficult to ascertain which tracts were responsible for decreased FA in each TBSS cluster because of coarse DTI resolution.

A two part study by Camchong et al. (2009) used TBSS to investigate differences in white matter FA between monozygotic twin pairs, unaffected first-degree relatives of a schizophrenia cohort and healthy controls. FA values were more strongly correlated between MZ twin pairs than between randomly generated pairs in genu of corpus callosum, anterior cingulum and

forceps minor. In unaffected relatives, reduced FA in medial frontal white matter was demonstrated, suggesting that anatomical connectivity in medial prefrontal cortex is significantly heritable within MZ twin pairs, an important criterion in the development of an endophenotype. In addition, altered medial frontal white matter integrity found in relatives of schizophrenia patients suggests that reduced white matter integrity in medial frontal regions of the brain might be associated with the genetic liability to schizophrenia. In adolescent onset schizophrenia, which often follows a more severe course of illness than adult onset schizophrenia, TBSS analysis has shown that white matter FA increases around the time of illness onset but remains stable in healthy adolescents (Douaud et al., 2009). This pattern of white matter disease progression is clearly different from adults, which showed that white matter FA is reduced or unchanged at first episode of psychosis in adult onset schizophrenia.

3.5 Magnetisation Transfer Imaging Studies in schizophrenia

Few studies have used magnetization transfer imaging (MTI) to investigate schizophrenia. MTI should be able to reveal more subtle effects of schizophrenia on brain tissue, with MTI abnormalities explained by changes to the neuropil which consist primarily of dendrites, axons and synapses (Glantz and Lewis, 2000; Selemon and Goldman-Rakic, 1999). It is thought that the magnetization saturation capacity of brain tissue decreases in disease states, hence the magnetization transfer ratio (MTR) will decrease. MTR is not a quantitative value and does not reflect the absolute degree of saturation with a pulsed gradient in the tissue. A more detailed description of the basic principles of MTI have already been described in chapter 2.

The first published findings of MTI in schizophrenia by Foong et al. (2000a), reported reduced MTR in temporal lobe white matter of 25 chronic schizophrenia patients, compared with 30 healthy controls. When this analysis was repeated using whole brain VBM on the same group, MTR reductions were found predominantly in the fronto-temporal regions of the cortex extending into white matter only in the temporal lobes (Foong et al.,

2001). In a study of 30 first episode psychosis patients and controls, a VBM whole brain analysis showed reduced MTR bilaterally in the medial prefrontal cortex, insula and white matter incorporating the uncinate fasciculus in the patients in the absence of any volumetric differences between groups (Bagary et al., 2003). An earlier study using the thalamus as a region of interest revealed no volumetric or MTR differences between patients and controls (Bagary et al., 2002).

A small study investigating the hippocampus as a ROI and consisting of 14 schizophrenia patients and 14 controls (Kiefer et al., 2004) found no group differences in MTR or volume. Kubicki et al. (2005a) found widespread reduction in MTR of the corpus callosum, fornix, right internal capsule, and the superior occipito-frontal fasciculus bilaterally in a whole brain analysis of 21 patients with schizophrenia and 26 controls. Concurrent DTI scanning revealed that FA was also reduced in some of these tracts, suggesting that schizophrenia may cause abnormal coherence of fibre tracts and these abnormalities may be attributed to coincide with myelin/axonal disruption. Another study (Kalus et al., 2005) looked at the amygdala as a ROI and used DTI and MTI in addition to volumetric MRI. Although no difference in amygdala volumes were identified between 14 schizophrenia patients and controls, diffusion anisotropy and quantitative MTI parameters were reduced in the patient group although there was no significant difference in MTR between groups.

Using a higher resolution 3T scanner to perform whole brain MTI, no differences in MTR were found between 20 schizophrenia patients and 23 healthy controls (Anostik-Biernacka et al., 2006). Although there were trends for reduced MTR in the left superior temporal gyrus, right occipital cortex, and left periventricular white matter in patients, these were lost after correction for multiple comparisons.

A more recent study compared whole brain MTR and volume in a VBM analysis of 48 first episode psychosis patients and 47 healthy controls (Price

et al., 2010). In patients, MTR was reduced in right entorhinal cortex, fusiform, dentate and superior frontal gyri and in left superior frontal and inferior/rostral cingulate gyri, with volumetric differences between groups in fronto-temporal areas only. This suggests neuroaxonal and myelin changes are more extensive in patients than can be detected using conventional volumetric MRI.

Although findings from MTI studies of schizophrenia have varied, it appears that investigations of smaller, well defined ROIs did not find differences between patient and control groups, while studies comparing whole brain volumes generally found reduced MTR in patients. As no longitudinal MTR studies have been published, it is difficult to ascertain if MTR changes indicative of neuropathology accumulate over time with disease progression.

3.6 Imaging studies linking bipolar affective disorder and schizophrenia

Both bipolar affective disorder (BPAD) and schizophrenia have overlapping psychopathology and it is increasingly apparent that they share common genetic and neurochemical abnormalities (Lin and Mitchell, 2008). Some imaging studies have directly compared these two conditions to seek similarities in neuropathology which would support the hypothesis of psychosis being on a continuum with affective disorder.

Patients with first episode psychosis showed differences in GM volume at baseline and in their pattern of disease progression depending on whether they were found to have schizophrenia or affective disorder at follow-up. Initial differences and progressive changes in patients with affective disorder were confined to the subgenual cingulate, whereas patients with schizophrenia initially had widespread but progressively smaller volume changes (Koo et al., 2008). Progressive GM loss has also been described in the hippocampus, fusiform gyri and cerebellum of bipolar disorder patients in a longitudinal study (Moorhead et al., 2007). Just as medication effects of

clozapine and risperidone have been linked with increased cortical GM volume, patients treated with lithium have been shown to have increased GM volume, compared to bipolar patients on valproate and unmedicated controls who did not show GM volume changes over time (Lyoo et al., 2010). In a similar manner to schizophrenia, reduction in temporal lobe GM of bipolar patients correlated with intellectual function decline and number of relapses (Moorhead et al., 2007), with duration of illness demonstrated as being inversely correlated with total GM volume (Frey et al., 2008).

Decreased FA as a marker of compromised white matter integrity has been described, with the distribution of affected white matter tracts in BPAD over-lapping with those affected in schizophrenia. McIntosh and colleagues found that both bipolar and schizophrenia patients showed reduced FA in the uncinate fasciculus and anterior thalamic radiation in a whole brain VBM study (McIntosh et al., 2008a). Meanwhile, a region of interest analysis published several years earlier by the same group, found that both schizophrenia and bipolar disorder patients had reduced white matter density in the anterior limb of the internal capsule compared to their unaffected relatives (McIntosh et al., 2005). In a longitudinal study comparing change in bipolar and schizophrenia brain volumes, GM deficits were observed in lateral and medial frontal regions and bilateral posterior temporal lobe regions, with extensive losses over time in lateral fronto-temporal regions and left anterior cingulate gyrus in patients with schizophrenia. GM deficit in bipolar patients was however localized to bilateral inferior temporal gyri with additional loss over time observed only in the anterior cingulate cortex (Farrow et al., 2005). Therefore, GM volume differences probably predate the onset of symptoms and neurodegenerative GM volume loss is diagnosis-related. Research findings may be restricted because studies are diagnosis orientated rather than covering the broader remit of psychosis, which would include the affective disorders spectrum. Some structural differences include more pronounced global and regional volumetric deficits in schizophrenia, particularly in the thalamus, hippocampus, STG and volume increase in the third ventricle (Emsell and McDonald, 2009).

In a review of brain imaging studies in psychosis (Gur et al., 2007), the authors observed that studies rarely provided direct comparisons between different psychotic disorders using integrated investigation methods and there is a need to implement sufficiently powered studies if psychosis is to ever be deconstructed. With this in mind, future studies should be designed to include patients with various diagnoses in order to compare psychosis as a common symptom arising from different disease models.

3.7 Conclusions

The MRI studies reviewed in this chapter showed changes in brain volumes in patients with varying illness duration at various stages of disease and lend support to hypotheses of progressive neuropathology (Gur et al., 1998; Lieberman et al., 2001; Mathalon et al., 2001). As Weinberger and McClure (2002) commented, the 2% annual rate of GM volume loss and similarly the ventricular enlargement rate of 13% per year as reported by the latter study, is similar to the degree of change reported in Alzheimer's Disease but post-mortem brains of schizophrenia patients clearly do not show the same gross neuropathology. With a model of cumulative loss you would expect no brain tissue to be left in older schizophrenia patients if atrophy continued at such an alarming rate. This would suggest that there is an initial insult in early development that predisposes to schizophrenia but time of onset is variable. In summary, the neuropathological changes evidenced in the current literature include:

1. Ventricular enlargement
2. Cortical and deep GM volume loss
3. Loss of WM integrity

The longitudinal imaging studies that have been reviewed in this chapter demonstrate that schizophrenia is not purely a neurodevelopmental disorder but may be due to an accumulation of neuropathological changes. Similarly, the evidence for neurodegeneration is limited and not supported by post-mortem studies. More conceivable perhaps is a hypothesis of neurotoxicity, which suggests that processing of stimuli is different in a brain affected by

schizophrenia and due to cortical plasticity unique adaptations are made dependent on environmental exposure. Neuropathological changes therefore accumulate in a non-linear fashion and lead to variation between individuals. This may also explain why imaging studies of schizophrenia have shown such diverse findings and why the course of this disease is so heterogeneous.

4. METHODS AND STUDIES PERFORMED

4.1 Introduction

The five studies that comprise this thesis, investigate neurobiological abnormalities in patients with first episode psychosis and schizophrenia spectrum disorders. Using structural imaging techniques sensitive to subtle neuropathological changes, magnetic resonance imaging (MRI), magnetisation transfer imaging (MTI) and diffusion tensor imaging (DTI) were used to investigate brain tissue compartments. Optical coherence tomography (OCT) was used to study thickness of the unmyelinated retinal nerve fibre layer (RNFL) and I also investigated hue discrimination ability in schizophrenia as a possible screening tool for the disease. These findings were correlated with clinical and cognitive parameters to examine their possible utility in predicting severity of the condition and functional outcome.

Experiments were primarily designed to examine whether differences between patient and control groups might provide evidence to support either a neurodevelopmental or neurodegenerative explanation of schizophrenia. A first episode psychosis patient cohort was used in a cross-sectional study to look for the earliest signs of disease affecting white matter integrity which might provide evidence of a neurodevelopmental abnormality affecting myelination (chapter 5). A longitudinal study (chapter 7) was designed to track patients from first episode of psychosis, to look for structural brain changes occurring early on in the course of disease. It was predicted that grey matter volume loss suggesting neurodegeneration might be seen over time, whilst MTI would reflect more subtle structural changes occurring. The cross sectional study of oculomotor function and grey matter volume (chapter 9) also utilised a first episode patient cohort to investigate whether grey matter volume loss suggestive of neurodegeneration, has already occurred early in the disease. In a cross-sectional study involving patients with established schizophrenia or schizoaffective disorder (chapter 6), a novel method of imaging in schizophrenia was used to measure RNFL thickness

and neurodegeneration by directly visualising this structure. The cross-sectional study on hue discrimination and cognition (chapter 8) was designed to investigate the visual system at a functional level in patients with established schizophrenia or schizoaffective disorder. Comorbid hue discrimination and cognitive deficits in patients might suggest a neurodevelopmental abnormality along a common pathway.

The remainder of this chapter details the patient and control samples common to all studies and provides a hypothesis for the studies with a brief introduction to the methods used, in addition to a short description of the five studies I carried out. Each study is individually discussed in greater detail within chapters 5 to 9.

4.2 Study Subjects

Patients were recruited from the West London Mental Health Trust and the South West London and St George's Mental Health Trust. Permission to conduct all parts of the study were obtained from Merton, Sutton and Wandsworth, Riverside and Ealing, and The National Hospital for Neurology and Neurosurgery & Institute of Neurology Joint Research Ethics Committees. Consultant psychiatrists in all local CMHTs were requested to refer patients between the ages of 16 and 60 years of age, who were presenting to psychiatric services for the first time with psychosis and interested in research participation. Two clinical research nurses additionally visited in-patient wards on a regular basis to identify potential patients for inclusion to the study. All patients were recruited within 12 weeks of first episode psychosis onset.

Patients in all of the studies discussed in my thesis formed part of the larger West London First Episode Psychosis Longitudinal Study cohort. This cohort consisted of over 200 first episode psychosis patients with baseline structured clinical interview, neuropsychometry and oculomotor function testing, follow-up of clinical outcomes and neuropsychometry were continued over the next 5 year period. Studies have already been published from this

dataset describing the cognitive trajectory (Leeson et al., 2011) and social function outcomes (Barnes et al., 2008).

All subjects included in the studies described in my thesis had expressed an interest in participating in the neuroimaging part of the study. I contacted them by telephone to explain the scanning process and to discuss my study before booking them an appointment at the UCL Institute of Neurology, London. At the appointment, I explained the MRI process before taking written informed consent for the study. In addition I carried out a safety checklist screening tool, assessed handedness using the Annett scale (Annett, 1970) and performed a routine clinical neurological examination. All subjects were seen by me at both baseline and approximately 18 months later at follow-up, when visual function testing and optical coherence tomography (OCT) scanning were offered. Although there was some overlap between patients and controls used for the different studies, all collected material was from new data.

Controls from the West and South West London areas were recruited from a variety of sources including via advertisements on a website (www.gumtree.com), job centres, bus depots and a college of further education, some control subjects also became involved in the study via word of mouth. The main inclusion criteria were good physical and mental health; all suitable controls were offered neuroimaging, neuropsychometry and oculomotor function testing with repeat testing at follow-up after a mean of 18 months. Control participants were also offered visual function testing and optical coherence tomography (OCT) scanning as part of the follow-up appointment.

All participants had to meet the following exclusion criteria: previous head injury resulting in loss of consciousness, previous episode of psychiatric illness requiring treatment by a psychiatrist and drug or alcohol dependency. All participants gave written, informed consent and received an honorarium.

4.3 Clinical Diagnosis

All prospective patients were interviewed by a qualified psychiatric, clinical research nurse, trained in gathering information on medication, using a battery of rating scales and finding out detailed information about each patient's course of illness at baseline and at follow-up. Eligible patients were screened using the WHO Psychosis Screen (Jablensky et al., 1992) and excluded if disease criteria for the schizophrenia spectrum were unmet.

Diagnosis was ascertained using a structured interview, the diagnostic module of the Diagnostic Interview for Psychosis (DIP-DM) (Jablensky, 2000), including items from the Operational Criteria Checklist for Psychosis (OPCRIT) (McGuffin et al., 1991) and the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). A computerized algorithm generated diagnoses under DSM IIIR and ICD 10 classification systems and the DSM IIIR diagnoses were subsequently checked against DSM IV criteria by entering data into OPCRIT for Windows (http://sgdp.iop.kcl.ac.uk/opcrit/). Patients were reviewed and their case notes assessed by two experienced consultant psychiatrists at one year after inclusion into the study to confirm the clinical diagnosis.

4.4 Symptom Ratings and Clinical Assessments

Symptoms experienced by patients were assessed using the Scales for Assessment of Positive Symptoms (Andreasen, 1983) and Negative Symptoms (Andreasen, 1981), a clinician administered tool which consists of a semi-structured interview. Affective symptoms were measured with the Hamilton depression rating scale (HamD), an administered questionnaire consisting of 21 items, with a closed rating score of 1 to 5 for each item (Hamilton, 1960) and the Young Mania Rating Scale (Young et al., 1978), an 11 item questionnaire with a similar closed scoring system. Age of onset, duration of untreated psychosis and duration of illness were established using the Symptom Onset in Schizophrenia Inventory (Perkins et al., 2000). Handedness was assessed using the Annett scale (Annett, 1970) and criteria

for substance abuse and dependence established, using the Alcohol and Drug Use Scales (Drake et al., 1990).

4.5 Magnetic Resonance Imaging

In brief, all study participants underwent a series of magnetic resonance imaging (MRI) brain scans following completion of a standard MRI safety checklist. Volumetric MRI, magnetization transfer imaging (MTI) and diffusion tensor imaging (DTI) data were collected at baseline using a 1.5 Tesler scanner (GE, Milwaukee). The scanning process lasted approximately 60 minutes, with a short break while the head coil was changed over for the DTI sequence and pulsed cardiac gating applied. At the follow-up appointment approximately 18 months later, scanning sequences were repeated with exception of the DTI, in order to reduce the scanning time. Detailed MRI methodology and statistical analysis of the data obtained are described in the following chapters.

4.6 Neuropsychometry

A large, neuropsychometric test battery was administered to all participants at baseline, one year and three year follow-up by the research psychologists. Data relevant to studies described in later chapters of this thesis included measures of current and premorbid IQ, working memory, verbal learning and processing speed. Correlations between cognitive function and brain structure were sought.

Current full scale IQ was measured using the Weschler Adult Intelligence Scale (WAIS) composed of 14 sub-units, of which there are 7 performance IQ and 7 verbal IQ measures (Wechsler, 1997). An abbreviated form of the WAIS- III comprising subtests of information, arithmetic, block design and digit symbol has been validated for use in schizophrenia (Blyler et al., 2000) and was used in this study.

Estimated premorbid IQ was obtained using the National Adult Reading Test (NART), a reading list of 50 irregularly spelt words in the English language, with accuracy of pronunciation scored to give an estimate of premorbid IQ in native English speakers (Nelson and Willison, 1991).

Spatial working memory was measured using the computerised Cambridge Neuropsychological Test Automated Batteries (CANTAB), with subjects required to find a token by searching only once in each of a number of boxes without returning to the same box (Fray et al., 1996). Total errors were used as an index of working memory manipulation.

Verbal learning was measured using the Rey Auditory Verbal Learning Task (Rey, 1964), which required 15 nouns to be read aloud in five consecutive recall trials, an interference list was then presented and effects on immediate recall measured. A score was derived from the maximum number of words recalled from the list in the best of five trials.

Processing speed was measured using the digit symbol subtest of the WAIS. In this pen and paper task, participants were required to match as many digit-symbol pairs as possible within 90 seconds.

4.7 Visual Function Testing and Optical Coherence Tomography (OCT)

The visual testing battery consisted of measurements of visual acuity, visual fields, colour hue discrimination and optical coherence tomography (OCT). All tests were performed on both right and left eyes.

- **Visual acuity** testing required subjects to sit at a distance of 4m from a light box and read aloud progressively smaller and fainter letters from Sloan letter charts to measure contrast visual acuity.

- **Visual field** testing was performed using the automated Humphrey field analyzer HFA 2i, (Carl Zeiss, Meditec Inc. USA).

- **Colour vision** was assessed using the Farnsworth-Munsell 100 Hue test.

- **OCT scanning** was carried out by a neurologist trained to use the Stratus OCT3, (Carl Zeiss, Meditec Inc. USA) to measure retinal nerve fibre layer (RNFL) thickness and macula volume in both eyes.

4.8 Oculomotor Function

A more detailed description of the collection and analysis of oculomotor function is provided in chapter 6. In brief, eye tracking data were collected at baseline by a research psychologist trained in measuring eye movements with an Eyelink I eye tracker (SR-Research, Osgoode, Ontario). The right eye was sampled at 250Hz in all subjects.

4.9 Description of the Five Studies in this Thesis

1. Diffusion Tensor Imaging and Cognitive Correlations

This study examined differences in white matter (WM) tract integrity by using DTI to measure fractional anisotropy (FA) in first episode psychosis patients and matched healthy controls. A comparison of between-group FA was made using tract based spatial statistics (TBSS). Cognitive performance measures were compared between groups and their correlations with WM FA were investigated. The hypothesis that first episode schizophrenia patients have a lower FA than controls and worse cognitive performance in patients would be correlated to lower FA was tested.

2. Imaging of the Retinal Nerve Fibre Layer Thickness

This study investigated axonal integrity in schizophrenia using optical coherence tomography (OCT) to measure retinal nerve fibre layer (RNFL) thickness. Comparisons were made between patients with established

diagnoses of schizophrenia or schizoaffective disorder and healthy controls. The hypothesis that patients have a thinner RNFL than healthy controls due to disrupted axonal structure was tested.

3. A Follow-up Imaging Study Using MRI and MTI

Structural changes were investigated in this longitudinal imaging study, with patients recruited at first episode of psychosis and matched to a healthy control group. MRI and MTI were carried out at baseline and a mean of 18 months later. Changes in GM, WM and CSF volume were sought, in addition to GM and WM MTR changes. Changes in cognitive performance measures over this time frame were also investigated and correlated with imaging variables. The hypothesis was tested that in schizophrenia patients, GM volume loss would be accompanied by CSF volume increase, while GM and WM MTR would become increased over time.

