COMMONALITIES AND DIFFERENCES BETWEEN SCHIZOPHRENIA AND BIPOLAR DISORDER

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I, Andrew M McIntosh declare that:

a) I have composed the work contained in this thesis.

b) The work contained in it is my own.

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ABSTRACT OF THESIS

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Schizophrenia and bipolar disorder share many symptoms but are difficult to separate on the basis of treatment response or prognosis. This had led some to question their validity as disease entities. The evidence concerning their validity is introduced in chapter 1 of this thesis and chapter 2 discusses the evidence for structural and neuropsychology abnormalities in both disorders, and specifically whether these form a basis by which they can be separated. Particular attention is given to magnetic resonance imaging (MRI) studies in affected individuals and in unaffected family members. Chapter 3 is a systematic review and meta-analysis of structural MRI studies of bipolar disorder, comparing affected patients with both healthy controls and with schizophrenic subjects. Some evidence is found for regions which may separate patients with bipolar disorder from controls and from patients with schizophrenia.

Chapter 4 outlines the methods for the main neuropsychological and MRI study of families affected by schizophrenia, bipolar disorder or both. The clinical and neuropsychological results are given in chapter 5 and the MRI results in chapter 6. This study finds some evidence that certain neuropsychological impairments are specific to a family history of schizophrenia. Certain reductions in grey matter, particularly in prefrontal areas, appear to be relatively specific to a genetic liability for schizophrenia. Other regions, particularly the anterior thalamus, may be affected in all patients and relatives. Furthermore these grey matter findings are associated with complimentary white matter density reductions.

Chapter 7 discusses some of the outstanding issues in terms of the separation of schizophrenia and bipolar disorder, and discusses the future of neuropsychological and brain imaging research in this area.

Preface

For over 100 years the diagnostic categories of manic-depressive illness, bipolar disorder, and schizophrenia have been used as a basis for diagnosis, targeted treatments and to convey meaning to both patients and clinicians about the likely course and outcome in an individual patient. These categories have also been adopted for psychiatric research in spite of their imperfect reliability and validity.

However, the lack of a validation for the schizophrenia/affective illness dichotomy does not in itself mean that the model is wrong. Indeed, many diseases in other parts of medicine were recognised by clinicians as discrete syndromes long before aetiological validation was eventually forthcoming.

This thesis considers only the two 'functional psychoses' for which the clinical and aetiological overlap appears to be the greatest, namely schizophrenia and bipolar disorder.

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Chapter 1: The Validity of the Concepts of Schizophrenia and Bipolar Disorder, a Historical Perspective

1.1 Classification of functional psychosis in the classical period

Skulls dated to around the time of Neolithic man have been found with bore holes drilled in order, it is thought, to allow the release of evil spirits. It is likely that shamen who practiced trepanning may have been attempting to relieve the mental or physical ills of their patients. Paintings have also been found on cave walls of human figures, adorned will deer antlers who may have been the prototype doctors or psychiatrists. Some of these paintings, found in the south of France, date to as early as 15 000 BC. Mental illness is often referred to in the writings of the Old and New Testament. King Saul is said to have been 'beset with paranoia' and Nebuchadnezzar troubled by persistent melancholia. Descriptions of mental disorder also appear in the Hindu *Ayurveda* (c1400 BC), and have been interpreted by some as similes of dementia or delirium (Romm 1994).

Clear references to mental illness, and probably psychotic illness, precede the bible. Insanity was referred to in Homer's Iliad when Podaleirios 'diagnosed' mental insanity in Ajax by examining his 'lightening eyes'. Hippocrates (c460-377 BC) classified mental disorders into three categories: mania, melancholia and phrenitis (probably febrile delirium) on the basis of their conspicuous symptomatology (Simon 1973). Paranoia was also used as a descriptive term later incorporated under the term insanity. However, these descriptive classes of observation incorporated clearly heterogeneous cases. Mania was used to describe an agitated form of melancholia and a relatively quiet form of insanity. Aristotle (c384-322 BC), a student of Plato, was perhaps the first to attempt to classify human emotions (desire, fear, envy and joy) (Romm 1994). However, he questioned Hippocrates's categorical classification and saw

no clear distinction between health and illness (Roccatagliata 1986). In spite of much attention, none of the early Greek philosophers published a separate text on insanity. Mania was however a popular 'diagnosis' amongst Greek physicians who thought it was particularly common amongst young men who drank to excess (Romm 1994). Mania was punctuated by silliness, rage and fear and was treated by placing the sufferer in a room with windows 'high enough to discourage jumping'.

A basic classification emerges in the writings of the Cappadocian physician Arataeus (c100 AD). In the second century AD, Arataeus described mania and melancholia occurring in the same individual and in doing so, anticipated Falret and Baillarger by more than 1800 years (Roccatagliata 1986). Arataeus also suggested that melancholia and mania had the same aetiology, namely disturbances of the brain and some other organs. Marneros and Angst (2000) clearly identify Arataeus as the first descriptor of 'manic-depressive' illness, although not all authors would agree (Ackerknecht 1959;Fischer-Homberger 1968). Arataeus was also one of the first to use prognosis as a basis for the classification of illness.

Roman philosophers also considered conditions which retrospectively were probably psychotic illness. Celsus (c30 AD) wrote about melancholia and mania and advocated that they be treated by ducking the sufferer under water so that the evil demons that caused the affliction would run away (Romm 1994). Galen (130-210 AD) also used the terms mania and melancholia and claimed to localise mania's cause in the blood and stomach although a scientific basis for such a claim was clearly absent.

The medieval era (c500 AD to c 1450 AD) appears to have been a time when rational enquiry about the nature of insanity was abandoned in favour of demonology

and superstition. The diagnosis and treatment of insanity was dictated by the church. Although some 'madmen' were thought to be gifted or chosen by god for rewards to be bestowed after death, many were tortured or subject to cruel and inhumane treatments. During the same period however, the Muslim world had a more humane attitude to the insane. Lunatics were housed in asylums and treated with baths, soothing music and visits from prostitutes. Recorded examples of such asylums have been found in Baghdad, Damascus, Cairo and Fez. Little is known of their approach to classification (Alexander and Selesnick 1966).

1.2 The medieval period and Renaissance

During much of the Renaissance (c1350-c1650) scientific enquiry into the aetiology and classification of mental disorder was also sparse. Descriptions of the insane being drowned at sea have been found in the early Renaissance period and witchcraft was a common aetiological theory of madness which pervaded at the time (Sprenger and Kramer 1486).

Paracelsus (1493-1541) was one of the few Renaissance thinkers who viewed lunatics as sick people and attempted to provide a possible classification. He believed that mental disorders could be classified as mania, vesania (true insanity), chorea lasciva (St Vitus Dance) and suffocatio intellectus (hysteria). Mania was a disorder of reason, not of the senses as in true insanity. Vesania was subdivided into many further classes including the melancholia, the insania (disease in which the affected were born mad or defective) and obsessional disorders.

Felix Plater (1536-1614), a Swiss Renaissance physician, decided to classify mental conditions by whether they were inherited, congenital or acquired. Plater advanced four diagnoses for those who were deemed insane: imbecility, consternation, alienation and defatigatio (Lorr *et al.* 1963). Imbecility included those with bizarre psychotic states. Consternation included various disorders including stupor and delirium. Alienation was a diverse group of disorders including St Vitus Dance, melancholia, mania, alcoholism and hypochondriasis. Defatigatio was identified by the presence of insomnia and was attributed to god or the devil.

Interest towards the end of the Renaissance was directed towards the brain. Vieussens (1641-1716), Descartes (1596-1650) and Willis (1621-1675) all proposed theories which made a link between brain structure and mental functions. Stahl (1660-1734) observed that powerful physiological reactions often accompanied emotional states and that brain disorder may also lead to psychological symptoms. He proposed a distinction between organic and functional mental disorders which became a classifying criterion in many diagnostic nosologies (Lorr et al. 1963).

1.3 Classification in the eighteenth and nineteenth centuries

Influenced by Linnaeus's botanical classification of plants, the eighteenth century and 'age of enlightenment' were a time where many nosologies of disease were advanced (Mack *et al.* 1994). Francois de Sauvages (1706-1767) wrote the Nosologie Methodique (Veith, 1957), based directly on Linnaeus's botanical model. He distinguished a class of Folies under which he distinguished four orders, errors of reason, bizarreries, deliria and anomalies. Mania and melancholia was subsumed under

disorders of reason. People whom we would now refer to as schizophrenic would probably have been classified under the bizarreries (Lorr et al. 1963).

William Cullen (1712-1790) in Edinburgh provided an extensive list of mental illnesses which were catalogued by symptoms, signs and treatments and also introduced the term neurosis (Berrios and Beer 1995). Esquirol (1772-1840) in France was of the first to used statistical methods to address the problems of aetiology and classification. He rediscovered the difference between illusions and hallucinations and separated psychotics into those who were preoccupied with a single thought or set of thoughts (monomania) from people with melancholia (Lorr et al. 1963). Also in France, Georget (1795-1828) asserted that there was only one psychosis, which was due to a single brain disease. His ideas may have anticipated those of Griesinger by many years, although this point is a matter of some debate (Lorr et al 1963).

Jean-Paul Falret (1794-1870), a student of Esquirol and a Parisian psychiatrist at the Salpêtriere, is credited by some as the father of the modern concept of bipolar disorder. In 1851 he published a statement in which he described a mental disorder called 'folie circulaire' characterised by a continuous cycle of depression, mania and intervening periods of varying length. Three years later Jules Baillarger (1809-1890) published his concept of 'folie à double forme' in which he described recurrent periods of melancholia and mania (Baillarger 1854). Falret differed from Baillarger in that he considered the intervening period as part of the illness whereas Baillarger considered it apparently unimportant.

The concepts of 'folie circulaire' and 'folie a double forme' found widespread acceptance in both France and also in German speaking nations. Karl Kahlbaum

introduced both terms into mainstream German psychiatry in his famous book 'The grouping and classification of mental disorders' in which he also introduces the term 'Katatonia' (1874) a prototype of the current concept of catatonic schizophrenia (Berrios 1995).

In German and English speaking psychiatry, it is Wilhelm Griesinger's (1817-1868) name that is most often associated with the term 'unitary psychosis' or 'Einheitspsychose' (Berrios and Beer 1995). This general view asserts that there is only one psychosis and that differences between patients are variously due to the pathoplastic effects of personality, life events or observer bias. Wilhelm Griesinger (1817-1868) graduated at a time when questions were starting to be asked about the biological substrate of illness, and the techniques of chemistry, physiology and microscopy were just being developed to answer them. He famously asserted that mental disease was brain disease. His views were so influential he has sometimes been called the father of biological psychiatry.

Many people shared Griesinger's views about the unitary nature of psychosis. Kant (1724-1804) believed that madness resulted from impairment of the brain and that classification should reflect only which faculty of the mind was involved. Zeller (1804-1877) and Neumen (1814-1884) also believed that insanity had a unitary cause and Benedict Morel's (1809-1873) concept of degeneration theory has also been interpreted in this context. It is interesting that in his later years, Wilhelm Griesinger came to doubt his unitary classification of psychosis. In 1861 he wrote 'from our observations there are two groups of insanities: firstly the affective ones and secondly the primary disturbances of perception and will' (Berrios and Beer 1995).

1.4 Twentieth century approaches to classification

Although many attempts to classify mental disorders, and in particular psychotic illness, predate Kraepelin (1856-1926). Kraepelin was the first to propose a systematic nosology which has come into widespread acceptance (Shorter 1997). Kraepelin, in the Platonic tradition, hoped to discover natural disease entities and hypothesised that patients with the same course of illness might suffer from the same disease and, like Sydenham before him, he classified on the basis that common characteristics would co-occur across patients with the same disease.

On the basis of meticulous clinical observation, Kraepelin proposed that psychotic illness could be divided into those with recurrent episodes of mania or melancholia with intervening periods of remission and good outcome and those with a chronic persistent illness who showed a tendency to deteriorate over time. He referred to the former disease as manic-depressive insanity and the latter as dementia praecox and emphasised that auditory hallucinations and lack of volition were relatively more common in dementia praecox. He later subdivided dementia praecox into Hebephrenia, Katatonia and Dementia Paranoides (Shorter 1997). He expected that researchers would in future find definite anatomical correlates or specific risk factors which would eventually confirm his classification.

It is sometimes not appreciated that Kraepelin came to doubt his own classification. In 1920 he said:

> "No experienced psychiatrist will deny that there are an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect" (Kraepelin 1920).

His system was however widely adopted and continues to influence many modern classifications. His unification of bipolar and unipolar illness into one category caused strong opposition in Germany, especially by Carl Wernicke (1848-1905) who distinguished five separate types of unipolar melancholia, 'folie circulaire', 'folie a double forme' as well as recurrent unipolar mania. Wernicke's opinions were the basis for future work by Kleist (1911;1926) in Frankfurt and Leonard (1957) in Berlin. Kleist and Leonard both regarded recurrent unipolar melancholia, recurrent unipolar mania and manic depressive insanity as separate disorders. Leonard (1979) added a further category of cycloid psychosis which he described as a recurrent non-affective illness of good prognosis which in which delusions or hallucinations are present. Wernicke's, Kleist's and Leonard's ideas never gained widespread acceptance. This may have been due in part to their relative complexity.

It was generally acknowledged that some people who displayed psychotic features fell between the descriptions of dementia praecox (schizophrenia) and manic-depressive psychosis. In 1933 a further diagnostic category termed 'Schizoaffective Psychosis' (Kasanin 1933) was introduced to account for those cases in which the signs

of schizophrenia and manic-depressive psychosis were found in equal measure. Gabriel Langfeldt (1939) separated schizophrenia into three varieties: process, reactive and atypical. In the process variety, the course was usually deteriorating and patents would show blunting of affect and loss of will. In reactive schizophrenia, the outcome was much more favourable and the symptoms displayed were almost equivalent to that described in schizoaffective psychosis. The atypical group comprised patients who were difficult to fit into the other two categories. Typically patients would suffer from vague, shifting delusions and hallucinations which lacked a bizarre and alien quality. In a 7-10 year follow up of patients with the atypical subtype, 1 out of 13 patients followed up had completely recovered. Langfeldt (1939;1969) coined the term schizophreniform psychosis to refer to the group of patients with 'atypical schizophrenia'.

Eugen Bleuler (1898-1927), like Kraepelin, assumed that the cause of schizophrenia lay in the substance of the brain but was more influenced by the psychological theories of his time. Bleuler proposed that that the fundamental features of schizophrenia were not poor outcome but the presence of five core symptoms (Bleuler 1911;1924).

Bleuler referred to his concept as schizophrenia, and for him symptoms such as hallucinations and delusions were regarded as of only secondary importance. It is clear that Bleuler's concept is considerable broader than that of Kraepelin, and the degree of interpretation involved in deciding whether the fundamental symptoms are present or absent is great. His ideas primarily concerned schizophrenia (dementia praecox), he did little to explicitly alter the concept of manic-depressive insanity.

Bleuler's concept of schizophrenia became very popular in North America whereas in Europe Kraepelin's concept of dementia praecox remained dominant. Consistent with this transatlantic difference in thinking, diagnostic practices diverged widely. Schizophrenia, being a relatively broad concept in North America, was a common diagnosis which was used in people we would not now regard as suffering from psychotic symptoms. In Europe, Schizophrenia was a relatively narrower concept and patients with psychotic symptoms were much more likely to receive a diagnosis of manic-depression than schizophrenia. This was clearly demonstrated in the US-UK Diagnostic Project (Cooper et al. 1972).

Using identical interviewing methods and diagnostic criteria, psychiatrists in the US and in the UK made detailed studies of consecutive admissions to mental hospitals in the two countries (Cooper et al. 1972). These comparisons showed that, while that the symptoms displayed by patients in the two countries were virtually identical, the proportion of people diagnosed with schizophrenia was far greater in New York and the proportion of people diagnosed with affective disorders greater in London. This appeared to be due to the fact that US psychiatrists had a much broader concept of schizophrenia than UK psychiatrists, and that the diagnosis embraced many patients who would have received a diagnosis of depression, manic-depression or even neurosis in the UK. A later study (The International Pilot Study of Schizophrenia, WHO 1973) also confirmed that psychiatrists in Washington and Moscow had much broader concepts of schizophrenia than psychiatrists in the other centres (Columbia, Czechoslovakia, Denmark, India, Nigeria, Taiwan and the UK).

Jaspers (1883-1969) made no attempt to devise a diagnostic classification of his own, but was interested in the assumptions made by those who had. He pointed out that by assuming each disease had its own distinct cause, symptoms, course, outcome and pathology that the same classification would result regardless of which criteria were used (Jaspers 1963). He also pointed out that no entities found within the field of psychiatry had been found had ever fulfilled these exacting criteria. Many non-psychiatric conditions (e.g. TB, lung cancer) would also fail these criteria in spite of detailed knowledge of their pathology. Jasper's believed instead that disease entities were concepts which could be endlessly refined.

Kurt Schneider (1887-1967) made further refinements to the diagnosis of schizophrenia by introducing symptoms 'first rank features' which, in the absence of organic brain disease, were pathognomic of schizophrenia (Schneider 1959). Many of these 'first rank features' may be interpreted as a failure to distinguish ideas or impulses which arise from within an individual from those which are imposed from outside. Schneider did not regard them as having any special theoretical significance. Instead he regarded them simply as convenient diagnostic aids and accepted that not all people who suffered from schizophrenia would show the symptoms. Modern diagnostic criteria incorporate his fist rank features to varying degrees. Although some studies of people with manic-depressive psychosis would show that they also display first rank symptoms, perhaps Schneider's greatest contribution was to the establishment of core symptoms whose presence or absence could be agreed upon with greater reliability than had previously been realised.

Twentieth century *unitarian* thinkers are considerably less common than in the 19th century. This probably reflects the increasing interest in Kraepelin's binary classification and the search for disease entities. Bonhoeffer (1909) believed that the brain was endowed with only a few stereotyped responses to disease. Although he divided psychosis into organic and functional, his writings emphasise the importance of careful description over the search for specific causes. Karl Menninger (1963) and other writers of a psychodynamic persuasion believed that mental illness was a continuum from health to disease, and that each person was unique. Crow (1987) and Kendell's (1980) work has also been interpreted in a Unitarian context. Crow (1987) expressed the view that schizophrenia and manic-depressive psychosis were parts on a continuum of psychosis to which he has variously attributed to genetic causes or viruses. Kendell (1980) made an unfruitful search for discontinuities within the symptoms and outcome of functional psychoses and also within the various subtypes of depression that existed at one time. His work is cited by some as support for a unitary concept of psychosis.

1.5 The reincarnation of bipolar disorder

Kraepelin's classification of affective disorders assumed that there was only one endogenous affective psychosis, namely manic-depressive insanity. Although this formulation was criticised widely, its detractors failed to convince practicing clinicians (Angst and Marneros 2001). In 1966 two large scale studies were published which separated manic-depressive insanity into bipolar and unipolar disorders. The first (Angst 1966) study examined 326 patients treated at the University Hospital of Zurich between 1959 and 1963, 638 parents, 1236 siblings, 111 half siblings, 425 children and

189 husbands and wives. Angst (1973) and others applied diagnoses, which were apparently non-operationalised, to the subjects themselves and their probands. Information was obtained from several sources including case records, relatives and employment records. Groups of patients and their relatives were compared in terms of gender, family history, age of onset, precipitating factors and comorbid medical and psychiatric conditions. The study is published only once in English (Angst 1973 and personal communication) although the conclusions were re-published in an article by Angst and Marneros (2001), shown in the following table.

Table 1.5: Conclusions from Angst's 1966 study

1.	Genetic and environmental factors have independent and interactive effects on the aetiology of endogenous depression
2.	Endogenous unipolar depression has a female preponderance whereas in bipolar disorder, the sexes are equally represented
3.	Manic-depressive insanity is not homogeneous. The unipolar form differs from bipolar disorder in several important respects (genetics, gender, course, premorbid personality)
4.	Depression of late onset seems to 'belong to unipolar depression having only a weak relationship to bipolar disorder

A second study (Perris 1966) concerned 138 bipolar and 139 unipolar depressive probands treated on one or more occasions at the Sidsjön Mental Hospital in Sundsvall

during the period 1950-1963. Like Angst (1966) the risk of illness in close relatives, precipitating factors and course were examined. In addition, assessments were also made of childhood environment, celibacy rate, body build, personality, perception (flicker fusion and colour), the EEG, therapy and mortality. Like Angst (1966) the study concludes that unipolar and bipolar disorders are separate in terms of heredity, celibacy rate, personality, flicker threshold, EEG profile, ECT response, course and mortality. Later studies generally confirmed their findings and more recently, and for similar reasons, bipolar disorder has been further subdivided into recurrent mania and depressive or mixed episodes (Bipolar I Disorder) and recurrent depression with episodes of hypomania (Bipolar II disorder).

1.6 The International Classification of Diseases

At the Congress of Mental Medicine held in Antwerp in 1885 a commission was appointed under the chairmanship of a Dr Morel from Ghent to consider whether existing classifications could be combined and a typology of mental disorders derived upon which the majority of psychiatrists could agree. The resulting classification, a forerunner of the International Classification of Diseases, consisted of 11 categories devised on the basis of majority verdict within the committee itself. The classification included melancholia, periodic insanity (folie a double forme by another name), progressive systematic insanity and insane neurosis amongst others. Whilst Morel and his colleagues were engaged in this ultimately fruitless process others were engaged in the same task. Even when the various conflicting classifications were eventually

published, many organisations insisted on using their own (e.g. The New York State Commission on Lunacy used their own classification as late as 1968).

Probably because of the obvious importance of mortality statistics to governments a International List of Causes of Death was produced which gained progressively widespread acceptance. The list was produced by the International Statistical Institute who in 1899 recommended that it should be taken over by a more weighty governmental body. In 1948 the 6th revision of the list was published as the International Statistical Classification of Diseases, Injuries and Causes of Death by the World Health Organisation (WHO). Section V of this publication entitled 'Mental, Psychoneurotic and Personality Disorders' consisted of 10 categories of psychosis and nine of psychoneurosis. Most were subdivided further. Although the classification was recommended for use by all member states of the WHO, it did not come into widespread use and in the US it was completely ignored.

Within psychiatry there was widespread disenchantment with international classification, despite the fact that most psychiatrists recognised the need for one. There was a growing recognition of the low reliability of clinical diagnosis and recognition that, whatever classification was used, a large number of patients seemed to fall between categories. A report by Stengel (1959) commissioned by the WHO concluded that the main reason for the current impasse lay in the aetiological implications of diagnostic terms, upon which there was widespread disagreement. Many categories carried explicit assumptions (e.g. psychogenic psychosis, reactive depression) whilst others were less obvious but nonetheless implied (involutional melancholia). Stengel recommended that all diagnoses should therefore be explicitly shorn of their aetiological underpinnings and

regarded simply as 'operational definitions' for certain types of abnormal behaviour. This conclusion was reached simultaneously by another psychiatrist Carl Hempel, although his recommendations were based upon considerations of low reliability.

The seventh edition of the International Classification contained a mental disorders section identical to that of the 6th. The 8th edition was entirely self-sufficient consisting of categories for all types of psychiatric disturbance and, in contrast to the preceding editions, were based on extensive international collaboration. Two separate glossaries were produced in the US and UK which contained authoritative diagnostic criteria by which the classification could be applied. The classification was referred to extensively in the literature but contained no operational definitions for specific mental disorders, failed to define 'mental disorder', failed to follow a consistent textual form throughout and some disorders continued to include aetiological underpinnings.

The 9th edition of the International Classification of Diseases was introduced in 1975 and although only minor modifications were made to the form of the previous edition, the scope was expanded dramatically to reflect the expanding boundaries of psychiatric practice. The category of involutional melancholia was also dropped but the categories of neurotic depression and reactive psychosis remained. Manic-depression and schizophrenia remained as separate categories although patients with both symptoms of affective disorder and schizophrenia were classified as having schizophrenia.

The 10th edition of the International Classification finally made the shift to operational definitions of mental disorder. Like its predecessors, it has a hierarchy of classification in which organic disorders take precedence over other categories when two

or more separate criteria are met by the same patient. Affective disorders and schizophrenia are at the same level. A diagnosis of schizophrenia may not be made if a full manic or depressive syndrome is present, unless the schizophrenic symptoms clearly predated the affective disturbance. In the 10th edition (revised), the distinction between psychosis and neurosis was dropped and mood disorders were all subsumed under one category, mood disorder. 'Manic-depressive psychosis' was also replaced with the term 'bipolar disorder'.

1.7 The American classification

By the early 1940s American Psychiatry had three competing official nosologies, none of them in line with the International Classification. It was obvious that this made communication between clinicians or researchers unnecessarily difficult and so in 1944 the American Psychiatric Association's Special Committee on Reorganisation was formed. William Menninger and a group of like-minded psychiatrists, fearful that psychosocial and psychodynamic concerns would be ignored, formed the Group for the Advancement of Psychiatry (GAP). The Diagnostic and Statistical Manual of the American Medical Association (DSM-I) was finally published in 1952 and its content was probably disproportionately influenced by GAP. DSM I was never accepted by the American Medical Association and there were difficulties in translating its categories into those of the International Classification. DSM-II was finally published in 1968 dropping several terms, such as 'schizophrenic reaction', in an attempt to distance classification from aetiological theory. However, DSM-II was not a major transformation over DSM-I and the majority of American Psychiatrists continue to value

psychodynamic and social theories over ones based on description, statistics and neurobiology.

DSM-III and DSM-IIIR reflect a major shift in psychiatric thinking within the US. Interest in psychodynamic theory was in rapid decline and the forthcoming ICD-9 prompted large revisions to the previous version. DSM-III and IIIR attempt to be *atheoretical* although concepts such as melancholic depression persisted. The manuals were based on a greater consideration of empirical patient data and the criteria for each disorder were spelled out in much greater detail than before. The move to operationalised diagnostic criteria in DSM-IIIR reflects a growing move to make psychiatric diagnoses more reliable. The concept of schizophrenia presented in DSM-III and IIIR is considerably narrower than that of its predecessors, reflecting the findings of the US/UK diagnostic project and the International Pilot study. Manic-depression is removed altogether and replaced with bipolar disorder. It is also further subdivided into type I, recurrent depression with mania, and bipolar II, recurring depression and hypomania.

DSM-IV borrowed extensively from ICD-10 and incorporated several new ideas over its predecessor. However, issues regarding the validity of psychiatric diagnoses are as pertinent today as they were centuries ago. Although two classifications now exist, each with high inter-rater reliability, there is still some disagreement about the correct nosology of mental disorders. The differences between the current classifications are illustrated in the following tables. Diagnoses in medicine as a whole appear to be more widely accepted and generate less debate amongst practising clinicians (with occasional

exceptions). The models on which these disease entities are based may also inform the debate surrounding the validity of mental disorder.

Table 1.6 and 1.7: American and WHO classifications of mental disorders

DSM-IV Schizophrenia	ICD-10 Schizophrenia
A. Characteristics of Symptoms: two or more of the following, each present for a significant portion of time during a one month period (or less if successfully treated): • Delusions • Hallucinations • Disorganised speech • Grossly disorganised or catatonic behaviour • Negative symptoms, i.e. affective flattening, alogia or avolition (Note: Only one "A" symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two more voices conversing with each other). B. Social/Occupational Dysfunction C. Duration: continuous signs of the disturbance persist for at least six months. This six month period must include at least one month of symptoms that meet criterion A.	1. At least one of the following: • Thought echo, thought insertion or withdrawal and thought broadcasting. • Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations, and delusional perception. • Hallucinatory voices giving a running commentary on the patient's behaviour or discussing him/her between themselves or other types of hallucinatory voices coming from some part of the body. • Persistent delusions of other kinds that are culturally inappropriate or implausible, such as religious or political identity, superhuman powers and ability etc. 2. Or, at least two of the following: • Persistent hallucinations in any modality, when accompanied by either fleeting or half-formed delusions without clear affective content or by persistent over-valued ideas or when occurring every day for weeks or months on end. • Breaks of interpolations in the train of thought, resulting in incoherence or irrelevant speech or neologisms. • Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor. • Negative symptoms such as marked apathy, paucity of speech and blunting or incongruity of emotional responses. • A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

DSM IV Bipolar Disorder	ICD-10 Bipolar Disorder
Bipolar I A. Criteria, except for duration, have been met for a Manic, Hypomanic, Mixed, or Major Depressive Episode. B. There has previously been at least one Manic Episode or Mixed Episode. C. The mood symptoms cause clinically significant distress or impairment. D. The mood episodes in Criteria A and B are not better accounted for by another psychotic disorder. E. The mood symptoms in Criteria A and B are not due to the direct physiological effects of a substance or a general medical condition. **Bipolar II** A. Presence (or history) of one or more Major Depressive Episodes. B. Presence (or history) of at least one Hypomanic Episode. C. There has never been a Manic or Mixed Episode. D. The mood episodes in Criteria A and B are not better accounted for by another psychotic disorder. E. The symptoms cause clinically significant distress or impairment.	A. There has been at least one hypomanic or manic episode in the past B. In addition, there must have been at least one other affective episode, hypomanic, manic, depressive or mixed

DSM	ICD
Mania Distinct periods of elation, irritability or mood disturbance for ≥ 1 week Three of the following: Inflated self-esteem or grandiosity (may be delusional) Decreased need for sleep Increased talkativeness or pressure of speech Flight of ideas or racing thoughts Distractibility Increase in goal directed behaviour or psychomotor agitation Indiscreet behaviour with poor judgement Symptoms do not meet criteria for mixed episode Marked impairment in function Not due to drug misuse / physical illness	**Mania** Elated, expansive or irritable mood for ≥ 1 week Three of the following, or four if mood is irritable: Increased activity or physical restlessness Increased talkativeness Flight of ideas / racing thoughts Loss of normal social inhibitions resulting in inappropriate behaviour Decreased need for sleep Inflated self esteem or grandiosity Distractibility or constant changes in activity or plans Reckless or foolhardy behaviour Marked sexual energy or sexual indiscretions Not due to drug misuse or organic disorder
Hypomania Persistently elevated, expansive, or irritable mood, lasting 4 days, different from the usual mood and three of the following: Inflated self-esteem or grandiosity Decreased need for sleep More talkative than usual or pressure to keep talking Flight of ideas or subjective experience that thoughts are racing Distractibility Increase in goal-directed activity or psychomotor agitation Excessive involvement in pleasurable activities that have a high potential for painful consequences The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.	**Hypomania** Elevated or irritable mood for at least 4 days, definitely abnormal for the individual concerned and at least three of the following: Increased activity or physical restlessness Increased talkativeness Difficulty in concentration or distractibility Decreased need for sleep Increased sexual energy Overspending or other types or reckless or irresponsible behaviour Increased sociability or overfamliarity The episode is not severe enough to cause marked impairment in functioning, social rejection or to necessitate hospitalization, and there are no psychotic features.

Depression (major depressive episode)	**Depression (mild)**
At least five of the following symptoms during the same two week period. One should be either depressed mood or loss of interest or pleasure. 1. Depressed mood 2. Diminished interest or pleasure 3. Weight loss or decrease in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness / guilt 8. Reduced concentration 9. Recurrent thoughts of death or suicidal ideation	At least 2 from: 1. Depressed mood (≥ 2 weeks) 2. Loss of interest or pleasure 3. Decreased energy / increased fatigueability Additional symptoms from the following to give a total of 4: 1. Loss of confidence/self esteem 2. Unreasonable self reproach or guilt 3. Recurrent thoughts of death or suicide 4. Diminished capacity to think or concentrate 5. Psychomotor agitation or retardation 6. Sleep disturbance 7. Change in appetite

1.8 Issues relating to disease in general

1.8.1 The medical model of disease

Early models of disease were usually based on the premise that diseases had a *real* existence outside the observer and were waiting to be discovered. This approach had shown early promise in the classification of species. Its application to medicine also had considerable initial success. Sydenham (1696) conceptualised disease as a collection of symptoms with a characteristic prognosis, but with the invention of the microscope by Leeuwenhoek and the study of post mortem tissue led to the discovery that many human illnesses seemed to be associated with an underlying bodily pathology and with the presence of identifiable microscopic pathogens. This shifted the predominant model of disease to one based on pathological rather than symptomatic criteria. Kreapelin's description of Dementia Praecox was consistent with Sydenham's syndromal model of disease, although he also believed that a defining pathological lesion would eventually be discovered by which the diagnosis would be confirmed.

This pathological model of disease continues to pervade both 'physical' and 'psychological' medicine. In the former, physical diseases are associated with pathology of the soma, whereas in the latter they were associated with disordered function or psychopathology. The term 'psychopathology' carries with it an implied psychological lesion contingent on the fact that, for most functional psychiatric illnesses, no obvious structural abnormality had been found. The ontological separation of mind and body (Descartes 1649) remained the dominant view in philosophy and medicine for many years. However, the concept of mental disease has received severe criticism from several quarters. A particularly vociferous critic, Thomas Szasz (1960;1991) wrote:

> If mental illnesses are diseases of the CNS, they are diseases of the brain not the mind. If they are the names of (mis)behaviour, they are forms of behaviour, not diseases. Psychiatrists have persuaded the scientific community, the courts, the media and the general public that the conditions they call mental disorders are diseases, that is, phenomena independent of motivation or will. The literal language of psychiatry allows motivated actions [kleptomania, pyromania, transvestism] to be called 'diseases'. (Szasz 1991)

Szasz assumes that diseases must be bodily disorders occurring as the result of a recognisable change in bodily structure. He asserts that because psychiatric disorders are defined by symptoms and behaviours, and because psychiatric diagnoses are subject to the social and political opinions of the time, they cannot be diseases. Szasz assumes robustness to physical (somatic) disease which doesn't stand up to closer scrutiny. Some physical diseases (e.g. migraine) continue to be defined on the basis of symptoms. Others (hypertension, diabetes) appear to be defined on the basis of an arbitrary criterion or are without a unifying single pathology.

The concept of illness itself is also a relatively insubstantial concept but is often defined as the subjective awareness of distress. People who are ill then exhibit 'illness behaviour' such as seeking help from a doctor. Although illness is often the reason that patients present to their doctors, this behaviour is subject to their perception of what the doctor is likely to offer. Patients may complain of illness to a doctor on the assumption

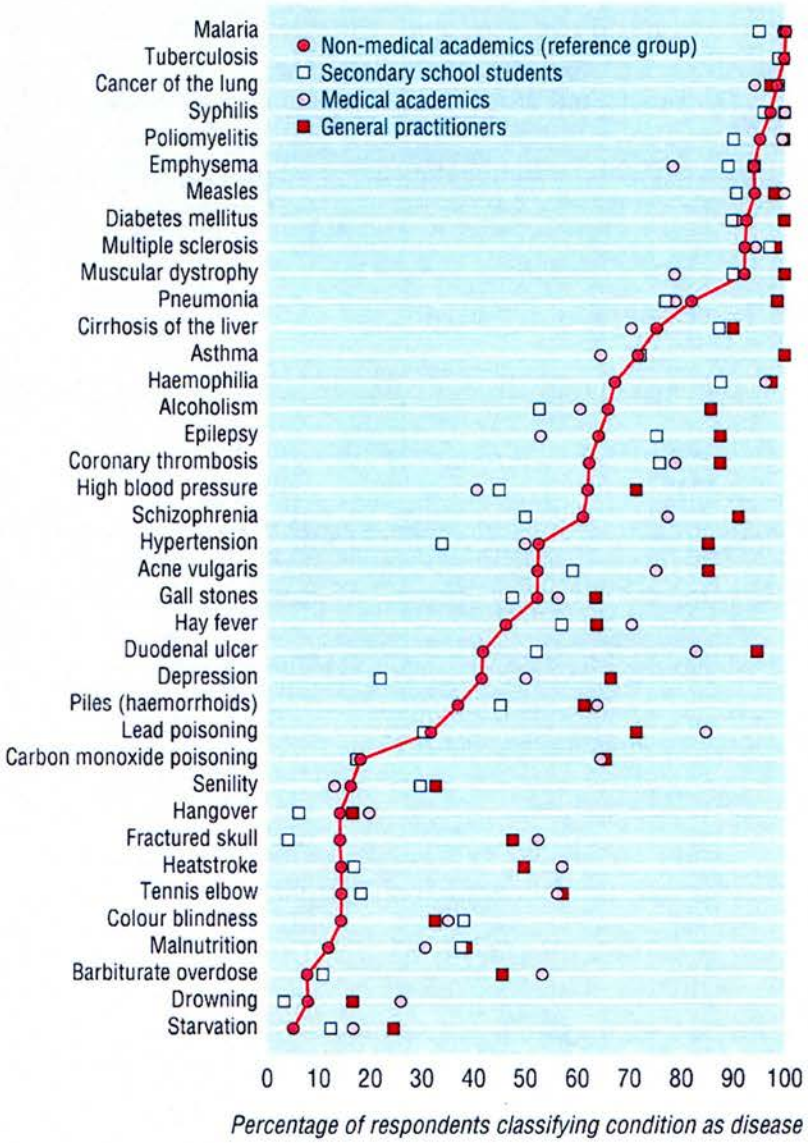
that this may be a more effective strategy than going to visit a priest for example. In this way diseases may be formed by doctors to explain what doctors treat rather than to define a natural entity which they have 'discovered'.

Finally, the notion that somatic illnesses affect the soma whereas mental illnesses affect the mind has also become progressively more unsafe. Although it has been known for a century that mercury poisoning could cause madness, the appreciation that mental illness might, in general, be the manifestation of brain disease has taken considerably longer. Modern neuroscientific techniques have demonstrated links between brain structure and mental illness. However, the finding of a brain abnormality does not in itself redefine a mental illness as a disease. By the medical model stated above, it would have to be a cause in each sufferer. Currently the evidence falls somewhat short of this criterion.

In spite of some limitations, the somatic model of disease continues to pervade (somatic) practice. It could be argued that an appreciation of what is meant by illness and disease is unimportant to clinical practice either because the issues are either self explanatory or because they are not of practical significance. However, the status-quo is sometimes disturbed when illnesses purporting to be diseases arise (e.g. neurasthenia, chronic fatigue syndrome). These situations stimulate lively debate amongst doctors, patients and even politicians. Usually the arguments appear polarised, either you believe chronic fatigue syndrome (CFS) is a physical disease which doctors should diagnose or you believe it is non-disease with no recognisable pathology and no real existence. Proponents of the concept are usually eager to search for causes and to describe possible pathologies.

To illustrate the lack of agreement amongst doctors about what constitutes a disease, two studies from the British Medical Journal are relevant (Campbell *et al.* 1979;Smith 2002). In the original 1979 study non-medical academics (the reference group), medical academics, general practitioners and secondary school students were asked which items from a list of 38 conditions, they considered to be diseases. Depression ranked 14th from bottom with around 40% of non-medical academics believing it to be a disease, schizophrenia was rated somewhat higher at position 20 from bottom with around 60% of non-medical academics believing it to be a real disease. The role of the doctor in diagnosis and treatment correlated strongly with the perception of the condition as a disease. Interestingly, whether the condition was defined in terms of an external cause, structure, function or syndrome was an important consideration for infectious diseases only.

Figure 1.8.1: Percentage of respondents classifying a condition as a disease. Figure originally appeared in BMJ (Smith 2002; Campbell et al 1979) and appears here with the permission of The BMJ Publishing Group



The second study (Smith 2002) asked clinicians to rate which conditions from a list of 200 they regarded as non-diseases. Chronic fatigue syndrome (27^{th}), adjustment reaction (38^{th}) and ADHD (46^{th}) all ranked relatively highly but few respondents regarded

depression or hallucinations (schizophrenia was not listed) as non-diseases. Many high ranking non-diseases shared a common aesthetic discomfort that could be attributed to the spectrum of normal variation. It is interesting that many more people now regard affective disorders and probably also schizophrenia as legitimate diseases in spite of the fact that criteria for a traditional medico-pathological cause are not fulfilled.

1.8.2 The biological disadvantage of disease

Scadding, a chest physician, has written extensively on the subject of disease. He noticed that patients with respiratory disease exhibited a limited number of stereotyped symptoms none of which were diagnostic of a specific condition. Scadding stated that the definitions used for individual diseases had in common the following factual implications in spite of their logical heterogeneity:

> A disease is the sum of the abnormal phenomena displayed by a group of living organisms in association with a characteristic or set of characteristics by which they differ from the norm of their species in such a way as to place them at a biological disadvantage (Scadding 1959;1967;1988)

Scadding pointed out that he was not attempting to define disease in general and that all attempts to do so were 'doomed to failure' (Mindham *et al.* 1992). However, he suggests that if a condition were manifest so that the sufferer was not placed at a biological disadvantage (i.e. reduced lifespan or fertility), then this would be outwith the remit of medicine.

Scadding and Kendell wrote specifically about the problems of applying a 'biological disadvantage criterion' to psychiatry (Kendell 1975;Scadding 1990). Biological disadvantage (i.e. reduced fertility or survival) might not be easy to apply to neurotic illness if the term disease is to define the legitimate territory of medicine. Schizophrenia and affective disorders limit the social and occupational function of sufferers and mortality and fertility are both adversely affected. However, depressive symptoms occurring after loss events are sufficiently common to cast doubt on whether the sufferers are indeed biologically disadvantaged compared to the general population. Such a deviation might be seen as an understandable reaction and not abnormal by any statistical definition. Homosexuality might also be regarded in this framework as a disease since is associated with the biological disadvantage of reduced fecundity. Diseases such as sickle cell anaemia also point to the environmental dependence of Scadding's definition since some diseases, like sickle cell disease, may be advantageous in some environs (e.g. areas where malaria is endemic).

1.8.3 Alternative models of disease

Attempts to clarify the concept of disease have been offered from many quarters. Many more models of mental disorder exist outside medicine although these have not traditionally been the concern of doctors and do not suggest a natural disease classification.

Disease is often interpreted as implying qualitative imperfection or departure from what is normal. Unfortunately there have been too many definitions of 'normal' to

make this definition any less ambiguous. Consider the following statistical rule: if a physical or psychological measurement lies outside the range defined by the mean, plus or minus two standard deviations, then that individual is diseased. Under such a rule, 5% of all individuals would be classified as diseased on a single measurement and the number classified as diseased would rise with each test performed. People of high stature or intelligence would also be so classified as diseased. Imperfection might also be interpreted as socially undesirable. This definition would lead to large cultural variations in disease definition although some would argue that imperfection is already the model adopted for disease in general, explains why some diseases become non-diseases (e.g. homosexuality) and why the insane are revered in some cultures but not others.

Disease might also be conceived of as 'what doctors treat'. Kraupl-Taylor (1971) attempted to define disease as having a statistical abnormality by the standards of the population, therapeutic concern by the patient and by those in his social environment and medical concern. This definition has attracted very heavy criticism (Kendell 1975;Scadding 1990) because of its obvious tautology. However, its legacy exists in both modern classification schemes as a clinical significance criterion.

Patients diagnosed as suffering from a disease are usually then offered a medical treatment. Some have suggested that the disease label itself is nothing but a disguised prescription (Linder 1965) or plan of action. In the BMJ survey of non-diseases (Campbell et al. 1979) non-medical academics were significantly more likely to regard a condition as a disease when the doctor had a role in its management. Conditions such as chronic fatigue syndrome, club foot or multiple personality disorder are regarded by a

proportion of clinicians as diseases. Those who regard the patient as ill will usually regard treatment or further investigation as necessary. However, debate surrounding the publication of the BMJ's most recent non-disease articles (Smith 2002) and the involvement of doctors in the normal process of childbirth suggest that this is an inconsistently applied criteria and that some doctors would pragmatically treat conditions they did not regard as diseases (e.g. big ears/nose, unsightly mole, anxiety about penis size) on the basis that their intervention would do more good than harm.

Table 1.8.3: Definitions of disease

Model	Summary of assumptions
Medical-pathological definition (Sydenham 1696;Szasz 1960)	Assumes diseases are associated with a necessary cause (e.g. bacterial infection of lesion) or have a replicable morbid anatomy
Biological disadvantage (Scadding 1972)	Assumes that sufferers from a disease possess a common characteristic such as to place them at a biological disadvantage compared to a normal population
Plan of action (Linder 1965)	Assumes disease labels are justifications for treatments and further investigations.
Syndrome with characteristic symptoms and outcome (Kendell 1975)	Assumes diseases represent circumscribed concepts distinguished from others by a bimodal distribution of scores on a discriminant function.
Disease as imperfection (Cohen 1943;1953)	Assumes diseases are quantitative or qualitative deviations form a desirable norm
Disease as 'concept' (Aristotle)	Assumes diseases are man-made abstractions with no independent existence.

1.8.4 Diseases as concepts

The disease model is based on the Platonic or Realist notion that diseases have a real existence independent of the observer. Even those criteria which define diseases by less stringent criteria, short of a necessary cause, may make assumptions that diseases are real phenomena and consequently search endlessly for an elusive lesion or characteristic pathology.

An alternative view of disease was proposed by Aristotle (384-322 BC) and Hippocrates (460-377 BC) both of whom believed that diseases were man-made abstractions with no independent existence of their own and justified only by their utility. Their view of disease has been named Hippocratic, biographical, Nominalist or empirical. Kendell suggests that the dominant views of psychiatrists in this country are empirical in nature. Psychiatrists, in general, probably do not believe that schizophrenia or depression have a real existence of their own, but are simply names given to recognisable syndromes on the basis that their identification has some utility (Kendell 1975).

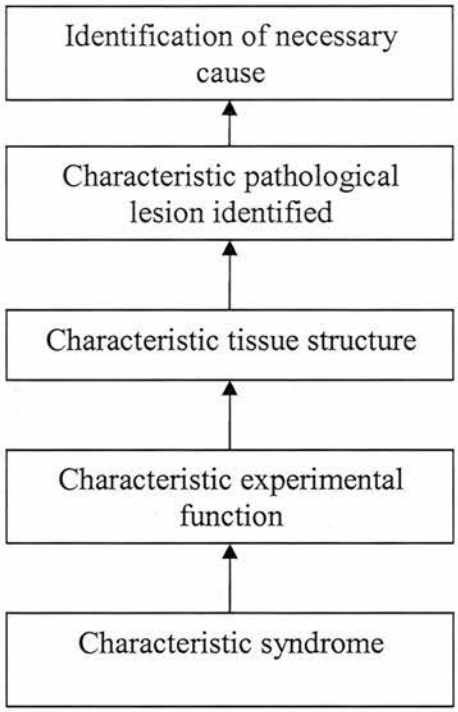
It is difficult to be critical of the 'concept model' since it seems to have obvious face validity. Critics might claim that malaria was 'discovered' since the plasmodium organism is believed to be the necessary cause of every single case. Isolation of an infective agent might therefore be taken as evidence that the associated disease is a real disease entity. However, the cause of TB, to take one example, might be regarded as multi-factorial (e.g. poverty, host immunosuppression) in that classification by infective organism defines a disorder at a point where medical intervention is likely to yield the greatest benefit.

1.8.5 The spectrum of disease

The search for a unifying concept of disease may be an ultimately fruitless unscientific quest. Advances in the aetiology of mental disorders will probably not be achieved by a better definition of what is meant by 'disease'. The meaning of the term disease is a slippery concept which relies as much on pragmatic issues as it does on scientific considerations.

The utility of a classification based on characteristic tissue pathology has been shown for centuries. The pathology enables relatively reliable and objective assessments to be made, even when the definition of disease is based on an arbitrary criterion. Other definitions may be achieved using indirect assessments of tissue structure such as x-rays or other radiological investigations. These also provide a relatively reliable and objective means of disease identification, although because the diseased organ is not visualised directly, the diseases thus identified are probably less robust than those identified directly by their pathology. Still less reliable are indirect and direct measures of patient function (e.g. symptoms, neuropsychology, and neurophysiology). These measures are affected by patient effort, the effects of medication, personality, intelligence and social background to a greater or lesser extent. Functional imaging studies are assumed to be more reliable than patients' self report because the experimental paradigm controls for factors which confound patient interviews or self report.

Figure 1.8.5: The hierarchy of disease



At each stage the term characteristic is used to imply that the measurement or finding should usually be found in the disorder and be useful in distinguishing it from other disorders with similar presentations. For a characteristic to be useful it must separate diseased and non-diseased individuals so that the substantial majority can be allocated to one category or another with few intermediate or equivocal cases.

1.9 Diagnostic validity applied to schizophrenia and bipolar disorder

Psychiatric disorder differs from the disease concept used in the majority of physical medicine in that it is usually defined on the basis of symptoms and signs rather than on the presence of a lesion or other demonstrable abnormality. Often the term

disorder is usually preferred over disease (Rather 1959) presumably because classifiers feel that to designate psychiatric 'conditions' as disease is somewhat premature without a more detailed knowledge of their physical pathology. However, the definition of what is meant by disorder is not without many of the same semantic difficulties.

Schizophrenia and bipolar disorder are both defined on the basis of their symptoms. It is uncertain as to whether they constitute separate disease entities since the aetiology of these disorders is uncertain and the predictive value of each diagnosis in terms of treatment response and prognosis is not particularly strong. This uncertainty is reflected in both DSM-IV and ICD 10 with the use of the term disorder instead of disease.

The diagnostic validity of schizophrenia and bipolar disorder has been tested using several criteria. The remainer of this chapter will discuss the genetic evidence before considering those studies which have used multivariate statistics to examine their separation on clinical or other grounds. The following chapter will review the neuroimaging and neuropsychological literature.

1.10 Genetic considerations

A family history of psychosis has long been established as one of the strongest risk factors for the development of the disorder in unaffected probands (Mitchell et al. 1993;Cannon and Jones 1996). Although the heritability estimates for schizophrenia and bipolar disorder suggest one or more major environmental influences, in practice it has been difficult to establish what these are. Obstetric complications, cannabis, winter birth and maternal influenza are all replicated risk factors. However, the population fraction

of schizophrenia and bipolar disorder for which these environmental factors appear responsible suggests that there may be many more environmental risk factors still to be found (Jones and Cannon 1998;Murray *et al.* 2003).

The model of genetic liability applied most often in medicine is typically that of Mendelian transmission (autosomal dominant, recessive and sex linked). Schizophrenia and bipolar disorder have been extensively investigated from this standpoint. However, several problems with this model emerged early on. Firstly, the pattern of affected family members within families frequently did not follow a typical Mendelian pattern. In order to accommodate this, genetic models have been used which allow the assumption of complete penetrance to be relaxed, allowing genes to be expressed in only a proportion of people who carry them. This model is typically used in molecular genetic studies where researchers look for linkage between a given region of DNA and a psychiatric disorder or alternatively, start with a candidate gene in mind and search for families in which the disorder and candidate gene co-occur.

Many molecular genetic studies of both schizophrenia and bipolar disorder have been completed. However, it is commonplace for initial claims of genetic linkage to be unconfirmed by future genetic studies and even in those studies where linkage has been replicated; it is common for there to be at least some negative studies. This suggests either the phenotype is itself sub-optimally defined, that the genes themselves are specific to certain populations, that there are instead many genes for psychosis or that the studies finding negative results have insufficient statistical power. In any case, substantial evidence that there are one or more genes of major effect in either schizophrenia or bipolar disorder is still lacking. Furthermore, most studies that have

tried to establish whether schizophrenia and bipolar disorder breed true have failed to find evidence that this is so (see table 1.10). This suggests that, either the disorders are themselves sub-optimally defined and/or there must be at least some genes which predispose to both disorders.

Table 1.10: Studies examining whether schizophrenia and bipolar disorder 'breed true'

Study	Summary
Rüdin (1916)	Showed that the risk of an unaffected sibling of a schizophrenic proband developing a non-schizophrenic (usually affective) psychosis was (10.3%). Also showed that the risk of a unaffected sibling developing schizophrenia was higher if the affected sibling had a non-schizophrenic (usually affective) psychosis (8.2%) than if the affected sibling was schizophrenic (6.2%)
Odegaard (1972)	Showed that 19%of the ill relatives of probands with manic-depression were diagnosed as schizophrenic. Showed also that 15% of the ill relatives of "severe defect" schizophrenics were affectively unwell.
Mendelwicz et al (1980)	Found a risk of 8.6% for affective illness in the first degree relatives of schizophrenic probands
Tsuang et al (1980)	Relatives of people with schizophrenia were more likely to receive a diagnosis if affective disorder (7.7%) than controls (5.0%). An increased risk of schizophrenia was also found in the relatives of people with a previous diagnosis of 'mania' (3%) or depression (1.6%) compared to controls (0.6%). Relative diagnoses were based on personal or 'approximate' interviews.
Kendler et al (1986)	The risk of schizophrenia in the relatives of people with psychotic affective disorder was increased (4.3%) compared to normal controls (0.2%).The morbid risk of bipolar disorder was higher in the relatives of patients with schizophrenia (1.2%), schizophreniform disorder (1.3%) and schizoaffective disorder (3.8%) compared to surgical control probands (0.3%).
Kendler et al (1993a;1993b)	The risk of schizophrenia was increased in psychotic affective disorder (2.8%) but not in non-psychotic affective disorders (0.6%) compared to controls (0.5%) using operational criteria applied at personal interview.

Study	Summary
Sham et al (1994)	The morbid risk of bipolar disorder in the first degree relatives of schizophrenic probands was approximately 2.1% (95%CI 0 to 4.5). Diagnoses were made by maternal interviews. The morbid risk of schizophrenia in the first degree relatives of bipolar probands was approximately 4.3% (95%CI 0 to 10.3). Diagnoses were made by maternal interviews and no control group was assessed.
Henn et al (1995)	Families with one or more schizophrenic siblings found that 8.3% had a family history of affective disorder only.
Erlenmeyer-Kimling et al (1997)	Relatives of schizophrenia subjects were more likely to develop either broadly defined affective disorder (6%) or Bipolar I Disorder (2.4%) compared to controls (0%). None of the unaffected relatives or controls developed Bipolar II Disorder. The lifetime risk of schizoaffective psychosis in families affected by affective disorder was increased (6%) compared to controls (0.7%). If a more stringent definition of schizophrenia was adopted, none of the unaffected relatives or controls satisfied this definition.
Valles et al (2000)	Relatives of patients with bipolar disorder had an increased risk of schizophrenia. RR=4.9 (95%CI 1.3 to 18.8). The presence of more than one affected family member also increased the risk but the presence psychotic symptoms conferred no additional liability to schizophrenia in relatives.

Molecular studies which were not primarily designed to test this specific hypothesis have also cast some light on the on the issue. St Clair et al (1990) showed that in a family with a balanced 1:11 translocation, those with the translocation suffered from several diagnoses including schizophrenia and affective illnesses. In several studies of regions from chromosome 22, linkage has also been shown to both schizophrenia and bipolar disorder from the same loci (Saleem *et al.* 2001;Kelsoe *et al.* 2001;Berrettini 2000).

It would appear therefore that schizophrenia and bipolar disorder do not breed true and that the mode of genetic inheritance is either polygenetic, although the presence of one or more major genes in some population remains a possibility. This latter assertion has also been confirmed using structural equation models in which the likely model of genetic transmission has been chosen on the basis of which one best fits the observed data. In each of the studies which have addressed this particular issue, the presence of multiple loci of quantitative effect has been suggested (O'Rourke *et al.* 1982;Risch and Baron 1984;McGue *et al.* 1985).

1.11 Multivariate methods to derive or confirm categories

1.11.1 Discriminant function analysis

Discriminant function analysis (DFA, Fisher 1936) is used to determine which variables discriminate between two or more naturally occurring groups. For example, a researcher may want to investigate which variables discriminate between schizophrenia and manic-depression. Discriminant function analysis could be used to determine which variables are the best predictors of a person belonging to a given diagnostic group. Although the technique is able to ascertain which combination of variables fits the data best, if the model is 'fitted' on the dataset on which it is also used to predict, then the model is likely to show greater predictive value than is likely to be borne out in practice. For this reason, DFA should be combined with techniques which predict the group membership of an observation without using that observation to fit the discriminant function itself. This process is known as Jacknifing.

There are few established rules for how the success of a discriminant function analysis should be measured. The performance of the predicted categories can be compared against the known clinical diagnosis and error rates for each prediction (i.e. sensitivity and specificity) can be calculated. Alternatively, Moran (1966) and Kendell (1968) have both suggested that a bimodal distribution of scores on a discriminant function, obtained on an unselected population and cross validated on a second should be an accepted criterion of validity for diagnostic categories. However, this approach could be criticized for being somewhat tautological since the model derived will be the one which discriminates best between two populations and will tend to be at least bimodal.

Using DFA Kendell and Gourley (1970) tried to establish bimodality on a discriminant function within a sample of 250 admissions to the Netherne Hospital in Surrey, studied as part of the US/UK Diagnostic project (Cooper et al. 1972). With unselected functional psychoses and also in 105 patients with schizoaffective admitted to one of three London Hospitals during a similar period. They attempted, but failed to show that the relationship between a discriminant function and outcome was non-linear (i.e. not unimodal). The details of their methods are unclear and would not allow replication.

Cloninger et al (1985) applied DFA to two random and equal samples (n=250 each) of psychiatric outpatients. Two samples were used, one to extract a discriminant rule and the other for its validation. On the basis of a symptom score derived from patient interviews a linear discriminant rule was derived on the first sample of patients. The authors report than in this first sample 83.7% of the schizophrenic patients were

correctly allocated using this rule and only 4.4% of non-schizophrenic patients were wrongly allocated (specificity 95%). In applying the rule to the second sample, sensitivity was similar at 96%, but specificity diminished slightly to 77.5%. Sensitivity and specificity were not reported separately for bipolar disorder. These results suggest that although patients with schizophrenia may be separated from the majority of people with other psychotic illnesses, as significant number of people without schizophrenia are falsely allocated to the schizophrenic group. In essence this study supports the substantial but imperfect separation of schizophrenia from other psychoses on the basis of symptoms. Unlike Kendell et al (1970), the study uses a valid technique and is well reported.

Later studies have also examined symptoms and their linear combination as a discriminator between traditional diagnostic boundaries. Brief Psychiatric Rating Scale scores were used to classify a sample of 207 inpatients (schizophrenia, bipolar disorder, unipolar depression) admitted to inpatients psychiatric care in an 8 month period (Hopko et al. 2001). 68% of schizophrenic subjects, 60% of bipolars and 74% of unipolar depressive subjects were correctly allocated according to the analysis. However, no validation was conducted on a separate data set and there is some evidence that the discriminant analysis was 'overfitted'. Given these limitations, the ability of BPRS items to discriminate between schizophrenic and affective psychoses appears particularly disappointing.

Since personality, drug misuse and life events may all confound the presenting symptoms of psychotic illness, others have used DFA to attempt of validate clinical syndromes on the basis of objectively measured biological indices. Such an analysis

assumes that the biological variables measured are more closely related to the fundamental biology of the disorder. Few such analyses have been undertaken. Although some success has been achieved in separating schizophrenic patients from controls (e.g. dermatoglyphic abnormalities, Akabaliev et al. 2001) and other non-psychotic illnesses (e.g. autism, Bolte et al. 2002), fewer studies have compared schizophrenia with affective disorder. A study comparing 20 schizophrenic patients with an equal number of bipolar patients and healthy volunteers examined the ability of reaction time parameters to discriminate between the three groups. According to the discriminant function obtained, 78.3% of the entire sample was allocated to the correct group compared to the 33% expected by chance. 100% of the healthy control group was correctly classified compared to 80% of the schizophrenic group and 55% of the patients in the bipolar group (Fleck et al. 2001). Of the 20% of schizophrenics misclassified by the analysis, 15% were falsely allocated to the bipolar group and 5% to controls. Patients with bipolar disorder were mis-allocated more equally between the schizophrenic and healthy control groups (25% vs. 20%). The study did not validate the results in a second sample or use the method of Jacknifing to estimate the actual classification rate. An earlier study also attempted to discriminate between schizophrenia, bipolar disorder and healthy controls using tests of information processing (Tam *et al.* 1998). The study used a combination of 5 psychophysiological and neuropsychological tests and correctly classified 76% of the schizophrenic and bipolar samples.

The results of most published DFAs are probably more optimistic than would be borne out in practice. However, the results of both symptom and experimental studies appear to support the fact that schizophrenia can be consistently but imperfectly

discriminated from healthy controls and affective psychotic illness. Patients with bipolar disorder however, appear to be less well discriminated from schizophrenia, unipolar disorder and healthy controls. It may be the case that the disorders are imperfectly defined or that the biological indices which most efficiently separate the disorders have yet to be discovered. Alternatively the possibility that there are no 'disease entities' just continuous variation remains a possibility which remains to be excluded. The fact that schizophrenia can usually be discriminated from other disorders and healthy controls is however evidence against continuous variation.

1.11.2 Cluster and latent class analysis

Latent class analysis (LCA) and cluster analysis (Titterington et al. 1985;Gordon 1999) are a rather loose collection of statistical methods that can be used to assign cases to groups or classes (clusters). Group members are assigned so that they share certain properties with other members of their class and are differentiated from those in other groupings. Both LCA and cluster analysis have been used in an attempt to empirically separate the broadly defined psychosis into sub-categories. Studies have then compared the clinical diagnosis with the categories derived by LCA or cluster analysis in order to see if there is a match.

One of the first studies to apply cluster analysis to the problem of psychiatric classification was conducted by Lorr et al (1963) on a sample of patients from several hospitals, although the clinical characteristics of the patients are poorly described. The cluster analysis separated the sample in 6 clusters none of which closely resemble current or past diagnostic syndromes. The method of cluster analysis is not stated and

the patients do not appear to have been subject to standardized assessments according to operationally defined criteria. As a result, it is extremely difficult to draw any firm conclusions from the study. Subsequent studies have explicitly stated their method of patient ascertainment and have used structured schedules to determine diagnostic status according to pre-specified criteria. Most studies (Everitt et al. 1971;Kendler et al. 1998;Jorgensen and Jensen 1990;Manton et al. 1994) identified one or more clusters with a high proportion of schizophrenic members. One which failed to find a 'schizophrenic cluster' was based on a sample of patients with cycloid psychoses (Mojtabai 2000). A second used psychophysiological and dermatoglyphic variables as parameters by which to derive clusters (Sponheim et al. 2001). Clusters containing a high proportion of patients with bipolar disorder (Everitt et al. 1971) were found in only one study. Other studies found clusters which contained patients with mania and another psychotic disorder, usually schizophrenia (Jorgensen and Jensen 1990;Manton et al. 1994;Kendler et al. 1998). Its is interesting to note that the only study using biological variables determined in an experiment failed to derive clusters corresponding to traditional psychiatric disorders (Sponheim et al. 2001).

Attempts to derive diagnostic groupings using cluster analysis and latent class analysis

Study	Method	Patient sample	Findings
(Lorr et al 1960)	Cluster analysis based on statistical distance. Exact method unclear. Study methods and results are poorly reported.	566 patients from several hospitals, although the number 296 is also quoted in the sample methods and it is not clear which sample was used	C1: Excited-grandiose C2: Excited-hostile C3: Retarded C4: Intropunitive C5: Hostile-paranoid C6: Disorganized All clusters overlapped with two or more clinical diagnoses
(Everitt et al 1971)	Class I and Normap cluster analysis of symptom and historical data derived from mental state (PSE) and relative interview	Patients in Netherne (n=244, UK) and Brooklyn (n=236, US) hospitals formerly examined in US-UK diagnostic project	C1: Mania C2: Depressive psychosis C3: Paranoid schizophrenia C4: Chronic schizophrenia * 79% of C1 had a clinical diagnosis of mania, 70-80% of C3 had schizophrenia. More diagnostic heterogeneity was observed in C2 and C4 and in sample from Brooklyn Hospital
(Jorgensen et al 1990)	Latent class analysis of 11 items from the PSE	88 deluded first-episode inpatients. All items used for LCA were from the PSE	C1: Low levels of all psychotic symptoms C2: Schizophrenia* * Assignment to C2 had a 91% specificity and 84% sensitivity for CATEGO S+ schizophrenia
(Manton et al 1994)	Cluster analysis ('grade of membership analysis') of symptom, historical and follow-up data of patients included in the WHO IPSS	1202 patients in 9 countries (China, Columbia, Czechoslovakia, Denmark, Nigeria, UK and USSR)	C1: Positive psychotic symptoms with predominating auditory hallucinations C2: Positive psychotic symptoms with predominating depersonalization/derealisation C3: Negative symptoms C4: Severe depression (with delusions) C5: Mania/schizomania

			C1, C2 and C3 showed some agreement with the CATEGO S+ schizophrenia but C5 showed less agreement with a clinical diagnosis of mania. Individual patients could be members of 2 or more clusters.
(Kendler et al 1998)	Latent class analysis of historical symptom data collected using the OPCRIT symptom checklist	343 patients with broadly defined schizophrenia or affective illness ascertained from a population-based register.	C1: Classic schizophrenia* C2: Major depression* C3: Schizophreniform disorder C4: Bipolar schizomania C5: Schizodepression C6: Hebephrenia *High level of agreement with DSM criteria
(Mojtabai 2000)	Latent class analysis of three variables (affective episodes, anxiety-elation, family history of affective disorder)	60 patients drawn from Perris (1974) with cycloid psychoses	C1: Affective psychosis (13%) C2: Non-affective psychosis (87%) History of clinically defined 'affective psychosis' was associated with membership of C1.No subgroups reported.
(Sponheim et al 2001)	Ward's hierarchical cluster analysis of 4 biological measures (eye tracking, EEG, nail fold visibility and electro-dermal skin response)	163 psychotic patients	C1: 'Electrodermal deviant' C2: 'non-deviant group' C3: 'Combined nail fold plexus high visibility and ocular-motor dysfunction'' Clusters contradicted traditional diagnostic boundaries. Support for clustering was made by examination of 1st degree relatives who showed deficits which were more similar to the assigned cluster of their ill relative than those of other groups.

1.12 Conclusions

The diagnoses of schizophrenia and bipolar disorder have emerged over many centuries of observation. During this time, others have advanced their own theories which have been accepted or rejected usually on grounds of clinical consensus or sometimes because of their inherent simplicity. Few studies have been conducted which attempt to confirm or refute these diagnostic categories on scientific grounds. However, the basis on which to derive valid diagnostic categories is far from clear. In medicine as a whole, categories have emerged based on the pathological appearance of diseased tissue; although no characteristic tissue pathology has yet been found for any psychiatric disorder. Studies have instead concentrated on whether psychiatric disorders breed true or used computer intensive multivariate methods to derive or confirm diagnoses on the basis of their symptoms and history. Family studies have in general showed that the type of psychosis does not breed true, although more restrictive definitions of schizophrenia have showed a tendency to run in families. Cluster and latent class analysis have also shown a tendency to derive the category of schizophrenia but are less successful at confirming the presence of delineated affective syndromes and may be influenced by the diagnostic bias of the observer. Furthermore, such studies use a variety of different techniques and have failed to show consistency over time. The process of attempting to confirm diagnostic categories using discriminant function analysis has shown mixed results and there now seems little continuing research effort using this technique.

It could be argued that a failure to derive or confirm diagnoses on the basis of symptoms is likely to fail since clearly separate tissue pathologies in the rest of medicine

may underlie conditions with similar presenting features (e.g. lung cancer and tuberculosis) and presenting symptoms are likely to be coloured by premorbid personality, life events and other complicating factors. Under such circumstances, investigating which biological variables distinguish between bipolar disorder and schizophrenia might be a more fruitful way of determining whether they can be separated from one another. Even if such an effort were to fail, an exploratory analysis of such data might suggest the presence of disease entities amenable to further investigation.

Biological variables could include any functional or physical substrate which could be objectively measured, and which has been shown in previous studies to distinguish patients with psychosis from healthy controls. The majority of contemporary clinical research has focussed on the fields of neuroimaging and neuropsychology. This thesis will review the body of neuropsychological, structural and functional neuroimaging research as it applies to schizophrenia and bipolar disorder.

Chapter 2: Neuropsychology and Brain Structure in Schizophrenia and Bipolar Disorder

2.1 Neuropsychology

2.1.1 Methodological considerations

Numerous neuropsychological studies have been conducted in people with schizophrenia and depression but, until recently, bipolar disorder has received relatively little attention. Neuropsychological tests have been grouped by domain of cognitive function, anatomical associations or by cluster analysis. The first categorization is probably the most useful as they enable interpretation of tests scores by domain of function (e.g. memory, IQ, attention, executive function) and they also sometimes correspond to an anatomical location. However, no test has been isolated to a single function or anatomical location and current symptoms and medication may always confound the picture. Nevertheless, testing cognition in schizophrenia and bipolar disorder is relevant to their validity since neuropsychological functions may be closer to the fundamental biology of these disorders than symptoms which are probably influenced by personality and life events to a greater degree.

The role of medication and current psychiatric symptoms on the neuropsychological performance of subjects has been addressed in several studies. Data from controlled trials has demonstrated that anticholinergic medication, lithium, benzodiazepines and antipsychotics may all affect memory and psychomotor performance. The role of medication in individual test performance is however unclear as most studies use subjects who are medicated and fail to address its effect as a confounder. Sharma et al (1999) reviewed several studies examining the effects of typical and atypical antipsychotic medication on cognition in schizophrenic patients. Several studies found that conventional antipsychotic drugs worsen attention (e.g. using

the Continuous Performance Test, CPT) and motor performance acutely, but that the impairments diminish with chronic exposure and one study found that conventional antipsychotic drugs ameliorate performance on the CPT. Memory does not appear to be consistently affected by conventional antipsychotics, although there are studies which show reductions, improvements and no change. The Wisconsin Cart Sort Test (WCST), Digit Symbol Substitution Test (DSST) and digit span however appear to relatively unaffected by conventional antipsychotic treatment. The atypical antipsychotics (excluding clozapine) appear to have no deleterious effects on cognition in schizophrenic subject and in some studies improved performance on tests of working memory. However, it is possible that lower relative dosages of atypicals may exaggerate their apparent superiority over conventional drugs in terms of cognition. This possibility has some prima-facie support from a meta-regression which showed dosage effects explained most of the supremacy of atypical drugs in terms of efficacy and tolerability (Geddes et al. 2000). However, an advantage for atypicals in terms of extrapyramidal side effects (EPSE) remained, even after dose was taken into account. It is possible that this advantage in EPSE could favourably affect cognitive tasks with a motor component compared to patients on typical drugs. Anticholinergic medication and benzodiazepines have been shown in several studies to adversely effect memory (Nishiyama et al. 1998;Mizusawa 1998;Verster et al. 2002;McAndrews et al. 2003). However, the cognitive effect of most antipsychotic medication with a strong affinity for antimuscarinic receptors is as yet unclear, with the possible exception of clozapine which has been shown to adversely affect psychomotor speed in randomised controlled trials, although many other cognitive abilities were apparently spared (Wahlbeck et al.

2004). The effects of antipsychotic medication on cognition are further clouded by their positive effects on positive symptoms which may conceal any negative effect of the antipsychotics themselves.

Psychiatric symptoms themselves may confound tests of cognitive function. In schizophrenia, negative (but not positive) symptoms were positively associated with memory impairment in one review (Aleman et al. 1999). However, Liddle et al (1987;1991) found that in chronic schizophrenic subjects, the syndrome of disorganisation was associated with poorer performance on certain executive tasks, a finding which was later replicated in a separate sample (Baxter and Liddle 1998). The syndrome of psychomotor poverty (which generally corresponds to negative symptoms) was also associated with a general slowing in mental activity. In bipolar patients performance IQ, verbal IQ and tests of attention and executive function all appear to be impaired in symptomatic patients (Quraishi and Frangou 2002) and there is some evidence that verbal memory impairment is also impaired in euthymic patients (Atre-Vaidya et al. 1998;Krabbendam et al. 2000). In a recent article by Martinez-Aran et al (2004) controls were compared with both symptomatic (manic and depressed) and non-symptomatic bipolar subjects on 19 measures of neuropsychological function. Although differences were found between controls and bipolar subjects on 16 of the 19 tests used, there were few significant differences between manic, depressed and euthymic subgroups. Depressed patients scored lower than euthymic patients on a test of verbal fluency and on a test of attention. The effect of current symptoms appears more likely to confound cognitive performance than that of concurrent medication in both schizophrenia and bipolar disorder. However, patients with ongoing positive symptoms

are often those with worse functional outcomes and likely to receive higher doses of medication. Some studies examining the role of symptoms in unmedicated people with sub-syndromal illness have not found a relationship with cognition (Byrne et al. 2003). However, almost all domains of cognitive impairment could usefully be re-examined in either asymptomatic subjects or by accounting for them in the statistical analysis.

2.1.2 Premorbid intelligence

Premorbid intelligence concerns the general intellectual ability of a subject before they have begun to manifest signs of illness. Because of practical considerations, premorbid IQ is generally inferred from tests administered in people once the matter of whether they will become ill has already been resolved. The most commonly used index of premorbid function is the National Adult reading Test or NART (Nelson 1982). The NART uses knowledge about the correct pronunciation of irregular nouns to infer an individual's premorbid intelligence. This is based on two assumptions, that individuals acquire few new words in the course of their adult life and secondly that such abilities are relatively robust to pathological processes which affect other cognitive functions. Studies of patients with neurological illness have suggested that the NART is a valid and reliable method of measuring IQ (Gladsjo et al. 1999;Watt and O'Carroll 1999). However, few studies have considered the validity of the NART in psychiatric patients. In a review by Heinrichs and Zakzanis (1998) NART scores were found to have a large distribution of effect sizes when schizophrenic subjects and healthy controls were compared. The authors attribute this finding to reduced reliability in this patient group. A later study by Russell (2000) compared estimates of premorbid IQ measured using the

WAIS-R in childhood and compared them to the NART scores obtained in adult life. The study found that the NART scores obtained once the illness had developed overestimated premorbid intelligence when compared to the WAIS-R scores obtained premorbidly. Higher NART scores are also associated with greater educational opportunity and are of limited value in those whose first language is not English (Filley and Cullum 1997). Nevertheless, the NART has become the accepted measure of premorbid IQ in psychiatric research.

Prospective cohort studies of children have shown that IQ is reduced in those who develop schizophrenia many years later (Jones et al. 1994b;Crow et al. 1995;David et al. 1997). This finding is confirmed by further studies of adults at high risk of schizophrenia for genetic reasons, in that it is those subjects with greatest premorbid impairments that are most likely to become manifestly unwell in the course of the study (Byrne et al. 1999;2003).

Prospective studies of individuals at high risk of developing bipolar disorder have yet to be conducted. Therefore differences between bipolar subjects and controls are generally inferred from the results of the NART, with all the aforementioned difficulties that entails. Several studies have also been conducted which compare bipolar subjects with either controls or schizophrenic subjects. Generally these studies show that bipolar subjects perform as well as healthy controls (Ferrier et al. 1999;Rubinsztein et al. 2000) and better than schizophrenic subjects (Souza et al. 1995;Gilvarry et al. 2000;Seidman et al. 2002b). Two studies have also suggested that premorbid intellectual deficits may also be present in unaffected relatives of schizophrenic subjects (Gilvarry et al. 2000) and related to paranoid personality traits (Gilvarry et al. 2001). These results

suggest that premorbid intellectual deficits may be related to genetic liability to schizophrenia but not bipolar disorder, although the research base for bipolar disorder is relatively weak compared to that of schizophrenia.

2.1.3 Current intelligence

There are several commonly used measures of intellectual ability in general use from which measures of performance, verbal and full scale IQ may be made. The most common test of intelligence is probably the Wechsler Adult Intelligence Scale (WAIS) and its revised (WAIS-R) and abbreviated (WASI) forms. The WAIS has several subtests from which full-scale, performance and verbal IQ scores can be derived. The difference between WAIS full-scale (current) IQ and NART (premorbid) IQ has also been used to infer a change in intellectual ability over time.

Numerous studies have found schizophrenic subjects to have lower current IQ that appropriately matched controls (Heinrichs and Zakzanis 1998). Most interest in this finding has concentrated on whether this deficit predates the onset of illness or is acquired as patients become unwell. Data obtained from prospective studies of children and from high risk studies of adults suggest that the IQ difference is both present before the illness and worsens as people become unwell (Aylward et al. 1984;Cannon et al. 1999). Unaffected relatives of people with schizophrenia also appear to have a lower current IQ than matched controls (Cannon et al. 1994;Faraone et al. 1995) suggesting that at least some of the genetic liability for schizophrenia is expressed as reduced full-scale IQ. Performance IQ (mean effect size=1.26) also appears to be relatively more affected than verbal IQ (mean effect size=0.88) (Heinrichs and Zakzanis 1998;O'Carroll

2000) although it is at least a theoretical possibility that tasks which depend more on motor function may be relatively more prone to the effects of medication.

Research into the intellectual ability of subjects with bipolar disorder is at a much earlier stage than that of schizophrenia. A study which compared full-scale IQ in bipolar subjects in remission found no significant differences between patients and controls (Coffman et al. 1990). Most other studies involve patients with variable degrees of affective symptoms. Dalby and Williams (1986) studied 15 bipolar inpatients and 21 controls and found that patients scored significantly lower in terms of full-scale and performance, but not verbal IQ. The finding was later partially replicated by Morice (1990) who found that bipolar subjects had lower performance IQ, but were approximately equal in terms of full-scale and verbal IQ compared to controls. Robertson and Taylor (1985), using a remand prison population found IQ differences which found bipolars performed better in terms of verbal IQ than healthy controls. The balance of this research seems to indicate that full-scale and verbal IQ is probably spared in bipolar disorder. There is insufficient evidence to draw any conclusions about performance IQ since studies have not yet adequately addressed whether observed differences are due to confounding by medication or current psychiatric symptoms. A verbal-performance IQ deficit of 6 points has also been found in studies of bipolar patients, although this difference may also be dependent on current clinical state (Bearden et al. 2001). Unaffected people from families affected by bipolar disorder have been examined in at least two studies. Both studies found that unaffected individuals had similar full-scale IQs to normal controls although some evidence was found for a

performance-verbal IQ deficit in the children of bipolar subjects compared to normal control children (Decina et al. 1983;Gourovitch et al. 1999).

Several studies have compared schizophrenic and bipolar patients directly using the full WAIS although in only one study were the bipolar patients described as in remission. All studies appear to find that bipolar patients perform either equally or better than schizophrenic patients in terms of full-scale, performance and verbal IQ (Abrams et al. 1981;Morice 1990;Goldberg et al. 1993;Souza et al. 1995;Mojtabai et al. 2000;Seidman et al. 2002b) and only one study, using acutely manic subjects, found no difference (Hoff et al. 1990). On the basis of these studies, performance IQ appeared to discriminate the least between schizophrenic and bipolar patients, although this issue could be clarified further.

2.1.4 Memory

Although memory was considered by Kraepelin (1919) to be preserved in schizophrenia and bipolar disorder, numerous studies conducted in the second half of the twentieth century have demonstrated that this is certainly not the case (Heinrichs and Zakzanis 1998;Aleman et al. 1999;Bearden et al. 2001).

In an early systematic review and meta-analysis (Heinrichs and Zakzanis 1998) memory was found to be impaired in schizophrenic subjects compared to controls. Verbal memory was more impaired than non-verbal, a finding confirmed by a later review (Aleman et al. 1999) which also found that differences were present irrespective of whether the recall condition was immediate or delayed. Cued recall and recognition conditions reduced the differences observed between schizophrenics and controls,

although the differences remained statistically significant. Working memory was also impaired compared to controls (Aleman et al. 1999) and subsequent studies suggest that working memory deficits are also present regardless of whether the stimuli are presented verbally or visually (Barch et al. 2002;Coleman et al. 2002;Gold et al. 2003;Glahn et al. 2003) and may also be manifest in unaffected relatives (Toulopoulou et al. 2003;Callicott et al. 2003).

Verbal memory has been assessed in several studies of remitted (van Gorp et al. 1998;Ferrier et al. 1999;Krabbendam et al. 2000) or stable symptomatic bipolar subjects (Coffman et al. 1990;Jones et al. 1994a). Most studies found a robust impairment of verbal memory in bipolar patients compared to controls (Quraishi and Frangou 2002) and an early study which correlated impairments to numbers of episodes (van Gorp et al. 1998), has recently been replicated (Cavanagh et al. 2002). Non-verbal memory impairments (e.g. visio-spatial memory) appear less consistently disturbed compared to controls with both positive (Atre-Vaidya et al. 1998;Quraishi and Frangou 2002) and 'negative' studies (Coffman et al. 1990;Jones et al. 1994a;Clark et al. 2002).

Unaffected relatives of bipolar subjects also show evidence of memory impairments compared to healthy controls. Gourovitch (1999) studied 7 MZ twin pairs discordant for bipolar disorder and 7 healthy concordant MZ twin pairs. Bipolars were impaired on measures of verbal memory and visiospatial functioning compared to unaffected co-twins and normal MZ twins. Unaffected co-twins were also impaired on a verbal list learning task and the overall Wechsler Memory Task Quotient.

Direct comparisons of schizophrenic and bipolar subjects have found mixed results. Goldberg et al (1993) found that symptomatic bipolar patients were less

impaired on the Wechsler Memory Scale (WMS) than schizophrenic patients, a finding which was replicated in a later study using the same scale (Mojtabai et al. 2000). However, another study (Albus et al. 1996) found no differences between schizophrenic and psychotic bipolar subjects in terms of verbal memory, but found a significant impairment in subjects with a history of psychotic symptoms compared to those without. Non-verbal memory also appears to be more impaired in schizophrenia on several non-verbal tasks, including tests of visual reproduction and visual short term memory (Goldberg et al. 1993;Mojtabai et al. 2000). However, there are also some 'negative' studies which find no differences in facial recognition (Goldberg et al. 1993) or in WMS visual reproduction (Verdoux and Liruad 2000). Hence the available evidence suggests that verbal and non-verbal memory tasks may be impaired in schizophrenia and bipolar subjects, but that the degree of impairment is greater in schizophrenia. It remains to be seen how the impairments relate to the presence or absence of psychotic symptoms in general.

2.1.5 Executive function

Executive function can be assessed by a number of cognitive tests, including ones that attempt to measure controlled output (e.g. verbal fluency), response inhibition (e.g. The Hayling Test) and planning (e.g. Tower of London, Stockings of Cambridge). Some of these tests have been used for over 50 years and evidence has gradually emerged of the relationship between tests of executive performance and frontal lobe function from lesion studies and from functional imaging.

Abnormalities of executive function have been extensively described in schizophrenic subjects, particularly using the Wisconsin Card Sort Test (WCST, Berg 1948). The WCST measures a subject's ability to match a presented card to a series of stimulus cards, according to an un-stated rule. A subject's performance can be measured by the number of categories they complete, or by the number of perseverations they make. Subjects with schizophrenia make both types of error more often than controls (Heinrichs and Zakzanis 1998) and performance on the WCST may be related to the syndromes of psychomotor poverty and disorganisation (Nieuwenstein et al. 2001). Close relatives of schizophrenic subjects also appear to be impaired on the WCST (Wolf et al. 2002;Rybakowski and Borkowska 2002;Saoud et al. 2000) although there are some 'negative' studies (Stratta et al. 1997;Laurent et al. 2001).

Performance on tests of response inhibition such as the Hayling Sentence Completion Test (HSCT, Burgess and Shallice 1996) and Stroop Test (Golden 1978) have also been shown to be impaired in schizophrenic subjects, their close relatives and also subjects at high risk of schizophrenia for genetic reasons (Byrne et al. 1999;Yucel et al. 2002;Rybakowski and Borkowska 2002;Byrne et al. 2003). Tests of spontaneous production such as the verbal fluency test (e.g. FAS, Spreen and Strauss 1991), also show a similar pattern of impairment (Chen et al. 2000a;Chen et al. 2000b) as do tests of planning ability (Morris et al. 1995;Morice and Delahunty 1996;Staal et al. 2000a).

Performance on frontal lobe tests also appear to be reduced in at least some patients with bipolar disorder (Bearden et al. 2001;Quraishi and Frangou 2002). Performance on the WCST is reduced in bipolar subjects, both in terms of categories completed (Morice 1990) and perseverative errors (Coffman et al. 1990;Morice

1990;McGrath et al. 1997). However, one study suggests found that the differences between bipolars subjects and controls could be explained by the inclusion of bipolar patients with psychotic symptoms (Albus et al. 1996).

In a study of remitted bipolar patients, Ferrier et al (1999) demonstrated decreased verbal fluency in bipolar patients compared to controls. Decreased verbal fluency has been confirmed in some (Docherty et al. 1996;Atre-Vaidya et al. 1998), but not all studies (Calev et al. 1989;van Gorp et al. 1998;Hawkins et al. 1997;Gruzelier et al. 1988) and many studies do not control for general intellectual function or psychiatric symptoms.

On tests of planning ability, two studies find no difference between bipolar subjects and controls (Ferrier et al. 1999;Rubinsztein et al. 2000). The first study initially found significant differences which were lost once the analysis was adjusted for current depressive symptoms. These studies are balanced by two further studies of symptomatic bipolar patients in which patients were significantly impaired compared to controls (Murphy et al. 1999;Sweeney et al. 2000).

There are only a few direct comparisons of executive function in schizophrenic and bipolar subjects. Docherty et al (1996) found that although bipolars and schizophrenics were both impaired compared to controls, schizophrenics performed significantly worse in terms of verbal fluency than the bipolars. Hawkins et al (1997) and Gruzelier et al (1988) also found significantly greater impairments of verbal fluency in schizophrenics compared to bipolar subjects. Morice (1990) however, found no difference between schizophrenic subjects and controls in terms of verbal fluency. Goldberg et al (1993) in a study of schizophrenic subjects and patients with both

unipolar and bipolar affective disorders found that the affective disorders group performed significantly better than schizophrenics on the WCST test. This finding has been replicated by at least one (Mojtabai et al. 2000), but not all later studies (Young et al. 1998;Verdoux and Liruad 2000). No studies identified compared schizophrenic and bipolar subjects on measures of planning ability.

2.1.6 Attention and psychomotor performance

Heinrichs and Zakzanis (1998) reviewed four attentional variables (Digit Span, Continuous Performance, Stroop, Trail Making) in their meta-analysis of neuropsychological test scores in schizophrenia. Digit span would generally now be regarded as a test of working memory and the Stroop test would be regarded as a test of executive function (probably suppression/control, see Lezak 1995). The trail making test had an average effect size in schizophrenic subjects compared to controls of 0.95 (part A) and 1.07 (part B), although the confidence intervals overlapped zero (Heinrichs and Zakzanis 1998). Subsequent studies have however found that Trail Making Test scores are lower in schizophrenic subjects than in controls (Grawe and Levander 1995;Liddle and Morris 1991;Wolwer and Gaebel 2002), and are reduced in the unmedicated close relatives of affected subjects (Pogue-Geile et al. 1991;Franke et al. 1993).

The Span of Apprehension Test (SPAN, Arsanow et al. 1991), Continuous Performance Test (CPT, Cornblatt et al. 1988) and their many forms are probably the most often used standardised tests of attention in schizophrenia research. The tests involve the identification of a target stimulus from a background of other stimuli. More than forty studies using the CPT have been conducted in schizophrenic subjects

(Cornblatt and Keip 1994). Studies using the classic CPT consistently find differences between schizophrenic subjects and controls (Mirsky et al. 1992), but it tends to be the task's more challenging versions which find impairments in the healthy relatives of affected patients (e.g. Nuechterlein 1983;Cornblatt and Keip 1994).

Studies of patients with bipolar disorder reveal that stable bipolar subjects have significant impairments on the CPT (and its variants) and SPAN which are greater than controls, but less than that of schizophrenic subjects (Arsanow and MacCrimmon 1981;Docherty et al. 1996;Addington and Addington 1997;Clark et al. 2002). Other studies, using acutely symptomatic patients, have found that bipolar subjects perform as poorly as schizophrenic subjects (Strauss et al. 1984) and that those bipolar patients who perform the worst are more likely to have psychotic symptoms (Albus et al. 1996). Studies using the Trail Making Test also find that bipolar subjects consistently score worse than controls (Ferrier et al. 1999;Mojtabai et al. 2000), but although symptomatic bipolars perform better than symptomatic schizophrenic patients in the acute phase of illness (Mojtabai et al. 2000;McGrath et al. 1997), the difference was lost after 4 weeks of medical treatment in one study (McGrath et al. 1997).

The Digit Symbol Substitution Test (DSST, Kaplan et al. 1991) and the Reaction Time Test (RT, e.g. Lezak 1995) are tests of psychomotor performance which tend also to correlate highly with measures of attention (Spreen and Strauss 1991). Digit Symbol test scores appear to be impaired in schizophrenia (Jogems-Kosterman et al. 2001;Brebion et al. 2000) although it is still unclear whether there are abnormalities in bipolar disorder and whether the test can discriminate between the disorders. Reaction Time test scores are also reduced in schizophrenic (Krieger et al. 2001;Jogems-

Kosterman et al. 2001;Ngan and Liddle 2000;Gale and Holzman 2000) and bipolar subjects (Strauss et al. 1987;Pierson et al. 2000) and there is also an unreplicated study which finds that reaction time may have the ability to discriminate between schizophrenic and bipolar subjects when used in alongside the CPT (Fleck et al. 2001). Fleck et al (2001) studied a sample of 40 patients (20 bipolars with psychotic features, 20 schizophrenics) and 20 non-related healthy controls. Using discriminant function analysis, the diagnoses of each patient an could be made with 80% accuracy using a weighted combination of three reaction time variables reflecting psychomotor speed. Since the study did not confirm their results using the techniques outlined at the end of chapter 1 (e.g. jacknifing, confirmation with a second sample) the results should be regarded as preliminary.

2.2 Neuropathology

Neuropathological investigations of schizophrenia began in the hope that an identifiable lesion would be identified in the brain of affected people. Early studies using primitive histological techniques (Alzheimer 1897;Wernicke 1900) were often positive and lacunae or neuronal atrophy was frequently described in the histological specimens of affected subjects (Bruton et al. 1990). These early studies were conducted when the need to control for fixation and other artefacts was not appreciated and were contradicted by later, more methodologically rigorous studies (Lewis 1923;Dunlap 1924). Neuropathological study of schizophrenia was given fresh impetus following Johnstone's (1976) finding of ventriculomegaly on computed tomography. The notion that there may be a neuropathological abnormality in schizophrenia was based on many

strands of evidence. Firstly, people with schizophrenia showed a tendency to have static or progressive abnormalities in terms of symptoms. Secondly, it was also appreciated that cognitive impairments were also present. Thirdly, some organic brain syndromes were known to present with psychotic symptoms and finally, case studies of people with focal brain lesions also occasionally showed cognitive and behavioural abnormalities similar to schizophrenic subjects.

Post-mortem studies have been relatively infrequent in bipolar disorder. This is perhaps because subjects show a tendency to remit over time and neuroimaging studies have not, until recently, begun to show evidence of brain abnormality. However, advanced techniques (e.g. immunological techniques, mRNA measurement) have the potential to reveal subtle degrees of abnormality which may not be apparent to the naked eye or using conventional staining techniques.

2.2.1 Methodological considerations

Diagnostic validity and heterogeneity, medication effects, selection of controls and blind assessment are all methodological issues which, in common with all psychiatric brain research, may limit the validity of study findings. However, in addition to these general problems, neuropathological studies face other specific methodological difficulties.

The diagnosis of psychiatric patients whose brains become available for neuropathological research will rarely have been confirmed in life using operational criteria, except perhaps in disorders of late life such as Alzheimer's disease or disorders related to Parkinson's disease. Detailed case notes may not be available after death in

some cases limiting any further diagnostic clarification. Where case notes are available, it is sometimes possible to apply modern diagnostic criteria, and schedules exist for this very purpose (Zalcman and Endicott 1983). However, the tendency for diagnostic confusion with other disorders is perhaps greater than for studies carried out on live volunteers. Unsuspected neuropathological abnormalities may be discovered at post-mortem, some of which may be related to the cause of death and indeed some may suggest that the psychotic illness manifested was secondary to an undiagnosed neurological condition. In either case, the potential of such findings to cloud the micro and macroscopic picture is significant. Furthermore most patients develop schizophrenia in their 3rd decade and often do not die until their 7th or 8th. Much may happen over the intervening 40-50 years including physical treatments, some which have been out of favour for many years, substance misuse and intercurrent disease.

The decline in autopsy rates internationally has limited the numbers of brains which can be collected for research. This problem has been compounded in the UK by several widely publicised scandals regarding the inappropriate acquisition of human brains without the consent of the individual or their relatives. Prospective identification of individuals willing to donate their brains to psychiatric research might improve the rate at which brains may be collected and also improve the quality of diagnostic information collected. However, to the best of my knowledge, no scheme of this sort has begun for 'functional' psychiatric illness, although prospective brain collections do exist for Alzheimer's disease. Unfortunately, in the current political climate, there seems little prospect of developing new collections.

The quality of brain tissue obtained is dependent upon many factors. In addition to the confounding effects of medication, overdoses of prescribed medication and the use of illicit substances both have the potential to cause significant brain injury. Drug analysis of blood, urine or hair is possible but is rarely performed. Other peri- and post-mortem factors also influence the quality of brain tissue (see figure below) and their effects may be greater than those of the mental illness under study.

Figure 2.2.1: Factors influencing tissue quality in post-mortem studies

Mode of death
Time from death to refrigeration
Time from refrigeration to fixation or freezing
The duration of fixation
Methods of embedding and fixation

2.2.2 Brain dimensions

Brain weight in schizophrenia has recently seen subject to a systematic review and meta-analysis (Harrison et al. 2003) in which published and unpublished studies comparing schizophrenic subjects to normal controls were identified. Seventeen studies of 540 schizophrenics and 794 comparison subjects were located which recorded whole brain weight on adult patients to whom operational criteria had been applied. After controlling for age, sex and series-diagnosis interactions, brain weight in schizophrenic subjects was found to be approximately 24g lighter than in control subjects. Brain weight was lower in women than in men and found to decrease in all groups at a rate of approximately 2.4g per year. The effect size was not related to duration of illness or to age at death although patients with a later age of onset had significantly lower brain

weights in an exploratory analysis. There is evidence from this systematic, and other non-systematic reviews that the methods used in each study varied considerably. The number of post-mortem studies reporting brain length or width is somewhat more disappointing (Bruton et al. 1990). The few studies that exist appear to suggest that brain length is reduced.

In contrast to schizophrenia, no studies could be identified which measure brain weight in a sample of people with bipolar disorder.

2.2.3 Frontal lobes

Few studies have examined the size or weight of the prefrontal cortices, in either schizophrenia or bipolar disorder. However, in schizophrenia there is some evidence that the neuronal morphology of frontal neurones is abnormal. Several studies have found a decrease in neuronal density in layers II, III and VI of the cortex (Benes et al. 1986;1991;1993) and a reduction in neuronal size (Benes and Bird 1987;Rajkowska et al. 1998). However, there are several contradictory studies and some suggestions that particular types of neurones may be affected (Selemon et al. 1995;Akbarian et al. 1996;Anderson and Rutledge 1996). Brodmann's areas 4, 10 (lateral) and, 24 (anterior cingulate) appear to be the most consistently implicated areas.

Most neuropathological studies of the frontal cortex in bipolar disorder have considered the anterior cingulate cortex specifically, based primarily on the functional imaging data which also implicates this region and a structural study also finding a volumetric deficit in the sub-genual prefrontal cortex (Drevets 2001). Drevets and colleagues (Ongur et al. 1998) subsequently found reductions in BA24 (sub-genual)

volume and in glial density. A further study of brains from the Stanley foundation found that glial density and number was reduced in both bipolar and unipolar disorder, but not in schizophrenics. Reductions were also found in the orbitofrontal cortex. Bouras et al (2001) also replicated these findings, but found reductions only in the dorsal part of BA24. His study also found that neuronal density and lamina depth was reduced but did not replicate reductions in glial density. Cotter (2001) was the first study to fail to replicate these findings, although non-significant trends in the same direction were found. Benes et al (2000;2001) also found a reduction in neuronal density in BA24 (rostral, pre-genual part) but no differences in glial density or neuronal size. Molecular studies of the same region find reductions in growth associated protein (GAP-43), dendritic microtubule associated protein and synaptophysin all of which point to a synaptic pathology (Eastwood and Harrison 2001;Bouras et al. 2001). Reductions in both glial and neuronal density have been found in other parts of the prefrontal cortex, including BA9 (Rajkowska et al. 1999;Cotter et al. 2002).

2.2.4 Temporal lobes

Several neuropathological studies support the finding of reduced temporal lobe volume in schizophrenia (Bogerts et al. 1985;1990;Brown et al. 1986;Falkai and Bogerts 1986;1988;Altshuler et al. 1990;Vogeley et al. 1998). Studies find reductions in neuronal number or density in cortical areas (Akbarian et al. 1993), although the hippocampal complex and amygdala have been subject to greater study. Studies consistently find reductions in neuronal cell size, number and density within the hippocampus (Falkai and Bogerts 1986;Jonsson et al. 1997b) and entorhinal cortex

(Falkai et al. 1988;Krimer et al. 1997) with only a couple of equivocal or contradictory studies (Christison et al. 1989;Pakkenberg 1993b). These studies have been extensively criticised in the neuropathological literature (Harrison 1999) and the most methodologically rigorous study to examine this region found no differences in neuronal cell number or density (Heckers et al. 1991a). Disarray of hippocampal neurones in schizophrenia has also been found in some studies (Kovelman and Scheibel 1984;Conrad et al. 1991) although these studies have implicated separate subfields of the hippocampus and have not been consistently replicated (see Harrison 1999 for a review).

In contrast to schizophrenia, temporal lobe structures have received little attention in bipolar disorder. Only two studies have compared more than four patients with bipolar disorder to controls (Damadzic et al. 2001;2002), both by the same group, and only glial fibrillary acidic protein (GFAP) positive astrocytes were considered in the earlier of the two. No differences were found between the groups.

2.2.5 Subcortical structures

In parallel to structural imaging findings in schizophrenic subjects, neuropathological studies have also found macroscopic decreases in thalamic size (Pakkenberg 1990;1993a;Danos et al. 2002;2003) and increases in basal ganglia (Heckers et al. 1991b). The same studies also found cytoarchitectural evidence for decreased numbers of neurones in the dorsomedial nucleus and anteroventral nuclei, both of which project primarily to the prefrontal cortex. The evidence for other subcortical structures in bipolar disorder is too weak to make any conclusions (Vawter et al. 2000;Harrison 2002) but there is limited evidence that hypothalamic neurones may be

increased in number and raphe neurones may be reduced in mixed bi and unipolar samples (Zhou et al. 2001;Purba et al. 1996;Baumann and Bogerts 2001).

2.3 Pneumoencephalography

The technique of pneumoencephalography was introduced by Dandy in 1919 and its main use became the investigation and diagnosis of possible hydrocephalus. Pneumoencephalography was also used to detect cerebral atrophy and ventricular enlargement in other neurodegenerative conditions and was employed fruitfully as a research tool in schizophrenia for this reason.

2.3.1 Methodological considerations

Pneumoencephalography involved the introduction of air into the subarachnoid space by lumber puncture, and allowing it to ascend to outline the ventricular system and basal cisterns of the brain where it could be imaged using a plain x-ray of the skull (Lishman 1998). The technique was painful, was associated with a significant mortality and could cause tentorial herniation in the presence of space occupying lesions. Even cerebral atrophy itself could be worsened, at least temporarily, by this technique. The spatial resolution of pneumoencephalography is poor compared to MRI and modern CT and the technique does not allow the direct visualisation of brain substance or allow images to be acquired in several different planes. Because of safety concerns the American Rotengen Ray Association stated that the use of pneumoencephalography on healthy controls was unethical in 1929 which led in part to the demise of the technique

and of neuroimaging in psychiatry until more advanced in vivo techniques became available with the advent of CT (Johnstone et al. 1976).

2.3.2 Findings in affected patients

The first pneumoencephalography study in psychiatry was published by Jacobi and Winkler (1927) and showed 'unmistakable hydrocephalus' in the brains of people with chronic schizophrenia. The findings were replicated by other groups with very few negative or equivocal results.

Table 2.3.2: Pneumoencephalography studies in the functional psychoses

Study	Summary of findings
(Jacobi and Winkler 1927)	Internal hydrocephalus in 18 out of 19 schizophrenic subjects
(Moore et al. 1933)	Increased ventricular and cisternae in 21 of 60 schizophrenics
(Lemke 1935)	Ventricular dilatation found in 50% of schizophrenics and 12% of controls
(Borenstein et al. 1957)	118 of 134 schizophrenic cases described as abnormal
(Huber 1957)	135 of 195 schizophrenics had dilated ventricles. Dilated ventricles were more common in those with defect state
(Haug 1962)	Ventricular enlargement greater in schizophrenics than controls and associated with poor outcome
(Nagy 1963)	260 cases (mixed schizophrenia and manic-depressive illness). 58% of schizophrenics and 28% manic-depressives showed cerebral 'atrophy'.
(Storey 1966)	No differences found between schizophrenics and controls. Scans were performed as investigations for suspected neurological disease.
(Asano 1967)	Lateral and 3rd ventricular enlargement found in schizophrenic subjects. Greatest in 'nuclear' group of schizophrenics.
(Hunter et al. 1968)	Lateral ventricular enlargement in 15 of 27 cases with a tendency to L>R
(Young and Crampton	In schizophrenics referred for investigation of suspected

1974)	neurological disease, 'atrophy' found in 24 of 36 patients.
(Haug 1982)	Qualitative ventricular abnormalities found in 58 of 101 chronic schizophrenics reported previously by Haug (1962)

Ventricular enlargement was repeatedly found in schizophrenics without suspected neurological disease. In a single study (Nagy 1963) comparing schizophrenic subjects with manic-depressive subjects, cerebral atrophy was reported in a substantial proportion of patients with affective illness.

Pneumoencephalography increased interest in the neuropathology of schizophrenia and led to further studies with more advanced techniques. It had little effect on the study of bipolar disorder. This is to some extent surprising since many studies included people who were simply 'psychotic' or used outdated criteria which were not operationally based. Therefore, many groups of individuals described either as 'psychotic' or schizophrenic' would have been likely to include people with bipolar disorder as it is now defined.

2.4 Computed tomography

2.4.1 Methodological considerations

Computed Tomography (CT) uses a thin x-ray beam which rotates 360 degrees around a patient in order to obtain an axial image of the underlying structures. The absorption of x-rays is detected at each point on the trajectory of the beam and the resultant structure reconstructed by back projection. Whereas conventional x-rays are unable to visualise white/grey matter contrast, this is improved in CT by allowing the

range of x-ray absorption to be widened to a stage where it can be appreciated by the human eye.