4. Colour Hue Discrimination

The Farnsworth Munsell 100 Hue Colour Test was used to compare colour hue discrimination ability between patients with schizophrenia and healthy controls. The hypothesis that patients would perform worse than controls in colour hue discrimination was tested and correlations with measures of cognitive function were sought.

5. Oculomotor Function and Correlations with Grey Matter Volume

Oculomotor function was measured using an infra-red eye tracking device to look at smooth pursuit, antisaccade error rate and prosaccade latency. GM volume was measured using voxel-based morphometry in a first episode schizophrenia cohort and associations with oculomotor function measured. The hypothesis that oculomotor function is impaired in first episode schizophrenia and associated with reduced GM volume was tested.

5. An Investigation of White Matter Tract Integrity and Cognitive Correlations Using Tract Based Spatial Statistics

5.1 Introduction

The notion that schizophrenia may be due to “anatomical disruption of association fibre tracts” was initially suggested by Carl Wernicke. This hypothesis has since been reiterated with a biological model of schizophrenia describing a syndrome of disconnectivity, affecting white matter connections between cerebral cortical areas (Friston and Frith, 1995).

Neurological diseases that typically affect white matter development, appear to be associated with higher rates of schizophrenia-like psychosis, including metachromatic leukodystrophy (Merriam and Hegarty, 1993) and Niemann-Pick disease (Josephs et al., 2003) where psychosis occurs in 25 to 40% of cases. By contrast, multiple sclerosis is a disease of demyelination (where normally formed myelin is lost) and rates of psychosis are much lower, only occurring in up to 5% of cases (Feinstein et al., 1992). A review by Walterfang et al. (2005) concluded that diseases disrupting myelin formation appeared to be associated with higher risk of developing psychosis compared to diseases disrupting mature myelinated structures. Additionally, diffuse rather than discrete lesions affecting fronto-temporal areas, were more strongly associated with schizophrenia-like psychosis.

Imaging studies have consistently reported reduced cortical grey matter volume in patients with schizophrenia (Hazlett et al., 2008; Hulshoff Pol et al., 2002; van Haren et al., 2007) but white matter volume loss appears to be more subtle and has been less frequently reported (Bose et al., 2009; Okugawa et al., 2002; Price et al., 2006). There is certainly a lack of evidence for gross neurodegeneration from neuropathology studies (Weinberger and McClure, 2002). Gene expression studies investigating the dorsolateral prefrontal cortex (DLPFC) in schizophrenia describe a significant

decrease in the expression of myelin-related genes in oligodendrocytes, which supports the hypothesis for an underlying pathology of myelination occurring in schizophrenia (Hakak et al., 2001).

Diffusion tensor imaging (DTI) reflects tissue integrity and microstructure by quantifying the diffusion of water in a scalar value known as fractional anisotropy (FA) (Basser and Jones, 2002). Reduced FA reflects the degree of disruption of white matter integrity. If barriers to water molecules diffusing between parallel axons in white matter tracts are decreased as a result of pathology, FA decreases as the water molecules are less restricted and can move more freely in a perpendicular plane. (A detailed explanation of FA has been provided in chapter 2, section 2.5). With DTI data, maps can be constructed to reveal white matter FA of the whole brain and allows voxelwise comparisons of FA to be made between subjects. In schizophrenia, reduced FA has been reported even in the absence of any volume decrease (Lim et al., 1999); this is now a well-replicated finding (Kubicki et al., 2005a; Kubicki et al., 2007; Minami et al., 2003; Okugawa et al., 2005; Wang et al., 2003) and suggests that the neuropathology of schizophrenia may lie in a disorder of the myelin sheath.

DTI data can be analysed using tractography, which allows three dimensional reconstruction of white matter tracts by estimating the orientation of greatest diffusion between neighbouring voxels and predicting pathways between two or more seed points. Although not always anatomically correct, the most likely path of white matter tracts can be mapped using this method. Tractography appears to have greater sensitivity for detecting reduced FA in the corpus callosum compared to conventional FA mapping in the same region of interest (ROI), in schizophrenia (Kanaan et al., 2006). A tractography study of first episode psychosis (Price et al., 2007), described reduced FA in the genu and splenium of the corpus callosum, some of those study subjects overlap with the cohort described in this chapter.

When an apriori hypothesis is present, a specific region-of-interest can be investigated but problems arise with placement of seed points along with issues relating to the size, shape and number of ROIs selected (Kanaan et al., 2005). In schizophrenia there is diffuse and subtle white matter pathology, hence a global searching strategy using voxel-based approaches applied to DTI may be more appropriate. Tract Based Spatial Statistics (TBSS) (Smith et al., 2006) allows a fully automated comparison across whole brain white matter tracts in contrast to investigation of isolated tract reconstruction which is much slower and can be subject to operator error. TBSS registers all scans to a non-linear model to correct misinterpretation of residual alignments. A skeleton map consisting of the core of all white matter tracts is obtained; against which the study group's FA data are projected, the resulting "mean FA skeleton" is then subjected to voxel-wise cross-subject comparison.

TBSS has been used to investigate white matter pathology in neurological conditions such as motor neurone disease (Ciccarelli et al., 2009) and can identify localized abnormalities in preterm infants, even in the absence of focal lesions detectable using conventional MRI (Anjari et al., 2007). In schizophrenia, reduced white matter FA has been consistently reported by studies employing various techniques to analyse DTI data as described in reviews by Kanaan et al. (2005) and Kubicki et al. (2007). TBSS has already been used to demonstrate widespread WM FA reductions in chronic schizophrenia, particularly in fronto-temporal areas (Seal et al., 2007). Severe microstructural deficits in childhood onset schizophrenia have also been described, using TBSS to evidence reduced FA in multiple areas, including corticospinal/corticopontine tracts, superior thalamic radiations, left optic radiation, arcuate fasciculus, corpus callosum and brainstem (Douaud et al., 2007).

At onset of schizophrenia cognitive heterogeneity is reported, with a high proportion of patients already having undergone general cognitive decline (Joyce et al., 2005). Patients with established schizophrenia and cognitive

deficits have reduced white matter volume and larger lateral ventricles (Wexler et al., 2009). One DTI study (Lim et al., 2006) reported an association between higher FA and better verbal memory, attention and executive function in task relevant regions. Using TBSS in a ROI analysis, a positive correlation between working memory and FA in the left superior longitudinal fasciculus was reported (Karlsgodt et al., 2008). It would therefore appear reasonable to surmise that WM microstructural changes may be reflected by the cognitive deficits commonly seen in schizophrenia.

White matter maturation is the final stage of neurodevelopment and continues well into the third decade, WM tissue might therefore be more vulnerable in a psychotic illness where onset typically occurs in early adulthood. If TBSS was able to demonstrate subtle differences in WM between first episode psychosis (FE) patients and healthy controls, this would provide evidence of disruption in the final stage of neurodevelopment and loss of WM integrity occurring early in the course of illness. Objectives of this study were primarily to compare FA differences in white matter tracts of FE patients and healthy controls. Secondly, cognitive performance (processing speed, verbal learning, spatial working memory, current and premorbid IQ) and their associations with white matter FA were sought. It was therefore hypothesised that:

1. FE patients would have lower FA compared to controls.
2. FE patients would perform worse than controls on cognitive measures which would correlate with reduced FA.

5.2 Methods

5.2.1 Subjects

All patients recruited to this study formed part of the West London First Episode Psychosis Study cohort as described in chapter 4.

Thirty-two, right-handed FE patients (25 males, 7 females) and mean age 28.3 (range 16-49) years, participated in this study. Neuroimaging was performed within 12 weeks of first presentation to psychiatric services,

average duration of treatment with medication at time of imaging was 13 (range 0-27) weeks; with some patients prescribed medication by their primary care physicians prior to psychiatric referral. 26 patients were diagnosed with schizophrenia (SZ), 5 schizoaffective (SA) and 1 schizophreniform (SF) disorder. Diagnoses were subsequently confirmed 1 year later by patient interview and review of clinical notes by two consultant psychiatrists. The study was naturalistic with no restrictions on prescribed medication; at the time of scanning 31 patients had been prescribed second generation antipsychotics, 8 were additionally prescribed antidepressants and 1 a mood stabiliser.

Thirty-two, right-handed healthy subjects (17 males and 15 females), mean age 24.8 (range 16-35) years, were recruited as controls. Those with a previous psychiatric history or family history of psychiatric illness in first-degree relatives were excluded.

Exclusion criteria for all subjects were: a) history of neurological disease, b) previous head injury with loss of consciousness and c) a history of drug or alcohol dependence. This study was approved by the local Ethics Committees. All participants gave written informed consent obtained according to the Declaration of Helsinki and received an honorarium.

5.2.2 Clinical Assessment

In patients; positive, negative and disorganisation syndrome scores were calculated using the SAPS and SANS assessment tools (Andreasen, 1981; Andreasen, 1983). Inter-rater agreement (linearly weighted kappa) was assessed using a standard set of videotaped interviews. Using global subscale items, linearly weighted kappas of 0.76 for SAPS and 0.74 for SANS were achieved (Andreasen, 1990). Factor scores for positive, negative and disorganization symptoms were derived from these results.

5.2.3 Cognitive Assessment

Premorbid IQ was estimated using the Revised National Adult Reading Test (NART) (Nelson and Willison, 1991), shown to be valid in schizophrenia (Crawford et al., 1992; O'Carroll et al., 1992). Current IQ was measured using a short form of the WAIS III (Wechsler, 1997) validated for use in schizophrenia (Blyler et al., 2000), comprising of the Information, Arithmetic, Block Design and Digit Symbol subtests. The scaled digit symbol test scores were analyzed independently as a measure of information processing speed. In this pen and paper task, participants have to match as many digit-symbol pairs as possible within 90 seconds. A measure of working memory manipulation was obtained by the spatial working memory task (SWM) from the computerized CANTAB battery (Sahakian and Owen, 1992). This is a self-ordered search task measuring the ability to remember the location of previously found 'tokens' while searching for new tokens. An error occurs when a participant returns to the location where a token has already been found. The total errors score was used as an index of working memory manipulation. Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1995), a score was derived from the maximum number of words recalled from a list of 15 nouns in the best of five trials.

5.2.4 Magnetic Resonance Imaging Data Acquisition

MRI imaging was performed on a GE Signa 1.5T MRI scanner (General Electric, Milwaukee, WI, USA). Diffusion tensor imaging (DTI) for each subject was acquired with an 8-channel RF head coil and a single-shot echo planar imaging sequence. (TE=81.3ms, matrix=96x96, FoV=220x220mm, 60x2.3mm contiguous slices). Diffusion sensitizing gradients (b=1200s/mm^{-2}) were applied in 61 non-collinear directions (Cook et al., 2006), and seven images were acquired with no diffusion-weighting. Images were interpolated to a 128x128 matrix during reconstruction, yielding a final in-plane resolution of 1.72mm. To improve data quality, the acquisition was cardiac gated by pulse oximetry and head motion minimized with foam padding.

5.2.5 Image Processing

The diffusion weighted volumes were spatially aligned with a 12 parameter model to correct for subject motion and eddy current effects (Jenkinson et al., 2002). The diffusion tensors (Basser and Jones, 2002) were estimated using 'robust estimation of tensors by outlier rejection' (RESTORE) (Chang et al., 2005), which includes an algorithm for outlier rejection and is implemented in the Camino software package www.cs.ucl.ac.uk/research/medic/camino (Cook et al., 2006). Subjects whose images contained excessive motion or spike artifacts were rejected from the study; a rejection criterion of 5 or more artifacts per slice (>6.7%) was chosen in keeping with published reports (Chang et al., 2005). Spike artifacts were manually labeled as outliers to assist the RESTORE algorithm (Jackson et al., 2008). FA maps (Pierpaoli and Basser, 1996) were computed from the diffusion tensor using Camino.

FA maps were prepared for voxel-wise statistical analysis following the tract-based spatial statistics (TBSS) methodology (Smith et al., 2006) as described on the TBSS home page (www.fmrib.ox.ac.uk/fsl/tbss/index.html), using version 4.0.2 of the FSL software (www.fmrib.ox.ac.uk/fsl/). 1) Skull-stripped FA maps of all subjects were aligned to a template image using nonlinear registration (Rueckert 1999, www.doc.ic.ac.uk/~dr/software). 2) The aligned images were averaged and thinned to yield a group 'mean FA skeleton', then further thresholded at an FA value of 0.2 to represent the core of all white matter tracts common to the group. 3) Voxel values of each subject's FA map were projected onto the skeleton by searching for the local maxima along the perpendicular direction of the skeleton. 4) Voxel-wise statistical analysis was performed across the entire skeleton (see below). 5) White matter clusters of interest were anatomically located by overlaying the JHU (John Hopkins University) DTI-based white-matter atlas (http://cmrm.med.jhmi.edu) contained within the TBSS program.

5.2.6 Statistical Analysis

Chi-squared and independent samples t-tests were used to compare age, gender, cognitive measures and clinical ratings in patient and control groups.

Using the Randomise tool (www.fmrib.ox.ac.uk/fsl/randomise/index.html), a general linear model was applied to compute voxel-wise statistics and significant FA differences between patient and control groups were sought. Confound regressors of age and gender, were included in all analyses. The general linear model was also used to explore associations in regional FA variation and cognitive measures between groups. The resulting t-statistic maps were thresholded at t=3, with a cluster-wise significance level of $p<0.05$ as recommended on the TBSS homepage (www.fmrib.ox.ac.uk/fsl/tbss/index.html) and corrected at cluster level for multiple comparisons using permutation-based nonparametric inference (Hayasaka and Nichols, 2003).

5.3 Results

Patient and control groups were matched for age (t= -1.31, p=0.20) and gender (χ^2=3.39, p=0.07). Mean duration of untreated psychosis was 11.3 (sd 17.5) weeks but total duration of illness was an average of 30 (sd 39.3) weeks. Positive symptoms 0.67 (sd 0.26) were more prominent than negative 0.29 (sd 0.24) or disorganized symptoms 0.26 (sd 0.22).

5.3.1 Cognitive Measures

Cognitive data were available for 22 SZ patients, 4 SZ patients did not complete the test battery. SZ patients and controls had similar estimated premorbid IQ but SZ patients performed significantly worse in tasks measuring current IQ, processing speed, working memory and verbal learning (table 5.1).

	SZ (n=22)	Ctrl (n=32)	Comparison
Estimated premorbid IQ	100.3 (11.7)	105.7 (11.9)	t=1.85, df=62, p=0.07
Current IQ	94.8 (19.6)	110.6 (15.1)	t=3.62, df=62, p=0.001
Processing speed	6.4 (2.8)	10.2 (2.9)	t=5.31, df=62, p<0.001
Working memory	32.8 (15.2)	15.3 (16.1)	t=-4.47, df=62, p<0.001
Verbal learning	10.3 (2.1)	12.7 (2.2)	t=4.55, df=62 p<0.001

Table 5.1 Table of Cognitive Measures Comparing Schizophrenia Patients and Controls

Results displayed = mean (sd)

5.3.2 Mean FA differences

FE patients had significantly lower FA than controls. A lower FA was also seen in SZ patients but not in SA/SF patients compared to controls but as there were only 6 SA/SF subjects, no further analyses were run on this subgroup (table 5.2).

Groups	Mean FA (sd)	FA difference between pt and ctrls (95% CI)
FE patients (n=32)	5749.0 (374.7)	272.9 (84.7- 461.1); p<0.001
SZ (n=26)	5703.2 (373.1)	318.70 (119.8 – 517.6); p=0.02
SA/SF (n=6)	5947.4 (341.4)	74.53 (-262.6 – 411.6); p=0.64
Controls (n=32)	6021.93 (378.55)	

Table 5.2 Comparison of FA in Patients & Controls

Using TBSS, specific regions of reduced FA were identified corresponding to the right (t>3, p=0.04) and left (t>3, p=0.03) posterior thalamic radiations in FE patients (fig 5.1). When the TBSS analysis was repeated excluding the SA/SF patients, no regional FA differences were identified between SZ patients and controls.

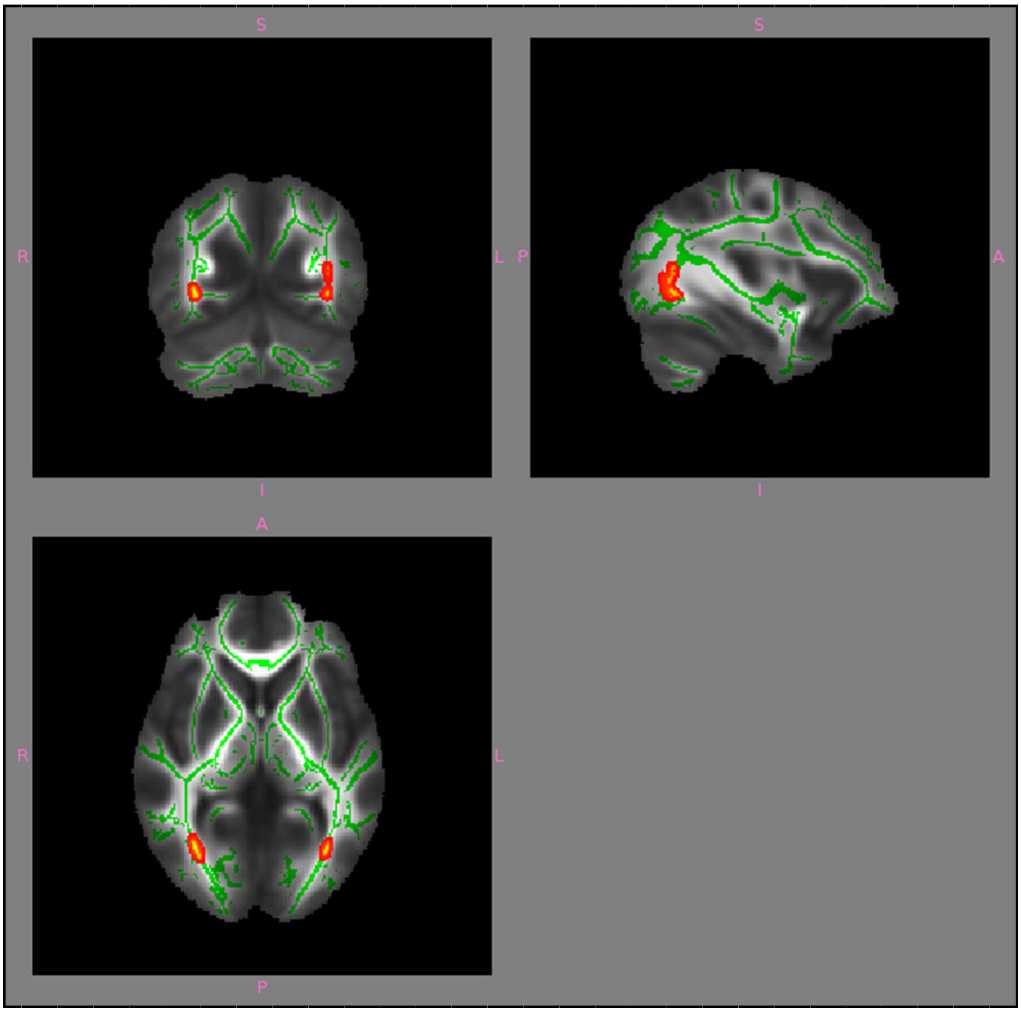


Figure 5.1 Regions of Posterior Thalamic Radiation with Reduced FA in First Episode Psychosis

(A=anterior, P=posterior, R=right, L=left, S=superior, I=inferior)

5.3.3 Cognitive measures and FA correlations

When FE patients and controls were considered as one group There was a positive correlation between mean FA and estimated premorbid IQ (r=0.28, df 55, p=0.04) but no significant correlation between mean FA and current IQ (r<-0.01, df 55, p=0.09), working memory (r=0.08, df 55, p=0.57), verbal learning (r=0.06, df 55, p=0.68) or processing speed (r=-0.03, df 55, p=0.84).

When SZ patients and controls were considered together, no correlations were found between mean FA and cognitive measures of estimated premorbid IQ (r=-0.13, df 50, p=0.25), current IQ (r=-0.13, df 50, p=0.34),

working memory (r=0.24, df 50, p=0.09), verbal learning (r=-0.11, df 50, p=0.43) or processing speed (r=-0.18, df 50, p=0.20).

Correlations between cognitive measures and mean FA in patients, showed premorbid IQ correlated with mean FA in FE patients (table 5.3). Mean FA in the SZ subgroup did not correlate with any cognitive measures.

	FE (r, df, p)	**SZ** (r, df, p)
Premorbid IQ	0.44, 24, 0.02	0.36, 18, 0.12
Current IQ	-0.19, 24, 0.36	0.18, 18, 0.44
Processing speed	0.13, 24, 0.54	0.49, 18, 0.84
Working memory	-0.63, 24, 0.76	0.04, 18, 0.88
Verbal learning	0.04, 24, 0.84	-0.03, 18, 0.91

Table 5.3 Correlations Between Mean FA & Cognitive Performance in Patients

FE=first episode, SZ=schizophrenia: results displayed=r, df, p value

Using TBSS, regional FA values did not correlate with cognitive measures of premorbid IQ (t>3, p=0.75), current IQ (t>3, p=0.79), WM (t>3, p=0.93), verbal learning (t>3, p=0.61) or processing speed (t>3, p=0.75) across both patient and control groups combined. Comparison between controls and FE patients showed group differences at a trend level (t>3, p=0.06), in the strength of association between FA and processing speed (fig 5.2) in an area of the left superior longitudinal fasciculus (SLF). No differences were seen between controls and FE patients for premorbid IQ (t>3, p=0.42), current IQ (t>3, p=0.79), working memory (t>3, p=0.49) or verbal learning (t>3, p=0.69).

When TBSS analysis was repeated excluding SA/SF patients, a significant difference between SZ patients and controls was seen in the strength of association between FA and processing speed (fig 5.3) in the left SLF (t>3, p=0.04) and right posterior thalamic radiation (PTR) (t>3, p=0.03). No significant group differences were found in the strength of association

between FA and estimated premorbid IQ (t>3, p=0.91), current IQ (t>3, p=0.42), working memory (t>3, p=0.87) or verbal learning (t>3, p=0.27).

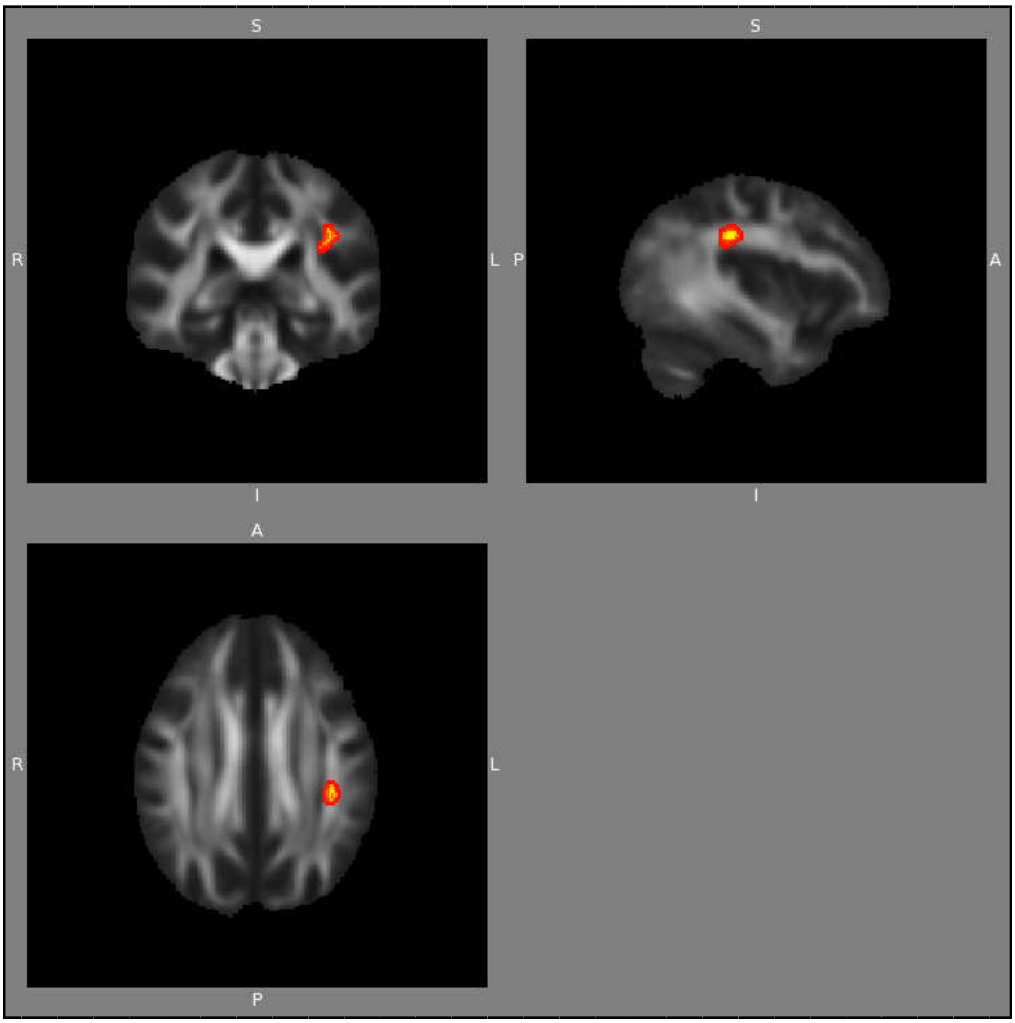


Figure 5.2 FA in the Left Superior Longitudinal Fasciculus is Associated with Processing Speed

(A=anterior, P=posterior, R=right, L=left, S=superior, I=inferior)

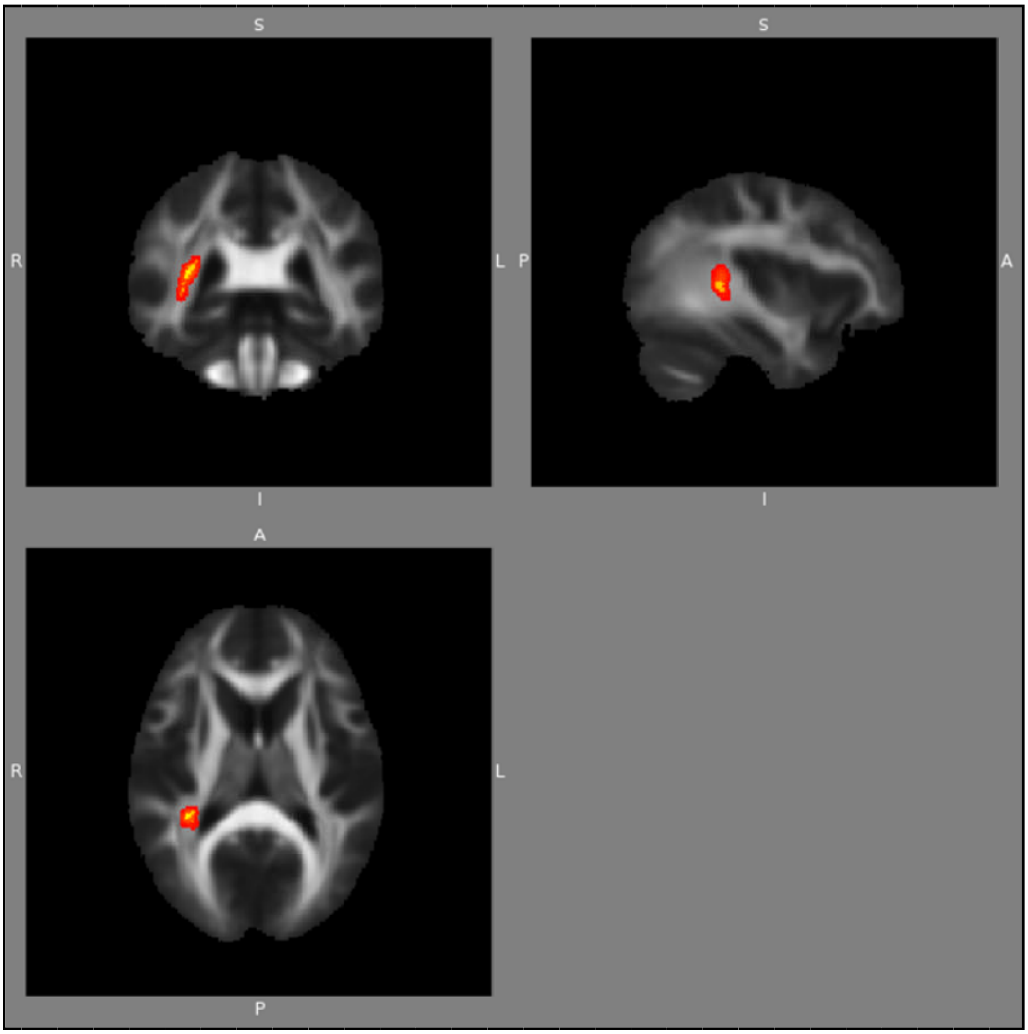


Figure 5.3 FA in the Right Posterior Thalamic Radiation is Associated with Processing Speed

(A=anterior, P=posterior, R=right, L=left, S=superior, I=inferior)

5.3.4 Post hoc analysis

To further investigate the regional FA differences associated with processing speed, a white matter mask of the 4 regions of interest (ROIs) were taken from the JHU atlas and used to extract mean FA values from the SLF and TR bilaterally in each subject.

	SLF FA mean (sd)		**PTR FA** mean (sd)	
Diagnosis	Left	Right	Left	Right
Controls n=32	4780.24 (270.49)	4820.25 (270.72)	4909.18 (380.86)	5537.33 (467.30)
Schizophrenia n=26	5737.00 (504.79)	4839.47 (257.60)	5040.24 (438.79)	5504.43 (447.27)

Table 5.4 Comparison of FA in Patients and Controls from Regions of Interest in Superior Longitudinal Fasciculi & Posterior Thalamic Radiations

SLF=superior longitudinal fasciculus, PTR=posterior thalamic radiation

FA in the left SLF of SZ patients was higher than that of controls (t=-8.12, df=-0.26, p<0.001) while FA in the right SLF and bilateral PTR were similar.

FA values obtained from the 4 ROIs of each participant were correlated with WAIS digit-symbol scores (as a measure of processing speed), while controlling for effects of age and gender. Processing speed and FA in the 4 ROIs were confirmed as normally distributed using the Kolmogorov-Smirnov test.

In controls, a positive correlation was found between FA in the right SLF and processing speed (r=0.37, p=0.04), suggesting faster processing speed corresponds to higher FA values. Correlations between FA and processing speed were seen at a trend level of significance in the left SLF (r=0.34, p=0.06) and right PTR (r=0.32, p=0.08).

In FE patients, there was a significant correlation between FA and working memory in the right SLF (table 5.5).

In SZ patients, a significant correlation was found between working memory and FA in the right SLF, suggesting that worse performance in the working memory task corresponded with lower FA. No other correlations were

observed between regional FA and cognitive measures in SZ patients (table 5.6).

	SLF		**PTR**	
Cognitive variable	Left	Right	Left	Right
Premorbid IQ	0.34, 0.09	0.22, 0.28	0.08, 0.70	0.11, 0.58
Current IQ	0.03, 0.87	0.19, 0.38	-0.01, 0.95	0.04, 0.83
Processing speed	0.29, 0.16	0.17, 0.41	0.12, 0.55	0.08, 0.71
Working memory	0.10, 0.64	-0.40. 0.04	0.12, 0.57	-0.06, 0.79
Verbal learning	-0.04, 0.85	-0.10, 0.61	0.06, 0.79	0.23, 0.25

Table 5.5 Correlations Between Cognitive Performance & FA in Four Regions of Interest in First Episode Patients

SLF=superior longitudinal fasciculus, PTR=posterior thalamic radius

Correlation co-efficient and p-values are shown, df=24

	SLF		**PTR**	
Cognitive variable	Left	Right	Left	Right
Premorbid IQ	0.33, 0.16	0.35, 0.14	0.04, 0.85	0.03, 0.89
Current IQ	0.07, 0.75	0.22, 0.35	-0.05, 0.84	0.02, 0.94
Processing speed	-0.14, 0.55	-0.07, 0.75	0.20, 0.41	0.24, 0.31
Working memory	-0.13, 0.60	-0.52, 0.02	0.11, 0.65	-0.06, 0.79
Verbal learning	-0.03, 0.92	0.29, 0.21	0.07, 0.79	0.21, 0.37

Table 5.6 Correlations Between Cognitive Performance & FA in Four Regions of Interest in Schizophrenia Patients

SLF=superior longitudinal fasciculus, PTR=posterior thalamic radius

Correlation co-efficient and p-values are shown, df=18

5.4 Discussion

Results of this study appear to support the hypothesis that FE patients have reduced white matter FA compared to healthy controls. Mean FA values (obtained as an average of all white matter tracts) were lower in both FE and SZ patients compared to controls; however, regional FA comparison using TBSS, identified bilateral areas of the PTR as having reduced FA in FE

patients only but not in the SZ subgroup. This may have been due to the smaller SZ patient group size having a weaker effect, therefore resulting in loss of what was already a subtle group effect. Other studies using TBSS to investigate FA in first episode schizophrenia have reported equivocal results. Lee and colleagues reported neither mean nor regional FA differences in patients compared to controls (Lee et al., 2012), while others have reported regional but not mean FA reduction (Chan et al., 2010;Tang et al., 2010) in FE patients.

The second hypothesis was partially supported by results of this study. As predicted SZ patients performed worse than controls on cognitive measures of current IQ, processing speed, working memory and verbal learning. Premorbid IQ estimates were similar in both groups indicating that cognitive decline had occurred following disease onset. Mean FA across all subjects correlated with premorbid IQ but not with current IQ, working memory, processing speed or verbal learning. When correlating regional FA differences, a trend for association was seen between processing speed and FA in FE patients. In SZ patients, FA in areas of the left SLF and right PTR correlated with processing speed.

When comparing mean FA, both FE and SZ patients had lower FA than healthy, matched controls. Using TBSS to investigate regional FA variation, reduced FA in FE patients was identified in an area of the occipital lobe where the PTR contributes most out of the multiple white matter tracts (including the inferior longitudinal fasciculus, posterior thalamic tract, fronto-occipital tract and optic radiations) that converge in this area.

In the post hoc analysis where FA values from 4 ROIs of SZ patients and controls were compared, FA was similar in the right SLF and PTR bilaterally; however FA values were higher in the left SLF of SZ patients than controls, this was an unexpected finding. Although tissue damage typically results in decreased FA, an apparent increase may occur where there is loss of tissue in one of the tracts intersecting a junction (Pierpaoli et al., 2001).

Paradoxically, increased FA is reflective of acute injury and is seen in axonal cytotoxic oedema (Chu et al., 2010); at an early stage of disease such as first episode schizophrenia, increased FA could indicate acute neuropathology.

Studies of cognitive function in schizophrenia tend to focus on fronto-temporal specific tasks in domains such as working memory, executive function and verbal fluency; however, no fronto-temporal areas of FA variation were identified in this study. The functional significance of FA measures have been demonstrated with verbal memory deficits in the uncinate fasciculus and executive function in the cingulate (Nestor et al., 2004), IQ, executive performance, verbal and visual memory (Kubicki et al., 2002). Karlsgodt et al. (2008) identified that aberrant fronto-parietal connectivity is implicated in first onset schizophrenia and worse verbal working memory is reflected by reduced FA in the SLF. In the current study, the SLF was also implicated but found to be associated with processing speed rather than verbal learning. Some higher cognitive tasks are speed dependent e.g. digit-symbol substitution task and multiple cognitive operations may be employed in any one task alone. The digit-symbol substitution task, (a measure of processing speed) is sensitive to various neuropsychiatric conditions (including schizophrenia) and highly correlated to overall cognitive performance (Dickinson et al., 2007); which may explain why processing speed correlated with regional FA variation in this study.

Across both FE patients and controls, mean FA showed a positive correlation with estimated premorbid IQ, so subjects with higher FA values had a higher premorbid IQ. When the group was reduced to SZ patients only, no correlation was identified, which suggests that the effect was too weak to be observed in a smaller group with fewer subjects.

In summary, mean FA is reduced in FE patients compared to healthy controls. Using TBSS to identify regional FA variation, a small area of the PTR in FE patients showed a lower FA than controls. FE patients performed worse than controls in cognitive tasks measuring current IQ, working

memory, processing speed and verbal learning; however, only processing speed and working memory correlated with FA. In controls and FE patients there was a trend for correlation between processing speed and FA in a small area of the left SLF. In controls and SZ patients, an association between processing speed and FA was identified in the left SLF and right PTR.

The current study provides evidence of disruption to white matter integrity in FE psychosis. This would support a neurodevelopmental explanation for schizophrenia and suggest problems with myelination are occurring early on in the illness. DTI studies concentrating on patients with established diagnoses of schizophrenia and schizoaffective disorder typically demonstrate more widespread FA changes. Although this is suggestive of progressive change in white matter microstructure, this can only be reliably determined by longitudinally designed studies. Considering there was evidence of early occipital lobe WM involvement, I decided to further investigate the visual system in schizophrenia.

6. A STUDY TO INVESTIGATE THE RETINAL NERVE FIBRE LAYER IN SCHIZOPHRENIA

6.1 Introduction

Schizophrenia lacks a clearly defined diagnostic pattern of neuropathological features, as discussed earlier (chapter 1). The best validated neuropathological abnormalities include possible reductions of neuronal density in the thalamus but not in the cerebral cortex or hippocampus; although in these structures, pyramidal neurons may have smaller bodies with reduced dendritic arborisation and spines (Harrison and Weinberger, 2005). Reductions in the number of some interneurons and in the number and function of oligodendrocytes, relevant to myelination and neuronal and synaptic integrity, complete the picture (Harrison and Weinberger, 2005). In keeping with these findings, cross-sectional neuroimaging studies have reported grey matter volume deficits in patients with chronic schizophrenia (Ellison-Wright and Bullmore, 2010; Shenton et al., 2001a), in those at first episode of psychosis (Bangalore et al., 2009), in prodromal illness (Pantelis et al., 2003) and even in those at high genetic risk of schizophrenia (Witthaus et al., 2009). Childhood onset schizophrenia also results in progressive grey matter volume loss in the early years of illness (Sporn et al., 2003). Compromised white matter integrity rather than white matter volume loss has been reported in first episode schizophrenia (Price et al., 2007) and in chronic schizophrenia (Kanaan et al., 2009a; Kubicki et al., 2002).

Longitudinal imaging studies (as discussed in chapter 3) have also suggested that in at least some patients there may be an accelerated loss of grey matter (GM) in comparison with healthy controls immediately after the first episode of schizophrenia (Sun et al., 2009b). Similar results of reduced GM volume have been documented in chronic schizophrenia (Brans et al., 2008b) and in those at ultra-high risk, i.e. even before the first episode of psychosis (Takahashi et al., 2010). The precise neuropathological changes

that underlie these neuroimaging findings however, have yet to be determined.

In-vivo visualization of the retinal nerve fibre layer (RNFL) can be achieved by optical coherence tomography (OCT), a non-invasive imaging technique originally developed to monitor retinal changes in glaucoma (Huang et al., 1991). This imaging technique opens a “window” into the brain by allowing measurement of RNFL thickness and macular volume (MV). The RNFL is composed of unmyelinated axons that traverse the retina, with the highest axonal density contained in the macula; these axons converge to form the optic nerve which is part of the central nervous system. OCT has recently been applied to the study of neurological conditions with diffuse and progressive brain pathology. RNFL thinning has been described in patients with mild cognitive impairment without dementia (Paquet et al., 2007) and is inversely correlated with the severity of cognitive impairment in patients with Alzheimer’s disease (Iseri et al., 2006). Even in the early stages of Alzheimer’s disease, RNFL thinning has been reported (Berisha et al., 2007). RFNL thickness is also reduced in patients with Parkinson’s disease in whom loss of dopaminergic neurons is known to occur, not only in the cortex and basal ganglia but also in the retinal ganglion cells (Altintas et al., 2007). Following an episode of optic neuritis, which commonly heralds the onset of multiple sclerosis (MS), OCT revealed a mean RNFL loss of 20% (Fisher et al., 2006; Pro et al., 2006; Sepulcre et al., 2007; Trip et al., 2005). Reduced RNFL thickness has also been described in MS patients without a history of optic neuritis and appears to correlate with MRI measures of brain atrophy in a condition which is characterized by inflammation, demyelination and axonal loss (Gordon-Lipkin et al., 2007; Siger et al., 2008). RNFL thickness has also been reported to be associated with cognitive performance of healthy individuals, particularly in those below 40yrs of age (van Koolwijk et al., 2009).