CT scans are subject to a number of important artefacts which limit their application to psychiatric research. If the x-ray beam paths do not intersect as they trace a 360 degree path around the patient then different intensity values may wrongly be assigned to the same voxel causing streaking. Probably the most common cause of this artefact is patient motion although similar problems can be caused by equipment misalignment. Artefacts are also created by objects such as bone or fillings which have high x-ray absorption. These structures tend to absorb low energy x-ray photons from the source and lead to the average energy of the transmitted signal increasing. This phenomenon is known as beam hardening and can also lead to 'streaking' in the resulting images. A final and important source of artefact on a CT image is the effect of 'partial voluming'. Each 3-dimensional volume of tissue in a patient's brain is converted to a two dimensional pixel on a photographic plate or computer screen. Where image pixels lie at the boundary of two tissue types then the resulting signal from that pixel will tend to represent weighted mean attenuation value from each tissue. This leads to poorer spatial resolution and contrast and is greatest at the periphery of the patient where the x-ray beam is at its widest.

Technical problems in terms of the measurement techniques used have also been a limitation to the use of CT. Although more recent studies have used semi-automated methods to trace regions using the original CT data, earlier studies involved tracing over the structures on photographic film, and were prone to lower reliability. However, both techniques were relatively subjective compared to modern methods. The ventricle to

brain ratio was commonly used as a measure of ventricular size/area, often traced on a single section of brain. This assumed that there was a linear relationship between brain and ventricle size, and that schizophrenic patients had similar head sizes to that of healthy controls. There is evidence that neither assumption was correct (See Lewis 1990 for a review of this area).

In addition to the technical limitations of this technique, each CT scan is associated with a significant exposure to ionising radiation. The health consequences of these exposures (e.g. foetal teratogenesis, neoplasm, genetic damage to germ cells) has generally limited the use of CT in children, adolescents, women of childbearing age and also in repeated measurements of adult subjects of both sexes.

2.4.2 Findings in affected patients

The first controlled study of psychiatric patients using CT was carried out at a time when psychosocial theories of schizophrenia were very fashionable (Johnstone et al. 1976). In her study of 17 chronic schizophrenics and 8 normal controls, lateral ventricles were significantly larger in affected patients. Between 1976 and 1990 there had been a further 30 CT studies, although most have also concentrated on the measurement of cortical atrophy, ventricular size, and their clinical associations. Two studies specifically addressed cerebral asymmetry and both reported a greater frequency of fronto-occipital asymmetry in schizophrenics than in normal controls (Naeser et al. 1981;Luchins et al. 1982). Ventricular enlargement was shown to be associated with neuropsychological impairment (Donnelly et al. 1980;Johnstone et al. 1978), negative symptoms (Andreasen et al. 1982;Takahashi et al. 1981), poor premorbid adjustment

(Pearlson et al. 1985) and extrapyramidal syndromes (Owens et al. 1985). Physical treatment including medication was shown not to be a confounder for the relatively consistent findings of these studies (Owens et al. 1985).

CT has also been applied to the study of unipolar and bipolar affective disorders (Beyer and Krishnan 2002). At least nine studies have specifically addressed ventricular enlargement and cerebral atrophy in bipolar disorder, although many more studies have compared individuals with unselected affective disorders to both healthy controls (Targum et al. 1983;Shima et al. 1984) and schizophrenics (Weinberger et al. 1982;Schlegel and Kretzschmar 1987a;1987b). Results in bipolar subjects are less consistent than in schizophrenia although the majority also find ventricular enlargement compared to controls (see table 2.4.2).

Table 2.4.2: CT studies in bipolar disorder and manic-depressive illness

Study	Sample	Summary
Pearlson and Veroff (1981)	16 MDP 22 SCZ 35 CTRL	Increased VBR in SCZ and MDP compared to CTRL
Nasrallah et al (1982b;1982a)	24 BPD* 55 SCZ 27 CTRL	Enlarged VBR in SCZ and BPD compared to CTRL
Tanaka et al (1982)	9 BPD 31 MDD 40 CTRL	BPD showed cortical 'atrophy' in temporal and occipital cortices at an earlier age than CTRL
Rieder et al (1983)	19 BPD 15 SCZAff 28 SCZ	No significant differences between groups. Each group showed qualitative cortical atrophy and ventricular enlargement
Pearlson (1985)	19 SCZ 27 BPD 27 CTRL	BPD had larger ventricles than controls. Increased VBR associated with greater hospitalisation and

		unemployment
Dewen et al (1988)	26 BPD 22 CTRL	Enlarged 3rd ventricle, increased white matter density and increased signal from caudate and thalamus in BPD
Andreasen (1990)	24 BPD 27 MDD 75 CTRL	BPD had larger ventricles than controls (males only)
Young et al (1999)	30 BPD 18 CTRL	Greater cerebral 'atrophy' in BPD compared to controls but no difference in ventricular size.

*defined by the presence of a manic episode, BPD – bipolar disorder, MDP – manic-depressive psychosis, MDD- major depressive disorder, CTRL - controls

2.5 Structural magnetic resonance imaging

The brain images created by MRI arise because of the properties of the component tissues, and in particular, the magnetic properties of protons (hydrogen nuclei).

When a tissue is placed in a magnetic field (B_0), a proportion of the hydrogen nuclei will align with the magnetic field and precess around it, at a frequency known as the Lamor frequency, at an angle to the direction of the magnetic field. The hydrogen nuclei will not be in phase with one another (i.e. at the same frequencies, as if 'marching in step with one another', Suckling and Bullmore 2000) and the tissue itself will generate no coherent signal under these conditions. When a radiofrequency pulse is applied to the tissue, the spinning nuclei tip further from the direction of the field and spin briefly in phase with one another. Over time the spins of the respective nuclei to return to their original state both by returning to their original angle of spin before the field was applied and also by de-phasing with one another. The tendency for nuclei to return from their 'tipped state' to their original angles occurs exponentially and can be summarised using

a rate constant called T1. The tendency for nuclei to de-phase from one another again also occurs exponentially at a rate which can be expressed using a constant called T2.

Figure 2.5a: Shows the increase in displacement of hydrogen nuclei following the application of a radiofrequency pulse.

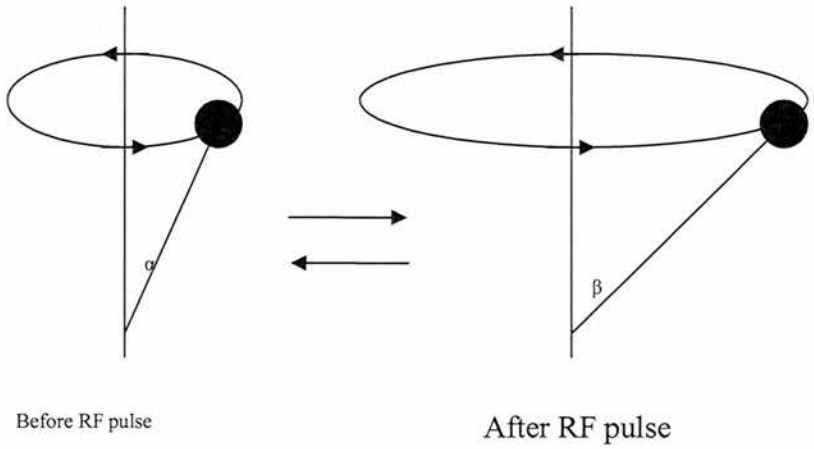
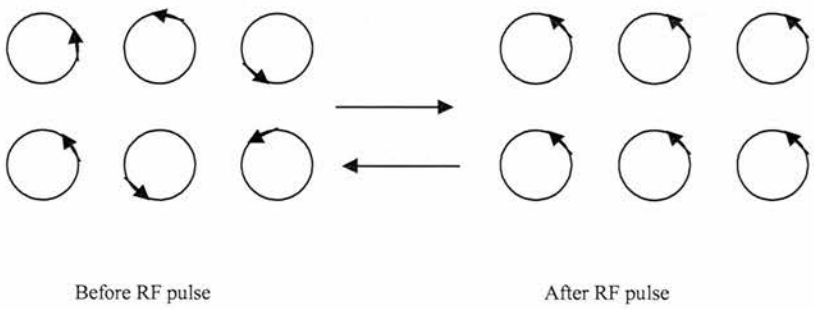


Figure 2.5b: The phasing of hydrogen nuclei after the application of a brief radiofrequency pulse. The tendency for protons to return (decay) to their original (out of phase) state is summarised using the T2 constant

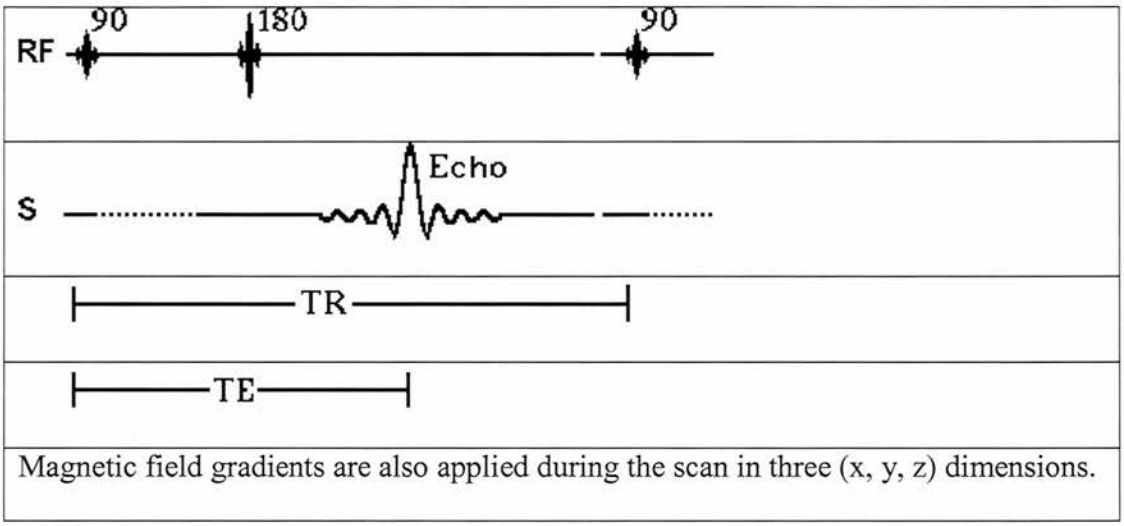


T1 is sometimes known as the spin-lattice rate constant while T2 is sometimes known as the spin-spin constant. Measuring the decay constants T1 and T2, as well as the overall proton density (PD) has many clinical applications as the values reflect the underlying anatomy and also physiology of the brain. T1, T2 and PD signals at each unit of brain volume (voxel) can be presented as a grey-scale image with the highest signals represented as white voxels and low signals as black. However, a single radiofrequency pulse as described above would produce signals from brain tissue decaying as a function of T1, T2 and proton density (PD) and also from brain tissue on many different slices. For this reason, sequences have been devised which generate signals that are highly dependent upon either the T1 or T2 decay constants or on PD and which are slice selective, acquiring image data from one slice of brain tissue at a time. The most common sequences used are the spin-echo sequence and gradient echo. Many other sequences exist (e.g. diffusion weighted, T2* etc).

2.5.1 Spin-echo sequence

Spin-echo sequences involve the application of a radiofrequency pulse at time 0 and, after a time TE/2 later, an inversion pulse of 180° to displace those protons that have decayed most from their 'excited' state. Images can be acquired during the period between the first two pulses, or after the 180° pulse and the beginning of the next sequence. By varying the timing of the image acquisition, the echo time (TE) and the repeat times, PD, T1 or T2 weighted images can be acquired from the same imaging sequence.

Figure 2.5.1: Typical spin echo scanning sequence. RF refers to radiofrequency pulse, S to signal and TR and TE refer to repeat and echo times respectively



Magnetic field gradients are also applied during the scan in three (x, y, z) dimensions.

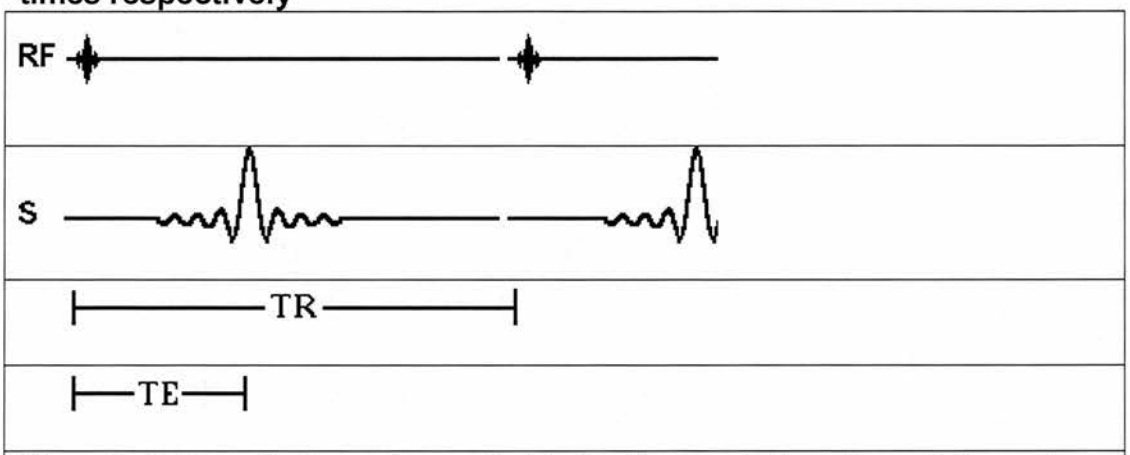
2.5.2 Gradient-echo

A typical gradient echo sequence is shown below. The first event in the sequence is the application of a radiofrequency pulse at time 0. This pulse can flip the protons by an angle, usually between 5 and 90 degrees, known as the 'flip angle'. At a given time (TE) after the radiofrequency pulse the image signal is acquired. After a further interval, the radiofrequency pulse is reapplied and the sequence is repeated. The time between cycles is called the repetition time (TR).

The flip angle, TR and TE together determine the scan time, image resolution and T1 or T2 weighting. Smaller flip angles phase spinning protons but do not displace them very far from their original axes. The images acquired from these sequences tend therefore to be T2 weighted. Conversely, larger flip angles tend to produce T1 weighted images. The gradient echo sequence can also be modified by the application of a 180°

pulse before the subsequent cycles. This 'pre' pulse allows the faster acquisition of T1 weighted images using low flip angles. These sequences are sometimes called magnetisation prepared gradient echo sequences (MPRAGE).

Figure 2.5.2: A gradient echo scanning sequence. RF refers to radiofrequency pulse, S to signal and TR and TE refer to repeat and echo times respectively



Magnetic field gradients are also applied during the scan in three (x, y, z) dimensions.

2.5.3 Measurement of tissue signal

The image itself is created from the measurement of energy 'released' from tissue by several radiofrequency detectors located in a coil placed around the head of the subject. Images are created using Fourier analysis of this information to make a 'back projection' of the properties of the tissue which gave rise to the signal in the first place.

2.5.4 Image acquisition

The first MRI study of schizophrenia was conducted by Smith et al (1984) with only 9 schizophrenic subjects and 5 controls using a single unreliably positioned slice.

No significant differences in cortical areas were found between the groups. The methods of MRI studies have greatly advanced over the last 20 years in parallel with advances in the technology of image acquisition and analysis.

Parameters influencing MRI image quality

- Magnet strength
- Field inhomogeneity
- Time to echo, repeat time, flip angle etc
- Slice thickness
- Contiguous vs. interleaved vs. spaced slices
- Plane of acquisition

The main factors influencing image quality are shown in the box above (Beck et al. 2002;Davidson and Heinrichs 2003). Greater magnetic strength has the effect of increasing signal to noise ratio and provides greater tissue contrast. However, magnetic field strength is usually maximal at the centre or core of the magnet and decays slightly at distances further away from the centre. This 'field inhomogeneity' can lead to differences in tissue contrast and quality which increases noise and may lead to unreliable results. Conventionally, field inhomogeneity is controlled for by scanning an object of homogeneous density and correcting the images for any inhomogeneity observed in the object. The object used is typically a fluid phantom which bears little resemblance to a complex structure like the brain. Slice thickness is an important consideration in MRI studies of the brain because thinner slices give rise to greater resolution and brain tissue present at one anatomical level is separated from that at another level more effectively. A signal in one plane of brain tissue from two adjacent regions is sometimes called a 'partial volume'. Early sMRI studies often acquired

images from several slices of the brain but left interslice gaps of the brain from which no data was acquired. This meant planar or volumetric data on a brain region was often incomplete and potentially inaccurate. Generally brain 'slicing' is now contiguous. Finally, volumes or areas are commonly acquired as T1 weighted coronal images and, for most purposes, this is probably adequate. However, some regions (e.g. the hippocampus) are better visualised in an oblique or transverse plane, parallel to the long axis of the structure.

2.5.5 Image Analysis

Methods of image analysis

- Region of interest
  - Manual
  - Semi-automated
  - Fully automated
- Voxel based
  - Statistical parametric mapping (SPM)
  - Other methods (e.g. those based on fuzzy logic)

The results from structural magnetic imaging studies are influenced by the method of image analysis as well as the method of image acquisition. Until the last five years studies have mainly used semi-automated methods which extract the brain from the surrounding tissues. A researcher then manually traces around regions of interest with a cursor with the aid of a tissue contrast facility. Tracings are usually made with the aid of an anatomical atlas and using previously established methods for delineating brain structures with *operationalised* criteria. Volumes are then calculated by multiplying each regional area by the slice thickness, summing all slice volumes over the brain region in

question. This technique involves a certain amount of subjectivity and it is essential to first establish adequate inter-rater and intra-rater reliability. Large structures (e.g. whole brain, temporal and frontal lobes) have high measurement reliability whereas smaller structures (e.g. hippocampus, amygdala, caudate) are generally subject to greater measurement error. In an attempt to measure smaller volumes more reliably parcellation techniques have been developed. These generally involve tracing in three dimensions simultaneously although this technique is very time consuming and subjective judgements continue to be necessary (Caviness et al. 2000).

An alternative approach to image analysis has been developed called voxel based morphometry (VBM). VBM involves the transformation of each brain into a common three dimensional space and segmentation into grey and white matter and cerebro-spinal fluid (CSF). Differences in e.g. grey matter density are then computed by comparing these 'normalised' brains from each group on a voxel by voxel basis (see chapter 6 for details of this and other automated techniques). VBM avoids subjective judgements about where a region of interest begins and ends, although the results obtained reflect differences in tissue density rather than volume and cannot be interpreted with the same ease as a mean difference in volume. However, the results obtained from samples using both region of interest analysis and VBM suggest that the results are generally similar (Wright et al. 1999;Lawrie et al. 2001;Job et al. 2002 and in press). VBM has the additional advantage in that very small structures can be investigated.

2.5.6 Patient and control selection

In sMRI studies of patients of schizophrenia, the usual study design is to compare a sample of cases with unaffected controls, healthy relatives or patients with another psychiatric disorder. The primary interest of such a study is to examine whether the volume of a brain region differs between groups. Where a significant difference is shown, the difference is usually attributed to the diagnosis. However, the many differences between controls and established patients with schizophrenia mean that anatomical differences may be attributable to treatment, the effects of an ongoing disease process or the effect of a risk factor. A more rigorous design is to follow unaffected patients prospectively before and as they become unwell. This is rarely feasible (see later), and for these and other practical reasons the predominant design, as in the rest of medicine, has been the case-control study.

Case-control studies are however susceptible to several sources of bias. Firstly, patients and controls may be dissimilar in many ways, in addition to their diagnostic status. Patients recruited from hospitals are often those with the most severe illnesses, greatest social adversities and complicating factors e.g. substance misuse. The recruitment of socially comparable well controls is not easy. Non-schizophrenic psychiatric or neurological controls can be used as an alternative control group, being more similar than groups of well volunteers in terms of potential confounders of brain volume such as social class and educational level for example. Healthy controls are however almost always required. It is sometimes possible to recruit healthy controls from the non-genetic relatives and social networks of the patients themselves, thereby establishing both a more generally comparable control group and one which may be more committed to the research in question (having first hand knowledge of the effects

of psychosis). However, studies using this design run the potential problem that the controls are themselves atypical of unaffected people from the general population. Many studies attempt to match schizophrenic patients to one or more controls for known influences on brain volume (e.g. age, sex, IQ). Matched designs have great value when the potentially confounding variables are well understood and can be measured accurately, but this may well not be the case for schizophrenia. IQ for instance has been shown to be both a risk factor and a state indicator (Cosway *et al.* 2000) such that matching patients with controls of equal current IQ might effectively select intellectually inferior controls and vice-versa for premorbid IQ matching. There is also the danger of over-matching patients and controls on variables which are important in the pathogenesis of schizophrenia itself (i.e. are on the causal pathway).

An ideal approach might be to randomly select affected subjects and healthy controls from a population. This is however easier said than done and still has hazards. Population sampling (e.g. from the electoral register) may select subjects who are relatively affluent and patients who are atypical of patients in general. Ethics committees might be reluctant to agree to the unsolicited approach of potential study participants and some participants will inevitably refuse to be scanned, but the design has obvious theoretical advantages over the aforementioned. I am unaware of any studies using this approach in sMRI studies of functional psychiatric illness.

In practice, the influence of methodological and descriptive variables on the results obtained from case control studies has been examined by very few studies. One study that has assessed the influence of methodological confounds on observed effect sizes is a study by Davidson and Heinrichs (2003) using meta-analytic methods. This

study found that sample size was negatively correlated with effect size overall, suggesting that publication bias may be an important source of bias in imaging studies of schizophrenia (but see Lawrie and Abukmeil 1998;Wright et al. 2000). In addition, the proportion of right handed males were also significant confounds (but see Nelson *et al.* 1998). Slice thickness and time to echo were also related to observed effect sizes, although magnetic strength was not. This study suggests that methodological issues are important sources of potential bias in sMRI research. Nonetheless, their effects are not as large as those of the illness.

2.6 Structural MRI findings in affected patients

Early sMRI studies were generally small in size and used area measures such as the ventricle to brain ratio (VBR). sMRI methodology has greatly improved and, in particular, thin contiguous slicing through the brain has facilitated accurately measuring regional brain volumes. Studies consistently show differences between controls and people with schizophrenia and two meta-analytic reviews of more than 50 individual studies have summarised our knowledge of the location and extent of these regional differences (Lawrie and Abukmeil 1998;Wright et al. 2000).

2.6.1 Whole brain

Whole brain volume in schizophrenia has been examined in multiple studies and reviewed in several systematic reviews and meta-analyses. Although whole brain volume is reduced compared to controls when studies are combined (Lawrie and Abukmeil 1998;Wright et al. 2000), most individual studies fail to find a significant

difference between schizophrenics and controls (Shenton et al. 2001). The effect size appears to be around -0.31 for grey and -0.19 for white matter. This corresponds to an average volume reduction of 4% in grey matter (95%CI 1-6%) and 2% in white matter (95%CI 0-5%) (Wright et al. 2000). Whole brain volume reductions appear to be more equivocal in first episode studies, with the majority of studies failing to find any differences (Bilder et al. 1994;Velakoulis et al. 1999;Lawrie et al. 1999) with only an occasional exception (e.g. in adolescents, James et al. 1999).

Several reviews of bipolar disorder consider the evidence for whole brain volume reductions compared to controls (Jeste et al. 1988;Elkis et al. 1995g;Videbech 1997;Bearden et al. 2001) . In view of the fact that they include substantially the same primary studies it is surprising that they come to differing conclusions. Elkis (1995f) in a quantitative review of the literature found that sulcal prominence was greater in bipolar subjects compared to controls (effect size d=0.42). However, it is far from clear which measures of sulcal prominence were used. Other reviews in this area are more cautious in their interpretation of the literature (Bearden et al. 2001) but point out that almost all primary studies have had negative results. The only systematic review and quantitative meta-analysis in this area which sets clear inclusion and exclusion criteria found that there were no significant differences in brain volume between bipolar subjects and controls (7 studies, 160 bipolars, 215 controls, d=0.04, 95%CI -0.17 to 0.25 Hoge et al. 1999).

Since the numbers of studies to examine whole brain volume in subjects with schizophrenia or bipolar disorder are relatively few, it is not surprising that the evidence comparing schizophrenia to bipolar disorder is weak. A single meta-analysis has

compared schizophrenic and affective disordered subjects from studies involving direct comparisons. (Elkis et al. 1995e). The review concludes that there is a statistically significant difference between schizophrenics and controls, with schizophrenics having a larger degree of sulcal prominence. It is however unclear which measure of sulcal prominence they use and many of the included studies also recruited unipolar patients. It is also possible that sulcal prominence does not reflect an underlying reduction in whole brain volume. From an indirect comparison of two reviews by the same group, (Ward et al. 1996;Hoge et al. 1999) the authors conclude that whilst schizophrenic subjects have significantly smaller whole brain volumes than controls, that no such difference is found in bipolar subjects. They present a graph of the two meta-analyses demonstrating that the confidence intervals for each effect size barely overlap further suggesting that whole brain volume is significantly different in schizophrenia and bipolar disorder.

There appears to be some doubt as to whether bipolar disordered subjects have whole brain volume reductions compared to controls. However, if present, it is likely to be somewhat less than found in schizophrenia. Since the publication of the only quantitative review to directly compare bipolars and schizophrenics, new studies have emerged which use higher magnetic field strengths, producing better images which have then been analysed using reliable semi-automated methods. Some of these studies have found whole brain reductions in bipolar subjects (Lim et al. 1999) and necessitate a further quantitative review of this area (see below).

2.6.2 Ventricles and CSF

An increased ventricle to brain ratio (VBR) was one of the first standardised measures to be used in psychiatric neuroimaging (Johnstone et al. 1976) and the results of studies using this measure showed increases in VBR (DeQuardo et al. 1996). However, the measure conflated whole brain width with ventricular width and provided results which had low reliability (Arndt et al. 1991). Most MRI studies measure ventricular size separately for all ventricles and occasionally divide the lateral ventricles into their inferior horn, anterior horn, and body.

In schizophrenia, the lateral and third ventricles appear to be larger than in controls (Lawrie and Abukmeil 1998;Wright et al. 2000;Shenton et al. 2001). Wright et al (2000) demonstrated that the bodies of the left and right ventricles contributed the largest amount to this effect being increased in volume by about 48% compared to control subjects and the frontal horns contributed the least. The fourth ventricle showed a non-significant increase of 7% in schizophrenic compared to control subjects. Studies of first episode patients and healthy relatives tend to confirm that differences in lateral and third ventricular volumes are present at first presentation (Barr et al. 1997;DeLisi et al. 1991;1998) and are related to genetic liability being present in unaffected close relatives (Seidman et al. 1997;Lawrie et al. 2001;McDonald et al. 2002).

Table 2.6.2: Increases in ventricular size in schizophrenic subjects compared to controls. Data from Wright et al (2000)

Ventricular Region	Effect size (Cohen's d)	% Increase compared to controls	
		mean	95%CI
Lateral ventricle (L)	0.51	130	120-141
Lateral ventricle (R)	0.39	120	113-128
Third ventricle	0.59	126	119-134
Forth ventricle	0.21	107	96-119

In bipolar disorder some early studies found that lateral ventricular size was also increased compared to healthy controls (Swayze et al. 1990a;Fiegiel et al. 1991). Not all studies were positive however (Johnstone et al. 1989), and some studies found that ventricular enlargement was greater in male patients or those with psychotic symptoms or poor early outcomes (see Bearden et al. 2001 for a review). However, overall, it appears likely that lateral ventricular volume is increased in bipolar disorder compared to controls (Elkis et al. 1995d). Third ventricular enlargement is also found in some studies compared to healthy controls (Strakowski et al. 1993b;Kato et al. 1994), but not all studies are positive (Botteron et al. 1995;Lim et al. 1999). However, the 'negative' studies tend to be small (≤ 25 patients).

Direct comparisons of schizophrenia and bipolar disorder are even fewer in number. Lateral ventricular enlargement appears to be greater in schizophrenic subjects compared to samples with mixed uni and bi-polar mood disorders (Elkis et al. 1995c). Studies comparing only bipolar subjects with schizophrenics either find no difference (Zipursky et al. 1997;Johnstone et al. 1989;Friedman et al. 1999) or find greater lateral ventricular volumes in schizophrenic subjects (Lim et al. 1999). Only two studies (Lim et al. 1999;McIntosh et al. 2001) to my knowledge have directly compared schizophrenic and bipolar patients in terms of third ventricular volume, and both were 'negative'. Both studies were small and only Lim (1999) was specifically designed to address the hypothesis but included only 9 bipolar and 9 schizophrenic patients.

2.6.3 Frontal lobes

Most studies of prefrontal cortex volume in schizophrenia have found lower volumes in schizophrenic patients compared to controls in their own right (Shenton et al. 2001), regardless of whether chronic (Andreasen et al. 1994b;Harvey et al. 1993) or first episode patients (Bilder et al. 1994;Gur et al. 2000) were examined (see Shenton et al. 2001 for a review). Overall, the volume reductions appear to be of the order of 2-8% (Wright et al. 2000). However, since prefrontal cortex accounts for approximately 30% of total cerebral volume and has diverse regional specialisation, the finding of reduced volume is not in itself very revealing. Frontal volume reductions have been further characterised using parcellation or voxel-based morphometry (VBM). Reductions in anterior cingulate, orbitofrontal, dorsolateral and ventromedial cortices have been found using parcellation (Crespo-Facorro et al. 1999;Goldstein et al. 1999;Gur et al. 2000), VBM (Wright et al. 1999;Chua et al. 1997) or a related technique call deformation based morphometry (DBM, Gaser et al. 1999). However, the studies tend to be small and each individual finding, with the exception of the anterior cingulate, has not been broadly replicated.

Early studies comparing bipolar disorder with healthy controls found mostly negative results (Zipursky et al. 1997;Strakowski et al. 1993a;1999) with only a few exceptions (Sax et al. 1999). However, positive findings from neuropathology and functional imaging have motivated a re-examination of this region using automated techniques and parcellation. Drevets (1997) examined blood flow in bipolar depressed subjects (n=6) and healthy controls (n=24) using low resolution PET. Finding reductions in blood flow in the subgenual region of the prefrontal cortex, grey matter volume was

then examined in a group of medicated depressed unipolar (n=17) and bipolar (n=21) subjects and compared to that of healthy controls (n=21). Reductions were found in left subgenual prefrontal cortex in mood disordered subjects compared to controls. Post-hoc tests found that his difference was also significant for the bipolar-control contrast, but that the difference was greater in patients with unipolar as opposed to bipolar mood disorders (48 vs. 39% reduction). However, in a larger and better reported study of unipolar (n=18) and bipolar (n=27) patients compared to controls (n=38), Brambilla et al (2002) failed to replicate the subgenual prefrontal cortex reductions found by Drevets et al. Instead, subgenual volumes were slightly, and non-significantly, increased in both familial and non-familial bipolar patients compared to healthy controls.

A further study (Sharma et al. 2003) has reported subgenual prefrontal cortex reductions, but on the opposite side to that of Drevets et al. However, their chosen hypothesis test was negative and the significant difference was only found on post-hoc testing. In another study of the frontal cortex in bipolar disorder, Lopéz-Larson (2002) found reductions in left middle and superior grey matter and also in right inferior and middle grey matter using ROI in 17 bipolar and 12 matched healthy volunteers. In the only VBM study of bipolar patients, Kubicki et al (2002a) compared fist episode schizophrenic (n=16), first-episode affective psychosis (n=14 bipolar plus 2 unipolar) and healthy controls (n=18) and found no differences between bipolar patients and healthy controls in the prefrontal cortex or insula but found that hippocampal and superior temporal gyral density reductions were greater in the schizophrenic sample.

2.6.4 Temporal cortex

Abnormalities of temporal cortex are well described in schizophrenic patients. Of 51 MRI studies of whole temporal lobe volume in schizophrenia, 61% were positive and showed reductions in schizophrenic patients compared to healthy controls (Shenton et al. 2001). Medial temporal lobe volume (typically hippocampus and amygdala combined) were significantly reduced in schizophrenic patients compared to controls in 74% of the 49 studies identified. Wright et al (2000) pooled the results from 25 studies comparing schizophrenic patients with controls and found a reduction of between 2 and 4% in affected patients. In first-episode studies however, temporal lobe reductions are less consistently found than for chronic patients, but medial temporal lobe volumes remain consistently smaller compared to controls (Lieberman et al. 1993;Lawrie et al. 1999). The reason for this is unclear, but there is some evidence that temporal lobe differences may progress over time (DeLisi et al. 1998;Jacobsen et al. 1998). Alternatively, the tendency for first-episode studies to be smaller may have led to insufficient statistical power.

Superior temporal gyrus (STG) volume in schizophrenia has also been the subject of several studies. The attention this region receives in perhaps because of its close association with language and because of functional imaging studies which have shown changes in perfusion in schizophrenic subjects with clinical associations. Superior temporal gyrus volume appears to be reduced in schizophrenic subjects compared to controls, with a relatively greater effect size for the left anterior superior and posterior superior segments (Cohen's $d \approx 0.4$) (Wright et al. 2000). Studies focussing on hallucinations or delusions have shown a tendency to implicate the temporal lobes, particularly on the left (Shapleske et al. 2002;Levitan et al. 1999;Barta et al. 1990) and

there is some evidence that these reductions are greatest in the left anterior superior temporal gyrus (Levitan et al. 1999;Rajarethinam et al. 2001). Reductions in left posterior superior temporal gyrus grey matter have also been repeatedly found in association with thought disorder (Shenton et al. 1992;Menon et al. 1995;Rajarethinam et al. 2000).

Unfortunately, no quantitative review of temporal lobe volume has been performed in bipolar subjects. There are several studies examining differences between bipolar subjects and healthy controls, but their results find decreases (Altshuler et al. 1991;Hauser et al. 1989a;Schlaepfer et al. 1994), no difference (Johnstone et al. 1989;Altshuler et al. 2000) and increases (Pearlson 1997;Harvey et al. 1994) in bipolar subjects compared to controls. Overall it is difficult to make any firm conclusions about the probable direction and size of effect without a quantitative review. Differences between bipolar and schizophrenic subjects appear a little clearer. Bipolar subjects have been found to have larger whole temporal lobe and STG volumes than schizophrenic subjects (Harvey et al. 1994;Pearlson et al. 1997) with no studies reporting significant changes in the opposite direction so far as I am aware.

The fusiform gyrus, has also been found to be abnormal in schizophrenic patients compared to controls (Paillere-Martinot et al. 2001;Onitsuka et al. 2003) using both ROI and VBM. Evidence from a single study suggests that fusiform gyrus volume reductions in schizophrenic patients, especially on the left, are specific to schizophrenia; whereas those on the right are found in both affective psychosis and schizophrenia (Lee et al. 2002). Visual inspection of the data suggests that there is considerable overlap between patients and controls and suggests further replication is required.

2.6.5 Amygdala

Of the 44 regions considered by Wright et al (2000) in their meta-analysis of regional volumes in schizophrenia the left and right amygdala had two of the largest volume reductions of all, in comparison to healthy controls (Cohen's d=-0.72 and -0.69, for left and right respectively) being reduced by around 10% in schizophrenic subjects. Wright et al (2000) considered ROI studies where regions were defined using established and operationalised criteria. Further evidence of grey matter loss has come from VBM studies which have shown reduced amygdala grey matter density in several studies (Wright et al. 1999;Job et al. 2002) and evidence of abnormal shape (Shenton et al. 2002) although there are some contradictory studies (Levitt et al. 2001) and some important methodological difficulties associated with its measurement (David et al. 2002).

Interestingly, there is some evidence in bipolar disorder that amygdala volumes are greater than those of controls (Altshuler et al. 1998;2000;Strakowski et al. 1999;Brambilla et al. 2003) with only a few contradictory results (Swayze et al. 1992) which can potentially be explained by sampling error. Since amygdala volumes may be decreased in schizophrenia and increased in bipolar disorder, the amygdala might provide the first structural measure by which schizophrenia and bipolar disorder can be discriminated from one another. Direct comparisons of schizophrenic and bipolar patients appear supportive (Pearlson et al. 1997;Altshuler et al. 1998;2000).

2.6.6 Hippocampus and parahippocampus

Early studies of the hippocampus in schizophrenia tended to incompletely image the structure using only a few interleaved slices which did not fully measure the structure, sometimes dramatically underestimating its true volume. The tendency for slices to be contiguous has greatly improved the accuracy of hippocampal measurement and there are now more than 30 well conducted studies which show a reduction of around 6% in both left and right hippocampi compared to healthy controls (Wright et al. 2000). The changes appear also to be present at first presentation (e.g. Whitworth et al. 1998;Velakoulis et al. 1999) although there is some doubt as to whether changes may be acquired as patients become unwell (Lawrie et al. 2001;2002b) and whether they progress once psychotic symptoms have become established (Gur et al. 1998a;Jacobsen et al. 1998). The pattern for left and right parahippocampus is also similar (8 studies, >350 subjects, Cohen's d≈-0.4 to -0.7) being smaller in schizophrenic subjects than in controls although there is evidence that studies vary by more than one would expect by chance alone, suggesting some unexplained clinical or methodological heterogeneity.

In contrast, few studies have measured hippocampal volume in bipolar disorder, and of those that have, most find no differences compared to healthy controls (Hauser et al. 2000;Altshuler et al. 2000;Brambilla et al. 2003). There is some evidence from one study that hippocampal volumes are smaller in schizophrenic than in bipolar subjects (Altshuler et al. 2000) although there is also at least one negative study (Brambilla et al. 2003). No studies were identified which considered parahippocampal volumes in bipolar patients.

2.6.7 Thalamus

Abnormalities in several psychophysiological measures (e.g. ERPs, gating and habituation of startle) could be attributed to a defective filtering of information from the sensory organs (Braff and Geyer 1990). It has been suggested that the role of the thalamus in modulating ascending sensory information makes it a likely candidate as a filter (Tennigkeit et al. 1998). Evidence suggesting a reduced volume of the thalamus in schizophrenia has come relatively recently in schizophrenia research (Andreasen et al. 1994a;Flaum et al. 1995), and has been replicated by some (Staal et al. 1998;Gur et al. 1998b;Gilbert et al. 2001), although not all (Deicken et al. 2002;Hazlett et al. 1999) subsequent studies. The thalamus is however a collection of several nuclei and the inability to clearly visualise each individual nucleus with MRI probably contributes to greater 'noise' and leads to some inconsistency. Voxel based morphometry is less reliant on the ability of operators to separate the thalamus into its constituent nuclei but has not confirmed the results of ROI analyses so far (Kubicki et al. 2002a;Job et al. 2002). There is also some evidence that antipsychotic medication may increase thalamic size, further confounding any association with diagnosis (Gur et al. 1998b).

Thalamic size in bipolar disorder has been assessed in a fewer number of studies, and although the rationale for the thalamus being involved in mood regulation is also a strong one, the available evidence form sMRI has not so far been supportive (Caetano et al. 2001;Strakowski et al. 1993a). The question of whether thalamic volumes differentiate schizophrenia and bipolar disorder is one which awaits appropriately designed studies.

2.6.8 Basal ganglia and nucleus accumbens

In contrast to other nuclei, there is good evidence that patients with schizophrenia have a larger left and right globus pallidus than healthy subjects of the same age. Several studies (Kelsoe, Jr. et al. 1988;Jernigan et al. 1991;Elkashef et al. 1994) have shown increases of around 18% (L) and 21% (R) overall (Wright et al. 2000) including some data from first episode studies. However, some studies measure lentiform nucleus rather than globus pallidus and putamen separately and the evidence for an increased volume of the putamen in chronic patients is somewhat weaker with both positive (Elkashef et al. 1994;Hokama et al. 1995) and 'negative' studies. First-episode studies do not generally find increases in putamen compared to healthy controls, although putamen and globus pallidus volumes are significantly smaller in first-episode compared to chronic patients (Gunduz et al. 2002;Lang et al. 2001). The possibility that such changes are an effect of antipsychotic treatment has been substantiated by several studies which correlate basal ganglia volumes with antipsychotic exposure (Chakos et al. 1994;Keshavan et al. 1994). However, both studies found associations between antipsychotic exposure and caudate volumes, and not globus pallidus or putamen volumes as expected. This finding is difficult to explain in the broader context of the MRI literature which does not consistently find increases in caudate volume compared to controls (e.g. Wright et al. 2000 10 studies, 565 patients). However, there is some evidence that caudate volume is decreased in first-episode patients (Keshavan et al. 1998) which might suggest that antipsychotic exposure minimises these reductions which predate treatment. No convincing evidence that the nucleus accumbens differs in size between schizophrenia and controls has yet been shown (Gunduz et al. 2002).

In bipolar disorder six studies have addressed basal ganglia volumes compared to controls and have had negative results (Swayze et al. 1992;Strakowski et al. 1993a;Harvey et al. 1994;Dupont et al. 1995;Sax et al. 1999;Brambilla et al. 2001a). Only two studies have so far been positive. Aylward (1994) examined 30 bipolar patients and 30 normal controls and found patients had significantly larger caudate nuclei than controls, but showed no differences in terms of putamen and globus pallidus volumes. Getz (2002) studied 12 bipolar patients, 12 controls and 12 patients with schizoaffective disorder. Bipolar patients had a larger globus pallidus, caudate and putamen than healthy controls and had a larger striatum (caudate and putamen combined) than patients with schizoaffective disorder. Harvey (1994) is the only other study to compare bipolar patients with schizophrenia and related psychoses, but produced no useable data in terms of individual basal ganglia volumes, combining several volumes together in one measure.

2.6.9 Insula

The insula is a region of cerebral cortex not usually included within the previously mentioned structures. It lies buried within the depths of the lateral sulcus, concealed by the frontal, temporal and parietal lobes and is situated overlying the site at which the telencephalon and diencephalons fused during embryological development (Nolte 1988). There is some evidence from both ROI (Kim et al. 2003) and VBM (Sigmundsson et al. 2001;Kubicki et al. 2002a;Shapleske et al. 2002) that there may be grey matter reductions in the insula in schizophrenic patients compared to controls. So far no evidence exists for volumetric reductions in bipolar patients.

2.7 Structural MRI findings in relatives

2.7.1 Monozygotic twin studies

Studies of monozygotic twins discordant for schizophrenia have the potential to distinguish environmental from genetic effects. In the context of these studies, greater neuroanatomical similarity would be presumed to reflect common genetic effects and greater difference to reflect environmental or disease contingent effects. Studies of discordant monozygotic twins are however limited by the unusual circumstances of twin birth and differences between twins may be a reflection of different gene expression or gene-environment interaction. Notwithstanding these potential limitations, studies of discordant MZ twins have enhanced our understanding of genetic and environmental influences in schizophrenia.

CT and MRI studies have generally been consistent. Unaffected relatives of schizophrenic patients have a degree of quantitative brain anomaly which is intermediate between that of their affected relatives and healthy controls. Such findings suggest that a degree of brain anomaly is inherited at least by a proportion of those who never develop schizophrenia. Studies of discordant monozygotic (MZ) twins have the added ability to quantify the effect of environmental factors on subsequent illness. In a study of 15 pairs of MZ twins discordant for schizophrenia (Suddath *et al.* 1990), it was the affected twin which had larger ventricles, reduced temporal lobe grey matter and reduced hippocampal volumes. These findings are difficult to explain without the effect of environmental factors or gene-environment interactions. However, no differences were found in either frontal lobe volume or white matter. Since frontal lobe volume has been

shown to be consistently reduced in schizophrenia (Lawrie and Abukmeil 1998;Wright et al. 2000) compared to non-related healthy controls, it is possible that a reduced frontal lobe volume may predispose to psychosis while a reduction in temporal lobe grey matter and hippocampal volumes might be associated more closely with the onset of illness itself.

A further study of monozygotic twin pairs discordant for schizophrenia used 15 pairs of discordant monozygotic twins,14 pairs of discordant dizygotic twins and 29 healthy twin pairs matched on a number of important confounders (Baare et al. 2001). Frontal brain volumes were smaller in affected versus unaffected monozygotic twins but not for the same sib-wise comparison within the discordant dizygotic twin group. Irrespective of zygosity however, affected twins had smaller whole brain, hippocampal and parahippocampal volumes than their healthy co-twin. Unaffected co-twins had smaller whole brain volumes than twins from unaffected sibships. These findings suggest that frontal brain volumes are associated with the development of illness itself and that small whole brain, hippocampal and parahippocampal volumes may also be associated with the development of illness. The relationship of these brain regions to genetic vulnerability could however not be excluded due to the relatively small sample sizes. Whole brain volume however, appeared to be both a marker both of illness and genetic vulnerability. A further study specifically examining differences in thalamic and caudate volumes in discordant MZ twins (Bridle *et al.* 2001) found larger caudate nuclei in affected twins but found no differences in thalamic volumes between twin pairs.

In an attempt to further characterise the significance and extent of grey matter deficits in affected and unaffected co-twins, Cannon (2002) conducted an MRI study of

discordant MZ and DZ twins along with a sample of demographically matched control twins. The study used a relatively novel technique of constructing three dimensional probabilistic maps of the cortex. Cortical maps were used to compute 3D vector deformation fields which allowed researchers to compute a measure to reflect grey matter density at each cortical point. Differences between well twins and their schizophrenic co-twin were found in the region of the dorsolateral prefrontal cortex, superior temporal gyrus and superior parietal lobule and were associated with measures of disease severity and cognitive function. No relationship was found with duration of illness or antipsychotic drug treatment. A cortical map of grey matter density associated with genetic proximity to affected patients found deficits in the polar and dorsolateral prefrontal cortex. These findings suggest that different cortical areas may be associated with genetic and disease specific influences. Medial prefrontal and medial temporal lobe structures could not be assessed in this approach as they could not be extracted using the surface extraction method employed in the study.

The functional significance of structural abnormalities in twins discordant for schizophrenia has been investigated in few studies, probably because of the practical limitations of this kind of research. Berman (1992) measured cortical blood flow in monozygotic twins discordant and concordant for schizophrenia and a group of health co-twins. Three conditions were studied: a resting task, the Wisconsin Card Sorting Test and a number matching task designed to act as a non-specific active control task. Affected subjects showed hypofrontality compared to their well sibling. However, well siblings of schizophrenic MZ twins showed no differences compared to healthy twins from unaffected pairs suggesting that hypofrontality is related to non-genetic factors.

Hypofrontality in the schizophrenic co-twins was also associated with a higher life time exposure to antipsychotic medication. A further publication by the same group (Weinberger *et al.* 1992) examined the relationship between functional deficits and regional brain volumes measured by MRI in both healthy MZ and twins discordant for schizophrenia. Differences between discordant MZ twin pairs in prefrontal dysfunction measured during the Wisconsin Card Sort Test were found to be related to differences in left hippocampal volume. Within the affected twin group alone, prefrontal activation was strongly related to both right and left hippocampal volumes. A third publication (Goldberg *et al.* 1994) from the group examined intra-pair differences in anatomic structures, prefrontal rCBF and cognitive function. The study found left hippocampal volume to be related to a parameter of verbal memory and prefrontal rCBF to be related to psychotic symptom scores and preservation on the Wisconsin Card Sort Test. These findings suggest that prefrontal and medial temporal lobe regions are important in the aetiology of psychotic symptoms and cognitive dysfunction.

MRI findings in twins discordant for bipolar study have only been published in two independent studies study (Noga et al. 2001;Kieseppa et al. 2002;2003). Noga et al (2001) studied 6 monozygotic twin pairs discordant for bipolar disorder and 11 healthy concordant MZ twin pairs. Affected MZ twins had smaller right hippocampi than their normal co-twins whereas caudate volumes were increased in both the healthy and ill co-twins compared to members of concordant MZ pairs. Kiesappa (2002;2003) studied 24 twins with bipolar I disorder, 15 healthy co-twins and 27 twins with no history of psychiatric disorder. Patients and co-twins showed reductions in left hemispheric white matter volume compared to control twins. No grey matter differences were found.

2.7.2 Findings in the extended family

The underlying rationale of examining the first degree relatives of patients with schizophrenia is that they share approximately 50% of their genome and that common differences versus controls probably reflect genetic factors, while differences between unaffected and affected relatives presumably represent disease specific effects. A similar degree of abnormality in relatives and patients implies that the volume alterations are not related to the disease itself but are probably related to genetic factors. In some cases however, studies may be small and of low statistical power rendering a conclusion of no-difference between two groups insecure. It is clear that these studies cannot distinguish genetic and environmental causation, but as schizophrenia is usually found to reflect mainly genetic factors, with a relatively small unique environmental effect, and almost no familial environment involvement (McGuffin *et al.* 1994), the commonalities between patients and their relatives are probably genetic in origin.

Most of these relatives' studies have examined the volumes of the lateral ventricles (LVs) and/or the AHCs. Only one study has reported significantly enlarged LVs in relatives as compared to controls (Sharma *et al.* 1998), although most of the studies in siblings (Cannon et al. 1998;Seidman et al. 1999;Staal et al. 2000b) or offspring (Keshavan et al. 1997;Schreiber et al. 1999;2002;Lawrie et al. 2001) give results in that direction. The few comparisons of patients and sibs are on the other hand universally significant (Cannon et al. 1998;Sharma et al. 1998;Staal et al. 2000b;McDonald et al. 2002) , as are the twin studies, suggesting stronger environmental and phenotypic effects. Indeed, in older 'obligate gene carriers' lateral

ventriculomegaly (Sharma et al. 1998;McDonald et al. 2002) has yet to be externally replicated (Steel *et al.* 2002). An increased VBR in relatives may therefore primarily reflect a reduction in brain volume, although the results on sMRI are equivocal. While some studies find the brain is smaller in relatives than controls (Cannon et al. 1998;Keshavan et al. 1997;2002) with no patient-relative differences (Cannon et al. 1998;McDonald et al. 2002;Seidman et al. 1999) many studies comparing relatives or obligates with controls find no differences (Seidman et al. 1999;Sharma et al. 1998;McDonald et al. 2002).

The evidence from relatives' studies is similarly inconclusive for most other brain regions, in some cases because of insufficient studies and in others due to low power. There are for example isolated reports of abnormal cerebral torque (Sharma *et al.* 1999), but the most consistent abnormalities in patients have not been found in relatives (Bartley *et al.* 1993;Frangou *et al.* 1997); and findings of abnormal sylvian fissure (Honer *et al.* 1995) and AHC asymmetry (Schreiber et al. 1999) have yet to be replicated (Bartley et al. 1993). There is however a degree of agreement with the twin and automated studies reviewed above for fronto-temporal differences with the changes greatest in schizophrenic subjects, intermediate in relatives and smallest in controls. The main support for this from ROI studies in relatives is as trends from a large study using sophisticated segmentation algorithms (Cannon et al. 1998), and studies contrasting patients with their unaffected relatives (Staal et al. 2000b;McDonald et al. 2002;Steel et al. 2002). Preliminary voxel based morphometry (VBM) analyses of the latter study suggest both frontal and temporal reductions, with common genetic and disease effects. Small (Keshavan et al. 1997;2002;Schreiber et al. 1999) and large studies (Lawrie et al.

2001) of high risk offspring have not found such differences, and neither have medium sized studies which do not control for family membership (Sharma et al. 1998). It appears that the relatively small effects require automated approaches and should control for within family clustering.

The importance of statistical power is again illustrated in studies of the third ventricle (3V) and the thalamus (the increase in the former probably reflecting reductions in the latter and other surrounding structures). The only negative studies of the third ventricle in relatives (n=15, Schreiber et al, 1999) and the thalamus (n=11, Keshavan et al, 1997) are the two smallest offspring studies and Keshavan et al (2002) found thalamus reductions when they increased the sample size to 19 (although differences have been found with samples as small as six). While most of the available literature suggests 3V increases and or thalamus reductions in relatives more than controls, the only significant patient-relative difference reported is for the thalamus (Staal *et al.* 1998). Thalamus reductions, which were related to genetic liability but not psychotic symptoms in the Edinburgh High Risk Study (Lawrie et al, 2001 and see below), may therefore be genetically mediated risk markers not related to the disease itself. Ventricular enlargement may be related to disease specific or other environmental effects rather than genetic liability.

Relatives' studies are relatively clear that amygdala-hippocampal complex (AHC) reductions are both genetic and disease related. Relatives have smaller AHCs than controls (Keshavan et al. 1997;Schreiber et al. 1999;Seidman et al. 1999;Lawrie et al. 2001;2002), and schizophrenics have smaller AHCs than relatives (O'Driscoll et al. 2001;Lawrie et al. 2001;Steel et al. 2002), although there are some negative studies

(Staal et al. 2000b). There are suggestions that the reductions may be more marked anteriorly (Keshavan et al. 2002;O'Driscoll et al. 2001), and on the left side (Lawrie et al. 2001;Keshavan et al. 2002). There is however good evidence for hippocampal differences as well (Waldo et al. 1994;Harris et al. 2002;Seidman et al. 2002a;van Erp et al. 2002).

Functional studies of unaffected family members and their close relatives have been conducted and are also relevant to the understanding of structural findings. A SPECT study of 19 schizophrenic patients, 36 first degree relatives and 34 unrelated healthy controls found decreased left inferior prefrontal cortex and anterior cingulate perfusion in both relatives and schizophrenic patients compared to controls (Blackwood *et al.* 1999). Increases in perfusion were also found in schizophrenics and relatives compared to controls in the periventricular white matter, occipital-frontal fasciculus and internal capsule. A further study by O'Driscoll et al (1999) used positron emission tomography (PET). The first degree relatives of schizophrenic patients with eye tracking dysfunction (ETD) showed decreased perfusion in the frontal eye fields compared to those without ETD and healthy controls. The authors suggest that hypoperfusion of the frontal eye fields may be caused by genes which predispose to schizophrenia.

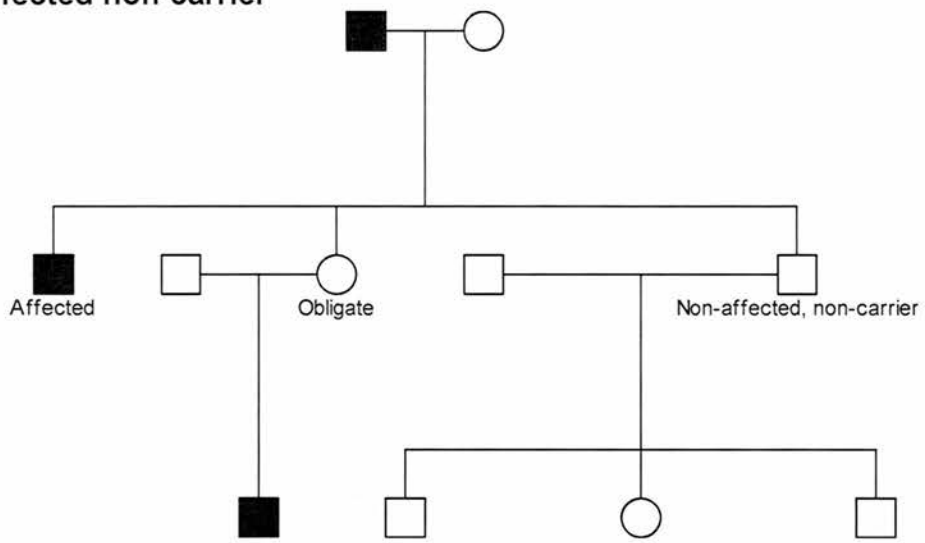
In bipolar disorder only one study could be found that examined MRI findings in the extended family (Ahearn et al. 1998). Twenty-one members of a single family with a strong family history of bipolar disorder were examined using MRI. Four of nine family members with bipolar disorder had deep white matter changes and eight had lesions of subcortical grey matter nuclei. Six of ten unaffected family members also had lesions of

subcortical grey matter nuclei, although only one had evidence of subcortical white matter changes.

2.7.3 Studies of obligate carriers

Studies of the healthy relatives of schizophrenic subjects have provided a useful design in which to study the effects of genes which raise the liability to schizophrenia. Such studies are generally unconfounded by the effects of medication and are not associated with the expression of the illness itself. However, the proportion of genes shared with the affected relative may be much less than 50% and the relative importance of shared genetic factors is likely to be less the more distant the relationship. A potentially stronger design is to consider the unaffected relatives of schizophrenic probands who have both a parent and a child with schizophrenia. Unaffected 'obligate carriers' can therefore be assumed to have transmitted the genotype from one generation to the next without succumbing to the illness themselves. They also share approximately 50% of their genes with both relatives, and since both are affected, the shared genes are more likely to contain alleles which increase the genetic liability to schizophrenia.

Figure 2.7.3: Family tree indicating affected patient, obligate carrier and non-affected non-carrier



Sharma et al (1998;1999) were one of the first to use the 'obligate carrier' approach to studying the effects of genes for schizophrenia. Thirty one people with schizophrenia were compared to 39 unrelated controls and 57 relatives, of whom 11 were presumed 'obligate carriers'. Obligate carriers had larger left and right lateral ventricles volumes than any other group. A subsequent study by Steel et al (2002) compared 6 affected sibships of three individuals in which one sibling was an affected subject with schizophrenia, one was a presumed obligate carrier with a child with schizophrenia and one sibling had no children with schizophrenia ('non-obligate'). In terms of cortical structures (WB, FL, TL), obligates resembled their non-obligate unaffected siblings, both having significantly larger volumes than their affected siblings. However, the amygdala-hippocampal complex was significantly smaller in schizophrenic siblings and their obligate siblings than it was in the non-affected non-

obligate sibling. Premorbid IQ, measured by the NART, was also unexpectedly higher in the sample of obligate carriers.

Positron emission tomography (PET) has been used to compare obligate carriers with stable schizophrenic patients and healthy controls in one study which used $H_2{}^{15}O$ to examine the functional correlates of verbal fluency (Spence *et al.* 2000). The 'normal' functional response is said to be characterised by left dorsolateral prefrontal cortex (DLPFC) activation and deactivation of the left superior temporal gyrus (STG) and was found in both normal controls, obligate carriers and affected patients. The same research group found similar results in asymptomatic patients with schizophrenia in an earlier study (Dye *et al.* 1999) who showed similar responses to both normal controls and a further group of six patients with schizophrenia. Previously replicated findings of reduced fronto-temporal connectivity (Frith *et al.* 1995;Fletcher *et al.* 1999;Lawrie *et al.* 2002a) in schizophrenia were not replicated in either study suggesting that at least some patterns of dysconnectivity may be related to psychotic symptoms rather than be markers of genetic liability.

2.7.4 Studies of familial and sporadic psychosis

Studies of the ventricle to brain ratio (VBR) in 'sporadic versus familial' schizophrenia provide less consensus, as one of the originators of the distinction noted in a review of the early studies (Lewis 1990). Patients without a family history of schizophrenia may have repeatedly been shown to have a higher VBR and more marked ventriculomegaly than family history positive patients (Vita et al. 1994;DeQuardo et al. 1996), and some notable large studies (n>100) may have failed to find an association

between family history and the VBR (Johnstone et al. 1989;Jones et al. 1994c); but several studies do report such an association (Owens et al. 1985), including those which go some way to supporting the distinction (Vita et al. 1994;Silverman et al. 1998). It may be that schizophrenics without an obvious genetic loading are more likely to have had environmental triggers which may increase the VBR, but determining sporadic status is not easy when many healthy relatives are likely to be carrying the gene(s) and, especially in families where there is a poor knowledge of family psychiatric history an affected subject may be misclassified as 'sporadic' (Johnstone *et al.* 1995). The limited resolution of CT studies increases measurement error and the use of VBR may have further compounded these difficulties. Indeed, the few sMRI studies to have adopted similar approaches have all reported similar or greater abnormalities in familial cases (Schwarzkopf et al. 1991;Roy and Crowe 1994;Falkai et al. 2002;Harris et al. 2002), with the exception of McDonald et al (2002), and some suggest specific genetic effects in frontal and temporal lobes, the ventricles and the basal ganglia.

Studies of familial and sporadic bipolar disorder are less frequent and have generally concerned a finding of reduced volume or density in the region of the subgenual prefrontal cortex (SGPFC). In the first study to report this finding, a reduced volume and blood flow in familial and non-familial bipolar disorder was shown by Drevets et al (Drevets et al. 1997). Unfortunately, this result was not replicated by Brambilla et al (2002) in a similar study which failed to find SGPFC volume reductions in either familial or non-familial bipolar disorder compared to controls.

2.7.5 High risk studies

Contemporary "high risk" studies follow a cohort of unaffected individuals at increased risk of schizophrenia prospectively through the period of high risk (circa 23 in males, 27 in women, see Hafner et al. 1989) in the knowledge that some subjects will become affected. This design overcomes several of the difficulties of case-control studies. Subjects can be scanned and interviewed repeatedly over the period of risk allowing any effects to be unaffected by medication or positive symptoms. Imaging findings may be associated to symptoms or neuropsychological performance and subjects who develop schizophrenia may be scanned before medication has been prescribed. In addition, because the matter of who will develop schizophrenia is not known, investigators are less liable to observer bias.

In spite of the considerable advantages of 'high risk' studies, they have many practical limitations. Patient attrition, cost and the tendency for both staff and technology to change over time has meant that few centres have undertaken this study design. The first high risk imaging study to be completed was the Copenhagen high risk project (CHRP), although the scans (CT) were not repeated over time (Cannon 1993). Two further studies are ongoing, both using sMRI, the Edinburgh high risk study (EHRS) and the Australian high risk study (AHRS).

The Copenhagen High Risk Study (Mednick 1966) concerned the children of mothers with schizophrenia Subjects received a CT scan of the brain and neuropsychological assessments. High risk subjects were compared to healthy controls with no family history of mental illness that were matched to high risk subjects on age, sex social class and IQ. CT scans were not repeated over time and the main results compare the scans from high risk subjects with healthy controls. Their results suggest

that widened fissures and sulci are positively associated to genetic risk but that only schizophrenic subjects have enlarged ventricles (Cannon *et al.* 1989). A subsequent study of 16 twin pairs discordant for schizophrenia (Zorrilla *et al.* 1997) found that the sulci to brain ratio and VBR differed between the twin pairs suggesting an environmental effect or gene-environment interaction.

Researchers in Melbourne have adopted a different but complementary approach. They have examined groups of people at 'ultra high risk' (UHR) of psychosis, those with first episode psychosis (FEP, including about 50% with schizophrenia or schizophreniform psychosis) and a large group of healthy controls. The UHR group consisted of referrals to a clinic in Melbourne, of people aged 14-30 with: 'attentuated' partial (positive) psychotic symptoms several times a week for one week to 5 years, transient symptoms of less than one weeks duration in the past year, and/or both trait and state risk factors for psychosis (a family history and a worsening in mental state or general functioning in the past year). Preliminary ROI results suggested non-significant hippocampal reductions in the UHR group and the sub-group of them that developed psychosis (Copolov et al, 2000). An early VBM study of nine who developed psychosis and twelve who remained well did however identify volume reductions in the hippocampus, entorhinal cortex, inferior frontal and fusiform gyri during the transition to psychosis (Pantelis et al. 2003).

Phillips et al (2002) recently reported on their traced whole brain and hippocampal volumes as possible predictors of psychosis. 75% of eligible referrals were scanned between 1995-8 and 5% of scans were lost due to movement artefact, leaving 60 scans. Twenty (33%) of those with usable scans developed an acute psychosis

(defined as an increase of one or more points on the BPRS or CASH, several times a week, for more than one week) within a year. A SCID interview identified diagnoses of schizophrenia spectrum disorder in 11, affective psychosis (3), bipolar disorder (3) and others (3). The UHR groups who did not develop psychosis included four patients with depression, and 11 with an anxiety state.

The scans were conducted at two sites and there was a weak tendency for the scanners to deliver different whole brain volumes and for more of those who developed psychosis (and of one sex) to be scanned at one site (Phillips et al, 2002). Nonetheless, controlling for a slightly smaller whole brain, the 60 UHRs has significantly smaller hippocampi (by about 11%, effect size≈ 0.9) than the controls but did not differ from the FEPs. However, the UHRs were on average 10 years younger and 11 points lower in premorbid IQ than the normals. The 20 who became psychotic were much more closely similar in demographics to the 40 who remained non-psychotic but, rather counter-intuitively, the (left) hippocampus was *larger* in those who went on to develop a psychosis. These confusing results may be attributable to scanner effects, selection bias and/or confounding by e.g. other diagnoses or gender.

Pantelis et al (2003) have recently reported on their VBM findings in a slightly extended sample. In 75 people with prodromal symptoms, defined as above, 23 (31% developed a psychotic disorder (roughly equal numbers of schizophrenia and affective psychoses). Compared to those who did not develop a psychosis, they had less grey matter in right medial temporal, lateral temporal and inferior frontal cortex, and in bilateral cingulate cortex. Twenty-one subjects had repeated scans at 1-2 year intervals – 10 of whom had become psychotic (five with schizophrenia). They showed reductions

over time in left parahippocampal, fusiform, orbitofrontal and cerebellar grey matter, while those who did not remain psychotic only exhibited cerebellar reductions. These are intriguing results that suggest grey matter reductions in the run up to psychosis and immediately after it. There are however some important issues outstanding – in particular, whether some of those in the UHR group actually had a psychosis before or at study entry, and why the ROI and VBM studies appear to have such different findings.

The Edinburgh High Risk Study concerns the families of known patients throughout Scotland whose consultant thought might have a family history of schizophrenia. Healthy family members were included if they had at least two close relatives with a confirmed diagnosis of schizophrenia using the OPCRIT computer program (McGuffin *et al.* 1991). 162 high risk subjects provided some data and 150 had at least one sMRI scan in the first phase of the study between 1994 and 1999. Two control groups were also recruited. The first consisted of healthy non-related controls matched as closely as possible for age and sex. The second consisted of patients with first schizophrenic episodes but without a known family history of psychosis. High risk subjects were further classified at each of up to 3 interviews, according to the Present State Examination, into those with schizophrenia, those with one or more psychotic symptoms and those without psychotic symptoms.

High risk subjects and controls were reassessed every eighteen months. Assessments performed included neuropsychological testing and clinical examinations and an MRI scan of the brain. Obstetric complications were also assessed from maternal recall and health service records (McIntosh et al. 2002) and the mothers of subjects and

controls were interviewed with a view to obtaining information about childhood behaviour (Miller *et al.* 2002).

Numerous differences in neuropsychological measures were shown (Byrne *et al.* 2003). In general controls performed best followed by high risk subjects followed by first episode patients. After controlling for IQ high risk subjects performed worse on the Hayling sentence completion test and the Rivermead Behavioural memory Test (RBMT) of delayed memory. Both measures were negatively correlated with both measures of genetic liability used in the study.

Early region of interest analysis of the first 100 MRI scans found the amygdala-hippocampal complex to be approximately 4% smaller than controls and about 4% larger than subjects with schizophrenia (Lawrie *et al.* 1999). Thalamic size was also smaller in high risks compared to controls. An increase in third ventricular volume was found in high risk subjects compared to controls, although this was not significant after the correlation in volumes between subjects from the same family had been taken into account (Lawrie et al. 1999). Voxel based morphometry confirms these early results and also shows medial prefrontal and temporal lobe reductions in grey matter density with a gradient which is greatest in first episodes, intermediate in high risks and lowest in controls (Job et al. 2002). Within high risk subjects, higher genetic liability was associated with smaller left and right prefrontal lobes and smaller left and right thalami (Lawrie et al. 2001).

Changes in brain size were also measured using repeat scans in the 66 high risk subjects and 20 healthy controls (Lawrie et al. 2002b). Changes within the high risk group were also compared for subgroups according to whether or not they had fully

rated psychotic symptoms in the first phase of the study. No differences were found between controls and high risk subjects. When high risks with symptoms were compared to those without symptoms however, several other differences emerged. Those with psychotic symptoms showed a greater reduction in right temporal lobe volume compared to those without symptoms and similar, though non-significant differences were also reported in respect of the left temporal lobe and the prefrontal cortex bilaterally. Over the same time period, neuropsychological measures also continued to favour controls over high risk subjects and those with psychotic symptoms performed less well than those without particularly in the area of memory (Cosway *et al.* 2002). Decline in memory performance also appeared greatest in those with symptoms though the change was not statistically significant

2.8 The molecular genetics of schizophrenia and bipolar disorder

2.8.1 Evidence for single gene loci

The increased risk to schizophrenia or bipolar disorder conferred by an affected relative has been established by many twin, family and adoption studies (Gottesman and Shields 1976;Kessler 1980;Tsuang et al. 1991;Mitchell et al. 1993). However, the genetic linkage and association studies which have sought to identify the genes responsible have so far failed to account for the majority of genetic liability to either disorder although several positive findings have been replicated in both disorders (Berrettini 2002;Levinson 2003). The failure to widely replicate most positive findings may be because gene effects are specific to a given population, because the effect is small and detectable only in large samples or because there is a tendency for small

positive studies to show a positive finding but for small negative ones to remain unpublished. The consistency of findings from one population to another, and the possibility of publication bias have been addressed in several reviews of this area.

In schizophrenia, a review of 20 genome wide linkage studies found evidence form linkage at several loci including 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q and 14p and further loci emerged as the threshold for statistical significance was lowered (Lewis et al. 2003). However, the study did not identify specific genes and neither publication bias nor heterogeneity was addressed. Linkage, but not association, has been found for the Catechol O-Methyltransferase Val allele and schizophrenia, although the linkage studies were generally smaller in number and in sample size (Glatt et al. 2003a). Other reviews have substantiated associations between the dopamine receptors D2 (Glatt et al. 2003b), D3 (Jonsson et al. 2003a;Shaikh et al. 1996) and D4 (Jonsson et al. 2003b). Recent evidence has also emerged regarding Neuroregulin, D-Amino Acid Oxidase and Dysbindin, although only Neurotrophin A3 has been subject to a confirmatory meta-analytic review (Jonsson et al. 1997a).

Linkage and association studies in bipolar disorder have not yet been subject to a systematic review and meta-analysis, although several narrative reviews exist. This is surprising since heritability estimates for bipolar disorder are generally greater than for schizophrenia and gene effects might be easier to detect under these circumstances, particularly if one or two genes of major effect exist. Linkage has been found, and subsequently replicated, to 18p11.2, 21q22, 22q11-13, 18q22, 12q24 and 4p15 (Berrettini 2002). Using both linkage and association techniques, polymorphisms have been found in the monoamine oxidase-A (MAO-A) gene which increase the risk of

bipolar disorder (odds ratio=1.49, Berrettini 1997;Furlong et al. 1999), although there are also several published negative studies (e.g. Norton et al. 2002). The negative studies tend to be underpowered however, and their presence is probably consistent with a modest effect size. Positive and negative findings have also been found for COMT (Kirov et al. 1998;Geller and Cook, Jr. 2000;Rotondo et al. 2002) and the serotonin transporter gene (5HTT, Collier et al. 1996;Oruc et al. 1997;Saleem et al. 2000) but it will be difficult to quantify their true effect without further large studies.

Linkage for 18p11, 13q32, 10p14 and 22q11 has been established in both schizophrenia and bipolar disorder and the COMT Val allele also appears to raise the probability to both disorders (Egan et al. 2001;Rotondo et al. 2002). However, most loci are not shared by both disorders and the majority of locus-dependent risk appears to be disease-specific (Bramon and Sham 2001). This is consistent with the twin, family and case-control studies referred to in the previous chapter which suggest that having a relative with schizophrenia increases the probability that an unaffected subject will develop bipolar disorder in the future, and vice versa. However, the apparent specificity of loci to either schizophrenia or bipolar disorder might be explained by a failure to systematically investigate disease specificity in the primary studies, the presence of small underpowered studies or the selective publication of small positive studies.

There are now several chromosomal and gene loci which appear to raise the risk for either schizophrenia, bipolar disorder or both. However, methodological problems have limited our confidence in these findings and the matter of which alleles raise the probability of either disorder in the general population has yet to be resolved. For each locus, the effect size is generally small (typically OR<2) which suggests that the

proportion of cases accounted for by 'known' mutations is very small. Given that the heritability of both schizophrenia and bipolar disorder is substantial and that genetic models examining their mode of inheritance tend to suggest several genes of minor effect, it seems likely that several genes of quantitative effect are responsible for the increased genetic liability. Certainly, classical *Mendelian* inheritance is an unlikely prospect given the nature of the data available.

2.8.2 Imaging gene effects in psychosis

The discovery of an allele associated with an increased liability to schizophrenia or bipolar disorder is not in itself very informative, unless it is related to the biology of the disorder. For example, the discovery of the gene for Huntingdon's disease 'Huntingtin' has not yet led to the discovery of a mechanism, although some theories have been suggested. Individual gene effects might best be quantified by relating their presence or expression to clinical features and/or regional brain volumes in both affected subjects and their well relatives. To date, however, very few studies have attempted to use this method. Difficulties with this approach are almost certainly contingent on the fact that few specific gene effects have been consistently replicated in schizophrenia. Kunugi et al (1999) looked at the relationship between the neurotrophin-3 A3 allele and regional brain volumes in schizophrenia and bipolar disorder. The results showed A3 allelic status to be associated with reduced volumes in schizophrenic but not bipolar subjects. This unconfirmed finding suggests that bipolar subjects may be subject to genetic or environmental factors which ameliorate the effects of this gene. Without further information about the clinical associations of A3 allelic status it is difficult to

draw any firm conclusions from this study. ApoE status has also been related to hippocampal volume in schizophrenia (Fernandez *et al.* 1999;Hata *et al.* 2002), although the results are inconsistent.

The catechol-O-methyl transferase (COMT) is a potential candidate gene for schizophrenia, having a role in dopamine metabolism and also a relationship between its expression and prefrontally medicated cognition. A study of 175 patients with schizophrenia, 219 unaffected siblings and 55 controls (Egan *et al.* 2001) demonstrated a dose like effect of COMT genotype expression and performance on the Wisconsin Cart Sorting Test. COMT allelic expression was further related to brain physiology during a working memory task in three subgroups (n=11-16) of the original sample. Met allele load predicted a stronger prefrontal response and in a subsequent analysis of 104 trios it was shown that the Val allele was preferentially transmitted to schizophrenic offspring. These findings suggest that the COMT Val allele may raise the liability to schizophrenia possibly by an impairment of dopamine function and consequent impairment of executive function. At the time of going to press, there had been no independent replication of this finding.

Studies attempting to image the effects of specific loci in bipolar disorder are much less common. A gene (NOTCH3) implicated in 'Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy' (CADASIL) has been investigated in a large family multiply affected family with bipolar disorder. Twenty-one family members were scanned using sMRI and, although subcortical white matter hyperintensities were common in both affected and unaffected family members, linkage was not shown to NOTCH3 (Ahearn et al. 2002). A further study examined the 5178

mitochondrial DNA polymorphism in 145 patients with bipolar disorder and 184 controls (Kato et al. 2000). The rate of the 5178C polymorphism was significantly higher in affected patients than in controls and was associated with higher brain pH (measured using 31P-MRS). No differences were found in subcortical hyperintensities between the bipolars with and without the polymorphism.

2.9 Conclusions

Early pneumoencephalography studies have clearly demonstrated that there are macroscopic anatomical differences between schizophrenic subjects and controls. CT has succeeded in this regard for bipolar disorder where pneumoencephalographic evidence has been lacking. However, advances in image acquisition, particularly MRI and in image analysis, have greatly increased our understanding of these disorders. There is good evidence that schizophrenic subjects have reductions in several cortical and subcortical regions and increases in ventricular CSF volume.

Many of the same regions are implicated in both bipolar disorder and schizophrenia. However, a few regions show some promise as discriminators between the disorders. In particular, the amygdala and thalamus may be larger in bipolar disorder than in schizophrenia. Furthermore, the amygdala may be larger in bipolar subjects than in healthy controls, suggesting that the degree of overlap with schizophrenic subjects may be much less than for other regions.

Neuropsychological abnormalities appear to be present in both schizophrenia and bipolar disorder. Verbal memory appears to be disrupted in both, but for virtually all other domains of neuropsychological function there is some doubt as to whether it

discriminates between the disorders. In particular, IQ appears to possibly separate the phenotypes although the effect of symptoms and possibly medication may also confound these findings.

Strong evidence of neuropsychological impairments in relatives of people with psychosis exists for schizophrenia only. The failure to demonstrate such deficits in relatives of patients with bipolar disorder may largely be because such studies have yet to be conducted.

2.10 Hypotheses and aims

This study seeks to clarify the neuropsychological and neuroanatomical differences between schizophrenia, bipolar disorder and their affected relatives. The neuropsychological domains of intelligence, executive function, psychomotor performance and memory will be measured in a sample of patients with schizophrenia, bipolar disorder and well relatives from both groups. Bipolar patients and their relatives will be of two types a) those with a family history of bipolar disorder only and b) those with a family history of both bipolar disorder and schizophrenia. In this way we hope to clarify which deficits are related to phenotype and which are related to family history. The patient and relative groups will be compared to a group of healthy controls with no personal or family history of either bipolar disorder or schizophrenia.

The same sample will also undergo an MRI scan of the brain to clarify similar issues with regard to brain anatomy. Amygdala volumes are hypothesised to discriminate between schizophrenic and bipolar patients. Thalamic volumes, having found to be reduced in both schizophrenia and their close relatives, are hypothesised to

be reduced in all patient groups reflecting a common underlying mechanism by which a liability to psychosis may be expressed.

The specific hypotheses are:

1. That reduced IQ will be associated with a genetic liability to schizophrenia, but not bipolar disorder
2. The executive function will be impaired to a greater extent in schizophrenia and relatives of patients with schizophrenia than in bipolar subjects of their relatives
3. That thalamic reduction will be found in schizophrenic subjects, but not in bipolar subjects or their close relatives.
4. That amygdala and hippocampal reductions will be found in schizophrenia and the relatives of schizophrenic subjects, but not in bipolar subjects, or their close relatives.

The general hypothesis is that the genes which are associated with an increased liability to schizophrenia or bipolar disorder act on regional brain systems. When certain brain systems are affected (e.g. the thalamus, cortical-thalamo-striatal loops) then the clinical picture is one of affective psychosis. Genes affecting prefrontal grey matter are *additionally* necessary for the development of schizophrenia and for the cognitive and other abnormalities shown by sufferers.

2.11 Power calculation

The number of people required to detect a standardised effect size of 1.0 with 80% power and at a significance level of p=0.05 in 2-groups is 38 in each group (STATA Software). Therefore, in comparison with controls, there should be about 76 subjects or more in the comparison.

Chapter 3: Systematic Literature Review: MRI Studies of Bipolar Disorder

3.1 Introduction

The question 'is the brain structure of people with bipolar disorder different from that of either healthy controls or people with schizophrenia?' is of some importance. Firstly, characterisation of differences between bipolars and controls may give clues to the biology of this illness, ranked by the WHO in the top thirty leading worldwide causes of disability (Murray and Lopez 1997). Such information could be combined in future studies, particularly ones which relate genetic liability to any volumetric differences found. Secondly, if the differences were large enough, and different from those found in schizophrenia, diagnostic testing, and the quantification of risk in subjects who have been hitherto unaffected, may be possible. Finally, by characterising the changes found in bipolar disorder, this might enable us to better understand the biology of mood.

There have been over 58 structural magnetic resonance imaging studies (sMRI) of over 1588 patients with schizophrenia compared to controls (Wright et al 2000). That there are established differences in cerebral, ventricular, amygdala and hippocampal volume is scarcely beyond doubt. However, attempts to compare patients with bipolar disorder to unaffected controls are sparser reflecting a general paucity of bipolar disorder research in general (Clement et al. 2003a). Combining the available studies might resolve uncertainty about the volumes of certain cerebral structures compared to both controls and schizophrenics (e.g. the amygdala and hippocampus) and any associated heterogeneity could also be measured and its potential causes investigated.

Several reviews of sMRI studies in bipolar disorder have been performed (Elkis et al. 1995b;Soares and Mann 1997b;Norris et al. 1997;Videbech 1997;Baumann and

Bogerts 1999;Hoge et al. 1999;Stoll et al. 2000;Bearden et al. 2001;Baumann and Bogerts 2001;Strakowski et al. 2002a;Sheline 2003). In many cases, a systematic search was either not reported in the text of the article, or was clearly not performed (Norris et al. 1997;Soares and Mann 1997a;Videbech 1997;Baumann and Bogerts 2001;Sheline 2003). In either case, because no search strategy was reported, the identification of articles may have been unsystematic and liable to represent the views of the authors rather than an unbiased estimate of effect size. Other reviews considered samples where unipolar and bipolar patients were taken together as one sample (Elkis et al. 1995a), others combined studies using CT or MRI (Hoge et al. 1999). Since it cannot be assumed that bipolar disorder and unipolar disorders are different expressions of the same process, it seems unsafe to combine them statistically. Similarly, the combination of CT and MRI studies in one meta-analysis is not without difficulty and it is perhaps surprising that the only systematic review to do this found no heterogeneity (Hoge et al. 1999). However, the review considered only whole brain size and does not address the many other regions of interest implicated in bipolar disorder.

In contrast, the review by Bearden et al (2001) appears systematic, comprehensive and has clear inclusion and exclusion criteria. However, the authors made no attempt to combine studies statistically. Given there is no up-to-date, comprehensive systematic review and meta-analysis of brain structure in bipolar disorder, this study sought to fill this publication gap in a way which would allow both direct and indirect comparison of bipolar disorder with schizophrenia.

3.1.1 Aims

The primary aim of this systematic review was to examine the evidence that the brains of people with bipolar disorder are different in structure from those of healthy controls and to describe and quantify any differences found. In addition, studies comparing patients with bipolar disorder and schizophrenia were also reviewed in order to assess the diagnostic specificity of any structural MRI findings compared to controls. In order to address these questions, observational studies meeting pre-specified criteria were sought and, where appropriate, combined mathematically.

3.2 Methods

3.2.1 Study ascertainment

Primary studies were considered for inclusion if they were published between 1984 and 2003 and compared patients with operationally defined bipolar disorder with a group of unrelated healthy controls or subjects with schizophrenia. Studies which included patients with unipolar as well as bipolar affective disorder were only included if the bipolar patients made up 80% of the sample size or more. Conference abstracts and letters were included only if there were other publications from the same study that had been published in full as peer reviewed articles. Studies reporting means and standard deviations were included in the meta-analysis, but if standard deviations were missing from the published articles, these were conservatively estimated from the largest standard deviation from other studies measuring the same structure in the same volumetric units. In order to facilitate an indirect comparison with the review by Wright et al (2000), the same brain regions were considered by this review. In addition, the total

volumes of lateralised brain structures were also considered in addition to their volumes for each hemisphere separately.

Studies were excluded if they failed to report means for each group, or if they reported volumes as a proportion of whole brain volume only. Similarly, studies reporting areas from a single slice only were excluded. Where a single study was published in several journal articles, the article reporting the largest group size for that volume of interest was used. Multiple publication of the same sample was suspected when two or more articles had the same grant numbers, reported the same means and standard deviations for a single structure and where at least two of the authors were named on all articles. Multiple publications were also identified when the text of an article referred to some of the patients or controls having participated in an earlier study which had already been judged eligible for inclusion. Multiple publications were identified by three of the authors (AM, SL and JC) and disagreements were resolved by discussion.

Studies were also excluded when there was a co-morbid diagnosis of learning disability, chromosomal or genetic disorder. Studies were included irrespective of slice thickness or inter-slice gap, though these factors were recorded as potential sources of heterogeneity. Studies were not included when control subjects were genetically related to affected probands.

3.2.2 Search strategy

The databases Medline, Embase and PsychINFO were searched using the search terms 'Bipolar Disorder' and 'MRI' and related terms both as free text and expanded

subject headings. Details of specific search strategies are given in tabular form below. Schizophrenia was also included as a subject heading in order to identify studies whose primary objective was to describe brain volumes in patients with schizophrenia, but which also included a bipolar group to examine diagnostic specificity.

Figure 3.2.2: Search strategy for location of articles

Medline (Ovid interface at http://gateway.ovid.com) 1. Explode Magnetic Resonance Imaging/ all subheadings 2. "MRI".ti,ab 3. Explode Bipolar Disorder/ 4. Explode Mania/ 5. Explode Mood Disorders/ 6. Explode Schizophrenia/ 7. 1 OR 2 8. 3 OR 4 OR 5 OR 6 9. 7 AND 8
Embase (Ovid interface at http://gateway.ovid.com) 1. Explode Magnetic Resonance Imaging/ 2. "MRI".ti,ab 3. Explode Bipolar Disorder/ 4. Explode Mania/ 5. Explode Mood Disorders/ 6. Explode Schizophrenia/ 7. 1 OR 2 8. 3 OR 4 OR 5 OR 6 9. 7 AND 8
PsychINFO (WinSPiRs interface at http://www.bids.ac.uk/) 1. Affective Disorder/ All subheadings 2. Manic-Depressive Psychosis/ 3. Schizophrenia/ 4. MRI 5. Nuclear Magnetic Resonance/ 6. 1 OR 2 OR 3 7. 4 OR 5 8. 6 AND 7

In addition, an online search of the journals Bipolar Disorders, Schizophrenia Research, Psychiatry Research: Neuroimaging, Psychological Medicine, British Journal of Psychiatry, American Journal of Psychiatry, Archives of General Psychiatry and the Journal of Neurology, Neurosurgery and Psychiatry. Most searches were completed through the web portals of the journals themselves or through the electronic resources of Elsevier (Science Direct, www.sciencedirect.com) or Blackwell Publishing (SwetsWise, www.swetswise.com). The initial search took place in November 2002 but was updated on the 21st November 2003 and 13th January 2004.

3.2.3 Study quality assessment

Abstracts were assessed for possible relevance by one reviewer (AM) and full text articles were obtained where appropriate. The threshold at which an article was retrieved in full text for further inspection was set very low. Full text articles were then reviewed by 3 reviewers (AM, GD, UK: AM read *all* full-text articles, GD and UK reviewed 50% each). Studies were included if they met the inclusion criteria above. An agreed pro-forma was used by all reviewers to extract the necessary information from all studies.

3.2.4 Data extraction and analysis

Data was extracted by a single reviewer (AM) and checked by a second (SL) who checked the spreadsheets containing the numbers, means and standard deviation from each group against the data given in the original articles . Extracted data (numbers, means, standard deviations and selected covariates) were then entered into STATA SE

version 8 for windows and stored in a flat text file. Where standard deviations were not available for a study, these were estimated conservatively from the largest standard deviation of all other studies included in that comparison.

Statistical analysis was conducted using STATA SE using the 'metan' computer program written by Michael Braidburn (Centre for Statistics in Medicine, Oxford, UK, Personal communication). Standardised mean differences were calculated using Cohen's d statistic:

$$\text{Cohen's d} = \frac{\bar{X}_1 - \bar{X}_2}{SD_p}$$

Where $\bar{X}_1$ and $\bar{X}_2$ are the mean volumes from the first and second groups respectively and Sp is the pooled standard deviation estimated from both groups:

$$Sp = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{(n_1 + n_2 - 2)}}$$

Where n_i and SD_i are the mean and standard deviation of the ith group. Standardised effect sizes were then combined using the inverse variance method. The variance of Cohen's d is estimated as:

$$SD(d) = \sqrt{\frac{N}{n_1 n_2} + \frac{d^2}{2(N-2)}}$$

Where N is the total sample size for the study, d is Cohen's d and n_1 and n_2 are as defined above. Random effects analyses (DerSimonian and Laird 1986) were used throughout to weight each study taking into account the between study heterogeneity Q:

$$Q = \sum w_i(\theta_1 - \theta_{IV})^2$$

Where w_i is the standard deviation of Cohen's d (given above), θ_i is the effect size (Cohen's d) from the ith study and θ_{IV} is the fixed effects estimate of overall effect calculated using the following formula.

$$\theta_{IV} = \frac{\sum w_i\theta_i}{\sum w_i}$$

The overall effect size for the comparison was then calculated using the following formula:

$$\theta_{DL} = \frac{\sum w_i'\theta_i}{\sum w_i'}$$

Where θ_{DL} is the pooled effect size, w' refers to the amended weight applied to the ith study and w' is:

$$w_i' = \frac{1}{SE(\theta_i^2 + \tau^2)}$$

And τ^2 (the variance of the effect size) is equal to:

$$\tau^2 = \frac{Q-(k-1)}{\sum w_i - \left(\frac{\sum w_i^2}{\sum w_i}\right)}$$

The more useful statistic I^2 can also be calculated as follows (Higgins et al. 2003):

$$I^2 = \frac{(Q-d.f.)}{Q}$$

and can be interpreted as the proportion of variation in effect size due to heterogeneity. Confidence intervals for the overall effect size θ_{DL} were calculated from its standard error:

$$SE(\theta_{DL}) = \frac{1}{\sqrt{\sum w_i^*}}$$

Where statistically significant heterogeneity was found and accounted for 50% or more of the variation in standardised effect size, Galbraith plots of the standardised normal deviate (z) were made against study precision. The Galbraith or Radial Plot was first described by Galbraith (1988) in the context of clinical trials. The numerical outcome from each study is divided by its standard error to give a deviation in standard normal deviation units (i.e. deviation in terms of a normal distribution with mean 0 and standard deviation 1, often referred to as z). The statistic z is then plotted on the y-axis or ordinate against study precision (1/standard error) on the x-axis or abscissa. The degree to which a study lies to the right of the graph is a measure of its weight in the meta-analysis. The gradient of the line from the origin to a particular study represents its effect size. The gradient of an unweighted regression line through all of the points represents the fixed-effects analysis of all studies combined. Studies which form a homogeneous group will scatter with constant variance along the regression line, with unit standard deviation. Points far away from the regression line indicate outlying studies which contribute greatly to the between study heterogeneity. The identification of such trials may be assisted by the addition of two lines indication the upper and lower 95% confidence intervals for the regression line. Studies identified as outliers were inspected for critical methodological differences from other trials and removed from the analysis where

appropriate. The estimates of effect size and heterogeneity were then re-calculated. In order to re-calculate I^2 with the heterogeneous studies removed, Galbraith plots were only conducted when there were 3 or more studies comparing a specific region of interest between 2 groups.

For comparisons where the Galbraith plot could not identify an obvious cause for heterogeneity, a meta-regression analysis was conducted. Meta-regression examines the relationship between summary effect size and methodological and clinical variables at a summary level. Effect size is effectively plotted against the characteristic of interest and the linear equation summarising their relationship is calculated using the restricted maximum likelihood technique (REML). However, unlike conventional regression analysis where each data point is given equal weight, meta-regression takes into account the individual study precision by weighting it by the inverse of its standard error squared.

A priori meta-regression analyses were conducted for the mean age of bipolar subjects and the proportion of males in each sample. The rationale for these analyses was to examine whether any differences exist between males and females, and also to examine whether any differences between subjects and controls are could be progressive. We considered using the years of elapsed illness as a more accurate measure of disease duration. However, in an earlier narrative review of this area it was evident that not enough primary studies provided this information to make the analysis practical.

3.3 Results

The search strategy (last updated 13 January 2004) identified 1746 unique articles of which 256 appeared were retrieved in full-text. Twenty-nine *studies* published in 41 separate articles met the pre-stated inclusion criteria and were tabulated (see table 3.3.1) and entered into STATA for further analysis.

3.3.1 Included studies

Twenty-seven studies compared patients with bipolar disorder with healthy, unrelated controls. Although one study (Noga et al., 2001) used a twin design, the control twins were unrelated to the concordant twins with bipolar disorder used in the analysis. Included studies are presented in table 3.3.1.1 by main publication and again in table 3.3.1.2 and 3.3.1.3 by region of interest. Table 3.3.1.2 considers studies comparing bipolar disorder with healthy controls whilst table 3.3.1.3 considers only those studies comparing bipolar with schizophrenic patients. Studies finding a larger volume in bipolar disorder are marked with a + sign and those finding a smaller volume in bipolar disorder are marked with a – sign. Studies finding an equal volume in bipolar subjects and controls are marked with a (NC). For most brain regions, measured in at least 3 studies, there is evidence of both increases and reductions in bipolar disorder compared to controls. However, no studies were identified finding an increased volume of the total prefrontal cortex in bipolars compared to controls, although differences were found in both directions when each side was considered separately. The left amygdala-hippocampal complex was smaller in bipolar patients compared to controls in all studies measuring this volume, although the differences were less one-sided when the amygdala and hippocampus were considered separately.

Table 3.3.1.1: Included studies

	Bipolar patients				Comparison group(s)	Methods		
Study	N	Diagnostic system	N (male)	Mean age	Type and number	Magnet (T)	Slice thickness	Contiguous slices
Swayze (1990a;1992)	48	DSM III	29	33.9	47 Unaffected 54 Schizophrenia	0.5	10mm	Y
Rossi (1991)	16	DSM III	NK	47	10 Schizophrenia	0.5	5mm	N
Strakowski (1993a)	17	DSM IIIR	7	28.4	16 Unaffected	1.5	6mm	Y
Aylward (1994)	30	DSM IIIR	16	39.2	30 Unaffected	1.5	5mm	N
Harvey (1994)	26	DSM IIIR	10	35.6	34 Unaffected 48 Schizophrenia	0.5	5mm	
Schlaepfer (1994) & Pearlson (1997)	27	DSM IIIR	16	34.9	60 Unaffected 46 Schizophrenia	1.5	5mm	Y
Botteron (1995)	8	DSM IIIR	5	11.3	5 Unaffected	1.5	4/5mm	Y
Dupont (1995)	36	DSM IIIR	24	36.6S	26 Unaffected 30 Unipolar Depression	1.5	5mm	N
Zipursky (1997)	14	DSM IIIR	3	35.9	17 Unaffected 23 Schizophrenia	1.5	5mm	N
Roy (1998)	14	DSM IIIR	3	35.9	15 Unaffected 22 Schizophrenia	1.5	1.5mm	N
Altshuler (1998;2000)	12/24	DSM IIIR	12/24	50.8/50.2	12/18 Unaffected 14/20 Schizophrenia	1.5	1.4mm	Y
Dassari (1999)	15	DSM IIIR	8	15.3	16 Unaffected 20 Schizophrenia	1.5	5mm	N
DelBello (1999)	30	DSM IIIR	18	26.3	15 Unaffected	1.5	1mm	Y
Lim (1999)	9	DSM IIIR	NK	44.4	16 Unaffected 9 Schizophrenia	1.5	5mm	N
Sax (1999)	17	DSM IIIR	10	27	12 Unaffected	1.5	1mm	Y

	Bipolar patients				Comparison group(s)	Methods		
Study	N	Diagnostic system	N (male)	Mean age	Type and number	Magnet (T)	Slice thickness	Contiguous slices
Strakowski (1999)	24	DSM IIIR	17	27	22 Unaffected	1.5	1mm	Y
Hauser (2000)	47	RDC	20	40.7	19 Unaffected	0.5T	5mm	Y
Brambilla (2001a;2001b;2001c;Brambilla et al. 2002) Sassi (2002;2001)	22-29	DSM IV	13-16	33.8-36	22-46 Unaffected 14-18 Unipolar Depression	1.5	1.5	Y
Caetano (2001)	25	DSM IV	15	34.4	39 Unaffected 17 Unipolar Depression	1.5	1.5	Y
McIntosh (2001)	14	OPCRIT	4	40.2	29 Unaffected 16 Schizophrenia 9 Unipolar Depression	1	1.9	Y
Noga (2001)	6	DSM IIIR	1	34.5	11 Unaffected MZ twins	1.5	2mm	Y
Getz (2002)	12	DSM IV	8	29.2	12 Unaffected 12 Schizoaffective	1.5	1mm	Y
Lopez Larson (2002)	17	DSM IV	11	29	12 Unaffected	1.5	1mm	Y
Strakowski (2002b)	35	DSM IV	17	23.5	32 Unaffected	1.5	1.5	Y
Kasai (2003b;2003a;2003c) and (Hirayasu et al. 1999;2000) and (Lee et al. 2002)	15-26	DSM IV	14	21.8	14-29 Unaffected 13-26 Schizophrenia	1.5	1.5	Y
Sharma (2003)	12	DSM IIIR	6	38.3	8 Unaffected	4.0	3.3	Unclear
Brambilla (2003)	24	DSM IV	15	35	36 Unaffected	1.5	1.5mm	Y
Blumberg (2003)	36	DSM)V	16	31	56 Unaffected	1.5	1.2	Y

Table 3.3.2.2: Volumes in bipolar disorder compared to healthy non-related controls.

Studies showing larger volumes in bipolars are marked with a (+) sign, differences in the opposite direction are given a (-) sign and (NC) is used the direction of overall effect is unclear.

Brain volume	Studies
Intracranial volume (ICV)	(-) (Harvey et al. 1994) (Kasai et al. 2003c) (Getz et al. 2002) (+) (Lim et al. 1999) (Sassi et al. 2001)
Whole brain volume	(-) (Harvey et al. 1994) (Strakowski et al. 1993a) (Strakowski et al. 2002b) (Schlaepfer et al. 1994) (Dasari et al. 1999) (McIntosh et al. 2001) (Getz et al. 2002) (Brambilla et al. 2001a) (+) (Roy et al. 1998) (Aylward et al. 1994) (Dupont et al. 1995) (Sax et al. 1999) (Strakowski et al. 1999) (DelBello et al. 1999) (Sharma et al. 2003)
Whole brain (grey matter only)	(+) (Strakowski et al. 1993a) (Sassi et al. 2002) (Sharma et al. 2003) (-) (Lim et al. 1999) (Lopez-Larson et al. 2002) (Schlaepfer et al. 1994) (Zipursky et al. 1997)

Brain volume	**Studies**	
Whole brain (white matter only)	(-)	(Strakowski et al. 1993a) (Lopez-Larson et al. 2002) (Pearlson et al. 1997)
	(+)	(Zipursky et al. 1997) (Lim et al. 1999) (Sassi et al. 2002) (Sharma et al. 2003)
Total left cerebellum	(+)	(Brambilla et al. 2001b) (DelBello et al. 1999)
Total right cerebellum	(-)	(Brambilla et al. 2001b) (DelBello et al. 1999)
Cortical limbic structures		
Left hemisphere	(-)	(Noga et al. 2001) (Botteron et al. 1995)
Right hemisphere	(-)	(Noga et al. 2001) (Botteron et al. 1995)
Prefrontal cortex	(-)	(Sax et al. 1999) (Strakowski et al. 1999) (Getz et al. 2002) (Strakowski et al. 1993a)
Left prefrontal cortex	(-)	(Strakowski et al. 1999) (McIntosh et al. 2001)
Right prefrontal cortex	(-)	(Strakowski et al. 1999) (McIntosh et al. 2001)
Left Subgenual prefrontal cortex	(-)	(Hirayasu et al. 1999) (Sharma et al. 2003)
	(+)	(Brambilla et al. 2002)
Right Subgenual prefrontal cortex	(-)	(Hirayasu et al. 1999) (Sharma et al. 2003)
	(+)	(Brambilla et al. 2002)
Temporal lobes	(-)	(Roy et al. 1998)
	(+)	(Altshuler et al. 2000)

Brain volume	**Studies**	
Left temporal lobe	(+)	(Harvey et al. 1994) (Swayze et al. 1992) (Hauser et al. 2000) (Brambilla et al. 2003) (Altshuler et al. 1998)
	(-)	(McIntosh et al. 2001) (Pearlson et al. 1997)
Right temporal lobe	(+)	(Harvey et al. 1994) (Pearlson et al. 1997) (Swayze et al. 1992) (Altshuler et al. 1998)
	(-)	(Hauser et al. 2000) (McIntosh et al. 2001) (Brambilla et al. 2003)
Amygdala	(-)	(Blumberg et al. 2003) (Getz et al. 2002)
	(+)	(Strakowski et al. 1999) (Altshuler et al. 2000)
Left amygdala	(+)	(Swayze et al. 1992) (Altshuler et al. 1998) (Strakowski et al. 1999) (Brambilla et al. 2003)
	(-)	(Pearlson et al. 1997)
Right amygdala	(+)	(Altshuler et al. 1998) (Strakowski et al. 1999) (Swayze et al. 1992) (Brambilla et al. 2003)
	(-)	(Pearlson et al. 1997)
Hippocampal-amygdala complex (AHC)		No studies identified
Left AHC	(-)	(Noga et al. 2001) (McIntosh et al. 2001) (Kasai et al. 2003a) (Swayze et al. 1992)

Brain volume	**Studies**	
Right AHC	(-)	(Noga et al. 2001) (McIntosh et al. 2001) (Kasai et al. 2003a)
	(+)	(Swayze et al. 1992)
Hippocampus	(+)	(Altshuler et al. 2000) (Strakowski et al. 2002b)
	(NC)	(Sax et al. 1999)
	(-)	(Strakowski et al. 1999) (Getz et al. 2002) (Blumberg et al. 2003)
Left hippocampus	(+)	(Strakowski et al. 1999) (Pearlson et al. 1997) (Hauser et al. 2000) (Noga et al. 2001) (Altshuler et al. 1998)
	(-)	(Swayze et al. 1992) (Brambilla et al. 2003)
Right hippocampus	(+)	(Strakowski et al. 1999) (Brambilla et al. 2003) (Altshuler et al. 1998)
	(-)	(Swayze et al. 1992) (Hauser et al. 2000) (Pearlson et al. 1997) (Noga et al. 2001)
Parahippocampus	(-)	(Altshuler et al. 2000)
Left parahippocampus	(+)	(Pearlson et al. 1997)
Right parahippocampus	(-)	(Pearlson et al. 1997)
Left entorhinal cortex	(+)	(Pearlson et al. 1997)
Right entorhinal cortex	(+)	(Pearlson et al. 1997)
Left STG	(+)	(Brambilla et al. 2003) (Kasai et al. 2003a)
Right STG	(-)	(Brambilla et al. 2003) (Kasai et al. 2003a)
Left anterior STG	(-)	(Pearlson et al. 1997) (Hirayasu et al. 1998)
Right anterior STG	(+) (-)	(Pearlson et al. 1997) (Hirayasu et al. 1998)

Brain volume	**Studies**	
Left posterior STG	(-)	(Pearlson et al. 1997) (Hirayasu et al. 1998)
Right posterior STG	(+)	(Pearlson et al. 1997) (Hirayasu et al. 1998)
Subcortical structures		
Caud ate	(+)	(Getz et al. 2002) (Aylward et al. 1994) (Strakowski et al. 2002b) (Dupont et al. 1995)
	(-)	(Sax et al. 1999)
Left caudate	(+)	(Noga et al. 2001) (McIntosh et al. 2001)
	(-)	(Brambilla et al. 2001c) (Swayze et al. 1992)
Right caudate	(+)	(Noga et al. 2001) (McIntosh et al. 2001)
	(-)	(Brambilla et al. 2001c) (Swayze et al. 1992)
Putamen	(+)	(Getz et al. 2002) (Strakowski et al. 2002b) (Aylward et al. 1994)
Left putamen	(-)	(Brambilla et al. 2001c)
	(+)	(Swayze et al. 1992)
Right putamen	(-)	(Brambilla et al. 2001c)
	(+)	(Swayze et al. 1992)
Globus pallidus	(+)	(Getz et al. 2002) (Strakowski et al. 1999) (Aylward et al. 1994)
Left globus pallidus	(+)	(Strakowski et al. 1999)
	(NC)	(Brambilla et al. 2001c)
Right globus pallidus	(+)	(Strakowski et al. 1999)
	(-)	(Brambilla et al. 2001c)
Striatum	(+)	(Getz et al. 2002) (Strakowski et al. 1999)
Left striatum	(+)	(Strakowski et al. 1999)

Brain volume	**Studies**	
Right striatum	(+)	(Strakowski et al. 1999)
Lenticular nucleus (LN)	(+)	(Dupont et al. 1995)
Left LN	(-)	(Noga et al. 2001)
	(+)	(McIntosh et al. 2001)
Right LN	(-)	(Noga et al. 2001)
	(+)	(McIntosh et al. 2001)
Thalamus	(-)	(Sax et al. 1999) (Strakowski et al. 2002b) (Getz et al. 2002)
	(+)	(Strakowski et al. 1999) (Caetano et al. 2001)
Left thalamus	(+)	(Strakowski et al. 1999) (McIntosh et al. 2001) (Caetano et al. 2001)
Right thalamus	(-)	(Strakowski et al. 1999) (McIntosh et al. 2001) (Caetano et al. 2001)
Ventricles		
Left and right lateral ventricle	(+)	(Swayze et al. 1990a) (Roy et al. 1998) (Getz et al. 2002) (Lim et al. 1999)
Left lateral ventricle	(-)	(Brambilla et al. 2001b)
	(+)	(Harvey et al. 1994) (Swayze et al. 1990a) (Strakowski et al. 2002b) (Botteron et al. 1995) (Strakowski et al. 1999) (McIntosh et al. 2001) (Hauser et al. 2000)

Brain volume	Studies	
Right lateral ventricle	(-)	(Harvey et al. 1994) (Brambilla et al. 2001b) (Hauser et al. 2000)
	(+)	(Swayze et al. 1990a) (Strakowski et al. 2002b) (Botteron et al. 1995) (Strakowski et al. 1999) (McIntosh et al. 2001)
Third ventricle	(+)	(Roy et al. 1998) (Pearlson et al. 1997) (Botteron et al. 1995) (Strakowski et al. 1999) (Lim et al. 1999) (Strakowski et al. 2002b)
	(-)	(McIntosh et al. 2001) (Brambilla et al. 2001b)
Fourth ventricle	(-)	(McIntosh et al. 2001)

In total 11 studies, that met inclusion criteria, compared bipolar patients with patients with schizophrenia. The volumes of several brain regions were not measured in any of the identified studies (e.g. total prefrontal cortex, subgenual prefrontal cortex (SGPFC)). Most studies reporting left or right temporal lobe volumes found reductions in bipolar compared to schizophrenic patients. In terms of direction of overall effect, the results for other brain regions were more discordant.