There is a growing body of evidence that early stage visual processing is impaired in schizophrenia, with well documented abnormalities of perceptual

organization (Butler and Javitt, 2005; Butler et al., 2006b; Butler and Javitt, 2005; Butler et al., 2006b) and visual evoked potentials (Mathalon et al., 2000). Additionally, electroretinogram (ERG) abnormalities which may represent a reduced number of rod photoreceptors or changes in inter-neuronal retinal architecture (a possible marker of dysfunctional neurodevelopment) have been described in unaffected offspring at genetic risk of schizophrenia (Hébert et al., 2009), in those with schizophrenia (Balogh et al., 2007; Warner et al., 1999) and in autism (Ritvo et al., 1988; Warner et al., 1999). No published OCT studies have reported using this technique to study the retina in patients with schizophrenia; although there is evidence of widespread, subtle neuropathological and cognitive abnormalities similar to those neurological diseases where OCT abnormalities have been reported.

The study described in this chapter of my thesis presents data from an investigation of RNFL thickness in patients with schizophrenia and schizoaffective disorder and explores the potential of using OCT to measure a possible disease biomarker.

6.2 Methods

6.2.1 Subjects

Patients recruited to this study were taken from the West London First Episode Psychosis cohort and had a firmly established diagnosis of schizophrenia or schizoaffective disorder. Full details of subject recruitment are available in chapter 4.

Forty-nine patients (37 males, 16 females), mean age 29.9yrs (range 18 to 56) with diagnoses of schizophrenia (38), or schizoaffective disorder (11) and median illness duration of 3.2 years (range 1.1 to 13.8) at the time of OCT scanning were recruited to this study. Forty patients were prescribed antipsychotics (39 atypical), 10 were prescribed antidepressants and 4 prescribed concurrent mood stabilising medication, 2 were prescribed mood stabilisers only, 1 night sedation only and 5 were unmedicated. The Schedule

for Assessment of Positive and Negative Symptoms (SAPS and SANS) (Andreasen, 1981; Andreasen, 1983) scores were available for a subset of 32 patients. Severity of negative symptoms ranged from 0 to 16 (mean 3.7) and positive symptoms ranged from 0 to 10 (mean 2).

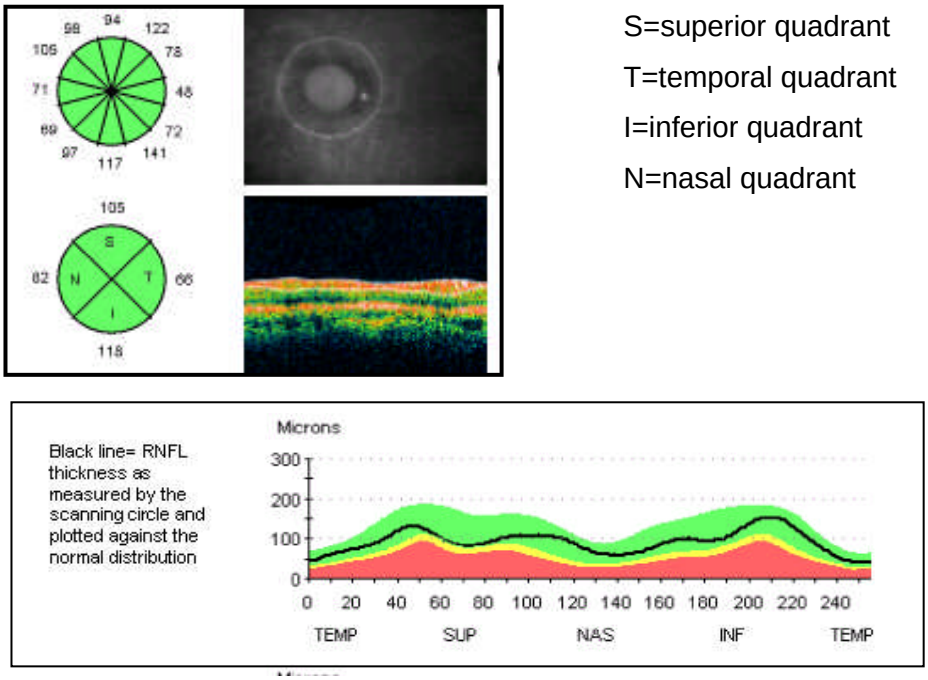
Forty healthy, control subjects, matched for age (mean 29.5yrs, range 20 to 46) and gender (25 males, 15 females), were recruited to this study for OCT imaging.

Exclusion criteria for all subjects were: a) concurrent or previous systemic disease (e.g. diabetes or autoimmune disease) that could involve the eyes, b) a neurological or ophthalmological condition (e.g. glaucoma) known to affect the visual pathway, c) severe myopia (>6.0D) as this may cause artefactual reduction in RNFL thickness (Kim et al., 2010) and difficulty in fixation, d) previous head injury with loss of consciousness, e) drug or alcohol dependence.

6.2.2 Optical Coherence Tomography

OCT produces a cross-sectional image of the retina by measuring the echo time delay of back-scattered infra-red light after it has passed into the eye and is bounced back using a low coherence light source and interferometer (Schuman et al., 1995). OCT data gathered for this study was obtained by a neurologist trained and experienced in using the Stratus 3 OCT device (fig 8.1) and software (Carl Zeiss Meditec Inc., California, USA) at UCL Institute of Neurology, London. RNFL images were acquired for each eye by taking a circumpapillary scan of 3.4mm diameter to effectively intercept all nerve fibres converging toward the optic disc while avoiding inaccurate measurements resulting from peripapillary atrophy (Schuman et al., 1996).

Figure 6.1 The Stratus 3 Optical Coherence Tomography Device



S=superior quadrant

T=temporal quadrant

I=inferior quadrant

N=nasal quadrant

Figure 6.2 The OCT Scanning Circle is Seen Around the Optic Nerve Head with a Cross-sectional View of the Retinal Nerve Fibre Layer Below

(red = RNFL thickness less than 2 sd below normal population, green = normal RNFL thickness)

6.2.3 Retinal Nerve Fibre Layer and Macular Volume Measures

The thickness of the RNFL quadrants (temporal, superior, nasal and inferior), were calculated by the OCT device software and represented by a graph indicating RNFL thickness at any point of the scanning circle (fig 8.2). Using the Fast RNFL protocol, the mean of three circular 3.4mm diameter scans, centred on the optic disc was used to express RNFL thickness. MV was measured in each eye by taking six consecutive radial linear scans centred on the fovea, to provide six sets of equally spaced and intersecting scans to obtain a single average value (using the fast macular thickness map scanning protocol). The Stratus OCT3 device assigns a signal strength out of 10 to all OCT images. These were rejected if signal strength was less than 7 or when the difference in signal strength between images for the two eyes was greater than 2 to ensure consistency in the quality of scans obtained. The OCT scanning in this study was carried out by a neurologist trained and experienced with carrying out the procedure on the Stratus OCT3.

6.2.4 Statistical analysis

Independent sample t-tests and chi-squared tests were used to compare age (normally distributed in patients and controls) and gender between groups. Relationships between patients and controls for whole retina and quadrant RNFL thickness and macular volume (MV) were investigated using linear regression with adjustment for age. In the patient group, linear regression analyses were used to investigate relationships between severity of illness duration, positive and negative symptoms with measures of RNFL thickness and MV in both eyes, while controlling for age. A computer-based statistical package (SPSS) was used throughout, with statistical significance reported at $p<0.05$.

A generalized linear mixed model (GLMM) approach was used to compare whole retina RNFL thickness, quadrant RNFL thickness and MV between the three groups (healthy controls, schizophrenia patients and schizoaffective disorder patients). Multilevel models were used to account for the fact that observations within each patient (i.e. right and left eyes) were not

independent, while also controlling for possible confounding effects of age, gender and disease duration (Laird and Ware, 1982). Where association was shown between eye and disease subtype, linear regression analysis was used to investigate the effect of disease subtype on each eye independently.

In the patient group, multiple linear regression analysis was used to investigate the relationship between severity of positive and negative symptoms with measures of RNFL thickness and MV in both eyes, while controlling for age and gender. Statistical significance was reported at $p<0.05$.

6.2.5 Power calculation

A power calculation was based on studies reporting subtle changes in RFNL thickness in the unaffected eyes of patients with MS due to subclinical axonal damage (Fisher et al., 2006). In order to detect a mean difference in RNFL thickness between groups of 9µm with standard deviation of +/-14µm and a standardized difference of 0.64, an estimated sample size of 38 patients and 38 controls would be needed to achieve an 80% probability of detecting differences between the two groups at a 5% significance level. Based on a study by Henderson et al (2008), a mean difference in MV of 0.27mm^3 between groups, would give a 70% probability of detecting a group difference at the 5% level of significance with a sample size of 38 patients and 38 controls.

6.3 Results

Patients and controls were matched for age ($t=0.27$, $df=85$, $p=0.79$) and gender ($\chi^2=0.27$, $p=0.36$). Across both patient and control groups combined, there was a weak negative correlation between age and RNFL thickness in the right ($r= -0.28$, $n=89$, $p=0.01$) and left ($r= -0.25$, $n=89$, $p=0.02$) eyes but not between age and MV, hence age was controlled for in all subsequent analyses. No correlations were found between gender and RNFL thickness or gender and MV.

6.3.1 RNFL and MV

Data collected for this study including RNFL, MV and illness duration in patients were confirmed as having a normal distribution according to Kolmogorov-Smirnov tests. Using linear regression analyses, whole retina and quadrant RNFL thickness, and MV were compared between patients and controls, there were no significant differences between groups for either right or left eyes (table 8.1). There were no significant differences between schizophrenia or schizoaffective disorder patient subgroups compared to controls for any of these measures.

6.3.2 Duration of illness

After adjusting for age, there was a significant correlation between longer duration of illness and smaller MV of the right ($r= -0.36$, $p=0.01$) and left eyes ($r= -0.36$, $p=0.01$). A correlation was also found between longer duration of illness and thinner RNFL in the left eye ($r= -0.28$, $p=0.05$), with a trend in the right ($r= -0.27$, $p=0.06$).

6.3.3 Symptom severity

There were no significant correlations between RNFL thickness and positive or negative symptom severity, but there was a negative correlation between severity of positive symptoms and right MV ($r= -0.39$, $p=0.03$) but not left MV ($r= -0.29$, $p=0.12$). This correlation was no longer significant when patients with ($n=13$) or without ($n=15$) positive symptoms were considered separately.

	Controls	Patients	Regression coefficients of retinal measures adjusted for age (95% CI)
Overall RNFL thickness (µm)	**Mean (sd)**	**Mean (sd)**	
Right eye	100.71 (10.08)	100.07 (11.61)	-0.64 (-5.28, 3.99) p=0.84
Left eye	101.24 (11.55)	98.80 (11.65)	-2.45 (-7.36, 2.47) p=0.35
Macular volume (mm^3)			
Right eye	6.81 (0.33)	6.86 (0.37)	0.05 (-0.19, 0.10) p=0.52
Left eye	6.91 (0.33)	6.92 (0.38)	0.01 (-0.16, 0.15) p=0.91
Temporal quadrant RFNL (µm)			
Right eye	70.63 (13.07)	67.00 (11.97)	-3.63 (-8.91, 1.66) p=0.17
Left eye	64.50 (9.56)	67.06 (10.45)	2.56 (-1.70, 6.82) p=0.23
Superior quadrant RNFL (µm)			
Right eye	128.03 (15.10)	125.18 (18.97)	-2.85 (-10.19, 4.50) p=0.47
Left eye	127.70 (14.00)	127.67 (18.03)	-0.03 (-6.95, 6.90) p=0.98
Nasal quadrant RNFL (µm)			
Right eye	81.53 (17.22)	84.47 (18.76)	2.94 (-4.72, 10.60) p=0.41
Left eye	83.17 (18.93)	76.59 (18.43)	-6.58 (-14.49, 1.32) p=0.11
Inferior quadrant RNFL (µm)			
Right eye	121.53 (15.53)	124.31 (17.13)	2.78 (-4.18, 9.75) p=0.42
Left eye	124.28 (15.39)	123.24 (19.58)	-1.03 (-8.58, 6.52) p=0.82

Table 6.1 Retinal Nerve Fibre Layer Thickness & Macular Volume Measures

	Unadjusted analysis		**Adjusted analysis**	
Whole Retina RNFL	Regression co-efficient (95% CI)	P value	Regression co-efficient (95% CI)	P value
Disease type: Control Schizophrenia Schizoaffective	 Ref -0.97 (-5.79, 3.85) -3.52 (-10.76, 3.73)	0.63	 Ref -0.78 (-5.58, 4.03) -1.93 (-9.32, 5.47)	0.86
Eye: left vs. right	-0.46 (-1.78, 0.86)	0.50	-0.46 (-1.78, 0.86)	0.50
Age: for each yr older	-0.38 (-0.66, -0.10)	0.008	-0.38 (-0.67, -0.08)	0.01
Sex: male vs. female	-2.72 (-7.54, 2.10)	0.27	-3.13 (-8.13, 1.87)	0.22
Disease duration: for each yr longer	-1.01 (-1.85, -0.16)	0.02	-	-
Temporal Quadrant RNFL				
Disease type: Control Schizophrenia Schizoaffective	 Ref -0.62 (-4.91, 3.68) -0.24 (-6.70, 6.21)	0.96	 Ref -1.33 (-5.76, 3.10) 0.68 (-6.14, 7.50)	0.79
Eye: left vs. right	-2.72 (-5.28, -0.16)	0.04	-2.72 (-5.28, -0.16)	0.04*
Age: for each yr older	-0.00 (-0.26, 0.26)	0.99	-0.01 (-0.29, 0.26)	0.92
Sex: male vs. female	2.66 (-1.61, 6.93)	0.22	3.19 (-1.42, 7.80)	0.18
Disease duration: for each yr longer	-0.65 (-1.37, 0.06)	0.07	-	-
Superior quadrant RNFL				
Disease type: Control Schizophrenia Schizoaffective	 Ref -1.09 (-8.02, 5.85) -2.64 (-13.06, 7.79)	0.87	 Ref -2.10 (-9.22, 5.01) 0.36 (-10.58, 11.31)	0.83
Eye: left vs. right	1.22 (-1.48, 3.93)	0.37	1.22 (-1.48, 3.93)	0.38
Age: for each yr older	-0.34 (-0.76, 0.07)	0.10	-0.36 (-0.81, 0.08)	0.11

Sex: male vs. female	2.09 (-4.86, 9.03)	0.56	2.52 (-4.89, 9.92)	0.51
Disease duration: for each yr longer	-1.75 (-3.00, -0.49)	0.006	-	-
Nasal quadrant RNFL				
Disease type: Control Schizophrenia schizoaffective	Ref 0.07 (-6.91, 7.05) -8.35 (-18.84, 2.14)	0.25	Ref -0.40 (-7.61, 6.82) -6.39 (-17.49, 4.72)	0.52
Eye: left vs. right	-3.60 (-7.56, 0.37)	0.08	-3.60 (-7.56, 0.37)	0.08
Age: for each yr older	-0.37 (-0.79, 0.05)	0.09	-0.29 (-0.74, 0.16)	0.21
Sex: male vs. female	1.73 (-5.36, 8.83)	0.63	0.45 (-7.06, 7.96)	0.91
Disease duration: for each yr longer	-1.19 (-2.36, -0.02)	0.05	-	-
Inferior quadrant RNFL				
Disease type: Control Schizophrenia schizoaffective	Ref 1.03 (-5.98, 8.05) 0.33 (-10.22, 10.87)	0.96	Ref 0.95 (-6.31, 8.20) 1.79 (-9.37, 12.94)	0.94
Eye: left vs. right	0.65 (-2.20, 3.51)	0.65	0.65 (-2.20, 3.51)	0.66
Age: for each yr older	-0.26 (-0.68, 0.16)	0.22	-0.28 (-0.73, 0.17)	0.23
Sex: male vs. female	-1.06 (-8.09, 5.97)	0.77	-1.24 (-8.79, 6.30)	0.75
Disease duration: for each yr longer	-0.65 (-1.95, 0.66)	0.33	-	-
Macular Volume				
Disease type: Control Schizophrenia schizoaffective	Ref 0.01 (-0.14, 0.16)	0.85	Ref 0.00 (-0.16, 0.16)	0.64

	0.07 (-0.16, 0.30)		0.11 (-0.13, 0.36)	
Eye: left vs. right	0.08 (0.05, 0.11)	<0.0001	0.08 (0.05, 0.11)	<0.0001**
Age: for each yr older	-0.00 (-0.01, 0.01)	0.46	-0.00 (-0.01, 0.01)	0.34
Sex: male vs. female	0.04 (-0.12, 0.19)	0.63	0.06 (-0.11, 0.22)	0.51
Disease duration: for each yr longer	-0.04 (-0.07, -0.01)	0.005	-	-

Table 6.2 Multi-level Analyses of Whole Retina and Quadrant RNFL and Macular Volume

* Quadrant RNFL thinner in left than right eye

**MV smaller in left than right eye but no evidence for interaction between eye and disease type (p=0.47).

6.4 Discussion

This study did not detect any statistically significant differences in the RNFL thickness or macular volume between patients and healthy controls. These negative findings suggest that in patients with schizophrenia or schizoaffective disorder there is no detectable loss of unmyelinated axons in the retina in the early years after disease onset. Based on average values from both eyes for means and standard deviations of the RNFL thickness of this study sample, a retrospective power calculation showed that at least 300 subjects would be required in each arm of the study to detect any significant differences between groups (if they were present), with 80% power at a 5% level of significance. It can therefore be concluded, that using the OCT measurements described, RNFL variations are too subtle to be of value as a clinically useful biological marker for schizophrenia.

Several factors (not mutually exclusive), may be contributing towards the negative results seen in this study. The most obvious limitation is low resolution, which may be inadequate to detect the subtle abnormalities that may be present in the early years of schizophrenia. Transverse resolution

can reach a maximum of 10µm in tissue and 15µm in air using the Stratus 3 OCT device (Fujimoto et al., 2004), hence sensitivity is too low to visualize individual axons typically 1 µm in diameter. This point has been made in a recent study (Naismith et al., 2009) where OCT detected RNFL thinning in optic neuritis in only 60% of cases and detection rates were lower in those with mild onset and good recovery. Newer technology using spectral domain OCT (e.g. the Cirrus HD-OCT device) can offer better axial resolution (5µm compared to 10µm), in addition to macular thickness measurement and a higher scanning speed (50x faster) than the Stratus 3 OCT device used in this study.

Results of this study also suggest that axonal damage may be less important than myelin abnormalities in explaining the frequently reported reductions in brain volume in schizophrenia. There is growing evidence for disruption of white matter integrity in the early stages of schizophrenia (Price et al., 2006; Price et al., 2007; Pérez-Iglesias et al., 2010), which lends support to this possibility. The negative findings are also in keeping with earlier studies published on patient samples overlapping with the one described here, that failed to demonstrate differences in cortical thickness between patients and controls using surface-based morphometry (Gutiérrez-Galve et al., 2010) and only fronto-temporal white matter volume loss in patients but no cortical changes using magnetization transfer imaging or volumetric MRI (Price et al., 2006).

Longer duration of illness was associated with decreased RNFL thickness and smaller MV but the significance of these correlations, given the normal range of RNFL thickness and MV, needs to be further investigated in a longitudinal study to specifically determine the effects of illness chronicity and identify the stage at which possible changes in RNFL and MV may occur. While the RNFL measures reflect axons, MV measures are thought to reflect neurons as the macula area of the retina contains the highest concentration of retinal ganglion cells (Sakata et al., 2009). The tentative association between severity of positive symptoms and MV also needs replicating in a

larger sample, as it may represent state-dependent abnormalities similar to that reported by a previous ERG study (Balogh et al., 2007) that described transient retinal changes (i.e. decreased amplitude of the α-wave indicative of altered early visual information processing); which during acute relapses correlated with the severity of positive symptoms and was attributed to state-dependent alterations in phospholipid metabolism and/or impaired dopaminergic transmission.

Finally, most of the patients (40 out of the 49) were prescribed atypical antipsychotic medication at the time of OCT scanning and it is impossible to exclude the potential neuroprotective effects of these drugs (Navari and Dazzan, 2009), which could have obscured any minor differences in RNFL between the groups. Despite the largely negative results of this exploratory study using OCT scanning in schizophrenia, there is a need for further OCT studies to replicate and further investigate our findings of RNFL thinning and decreased MV in patients with longer illness duration. A longitudinal study design would additionally be able to detect whether progressive retinal changes occur and whether these measures could be utilized as a trait or state marker for schizophrenia or schizoaffective disorder.

In this study, exploration of the beginning of the visual pathway demonstrated no RNFL thinning in schizophrenia patients. Neurodevelopmentally, both the RNFL and forebrain (which contain neurons involved in higher cognitive processes) are derived from the same embryonic origins of the prosencephalon. Any predisposing biological marker of schizophrenia might therefore be expected to lie in the RNFL, especially considering the many neuroimaging and cognitive studies that provide evidence of fronto-temporal deficits in schizophrenia. The next chapter describes a longitudinal imaging study designed to examine progressive structural brain changes and explores correlations with cognitive function occurring early in the course of illness.