Table 3.3.2.3: Volumes in bipolar disorder compared to patients with schizophrenia.

Studies showing larger volumes in bipolar patients are marked with a (+) sign, differences in the opposite direction are given a (-) sign and (NC) is used the direction of overall effect is unclear.

Brain volume	**Studies**	
Intracranial volume (ICV)	(-)	(Harvey et al. 1994)
	(+)	(Kasai et al. 2003c) (Lim et al. 1999)
Whole brain volume	(+)	(Harvey et al. 1994) (Roy et al. 1998) (Schlaepfer et al. 1994)
	(-)	(Dasari et al. 1999) (McIntosh et al. 2001)
Whole brain (grey matter only)	(+)	(Lim et al. 1999) (Schlaepfer et al. 1994) (Zipursky et al. 1997)
Whole brain (white matter only)	(-)	(Zipursky et al. 1997)
	(+)	(Pearlson et al. 1997) (Lim et al. 1999)
Total left cerebellum		No studies
Total right cerebellum		No studies
Cortical limbic structures		
Left hemisphere		No studies
Right hemisphere		No studies
Prefrontal cortex		No studies
Left prefrontal cortex	(-)	(McIntosh et al. 2001)
Right prefrontal cortex	(-)	(McIntosh et al. 2001)
Left Subgenual prefrontal cortex		No studies
Right Subgenual prefrontal cortex		No studies
Temporal lobes	(+)	(Altshuler et al. 2000)

Brain volume	Studies
Left temporal lobe	(+) (Harvey et al. 1994) (Rossi et al. 1991) (Swayze et al. 1992) (Pearlson et al. 1997) (Altshuler et al. 1998) (-) (McIntosh et al. 2001)
Right temporal lobe	(+) (Harvey et al. 1994) (Rossi et al. 1991) (Swayze et al. 1992) (Pearlson et al. 1997) (Altshuler et al. 1998) (-) (McIntosh et al. 2001)
Amygdala	(+) (Altshuler et al. 2000)
Left amygdala	(+) (Altshuler et al. 1998) (-) (Pearlson et al. 1997)
Right amygdala	(+) (Altshuler et al. 1998) (Pearlson et al. 1997)
Hippocampal-amygdala complex (AHC)	No studies identified
Left AHC	(-) (McIntosh et al. 2001) (Kasai et al. 2003a) (+) (Swayze et al. 1992)
Right AHC	(-) (McIntosh et al. 2001) (Kasai et al. 2003a) (Swayze et al. 1992)
Hippocampus	(+) (Altshuler et al. 2000)
Left hippocampus	(+) (Pearlson et al. 1997) (Altshuler et al. 1998) (-) (Swayze et al. 1992)
Right hippocampus	(+) (Pearlson et al. 1997) (Altshuler et al. 1998) (-) (Swayze et al. 1992)
Parahippocampus	(+) (Altshuler et al. 2000)
Left parahippocampus	(+) (Pearlson et al. 1997)
Right parahippocampus	(+) (Pearlson et al. 1997)
Left entorhinal cortex	(+) (Pearlson et al. 1997)

Brain volume	**Studies**
Right entorhinal cortex	(+) (Pearlson et al. 1997)
Left STG	(+) (Kasai et al. 2003a)
Right STG	(-) (Kasai et al. 2003a)
Left anterior STG	(+) (Pearlson et al. 1997) (Hirayasu et al. 1998)
Right anterior STG	(+) (Pearlson et al. 1997) (Hirayasu et al. 1998)
Left posterior STG	(+) (Pearlson et al. 1997) (Hirayasu et al. 1998)
Right posterior STG	(-) (Pearlson et al. 1997) (+) (Hirayasu et al. 1998)
Subcortical structures	
Caudate	No studies
Left caudate	(+) (McIntosh et al. 2001) (-) (Swayze et al. 1992)
Right caudate	(+) (McIntosh et al. 2001) (-) (Swayze et al. 1992)
Putamen	No studies
Left putamen	(-) (Swayze et al. 1992)
Right putamen	(-) (Swayze et al. 1992)
Globus pallidus	No studies
Left globus pallidus	No studies
Right globus pallidus	No studies
Striatum	No studies
Left striatum	No studies
Right striatum	No studies
Lenticular nucleus (LN)	No studies
Left LN	(-) (McIntosh et al. 2001)
Right LN	(-) (McIntosh et al. 2001)
Thalamus	No studies
Left thalamus	(+) (McIntosh et al. 2001)
Right thalamus	(+) (McIntosh et al. 2001)
Ventricles	
Left and right lateral ventricle	(+) (Roy et al. 1998) (-) (Lim et al. 1999)

Brain volume	Studies	
Left lateral ventricle	(-)	(Harvey et al. 1994) (Swayze et al. 1990a)
	(+)	(McIntosh et al. 2001)
Right lateral ventricle	(-)	(Harvey et al. 1994) (Swayze et al. 1990a)
	(+)	(McIntosh et al. 2001)
Third ventricle	(-)	(Roy et al. 1998) (Lim et al. 1999) (McIntosh et al. 2001)
	(+)	(Pearlson et al. 1997)
Fourth ventricle	(-)	(McIntosh et al. 2001)

3.3.2 Excluded Studies

Thirty articles were retrieved which compared patients with bipolar affective disorder with either controls or patients with schizophrenia, but which either a) failed to present mean volumes for each group separately, b) expressed volumes as a proportion of whole brain only, or c) reported a summary measure conflating two volumes (e.g. ventricle to brain ratio, VBR). Seven studies provided useable data for patients with affective disorder compared to either controls or patients wit schizophrenia. However, these studies could not be included because patients with bipolar disorder comprised less than 80% of the affective disordered sample. The studies excluded are listed in table 3.3.2.1.

Table 3.3.2.1: Studies excluded from the review

Study	Reason for exclusion
Besson (1987), Hauser (1989b), Johnstone (1989), Swayze (1990b), Olson (1990), Altshuler (1991), Risch (1992), Jurjus (1993a;1993b), Strakowski (1993b), Bullmore (1994), Kato (1994), Altshuler (1995), Lewine (1995), Shiori (1996), Hirayasu (1998), Loeber (1999), Friedman (1999), Bilder (1999), McDonald (1999), Krabbendam (2000), Deicken (2001), Moore (2001a), Moore (2001b), Pillai (2002), Cecil (2002), Loeber (2002), McCarley (2002), Kieseppa (2003), Sassi (2003)	No useable data reported. Variety of reasons (no volumes, VBR only, volumes expressed as proportion of whole brain volume)
O'Brien (1996a), O'Brien (1996b), O'Brien (1997), Velakoulis (1999), Wood (2001), Kegeles (2003), Keshevan (2003)	Affective disordered group contained <80% bipolar patients

3.3.3 Meta-analysis of region of interest studies

Random effects analyses were conducted for 60 separate regions of interest for the bipolar versus control comparison. However, many of these regions have not been compared between patients with bipolar disorder and schizophrenia, which limited the number of analyses that could be performed.

Statistically significant evidence of an increase in volume in bipolar compared to controls was found for the following structures: right amygdala (5 studies, 318 subjects), total globus pallidus (3 studies, 130 subjects), left (1 study, 44 subjects), right (1 study, 44 subjects) and total striatum (2 studies, 70 subjects), left thalamus (3 studies, 153 subjects), left (8 studies, 434 subjects) and total lateral ventricles (3 studies, 78 subjects). Left anterior STG (2 studies, 121 subjects) volume was reduced in bipolar patients compared to controls. Evidence was also found for larger total temporal lobe (1 study,

44 subjects), total hippocampus (1 study, 44 subjects), left (1 study, 73 subjects) and right (1 study, 73 subjects) entorhinal cortex, total (1 study, 34 subjects) and right (2 studies, 99 subjects) amygdala, left total STG (1 study, 28 subjects), and left posterior STG (2 studies, 106 subjects) in bipolar disordered patients compared to those with schizophrenia. Bipolar patients showed significant reductions in right prefrontal cortex (1 study, 30 subjects) compared to patients with schizophrenia, and left lateral ventricle volume showed a non-significant trend in this direction.

There was evidence of considerable heterogeneity, both in terms of magnitude and statistical significance. The variation in effect size due to statistical heterogeneity was in most cases greater than 40%, and in some cases (e.g. total and left amygdala volume for bipolar-control, and left and right hippocampus for bipolar-schizophrenia) greater than 80%. However, in comparisons using fewer than 3 studies, the magnitude of heterogeneity could not be quantified using I^2 although statistical significance can be calculated with a few as two studies. Statistical heterogeneity was present in all cases where I^2 was greater than 70% and also in some comparisons where there were only two studies (e.g. right globus pallidus for bipolar-control comparison). The results of the meta-analysis are shown in the following 2 tables.

Table 3.3.3.1: Bipolar disorder versus controls

Brain region	N_s	Bipolar	Control	Estimate	95%CI	I^2 (%)	Egger (p)
Intracranial volume	5	102	137	0.11	-0.20, 0.41	24.1	0.84
Whole brain	16	367	405	-0.13	-0.31, 0.04	24.9	0.95
Whole brain (grey)	7	125	175	-0.18	-0.61, 0.26	66.9*	0.61
Whole brain (white)	7	125	175	-0.04	-0.32, 0.24	22.0	0.89
Left cerebellum	2	52	37	0.023	-0.41, 0.45	IC	IC
Right cerebellum	2	52	37	-0.09	-0.51, 0.34	IC	IC
Left hemisphere	2	14	27	-0.49	-1.2, 0.22	IC	IC
Right hemisphere	2	14	27	-0.50	-1.21, 0.22	IC	IC
Prefrontal cortex	4	70	62	-0.37	-0.72, -0.02	0.0	0.19
Left prefrontal cortex	2	38	51	-0.30	-0.73, 0.13	IC	IC
Right prefrontal cortex	2	38	51	-0.30	-0.79, 0.19	IC	IC
Left SGPRC	3	63	66	-0.17	-0.70, 0.36	50.2	0.40
Right SGPFC	3	63	66	-0.33	-0.9, 0.25	56.6	0.19
Temporal lobes	2	38	33	0.15	-0.49, 0.17	IC	IC
Left temporal lobe	7	198	243	0.05	-0.21, 0.31	41.3	0.22
Right temporal lobe	7	198	243	-0.07	-0.30, 0.16	25.1	0.29
Amygdale	4	96	108	-0.12	-1.19, 0.95	91.8**	0.61
Left amygdala	5	135	183	0.33	-0.35, 1.02	87.7**	0.28
Right amygdala	5	135	183	0.32	0.02, 0.62	39.5	0.38
Left AHC	4	83	102	-0.21	-0.53, 0.10	7.0	0.25
Right AHC	4	83	102	-0.19	-0.50, 0.13	6.7	0.06
Hippocampus	6	148	152	-0.18	-0.51, 0.14	44.8	0.63
Left hippocampus	7	166	214	0.05	-0.16, 0.26	0.0	0.12
Right hippocampus	7	166	214	-0.05	-0.28, 0.18	20.1	0.14
Parahippocampus	1	24	18	-0.09	-0.70, 0.52	IC	IC
Left parahippocampus	1	27	60	0.03	-0.42, 0.48	IC	IC
Right parahippocampus	1	27	60	-0.23	-0.69, 0.23	IC	IC
Left entorhinal cortex	1	27	60	0.30	-0.15, 0.76	IC	IC
Right entorhinal cortex	1	27	60	0.23	-0.23, 0.69	IC	IC
Superior temporal gyri (STG)	1	14	15	-0.22	-0.95, 0.51	IC	IC
Left STG	2	39	50	0.14	-0.28, 0.57	IC	IC
Right STG	2	39	50	-0.20	-0.62, 0.22	IC	IC
Left anterior STG	2	43	78	-0.49	-0.87, -0.10	IC	IC
Right anterior STG	2	43	78	-0.13	-1.15, 0.90	IC*	IC

Brain region	N_s	Bipolar	Control	Estimate	95%CI	I^2 (%)	Egger (p)
Left posterior STG	2	43	78	-0.17	-0.55, 0.21	IC	IC
Right posterior STG	2	43	78	0.12	-0.26, 0.50	IC	IC
Subcortical structures							
Caudate	5	130	112	0.19	-0.17, 0.55	46.0	0.50
Left caudate	4	90	110	0.02	-0.33, 0.37	26.6	0.15
Right caudate	4	90	110	0.05	-0.37, 0.48	47.4	0.15
Putamen	3	77	74	0.38	-0.10, 0.87	50.5	0.35
Left putamen	2	70	69	0.09	-0.25, 0.42	IC	IC
Right putamen	2	70	69	0.08	-0.25, 0.41	IC	IC
Globus pallidus	3	66	64	0.89	0.05, 1.74	79**	0.08
Left globus pallidus	2	46	44	0.39	-0.38, 1.17	IC	IC
Right globus pallidus	2	46	44	0.11	-0.97, 1.20	IC**	IC
Striatum	2	36	34	0.84	0.35, 1.33	IC	IC
Left striatum	1	24	22	0.64	0.05, 1.23	IC	IC
Right striatum	1	24	22	2.29	1.54, 3.04	IC	IC
Lenticular nucleus (LN)	1	36	26	0.32	-0.19, 0.82	IC	IC
Left LN	2	20	41	0.25	-0.29, 0.79	IC	IC
Right LN	2	20	41	0.13	-0.41, 0.67	IC	IC
Thalamus	5	113	117	0.05	-0.37, 0.46	57	0.99
Left thalamus	3	63	90	0.41	0.06, 0.77	13.1	0.57
Right thalamus	3	63	90	0.46	-0.06, 0.98	57.8	0.37
Ventricles							
Left and right lateral ventricle	4	83	90	0.36	0.06, 0.66	0.0	0.30
Left lateral ventricle	8	224	210	0.19	0.00, 0.37	0.0	0.69
Right lateral ventricle	8	224	210	0.12	-0.07, 0.32	0.0	0.45
Third ventricle	6	94	147	0.13	-0.26, 0.52	48.2	0.83

*p<0.05, **p<0.01

Table 3.3.3.1: Bipolar disorder versus schizophrenia

Brain region	N_s	Bipolar	Schizophrenia	Estimate	95%CI	I^2 (%)	Egger (p)
Intracranial volume	3	61	84	0.49	-0.39, 1.36	81.4**	0.05
Whole brain	5	96	152	-0.02	-0.28, 0.24	0.0	0.12
Whole brain (grey)	3	50	78	0.41	-0.15, 0.96	49.7	0.24
Whole brain (white)	3	50	78	0.38	-0.27, 1.13	71.1*	0.63
Left cerebellum	No studies						
Right cerebellum	No studies						
Left hemisphere	No studies						
Right hemisphere	No studies						
Prefrontal cortex (PFC)	No studies						
Left prefrontal cortex	1	14	16	-0.48	-1.21, 0.35	IC	IC
Right prefrontal cortex	1	14	16	-0.76	-1.50, -0.01	IC	IC
Left Subgenual PFC	No studies						
Right Subgenual PFC	No studies						
Temporal lobes	1	24	20	0.86	0.24, 1.48	IC	IC
Left temporal lobe	6	143	187	0.18	-0.05, 0.40	0.0	0.48
Right temporal lobe	6	143	187	0.19	-0.04, 0.41	0.0	0.87
Amygdale	1	14	20	0.93	0.30, 1.55	IC	IC
Left amygdala	2	39	60	0.30	-1.44, 2.04	IC**	IC
Right amygdala	2	39	60	0.59	0.17, 1.00	IC	IC
Left AHC	3	77	82	-0.01	-0.33, 0.30	0.0	0.05
Right AHC	3	77	82	-0.13	-0.44, 0.19	0.0	0.10
Hippocampus	1	24	20	1.08	0.44, 1.72	IC	IC
Left hippocampus	3	87	113	0.35	-0.37, 1.06	81.1**	0.29
Right hippocampus	3	87	113	0.36	-0.37, 1.09	81.7**	0.14
Parahippocampus	1	24	20	0.57	-0.04, 1.17	IC	IC
Left parahippocampus	1	27	46	0.18	-0.28, 0.63	IC	IC
Right parahippocampus	1	27	46	0.17	-0.28, 0.63	IC	IC
Left entorhinal cortex	1	27	46	0.82	0.33, 1.32	IC	IC
Right entorhinal cortex	1	27	46	0.74	0.25, 1.24	IC	IC
Superior temporal gyri (STG)	1	14	22	-0.56	-1.24, 0.13	IC	IC
Left STG	1	15	13	1.36	0.52, 2.19	IC	IC
Right STG	1	15	13	0.20	-0.55, 0.94	IC	IC
Left anterior STG	2	43	63	0.03	-0.36, 0.42	IC	IC

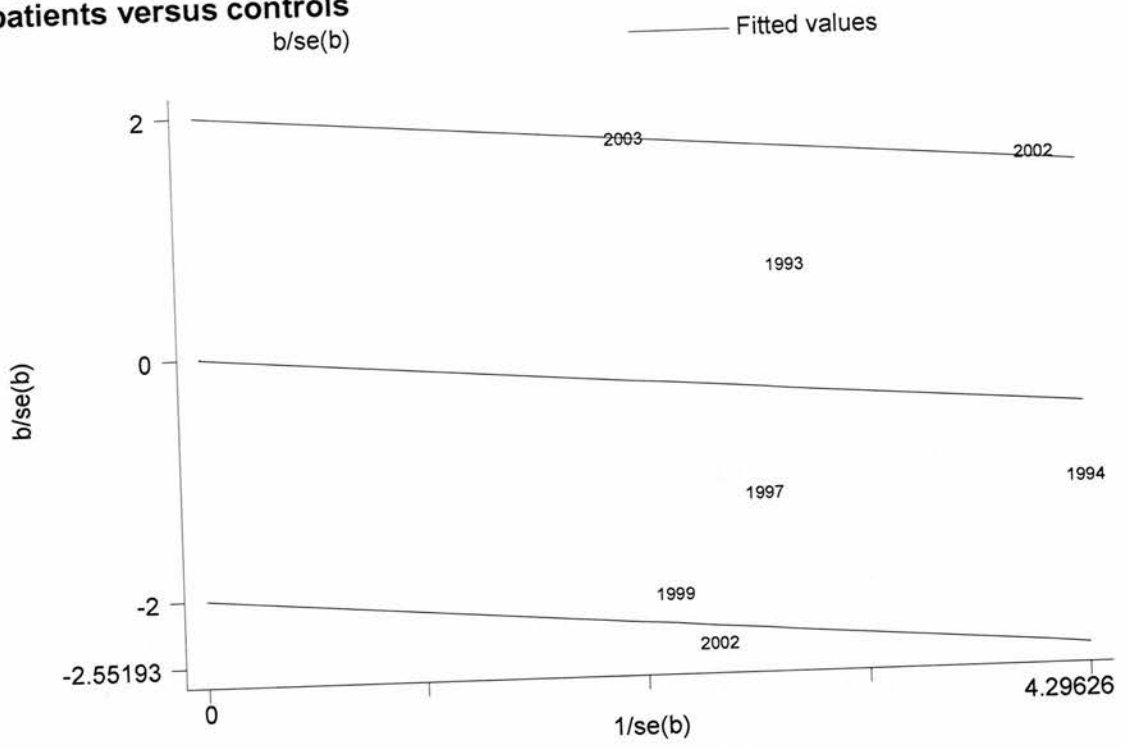
Brain region	N_s	Bipolar	Schizophrenia	Estimate	95%CI	I^2 (%)	Egger (p)
Right anterior STG	2	43	63	0.50	-0.09, 1.08	IC	IC
Left posterior STG	2	43	63	0.53	0.14, 0.93	IC	IC
Right posterior STG	2	43	63	0.02	-0.37, 0.41	IC	IC
Pituitary volume	No studies						
Subcortical structures							
Caudate	No studies						
Left caudate	2	62	69	-0.30	-0.77, 0.18	IC	IC
Right caudate	2	62	69	-0.30	-0.72, 0.11	IC	IC
Putamen	No studies						
Left putamen	1	48	53	-0.25	-0.64, 0.14	IC	IC
Right putamen	1	48	53	-0.31	-0.71, 0.08	IC	IC
Globus pallidus	No studies						
Left globus pallidus	No studies						
Right globus pallidus	No studies						
Striatum	No studies						
Left striatum	No studies						
Right striatum	No studies						
Lenticular nucleus (LN)	No studies						
Left LN	1	14	16	-0.60	-1.33, 0.14	IC	IC
Right LN	1	14	16	-0.57	-1.30, 0.16	IC	IC
Thalamus	No studies						
Left thalamus	1	14	16	0.22	-0.50, 0.94	IC	IC
Right thalamus	1	14	16	-0.36	-0.36, 1.09	IC	IC
Ventricles							
Left and right lateral ventricle	2	23	31	0.07	-0.47, 0.61	IC	IC
Left lateral ventricle	3	88	116	-0.27	-0.56, 0.02	2.3	0.06
Right lateral ventricle	3	88	116	-0.16	-0.44, 0.12	0.0	0.06
Third ventricle	4	64	93	-0.05	-0.52, 0.43	48.6	0.14

3.3.4 Sensitivity analyses

Sensitivity analyses were conducted for those brain regions where the proportion of variation in effect size attributable to heterogeneity (I^2) exceeded 50% and the number of included studies for that region was greater or equal to 3. Standardised effect size was plotted against study precision in order to identify those studies contributing most to heterogeneity. The summary effect size was then re-calculated excluding those studies whose contribution to overall heterogeneity was the greatest. Possible methodological reasons for the observed heterogeneity were identified by inspecting the methods sections of the excluded articles.

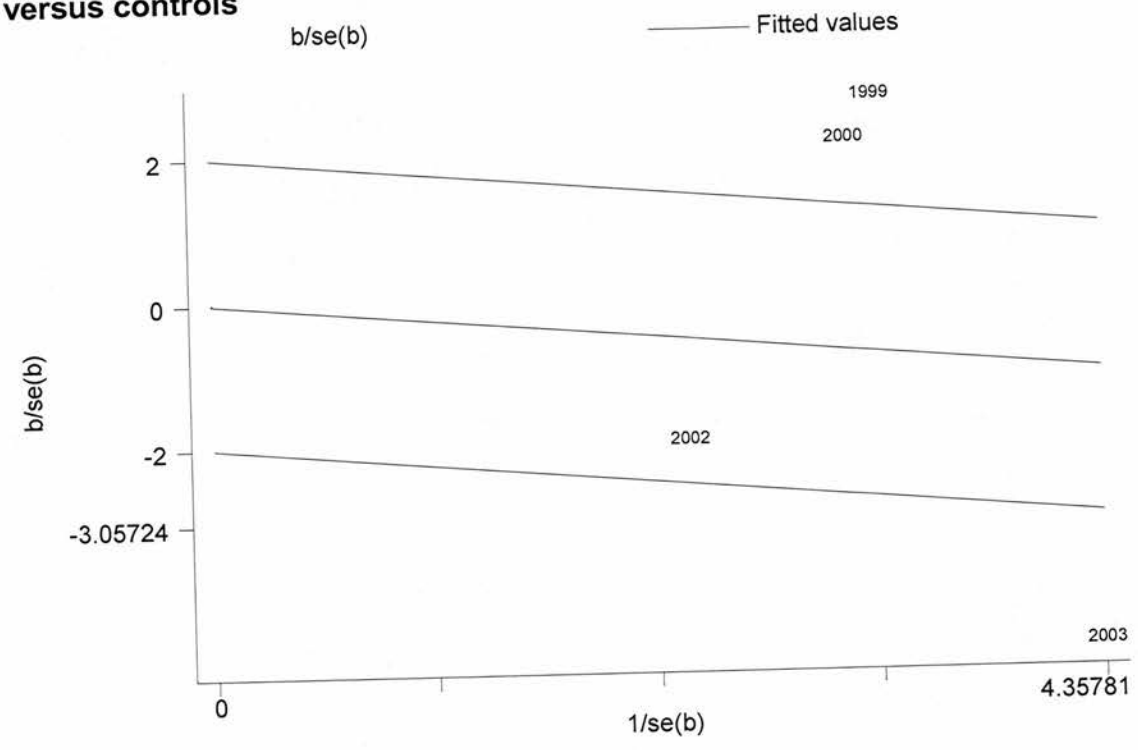
For the bipolar versus control comparison, four brain regions merited further consideration using the planned sensitivity analysis described above (whole brain grey matter, total amygdala, left amygdala and total globus pallidus). Similarly, in bipolar patients compared to patients with schizophrenia, four regions merited further consideration using sensitivity analysis (intracranial volume, whole brain white matter, left hippocampus and right hippocampus). The results of the sensitivity analyses are given in the following Galbraith plots along with explanatory text.

Figure 3.3.4.1: Galbraith Plot for Whole Brain Grey matter in bipolar patients versus controls



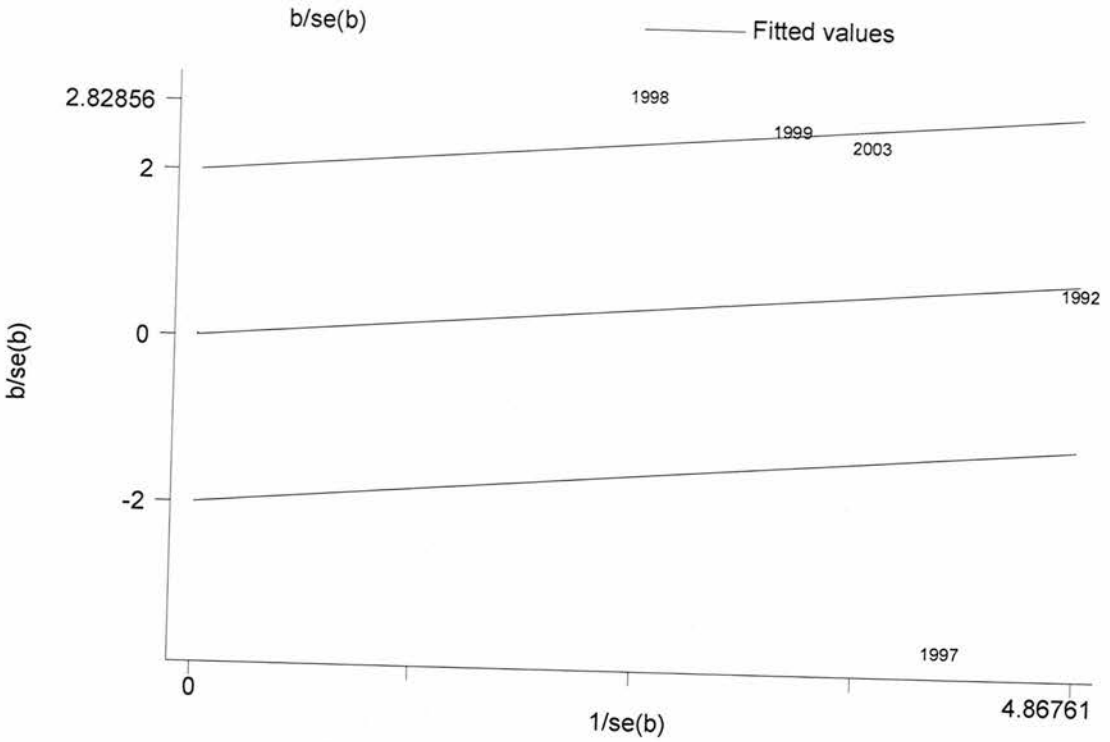
The only study to lie outside the 95% confidence intervals was the study by Lopez-Larson et al (2002). However, the exclusion of this study made little difference to the effect size (-0.05, 95%CI -0.48 to 0.37) or heterogeneity which remained high and statistically significant (I^2=0.61, p=0.03). Since there seemed to be no obvious methodological reason to exclude this study in the final analysis, it was retained for the next stage of meta-regression.

Figure 3.3.4.2: Galbraith plot of total amygdala volume in bipolar patients versus controls



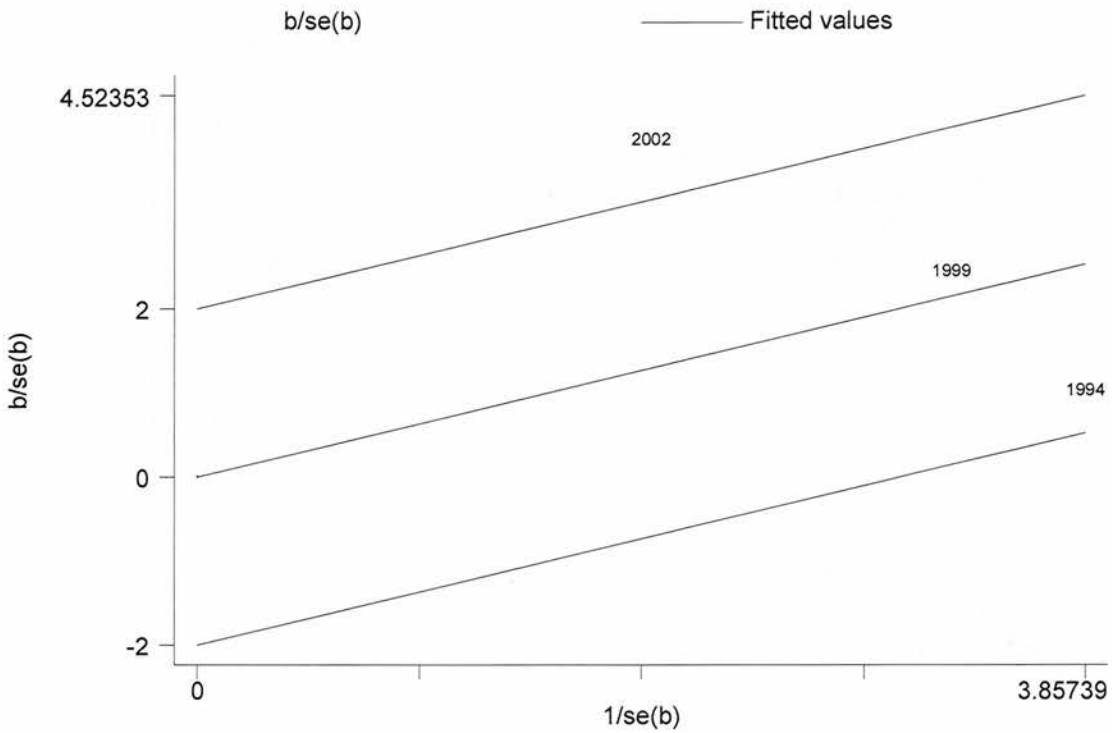
Three studies lay outside the 95% confidence intervals (Strakowski et al. 1999;Altshuler et al. 2000;Blumberg et al. 2003). Exclusion of these studies left a single study (Getz et al. 2002) from which heterogeneity could not be calculated. There seemed to be no methodological reason to exclude the three studies contributing most to overall heterogeneity. However, a visual inspection of the Galbraith Plot revealed a possible relationship between year of publication and effect size, with more recent studies tending to find reductions in bipolar subjects compared to controls. All studies were therefore retained for meta-regression analysis.

Figure 3.3.4.3: Galbraith plot of standardised effect size for left amygdala in bipolar patients versus controls



Two studies lay clearly outside the 95% confidence intervals (Pearlson et al 1997; Altshuler 1998) but in opposite directions. Exclusion of these studies changed the results such that there was an effect size of 0.47 (95%CI 0.06 to 0.88) and no statistically significant heterogeneity (I^2=0.50, p=0.14). This result excluding these two studies suggests that left amygdala volumes are increased in bipolar patients compared to controls. However, since there appeared to be no sound methodological basis on which to exclude these studies, they were retained and analysed further by meta-regression.

Figure 3.3.4.4: Galbraith plot for total globus pallidus volume in bipolar subjects versus controls

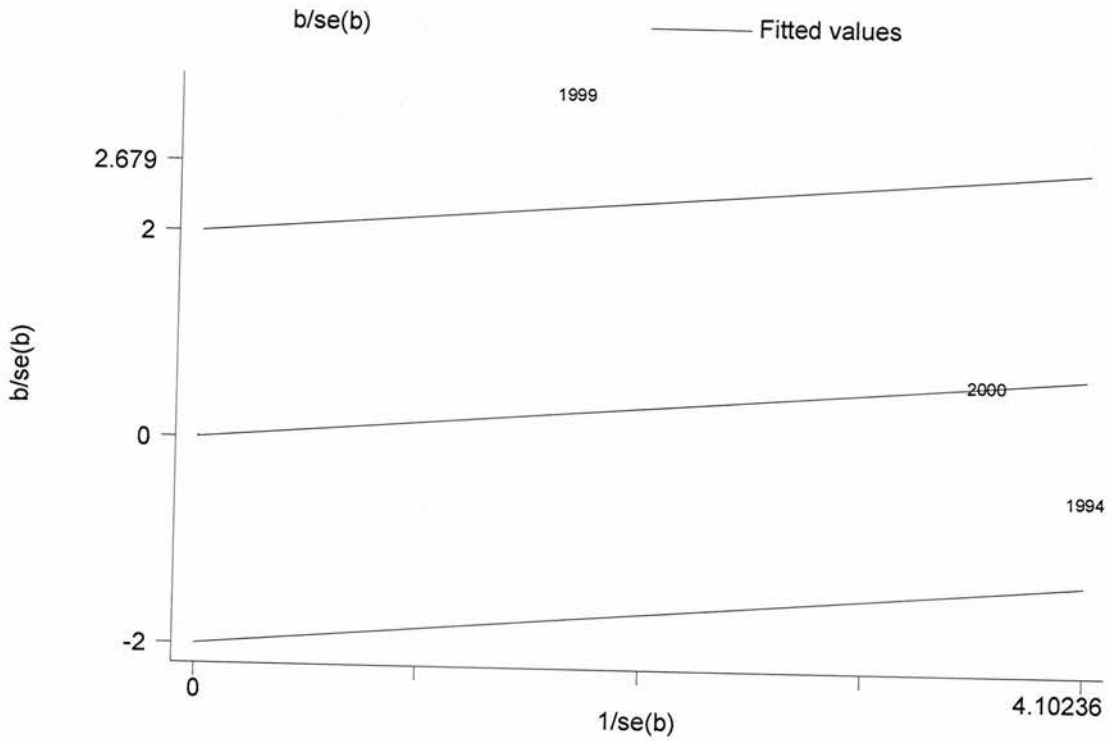


One study lay outside the 95% confidence intervals for standardised effect size (Getz et al., 2002). After removal of this study, the effect size became marginally non-significant (test for overall effect z=1.95, p=0.051) showing a trend to larger total globus pallidus volumes in bipolar patients compared to healthy controls (effect size=0.46, 95%CI 0.00 to 0.93) with no statistically significant heterogeneity (χ^2=1.42, p=0.23). Unfortunately, since only two studies were then included in this compassion, the magnitude of any associated heterogeneity could not be quantified. Methodological differences between two of the studies were slight (Strakowski et al 199;Getz et al 2002) although the third study used interleaved rather than contiguous slicing to image the

whole brain (Aylward et al, 1994). Consequently, a obvious cause for the relatively extreme effect size found in Getz et al (2002) could not be identified.

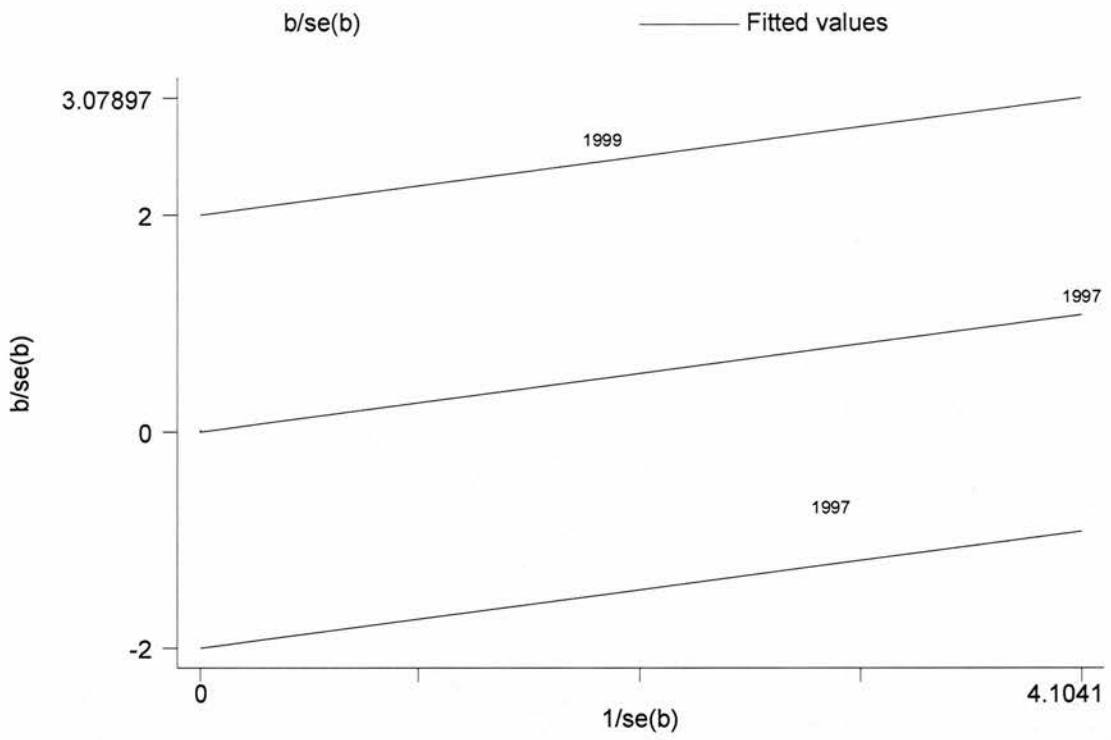
The Galbraith plots presented in the following pages concern bipolar disorder versus schizophrenia comparisons.

Figure 3.3.4.4: Galbraith Plot of intracranial volume in bipolar patients versus patients with schizophrenia



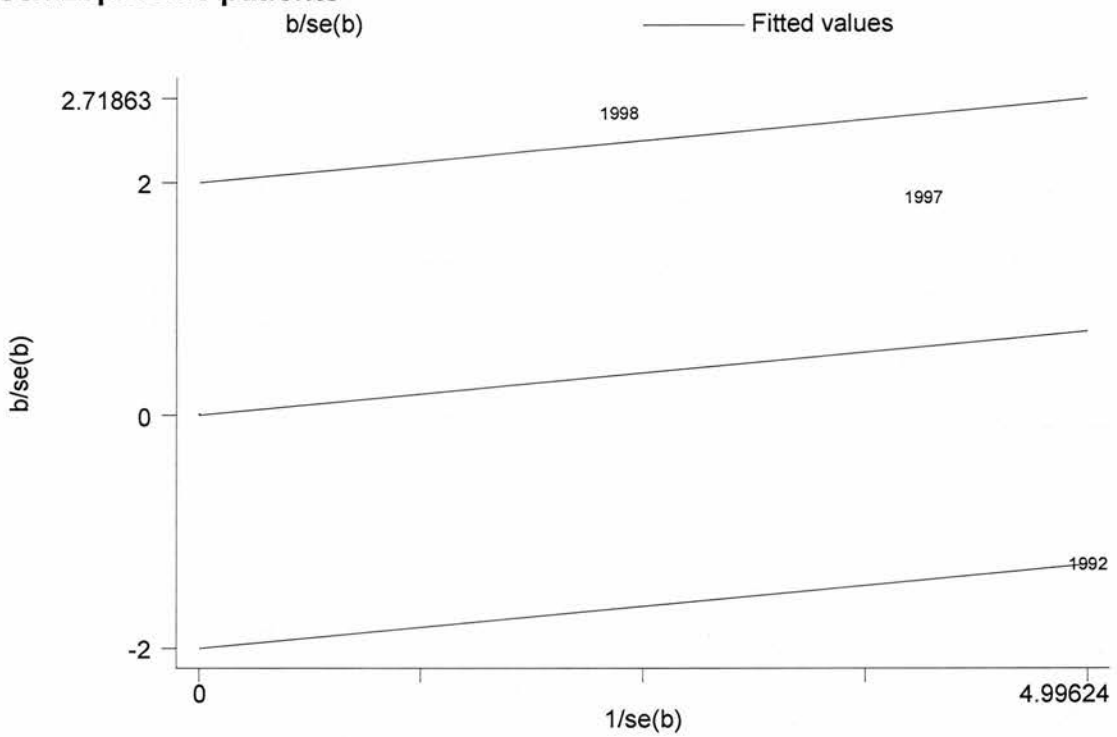
The study by Lim et al (1999) lay clearly outside the 95% confidence intervals. Because this study used an automated instead of conventional region of interest analysis (ROI), we decided to remove it from the analysis. Once removed, the effect size was estimated as -0.13 (95%CI -0.46 to 0.20) with no statistically significant heterogeneity (I^2=0.12, p=0.32). This result suggests that, after excluding the study using automated instead of ROI, no statistically significant differences between bipolar and schizophrenic patients were found.

Figure 3.3.4.5: Galbraith plot of whole brain white matter in bipolar versus schizophrenic patients



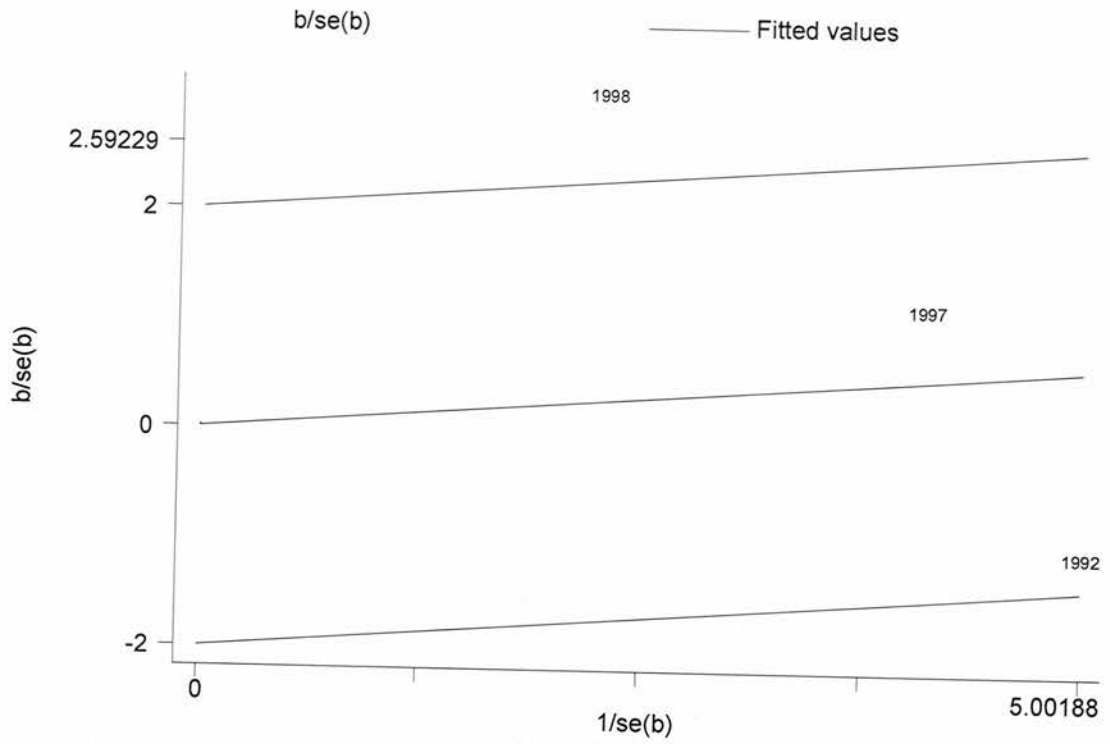
The study using an automated rather than a conventional ROI approach was the only study to lie clearly outside the 95% confidence limits. Removing this single study lead to an observed effect size of 0.07 (95%CI -0.46 to 0.60) with no statistically significant heterogeneity (p=0.19). However, since the exclusion of Lim et al (1999) left only two remaining studies, I^2 could not be quantified.

Figure 3.3.4.6: Galbraith plot of left hippocampal volume in bipolar versus schizophrenic patients



The plot shows that the study by Altshuler et al (1998) is the only one to lie outside the 95% confidence limits. Exclusion of this single study resulted in an effect size of 0.08 (95%CI -0.63 to 0.78). However, heterogeneity remained statistically significant (p=0.02), although I^2 could not be calculated with only 2 remaining studies. However, since there was no obvious methodological reason to exclude this study, it was retained for further analysis.

Figure 3.3.4.7: Galbraith plot of standardised effect size for right hippocampus in bipolar patients versus schizophrenics



The Galbraith Plot shown above demonstrates that Altshuler (1998) is an extreme observation and lies outside the 95%CI for standardised effect size. Excluding this study results in a standardised effect size of -0.003 (95%CI -0.49 to 0.48) with no statistically significant heterogeneity (p=0.12). However, since only two studies were included, I^2 could not be calculated and since there appeared to be no strong methodological reason to exclude this study, it was retained for further analysis.

3.3.5 Meta-regression

Since some of the heterogeneity was reduced and explained by the inclusion of a study using automated rather that semi-automatic analysis, meta-regression was used

only for the comparisons where this methodological difference between studies did not apply, and where there were three or more studies. Therefore, meta-regression analyses were performed for intracranial, total grey matter, left and right amygdala and total globus pallidus volumes for the bipolar-control comparison, and also for left and right hippocampal volumes for the bipolar-schizophrenia comparison.

Figure 3.3.5.1: Meta-regression analyses

	Age		Patient proportion of male sex		Year of article publication	
Region	**Beta (95%CI)**	**P-value**	**Beta (95%CI)**	**p-value**	**Beta (95%CI)**	**P-value**
BPD vs. CTRL						
WB (Grey)	-0.01 (-0.2, 0.09)	0.78	-1.06 (3.25, 1.14)	0.35	0.02 (-0.12, 0.15)	0.81
Total amygdala	0.04 (-0.09, 0.16)	0.55	0.02 (-0.01, 0.05)	0.26	-0.53 (-0.70, -0.35)	**<0.001**
Left amygdala	0.03 (-0.07, 0.13)	0.54	10.4 (-3.7, 24.47)	0.15	0.07 (-0.14, 0.28)	0.51
Total GP	-0.08 (-0.28, 0.23)	0.46	0.02 (0.00, 0.04)	**0.013**	0.18 (0.02, 0.35)	**0.03**
BPD vs. SCZ						
Left hippocampus	0.06 (-0.02, 0.15)	0.14	IC	IC	0.17 (0.06, 0.28)	**0.002**
Right hippocampus	0.08 (0.02, 0.15)	**0.012**	IC	IC	0.19 (-0.05, 0.42)	0.12

*Proportion of bipolar group who are male, GP: Globus Pallidus, IC: Incalculable because proportion of male subjects not reported in >2 studies

Meta-regression analyses found that higher proportions of male patients tended to find larger effect sizes for total globus pallidus volume compared to controls, suggesting that the enlargement found in bipolar patients may be greater in males than in females.

Larger right hippocampi in bipolar subjects compared to schizophrenic subjects were also positively associated with advancing years compared to schizophrenic patients.

Year of study publication was associated with smaller amygdala sizes in bipolar subjects compared to controls, larger globus pallidus volumes in bipolars compared to controls and larger hippocampi in bipolars compared to patients with schizophrenia.

3.4 Discussion

3.4.1 Main Findings

This review found that compared to controls there is good evidence that patients with bipolar disorder have a smaller total frontal lobe volume (4 studies) and left anterior superior temporal gyrus (2 studies). Bipolar subjects also appear to have a larger right amygdala (5 studies), left thalamus (5 studies), total globus pallidus (3 studies), total striatum (2 studies) and total lateral ventricles (3 studies).

Limited evidence was also found for a larger right thalamus and larger left and right lateral ventricles, although these findings were not statistically significant at a p-value of less than 0.05. Large standardised effect sizes ($d > 0.6$) were found for total striatum and for left and right ventricle combined, without significant heterogenity. This meta-analysis did not find a decrease in subgenual prefrontal cortex volume based on three studies of 129 subjects. This direction of effect size suggests a possible reduction but there are insufficient studies to investigate potential sources of heterogeneity or publication bias.

The number of studies comparing bipolar and schizophrenic patients was much less. Right amygdala volume was increased in bipolar subjects with a greater effect size than that seen for the bipolar-control comparison. This suggests that amygdala volumes are decreased in schizophrenia but increased in bipolar disorder. This finding has further support from a systematic review and meta-analysis of schizophrenic subjects which showed reductions in patients compared to controls (Wright et al. 2000). Left posterior STG was also significantly larger in bipolar subjects compared to those with schizophrenia. Limited evidence was found for larger temporal lobe and left lateral ventricle volumes in bipolar subjects, although these findings did not reach statistical significance. The largest effect size was for right amygdala enlargement in bipolar disorder, although this was based on only two studies with a total of 99 subjects and although there was no statistical significant heterogeneity, the number of studies was inadequate to investigate this rigorously.

Heterogeneity was found for many bipolar-control and bipolar-schizophrenia comparisons. Some of this heterogeneity was explained by the presence of a single study which used an apparently automated technique (Lee et al, 2002) which appeared to find a systematically different result from the other studies. This does not necessary imply that the remaining studies provide a more accurate or true estimate; it is possible that the reverse is the case. However, the fact that the heterogeneity was largely accounted for by this methodological difference justified the re-calculation of summary effect size with it excluded from the analysis.

Heterogeneity was also partially explained by age, proportion of male subjects or year of publication. The greater volume of the right hippocampus found in bipolar

subjects compared to schizophrenic patients appears to increase in magnitude with increasing age. This may be due to a tendency for the hippocampus to diminish in size in schizophrenia as successive years of illness pass by in affected patients (Jacobsen et al. 1998). The proportion of male subjects in each study was also associated with larger total globus pallidus volume in patients compared to controls. This finding suggests that males have a greater degree of striatal enlargement than females and this may be associated with antipsychotic medication exposure. It is unfortunate that this could not be investigated directly in this study, although it may provide a basis for future analyses. Finally, the degree to which amygdala, globus pallidus and whole brain volumes differed between controls and schizophrenic patients differed according to the year of publication. We suggest that these differences may be due to advances in image acquisition and analysis that have occurred over time, but may also reflect a tendency for studies to vary in their inclusion and exclusion criteria over time.

The relationship of brain structure to the development of bipolar disorder has been hampered by the lack of appropriately designed and sufficiently powered studies. The case-control studies identified by this review are generally small and are unable to address whether brain differences arose prior to illness or are as a consequence of the disease process or its treatment. The added difficulty of multiple publication from one centre (particularly Kasai, Hirayasu, Lee and others) is likely to afford that study more weight in the literature than if it had been published only once.

There is however, some evidence from this review that bipolars may differ from controls in terms of prefrontal cortex, amygdala, anterior STG, striatum and thalamus. There is also some (lesser) evidence that bipolars differ from schizophrenic patients in

prefrontal cortex, amygdala, temporal lobe, entorhinal cortex and left STG. Many of the regions implicated in this review have been associated with abnormalities in emotional processing (Phillips et al. 2003). In depressed and manic states, abnormal activity in the dorsal prefrontal cortex has been found in several studies (O'Connell et al. 1995;Ketter et al. 2001), although the direction of difference compared to controls is not always the same. Amygdala and thalamic perfusion may increase in depressed bipolar patients compared to controls during the performance of executive tasks (Ketter et al. 2001) although the results for manic patients are more conflicting (O'Connell et al. 1995;Gyulai et al. 1997) but also suggest a possible decrease in striatal activity during these tasks (Blumberg et al. 2000). The findings in euthymic patients have not been investigated to the same degree but generally suggest an lower degree of abnormality compared to depressed or manic subjects (Phillips et al. 2003). However, a study examining cerebral perfusion during facial expressions of fear found reduced prefrontal and increased amygdala perfusion in bipolar subjects (Yurgelun-Todd et al. 2000).

It is not easy to suggest a single common mechanism for the structural and functional imaging findings found in bipolar disorder. There is no doubt that connections exist between temporal lobe, prefrontal cortex and amygdala, that many of these connections involve the thalamus (Nolte 1988) and that researchers have proposed several sub-cortical loops each sub-serving a specific function (Papez 1937;Alexander et al. 1990). Dysfunction in any one of these structures *might* give rise to problems in emotional sensitivity or regulation in itself. Since abnormalities are found in several of these structures in bipolar patients, it is possible that these circuits may require several 'hits' before symptoms of bipolar disorder emerge.

3.4.2 Strengths and Limitations

3.4.2.1 Publication bias

Statistically significant evidence of publication bias was evident for two structures. Total amygdala volume in bipolar subjects compared to controls, and left amygdala-hippocampal complex for the bipolar-schizophrenia comparison (see following funnel plots). Total amygdala volume in bipolar disorder shows a significant tendency for smaller studies to find a larger volume in healthy controls. This may have been because a finding in this direction was initially viewed as more plausible and small studies finding a similar effect, but in the opposite direction, have been difficult to publish. Studies measuring amygdala-hippocampal complex volumes in bipolar disorder show a tendency for smaller studies to find greater reductions in schizophrenic subjects. The largest study finds no significant difference between bipolar and schizophrenic subjects in either direction. This finding may reflect a perception amongst researchers that amygdala-hippocampal volumes were specific to schizophrenia and a tendency for small studies finding no difference to be less interesting and therefore less likely to be published.

The explanation of publication bias using the funnel plot is however somewhat speculative. Funnel plot asymmetry may reflect a bias in the location, identification as well as the publication of articles. Therefore the observed funnel plot asymmetry may reflect the fact that other evidence is available in non-indexed journals, foreign languages, and conference proceedings. Alternatively, small studies showing results in the opposite direction may not have been identified by the search strategy.

Figure 3.4.2.1: Funnel plot of standardised mean difference against standard error for total amygdala volume in bipolar subjects versus controls.

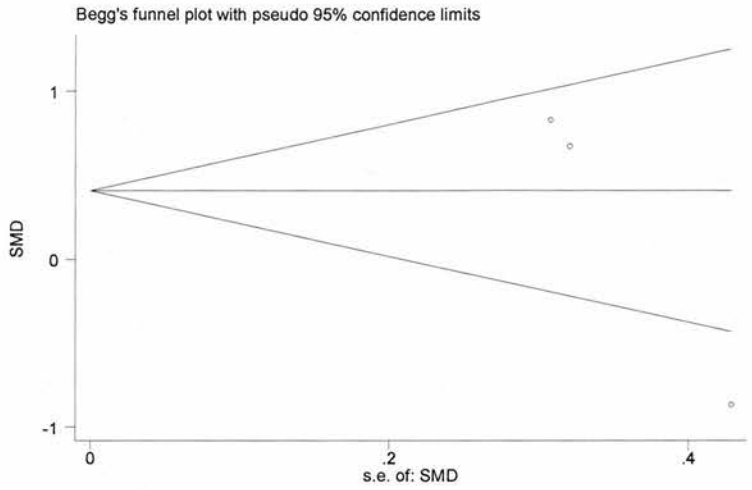
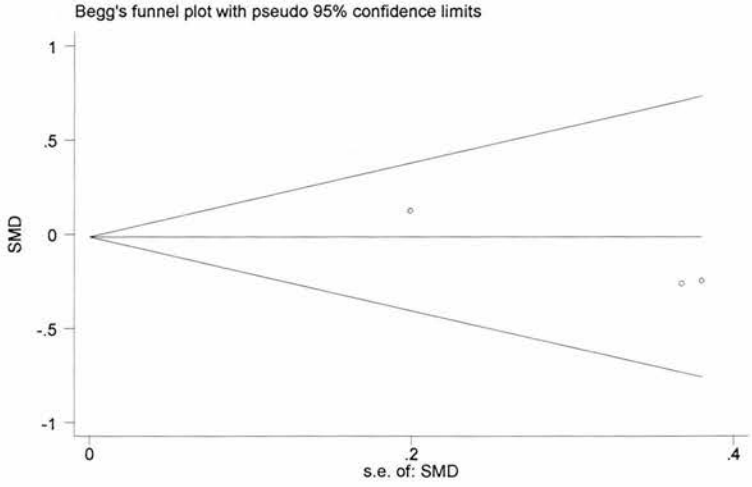


Figure 3.4.2.2: Funnel plot of standardised mean difference against standard error for left amygdala-hippocampal volume in bipolar subjects versus schizophrenics.



3.4.3 Future studies

The differences between healthy controls and patients with bipolar disorder are in general more modest than those found in schizophrenia and many show considerable heterogeneity. However, the average sample size is small and most studies are underpowered to detect the magnitude of effect sizes quoted in table 3.3.3. When bipolar subjects are compared to subjects with schizophrenia, the problem is compounded further by a lack of any publications for several regions of interest.

The comparison of bipolar and schizophrenic patients has much to tell us about the biology of both disorders and their component symptoms. Unfortunately, until studies with at least modest sample sizes of more than fifty are conducted, it is likely that sMRI research in bipolar disorder will trail that of schizophrenia by several years. Studies should not consider the distinction between Bipolar I and Bipolar II disorders prematurely since several issues for bipolar disorder as a whole continue to require clarification. The emphasis on sub or endophenotypes of bipolar disorder is likely to pose practical problems for researchers that will limit sample sizes.

Chapter 4: Clinical, Neuropsychological and Imaging Methods

4.1 Patient identification and recruitment

At the beginning of 2001 a study protocol was sent to all consultant psychiatrists in Lothian informing them of the proposed study. A letter enclosed with the protocol invited them to refer patients aged 18-65 who belonged to one of the following groups.

- Patients with a diagnosis of schizophrenia who had one or more close relatives with either bipolar disorder or schizophrenia.

- Patients with a diagnosis of bipolar disorder who had one or more relatives with either bipolar disorder or schizophrenia.

Consultants were asked not to refer patients with a history of neurological illness, learning disability or those with a diagnosis of alcohol dependence syndrome. Patients were also identified through informal contacts with Specialist Registrars in Psychiatry, General Practitioners and also from families already known to the Department of Psychiatry. Permission from the patient's responsible consultant was sought in all cases.

Once a potentially suitable patient had been identified, they were then approached in writing with a view to obtaining their informed consent. Those patients who gave their consent were then invited to attend the Division of Psychiatry at the Kennedy Tower, Royal Edinburgh Hospital with a view to their involvement in the current study.

4.2 Recruitment of well relatives

Well relatives were identified from the families of affected patients by referring to psychiatric records and from family history data given by the subjects themselves. The permission of the affected subject was also sought before unaffected relatives were approached and there was always some discussion about what historical material may or may not be revealed to their well relative. In most cases the affected subject themselves would then approach their well relative with the department's contact details, although on some occasions patients asked if we would approach their relatives directly, either in writing or by telephone. Relatives giving informed consent were then invited to the Division of Psychiatry with a view to their involvement. All relatives were then screened with the schedule for affective disorders and schizophrenia to ensure a lifetime absence of schizophrenia, bipolar disorder or major depression.

4.3 The Present State Examination (PSE)

All patients and healthy relatives were interviewed using the Present State Examination version 9 (Wing et al. 1974) with a view to categorising their current symptoms according to one of the following groups:

1. No symptoms
2. Unspecified symptoms from the PSE not rated in items 2 or 4 (below)
3. Any *partially* rated psychotic symptoms from sections 55-92 or 49-54
4. Any *fully* rated psychotic symptoms from sections 55-92 or 49-54

Patient relatives who met CATEGO criteria for affective disorder or schizophrenia were excluded from the study. Information obtained from the PSE was also used to supplement information obtained from psychiatric records.

4.4 Case note assessment

The psychiatric records of index patients were obtained in all cases. In addition the psychiatric records of other affected family members were also sought.

4.4.1 The OPCCI

Using the psychiatric records and information obtained from the PSE the lifetime ever occurrence of 90 signs, symptoms and other variables was recorded using the Operational Criteria Checklist (McGuffin et al. 1991). Additional information was obtained on age of onset, the relationship between affective and psychotic symptoms and several other clinical and demographic variables.

4.4.2 The OPCRIT computer program

The data obtained from psychiatric records and the PSE using the OPCCI was entered into the OPCRIT computer program. The OPCRIT computer program runs in a Microsoft DOS operating environment and generates operational diagnoses according to several international classifications. The clinical diagnoses of patients referred with Bipolar Disorder or Schizophrenia were confirmed according to the Diagnostic and Statistical Manual of the American Psychiatric Association (volume 4) using this

instrument. Subjects who failed to meet diagnostic criteria for either bipolar disorder or schizophrenia were excluded from the study

4.5 Recruitment of healthy controls

4.5.1 Method of identification

Healthy controls aged 18-65 were identified first from the social networks and non-genetic family members of the patients themselves. Additional healthy controls were also recruited using a number of other methods including:

- Advertising through two local village newsletters
- Advertising through the notice board of a local leisure centre
- By asking controls who had completed all assessments to identify other potential control subjects

Controls giving written informed consent were then invited to attend the Division of Psychiatry with a view to their involvement in the current study.

4.5.2 Control screening procedure

Controls without a known personal or family history of affective disorder or schizophrenia were then interviewed by the principle researcher (AM) with the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). Those meeting criteria for major depressive disorder, bipolar disorder or schizophrenia were excluded

from further consideration. Relatives of affected probands were also screened using this instrument to ensure that they too had no lifetime history of affective disorder or schizophrenia.

4.6 Demographic data set collected on all subjects and controls

4.6.1 Personal and paternal socio-economic status

The occupation of all subjects and controls was recorded at the time of participation in the study. These occupations were then classified according to the Register Generals Occupational Classification into the following mutually exclusive ordinal categories.

Table 4.6.1: Classification according to occupation

Socioeconomic Status	Description
I	Professional
II	Semi-professional
IIIa	Skilled non-manual
IIIb	Skilled manual
IV	Semi-skilled manual
V	Unskilled manual

Socioeconomic status is a potential covariate in neuropsychological and neuroimaging studies. However, its role may be partly explained by other factors such as IQ. Furthermore, socioeconomic status may decline at the time of illness and be a poor measure of the original socio-economic group to which patients would have originally belonged. Therefore, no attempt was made to match groups on social class since this might have the effect of selecting controls that were from relatively disadvantaged

backgrounds compared to the affected patients. Since individual levels of social class are ordinal and unlikely to be linearly related to any neuropsychological or brain measures, socio-economic status was tabulated as manual (IIIb to V) or non-manual (I To IIIa). This also had the additional effect of collapsing tables which had expected cell counts of less than 5, and enabled socioeconomic status to be entered, where necessary, as a single 2-level dummy variable, rather than as 6 2-level dummy variables with the consequent reduction in degrees of freedom and added complexity that would have entailed.

4.6.2 Alcohol, substance and cigarette History

All participants were asked about their weekly alcohol consumption in the weeks leading up to the study. In particular participants were asked on average how many days a week they drank and on each occasion how much they drank. By multiplying these figures together we obtained an approximate weekly consumption of alcohol in standard 8g units of ethanol. Information was also collected on alcohol consumption on the day preceding neuropsychological testing. Patients were also asked how many cigarettes they smoked on an average day.

Information regarding illicit drug misuse was also recorded at face-to-face interview. Participants were asked in particular whether they had ever used cannabis, cocaine, heroin, LSD, barbiturates, benzodiazepines or ecstasy. Current use was also recorded, but if participants were clearly dependent on illicit substances they were excluded from further consideration.

4.6.3 Height, weight and handedness

The height of each participant was recorded at interview in centimetres. Later, when patients attended for an MRI scan of the brain, they were routinely weighed and each weight was recorded in kilograms. Handedness was recorded by asking which hand people used for writing. Where patients were able to use both hands equally well, handedness was recorded as ambidextrous.

4.6.4 Educational history

The educational history of each participant was recorded by asking the age at which they left full time education. In those subjects who left education at 16 or under, their educational attendance was recorded as 'compulsory only'. Where participants left school after the age of 16, or immediately went onto further or higher education, the educational history was recorded as 'more than compulsory'.

4.6.5 Marital status

Marital status was recorded as married, when subjects were currently married, single when they had never been married and divorced when they had previously been divorced from a spouse but had not remarried.

4.6.6 Current medication

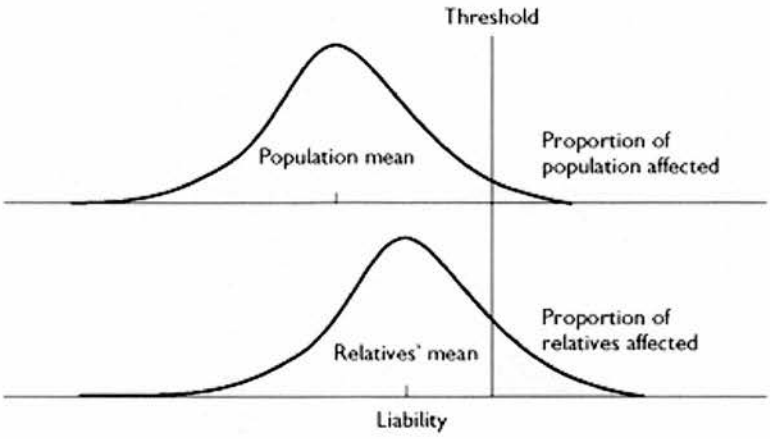
Current medication was recorded at face-to-face interview. When participants could not remember the drugs or doses being prescribed, this information was sought from psychiatric records. The prescription of conventional and 'atypical' antipsychotics, benzodiazepines, lithium and antidepressants were recorded as 'yes' or 'no'.

Additionally, conventional antipsychotic doses were converted into chlorpromazine equivalents and all lithium prescriptions were converted to bioequivalent doses of lithium carbonate.

4.7 Measurement of genetic loading for psychosis

Most common psychiatric conditions, including schizophrenia do not show a Mendelian pattern of inheritance. However, those who are affected can be graded along a continuum of severity and even those who are unaffected, but closely related to one or more schizophrenic relatives may show partial signs of the disorder. It is possible to fit a genetic model to this data which assumes an underlying liability to the disorder which is continuously distributed in thee general population (Pearson and Lee 1901). Individuals who pass a threshold on genetic liability would therefore be expected to manifest the condition. If the underlying liability is mediated by many genes, then it can be assumed that genetic liability to schizophrenia is approximately normally distributed. Furthermore, the relatives of affected probands would also be expected to have an approximately normally distributed genetic liability whose modal value would be shifted to the right compared to the general population. Since higher numbers of people would be expected to cross the threshold of genetic liability, more relatives would be predicted to develop symptoms than unselected members of the general population.

Figure 4.7.1: Genetic liability-threshold model of disease



4.7.1 Method of calculation

Assuming that genetic liability (z) has normal distribution and that at a given threshold (z=t) people with liabilities greater than t develop schizophrenia; a mathematical model can be fitted. The area under the normal curve to the right of a given threshold represents the probability of being affected and, taking the example of schizophrenia, the area bounded by the curve, infinity and the threshold liability (z=t) will equal the prevalence of the disorder (p). In order to fit the model, we first assume that the genetic liability of an individual selected at random for a population is zero. The value of t is then calculated from the cumulative normal distribution as follows:

$$\int_{-\infty}^{t} \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}} dz = \mathbf{1\text{-}p}$$

or, alternatively

$$t=\Phi^{-1}(1-p)$$

Where Φ^{-1} is the inverse standard cumulative normal distribution function. For schizophrenia, p can be assumed to take the value 0.005 (Jablensky 1997), from which t=2.58 ($\Phi^{-1}(0.995)$) can be calculated. The mean liability of those affected and unaffected can then be calculated as follows:

The general formula for the mean of a continuous variable:

$$\int_{\text{all z}} z.f(z)\,dz$$

where f(z) is the probability density function. The denominator of this function disappears because the sum of all probabilities for a continuous probability density function is 1. Therefore the average genetic liability of unaffected individuals is therefore:

$$\frac{\int_{-\infty}^{t} z.f(z)dz}{(1-p)}$$

and the average genetic liability of those above threshold (i.e. affected) is therefore:

$$\frac{\int_{t}^{\infty} z.f(z)dz}{p}$$

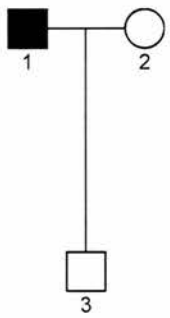
For schizophrenia (prevalence=0.005) and bipolar I disorder (prevalence=0.008) (Judd and Akiskal 2003), the equations can be solved to give the following result:

Table 4.7.1: Expected liabilities in schizophrenia and bipolar disorder

	Schizophrenia	Bipolar I Disorder
Expected liability of unaffected individual	-0.014	-0.022
Expected liability of affected individual	2.85	2.74

However, the above expected liabilities do not take in account sample information about the affected or unaffected status of family members. In order to take this information into account, the relatedness of family members to each other and the genetic contribution to the disorder needs to be expressed. Relatedness of family members to one another is usually expressed as $(0.5)^n$. For example, a given person shares 100% of his genetic liability with himself, so his relatedness is 1 or 0.5^0. The same individual shares only 50% of his genetic material with his parents, siblings and children and only 25% with his grandparents, grandchildren, nieces, nephews, aunts and uncles. The relatedness is therefore expressed as 0.5 (0.5^1) and 0.25 (0.5^2) respectively. The matrix of relatedness for a given family can be expressed as a square matrix.

For a given family with one affected family member:



Then the matrix of 'relatedness' is:

$$R=\begin{pmatrix} 1 & 0 & 0.5 \\ 0 & 1 & 0.5 \\ 0.5 & 0.5 & 1 \end{pmatrix}$$

Where the rows and columns of the matrix represent the members of the family numbered in figure X.

If a disorder was not genetic however, the degree of relatedness would not need to be taken into account, since an affected relative would not be a risk factor for the disorder in other healthy probands. If however, the genetic contribution to a disorder is expressed as h^2, then the liability posed by an additional relative would be h^2 x relatedness. Therefore, in order to reflect this fact, the off diagonals of the matrix of relatedness are multiplied by h^2. Taking h^2 to be 0.7 for schizophrenia, then the matrix becomes:

$$\mathbf{V} = \begin{pmatrix} 1 & 0 & 0.5x0.7 \\ 0 & 1 & 0.5x0.7 \\ 0.5x0.7 & 0.5x0.7 & 1 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0.35 \\ 0 & 1 & 0.35 \\ 0.35 & 0.35 & 1 \end{pmatrix}$$

The vector of expected liabilities for the above family can be expressed as:

$$\mathbf{X} = \begin{pmatrix} 2.85 \\ -0.014 \\ -0.014 \end{pmatrix}$$

In order to calculate the actual genetic liabilities for each family member, the product $RV^{-1}X$ is calculated to give another 3 cell column vector:

$$\mathbf{(RV^{-1})X} = \begin{pmatrix} 1 & 0 & 0.5 \\ 0 & 1 & 0.5 \\ 0.5 & 0.5 & 1 \end{pmatrix} \times \begin{pmatrix} 1 & 0 & 0.35 \\ 0 & 1 & 0.35 \\ 0.35 & 0.35 & 1 \end{pmatrix}^{-1} \times \begin{pmatrix} 2.85 \\ -0.014 \\ -0.014 \end{pmatrix}$$

$$\text{Estimated} = \begin{pmatrix} 2.64 \\ -0.36 \\ 0.42 \end{pmatrix}$$

Therefore the liability for the affected father, unaffected mother and unaffected son are 2.85, -0.19 and 0.81 respectively. This method was used to calculate the genetic liability of all individuals in the current study from their family's pedigree. Pedigrees

were constructed from information obtained from the subjects themselves, their well relatives and from psychiatric case notes. For families in whom some individuals were affected with bipolar disorder and others schizophrenia, the genetic liability for both disorders was calculated separately. Affected relatives with bipolar disorder were assumed to be unaffected when calculating the genetic liability for schizophrenia and vice versa. This method was chosen partly for the sake of simplicity and partly because the degree to which a family history of schizophrenia predisposes to affective disorder had not been adequately quantified at the time of the experiment.

4.8 Baseline clinical data set collected on all subjects and controls

In addition to the demographic and historical information collected on all participants, a core dataset of current manic, depressive and positive psychotic symptoms was also collected. Symptoms were assessed using established rating scales administered to all subjects no more than 24 hours from the time of their neuropsychological assessments. The details of each assessment are given in the following sections.

4.8.1 The Positive and Negative Symptom Scale

The positive and negative symptom scale (PANSS, Kay et al. 1987) is a 30 item scale derived partly from the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962). The scale is subdivided into three subscales: positive, negative and general psychopathology. The individual items of each scale are shown in the table below. Each

item is rated according to a glossary definition. All assessments using the PANSS were completed by the same researcher (AM) after a period of training.

Table 4.8.1: Positive and Negative Symptom Scale Items

Positive subscale
Delusions
Conceptual disorganisation
Hallucinatory behaviour
Excitement
Grandiosity
Suspiciousness/persecution
Hostility
Negative subscale
Blunted affect
Emotional withdrawal
Poor rapport
Passive/apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity & flow of conversation
Stereotyped thinking
General Psychopathology
Somatic concern
Anxiety
Guilt feelings
Tension
Mannerisms & posturing
Depression
Motor retardation
Uncooperativeness
Unusual thought content
Disorientation
Poor attention
Lack of judgement& insight
Disturbance of volition
Poor impulse control
Preoccupation
Active social avoidance

Rating of individual items from the Positive and Negative Symptoms Scale

1 = Absent	
2 = Minimal	5 = Moderately severe
3 = Mild	6= Severe
4 = Moderate	7= Extreme

4.8.2 The Young Mania Rating Scale

Table 4.8.2: The Young Mania Rating Scale

Elevated Mood 0. Absent 1. Mildly or possibly increased on questioning 2. Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content 3. Elevated, inappropriate to content; humorous 4. Euphoric, inappropriate laughter	**Language-Thought Disorder** 0. Absent 1. Circumstantial; mild distractibility; quick thoughts 2. Distractible; looses goal of thought; changes topic frequently; racing thoughts 3. Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia 4. Incoherent; communication impossible
Increased Motor Activity-Energy 0. Absent 1. Subjectively increased 2. Animated; gestures increased 3. Excessive energy; hyperactive at times; restless (can be calmed) 4. Motor excitement; continuous hyperactivity (cannot be calmed)	**Content** 0. Normal 2. questionable plans, new interests 4. Special project(s), hyperreligious 6. Grandiose or paranoid ideas; ideas of reference 8. Delusions or hallucinations
Sexual Interest 0. Normal; not increased 1. Mildly or possibly increased 2. Definite subjective increase on questioning 3. Spontaneous sexual content; elaborates on sexual matters 4. Overt sexual acts (towards patients, staff or interviewer)	**Disruptive-Aggressive Behaviour** 0. Absent, cooperative 2. Sarcastic; loud at times, guarded 4. Demanding, threats on ward 6. Threatens interviewer, shouting; interview difficult 8. Assaultive, destructive; interview impossible
Sleep 0. Reports no decrease in sleep 1. Sleeping less than normal amount by up to one hour 2. Sleeping less than normal amount by more than one hour 3. Reports decreased need for sleep 4. Denies need for sleep	**Appearance** 0. Appropriate dress and grooming 1. Minimally unkempt 2. Poorly groomed; moderately dishevelled; overdressed 3. Dishevelled; partly clothed; garish make-up 4. Completely unkempt; decorated; bizarre gard
Irritability 0. Absent 2. Subjectively increased 4. Irritable at times during interview; recent episodes of anger or annoyance on ward 6. Frequently irritable during interview; short, curt throughout 8. Hostile uncooperative; interview impossible	**Insight** 0. Present 1. Possibly ill 2. Admits behaviour change but denies illness 3. Admits possible behaviour change, but denies illness 4. Denies any behaviour change
Speech (rate and amount) 0. No increase 2. Feels talkative 4. Increased rate or amount at times; verbose at times 6. Push; consistently increased rate and amount; difficult to interrupt 8. Pressured; uninterruptible, continuous speech	

The Young Mania Rating Scale (Y-MRS) (Young et al. 1978) is an eleven item rating scale conducted at face-to-face interview. All participants were rated using this instrument (AM).

4.8.3 The Hamilton Depression Rating Scale

The Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) is a 21 item rating scale completed at face-to-face interview with subjects. Each item consists of a symptom or sign which is rated according to an ordinal scale. By adding the score from each item a total score is generated which is thought to reflect the severity of depressive symptoms. All participants in the study were rated using the HRSD by single researcher (AM).

Table 4.8.3: Items of the Hamilton Depression Rating Scale

Item	Description
1	Depressed mood
2	Feelings of guilt
3	Suicide
4	Insomnia early
5	Insomnia middle
6	Insomnia late
7	Work and activities
8	Retardation: psychomotor
9	Agitation
10	Anxiety (psychological)
11	Anxiety (somatic)
12	Somatic symptoms (gastrointestinal)
13	Somatic symptoms (general)
14	Genital symptoms

15	Hypochondriasis
16	Loss of weight
17	Insight
18	Diurnal variation
19	Depersonalisation and derealisation
20	Paranoid symptoms
21	Obsessional and compulsive symptoms

4.9 Neuropsychological battery

The test battery chosen was designed to include tests which had previously been shown to distinguish individuals with schizophrenia or bipolar disorder from controls. The battery was organised according to domain of neuropsychological function in accordance with standard practice.

Table 4.9: Neuropsychological test battery

NEUROPSYCHOLOGICAL FUNCTION	TESTS
Current intellectual function	Wechsler Abbreviated Scale of Intelligence (WASI)
Premorbid intellectual function	National Adult Reading Test
Memory	Rivermead Extended Behavioural Memory Test (version A)
Executive function	Hayling Sentence Completion Test (Response inhibition) Verbal Fluency (FAS) and semantic category (Animals) (Spontaneous production) CANTAB Stockings of Cambridge Test (Planning)

Psychomotor performance	Digit Symbol Substitution Test CANTAB Simple and Choice Reaction Time
Handedness	Hand preference for writing

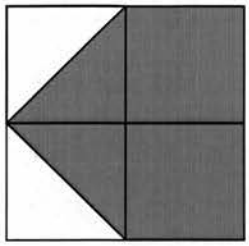
4.10 Current and premorbid functioning

4.10.1 The Wechsler Abbreviated Scale of Intelligence

Current intellectual functioning was measured using the Wechsler Abbreviated Scale of Intelligence (WASI). The WASI consists of 4 subscales: vocabulary, block design, similarities and matrix reasoning that were selected to provide accurate and reliable measures of verbal, performance and full scale IQ. The test itself has been subject to numerous pilot, scoring and quality control studies and has been shown to be valid and reliable for the age range 6 to 89 years.

All subtests are completed at face-to-face interview with a subject. Directions for the administration and scoring of each subtest are provided in an accompanying text. The first (vocabulary) subtest requires subjects to define a word presented to them verbally. For example, the examiner would say 'tell me what DANCE means'. The second task (block design) requires the examinee to arrange a series of 4 or 9 coloured blocks to fit a template pattern within a pre-specified period of time.

Figure 4.10.1: A pre-specified pattern from the block design subtest



The third (similarities) requires subjects to define a rule which explains why two items are similar. For example, the examiner would ask 'In what way are a PEN and a PENCIL alike' to which the subject would be expected to respond along the lines of 'they are both for writing'. The forth and final subtest (matrix reasoning) requires the examinee to look at a matrix of items from which a single item is missing. The examinee then selects an item from a list which completes the pattern.

4.10.2 The National Adult Reading Test

The National Adult Reading Test (NART, Nelson 1982) was used to estimate the subject's premorbid full-scale IQ (NART FSIQ). The test consists of 50 short words, which the subject is required to read aloud. Each word is selected because of its atypical grapheme-phoneme conversions (e.g. gauche, leviathan) and each word is presented in order of increasing difficulty. Therefore subjects must have prior knowledge of how the word is pronounced in order to read it accurately. The number of pronunciation errors made is used to estimate premorbid intelligence. The test was originally developed in order to measure the premorbid IQ of individuals in whom intellectual decline was

suspected. Reading ability is known to correlate highly with IQ in the general population. Conclusions can be made about the probable extent of intellectual decline by subtracting NART full scale IQ from the WASI estimate of full scale IQ. However, a negative difference could be taken to infer that the subject is currently functioning at a higher level than in the past.

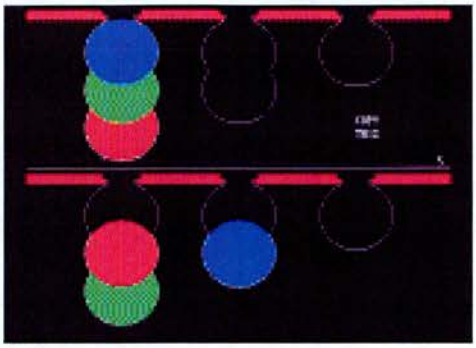
4.11 Executive functioning

Executive functioning was measured using three tests designed to measure specific domains: The Stockings of Cambridge Test (planning) from the Cambridge Neuropsychological Testing Automated Battery (CANTAB, Sahakain and Owen 1992), The Hayling Sentence Completion Test (HSCT-response inhibition, Burgess and Shallice 1996) and FAS/Animals (verbal fluency, Benton 1978).

4.11.1 The Stockings of Cambridge Test

The Stockings of Cambridge Test is a spatial planning test based upon the 'Tower of London' test. The subject is shown two displays containing three coloured balls, presented so they can be perceived as stacks of coloured balls in stockings. In each trial, the subject must move the balls in the lower display to copy the pattern shown in the upper. A later motor control task, in which the subject simply copies earlier moves, allows planning time (versus movement time) to be calculated and taken, relative to the number of moves required to complete each trial, as a measure of the subject's planning ability.

Figure 4.11.1: A typical screen from the CANTAB stockings of Cambridge sub test



4.11.2 The Hayling Sentence Completion Test

The Hayling Sentence Completion Test (HSCT) is a timed test of response suppression and is comprised of two sections. In both sections the subject is presented verbally with sentences from which the last word is missing and in each case the subject is asked to provide a one word answer. In the first section (A, response initiation), the subject is required to provide an answer which sensibly completes the sentence. In the second section (B, response suppression) the subject is required to give a ridiculous answer which no sense in the context of the sentence. The errors are scored according to the degree of sense made by the sentence completion. Category A errors are scored if the sentences in the incongruous condition are completed correctly. Category B errors are scored if the sentence completion makes some sense (e.g. 'The whole town came to hear the Mayor __' answer: 'sing'. Raw scores are then converted to scaled scores.

4.11.3 Verbal fluency

The test used to measure verbal fluency is known by the names 'FAS', 'FAS/Animals' and also 'The Controlled Oral Word Association Test' (Spreen and Strauss 1991). The purpose of this test is to provide as many words beginning with a specific letter, or belonging to a specific category, within a limited amount of time. The subjects were asked to verbally provide as many words beginning with letters F, A and S as possible in 1 minute without any repetitions (verbal association fluency). Subjects were also required to name as many four legged animals as possible in 1 minute, again without repetition (semantic fluency). An egg timer was used to keep account of time and one minute was used for each letter and animal category. Inadmissible words were not positively scored as correct or negatively as incorrect. Preservative answers were deducted from the overall score. Inter-rater reliability for this test is reported to be near perfect (Spreen and Strauss 1991) and impairment on this task is also been associated with frontal lobe impairment in both brain injured subjects (Lishman 1998) and in functional imaging studies of psychotic patients (Frith et al. 1995).

4.12 Sustained attention

4.12.1 Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale Revised (WAIS-R) and is a test of perceptual motor speed. The test consists of four rows of 100 blank squares, each paired with a randomly assigned number from between 1 and 9. Above the test is a key which pairs each number with a nonsense symbol. The objective of the test is to fill in as many of the 100 consecutive blank squares in 90 seconds as possible. The test is purported to be a measure of

psychomotor performance and is relatively unaffected by intelligence, memory or learning (Erber 1976;Glosser et al. 1977).

4.13 Perceptual and motor speed

4.13.1 The Simple and Choice Reaction Time

The Simple and Choice Reaction Time Test is designed to measure psychomotor performance. The materials for the task consist of a depressible paddle and a touch sensitive computer screen which can display a target for the examinee to touch. The target can be presented within a single area within the computer screen, or presented at one of five possible areas. There are four conditions:

Condition 1: The subject is asked to depress the paddle and wait for a circular target to appear on the computer screen within a single location. When the target appears, the subject is instructed to release the paddle. The task is repeated several times and the time between target presentation and the release of the paddle is recorded.

Condition 2: The subject is asked to depress the paddle and wait for a circular target to appear on the computer screen within a single location. When the target appears, the subject is instructed to release the paddle and then to touch the location on the screen where the target has just appeared. The task is repeated several times and the time between target presentation and the screen contact is recorded.

Condition 3: The subject is asked to depress the paddle and wait for a circular target to appear on the computer screen within 5 possible locations. When the target appears, the subject is instructed to release the paddle. The task is repeated several times and the time between target presentation and paddle release is recorded.

Condition 3: The subject is asked to depress the paddle and wait for a circular target to appear on the computer screen within 5 possible locations. When the target appears, the subject is instructed to release the paddle and then to touch the location on the screen where the target has just appeared. The task is repeated several times and the time between target presentation and the screen contact is recorded.

The times recorded can be used to construct four parameters: simple reaction time, choice reaction time and simple movement time and simple reaction time. Reaction times are assumed to represent processing speed and movement time.

4.14 Learning and memory

4.14.1 The Extended Rivemead Behavioural Memory Test

The original Rivermead Behavioural Memory Test (RBMT) was first devised in 1985 (see Wilson et al. 1989 for a description) and was designed to predict everyday memory problems in people with acquired, non-progressive brain injury. The RBMT comprises tasks analogous to situations found in daily living that often appear troublesome for memory impaired people and population norms exist for people aged 5 to 96 years.

Using the non-extended version of the test, most non-memory-impaired people would be at ceiling on the test, and hence the RBMT might not be suitable for picking up very mild memory impairment. In an attempt to refine the test for use in people with very mild memory impairments the extended version has been developed (de Wall et al. 1994). In order to make the RBMT-E more sensitive to mild memory impairment than its predecessor, the amount of material to be remembered has been increased and many items have been made more complicated.

Studies using the RBMT-E have shown that it is sensitive to age and IQ effects in non brain injured subjects. The stimuli are presented in standing books so that the tester is able to read the relevant instructions while at the same time viewing a miniature representation of each stimulus as it is presented to the subject. The task itself consists of 11 subtests described in table.

Table 4.14.1: The subtests of the Extended Rivermead Memory Test (E-RBMT)

NUMBER	NAME	DESCRIPTION
1 and 2	First and second names	The subject is shown three photographic portraits and asked to remember the first and second names of all three people in the photographs. The subject is then asked to recall the fist and second names later in the test.
3	Belongings	The subject is asked to provide two of their belongings which are borrowed and secreted (in full view of the subject) in two hidden locations. The subject is instructed to ask for their belongings back when the examiner says 'we have now finished the test'.
4	Appointments	An alarm is set for 20 minutes. When the alarm rings the subject is required to ask two questions 'when do I have to see you again' and 'when will this session end'. The degree to which these two tasks are correctly performed is recorded.
5	Picture recognition	Twenty line drawings of everyday objects are presented on a card and the subject is asked to remember as many as possible in 15 seconds. After 15 seconds has elapsed, the card is turned over so that the items are no longer visible. After subtest 6 the subject is then presented with 40 pictures containing the 20 original images. The subtest is then asked to correctly identify the original images.
6	Story	The subject is instructed to listen to a short passage of prose and to recall of much of it as possible both immediately and after 5 further tests have been administered.
7	Face recognition	The subject is presented with pictures of 15 faces, one at a time for a period of 3 seconds each. After the faces have been presented the subject is later asked to recall the faces correctly from amongst a set of 30.
8 and 9	Route and messages	The examiner takes two items (an envelope and a book) and traces a path around the room comprising 7 sections leaving the two items at two separate locations. The subject is then asked to retrace the steps of the examiner immediately and after the end of all other subtests.
10 and 11	Orientation and time	The subject is presented with 13 questions regarding their orientation in time, place and person. Scores reflect the accuracy of their answers.

Raw scores from the above tests were then converted into profile scores which take account of the subject's age and current full scale IQ.

4.15 Statistical analysis of neuropsychology data

The following data set was obtained from the neuropsychology test battery:

Table 4.14: Data obtained

Variable	Description
Predfsiq	Predicted NART full-scale IQ
Fastot	Verbal fluency (total number of words from FAS and animals
Waisdgsy	Digit-symbol substitution test, number of correct substitutions
RBMTfnp	RBMT, fist names profile score
RBMTsnp	RBMT, second names profile score
RBMTaptp	RBMT, sum of belongings and appointments profile score
RBMTprcp	RBMT, picture recognition test profile score
RBMTstip	RBMT, immediate story recall profile score
RBMTstdp	RBMT, delayed story recall profile score
RBMTfrcp	RBMT, face recognition profile score
RBMTrtip	RBMT, route immediate profile score
RBMTrtdp	RBMT, route delayed profile score
RBMTmsip	RBMT, message immediate profile score
RBMTmsdp	RBMT, message delayed profile score
RBMTodtp	RBMT, orientation profile score
RBMTtotp	RBMT, total profile score
HSCT	Hayling sentence completion test,
HSCT	Hayling sentence completion test,
WASIvbiq	WASI predicted verbal IQ
WASIpriq	WASI predicted performance IQ
WASI4iq	WASI predicted full-scale IQ
Rtsmt	CANTAB simple movement time
Rtsrt	CANTAB simple reaction time
Rtcmt	CANTAB choice movement time
Rtcrt	CANTAB choice reaction time
Socsmntt	CANTAB Stockings of Cambridge Test, number of trials in minimum

	number of moves

Emboldened variables represent those used primarily in subsequent analyses

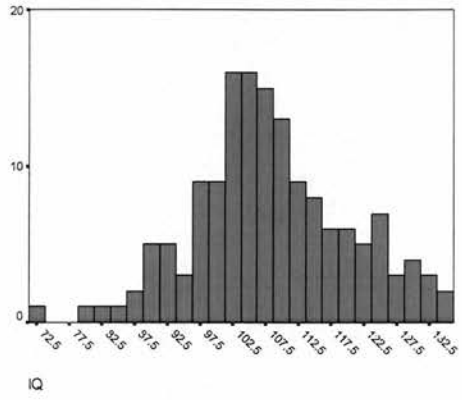
Key to preceding table	
NART	National Adult Reading Test
RBMT	Extended Rivermead Behavioural Memory Test
WASI	Wechsler Abbreviated Scale of Intelligence
CANTAB	Cambridge Neuropsychological Test Automated Battery

4.15.1 Outlier detection and assessment of normality

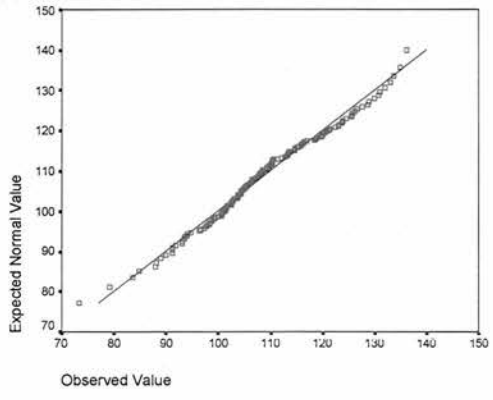
The distribution of each neuropsychological variable was examined for normality. Normality was assessed in two ways: a) by examining a histogram of the variable for each group individuals and b) by plotting the observed quantile against that expected under a normal distribution to produce a normal probability plot (Q-Q plot) for each group. Where the observed and expected quanitiles are equal, the observations will tend to cluster along the line of equality. Observations situated away from the line, especially at the extremes, were checked against the written record of the neuropsychological assessment to ensure they had been transcribed correctly. Where multivariate tests were used, the assumption of multivariate normality was checked by examining the Mahalanobis plot of statistical distance squared versus that expected under the Chi-squared distribution. Standardised residual plots from the many mixed-effects ANOVAs conducted were also examined for normality.

Figure 4.15.1: Example of a normally distributed variable

Histogram of a normally distributed variable (150 observations)



Q-Q Plot of a normally distributed variable (150 observations)



Where data were not normally distributed, transformations were applied to improve the approximation to a normal distribution. Where the Q-Q plot remained incompatible with an underlying normal distribution, subsequent hypothesis tests were conducted using non-parametric statistics.

4.15.2 Multivariate analyses

Domains of neuropsychological function (IQ, memory, executive function) were compared between groups using a mixed model multivariate analyses of variance (mixed MANCOVA) controlling for WASI full scale IQ (memory and executive function), psychiatric symptoms (HDRS, PANSS positive and YMRS) and age. A mixed model MANOVA was used instead of a conventional 'fixed-effects' MANOVA to take account of the non-independence of observations within families. Family membership

was modelled as a 'random effect', assumed to represent a sample of possible families taken from a normal probability distribution. All multivariate analyses were conducted using the PROC GLM procedure within the statistical package SAS (SAS Institute, Cary, NC).

A mixed model MANOVA was chosen in order to test the equality of mean vectors, rather than individual group means, and consequently controls for the experiment-wise error rate by reducing the number of individual tests required.

4.15.3 Between-group comparisons

Where the mixed model MANOVA showed an overall difference within a domain of neuropsychological function, further tests were conducted to examine a) which specific neuropsychological variable means differed between the groups and b) specific pairwise effect sizes. Both analyses were conducted using a mixed model ANOVA, with family modelled as a random factor. Where differences were found in the overall ANOVA, controlling for WASI full scale IQ (for memory and executive function) and psychiatric symptoms (HDRS, PANSS positive, YMRS) the pairwise between group differences were estimated from the model. All analyses were conducted using the PROC MIXED procedure within the statistical package SAS (SAS Institute, Cary, NC).

The results of the various neuropsychological analyses conducted are given in chapter 5 of this thesis.

4.16 Image acquisition

All participants were scanned on a 1.5 Tesla GE MRI scanner. Midline saggital localisation was followed by two further sequences to image the whole brain. The first sequence was a transverse spin-echo scan which acquired both T2 and proton density weighted images of the brain. These images were subsequently reported by a consultant in neuroradiology. The third and final sequence was a coronal gradient echo sequence with magnetisation preparation (MPRAGE) and produced 128 coronal high-resolution T1 weighted images which were used for structural image analysis.

Table 4.16.1: Imaging Sequences

Sequence	Parameters
T1 saggital spin echo sequence 'localiser'	TR=400ms, TE=14ms, FOV=24, slice thickness=3mm, matrix=256x160
T2/PD transverse spin echo 'clinical scan'	TR=5000ms, TE=15ms &102ms, FOV=24, slice thickness=5mm, matrix=256x256
T1 gradient echo 'structural scan'	TI=600ms, TE=3.4ms, Flip angle=15°, FOV=22, slice thickness=1.7mm, matrix=256x192

All images were acquired in Dicom © format and were then transferred to a SPARC SUN STATION computer (Sun Microsystems) and backed up onto optical discs.

4.17 Voxel based morphometry

Stored images were converted from DICOM to Analyze format using a script written in the C programming language. Once converted, images were then transferred to a Dell © computer running Red Hat Linux.

4.17.1 Conversion from Dicom© to Analyze© Format & Origin Setting

Images were initially acquired and stored in Digital Imaging and Communications in Medicine (DICOM) format. The DICOM format encodes each brain 'slice' as a separate 2 dimensional image file. Since these files could not be processed by SPM99, they were then converted into ANALYZE 3-dimensional file format for further processing. Each image was the viewed using SPM99, an automated image analysis program developed in the Wellcome Department of Imaging Neuroscience (London, UK) on s SUN SPARC microcomputer (Sun MicroSystems Inc., Mountain View, CA, USA). Images were inspected for orientation and movement artefact and the origin was set at the anterior commisure. Images were then transferred to a computer running SPM99 on MATLAB 6.5 using the Red Hat Linux 8.0 platform.

4.17.2 Template generation

Two optimised T1 study specific templates were made from all 192 T1 MRI scans, from all subject groups. Images were first re-orientated to neurological convention and then spatially normalised to the generic MNI 152 T1 template (Montreal Neurological Institute) provided as part of the SPM99 package using linear affine normalisation and nearest neighbour interpolation. A grey-matter optimised template

was made by using the grey matter distribution to normalise the source images to MNI template. The white-matter optimised template was made by using the white matter distribution to normalise images. The MATLAB script authored by John Ashburner was used for the purposes of template generation in both cases (supplied via the SPM mailbase, www.jiscmail.ac.uk). Extracerebral voxels were removed using the "Xtract Brain" render function. This function uses the combined grey and white segments and uses them as a mask to remove extracerebral voxels. This process is accomplished by multiplying the rendered image by the original grey matter segment. A mean image was then calculated and smoothed using an 8mm full width at half maximum (FWHM) Gaussian Kernel. All normalised and segmented images used to construct the template were subsequently checked to ensure the images had not become corrupted.

4.17.3 Normalisation

All images were spatially normalised to the study-specific T1 template. This process attempts to register all images in the same 3 dimensional stereotactic space so that differences in grey matter density can be assumed to relate to the underlying anatomic space. This was accomplished using a method which attempts to minimize the sum of squared differences between each image and the T1 template. The twelve point simple (linear) affine transformation is usually expressed as:

$$\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ 1 \end{pmatrix} = \begin{pmatrix} p_1 & p_4 & p_7 & p_{10} \\ p_2 & p_5 & p_8 & p_{11} \\ p_3 & p_6 & p_9 & p_{12} \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ 1 \end{pmatrix}$$

Where y_1, y_2 y_3 are the transformed coordinates of the original coordinates x_1, x_2, x_3. The 4x4 matrix describes the 12-point transformation applied to the original coordinates in order to map them to the new coordinates. This matrix actually describes a rigid body transformation, zoom transformation and shear transformation in one matrix. These matrices can be calculated separately and multiplied together to give the same solution. Alternatively, the equation can be given in matrix notation as:

$$\mathbf{Y} = \mathbf{Mx}$$

The transformation M is chosen such that the sum of squared differences between the new coordinates and the template image are minimised. Therefore, the function minimised is:

$$\sum_i (f(\mathbf{M}\mathbf{x}_i) - p_{13} g(\mathbf{x}_i))^2$$

Where x_i denotes the reference points in the template image, M_{xi} represents the points in the source image (M is the transformation applied) and p_{13} is a scaling parameter to correct for differences in spatial scaling between source and reference images.

Optimal linear normalisation was performed using a Bayesian framework, whereby the maximum *a posteriori* estimate of the spatial transformation is made using prior information about variability in brain size. Linear affine transformations, used for the *construction* of a study specific T1 template were also supplemented with non-linear

basis functions for the normalisation of images *to the* study specific T1 template. Non-linear basis functions consist of discrete cosine transformations (DCT) which produce a better fit between image and template whilst maximising the smoothness of the transformations.

The result of transforming the source images to the study-specific template image is imperfect in the sense that they do not match individual gyri in each source image with that of the template. Instead, they attempt to correct for overall shape differences such that differences in grey matter density at each voxel reflect volumetric and not shape differences between source and template.