7. A Longitudinal Study of First Episode Psychosis Using Magnetic Resonance and Magnetisation Transfer Imaging: Structural Brain Changes and Correlations with Cognitive Function

7.1 Introduction

Different forms of magnetic resonance imaging (MRI) have been utilised to measure brain volume changes over time in longitudinal studies of schizophrenia (as discussed in chapter 3). There are fewer first episode schizophrenia studies investigating brain changes early in the disease, presumably because of difficulties with recruitment. One longitudinal study following first episode schizophrenia patients over a 10 year period described ventricular enlargement occurring at variable rates of progression, with some patients exhibiting active structural changes only early in the illness or not at all after first episode, while others exhibited continuous ventricular changes spanning the decade (DeLisi and Hoff, 2004). Another longitudinal first episode study reported that temporal lobe volume loss is not progressive (DeLisi et al., 2005). Both these findings appear to be at odds with an earlier review (Shenton et al., 2001) and meta-analysis (Wright et al., 2000); one possible reason for this discrepancy would be the long follow-up duration with data collected from an early stage of the illness.

During the course of schizophrenia, volume decrease in cortical grey matter has been found to be particularly prominent in the prefrontal cortices and medial temporal areas (Lawrie and Abukmeil, 1998). Such structural changes may contribute to behaviours typically described as negative symptoms (Andreasen et al., 1995) in addition to a distinctive profile of cognitive deficits (Bilder et al., 1992). Early CT imaging studies by Johnstone and colleagues showed enlargement of the lateral ventricles (Johnstone et al., 1976) this has been a robust finding supported by both post-mortem neuropathology (Brown et al., 1986) and in-vivo MRI studies (Shenton et al., 2001). Timing of the

ventricular enlargement is unclear but may have relation to grey matter abnormalities which have been described in the prodromal phase of illness before first episode psychosis onset (Pantelis et al., 2005) and may also be present to a lesser extent in unaffected first degree relatives (McIntosh et al., 2004). There is also evidence that perinatal complications may contribute to an increased risk of psychotic illness in later life, presumably due to neuronal insult (Murray et al., 1992). In post-mortem neuropathology studies there is a lack of neurodegenerative lesions and no evidence of post-maturational brain injury (Arnold and Trojanowski, 1996). It therefore appears that aberrant neurodevelopment in fronto-temporal regions give rise to schizophrenia.

White matter volume loss has been described in published literature but the evidence is perhaps less convincing, a review of 193 studies by Wright and colleagues (Wright et al., 2000) described 1% loss of whole brain white matter but this magnitude of reported volumetric loss is close to the limit of detection by MRI (Steen et al., 2006). Loss of fronto-temporal white matter volume has been reported in first episode psychosis (Ho et al., 2003; Whitford et al., 2007b) suggesting that changes may occur early on in the disease. White matter volume loss has also been reported in patients with schizophrenia and their unaffected first degree relatives (McIntosh et al., 2005), indicative of a genetic trait. Others studies however, report no evidence of white matter volume changes, even with increasing duration of illness (Steen et al., 2006). A different hypothesis has proposed that it is the integrity of white matter fibre bundles that are affected in schizophrenia rather than a reduction of tissue volume (Friston and Frith, 1995). White matter integrity is quantifiable and measured as fractional anisotropy (FA) using diffusion tensor imaging (DTI) as discussed in chapter 2.

Magnetisation transfer imaging (MTI) is also believed to be able to identify tissue integrity and has been described in chapter 2. A reduced magnetisation transfer ratio (MTR) has been reported in the temporal lobe WM of patients with chronic schizophrenia (Foong et al., 2000a); while in first episode patients reduced MT in focal areas have been reported in the medial

pre-frontal cortex, insula and uncinate fasciculus with no evidence of atrophy (Bagary et al., 2003). A longitudinal MTI study of first episode patients (Price et al., 2010) described reduced MT in patients for all areas where volumetric differences between patient and control groups had been identified, suggesting that volume and MT measures are related.

Cognitive deficits are a well-recognised feature of schizophrenia (Keefe and Harvey, 2012) but fewer studies have investigated associations between cognitive function and brain tissue volume changes. Guttierez and colleagues described a significant association of premorbid IQ and IQ at disease onset with area of frontotemporal cortex, while working memory was associated with area of frontal cortex (Gutiérrez-Galve et al., 2010). Grey matter volume loss in the left inferior parietal and right middle temporal cortex has also been associated with deficits in attention (Wolf et al., 2008). A cross-sectional study found that subjective reports of poor working memory were associated with reduced frontal lobe volume (Garlinghouse et al., 2010).

The primary aim of this study was to investigate structural brain changes in the period immediately following first episode psychosis in patients who subsequently developed schizophrenia or schizoaffective disorder. A longitudinal design was employed and the following were measured:
1) Whole brain, CSF, grey and white matter volumes.
2) Magnetisation transfer ratio (MTR) of grey and white matter.
A secondary objective was to investigate if any identified areas of structural change were associated with cognitive performance.

7.2 Methods

Participants in this study were taken from the West London Longitudinal First Episode Psychosis study cohort as described in chapter 4.

7.2.1 Subjects

Nineteen patients (12 males, 7 females), mean age 31.1yrs (range 21 to 52) and 23 controls (13 males, 10 females), mean age 28.7yrs (range 18 to 46)

underwent baseline and follow-up MRI scanning. Average duration of treatment with medication at time of baseline imaging was 71 days (range 0 - 176). Fifteen patients had been prescribed an atypical antipsychotic (6 were additionally prescribed antidepressants and 2 were additionally prescribed benzodiazepines), 2 patients were prescribed typical antipsychotics while 2 were unmedicated. Diagnoses were confirmed by two consultant psychiatrists through patient interview and clinical information obtained from the medical notes. Twelve patients were diagnosed with schizophrenia and 7 with schizoaffective disorder.

All subjects returned for follow-up MRI scanning on the same 1.5T MRI scanner, in the NMR Unit, UCL Institute of Neurology, London. The original study protocol for a 3 year follow-up period had to be shortened due to planned replacement of the departmental scanner. As a result, the scanning interval was a mean of 1 year 8 months (sd 2 months) in controls and 1 year 10 months (sd 7 months) in patients.

7.2.2 Cognitive Assessment

Patients and controls underwent cognitive assessment (as described in chapter 4) at time of baseline MRI scanning, the same test battery was repeated at the time of follow-up MRI. Current IQ was measured using a short form of the Wexler Adult Intelligence Scale (WAIS III) comprising of the information, arithmetic, block design and digit symbol subtests (Wechsler, 1997). The digit symbol subtest scores were analyzed independently as a measure of information processing speed. A measure of working memory was obtained via the token search task using the computerized CANTAB battery (Sahakian and Owen, 1992). The “between error score” was used as an index of the ability to manipulate information in working memory. Verbal memory was assessed using the Rey Auditory Verbal Learning (RAVLT) (Lezak, 1995). Change in cognitive performance was obtained for each subject on each of the four measures (IQ, processing speed, working memory, verbal learning) by subtracting baseline scores from those obtained at follow-up.

Cognitive performance was compared between patient and control groups at baseline and follow-up, with change in performance compared using independent sample t-tests. At baseline, cognitive measures were available from 19 patients and 22 controls with 18 patients and 16 controls completing repeat cognitive testing at the time of their follow-up MRI and MTI.

7.2.3 Magnetic Resonance Imaging

MRI scans were obtained using a standard quadrature head coil on a GE Signa 1.5 Tesla scanner (General Electric, Milwaukee, WI), which underwent weekly quality-assessment checking. A preliminary sagittal localizing scan was acquired and used to check head position for the follow-up scan. High-resolution axial volumetric images were acquired using a 3-dimensional inversion-recovery prepared T1-weighted spoiled gradient recalled (SPGR) echo sequence generating 156 contiguous, 1.2mm axial slices (echo time [TE] 5ms, repetition time [TR] 14 ms, inversion time [TI] 450 ms, field of view [FOV] 31cm^2, 256 × 256 matrix, flip angle 20°). The 1.2 × 1.2 × 1.2mm voxel size at acquisition was determined by scan time constraints.

Axial magnetization transfer (MT) images were acquired using a 3D MT-prepared SPGR dual spin-echo-based MT sequence (TE 5ms, TR 23ms, 28 contiguous 5mm axial slices, 256 × 256 pixel image matrix, 31cm^2 FOV), two volumes with and without a saturation pulse were generated. The 1.2 × 1.2 × 1.2mm voxel size was again determined by scan time constraints.

7.2.4 Processing of Magnetic Resonance Imaging for Brain volumes

MRI scans were processed on a Sun workstation (Sun Microsystems, Santa Clara, CA). The FSL Brain extraction tool was used to remove voxels which might include non-brain tissue from the periphery from each subject (http://www.fmrib.ox.ac.uk/fsl/bet2/index.html). Image processing was performed using Statistical Parametric Mapping (SPM5; Wellcome Dept of Cognitive Neurology, Institute of Neurology, London, UK), running in Matlab 6.5 (The MathWorks, Inc., Natick, MA, USA). T1 weighted scans were segmented in native space to determine grey matter, white matter and CSF

voxels, http://www.fil.ion.ucl.ac.uk/spm/software/ was used to calculate the volume (in cm^3) of each tissue compartment, using the following command line *spm_volume –v SPM5 –f.*

7.2.5 Processing of Magnetisation Transfer Imaging Data

The proton-density weighted scans (MTI data) from baseline and follow-up were co-registered to the corresponding SPGR volume, with the SPGR at follow-up co-registered to the SPGR at baseline. The transformation determined was applied to the follow-up MTR so all volumes were in baseline SPGR space. Methods for processing of MTR data were the same as those described by Price et al. (2010).

MTR maps were created from the segmented MRI images and measures of peak MTR height, peak MT location and mean MTR obtained. Whole brain MTR maps were created pixel-by-pixel using the formula: $MTR = \{[M_o - M_s]/M_o\} \times 100$, where M_s was mean signal intensity with saturation pulse and M_o was mean signal intensity without saturation pulse.

7.2.6 Volumetric and MTR group comparisons

The SPGR volumes and MTR images were then segmented into grey and white matter masks and a “difference map” created for each subject in the grey and white matter, reflecting changes in tissue density between the two time points, calculated by subtracting the baseline from the follow-up image for each tissue class. This difference map was normalised to the MNI52 template using the optimized VBM method (Good et al., 2001b), modulated and smoothed with an 8mm FWHM Gaussian kernel to address residual registration errors and inter-individual variability to ensure normality of parametric statistics were met. As smoothing kernel size can affect results (Jones et al., 2005), an 8mm kernel was selected as only small group differences were expected.

7.2.7 Statistical Analysis

Differences in age, gender and scanning interval between patient and control groups were calculated.

Differences between patient and control groups were sought for grey matter, white matter and CSF volumes at both baseline and follow-up. Changes in each of the tissue compartments were calculated for patient and control groups, differences between groups were sought using independent sample t-tests.

Using SPM5 in the general linear framework, a multiple regression model was used to investigate changes over time in grey matter, white matter and CSF volumes across patient and control groups. Between group differences with and without the effect of time were investigated while controlling for confounding effects of age and gender.

Differences were sought between groups for change to grey and white matter volumes and MTR measures using a multiple regression model containing the following regressors: group, time to follow-up, gender, age and change in cognitive performance; with IQ, working memory, processing speed and verbal learning incorporated into separate design matrices. Results were corrected for multiple comparisons using family-wise error correction at a statistical significance of $p<0.05$ and statistical parametric maps depicting regions of significant difference were compared. Only clusters greater than 10 voxels in size were reported.

7.3 Results

Patients and controls were matched for age ($t= -1.26$, $df=40$, $p=0.21$), gender ($\chi^2=0.19$, $p=0.66$) and scanning interval ($t= -1.66$, $df=40$, $p=0.1$).

7.3.1 Brain Volumes

There were no significant differences in grey or white matter volumes between patient and control groups at baseline or follow-up but CSF volume was

greater in patients than controls at both baseline (t= -3.1, df=40, p=0.003) and follow-up (t= -2.9, df=40, p=0.006) as shown in table 7.1. Analysis of variance identified a significant effect of age (p=0.01) on CSF volume across both patients and controls. Across both groups, GM, WM and CSF volumes showed no significant change between baseline and follow up. Patients showed no significant change in GM, WM or CSF volumes between baseline and follow-up. Controls showed no significant change in GM or CSF volumes but a WM volume increase (t= -3.7, df=22, p=0.001) was identified over time.

Tissue	Group	Baseline	Follow-up	Change
Grey Matter	Pt	705.60 (72.93)	701.51 (68.72)	-4.09 (15.75)
	Ctrl	694.08 (74.36)	695.16 (76.03)	1.08 (11.22)
White Matter	Pt	470.37 (46.28)	468.72 (44.20)	-1.65 (12.71)
	Ctrl	446.64 (53.19)	449.50 (54.03)	2.86 (3.71)
CSF	Pt	370.71 (88.93)	372.56 (98.00)	1.85 (36.28)
	Ctrl	292.41 (72.60)	294.86 (74.30)	2.44 (16.95)

Table 7.1 Brain Tissue Volumes at Baseline, Follow-up & Change Over Time to Follow-up

mean volume (sd) cm^3

7.3.2 Volumetric group comparisons

VBM analysis showed that patients and controls had similar grey and white matter volumes at both baseline and follow-up. There were no significant changes in grey matter volume over time to follow-up, either between or across both groups; however WM volume increase over time was identified in 3 small areas across both groups (table 7.2, fig. 7.1).

Cluster size (voxels)	Max Talairach Co-ordinates (x, y, z)	Area
48	18, -22, 78	Right corticospinal tract
14	4, -8, 68	Right cerebral white matter
11	-22, 8, 68	Left cerebral white matter

Table 7.2 Cluster Sizes & Areas of White Matter Volume Increase in Patients & Control

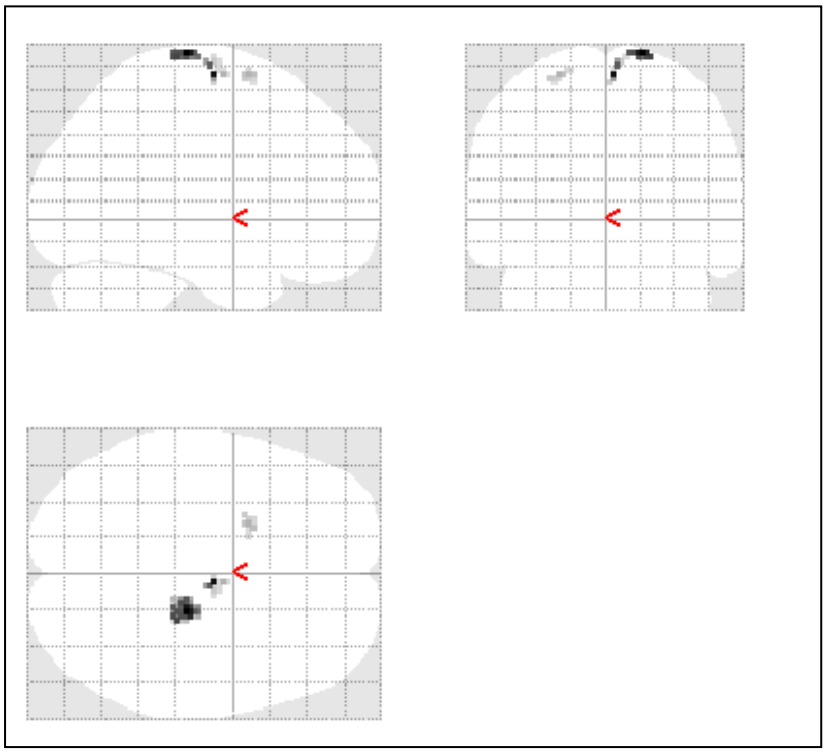


Figure 7.1 Position of Increased White Matter Areas in Patients and Controls

7.3.3 MTR group comparisons

Both patients and controls had similar grey and white matter MTR at baseline and follow-up time points. There were no changes in grey or white matter MTR over time to follow-up either between or across both patient and control groups.

7.3.4 Cognitive Performance

Estimated premorbid IQ was similar between patients and controls. At baseline, patients performed significantly worse than controls in measures of IQ (t=2, df=30.8, p=0.05), processing speed (t=2.4, df=39, p=0.001) and verbal learning (t=3, df=38, p< 0.001). At time of follow-up there were significant differences between groups in IQ (t=2.4, df=32, p=0.02), processing speed (t=5.3, df=32, p=0.001), and working memory (t= -2.1, df=32, p=0.04). Changes between baseline and time to follow-up in patients were a decrease in IQ and worse spatial working memory. Meanwhile, controls showed an increase in IQ and processing speed and better working memory (table 7.3). Differences between groups were statistically significant for changes from baseline to follow-up in IQ (t=2.6, df=32, p=0.01) and processing speed (t=3.6, df=32, p=0.001) but not spatial working memory or verbal learning.

	Pt base-line	**Pt follow-up**	**Pt change**	**Ctrl base-line**	**Ctrl follow-up**	**Ctrl change**
Premorbid IQ (NART)	104.5 (12.0)	-	-	109.0 (9.2)	-	-
Current IQ (WAIS)	103.3 (17.6)	101.2 (20.1)	-1.2 (19.5)	110.8 (11.8)	118.3 (17.6)	12.1 (12.2)
Processing speed (WAIS digit symbol)	7.5 (2.5)	7.5 (2.9)	0 (2.2)	10.3 (2.6)	13.0 (3.1)	2.7 (2.1)
Working memory (Token search)	33.5 (5.7)	34.2 (7.5)	0.1 (5.3)	30.7 (5.3)	29.4 (5.4)	-1.1 (7.0)
Verbal learning (REY AVLT)	11.2 (2.0)	12.6 (2.6)	1.2 (2.9)	13.4 (1.4)	13.9 (1.4)	0.3 (1.4)

Table 7.3 Cognitive Performance at Baseline and Follow-up, with Change Over Time to Follow-up in Patients & Controls

results shown = mean (sd)

*higher score = worse performance in working memory, in all other cognitive measures higher score = better performance

7.3.5 Imaging and Cognitive Correlations

VBM analysis found no effect of cognitive performance (IQ, processing speed or working memory) on GM or WM volumes either across patients and controls considered as a single group or when investigating between group differences. Across both groups there was an effect of time on white matter volume increase in the right corticospinal tract, while controlling for effects of age, gender and any of the three cognitive variables of IQ, processing speed or working memory (table 7.4). No between group differences were identified using this matrix.

Cognitive variable	Cluster size (voxels)	Max Talairach Co-ordinates (x, y, z)	Area
Current IQ	20	18, -22, 78	Right corticospinal tract
Processing speed (WAIS digit symbol)	23	18, -22, 78	Right corticospinal tract
Working memory (Token search)	23	18, -22, 78	Right corticospinal tract

Table 7.4 Cluster Sizes and Positions of White Matter Increase Over Time Seen Across Both Groups

7.4 Discussion

Results from this VBM study did not identify any significant change in grey matter volumes for patients or controls during a relatively short follow-up period of under 2 years. Small areas of white matter volume increase were observed across both groups over time in a distal region of the right corticospinal tract and in right and left superior frontal lobes. Patients had larger CSF volumes than controls at both baseline and follow-up time points.

The present study shows that patients at first episode of schizophrenia or schizoaffective disorder already appear to have larger CSF volumes than healthy controls. This finding lends support for the hypothesis that ventricular

dilatation is already present at first episode psychosis, as described by Vita and colleagues (Vita et al., 2006). There was no significant change in CSF volume over time but follow-up was fairly short in the current study. In a meta-analysis of longitudinal studies of lateral ventricular volume, progression of ventricular dilatation in first episode patients was similar to that of chronic patients (Kempton et al., 2010).

Diffuse single voxels of grey matter volume loss were seen across all subjects over time but there were no sizeable clusters of note were identified in this study where a short follow-up duration was utilised. These results appear to suggest that cortical grey matter volume may be changing very slowly in this study cohort. Other studies with short follow-up duration have reported grey matter volume reduction in first episode schizophrenia patients (Cahn et al., 2002) and identified this occurring within the neocortical grey matter of the fronto-temporal lobes (Nakamura et al., 2007). Meanwhile other authors reported no change in grey matter volume over time (Lieberman et al., 2001; Whitworth et al., 2005), with Whitworth and colleagues reporting higher between-subject variability in schizophrenia patients, which may represent morphologically visible disease progression in some patients but not in others. Price and colleagues reported a simultaneous increase and decrease of cortical grey matter in different areas with no overall volume change (Price et al., 2010), a finding which could be explained by the hypothesis that “some brain volume abnormalities may be reversible and possibly associated with a better illness course” (Schaufelberger et al., 2011). Patients in the current study were all well enough to be living in the community at time of follow-up, which suggests a “better illness course” this may explain why little overall change in cortical grey matter volume was observed.

Regions where white matter increases were identified in the current study appear to include the cortico-spinal tract and arcuate fibres. Although the regions of interest are small and superficial, they are unlikely to be an artefact due to stringent correction of scans during processing. In a large

longitudinal study of 96 schizophrenia patients, change in white matter volume during the scanning interval was reflected by an excessive WM increase in patients between 18 and 32 years of age (van Haren et al., 2008b). White matter maturation (myelination) continues into the third decade of life and is the final stage of neurodevelopment (Lebel and Beaulieu, 2011); therefore findings from the current study may have been driven by larger numbers of younger subjects.

In the current study, no grey or white matter MTR differences between patients and controls were found and there were no significant changes in MTR over time to follow-up. MTR decreases typically occur in states of pathological tissue damage and post-mortem studies suggest that MTR in white matter depends on myelin integrity (Schmierer et al., 2007). A study using MTI on a cohort of chronic schizophrenia patients reported MTR reductions of left inferior frontal, right superior occipital and right inferior temporal cortical regions and temporal lobe white matter (Foong et al., 2001). In a cohort of first episode schizophrenia patients, small areas of MTR reduction were reported in the prefrontal cortex, insular cortex, and uncinate fasciculus in the absence of volumetric differences between patients and controls (Bagary, 2003). In a first episode cohort study, Price et al. (2010) reported MTR decreases in fronto-temporal grey and white matter regions which were more extensive than the areas of volume reduction, concluding that MTI suggests neuroaxonal and myelin changes may be more extensive than what can be detected using conventional MRI. In a study comparing DTI and MTI abnormalities in schizophrenia, different findings using both imaging modalities were ascribed to different neuropathological processes of abnormal coherence or organization of the fiber tracts and disruption of myelin or axons (Kubicki et al., 2005a). The lack of MT findings in the current study was unexpected considering that this method should be more sensitive to detection of neuropathological changes than conventional MRI but our study sample of just 19 patients was relatively small and it has already been demonstrated that MTR and volumetric changes do not necessarily overlap as they appear to indicate different pathological processes.

In the current study, patients showed deficits in IQ, processing speed and working memory at baseline and lower IQ and slower processing speed at follow-up compared to controls. Cognitive performance was not associated with brain tissue volume changes over time. In a longer follow-up study (2 to 3 years) of first episode patients (Zipparo et al., 2008), mild improvement in IQ and visual memory were associated with progressive GM atrophy. Cognitive performance may therefore vary, depending on follow-up duration.

The final number of subjects reported in this study was much lower than the number originally recruited because of strict exclusion criteria and subjects unable to tolerate the MRI scanning. Time to follow-up was shorter than originally intended and perhaps not long enough for any significant neuropathology to manifest itself; considering the subtle changes (if any) reported in previous scanning studies.

This study demonstrates that structural brain changes such as ventricular dilatation are already present at disease onset. Additional absence of MTR or GM volume changes at this early stage of schizophrenia suggest that these events occur at a stage beyond the first 18 months of illness eventually resulting in cortical volume loss. The small increase in WM volume seen across both groups supports the hypothesis of myelination continuing well into adulthood but in schizophrenia this process could be aberrant at disease onset and reflected in measures of WM integrity rather than volume. The cognitive deficits demonstrated in schizophrenia do not appear to be related to any structural imaging findings. Returning to the earlier theme of vision in psychosis, the next study was designed to look at processes further along the visual pathway and investigated hue discrimination.

8. ABNORMAL HUE DISCRIMINATION IS RELATED TO COGNITIVE DEFICITS IN SCHIZOPHRENIA SPECTRUM DISORDERS

8.1 Introduction

Visual information is transmitted from the retinal nerve fibre layer (RNFL) through the optic nerve. Most optic nerve axons terminate in the lateral geniculate nucleus (LGN) of the thalamus, with the optic radiation continuing in a posterolateral direction to the occipital cortex (Ellis, 1992). From the LGN there are two main routes into the primary visual cortex (V1). The magnocellular 'M pathway' carries information about luminance contrast and movement discrimination to the visual cortex (Perry and Cowey, 1981), while parvocellular 'P pathway' (Merigan and Maunsell, 1993) carries information about chromatic (colour) vision, central acuity and fine stereopsis to the visual cortex (Schiller et al., 1990). From the visual cortex the M pathway continues in the dorsal stream projection to the parietal cortex and is involved in attentional processes - the so-called 'where pathway'. This is in contrast to the P pathway which continues as the ventral stream to the temporal lobe association cortex contributing to object and face recognition - the so-called 'what pathway'. The M and P pathways also interact with each other; for example the P pathway is under attentional control via inputs from the M pathway as well as the frontal cortex (Butler et al., 2008).

In a study by Phillipson and Harris (1985), over 80% of patients with probable schizophrenia reported visual distortions with subjective difficulty in perceiving brightness, motion and/or colour compared to 27% of healthy comparison subjects. These abnormalities appeared linked to the development of visual hallucinations, with nearly half the patients reporting improvement in visual distortions following treatment with antipsychotic medication.

Precise assessment of visual processing in schizophrenia has been mainly investigated using “masking” paradigms where a target stimulus is quickly followed (backward masking) or proceeded (forward masking) by another stimulus or “mask” that overlaps or surrounds the target stimulus. Backward masking paradigms in particular, have demonstrated larger and more prolonged masking effects (i.e. greater difficulty in identifying the target stimulus) in schizophrenia patients than controls (Green et al., 1999). Backward masking effects correlate with poor premorbid social functioning and negative symptoms of schizophrenia as described in a review by Green et al. (2011) but not with severity of psychosis or positive symptoms (Slaghuis and Bakker, 1995). Masking abnormalities have also been observed in unmedicated patients (Butler et al., 1996) and in unaffected siblings (Green et al., 2006), suggesting that they may be a marker of vulnerability to schizophrenia.

Masking effects appear to originate at a stage of processing beyond basic sensory input, and M pathway alterations are thought to explain these deficits in schizophrenia (Schechter et al., 2003; Green et al., 2011). Using masks that separately biased activation towards either the P (using colour contrast) or M (using very low luminance) pathways, Schechter et al (2003) found evidence of impaired M but not P pathways in schizophrenia. Furthermore, as these deficits correlated with negative symptoms, they suggested that it is impaired M pathway functioning that is related to poor outcome.

8.1.1 Colour vision in schizophrenia

Chromatic vision, a visual function mainly subserved by the P pathway has received less attention in schizophrenia, despite deficits having been reported several decades ago by Young (1974). The finding that retinal dopamine is involved in a number of visual functions, including chromatic vision, and that patients with reduced dopamine neurotransmission, as in Parkinson’s disease, had deficits in colour discrimination in the blue-yellow hue-specific axis (Desai et al., 1997; Haug et al., 1997), generated further

interest, the hypothesis being that abnormal intrinsic or medication related dopamine function may be detectable at the level of the retina.

Early studies failed to show that antipsychotic medication affected colour vision (Gagrat, 1979; Haug, 1997). A later, more detailed study (Shuwairi et al., 2002) which used 5 different measures of hue discrimination with variable cognitive requirements reported that medicated, male schizophrenia patients made more errors than controls across all colour hues. These deficits, which were general and non-specific to the blue-yellow axis suggested that abnormal hue discrimination in schizophrenia is unrelated to dopamine function. It was concluded that these deficits were more likely to reflect poor attention and fatigue in patients.

The current study had two aims: 1) to determine whether hue discrimination is impaired in patients with schizophrenia spectrum disorder compared to healthy controls with a larger sample sizes than previous studies; 2) to investigate the relationship between hue discrimination and cognitive performance.

8.2 Methods

8.2.1 Subjects

All subjects were part of The West London Longitudinal First Episode Psychosis Study and had responded to a written invitation and follow-up telephone call.

Exclusion criteria for all participants were: i) medical history of neurological disease or systemic medical condition that might affect the eyes (e.g. diabetes or hypertension), ii) previous head injury with loss of consciousness, iii) a history of drug or alcohol dependence, iv) abnormal findings on ophthalmological screening tests (Sloan Letter Chart assessment of visual acuity, visual field assessment and visualisation of the retina), v) history of achromatopsia.

8.2.2 Patients

Forty-six schizophrenia spectrum disorder patients (34 males, 12 females), mean age 30yrs (range 18 to 56) were included in this study. Thirty-six had a diagnosis of schizophrenia and 10 of schizoaffective disorder; all patients were analysed as a single group. At the time of this study, thirty-five patients were prescribed atypical and two prescribed typical antipsychotic medication, one was prescribed a mood-stabiliser plus an antidepressant; eight patients were not taking medication.

Symptom type and severity were assessed in patients at the time of recruitment to the present study using the Scales for the Assessment of Positive Symptoms (Andreasen, 1983) and Negative Symptoms (Andreasen, 1981). Scores for the three syndromes of schizophrenia (Liddle & Barnes, 1990) were calculated and expressed as the ratio of the maximum possible score. Symptoms scores were available for a subset of 33 patients: of these 15 patients had no symptoms, 14 had positive symptoms with a mean factor score of 0.13 (range 0 to 0.6), 13 patients had negative symptoms (of whom nine also had positive symptoms) with a mean factor score of 0.2 (range 0 to 0.8) and three had disorganisation symptoms (in addition to negative and/or positive symptoms), mean factor score of 0.02 (range 0 to 0.3).

8.2.3 Controls

Thirty-nine healthy controls, mean age 29yrs (range 20 to 46), 24 males and 15 females were recruited. Controls were matched to patients for age ($t=0.09$, $df=83$, $p=0.93$) and gender ($\chi^2=0.22$, $p=0.25$).

8.2.4 Colour hue discrimination task

Hue discrimination was assessed in all subjects, using the Farnsworth-Munsell 100-Hue Colour Test (FMHH) (Farnsworth, 1943). The FMHH is recognized as the “gold standard” hue discrimination test and is widely used in industrial and clinical settings. The test consists of 85 colour caps of incremental hue variation split between four trays (fig. 8.1). Subjects were

instructed to line up the caps in a consistent colour continuum, always seeking the hue closest to the one just matched. The two end points of each tray were indicated by fixed colour caps and all four trays completed in consecutive order. The right eye was always tested first and an eye patch was worn contralateral to the eye being tested.

Figure 8.1 The Farnsworth Munsell Hundred Hue Colour Test

An error score was generated by the FMHH computerized scoring system for each of the four trays in right and left eyes. Differences in performance between trays 1 and 4 were calculated for both eyes and used as a surrogate marker of attention, with a greater difference in the left than the right eye taken to indicate reduced attention during the second half of the task.

For each of the 4 trays, a score was calculated using results averaged from both eyes for each subject. A total error score (TES) was obtained using the FMHH computerized scoring system incorporating results from all 4 trays to provide a marker of hue discrimination performance. Square root of TES (√TES) was used in all subsequent analyses as it follows a normal distribution (Farnsworth, 1943).

8.2.5 Cognitive Assessment

Thirty-one patients and 20 controls completed a cognitive battery measuring estimated premorbid IQ (National Adult Reading Test) (Nelson, 2013), current IQ (four subtests version of the Weschler Adult Intelligence Scale III) (Blyler et al., 2000), spatial working memory (token search task from the CANTAB battery) (Sahakian and Owen, 1992), verbal learning (Rey Auditory Verbal Learning Test) (Rey, 1964) and processing speed (digit symbol test) (Wechsler, 1981).

8.2.6 Statistical analysis

An independent samples t-test of √TES values was used to compare hue discrimination between patient and control groups. Linear regression was used to examine effects of group, age and gender for each of the 4 trays.

As a surrogate marker of sustained attention, difference in scores for trays 1 and 4 were calculated for both eyes and differences between patient and control groups sought using a paired t-test.

Correlations between hue discrimination and symptom severity as indicated by three symptom clusters (positive, negative and disorganisation) were investigated using linear regression.

Partial correlations were sought between hue discrimination and the cognitive variables of premorbid IQ, current IQ, spatial working memory (total errors), verbal learning (maximum number of words recalled over 5 attempts) and information processing speed, while controlling for age and gender.

8.3 Results

8.3.1 Colour hue discrimination

Linear regression analyses showed no effect of age or gender on hue discrimination. There was a significant effect of group across all colour hues (table 8.1). Patients performed worse than controls on all four trays of the

FMHH, indicating impaired hue discrimination across all colour spectra (table 8.2).

	Group	**Age**	**Gender**
Tray 1	β=0.38, p<0.001	β=-0.10, p=0.32	β=0.01, p=0.96
Tray 2	β=0.38, p<0.001	β=-0.10, p=0.31	β=0.07, p=0.52
Tray 3	β=0.38, p<0.001	β=-0.08, p=0.42	β=0.15, p=0.13
Tray 4	β=0.31, p=0.003	β=-0.19, p=0.08	β=0.11, p=0.30
√TES	β=0.45, p<0.001	β=-0.09, p=0.38	β=0.12, p=0.90

Table 8.1 Results of linear regression showing a significant effect of group on hue discrimination across all 4 trays

	Patients Mean (sd)	**Controls** Mean (sd)	**Significance**
Tray 1	69.67 (22.02)	55.62 (9.92)	t=3.89, df=64.74, p<0.001
Tray 2	85.13 (26.19)	67.51 (12.35)	t=4.06, df=66.30, p<0.001
Tray 3	85.39 (27.16)	66.33 (14.22)	t=4.14, df=70.13, p<0.001
Tray 4	76.30 (25.48)	62.13 (13.46)	t=3.27, df=70.45, p=0.002
√TES	11.86	8.78	t=4.54, df=88.40, p<0.001

Table 8.2 Comparison of FMHH scores between patients and controls
Higher score indicates worse performance

8.3.2 Attention

Differences between patient and control groups were similar for hue discrimination between trays 1 and 4, for both right (t=0.26, df=64.66, p=0.80) and left (t= -0.33, df=83, p=0.74) eyes, suggesting that attention was maintained throughout the testing.

8.3.3 Hue Discrimination and Symptom severity

The severity of positive, negative and disorganisation symptoms were unrelated to hue discrimination ability in patients (table 8.3).

Symptoms	Mean (sd)	Correlation
Positive	0.13 (0.18)	β= 0.19, p= 0.46
Negative	0.20 (0.30)	β= -0.20, p= 0.44
Disorganised	0.02 (0.08)	β= 0.22, p= 0.27

Table 8.3 Correlation of hue discrimination with symptom severity in patients

8.3.4 Cognitive Performance

Estimated premorbid IQ (p=0.09) and spatial working memory scores (p=0.44) were similar between patients and controls but patients performed worse than controls in tests of current IQ (p=0.001) and verbal learning (p<0.001). Speed of information processing (p=0.06) was slower in patients at a trend level of significance (table 8.4).

	Patients mean (sd)	**Controls** mean (sd)	**Significance**
Premorbid IQ	102.77 (11.35)	107.35 (7.37)	t=1.75, df=49 p=0.09
Current IQ	98.48 (19.94)	118.20 (18.86)	t=3.52, df=49 p=0.001
Working memory[a]	31.90 (8.96)	30.10 (6.46)	t=-0.78, df=49 p=0.44
Verbal learning	11.32 (2.83)	13.85 (1.53)	t=3.65, df=49 p=<0.001
Processing speed	9.26 (8.30)	13.55 (7.20)	t=1.9, df=49 p=0.06

Table 8.4 Comparison of Cognitive Performance in Patient and Control Groups

[a]higher score = worse performance

Worse hue discrimination was associated with lower premorbid IQ in both groups. There were no significant correlations between hue discrimination and cognition in controls but in patients, worse hue discrimination was associated with lower premorbid IQ, significantly worse spatial working memory and verbal learning (table 8.5).

	All subjects	Patients	Controls
Premorbid IQ	**-0.51, p<0.001**	**-0.48, p=0.009**	-0.46, p=0.05
Current IQ	**-0.42, p=0.003**	-0.34, 0=0.07	-0.36, p=0.15
Spatial working memory[a]	**0.34, p=0.02**	**0.46, p=0.01**	-0.17, p=0.50
Verbal learning	**-0.54, p<0.001**	**-0.51, p=0.004**	-0.30, p=0.23
Processing speed	-0.27, p=0.07	-0.30, p=0.11	0.15, p=0.56

Table 8.5 Correlations between hue discrimination and cognition in all subjects, patients and control groups

[a]higher score = worse performance

8.4 Discussion

The main finding from this study was that schizophrenia spectrum disorder patients had worse hue discrimination ability than healthy controls across all colour spectra. This replicates the findings of Shuwairi et al (2002) in a larger group of patients who were earlier in their course of illness and suggests that impaired hue perception is a trait present from the earliest stages of schizophrenia. Shuwairi et al (2002) hypothesised that specific deficits in colour vision would be seen in the blue-yellow hue axis due to dopamine dysregulation, similar to that reported in Parkinson's disease. When a more generalised deficit was found, they suggested that this might be explained by inattention or fatigue. In the current study there was no evidence to support patients becoming more fatigued or less attentive during the FMHH task, as performance in both eyes was equally stable in both groups across all four colour trays which were presented sequentially. Furthermore, no association was found between information processing speed and hue discrimination ability.

On the other hand, worse auditory verbal learning, spatial working memory and, to a lesser extent, current IQ were associated with worse hue discrimination in patients but not in healthy controls. It has been

demonstrated that from the onset of schizophrenia, patients display persistent and widespread cognitive impairment, with verbal learning and working memory being particularly compromised (Leeson et al., 2009b). Cognitive impairment has also been demonstrated prior to onset of psychosis, with deficits already seen in childhood suggesting that it is intrinsic to the neurodevelopmental risk for schizophrenia (Khandaker et al., 2011). The association between impaired hue discrimination and cognitive impairment in the current study suggests that the underlying biological mechanism of hue perception is abnormal in schizophrenia and that this is also a facet of the neurodevelopmental abnormality.

An alternative explanation is that cognitive impairment caused a greater rate of hue discrimination errors in the schizophrenia group but this is unlikely as all subjects were given a practice trial of the task, to ensure they had understood the instructions and the task was not timed. Medication could not explain the difference between patients and controls as a post hoc analysis comparing medicated and unmedicated patients found no difference between groups on hue discrimination ability. This also supports the conclusions of Shuwairi et al (2002) who failed to find a dose related performance response on the same task.

Although age-related loss of hue discrimination has been reported (Jackson and Owsley, 2003), this could not explain the results of this study as age did not predict hue discrimination deficits. An earlier study of retinal nerve fibre layer (RNFL) thickness (described in chapter 6) failed to show differences in RNFL thickness between patients and controls (Chu et al., 2012). As those subjects also formed the patient and control groups described in the current study, hue discrimination deficits present in the same patients are unlikely to be explained by structural retinal abnormalities.

The human visual area V4 is located in the lingual and fusiform gyri of the occipital and occipto-temporal lobes and is the first area along the visual pathway to contain cells specialised for colour perception and hue

discrimination. Cells in this area project onward to the temporal cortex where colour perception combines with object perception to enable object recognition (Zeki et al., 1991). Results of the current study may therefore reflect a dysfunction of this occipito-temporal cortical system or, more broadly, of the P visual pathway.

The importance of our finding, and that of Shuwairi et al (2002), is that it challenges previous work suggesting that the visual processing deficit in schizophrenia is specific to the M pathway. Backward masking paradigms biased towards either the M or P pathway have pointed to intact P pathway and impaired M pathway function in schizophrenia (Schechter et al., 2003). Similarly, studies measuring P1 and N1 evoked potentials thought to reflect integrity of the M and P pathways respectively, have consistently reported changes in the amplitude of the P1 but not the N1 potential (Koychev et al., 2011). Conversely, a more recent psychophysiological study (Cadenhead et al., 2013) using a visual contrast sensitivity paradigm able to detect near threshold stimuli biased towards either M (luminance) or P (chromatic) pathways found that patients with schizophrenia were impaired on both conditions. These findings, along with results of the current study suggest impairments in both M and P pathways or a more general impairment in visual processing at a level where both pathways interact.