4.17.4 Segmentation

Spatially normalised images were then partitioned into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using an established method (Ashburner and Friston 2000). This step was accomplished using a maximum likelihood 'mixture model' clustering algorithm. Each voxel in a normalised image has intensity from 0 to 1 and these values represent the prior probability that a voxel is GM, WM or CSF. Further information is also available from MNI (Montreal Neurological Institute) representing the spatial distribution and variability of GM, WM and CSF clusters from a large numbers of brains. Using these two sources of information the probability that a voxel of intensity v belongs to a cluster c can be established using Bayes Theorem.

The segmentation process generates 3 probability maps, for grey, white and CSF. The solution obtained relies on several assumptions. Firstly, each voxel is assumed to consist of one several tissue classes (usually grey, white and CSF). Secondly, the

distribution of voxel intensities for each class has a normal distribution, but with unknown mean and variance. Thirdly, the distribution of voxel intensities can be described using the number of voxels within a cluster, the mean intensity and the variation around that mean. The MNI image represents a prior probability map representing the prior expectation or probability that a given voxel consists of grey, white or CSF. This prior information is combined with the sample image data to produce a posterior probability that each voxel consists of grey white or CSF. Sample image data is expressed as a likelihood function which is multiplied by the prior probability to give a posterior probability or likelihood function. The iterative process proceeds in order to maximise the posterior probability that a given voxel will belong to a particular tissue class. Nearest neighbour interpolation was used to preserve original tissue values and grey/white contrast.

4.17.5 Smoothing

Smoothing is a general statistical technique used whenever data contains 'noise' and an underlying 'signal'. In order to increase the ratio of signal to noise, data at several time points are averaged to give a mean value which should be less susceptible to short range fluctuations. The normal curve used to smooth voxel intensities has mean zero can be described in terms of a single parameter, the 'full width and half maximum' (FWHM), and is usually set at 12mm for voxel based morphometry. The FWHM kernels used for VBM represent the usual minimal spatial extent for two clusters to be regarded as anatomically separate.

Using a smoothing kernel has two further consequences. Firstly, data which contains a lot of noise is generally skewed towards high voxel intensity values and is therefore not normally distributed. This creates difficulties with the subsequent analysis of such data. However, by taking the weighted average intensity from a given voxel and the surrounding voxel, averaged data will converge towards a normal distribution more quickly. A further consequence of smoothing is to reduce the number of independent observations from an image. In a single image of 128 by 128 voxels there are 16384 observations. When an 8mm smoothing kernel is used, the effective observation size, termed 'resolution elements' (RESELS), becomes 8x8mm. Therefore, in an image of 128x128mm smoothed with a 8x8mm smoothing kernel contains 256 RESELS. By reducing the number of *independent* observations within an image, the problem of multiple hypothesis testing at each individual voxel is minimised somewhat.

A 12mm Gaussian kernel was used to smooth GM, WM and CSF voxel intensities in the current study.

4.17.6 Statistical analysis

Voxel based morphometry compares the mean voxel intensity for each group and performs a hypothesis test to see if these values differ between groups. The general linear model is used to model the voxel intensity (Y, response variable) in terms of one or more explanatory variables (X) and an error term (ε). The relationship between these variables can be stated in matrix form as:

$$\begin{pmatrix} Y_1 \\ Y_j \\ Y_J \end{pmatrix} = \begin{pmatrix} x_{11} & \ddots & x_{1L} \\ & & \\ x_{J1} & & x_{JL} \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_l \\ \beta_L \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_l \\ \varepsilon_L \end{pmatrix}$$

Or as,

$$\mathbf{Y = X\beta + \varepsilon}$$

where $\boldsymbol{\beta}$ is a vector of weights which describe the linear relationship between each explanatory variable and the response (dependent) variable. $\boldsymbol{\beta}$ is estimated using the method of least squares such that:

$$\hat{\beta} = \mathbf{(X'X)^{-1}X'Y}$$

The explanatory variables (X) can be explanatory variables (e.g. patient group) or covariates (e.g. height, sex etc). The vectors β and ε are not known from the data, and so must first be estimated using the least squares approach. Once these parameters have been determined, the significance of β can be determined for each explanatory variable using the matrix of residuals. Where β is significant, then the explanatory variable to which it corresponds could be said to be significantly associated with GM density at that voxel. Pairwise between-group comparisons were made using t-contrasts

4.17.7 Gaussian random fields

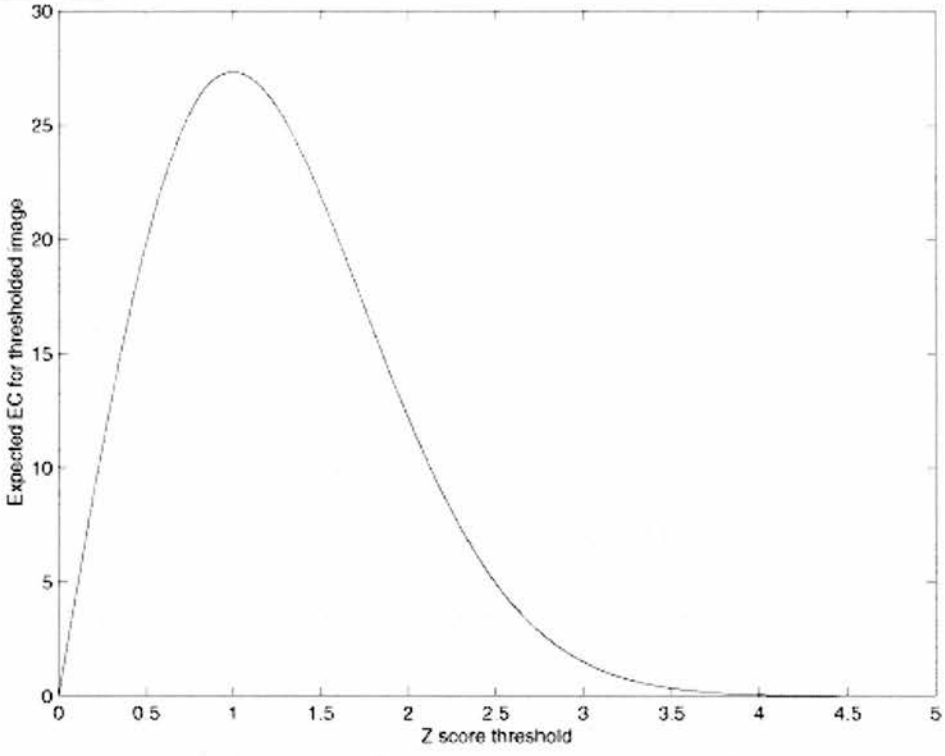
When an entire brain is imaged, the number of possible statistical tests conducted means that a proportion of statistical tests could be significant by chance alone. A

conventional method of correcting for multiple tests is the Bonferroni correction, whereby the probability of observing at least one significant test given that there is no overall difference between the groups is calculated. In order to use this correction, each observation is usually assumed to be independent under the null hypothesis. As regions of the brain are known to be integrated with one another, this is not a safe assumption. An alternative approach to the problem uses the principal of Gaussian random fields.

In order to correct for the multiple hypothesis tests conducted by SPM, firstly, the number of 'resolution elements' (RESELS) within an image is determined. Secondly, the expected Euler Characteristic (EC) of the image is calculated. For any statistical parametric map, the image generated can be thought of as the graphical representation of peaks of difference between one group and another. Each peak is measured in standard deviation units (Z scores). If an image is *'thresholded'* at Z=2.75, then all peaks of Z=2.75 or less are effectively set to zero. By setting the threshold higher, we will remove more peaks and the results obtained will be less likely to represent false positives. An inevitable consequence however, is that significant areas of difference (true positives) are removed erroneously.

The Euler Characteristic is the expected number of regions of difference in an image at a given threshold. As the Z score threshold is raised, the expected EC approaches zero and provides an approximate measure of observing one or more regions of difference at that threshold. For example, if we set a threshold of Z=x so that the expected EC is 0.05, then any regions of difference remaining will have a probability of occurring by chance of p=0.05 or less.

Figure 4.17.7: Expected Euler Characteristic for a smoothed image with 256 RESELS



Regions of significant difference between groups were projected onto a glass brain. Regions of significant difference were reported if the p-value (corrected, voxel level) ≤ 0.1 (trend) or ≤ 0.05 (significant).

In addition to the voxel-wise analysis of the whole brain, further specific hypotheses were tested using a small volume correction. A small volume correction adjusts for the number of false positives expected in an image over a pre-specified volume of interest. Because the volume of interest is smaller, the correction for multiple hypotheses is less severe, being based on a smaller number of individual comparisons. Each region of interest hypothesised to differ was traced onto a single image of the brain and used as a small volume correction. Brain regions hypothesised to differ between

schizophrenia and bipolar disorder in terms of grey matter density were contrasted between groups as before. Throughout all statistical analyses, age sex, handedness and height were included as covariates (nuisance covariates in the language of SPM).

The actual grey matter SVC image used in the study was constructed from the averaged scan of all 192 images. The thalamus and both amygdala-hippocampal complexes were traced on the image and the values of voxels outside this region set to zero. The image was then smoothed using an 8mm FWHM kernel used in the subsequent analyses to define a generous region encompassing thalamus and both amygdala-hippocampal complexes. The SVC image consisted of 12.3 RESSLS in total.

After the grey matter analysis was completed, analysis of white matter density was conducted using the white-matter optimised study-specific template and a small volume correction image. Further details of the small volume correction used and the contrasts performed are given in chapter 6.

4.17.8 Planned image analyses

Six broad groups of voxel based analyses were conducted (see table 4.17.8). Firstly, each patient group was compared to control subjects in order to examine grey matter differences contingent upon disease and genetic liability. Secondly, patients were compared to the appropriate relative group in order to examine differences contingent upon disease expression only. Thirdly, comparisons were made between patents groups directly. However, it was anticipated that the variance estimates might be greater for these comparisons since two diseased groups were being compared with one another. In conventional statistical analyses, it would be possible to test this possibility by plotting

residual values in each group, and also by plotting residuals against fitted values. In cases where the group variances were unequal, it would then be possible to conduct an analysis using a (Scatterthwaite) correction. To the knowledge of the investigators, neither solution is a possibility within SPM99. Therefore, a second analysis was conducted to maximise the precision of between patient comparisons. The control-patient comparisons were masked using the other control-patient contrasts. Hence differences between schizophrenic patients and controls not found in bipolar patients versus controls could be calculated using larger sample sizes and hence greater power and precision.

Table 4.17.8: Planned group wise analyses of grey matter density

	Comparison	**Explanation**
Patients vs. controls contrast	CTR-SCZ CTR-BPD CTR-MIX All contrasts were 2-sided	Examines differences contingent upon both disease and genetic liability
Patients versus patients	BPD-SCZ MIX-SCZ MIX-BPD All contrasts were 2-sided	Examines disease specificity
Changes in schizophrenic vs. controls families not found in bipolars vs. controls	**Contrast** **Mask** CTR-SCZ CTR-BPD CTR-SCZ CTR-MIX Contrasts were one-sided only in the direction specified	Examines disease specificity maximising precision by including control group in each contrast
Patients versus relatives	uSCZ-SCZ uBPD-BPD MIX-uMIX All contrasts were 2-sided	Examines differences contingent on *disease* between 2 groups both of which are at increased genetic liability
Relatives versus controls	CTR-uSCZ CTR-uMIX CTR-uBPD All contrasts were 2-sided	Examines differences contingent upon genetic liability

Abbreviations

Patients:SCZ: schizophrenic, BPD: bipolar from bipolar family, MIX: bipolar from mixed family
Relatives:uSCZ: schizophrenic family, uBPD: bipolar family, uMIX: mixed family

In addition, an analysis of white matter density was also conducted. Any significant differences in grey matter density were related to white matter density in associated tracts or subgyral areas. The results of the imaging analyses are given in chapter 6.

Chapter 5: Clinical & Neuropsychological Results

5.1 Introduction

5.2 Flow of patients through the study

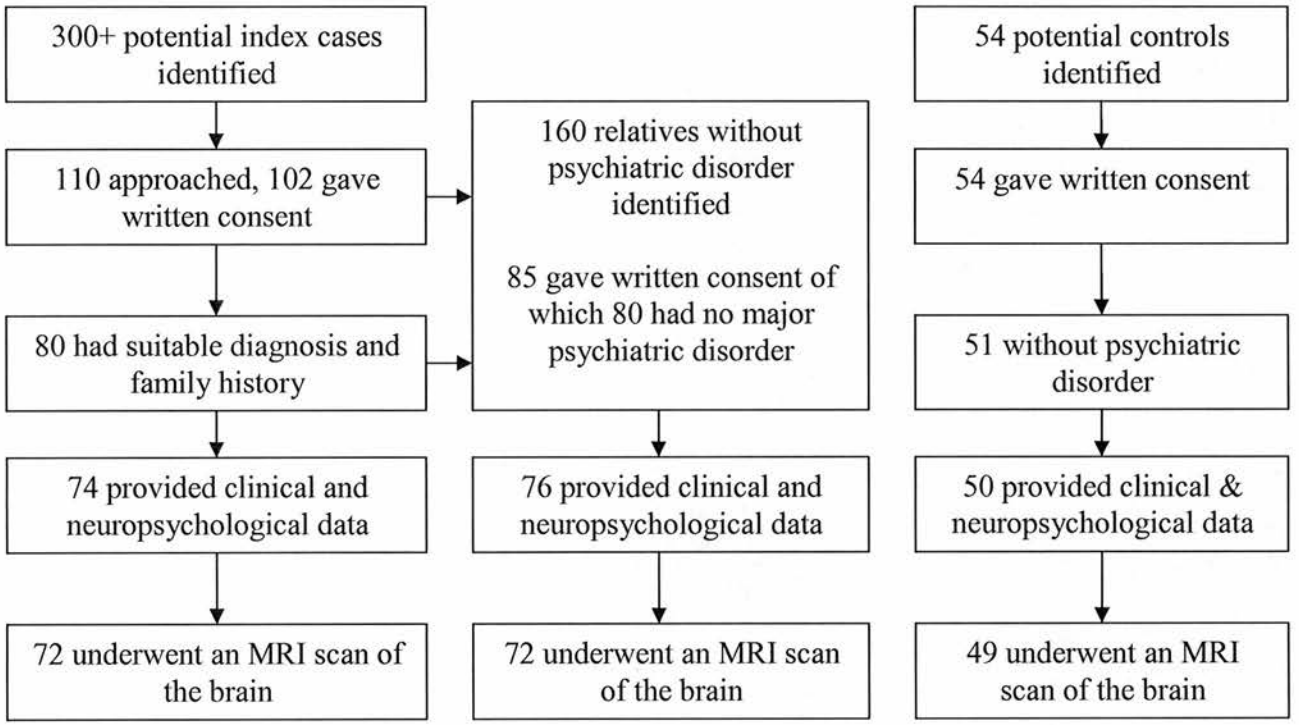
Over 300 patients with a clinical diagnosis corresponding to either schizophrenia or bipolar disorder were identified from the case loads of consultants across Edinburgh, the Lothians and Fife. All potential subjects were also believed to have a family history of either schizophrenia or affective disorder. One hundred and ten subjects were approached of which 102 gave their consent to undergo the Present State Examination (PSE) and for their case notes to be retrieved. On the basis of combined information from the PSE and case notes, 80 subjects met study inclusion criteria and 74 provided complete clinical data and near complete neuropsychological data. Incomplete neuropsychological data was obtained on three subjects because of equipment failure in two cases or because subjects had to leave the testing earlier than expected because of other commitments. Seventy-two patients also underwent complete MRI scan of the brain, although one patient left the scanner due to anxiety and one further scan was reported as abnormal (neurodevelopmental cyst).

A further 160 apparently unaffected close family members were identified from the families of eligible patients meeting study inclusion criteria. In each case, the unaffected relative belonged to one of the predefined groups described in the methods section. Eighty-five relatives gave consent and underwent a semi-structured interview about previous psychiatric problems using the PSE. This data set was supplemented with other information about psychiatric treatment obtained from the subjects themselves. On the basis of this information, 80 subjects met study inclusion

criteria of which 76 provided complete clinical data and near complete neuropsychological data and 72 underwent an MRI scan of the brain.

Fifty-four potential control subjects were identified through the social networks of the patients themselves, through adverts placed on notice boards at local leisure centres and through the social networks of previously recruited controls. All 54 controls gave consent to be interviewed and all completed a semi-structured interview using the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L, Endicott and Spitzer 1978). Three controls were excluded because of a history of previous psychiatric disorder (one with anorexia nervosa and two with a major depressive episode). 50 controls provided near complete neuropsychological data and all but one control subject underwent a complete MRI scan of the brain. The one subject who did not provide neuroimaging data could not tolerate the relatively confined space of the scanner itself. The flow of participants through the study is shown in the following figure.

Figure 5.2 Flow of participants through the study



5.3 Comparison of data from the Present State Examination

All patients and healthy relatives underwent the PSE version 9 to ensure they met eligibility criteria and to ascertain their current symptom profile. Complete information was obtained for all subjects. All patients and relatives were classified according to 4 levels of increasing psychopathology (see previous chapter): a) none, b) one or more affective or behavioural symptoms, c) one or more partially rated psychotic symptoms and d) one or more fully rated psychotic symptoms. The results are shown in table 5.3 below.

Table 5.3: Summary of psychopathological status of patients and well relatives

		Psychopathological category			
		No symptoms	1+ Affective / behavioural symptoms	1+ Partial psychotic symptoms	1+ Psychotic symptoms
SCZ from SCZ family	N	0	8	3	16
	%	0%	29.6%	11.1%	59.3%
OK from SCZ family	N	5	14	6	0
	%	20%	56%	24%	0%
BPD from BPD family	N	3	12	8	4
	%	11.1%	44.4%	29.6%	14.8%
OK from BPD family	N	3	13	8	0
	%	12.5%	54.2%	33.3%	0%
BPD from Mixed family	N	0	7	10	3
	%	0%	35%	50%	15%
OK from Mixed family	N	7	13	7	0
	%	25.9%	48.1%	25.9%	0%

Although all patients were deemed not to be in need of inpatient care by their treating clinicians, there were significant levels of psychopathology in all patient groups. Schizophrenic patients had the highest levels of psychopathology with many (59.3%) displaying one or more fully rated psychotic symptoms. Subjects with bipolar disorder from mixed and bipolar families had lower levels of psychopathology than that

displayed by the subjects with schizophrenia. None of the well relatives displayed any fully rated psychotic symptoms, although partial symptoms were relatively common with a rate of around 25%. Partial symptoms elicited consisted mostly of minor complaints which were not disclosed, except on direct questioning. Most would not be regarded as clinically significant.

5.4 Description of OPCRIT data

Complete case note data was available for all affected patients in the present study. This was supplemented with data obtained from structured interview (PSE) and combined to produce a data set of all recorded symptoms according to the OPCRIT scheme.

Of primary interest was the frequency with which psychotic symptoms were experienced by each group. All schizophrenic patients had been deluded in the course of their illness compared to 24/27 bipolar patients from families affected by bipolar disorder only and 17/20 bipolar patients from mixed families. No additional subjects were identified who had hallucinations but not delusions. Duration of illness was estimated from current age at interview minus the age of first psychiatric contact. This was similar for schizophrenics (mean=15.8 years, SD=11.4), bipolars from mixed families (mean=15.7 years, SD=10.5) and bipolars from bipolar families (mean=16.2 years, SD=9.2).

5.5 Comparison of demographic data

5.5.1 Age and gender

The groups spanned a 7 year interval in terms of mean age, with unaffected people from bipolar families having the lowest mean age (33.5 years) and bipolar subjects from mixed families having the greatest (40.5). Unaffected individuals from bipolar families also had the lowest proportion of males (36%) compared to other groups. Bipolar subjects from mixed families had the greatest proportion of males at 65%.

Table 5.5.1: Age and gender by group

Group	**Age** Mean (SD)	**Male** N (%)	**Female** N (%)
Control	35.5 (11.2)	23 (46)	27 (54)
SCZ from SCZ family	37.6 (14.0)	13 (48.1)	14 (51.9)
OK from SCZ family	38.8 (12.6)	11 (44)	14 (56)
BPD from BPD family	40.3 (11.9)	14 (51.9)	13 (48.1)
OK from BPD family	33.5 (12.8)	9 (35.5)	15 (62.5)
BPD from mixed family	40.5 (9.6)	7 (35.0)	13 (65.0)
OK from mixed family	34.4 (12.8)	14 (51.9)	13 (48.1)
Total	37.0 (12.2)	91 (45.5)	109 (54.5)

5.5.2 Marital status

Marital status differed widely between groups, with the schizophrenic group having the greatest proportion of single (81.5%) participants. The other groups were approximately equal in terms of the ratio of married to single people and the numbers of

divorced participants were not sufficiently frequent to make meaningful comparisons between the groups.

Table 5.5.2: Marital status of participants by group

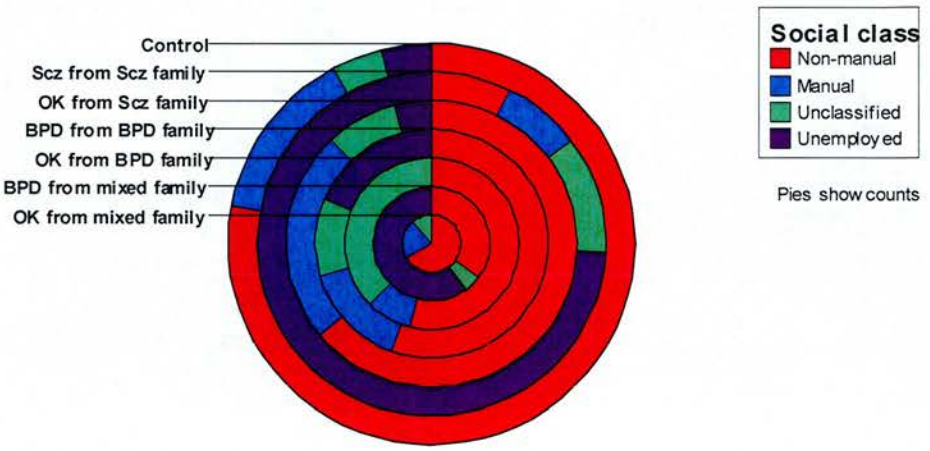
		Marital Status			
		Married	Single	Divorced	Total
Control	N	22	23	5	50
	%	44.0%	46.0%	10.0%	100.0%
Scz from Scz family	N	3	22	2	27
	%	11.1%	81.5%	7.4%	100.0%
OK from Scz family	N	13	11	1	25
	%	52.0%	44.0%	4.0%	100.0%
BPD from BPD family	N	11	13	3	27
	%	40.7%	48.1%	11.1%	100.0%
OK from BPD family	N	10	12	2	24
	%	41.7%	50.0%	8.3%	100.0%
BPD from mixed family	N	5	11	4	20
	%	25.0%	55.0%	20.0%	100.0%
OK from mixed family	N	14	13	0	27
	%	51.9%	48.1%	.0%	100.0%
Total	N	78	105	17	200
	%	39.0%	52.5%	8.5%	100.0%

5.5.3 Personal and paternal socio-economic atatus

Socio-economic status differed greatly between the groups. The pattern of impairment was somewhat as expected: schizophrenic patients showed the greatest socio-economic disadvantage (74.1% unemployed) followed by bipolar patients from mixed families and bipolar patients from bipolar families in order. Controls were, as expected, the least socially disadvantaged in terms of the proportions in non-manual employment, although were similar to the unaffected relatives in terms of the proportion who were unemployed. With the exception of the healthy relatives from mixed families,

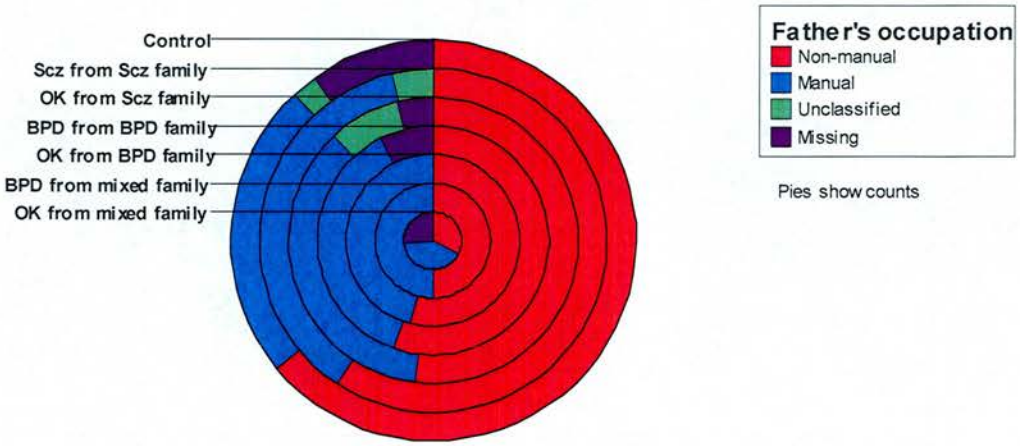
paternal socio-economic status was more similar between the groups. Unaffected relatives from mixed families had higher levels of missing data and lower levels of non-manual employment than all of the other groups.

Figure and table 5.5.3.1: Clustered pie chart and table of socio-economic status by group



		Social class				
		Non-manual	Manual	Unclassified	Unemployed	Total
Control	N	39	7	2	2	50
	%	78.0%	14.0%	4.0%	4.0%	100.0%
Scz from Scz family	N	2	2	3	20	27
	%	7.4%	7.4%	11.1%	74.1%	100.0%
OK from Scz family	N	16	6	2	1	25
	%	64.0%	24.0%	8.0%	4.0%	100.0%
BPD from BPD family	N	15	4	3	5	27
	%	55.6%	14.8%	11.1%	18.5%	100.0%
OK from BPD family	N	13	2	9	0	24
	%	54.2%	8.3%	37.5%	.0%	100.0%
BPD from mixed family	N	7	0	1	12	20
	%	35.0%	.0%	5.0%	60.0%	100.0%
OK from mixed family	N	18	6	3	0	27
	%	66.7%	22.2%	11.1%	.0%	100.0%
Total	N	110	27	23	40	200
	%	55.0%	13.5%	11.5%	20.0%	100.0%

Figure and table 5.5.3.2: Clustered pie chart and table of paternal socio-economic status by group



		Fathers social status				Total
		Non-manual	Manual	Unclassified	Missing	
Control	N	32	12	1	5	50
	%	64.0%	24.0%	2.0%	10.0%	100.0%
Scz from Scz family	N	16	10	1	0	27
	%	59.3%	37.0%	3.7%	.0%	100.0%
OK from Scz family	N	13	9	2	1	25
	%	52.0%	36.0%	8.0%	4.0%	100.0%
BPD from BPD family	N	15	10	0	2	27
	%	55.6%	37.0%	.0%	7.4%	100.0%
OK from BPD family	N	13	11	0	0	24
	%	54.2%	45.8%	.0%	.0%	100.0%
BPD from mixed family	N	10	10	0	0	20
	%	50.0%	50.0%	.0%	.0%	100.0%
OK from mixed family	N	9	11	0	7	27
	%	33.3%	40.7%	.0%	25.9%	100.0%
Total	N	108	73	4	15	200
	%	54.0%	36.5%	2.0%	7.5%	100.0%

5.5.4 Alcohol, substance and cigarette history

Within the sample, all groups were similarly balanced in terms of the number of units of alcohol consumed per week, and also in the number of units consumed in the 24hrs preceding their neuropsychological assessment. There was evidence of greater weekly alcohol consumption (mean 12.8u) and variability (SD=29.6) of alcohol intake within bipolar subjects from mixed families. Daily cigarette consumption was higher in affected patients than in either relatives or controls. Schizophrenic patients smoked the most and bipolar subjects from mixed and bipolar families smoked smaller quantities of tobacco which were only slightly greater than control subjects.

Table 5.5.3.1: Alcohol consumption and cigarette usage

Group		Statistic		
		Alcohol yesterday (U)	Alcohol per week (U)	Cigarettes per day
Control	Mean	1.43	11.53	3.73
	SD	2.481	9.226	7.590
Scz from Scz family	Mean	.65	5.46	19.15
	SD	1.917	10.069	17.066
OK from Scz family	Mean	2.01	9.08	5.33
	SD	4.787	8.861	10.025
BPD from BPD family	Mean	1.19	8.15	10.08
	SD	2.530	14.201	17.228
OK from BPD family	Mean	1.38	10.54	5.13
	SD	2.356	8.708	7.303
BPD from mixed family	Mean	1.05	12.80	9.20
	SD	3.137	29.643	12.493
OK from mixed family	Mean	1.28	14.43	2.91
	SD	2.300	13.993	5.316

Just over 50% of the sample reported using cannabis at some point in their lives. Current use was described in 11.1% of schizophrenic subjects, 18.5% of bipolar subjects from bipolar families and 10% of bipolar subjects from mixed families. Controls and relatives smoked less cannabis than patients with the exception of the healthy relatives of bipolar patients in whom a 20.8% rate of current use was recorded. The proportion describing past regular cannabis use was more closely matched between the groups (max=29.6%, min=18%).

Table 5.5.4.2: Cannabis use

		Cannabis				
		Never used	Once or twice	Past regular use	Current regular use	Total
Control	N	32	6	9	3	50
	%	64.0%	12.0%	18.0%	6.0%	100.0%
Scz from Scz family	N	16	0	8	3	27
	%	59.3%	.0%	29.6%	11.1%	100.0%
OK from Scz family	N	20	0	5	0	25
	%	80.0%	.0%	20.0%	.0%	100.0%
BPD from BPD family	N	11	5	6	5	27
	%	40.7%	18.5%	22.2%	18.5%	100.0%
OK from BPD family	N	9	4	6	5	24
	%	37.5%	16.7%	25.0%	20.8%	100.0%
BPD from mixed family	N	11	3	4	2	20
	%	55.0%	15.0%	20.0%	10.0%	100.0%
OK from mixed family	N	13	5	6	3	27
	%	48.1%	18.5%	22.2%	11.1%	100.0%
Total	N	112	23	44	21	200
	%	56.0%	11.5%	22.0%	10.5%	100.0%

Occasional use of 'ecstasy', heroin or amphetamine was disclosed by study participants. However, less than five people reported using these drugs overall and the numbers are too small to make any reasonable conclusions regarding between group differences.

5.5.5 Weight and height measurement

All groups were closely balanced in terms of height, weight and body mass index (see following table). Bipolar subjects from mixed families had the highest weight and BMI compared to the other groups.

Table 5.5.5: Height, weight and body mass index (BMI)

Group		Height in metres	Weight in kilograms	Body Mass Index
Control	Mean	1.72	72.90	24.31
	SD	.10	16.16	3.50
Scz from Scz family	Mean	1.70	76.93	26.69
	SD	.08	18.34	5.91
OK from Scz family	Mean	1.67	70.39	25.55
	SD	.07	13.91	5.17
BPD from BPD family	Mean	1.69	74.65	25.93
	SD	.11	17.93	5.61
OK from BPD family	Mean	1.70	66.93	23.08
	SD	.10	13.94	4.80
BPD from mixed family	Mean	1.69	80.08	27.83
	SD	.08	22.64	7.00
OK from mixed family	Mean	1.71	73.32	25.03
	SD	.10	16.81	4.72
Total	Mean	1.70	73.36	25.30
	SD	.10	17.13	5.21

5.5.6 Handedness

Left hand preference for writing was greatest in healthy people from schizophrenic families (20%). Healthy people from schizophrenic families and bipolars from bipolar families also had higher levels of left handedness than the other groups, although no participants in the bipolar group from mixed families who expressed a left

handed preference for writing (see table 5.5.6). For the sample as a whole, 91.5% of people stated that they used their right hand exclusively for writing.

Table 5.5.6 Handedness by group

		Handedness		
		R	L	Total
Control	N	47	3	50
	%	94.0%	6.0%	100.0%
Scz from Scz family	N	24	3	27
	%	88.9%	11.1%	100.0%
OK from Scz family	N	20	5	25
	%	80.0%	20.0%	100.0%
BPD from BPD family	N	24	3	27
	%	88.9%	11.1%	100.0%
OK from BPD family	N	23	1	24
	%	95.8%	4.2%	100.0%
BPD from mixed family	N	20	0	20
	%	100.0%	.0%	100.0%
OK from mixed family	N	25	2	27
	%	92.6%	7.4%	100.0%
Total	N	183	17	200
	%	91.5%	8.5%	100.0%

5.5.7 Educational history

The educational histories of the study groups differed widely. Patients with schizophrenia were the least likely to have studied beyond compulsory education, followed in turn by their well relatives, bipolars from mixed families and healthy subjects from mixed families. Bipolar patients and their well relatives had similar rates of continuing past the compulsory leaving age at around 27%. Controls were the most likely to continue past the compulsory school leaving age.

Table 5.5.7: Educational history

		Years of Full-time Education			
		Compulsory or less	More than compulsory only	Unclear or missing	Total
Control	N	8	39	3	50
	%	16.0%	78.0%	6.0%	100.0%
Scz from Scz family	N	17	10	0	27
	%	63.0%	37.0%	.0%	100.0%
OK from Scz family	N	13	11	1	25
	%	52.0%	44.0%	4.0%	100.0%
BPD from BPD family	N	7	20	0	27
	%	25.9%	74.1%	.0%	100.0%
OK from BPD family	N	7	17	0	24
	%	29.2%	70.8%	.0%	100.0%
BPD from mixed family	N	8	12	0	20
	%	40.0%	60.0%	.0%	100.0%
OK from mixed family	N	9	13	5	27
	%	33.3%	48.1%	18.5%	100.0%
Total	N	69	122	9	200
	%	34.5%	61.0%	4.5%	100.0%

5.5.8 Current medication

Data was collected on antipsychotics, lithium, antidepressants, anticonvulsants and antimuscarinic drugs. Controls were receiving no psychotropic medication from any category. Relatives of affected patients reported antidepressant use, though the rates of current prescription were low in all unaffected relative groups and were not associated with a major depressive episode. In most cases the prescription of antidepressants appeared to be associated with bereavement, isolated insomnia or anxiety. All affected patient groups reported extensive psychotropic medication use which is described in the following table. Antipsychotics (conventional and atypical) were most commonly

prescribed in the schizophrenic group, whereas anticonvulsants and lithium were more common in the bipolar subjects (table 5.5.8.1).

Table 5.5.8.1: Current medication status

Drug	Group						
	1	2	3	4	5	6	7
Antidepressant N (%)	0 (0)	5 (18.5)	1 (3.6)	10 (38.5)	2 (8)	7 (33.3)	1 (4.2)
Benzodiazepine N (%)	0 (0)	7 (25.9)	0 (0)	3 (11.5)	1 (4)	2 (9.5)	0 (0)
Antipsychotic N (%)	0 (0)	12 (44.4)	0 (0)	8 (29.6)	0 (0)	4 (20)	1 (3.7)
Atypical N (%)	0 (0)	13 (48.1)	0 (0)	3 (11.5)	0 (0)	7 (33.3)	0 (0)
Lithium N (%)	0 (0)	0 (0)	0 (0)	12 (46.2)	0 (0)	7 (33.3)	0 (0)
Anticonvulsant N (%)	0 (0)	1 (3.7)	0 (0)	9 (34.6)	0 (0)	6 (28.6)	0 (0)
Antimuscarinic N (%)	0 (0)	5 (18.5)	0 (0)	1 (3.8)	0 (0)	0 (0)	0 (0)

Key

1	Controls
2	Schizophrenic subjects from schizophrenic families
3	Unaffected from schizophrenic families
4	Bipolar subjects from bipolar families
5	Unaffected from bipolar families
6	Bipolar subjects from mixed families
7	Unaffected from mixed families

Table 5.5.8.2: Conventional antipsychotic and lithium doses

Group		Medication	
		Dose of lithium	Dose of antipsychotic
Scz from Scz family	Mean	.00	171.538
	Median	.00	.000
	Std. Deviation	.00	321.3060
	Interquartile Range	.00	200.000
BPD from BPD family	Mean	433.3333	37.037
	Median	.0000	.000
	Std. Deviation	538.51648	77.9455
	Interquartile Range	800.0000	.000
BPD from mixed family	Mean	173.6842	21.947
	Median	.0000	.000
	Std. Deviation	339.67649	64.3933
	Interquartile Range	100.0000	.000

5.6 Comparison of clinical data collected on all subjects

5.6.1 Clinical rating scales

Complete rating scale data was obtained for all subjects and controls. Positive symptoms were measured using the PANSS positive subscale, which has a minimum score of 7 when no positive symptoms are present rising to a possible maximum score of 49. All groups had relatively low positive subscale with higher scores being found in the patients. Depressive symptoms were measured using the Hamilton Depression Rating Scale (HDRS) which has a minimum score of 0 and a maximum of 66. Again, all groups scored closer to the lower end of the scale, although schizophrenics had the highest scores, followed in turn by bipolars from mixed families and bipolars from bipolar families. Mania was measured using the Young Mania rating Scale (minimum possible=0 maximum possible=60) and no group had a median score or greater than 5 or a mean greater than 6.

The results of the clinical rating scales are shown in the following table (table 5.6.1), along with the results of the PANSS negative and general psychopathology subscales. The primary purpose of collecting data on positive symptoms, depression and mania was to correct for the effect of current symptoms on the results of subsequent neuropsychological assessments. In order to do this effectively, data were collected on three relatively uncorrelated dimensions of psychopathology. The results of the general psychopathology subscale and negative subscales were not used to adjust for symptoms since they contain items which have counterparts within either the HDRS or YMRS.

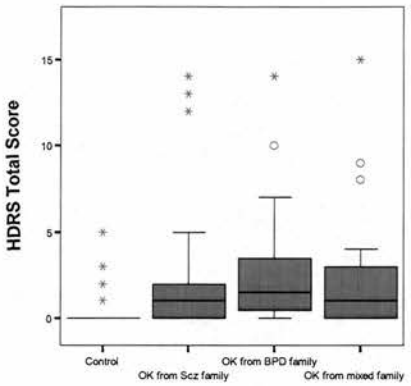
Table 5.6.1: Rating scale assessments

Group		Statistic				
		PTOTAL	NTOTAL	GENTOTAL	HAMTOT	YMRSTOT
Control	Mean	7.04	7.04	16.32	.46	.16
	Median	7.00	7.00	16.00	.00	.00
	SD	.198	.198	.768	1.034	.468
	IQR	.00	.00	.00	.00	.00
Scz from Scz family	Mean	12.22	12.41	26.70	11.22	5.74
	Median	12.00	11.00	27.00	10.00	3.00
	SD	4.458	4.466	7.645	8.959	5.096
	IQR	7.00	6.00	10.00	12.00	8.00
OK from Scz family	Mean	7.16	7.28	17.80	2.64	.40
	Median	7.00	7.00	17.00	1.00	.00
	SD	.624	.542	2.449	4.122	1.000
	IQR	.00	.50	3.00	2.50	.00
BPD from BPD family	Mean	9.56	8.41	22.63	7.33	4.19
	Median	8.00	8.00	21.00	5.00	2.00
	SD	2.847	3.104	6.103	7.312	5.485
	IQR	5.00	1.00	10.00	9.00	8.00
OK from BPD family	Mean	7.63	7.63	18.13	2.92	.79
	Median	7.00	8.00	17.00	1.50	.00
	SD	.970	.576	2.909	3.775	1.503
	IQR	1.00	1.00	3.00	3.50	1.00
BPD from mixed family	Mean	9.95	8.05	22.95	10.30	5.55
	Median	8.00	7.00	22.00	7.00	4.50
	SD	3.561	1.572	4.817	8.578	6.236
	IQR	5.75	2.50	5.25	14.25	6.50
OK from mixed family	Mean	7.04	7.15	17.26	2.33	.59
	Median	7.00	7.00	17.00	1.00	.00
	SD	1.556	1.680	4.311	3.464	1.394
	IQR	.00	1.00	3.00	3.00	.00

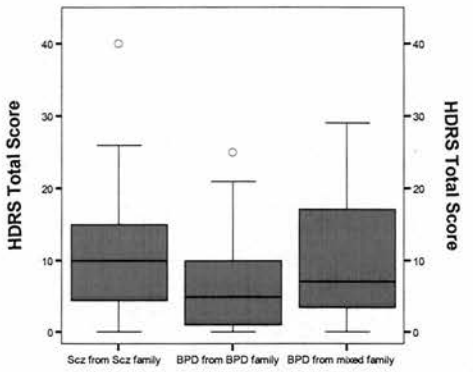
Key to table	
PTOT	PANSS positive symptoms total
NTOT	PANSS negative symptoms total
GENTOT	PANSS general symptoms total
HAMTOT	HDRS total score
YMRSTOT	YMRS total score

Figure 5.6.1: Box and whisker plots of rating scale assessments

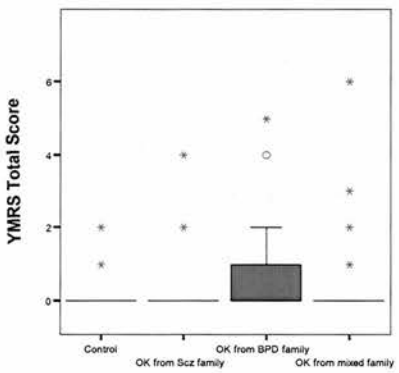
HDRS Scores for Unaffected Subjects



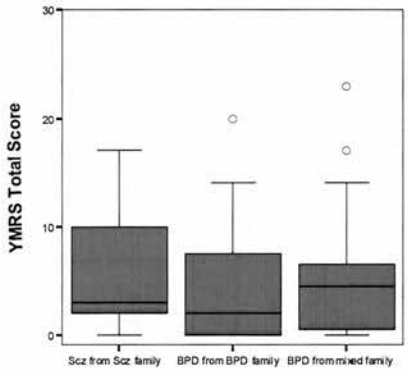
HDRS Scores for Affected Subjects



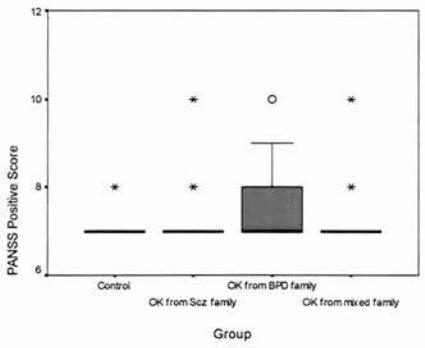
YMRS Scores for Unaffected Subjects



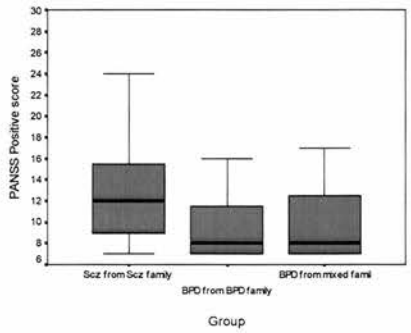
YMRS Scores for Affected Subjects



PANSS Positive Scores for Unaffected Subjects



PANSS Positive Scores for Affected Subjects



5.6.2 Measurement of genetic liability

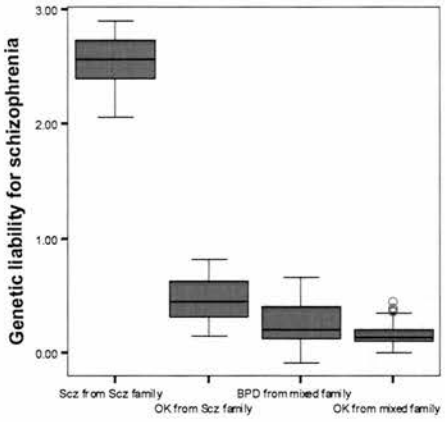
Genetic liability was calculated for all subjects affected by mental illness, and their well relatives. Genetic liability was approximately normally distributed in each group. As expected, patients with schizophrenia had the highest genetic liability for schizophrenia followed in order by unaffected people from schizophrenic families, bipolar patients from mixed families and finally unaffected subjects from mixed families. Genetic liability for bipolar disorder was highest in bipolar subjects from bipolar families followed in order by bipolar subjects from mixed families, unaffected subjects from bipolar families and finally unaffected subjects from mixed families.

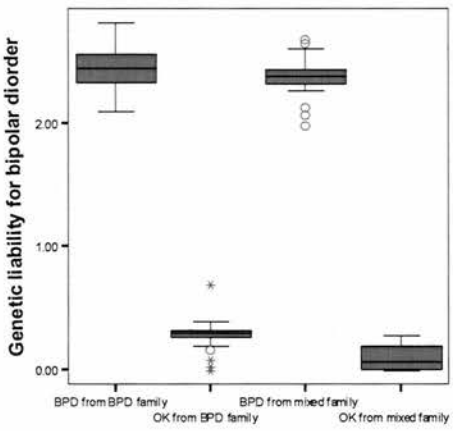
Table 5.6.2: Genetic liabilities by group

	Group		Value
Genetic liability for schizophrenia	SCZ from SCZ family	Mean	2.55
		SD	.23
	OK from SCZ family	Mean	.46
		SD	.20
	BPD from mixed family	Mean	.25
		SD	.19
	OK from mixed family	Mean	.17
		SD	.13
Genetic liability for bipolar disorder	BPD from BPD family	Mean	2.45
		SD	.19
	OK from BPD family	Mean	.28
		SD	.14
	BPD from mixed family	Mean	2.37
		SD	.18
	OK from mixed family	Mean	.09
		SD	.11

Figure 5.6.2 showing box and whisker plots of genetic liabilities to schizophrenia and bipolar disorder

Genetic liability to schizophrenia **Genetic liability to bipolar disorder**





5.7 Neuropsychological results

More than 90% of the sample provided complete data from all neuropsychological assessments. The results are given in the following sections, categorised by domain of neuropsychological function.

5.7.1 Intellectual function

On measures of intellectual function (NART FSIQ, WASI VIQ, PIQ and FSIQ), there was evidence from mixed model MANCOVA (with HDRS, YMRS and PANSS positive as covariates) that the groups differed significantly in terms of these measures ($F_{20,203}$=2.02, $p<0.01$). Individual pairwise effects were subsequently estimated using a multilevel model and 'pedigree' as a random factor. The results of the analyses

conducted are given in the following pages according to the domain of intellectual function affected.

Table 5.7.1: Mean intellectual function by group

Group		NART FSIQ	WASI FSIQ	WASI PIQ	WASI VBIQ
Control	Mean	110.8	114.0	113.5	111.2
	SD	8.5	13.3	13.1	12.9
Scz from Scz family	Mean	101.3	90.0	87.9	94.0
	SD	12.6	14.2	16.2	14.9
OK from Scz family	Mean	101.2	99.0	98.7	99.7
	SD	9.6	12.1	15.0	11.7
BPD from BPD family	Mean	111.5	106.7	102.0	109.9
	SD	10.9	13.3	13.6	13.1
OK from BPD family	Mean	104.4	105.3	104.1	105.4
	SD	11.1	12.1	14.2	12.2
BPD from mixed family	Mean	105.9	101.6	99.0	103.4
	SD	10.8	16.2	14.9	15.4
OK from mixed family	Mean	104.7	104.6	102.8	105.7
	SD	10.0	14.4	14.9	14.4

5.7.1.1 NART FSIQ

NART full scale IQ differed significantly between the groups ($F_{6,65}$=3.12, p=0.01). Schizophrenic subjects and unaffected subjects from schizophrenic families had significantly lower NART IQ's compared to healthy controls. Schizophrenic subjects also had significantly lower IQs compared to bipolar subjects and bipolar subjects had significantly higher NART IQs than their unaffected relatives. Overall, the results suggest that NART IQ is impaired in relationship to both the liability, and expression of schizophrenia. Neither the expression nor liability to bipolar disorder appeared to convey intellectual disadvantage.

Figure 5.7.1.1: Means and crude 95% confidence intervals for NART full scale IQ

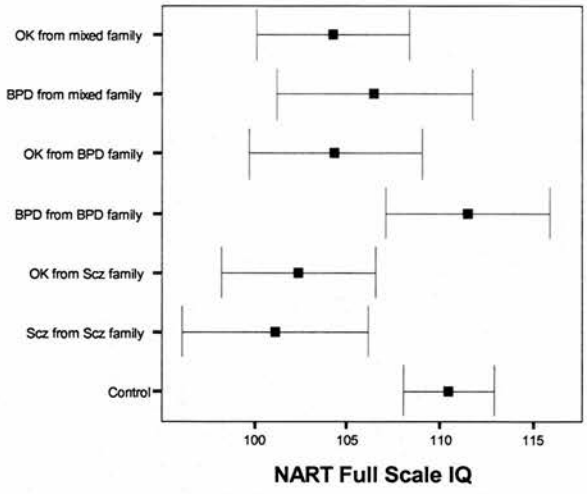


Table 5.7.2.2 Estimates of pairwise differences in NART FSIQ

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	8.85	2.83	2.61	15.08
Controls - Bipolars from Bipolar Families	-1.42	-0.50	-7.04	4.20
Controls - Bipolars from Mixed Families	4.04	1.28	-2.26	10.34
Controls - Unaffected from Schizophrenic Families	6.30	2.34	0.92	11.68
Controls - Unaffected from Bipolar Families	3.78	1.30	-2.04	9.60
Controls - Unaffected from Mixed Families	6.04	2.23	0.62	11.45
Schizophrenics - Unaffected from Schizophrenic Families	-2.54	-0.79	-9.00	3.91
Schizophrenics - Bipolars from Bipolar Families	-10.27	-3.31	-16.45	-4.08
Schizophrenics - Bipolars from Mixed Families	-4.80	-1.47	-11.33	1.72
Bipolars From Bipolar Families - Bipolars From Mixed Families	5.46	1.69	-0.99	11.91
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-7.72	-2.40	-14.13	-1.31
Bipolars From Mixed Families - Unaffected From Mixed Families	1.99	0.60	-4.68	8.67
Unaffected From Bipolar Families - Unaffected From Mixed Families	2.26	0.67	-4.48	8.99
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-2.52	-0.75	-9.21	4.16
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-0.27	-0.08	-6.60	6.07

5.7.1.2 WASI FSIQ

WASI full scale IQ differed significantly between the groups ($F_{6,64}$=6.42, $p<0.0001$). Schizophrenic subjects, bipolar subjects from mixed families and unaffected relatives from schizophrenic families had significantly lower WASI FSIQ's than healthy controls. A trend was also observed which indicated lower WASI FSIQ in the unaffected subjects from mixed families ($p=0.07$) compared to controls. Schizophrenic subjects also had significantly lower IQs than bipolar subjects from either bipolar or mixed families and indeed from their own healthy relatives.

Overall, the results suggest that WASI FSIQ is impaired in relationship to both the liability to, and expression of schizophrenia. Neither the expression nor liability to bipolar disorder appeared to covey an intellectual disadvantage.