Studies implicating impaired M pathway function in schizophrenia have also found an association with negative symptoms. Thus M pathway impairment has been considered not only a marker of schizophrenia but also relevant for clinical outcome (Schechter et al., 2003). No correlations were found between hue discrimination and symptom severity in our patients, but given that cognitive impairment at first episode of schizophrenia and schizoaffective disorder is predictive of poor functional outcome later on in the disease (Leeson et al., 2009a), the demonstrated association between cognitive and hue discrimination impairments of the current study also implicates dysfunction of the P pathway as being relevant for clinical outcome.

This study is limited by the use of only one type of task to assess P pathway function and the lack of a comparison M pathway task in the same participants. Further work using different paradigms are required to clarify the nature of visual processing abnormalities in schizophrenia and investigate if there may be utility in such tests to help predict clinical outcomes for patients.

In conclusion, results of this study suggest a deficit in the visual pathway lying somewhere along the occipito-temporal course of the P pathway. The current study supports a neurodevelopmental explanation of schizophrenia because hue discrimination deficits correlated with cognitive deficits, which are already established early on in the illness. Continuing on the theme of vision and combining this with structural imaging, the final study described in the next chapter was designed to examine the relationship between oculomotor function and grey matter volume.

9. A Study of Oculomotor Function in Relation to Grey Matter Abnormalities in First Episode Psychosis

9.1 Introduction

9.1.1 Oculomotor function in schizophrenia

Abnormalities in smooth pursuit (an eye movement which allows one to follow a moving stimulus in a single direction) were 'rediscovered' in patients with schizophrenia by Holzman (1974). This phenomenon was first described in 1908 by Diefendorf and Dodge; using a modified photochronograph to trace oculomotor movements onto a photographic plate they described "abnormally rapid eye movements" in 10 patients with dementia praecox (Diefendorf and Dodge, 1908). Other deficits of oculomotor function associated with schizophrenia have since been established, including delayed antisaccade latency (delay in making a saccadic movement towards the mirror image location after presentation of a stimulus) and increased antisaccade error rate (erroneous reflexive saccades made towards a peripheral target when subjects are instructed to look at a mirror image location) (Crawford et al., 1995; Katsanis et al., 1997; McDowell et al., 2002; Sereno and Holzman, 1995).

Abnormal oculomotor function is now considered to be a phenotype for schizophrenia, as this measurable characteristic is consistently observed, is not explained by other disease-related factors and is not state related (Thaker, 2000). Unaffected first degree relatives also demonstrate abnormal antisaccade and smooth pursuit measures and are impaired to a degree between that of healthy individuals and patients with schizophrenia, suggesting that oculomotor function measures may be a marker of genetic vulnerability for the disease (Clementz et al., 1994). This phenomenon is unlikely to be a medication effect as abnormal smooth pursuit and increased antisaccade error rates have also been reported in first episode psychosis

patients who have received minimal medication (Hutton et al., 2004; Lieberman et al., 1993).

Less attention has been given to measuring prosaccades (reflexive eye movements towards a stimulus) although existing studies demonstrate no difference in performance between patients with schizophrenia and healthy controls (Fukushima et al., 1990; Barton et al., 2006; Hutton et al., 2002; Reuter et al., 2006). This is perhaps surprising as motor reaction times are generally slower in patients with schizophrenia (Birkett et al., 2007). As prosaccade latency (the time delay to initiation of eye movement towards a stimulus) is a measure of reflex action, this was further investigated in the current study.

9.1.2 Oculomotor function and associated brain regions

The diagram and explanatory text in the paragraph below has been modified from an article by Munoz and Everling (2004).

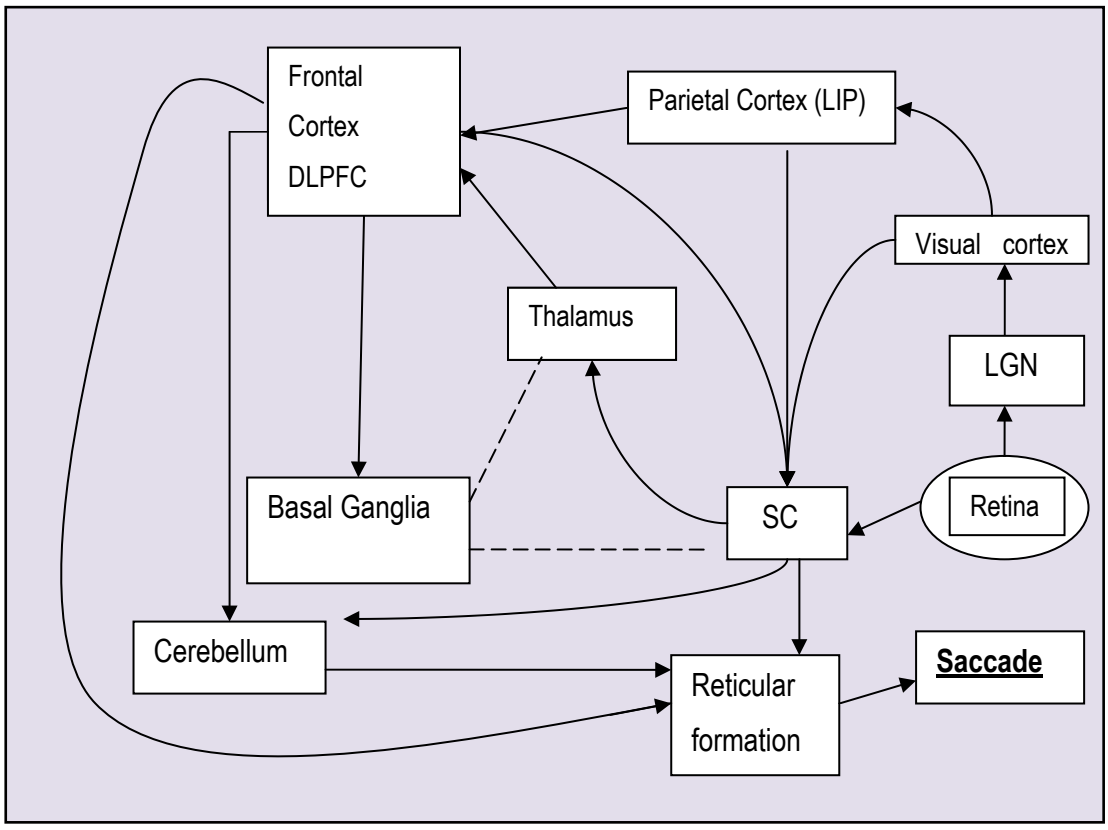


Figure 9.1 Neural Circuits Controlling Saccadic Eye Movements

Visual inputs arise from the retino-geniculo-cortical pathway to the primary visual cortex and from the retinotectal pathway to the superficial layers of the superior colliculus (SC). The lateral interparietal (LIP) area in the posterior parietal cortex is at the interface between sensory and motor processing and projects to intermediate layers of the SC and fronto-cortical oculomotor areas; which include frontal eye fields (FEF), supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (DLPFC). The FEF has a crucial role in executing voluntary saccades, the SEF guides decision-making and sequencing of saccades, while the DLPFC suppresses automatic reflexes. All these frontal regions project to the SC, a vital node in the premotor circuit. The FEF, SEF and SC project directly to the paramedian reticular formation to provide the necessary input to the saccadic premotor circuit so that a saccade is initiated or suppressed.

9.1.3 Neuroimaging of oculomotor function in schizophrenia

Neuroimaging studies, have allowed attempts to distinguish the neural networks associated with oculomotor movements. fMRI findings have shown varied results Fukumoto-Motoshita and colleagues (2009), described healthy subjects showing greater dorsolateral prefrontal cortex and thalamus activation in antisaccade than prosaccade tasks, while patients with schizophrenia showed no difference in degree of activation between the two tasks. Greater activation in the posterior hippocampi and right fusiform gyrus have also been described in patients with schizophrenia during smooth pursuit eye movements (Tregellas et al., 2004), while others have reported decreased activation in the lateral frontal regions and hyperactivity in temporal areas (Camchong et al., 2008). During antisaccades, fMRI showed failure of activation in schizophrenia patients of the left inferior frontal gyrus, thalami and lentiform nuclei bilaterally compared to healthy participants (Tu et al., 2006), while another study also described lack of prefrontal cortex activation (McDowell et al., 2002). In first-episode schizophrenia, it was found that visual pursuit abnormalities correlated with reduced magnetisation transfer ratio (MTR) in the right prefrontal cortex, while poorer performance

on the antisaccade task was associated with reduced GM volume in the right medial superior frontal cortex (Bagary et al., 2004).

The aim of the current study was to test the hypothesis that patients would perform worse than controls in smooth pursuit, antisaccade and prosaccade tasks and that these oculomotor function deficits would be associated with a reduction in GM volume.

9.2 Methods

9.2.1 Subjects

All subjects were recruited from the West London First Episode Psychosis study as described in chapter 4.

Eighteen first episode psychosis patients (12 males and 6 females) were recruited to the study, 8 were diagnosed with schizophrenia, 8 schizoaffective and 2 schizophreniform disorder. Seventeen patients were prescribed an antipsychotic and 4 were prescribed one additional psychotropic medication. A comparison group of twenty-two healthy controls (10 males and 12 females) were also recruited (Table 9.1).

	Patients (n=18)	**Controls (n=22)**
Mean age (sd)	22.6 (+/-5.7) yrs	30.1 (+/-6.7) yrs
Gender	12 male: 6 female	10 male: 12 female
Handedness	17 right: 1 left	17 right: 5 left
Diagnosis	8 schizophrenia 8 schizoaffective 2 schizophreniform	None
Antipsychotic medication	12 olanzapine 4 risperidone 1 amisulpiride 1 unmedicated	None
Other medication	2 benzodiazepines 1 citalopram 1 orphenadrine	None

Table 9.1 Demographic Information

9.2.2 Oculomotor Function Measures

All subjects had oculomotor function measurements performed in a quiet, dimly lit room. Eye movements were recorded with an Eyelink I eye tracker (SR-Research, Osgoode, Ontario), sampling the right eye at 250Hz by a research psychologist who was trained and experienced in measuring oculomotor function. Stimuli were presented on a 21" cathode ray tube (CRT) display with the refresh rate set to 100Hz. For all tasks the stimulus consisted of a red circle (luminance 15cd/m) presented on a black background, with the circle subtending approximately 0.5 degrees of visual angle. Participants were seated approximately 60cm from the display. Pupil position was monitored via two miniature infrared charge-coupled device video cameras mounted on an adjustable headband. A three-point horizontal calibration was performed at the start of each test, followed by a three-point calibration accuracy test. Calibration was repeated if the error at any point was more than 1° or if average error for all points was greater than 0.5°.

The following three measures were recorded:

1. Smooth pursuit velocity gain

The pursuit stimulus appeared on the left of the display and, after a drift correction procedure had been applied at that location, proceeded to move horizontally +/- approximately 20° at a constant velocity. Three blocks of 6 cycles of pursuit were recorded, with the drift correct procedure being applied before each block. The target moved at 0.125 Hz (5° per sec) in the first block, 0.25 Hz (10° per sec) in the second block and 0.5 Hz (20° per sec) in the third block. Participants were instructed to follow the target with their eyes and to refrain from blinking whilst the target moved. Velocity gain, the ratio of the eye velocity to the target velocity, was the measure used in subsequent analyses.

2. Antisaccade error rate

The antisaccade task employed the same methods and parameters as the prosaccade task, with the sole difference that participants were instructed that when the peripheral target appeared they should not look at it, but

should instead move their eyes as quickly and as accurately as possible to the mirror image location (an equal distance from central fixation but in the opposite direction). Participants performed 24 trials in total. Percentage error, calculated as the number of trials in which the participant made a saccade in the direction of the target as a function of the total number of successfully recorded trials, was used for further analysis.

3. Prosaccade latency

Each trial began with a red circle presented in the centre of the screen. Participants were instructed to look at the central stimulus, thus allowing a pre-trial drift correction procedure to be applied. This procedure could vary in length, taking longer if a participant blinked for example, but typically took no longer than 2 sec. The drift correct procedure was followed by a brief delay after which the central stimulus disappeared, and a target appeared simultaneously in the periphery. The target could be presented at one of four locations: +/-7.5 and 15 $^{\circ}$ from fixation. The target remained on screen for a further 2 sec before the trial ended and the central fixation stimulus reappeared signaling the onset of the next trial. Participants were instructed to look at the peripheral target as quickly and as accurately as possible. Participants performed 24 trials in total. Prosaccade latency, taken as the time in ms between the target appearing in the periphery and gaze being directed at the target in this new position, was the measure taken from this task.

9.2.3 MRI Acquisition and Processing

All subjects who had oculomotor function measured also had MRI scanning within a concurrent 2 week period. Brain MRI was performed on all subjects using a GE Signa 1.5T scanner (Milwaukee, Wisconsin, USA). High resolution T1 weighted images were acquired in the coronal plane with an SPGR gradient echo pulse sequence.

MRI images were processed using statistical parametric mapping (SPM2) software (http://www.fil.ion.ucl.ac.uk/spm) and the voxel based morphometry

(VBM) method was carried out as described by Good et al. (2001a). Segmented grey matter images were spatially smoothed with a 12mm FWHM isoptropic Gaussian kernel. Statistical parametric maps were calculated for the effects of interest within a general linear model.

Regions of significant effect were defined as having an extent of at least 100 contiguous voxels and reaching a threshold of significance at the cluster level ($p \leq 0.05$) following correction for multiple comparisons. Locations of local maxima were converted from MNI (Montreal Neurological Institute) to Talairach co-ordinates and referenced against the Jürgen-Mai brain atlas (Mai et al., 2004) http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach.

9.2.4 Data Analysis

Statistical differences were sought between patient and control groups for age, gender and oculomotor function measures.

A preliminary analysis was used to compare GM volume of patient and control groups. Total brain volume was calculated directly from segmented grey and white matter images (by taking the sum of the voxel intensity in the grey or white matter probability images, and multiplying by the voxel volume) and retained as a confounding variable in all subsequent analyses. Using a general linear model (GLM), each of the three different measures of oculomotor function were added in turn to the preliminary analysis model and their association with GM volume investigated across both patient and control groups, between groups and within groups. Regions where local maxima reached significance were then corrected for multiple comparisons using a family-wise error (FWE) correction.

9.3 Results

9.3.1 Demographics

Patients had a mean age of 22.6 years (sd=5.7) and were significantly younger (t= -3.8, df=38, p=0.001) than controls (mean age 30.1 years,

sd=6.7); age was therefore retained as a covariate in all subsequent analyses. Groups were similar for gender (χ^2=1.8, df=1, p=0.18) and handedness (χ^2=2.29, df=1, p=0.13). Average treatment duration with antipsychotics prior to MRI was 11 weeks (range 2-23 wks).

9.3.2 Oculomotor function

Results of oculomotor function measures are summarized in Table 9.2. Patients had slower smooth pursuit velocity gain than controls at 5°/sec (t= -2.639, df=38, p=0.012) and at 10°/sec (t= -2.059, df=38, p=0.046). As these measures were strongly correlated (Pearson's rho = 0.74), mean value for results at 5 and 10°/sec were used. Although recordings were obtained from both groups at 20°/sec these results were excluded from analysis as one patient outlier was >3sd below the mean, which severely skewed the data. Patients had slower smooth pursuit velocity gain than controls (t= -2.587, df=38, p=0.015).

Patients made more antisaccade errors than controls but this no longer reached statistical significance (t=3.178, df=37, p=0.339) after excluding one patient outlier who was performing at worse than chance level, with a 100% antisaccade error rate.

There was no difference in prosaccade latency (t=0.608, df= 38, p=0.547) between patients and controls.

Oculomotor Function	**Patient Mean (sd)**	**Control Mean (sd)**	**Sig (p value)**
Smooth pursuit (ratio)	0.96 (0.04)	0.98 (0.04)	0.01
Antisaccade error rate (%)	56.82 (26.85)	48.41 (26.93)	0.34
Prosaccade latency (ms)	183.93(68.01)	174.66 (20.31)	0.55

Table 9.2 Oculomotor Function Measures

9.3.3 Grey matter volume

Preliminary analysis found GM volume in first episode patients was similar to that of healthy controls (matched for handedness and gender). Any apparent differences in GM volume were explained by total brain volume and age; confounding variables of total brain volume, age and gender were therefore controlled for in all subsequent analyses.

9.3.4 Grey matter volume and smooth pursuit velocity gain

Smooth pursuit velocity gain was entered as the factor of interest on the GLM model across both groups, but this failed to explain variation in GM volume.

In the patient group, an association was found between smooth pursuit velocity gain and GM volume ($p<0.0003$), with local maxima in the striate area of the right occipital lobe, although the cluster also included bilateral cerebellar components (Figure 9.2). This suggests that the greater the smooth pursuit velocity gain, the greater the GM volume of these brain regions in patients. When patient and control groups were compared, the strength of association between smooth pursuit velocity gain and GM volume was greater in patients than controls ($p=0.024$) in bilateral cerebellar regions.

Across all subjects, an inverse association was found between smooth pursuit velocity gain and GM volume, with local maxima in the anterior cingulate ($p=0.006$) extending into the prefrontal cortex (Figure 9.3). This suggests slower smooth pursuit velocity gain was associated with greater GM volume in this region.

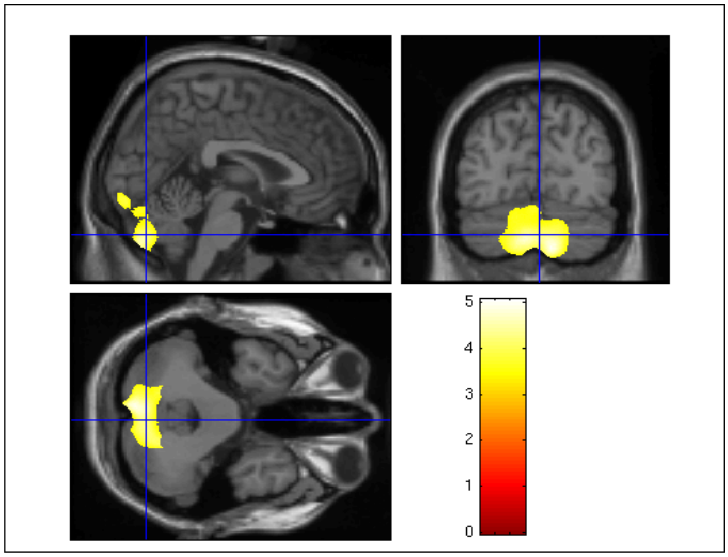


Figure 9.2 Right Striate & Bilateral Cerebellar Areas Where Grey Matter Volume is Associated with Smooth Pursuit in Patients

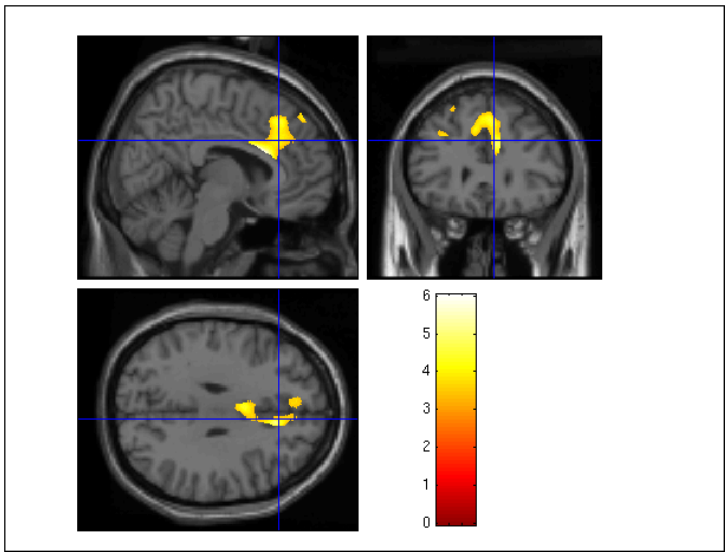


Figure 9.3 Anterior Cingulate Areas Where Grey Matter Volume is Inversely Associated with Smooth Pursuit in Patients & Controls

9.3.5 Grey matter volume and antisaccade error rate:

When antisaccade error rate was entered as the factor of interest on the GLM model, no regions of association between antisaccade error rate and GM volume were found either across or between both groups, or within either patient or control group alone.

9.3.6 Grey matter volume and prosaccade latency:

Prosaccade latency was entered as the factor of interest on the GLM model across both groups, but this failed to explain variation in GM volume beyond that of the nuisance variables (age and gender).

In the patient group, an inverse association was found between prosaccade latency and GM volume in the bilateral prefrontal cortices (Figure 9.4), suggesting that as prosaccade latency increases, GM volume decreases in these areas. Local maxima were found in the left (p=0.027) and right anterior frontal cortices (p=0.042). In the control group, there was no association between prosaccade latency and GM volume.

When patient and control groups were compared, association between prosaccade latency and GM volume was greater in patients than controls (Figure 9.5) in the right posterior inferior temporal region (p=0.015).

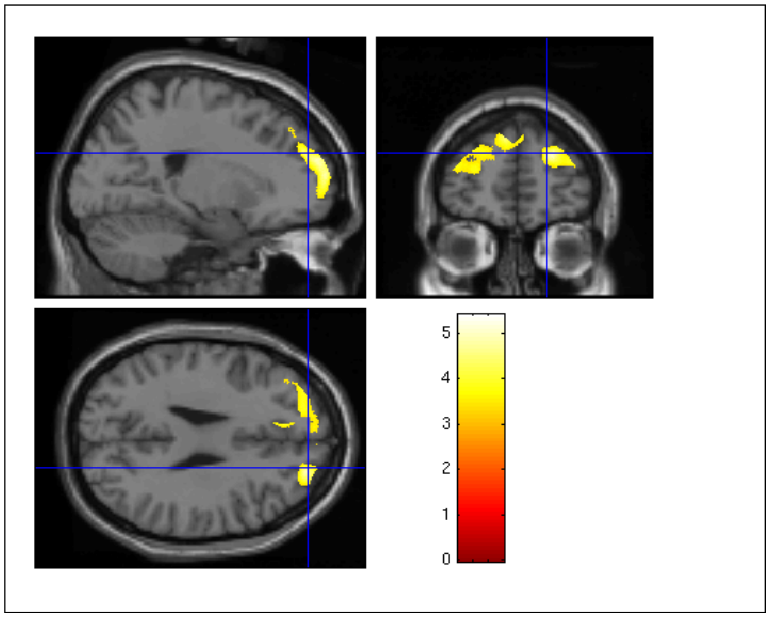


Figure 9.4 Bilateral Frontal Lobe Areas Where Grey Matter Volume Displays Inverse Association with Prosaccade Latency in Patients

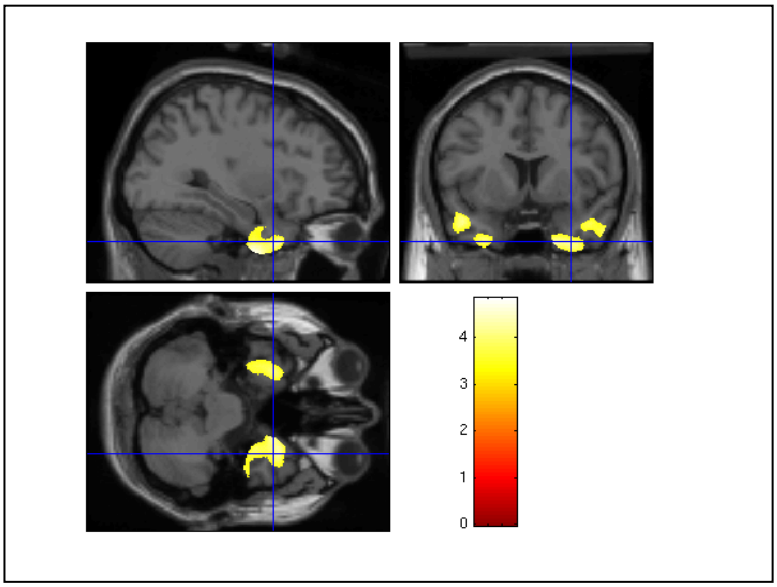


Figure 9.5 Right Inferior Temporal Lobe Areas Where Grey Matter Volume is Associated with Prosaccade Latency in Patients More than Controls

N.B. Only right hemisphere regions reached statistical significance

	Number of voxels in cluster	Max Talaraich coordinates (x, y, z)	Area	Association with GM volume and group
Smooth pursuit	23243	(11, -93, -11)	Right striate & bilateral cerebellar areas	Positive association in patients only
Smooth pursuit	6727	(34, -8, -49)	Anterior cingulate	Positive association across both groups
Prosaccade latency	6727	(34, -9, -41)	Right inferior temporal gyrus	Positive association greater in patients than controls
Prosaccade Latency	3718 3085 2730	(-18, 46, 34) (-10, 35, 26) (28,59,23)	Bilateral prefrontal cortices	Inverse association in patients only

Table 9.3 Cluster Sizes & Talaraich Co-ordinates Where Grey Matter Volume Showed Associations with Oculomotor Function Measures

9.4 Discussion

Smooth pursuit task performance was worse in patients than controls in this study. In the patient group, poor performance was associated with decreased GM volume in the striate area of the right occipital lobe and cerebellum. The striate region plays a crucial role in visual processing because most visual information is funneled through this area before reaching the rest of the visual cortex (Felleman and Van Essen, 1991). When patients and controls were compared, this association remained stronger in the posterior cerebellum of patients. Regions of the oculomotor vermis (lobuli vi-vii) in the posterior cerebellum are known to control ocular movements (Thier et al., 2002) and activation of this region using transcranial magnetic stimulation (TMS) has been demonstrated to correlate with increased visual pursuit velocity in “normal” subjects (Ohtsuka and Enoki, 1998).

Across patient and control groups combined, decreased GM volume in the anterior cingulate cortex (ACC) was associated with better performance on the smooth pursuit task in this study. This finding seems plausible considering the ACC directs spatial attention (Mesulam, 1981) and eye gaze, with the posterior dorsal ACC being specifically involved with volitional saccadic control (Gaymard et al., 1998). White matter (WM) underlying the ACC may be relevant in schizophrenia as reduced WM integrity of the cingulate in the right hemisphere has been described in chronic schizophrenia (Manoach et al., 2007b). If the WM tract underlying the ACC has reduced in volume, existing GM may spread to occupy the available space. Alternatively, although disruption of WM tract integrity may not affect volume; resulting MRI signal intensity may be reduced and come closer to that of GM, leading to misclassification of brain tissue by the segmentation algorithm.

Although studies consistently show that schizophrenia patients display an increased proportion of antisaccade errors compared to healthy controls (Turetsky et al., 2006) patients and controls recruited to the current study had a similar rate of antisaccade errors, which was unexpected. Antisaccade

impairment is known to be associated with genetic loading for schizophrenia (Petrovsky et al., 2009), considering diagnoses of patients in this study included schizoaffective and schizophreniform disorder, genetic loading for antisaccade impairment in our patient group may have been reduced.

Small sample sizes are a possible limitation of this study, although unlikely to explain the findings as other studies using small numbers of subjects reported that schizophrenia patients performed significantly worse than controls in an antisaccades task (McDowell et al., 2002). In the early stages of schizophrenia, GM volume changes may still be in a process of evolving (Szeszko et al., 2003), which may explain the lack of association between antisaccade errors and GM volume at first-episode psychosis.

Poorer performance on the prosaccade task was associated with reduced frontal cortex GM volume and increased right temporal GM volume, an effect of greater significance in patients than controls. This finding appears to lend support for the hypothesis of abnormal fronto-temporal connectivity in schizophrenia (Fletcher et al., 1999). It is the right hemisphere which plays a dominant role in spatial attention (Heilman and Valenstein, 1979) and eye gaze (De Renzi et al., 1982). One fMRI study reported hyperactive temporal regions and hypoactive frontal regions during visual pursuit tasks in schizophrenia patients (Tregellas et al., 2004). Increased regional cortical blood flow to the temporal region may be associated with increased local GM volume; furthermore the right temporal lobe is associated with visuo-spatial function of which prosaccadic tasks are a subset. Considering that both patients and controls performed at a similar level in the prosaccade task, this oculomotor function was unlikely to be associated with the GM volume differences seen in this study.

Most patients were taking atypical antipsychotics but medication effects are unlikely to affect smooth pursuit (Flechtner et al., 2002) or antisaccade task performance (Calkins et al., 2003). Although atypical antipsychotics are reported to affect brain structure, with reports of increased thalamic volume

(Dazzan et al., 2005) and increased cortical grey matter volume (Scherk and Falkai, 2006); this is unlikely to have affected our patient sample, as they had been prescribed medication for only a short period of time and all patients were in their first episode of psychosis.

This study is perhaps limited by the varied diagnostic distribution of our patient group as less than half were first episode schizophrenia. Inclusion of patients with schizoaffective and schizophreniform disorder may have diluted any findings of significance. A larger patient cohort would have allowed further subdivision of the schizophrenia spectrum disorders to examine whether oculomotor function varies according to diagnosis and whether there were any GM volume differences between healthy controls and patients with different diagnoses. Looking at patient and control groups separately, the sample size may be too small to pick up areas of true GM volume association if the effect size is only small and it is difficult to determine if associations found in only one of the two groups is truly due to a disease effect. If patients had reduced GM volume in addition to worse oculomotor function compared to controls, there would be an increased likelihood that this was due to a disease effect rather than simply the spread of results within a normal distribution.

With an increasing drive to reclassify illnesses within the schizophrenia spectrum into more meaningful endophenotypes as proposed in 2007 by the American Psychiatric Association and the Consortium on the Genetics of Schizophrenia; abnormalities of oculomotor function are once again under scrutiny as a potential biomarker for schizophrenia. Future studies coupling oculomotor function with neuroimaging may yield data of greater scientific value in the field of schizophrenia research.

10. SUMMARY AND CONCLUSIONS

The contents of this thesis have described a series of investigations to try and improve our understanding of the neurobiology of schizophrenia. By using a variety of brain imaging techniques the structural manifestation of schizophrenia was investigated and by examining ocular movement, visual function and retinal structure the eyes (which form a direct extension of the brain) were also investigated.

10.1 Summary of Findings

Chapter 5

A study of white matter FA using DTI techniques compared first episode psychosis patients with healthy controls using TBSS to measure average FA from the core of all white matter tracts. Patients performed worse than controls in cognitive measures of current IQ, working memory, processing speed and verbal learning. Reduced FA indicative of disrupted white matter integrity affecting the myelin sheath was found in the posterior thalamic radiations at first episode psychosis. Slower processing speed was associated with decreased FA in the left superior longitudinal fasciculus (SLF) and right posterior thalamic radius (PTR) in patients. This suggests that white matter changes start at the back of the brain and are only subtle at first episode of illness.

Chapter 6

The main focus of the projects in this thesis were based on experimental imaging techniques, hence a novel method of looking directly at an unmyelinated portion of the brain was investigated. Using the eyes as a "window into the brain" OCT enabled measurement of RNFL thickness and macular volume in patients with schizophrenia. No RNFL thinning was identified in the patients, suggesting that unmyelinated axons are unaffected by schizophrenia at least in the early years following illness onset. The neuropathology is therefore more likely to involve myelin early on and predominantly appears to affect white matter integrity. Visual pathways may

be affected further downstream in schizophrenia rather than at the start in the retina.

Chapter 7

The longitudinal follow-up study of first episode patients and healthy controls found a small increase in white matter volume for both groups over a short follow-up period of around 18 months but no change in grey matter volume. Patients had significantly larger ventricular volumes at both time points, demonstrating that increased CSF and ventricular dilatation is already present from early on in the course of illness. Grey and white matter MTR showed no significant changes in either group over time; although this negative finding was unexpected it appears to suggest an absence of structural change in grey or white matter early on in the course of illness. Cognitive deficits were present in patients at both time points with a further decline in performance over time in IQ and processing speed but this did not correlate with any structural brain changes. Ventricular dilatation and cognitive deficits appear to be the first markers of change and are present by the first onset of schizophrenia.

Chapter 8

Further investigation of the visual pathway using hue discrimination found that patients with schizophrenia had impaired colour hue discrimination across all colour spectra compared to healthy controls. In patients, hue discrimination correlated with premorbid IQ, verbal learning and working memory. In controls, hue discrimination did not correlate with any of the cognitive variables measured. Impaired hue discrimination in patients could not be explained by a deficit in attention but correlated with poor cognitive function. This suggests that visual pathway deficits may be present in the occipito-temporal P pathway in schizophrenia thus giving rise to deficits in both hue discrimination ability and cognition.

Chapter 9

This study combined structural brain imaging to examine associations between grey matter volume and oculomotor function. First episode psychosis patients performed worse than healthy controls in oculomotor function measurements of smooth pursuit while prosaccade latency and antisaccade error rates were similar in both groups. An association was found between better smooth pursuit performance and increased right striate and bilateral cerebellar areas in patients. An association was demonstrated between reduced prefrontal cortex grey matter and worse prosaccadic performance, an effect more marked in patients than controls. Conversely, increased grey matter in the right infero-posterior temporal lobe was associated with worse prosaccadic performance. This study demonstrates that oculomotor function deficits are already present by the first episode of schizophrenia and these appear to be related to grey matter volume.

10.2 Conclusions

Findings from the experiments described in my thesis suggest that the neuropathology of schizophrenia may manifest itself in a number of ways and at different time points. The limited neuroimaging findings from the first episode patients suggest that the neuropathology of schizophrenia arises from a combination of factors that cause “neurotoxicity” therefore these are not as evident early on in the course of illness.

The MRI scanning studies that were carried out and described in my thesis appear to demonstrate that in first episode psychosis, there is only a small degree of change in brain white matter affecting tract integrity in posterior brain regions. In at least the first 18 months following clinical diagnosis of a schizophrenic illness, there were no structural changes affecting grey matter volume although small areas of white matter volume increase were found. There was no loss of unmyelinated axons in the retinal nerve fibre layer observed, suggesting that the neuropathology of schizophrenia manifests itself first and foremost in the myelin sheath of white matter in the early years of illness. Hue discrimination ability was adversely affected by schizophrenia

and associated with impaired cognitive performance, indicative of occipito-temporal deficits. Cognitive deficits, increased CSF volume and impaired oculomotor smooth pursuit were present at first episode of psychosis in the cohort of patients used in my study, which replicates well-known findings from schizophrenia research.

10.3 Future Research

Although schizophrenia is typically thought of as being a disorder of fronto-temporal connectivity and much research has been concentrated specifically on these regions, the visual system runs a long and convoluted course as an extension from the retina at the front of the brain through the optic nerve to the occipital lobes at the back of the brain. Little is known about how the ocular system is affected by schizophrenia, yet abnormal oculomotor function and impaired hue discrimination are clearly present in this patient population. Important information about schizophrenia may perhaps be revealed by studying other visual function domains.

Suggestions for further work and possible research questions include:

1. Examining whether variation in density of DA receptors on the retina correlates with performance in colour hue discrimination.
2. A longitudinal MRI scanning study of longer duration e.g. introducing a third scan to track changes over different follow-up time points and using higher resolution, 3T MRI scanning.
3. Looking at long term functional outcome and seeing if this can be predicted by matching with earlier MTR measures.
4. DTI studies using tractography to look at the integrity of white matter tracts implicated in visual processing pathways.
5. A longitudinal OCT study to track whether there is any progressive RNFL thinning following repeated episodes of psychosis.

10.4 General Criticisms

One criticism of this series of studies was the high rate of attrition in patient data either through excessive movement artefacts or patients unable to tolerate the scanning process. In order for results to be more widely generalised and more meaningful, it would be necessary to scan a much larger number of patients. To do this effectively, a multi-centre trial would need to be set up in order to generate such large quantities of data but there are inherent complications with MRI scanner compatibility and the costs that such a study would incur.

With an increasing emphasis towards early intervention in the treatment of psychosis, it is becoming increasingly difficult to recruit medication naïve patients to studies. The precise cellular effects of antipsychotic medication are unclear and may; at least to some extent, be responsible for the large variation in results obtained by different MRI study groups. Efforts are therefore turning towards patients who are at “ultra high risk” or in the prodromal phase of a psychotic illness.

A further point for consideration is the age of subjects being recruited to studies. In the normal neurodevelopmental process a period of cortical pruning occurs during adolescence while white matter maturation continues well into adulthood in the third decade, so the age range of the subjects may have affected findings in the imaging studies.

Above all else, we should remember that patients who chose to engage in this set of research studies participated voluntarily and are therefore a self-selecting group of participants. A further feature of the first episode patients recruited to the studies described in my thesis is that they were all well enough to be living in the community (either independently within their own home or with family members) and were not severely ill. By accessing a community rather than a hospitalized sample of patients, any possible confounding effects of institutionalisation and environmental changes have been minimised. Because such patients are less unwell, this could explain

why any neuropathological features of disease in this group would be subtle. If a patient sample with a well-established, chronic course of disease had been selected to participate, abnormalities on imaging may have been much more pronounced and more readily observed.

10.5 Clinical and Research Implications

From a clinical perspective, one major difficulty facing clinicians is the classification of psychotic illness and this may have had implications on the validity of the studies I carried out. At the recruitment stage of the study, patients were experiencing their first clinical episode of psychosis but this could have arisen from a range of different psychiatric diagnoses. In view of this “first episode psychosis” was the term used to describe patients in chapters 5, 7 and 9 which encompassed those at first episode of schizophrenia, schizoaffective and schizophreniform disorder. With the absence of biological disease markers, current diagnostic criteria and boundaries which are based on clinical observations may not be entirely accurate. Caution is therefore required when interpreting findings from these studies as they may not be generalised to a broader range of patients with psychotic illness arising from different disorders.

The studies incorporated into my thesis (Table 10.1) appeared to provide some support for the neurodevelopmental hypothesis of schizophrenia. In foetal development both the retinal nerve fibre layer (RNFL) and neurons used in higher cognitive functions arise from the same embryonic origins of the prosencephalon. Although there was no RNFL thinning, cognitive deficits were already present in patients at first episode of psychosis and remained a feature in patients with established diagnoses of schizophrenia or schizoaffective disorder so this may be attributable to a neurodevelopmental abnormality.

Study	Hypotheses Tested	Findings	Conclusion
Comparison of FA between FE pts and controls	Pts have lower FA than controls. Pts perform worse on cognitive measures and this correlates with reduced FA.	Pts have lower FA in the posterior thalamic radius. Evidence of disrupted WM integrity in occipital lobe tracts early in the illness course.	No evidence of neurodegeneration Findings support the neurodevelopmental theory or may be evidence of neurotoxicity.
Comparison of RNFL thickness between sz/sa patients and controls	Pts have thinner RNFL than controls.	No difference in RNFL thickness between groups.	Sz does not appear to affect unmyelinated axons. No evidence to support neurodegeneration.
Longitudinal imaging study of FE pts	Pts have reduced brain tissue volumes compared to healthy controls.	No grey or white matter volume loss seen in patients. No correlations between brain tissue volumes and cognition.	No evidence to support neurodegeneration. Cognitive deficits already present at disease onset supports the neurodevelopmental theory.
Hue discrimination ability and cognitive function in sz spectrum patients	Pts perform worse in hue discrimination than controls.	Pts have worse hue discrimination ability than controls across all colour spectra, which correlates with cognitive performance.	No evidence to support or refute neurodegeneration .
Oculomotor function and correlations with grey matter volume in FE pts	FE pts have worse oculomotor function than ctrls. Performance is correlated with grey matter volume.	FE pts have slower smooth pursuit than ctrls. No difference in GM volume between groups.	Oculomotor impairments may be evidence of neurotoxicity. No evidence of neurodegeneration at FE schizophrenia

Table 10.1 Summary and Conclusions

There was unequivocal support for the neurodegenerative hypothesis of schizophrenia provided by the studies in my thesis. Although there was evidence of disruption to white matter integrity at first episode of psychosis, only small areas on two white matter tracts were affected and reduced FA may indicate neurotoxicity rather than neurodegeneration and cell death. This may have been the beginning of a more extensive neuropathological process but this could not be ascertained as only cross-sectional DTI scanning was carried out in this study cohort. As the longitudinal study showed no evidence of grey or white matter volume loss, neurodegeneration may occur at a later stage in the course of illness but not in the first 18 months following first episode psychosis. The small increase in white matter volume seen over time was possibly reflective of white matter maturation. A cross-sectional study correlating oculomotor function with GM volume failed to demonstrate differences in GM volume between FE patients and controls, again refuting the hypothesis of neurodegeneration at disease onset. However the presence of oculomotor function deficits may have arisen from neurotoxicity.

The rationale for using optical coherence tomography (OCT) was to investigate if this device might prove useful in helping with the diagnosis and clinical tracking of schizophrenia by measuring RNFL thickness as a biological disease marker. The negative RNFL finding provided evidence that unmyelinated axons are not affected by schizophrenia (or at least not in the optic nerve) and therefore the clinical utility of this instrument is limited. The absence of axonal loss that would result in RNFL thinning also refutes the neurodegenerative hypothesis of schizophrenia.

Colour hue discrimination in schizophrenia deserves further investigation. Although the exact mechanism for this deficit remains unclear it was associated with cognitive impairment in patients and may have clinical utility as a diagnostic tool and for tracking disease progression.

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