Figure 5.7.1.2: Means and crude 95% confidence intervals for WASI full scale IQ

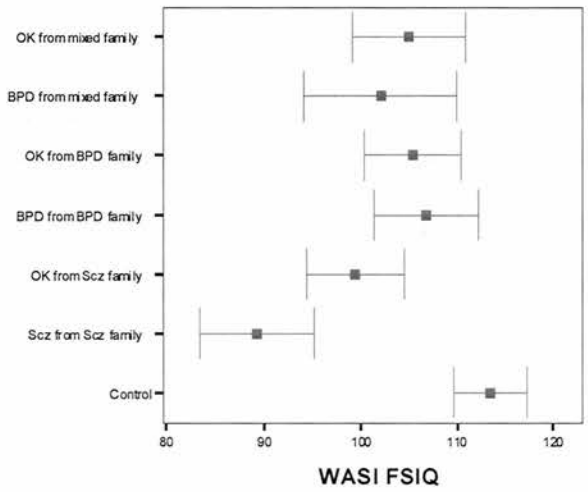


Table 5.7.1.2: Estimates of pairwise differences in WASI FSIQ

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	24.31	6.02	16.25	32.38
Controls - Bipolars from Bipolar Families	5.92	1.55	-1.71	13.55
Controls - Bipolars from Mixed Families	11.15	2.73	3.00	19.30
Controls - Unaffected from Schizophrenic Families	10.22	2.77	2.84	17.60
Controls - Unaffected from Bipolar Families	3.49	0.86	-4.59	11.56
Controls - Unaffected from Mixed Families	7.05	1.86	-0.53	14.63
Schizophrenics - Unaffected from Schizophrenic Families	-14.09	-3.78	-21.54	-6.65
Schizophrenics - Bipolars from Bipolar Families	-18.39	-4.44	-26.67	-10.11
Schizophrenics - Bipolars from Mixed Families	-13.17	-3.09	-21.67	-4.66
Bipolars From Bipolar Families - Bipolars From Mixed Families	5.22	1.20	-3.48	13.93
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-4.30	-0.98	-13.05	4.46
Bipolars From Mixed Families - Unaffected From Mixed Families	-4.10	-1.00	-12.25	4.06
Unaffected From Bipolar Families - Unaffected From Mixed Families	3.56	0.75	-5.93	13.05
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-6.73	-1.45	-16.02	2.55
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-3.17	-0.71	-12.06	5.72

5.7.1.3 WASI performance IQ

Performance IQ, as measured by the WASI (WASI PIQ) differed significantly between the groups ($F_{6,64}$=5.93, $p<0.0001$). Schizophrenics, bipolars from bipolar families and bipolars from mixed families all had significantly lower WASI PIQ's than controls. The effect size was greatest in schizophrenics, intermediate in bipolars from mixed families and least in bipolars from bipolar families. Unaffected relatives from schizophrenic families or mixed families were also significantly more impaired in terms of the WASIPIQ than healthy subjects. No trend to significance was found for the unaffected relatives of bipolar families. Schizophrenic subjects were significantly more impaired than either bipolar group or their own relatives. Bipolar subjects from either bipolar or mixed families did not differ from their well relatives. Although no significant differences between the unaffected subject groups were found, impairments were greatest in the unaffected relatives of schizophrenic subjects, intermediate in the unaffected relatives from mixed families and the unaffected relatives of bipolar subjects showed the least impairment.

Overall, the results suggest that WASI PIQ is impaired in relationship to the expression of psychosis, regardless of diagnosis. However, impairments in unaffected relatives were found only in healthy relatives where at least one person had schizophrenia. The genetic liability to bipolar disorder appeared to covey no intellectual disadvantage in terms of PIQ.

Figure 5.7.1.3: Mean and crude 95% confidence intervals for WASI performance IQ

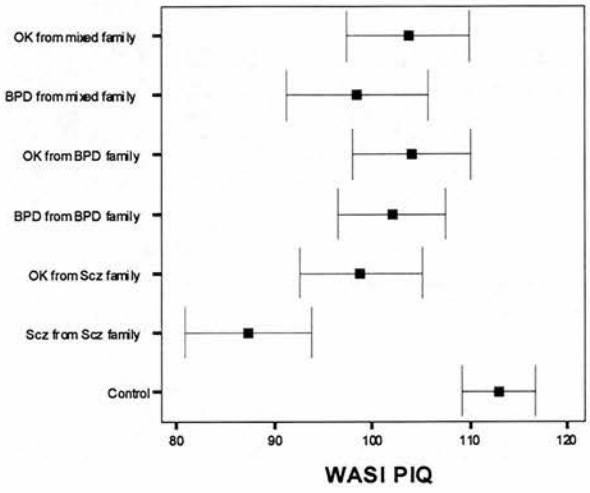


Table 5.7.1.3: Estimates of pairwise differences in WASI PIQ

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	25.30	5.86	16.68	33.92
Controls - Bipolars from Bipolar Families	10.43	2.63	2.50	18.37
Controls - Bipolars from Mixed Families	14.50	3.33	5.79	23.20
Controls - Unaffected from Schizophrenic Families	12.01	3.10	4.28	19.73
Controls - Unaffected from Bipolar Families	5.29	1.26	-3.09	13.66
Controls - Unaffected from Mixed Families	8.52	2.18	0.71	16.33
Schizophrenics - Unaffected from Schizophrenic Families	-13.29	-3.10	-21.85	-4.73
Schizophrenics - Bipolars from Bipolar Families	-14.86	-3.41	-23.56	-6.17
Schizophrenics - Bipolars from Mixed Families	-10.80	-2.38	-19.86	-1.74
Bipolars From Bipolar Families - Bipolars From Mixed Families	4.06	0.89	-5.03	13.16
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-1.57	-0.34	-10.75	7.60
Bipolars From Mixed Families - Unaffected From Mixed Families	-5.97	-1.32	-15.02	3.08
Unaffected From Bipolar Families - Unaffected From Mixed Families	3.23	0.66	-6.57	13.04
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-6.72	-1.38	-16.42	2.99
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-3.48	-0.75	-12.71	5.74

5.7.1.4 WASI verbal IQ

Verbal IQ, as measured by the WASI (WASI VIQ) differed significantly between the groups ($F_{6,64}$=4.04, p=0.002). Schizophrenic patients and their healthy relatives had significantly lower WASI VIQ than controls. However, both bipolar groups and their well relatives did not differ significantly from controls. A greater difference was observed between unaffected relatives from mixed families and controls than between unaffected relatives from bipolar families and controls. Schizophrenic subjects also had significantly lower WASI VIQ's than either their own relatives or either group of bipolar subjects. Bipolar subjects did not differ significantly from their well relatives, although there was a trend for unaffected relatives from bipolar families to have higher WASI VIQ's than their ill relatives.

Overall, the results suggest that WASI VIQ is impaired in relationship to both the liability to, and expression of schizophrenia. Neither the expression nor liability to bipolar disorder appeared to convey any intellectual disadvantage.

Figure 5.7.1.4: Means and crude 95% confidence intervals for WASI verbal IQ

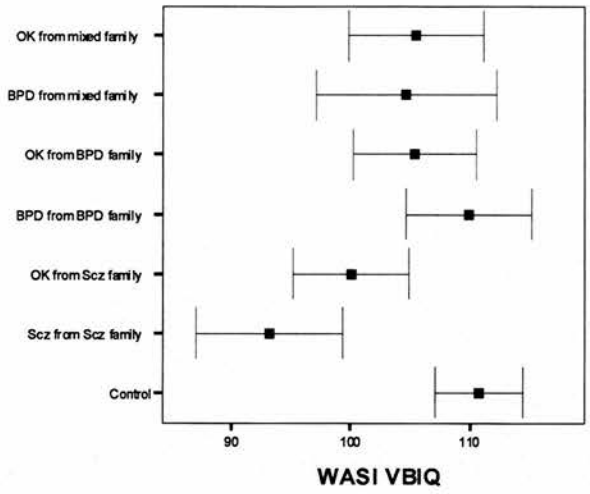


Table 5.7.1.4: Estimates of pairwise differences in WASI VBIQ

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	17.73	4.38	9.64	25.82
Controls - Bipolars from Bipolar Families	0.41	0.11	-7.03	7.84
Controls - Bipolars from Mixed Families	5.84	1.43	-2.34	14.01
Controls - Unaffected from Schizophrenic Families	7.85	2.16	0.61	15.09
Controls - Unaffected from Bipolar Families	1.99	0.51	-5.86	9.83
Controls - Unaffected from Mixed Families	4.77	1.30	-2.54	12.09
Schizophrenics - Unaffected from Schizophrenic Families	-9.88	-2.45	-17.94	-1.83
Schizophrenics - Bipolars from Bipolar Families	-17.32	-4.24	-25.48	-9.17
Schizophrenics - Bipolars from Mixed Families	-11.90	-2.80	-20.40	-3.40
Bipolars From Bipolar Families - Bipolars From Mixed Families	5.43	1.27	-3.10	13.95
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-7.44	-1.73	-16.04	1.16
Bipolars From Mixed Families - Unaffected From Mixed Families	-1.06	-0.25	-9.56	7.44
Unaffected From Bipolar Families - Unaffected From Mixed Families	2.78	0.61	-6.39	11.96
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-5.86	-1.29	-14.95	3.23
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-3.08	-0.71	-11.72	5.56

5.7.1.5 Premorbid versus current IQ difference

In studies of people with schizophrenia, a premorbid versus current IQ discrepancy is often found. This discrepancy is thought to represent a possible intellectual decline in schizophrenic subjects as they become unwell. The discrepancy between NART full-scale IQ and WASI full-scale IQ was computed by subtraction and then compared using a mixed model ANOVA taking the family into account as a random factor and the PANSS positive, HDRS and TMRS total scores as covariates. Comparisons were then made between each group and the control group by estimating the mean difference (NART FSIQ - WASI FSIQ) and its 95% confidence interval.

'NART-WASI IQ discrepancy' (NART FSIQ - WASI FSIQ) differed significantly amongst the groups ($F_{6,64}$=4.7, p<0.001). All patients groups differed from controls, although the difference was greatest for schizophrenic subjects (mean difference=15.6, 95%CI 9.5 to 21.7), whilst bipolars from mixed families (mean difference=7.8, 95%CI 1.6 to 13.9) and bipolars from bipolar families (mean difference=8.1, 95%CI 2.5 to 13.6) had similar levels of 'decline'. Unaffected relatives of patients with schizophrenia also showed evidence of a decline in intellectual functioning of about 5 points compared to controls, although the crude confidence interval for this IQ difference showns some overlap with the other unaffected relative groups. The data are represented graphically in figure 5.7.1.5.

Figure 5.7.1.5: Means and crude 95% confidence intervals for premorbid-current IQ difference

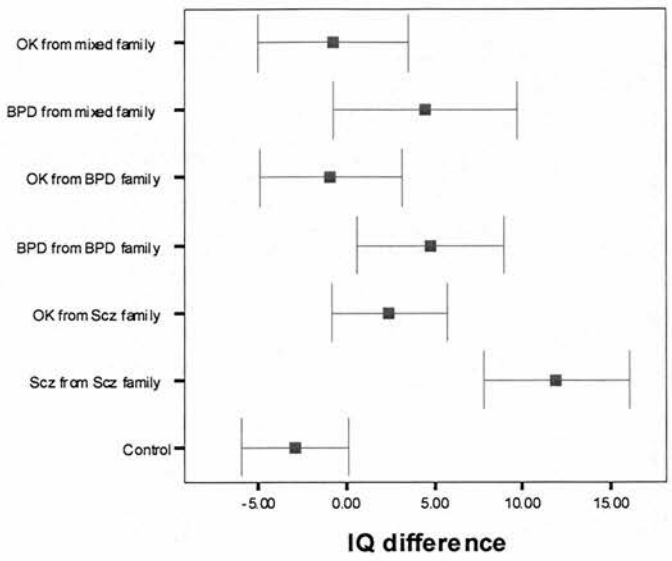


Table 5.7.1.5: Premorbid-current IQ differences by group

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls - Schizophrenics	-15.58	-5.11	-21.68	-9.49
Controls - Bipolars from Bipolar Families	-8.05	-2.90	-13.59	-2.51
Controls - Bipolars from Mixed Families	-7.77	-2.52	-13.92	-1.61
Controls - Unaffected from Schizophrenic Families	-5.71	-2.11	-11.11	-0.31
Controls - Unaffected from Bipolar Families	-1.73	-0.60	-7.53	4.07
Controls - Unaffected from Mixed Families	-2.13	-0.79	-7.53	3.27
Schizophreics - Unaffected from Schizophrenic Families	9.88	3.16	3.63	16.12
Schizophreics - Bipolars from Bipolar Families	7.53	2.47	1.44	13.63
Schizophreics - Bipolars from Mixed Families	7.82	2.44	1.43	14.21
Bipolars From Bipolar Families - Bipolars From Mixed Families	0.29	0.09	-6.07	6.65
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-2.34	-0.73	-8.75	4.06
Bipolars From Mixed Families - Unaffected From Mixed Families	5.63	1.74	-0.85	12.11
Unaffected From Bipolar Families - Unaffected From Mixed Families	-0.40	-0.12	-7.16	6.35
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	3.98	1.18	-2.76	10.71
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	3.57	1.12	-2.81	9.96

5.8 Memory

Memory was compared between groups using the Extended Rivermead Behavioural Memory Test (E-RBMT). As this was the only index of memory, a univariate mixed model ANOVA was used to compare mean total E-RBMT profiles scores between groups.

Table 5.8: E-RBMT total profile scores by group

	1	2	3	4	5	6	7
Mean	36.4	26.4	29.0	27.2	32.5	28.1	33.0
SD	4.4	5.3	6.3	6.8	4.9	6.2	4.6

Key

1	Controls
2	Schizophrenic subjects from schizophrenic families
3	Unaffected from schizophrenic families
4	Bipolar subjects from bipolar families
5	Unaffected from bipolar families
6	Bipolar subjects from mixed families
7	Unaffected from mixed families

5.8.1 Extended Rivermead Behavioural Memory Test

Extended Rivermead Behavioural Memory Test (E-RBMT) scores differed significantly between groups ($F_{6,64}$=8.8, $p<0.0001$), regardless of whether WASI FSIQ was included as a covariate ($F_{6,64}$=5.9, $p<0.0001$). Results are presented first without WASI FSIQ as a covariate, since WASI FSIQ may be related to genetic liability or

disease expression itself and hence not a true confounder. This is followed by analysis with WASI FSIQ as a covariate to highlight those differences which may not be explained simply by a reduction in general intellectual function.

E-RBMT scores were lower in all groups compared to controls. There was no evidence of disease specificity amongst affected subjects although unaffected subjects from schizophrenic families were more impaired than unaffected subjects from either bipolar or mixed families. Once WASI IQ was taken into account, the nature of the results changed little. Controls performed better than all other groups and, amongst affected subjects, there was little evidence of disease specificity. Bipolar subjects from mixed families performed worse than their well relatives (difference=3.8, 95%CI 0.5 to 7.1) and unaffected subjects from schizophrenic families performed worse than unaffected subjects from mixed families (difference=3.2, 95%CI 0.2 to 6.2). There was also a trend for unaffected subjects from schizophrenic families to do worse than unaffected members of bipolar families (difference=2.8, 95%CI -0.4 to 6).

Overall, these differences suggest that memory impairment is impaired in relationship to both genetic liability and phenotypic expression of psychosis and shows no evidence of diagnostic specificity. Amongst unaffected relatives, there was a suggestion than unaffected family members with only schizophrenic relatives may be relatively more disadvantaged in terms of memory than those with bipolar relatives.

Figure 5.8.1: Means and crude 95% confidence intervals for E-RBMT total scores between groups

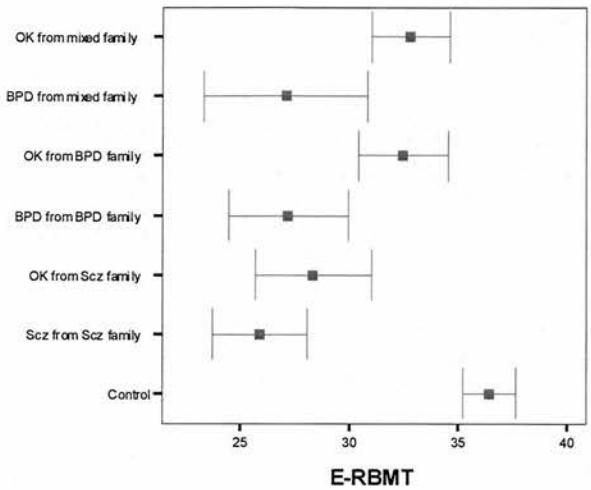


Table 5.8.1: Estimates of pairwise differences in E-RBMT, not WASI FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	8.61	5.41	5.43	11.78
Controls - Bipolars from Bipolar Families	7.59	5.27	4.71	10.47
Controls - Bipolars from Mixed Families	7.80	4.80	4.55	11.04
Controls - Unaffected from Schizophrenic Families	7.73	5.70	5.02	10.44
Controls - Unaffected from Bipolar Families	3.77	2.64	0.91	6.63
Controls - Unaffected from Mixed Families	3.62	2.71	0.95	6.30
Schizophrenics - Unaffected from Schizophrenic Families	-0.87	-0.52	-4.23	2.48
Schizophrenics - Bipolars from Bipolar Families	-1.02	-0.65	-4.13	2.09
Schizophrenics - Bipolars from Mixed Families	-0.81	-0.49	-4.11	2.49
Bipolars From Bipolar Families - Bipolars From Mixed Families	0.21	0.13	-3.04	3.45
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-0.14	-0.09	-3.36	3.07
Bipolars From Mixed Families - Unaffected From Mixed Families	-4.17	-2.41	-7.63	-0.71
Unaffected From Bipolar Families - Unaffected From Mixed Families	-0.15	-0.09	-3.41	3.12
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-3.96	-2.40	-7.25	-0.67
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-4.11	-2.61	-7.25	-0.97

Table 5.8.2: Estimates of pairwise differences in E-RBMT, FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	5.84	3.52	2.52	9.15
Controls - Bipolars from Bipolar Families	6.90	4.98	4.13	9.67
Controls - Bipolars from Mixed Families	6.52	4.11	3.35	9.69
Controls - Unaffected from Schizophrenic Families	5.91	4.36	3.20	8.62
Controls - Unaffected from Bipolar Families	3.11	2.28	0.39	5.84
Controls - Unaffected from Mixed Families	2.70	2.09	0.12	5.28
Schizophrenics - Unaffected from Schizophrenic Families	0.08	0.05	-3.24	3.39
Schizophrenics - Bipolars from Bipolar Families	1.07	0.68	-2.05	4.19
Schizophrenics - Bipolars from Mixed Families	0.68	0.42	-2.54	3.91
Bipolars From Bipolar Families - Bipolars From Mixed Families	-0.38	-0.25	-3.49	2.72
Bipolars From Bipolar Families - Unaffected From Bipolar Families	0.99	0.64	-2.12	4.11
Bipolars From Mixed Families - Unaffected From Mixed Families	-3.82	-2.31	-7.13	-0.51
Unaffected From Bipolar Families - Unaffected From Mixed Families	-0.41	-0.27	-3.50	2.67
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-2.80	-1.77	-5.96	0.36
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-3.21	-2.13	-6.23	-0.20

5.9 Attention and psychomotor performance

Cognitive and motor (psychomotor) performance was measured using the Digit Symbol Substitution Test (DSST) from the WAIS and the Simple and Choice Reaction Time Test from the CANTAB respectively. The combined vector of their means differed significantly between the groups ($F_{15,166}$=2.0, p=0.02). Summary statistics for each group are shown in table 5.9.1.

Table 5.9.1: Mean measures of psychomotor performance by group

		DSST	Choice RT (msec)	Simple RT (msec)
Control	Mean	63.8	323.6	313.8
	SD	11.7	35.8	40.3
Scz from Scz family	Mean	40.1	411.5	395.7
	SD	16.4	91.5	102.5
OK from Scz family	Mean	53.8	330.1	332.4
	SD	13.3	60.5	57.3
BPD from BPD family	Mean	47.2	418.4	379.5
	SD	13.5	271.2	110.8
OK from BPD family	Mean	58.6	309.0	332.3
	SD	9.4	42.5	50.9
BPD from mixed family	Mean	46.6	400.4	406.1
	SD	11.1	87.9	88.3
OK from mixed family	Mean	58.7	341.3	338.2
	SD	13.1	77.6	56.3

The number of correct digit symbol substitutions (DSST) differed significantly between groups ($F_{6,64}$=, p<0.0001). All patient groups were impaired relative to healthy controls. Similarly unaffected relatives from all families made fewer correct substitutions than controls although only unaffected subjects from schizophrenic families performed significantly worse than controls (difference=6.91, 95%CI 0.94 to

12.87). Schizophrenic subjects did significantly worse than their close relatives (difference=10.6, 95%CI 3.7 to 17.5) and showed a tendency to do worse than the other patient groups. There was no evidence of a difference between affected subjects from mixed or bipolar families and unaffected relatives showed no significant differences from one another.

Simple reaction time (SRT) also differed significantly between groups. All patient groups were significantly impaired compared to controls, although no differences were found between controls and any unaffected relative group. Bipolar subjects from mixed families did significantly worse than bipolars from bipolar families. Schizophrenic subjects and bipolar subjects from mixed families did significantly worse than their well relatives. No difference was found between bipolar subjects and healthy subjects from bipolar families.

Choice reaction time (CRT) also differed between groups. All patient groups were significantly impaired compared to controls, although no differences were found between controls and any unaffected relative group. Schizophrenic subjects performed less well than their well relatives and bipolar subjects also did les well than their well relatives. However, no significant differences were found between bipolar subjects from mixed families and their well relatives. Differences between affected or unaffected groups showed no diagnostic or familial specificity.

Figure 5.9.1: Means and crude 95% confidence intervals for DSST test (number of correct substitutions made in 90 sec), simple and choice reaction times

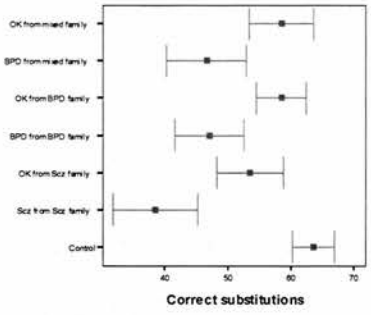
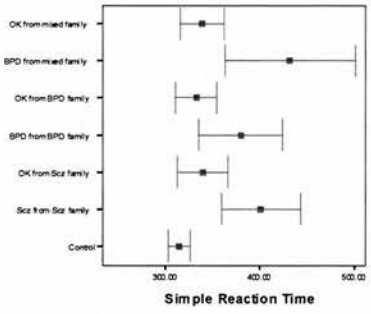
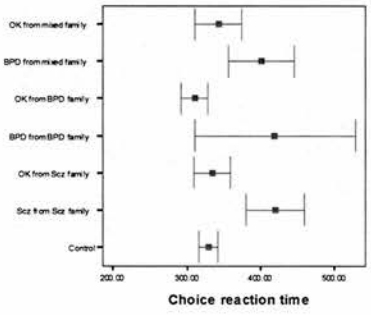
	**Digit symbol substitution test**
	**Simple reaction time**
	**Choice reaction time**

Table 5.9.2: Estimates of pairwise differences in DSST, not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	17.51	5.12	10.68	24.33
Controls - Bipolars from Bipolar Families	11.39	3.62	5.11	17.68
Controls - Bipolars from Mixed Families	11.15	3.21	4.20	18.10
Controls - Unaffected from Schizophrenic Families	6.91	2.31	0.94	12.87
Controls - Unaffected from Bipolar Families	4.44	1.37	-2.02	10.90
Controls - Unaffected from Mixed Families	4.80	1.59	-1.22	10.82
Schizophrenics - Unaffected from Schizophrenic Families	-10.60	-3.07	-17.49	-3.71
Schizophrenics - Bipolars from Bipolar Families	-6.11	-1.80	-12.89	0.67
Schizophrenics - Bipolars from Mixed Families	-6.35	-1.78	-13.47	0.76
Bipolars From Bipolar Families - Bipolars From Mixed Families	-0.24	-0.07	-7.33	6.84
Bipolars From Bipolar Families - Unaffected From Bipolar Families	4.49	1.27	-2.59	11.56
Bipolars From Mixed Families - Unaffected From Mixed Families	-6.35	-1.72	-13.71	1.01
Unaffected From Bipolar Families - Unaffected From Mixed Families	0.36	0.10	-7.15	7.88
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-2.47	-0.66	-9.93	4.99
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-2.11	-0.59	-9.21	5.00

Table 5.9.3: Estimates of pairwise differences in CANTAB simple reaction time, not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	-72.24	-3.11	-118.64	-25.83
Controls - Bipolars from Bipolar Families	-51.02	-2.44	-92.88	-9.15
Controls - Bipolars from Mixed Families	-107.43	-4.41	-156.16	-58.70
Controls - Unaffected from Schizophrenic Families	-24.31	-1.23	-63.73	15.10
Controls - Unaffected from Bipolar Families	-23.53	-1.13	-65.04	17.99
Controls - Unaffected from Mixed Families	-31.96	-1.61	-71.75	7.82
Schizophrenics - Unaffected from Schizophrenic Families	47.92	1.96	-1.04	96.89
Schizophrenics - Bipolars from Bipolar Families	21.22	0.94	-24.06	66.50
Schizophrenics - Bipolars from Mixed Families	-35.19	-1.43	-84.45	14.06
Bipolars From Bipolar Families - Bipolars From Mixed Families	-56.41	-2.32	-104.94	-7.89
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-26.70	-1.14	-73.36	19.95
Bipolars From Mixed Families - Unaffected From Mixed Families	75.47	2.90	23.52	127.41
Unaffected From Bipolar Families - Unaffected From Mixed Families	-8.44	-0.35	-56.46	39.58
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	0.79	0.03	-46.93	48.51
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-7.65	-0.33	-53.82	38.52

Table 5.9.4: Estimates of pairwise differences in choice reaction time, not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	-70.29	-2.06	-138.39	-2.18
Controls - Bipolars from Bipolar Families	-97.06	-2.79	-166.67	-27.44
Controls - Bipolars from Mixed Families	-66.63	-1.84	-138.81	5.56
Controls - Unaffected from Schizophrenic Families	7.65	0.24	-56.67	71.96
Controls - Unaffected from Bipolar Families	-54.50	-1.53	-125.63	16.63
Controls - Unaffected from Mixed Families	-41.64	-1.20	-110.74	27.46
Schizophrenics - Unaffected from Schizophrenic Families	77.93	3.26	30.11	125.76
Schizophrenics - Bipolars from Bipolar Families	-26.77	-0.76	-97.45	43.91
Schizophrenics - Bipolars from Mixed Families	3.66	0.10	-69.43	76.75
Bipolars From Bipolar Families - Bipolars From Mixed Families	30.43	0.77	-48.60	109.46
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-104.70	-2.82	-178.79	-30.61
Bipolars From Mixed Families - Unaffected From Mixed Families	24.99	0.83	-35.33	85.30
Unaffected From Bipolar Families - Unaffected From Mixed Families	12.86	0.31	-70.97	96.69
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-62.15	-1.59	-140.49	16.20
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-49.29	-1.27	-127.13	28.56

5.10 Executive function

The marginal distributions of each component of executive function were first inspected. Hayling Sentence Completion Test (HSCT) summary scores were found to be negatively skewed and were transformed to an approximately normal distribution by squaring each raw value. Using a mixed model MANCOVA, executive function (verbal fluency, transformed Hayling Sentence Completion Test, Stockings of Cambridge) did not differ significantly between

groups ($F_{20,196.6}$=1.29, p=0.19). Similarly, mixed effects 1-way ANOVAs did not differentiate the groups in terms of either measure of HSCT performance, whether corrected for current IQ or not. However, Stockings of Cambridge Test mean scores differed between the groups in the non-IQ corrected ($F_{6,62}$=3.53, p=0.005) but not in the IQ corrected analysis. Verbal fluency also differed between the groups in the non-IQ corrected analysis ($F_{6,64}$=2.98, p=0.013), but not once IQ had been added to the model ($F_{6,62}$=2, p<0.08).

Since the null hypothesis of no difference could not be rejected (the overall MANOVA was not significant), pairwise comparisons for each test were estimated as a means of data exploration rather than as a hypothesis test. Estimates are presented with and without WASI FSIQ as a covariate.

Table 5.10: Executive function summary statistics

		FAS Total	SOC Total	HSCT TSS	HSCT TES
Control	Mean	44.5	9.2	325.6	37.0
	SD	10.4	2.3	86.4	13.9
Scz from Scz family	Mean	31.9	6.8	241.4	24.2
	SD	11.6	2.2	96.5	13.3

OK from Scz family	Mean	42.0	7.6	273.5	29.2
	SD	10.4	2.3	98.6	14.1
BPD from BPD family	Mean	37.0	7.6	266.4	28.6
	SD	10.7	2.3	95.4	14.0
OK from BPD family	Mean	38.8	8.1	320.4	36.1
	SD	8.5	1.9	95.1	15.9
BPD from mixed family	Mean	34.8	6.8	262.2	28.2
	SD	11.5	1.9	104.9	15.6
OK from mixed family	Mean	41.6	7.5	315.6	34.4
	SD	14.0	2.7	73.3	10.7

FAS- verbal fluency, SOC- Stockings of Cambridge, HSCT – Hayling Sentence Completion Test. TSS- transformed (X^2) total score, TES- transformed (X^2) scaled error score

Verbal fluency (FAS) was lower in each patient group compared to controls (non-IQ adjusted). No significant differences were found for any unaffected groups compared to controls. Schizophrenic patients and bipolar patients were significantly more impaired than their well relatives. No difference was found between patients from mixed families and their well relatives. There was no evidence that differences were specific to diagnosis or familial history. After controlling for WASI FSIQ only two differences remained significant: schizophrenic subjects remained more impaired than their well relatives (difference=7.5, 95%CI 0.9 to 14.1) and bipolars from bipolar families performed significantly *better* than their well relatives (difference=10.0 95%CI 3.7 to 16.3). In addition, unaffected subjects from schizophrenic families performed significantly better than unaffected subjects from bipolar families (difference=7.2, 95%CI 0.7 to 13.8) and showed a tendency to perform better than controls (difference=4.8, 95%CI -0.7 to 10.3).

Hayling sentence completion tests (overall scaled scores) were significantly lower in unaffected subjects from schizophrenic families than in controls. This was the

only significant finding, although there was a tendency for schizophrenic subjects to also have lower scores than controls. After covarying for WASI FSIQ none of these differences remained significant and no new significant findings emerged. A similar pattern of results was also observed for the Hayling total scaled error scores.

The Stockings of Cambridge Test (number of trials completed in minimum number of moves) was significantly different between groups. All patient groups performed significantly worse than healthy controls with bipolars from bipolar families showing the smallest degree of impairment (difference=1.4, 95%CI 0.14 to 2.6). Similarly, unaffected subjects from schizophrenic and mixed families also performed significantly worse than controls. No significant difference was found between unaffected subjects from bipolar families and controls. Patient groups did not differ significantly from each other, or their healthy relatives. There was a tendency for bipolars from bipolar families to do better than those from mixed families, although this was not statistically significant (difference=1.2, 95%CI -0.18 to 2.6). After adjusting for IQ, only two significant findings remained. Bipolar subjects and healthy relatives from mixed families both did significantly worse than healthy controls. None of the other pairwise differences remained significant.

Table 5.10.1: Estimates of pairwise differences in HSCT (overall scaled score), not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	7.35	1.79	-0.86	15.57
Controls - Bipolars from Bipolar Families	3.03	0.82	-4.39	10.45
Controls - Bipolars from Mixed Families	1.89	0.45	-6.48	10.27
Controls - Unaffected from Schizophrenic Families	7.56	2.17	0.59	14.54
Controls - Unaffected from Bipolar Families	-0.44	-0.12	-7.77	6.88
Controls - Unaffected from Mixed Families	1.33	0.39	-5.54	8.20
Schizophrenics - Unaffected from Schizophrenic Families	0.21	0.05	-8.51	8.93
Schizophrenics - Bipolars from Bipolar Families	-4.32	-1.07	-12.37	3.73
Schizophrenics - Bipolars from Mixed Families	-5.46	-1.28	-14.00	3.08
Bipolars From Bipolar Families - Bipolars From Mixed Families	-1.14	-0.27	-9.51	7.23
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-4.53	-1.09	-12.81	3.75
Bipolars From Mixed Families - Unaffected From Mixed Families	-0.57	-0.13	-9.50	8.37
Unaffected From Bipolar Families - Unaffected From Mixed Families	1.77	0.42	-6.59	10.14
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-8.01	-1.89	-16.45	0.43
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-6.23	-1.55	-14.29	1.82

Table 5.10.2: Estimates of pairwise differences in HSCT (overall scaled score), FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	0.78	0.18	-7.87	9.43
Controls - Bipolars from Bipolar Families	1.20	0.33	-6.01	8.40
Controls - Bipolars from Mixed Families	-1.38	-0.33	-9.66	6.90
Controls - Unaffected from Schizophrenic Families	4.29	1.22	-2.73	11.31
Controls - Unaffected from Bipolar Families	-1.82	-0.52	-8.76	5.13
Controls - Unaffected from Mixed Families	-0.92	-0.28	-7.54	5.70
Schizophrenics - Unaffected from Schizophrenic Families	3.51	0.81	-5.20	12.22
Schizophrenics - Bipolars from Bipolar Families	0.42	0.10	-7.69	8.53
Schizophrenics - Bipolars from Mixed Families	-2.16	-0.51	-10.58	6.25
Bipolars From Bipolar Families - Bipolars From Mixed Families	-2.58	-0.64	-10.65	5.49
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-3.09	-0.77	-11.15	4.96
Bipolars From Mixed Families - Unaffected From Mixed Families	0.46	0.11	-8.18	9.10
Unaffected From Bipolar Families - Unaffected From Mixed Families	0.89	0.23	-6.89	8.67
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-6.11	-1.52	-14.13	1.91
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-5.21	-1.35	-12.91	2.48

Table 5.10.3: Estimates of pairwise differences in HSCT (scaled error score), not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	56.34	2.09	2.39	110.29
Controls - Bipolars from Bipolar Families	29.23	1.20	-19.37	77.83
Controls - Bipolars from Mixed Families	26.61	0.97	-28.44	81.66
Controls - Unaffected from Schizophrenic Families	55.50	2.44	10.04	100.97
Controls - Unaffected from Bipolar Families	1.62	0.07	-45.61	48.86
Controls - Unaffected from Mixed Families	6.47	0.29	-38.09	51.03
Schizophrenics - Unaffected from Schizophrenic Families	-0.84	-0.03	-58.51	56.84
Schizophrenics - Bipolars from Bipolar Families	-27.11	-1.03	-79.76	25.54
Schizophrenics - Bipolars from Mixed Families	-29.73	-1.06	-85.77	26.31
Bipolars From Bipolar Families - Bipolars From Mixed Families	-2.62	-0.10	-57.37	52.14
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-26.27	-0.97	-80.29	27.75
Bipolars From Mixed Families - Unaffected From Mixed Families	-20.15	-0.69	-78.81	38.52
Unaffected From Bipolar Families - Unaffected From Mixed Families	4.84	0.18	-48.81	58.49
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-53.88	-1.98	-108.26	0.50
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-49.04	-1.88	-101.11	3.03

Table 5.10.4: Estimates of pairwise differences in HSCT (scaled error score), FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	7.27	0.26	-48.69	63.23
Controls - Bipolars from Bipolar Families	15.44	0.66	-31.10	61.99
Controls - Bipolars from Mixed Families	1.50	0.06	-52.15	55.16
Controls - Unaffected from Schizophrenic Families	30.74	1.36	-14.36	75.84
Controls - Unaffected from Bipolar Families	-9.77	-0.45	-53.55	34.00
Controls - Unaffected from Mixed Families	-11.16	-0.53	-53.32	30.99
Schizophrenics - Unaffected from Schizophrenic Families	23.47	0.83	-33.16	80.10
Schizophrenics - Bipolars from Bipolar Families	8.17	0.31	-44.06	60.40
Schizophrenics - Bipolars from Mixed Families	-5.77	-0.21	-60.17	48.63
Bipolars From Bipolar Families - Bipolars From Mixed Families	-13.94	-0.54	-65.96	38.08
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-15.30	-0.59	-67.02	36.42
Bipolars From Mixed Families - Unaffected From Mixed Families	-12.67	-0.45	-68.52	43.19
Unaffected From Bipolar Families - Unaffected From Mixed Families	-1.39	-0.06	-49.83	47.05
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-40.51	-1.61	-90.79	9.76
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	-41.90	-1.72	-90.65	6.85

Table 5.10.5: Estimates of pairwise differences in SOC number of trials completed in minimum moves, not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	2.42	3.69	1.11	3.73
Controls - Bipolars from Bipolar Families	1.37	2.23	0.14	2.59
Controls - Bipolars from Mixed Families	2.59	3.78	1.22	3.97
Controls - Unaffected from Schizophrenic Families	1.39	2.37	0.22	2.56
Controls - Unaffected from Bipolar Families	0.72	1.14	-0.55	1.99
Controls - Unaffected from Mixed Families	1.75	2.93	0.55	2.94
Schizophrenics - Unaffected from Schizophrenic Families	-1.03	-1.62	-2.30	0.24
Schizophrenics - Bipolars from Bipolar Families	-1.05	-1.60	-2.37	0.26
Schizophrenics - Bipolars from Mixed Families	0.17	0.25	-1.22	1.57
Bipolars From Bipolar Families - Bipolars From Mixed Families	1.23	1.74	-0.18	2.64
Bipolars From Bipolar Families - Unaffected From Bipolar Families	-0.02	-0.03	-1.41	1.36
Bipolars From Mixed Families - Unaffected From Mixed Families	-0.85	-1.20	-2.26	0.57
Unaffected From Bipolar Families - Unaffected From Mixed Families	1.03	1.38	-0.46	2.52
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-0.67	-0.91	-2.14	0.80
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	0.36	0.51	-1.05	1.77

Table 5.10.6: Estimates of pairwise differences in SOC number of trials completed in minimum moves, FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	0.86	1.30	-0.47	2.19
Controls - Bipolars from Bipolar Families	0.87	1.56	-0.25	1.98
Controls - Bipolars from Mixed Families	1.70	2.60	0.39	3.00
Controls - Unaffected from Schizophrenic Families	0.66	1.20	-0.44	1.77
Controls - Unaffected from Bipolar Families	0.52	0.94	-0.59	1.64
Controls - Unaffected from Mixed Families	1.12	2.11	0.06	2.19
Schizophrenics - Unaffected from Schizophrenic Families	-0.20	-0.30	-1.50	1.10
Schizophrenics - Bipolars from Bipolar Families	0.00	0.01	-1.25	1.25
Schizophrenics - Bipolars from Mixed Families	0.83	1.28	-0.47	2.14
Bipolars From Bipolar Families - Bipolars From Mixed Families	0.83	1.30	-0.45	2.11
Bipolars From Bipolar Families - Unaffected From Bipolar Families	0.20	0.32	-1.06	1.46
Bipolars From Mixed Families - Unaffected From Mixed Families	-0.57	-0.85	-1.92	0.77
Unaffected From Bipolar Families - Unaffected From Mixed Families	0.60	0.93	-0.69	1.89
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	-0.14	-0.21	-1.45	1.17
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	0.46	0.74	-0.79	1.71

Figure 5.10: Means and crude 95% confidence intervals for total verbal fluency score (FAS & animals)

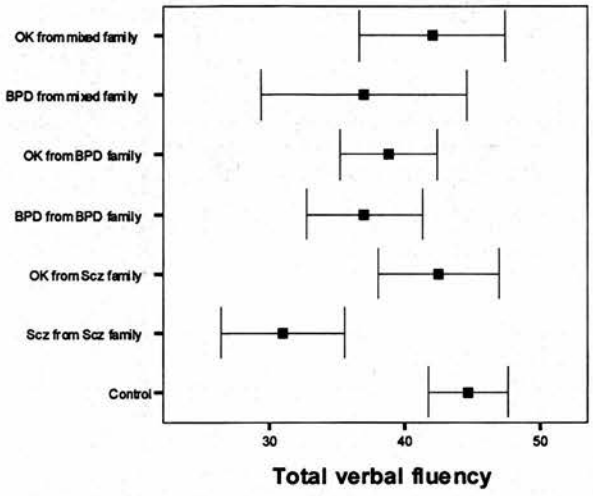


Table 5.10.7: Estimates of pairwise differences in FAS total words (verbal fluency), not FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	13.80	3.94	6.80	20.81
Controls - Bipolars from Bipolar Families	8.15	2.57	1.82	14.48
Controls - Bipolars from Mixed Families	8.06	2.25	0.90	15.21
Controls - Unaffected from Schizophrenic Families	1.70	0.57	-4.23	7.63
Controls - Unaffected from Bipolar Families	5.29	1.71	-0.91	11.48
Controls - Unaffected from Mixed Families	2.15	0.74	-3.67	7.98
Schizophrenics - Unaffected from Schizophrenic Families	-12.11	-3.24	-19.57	-4.64
Schizophrenics - Bipolars from Bipolar Families	-5.65	-1.65	-12.49	1.18
Schizophrenics - Bipolars from Mixed Families	-5.75	-1.58	-13.02	1.53
Bipolars From Bipolar Families - Bipolars From Mixed Families	-0.10	-0.03	-7.23	7.04
Bipolars From Bipolar Families - Unaffected From Bipolar Families	6.45	1.83	-0.59	13.50
Bipolars From Mixed Families - Unaffected From Mixed Families	-5.90	-1.55	-13.53	1.73
Unaffected From Bipolar Families - Unaffected From Mixed Families	-3.13	-0.89	-10.19	3.92
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	3.59	1.01	-3.54	10.73
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	0.46	0.13	-6.36	7.28

Table 5.10.8: Estimates of pairwise differences in FAS total words (verbal fluency), FSIQ corrected

Comparison	Estimate	T	Lower 95%CI	Upper 95%CI
Controls – Schizophrenics	2.70	0.81	-3.97	9.37
Controls - Bipolars from Bipolar Families	5.17	1.85	-0.42	10.76
Controls - Bipolars from Mixed Families	2.56	0.81	-3.79	8.92
Controls - Unaffected from Schizophrenic Families	-4.80	-1.75	-10.29	0.69
Controls - Unaffected from Bipolar Families	2.40	0.86	-3.20	8.00
Controls - Unaffected from Mixed Families	-1.96	-0.74	-7.24	3.31
Schizophrenics - Unaffected from Schizophrenic Families	-7.50	-2.27	-14.09	-0.91
Schizophrenics - Bipolars from Bipolar Families	2.47	0.78	-3.84	8.78
Schizophrenics - Bipolars from Mixed Families	-0.14	-0.04	-6.64	6.36
Bipolars From Bipolar Families - Bipolars From Mixed Families	-2.61	-0.83	-8.88	3.67
Bipolars From Bipolar Families - Unaffected From Bipolar Families	9.97	3.16	3.65	16.29
Bipolars From Mixed Families - Unaffected From Mixed Families	-4.53	-1.36	-11.17	2.12
Unaffected From Bipolar Families - Unaffected From Mixed Families	-4.36	-1.36	-10.76	2.04
Unaffected From Schizophrenic Families - Unaffected From Bipolar Families	7.20	2.21	0.68	13.71
Unaffected From Schizophrenic Families - Unaffected From Mixed Families	2.84	0.92	-3.35	9.02

5.11 Medication and substance effects on neuropsychological function

The mixed-effects analyses of variance quoted above (sections 5.7 to 5.10) did not include medication as a covariate for symptom effects are likely to be more important than medication effects. This is partly for reasons of simplicity but also because medication has been shown to have an ameliorating as well as deleterious effect on cognition in some studies (see chapter 2). However, to check the validity of the models chosen, the unstandardised residuals (unexplained variation) from each analysis were plotted against current conventional antipsychotic dose (chlorpromazine equivalents), lithium dose and weekly alcohol intake. Antimuscarinic medication and benzodiazepines were not prescribed in sufficient numbers to make the equivalent analyses possible and no bioequivalent dose information is available for antimuscarinic, antidepressant or anticonvulsant medications. However, the influence of these medications was investigated by labelling plots of fitted versus observed values by whether these medications had been prescribed at all and detecting any observed patterns graphically.

Table 5.11.1: Pearson correlation coefficients for residuals versus potential confounding variables. P-values are given in parentheses

	NART FSIQ	WASI FSIQ	WASI VBIQ	WASI PIQ	RBMT	HSCT OSS	HSCT SES	Simple RT	Choice RT	DSST
Antipsychotic	0.03 (0.70)	0.05 (0.48)	0.07 (0.34)	0.03 (0.66)	0.08 (0.21)	-0.04 (0.59)	-0.03 (0.66)	-0.02 (0.84)	0.03 (0.70)	-0.06 (0.38)
Lithium	-0.00 (0.96)	0.03 (0.70)	0.01 (0.89)	0.07 (0.34)	0.04 (0.59)	-0.03 (0.64)	-0.02 (0.80)	-0.13 (0.07)	-0.06 (0.40)	-0.06 (0.43)
Alcohol	-0.10 (0.17)	-0.01 (0.82)	-0.07 (0.33)	0.02 (0.73)	-0.03 (0.67)	0.09 (0.23)	0.08 (0.26)	0.02 (0.80)	0.02 (0.79)	0.00 (0.99)

RBMT: Rivermead Behavioural Memory Test, FSIQ: Full-scale IQ, HSCT OSS: Hayling Overall Scaled Score, SES: Scaled Error Score, VBIQ: Verbal IQ, RT: Reaction time.

Results from these correlational analyses are shown in table 5.1.1. There were no significant associations between any of the 10 neuropsychological measures and either antipsychotic dose, lithium dose or weekly alcohol consumption.

5.12 Relationship of neuropsychology to genetic liability

5.12.1 Genetic liability to schizophrenia and general intelligence

NART and WASI full scale IQ, WASI verbal IQ and WASI performance IQ were all reduced in schizophrenics and their healthy relatives. In addition, bipolars from mixed families and their unaffected relatives also performed less well than controls. These findings suggested that general intelligence might be related to the genetic liability to schizophrenia. In order to further investigate this relationship, Pearson product-moment correlation coefficients were computed between each measure of intelligence and the continuous measure of genetic liability to schizophrenia.

Within schizophrenic subjects themselves, genetic liability to schizophrenia was inversely related to NART FSIQ (r=-0.49, p=0.01), WASI FSIQ (r=-0.33, p=0.1, trend only) and WASI verbal IQ (-0.55, p=0.004) but not WASI performance IQ (r=-0.01, p=0.94). However, within the healthy relatives of schizophrenic subjects, genetic liability to schizophrenia was *positively* related to WASI performance IQ (r=0.45, p=0.03) and WASI FSIQ (r=0.36, p=0.08, trend only). No relationship was found between NART FSIQ (r=0.31, p=0.13) or WASI verbal IQ and genetic liability (r=0.06, p=0.78).

Figure 5.12.1a: Relationship between genetic liability to schizophrenia and verbal IQ in patients with schizophrenia

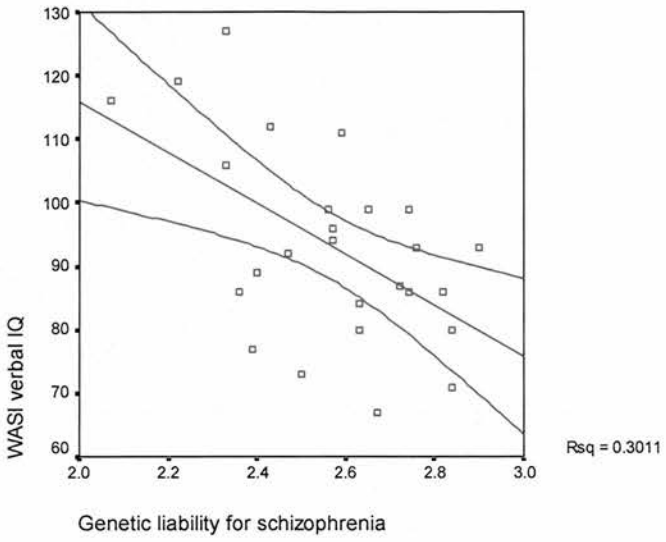
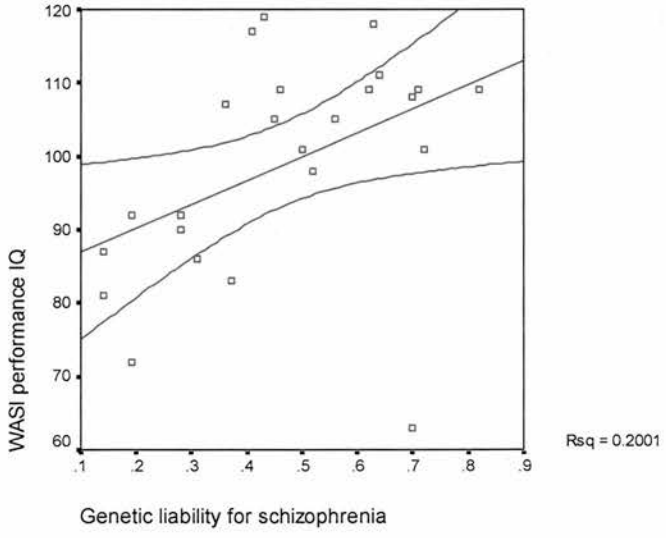


Figure 5.12.1b: Relationship between genetic liability to schizophrenia and performance IQ in the relatives of people with schizophrenia



Within bipolar subjects from mixed families there were no significant relationships between genetic liability to schizophrenia and measures of intelligence, and

no suggestion of any trends. Within unaffected subjects from mixed families however, genetic liability was negatively related to WASI FSIQ (r=-0.33, p=0.09, trend only) and WASI verbal IQ (r=-0.39, p=0.05). Genetic liability was not related to WASI performance IQ or NART FSIQ.

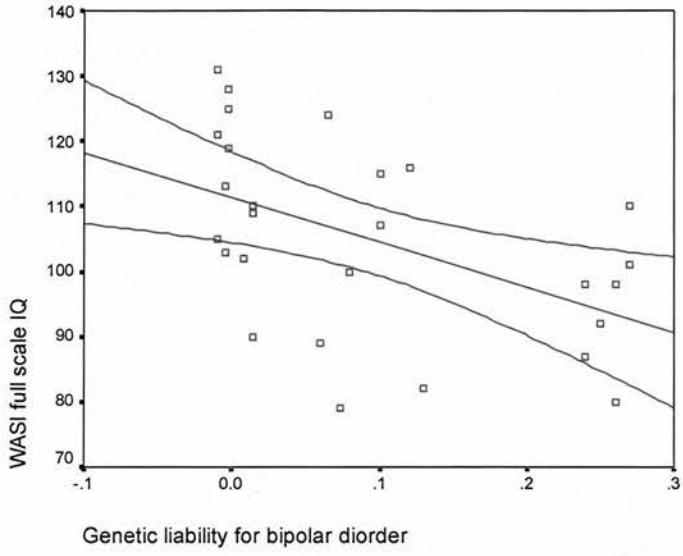
5.12.2 Genetic liability to schizophrenia and memory

There was no evidence of a relationship between genetic liability to schizophrenia and scores on the Rivermead Behavioural Memory Test within any group.

5.12.3 Genetic liability to bipolar disorder and general intelligence

There was no evidence of a relationship between genetic liability to bipolar disorder and any measure of general intelligence within bipolar subjects from bipolar families, their well relatives or bipolar subjects from mixed families. However, unaffected subjects from mixed families showed negative associations between genetic liability to bipolar disorder and WASI FSIQ (r=-0.50, p=0.009), WASI verbal IQ (r=-0.47, p=0.01), WASI performance IQ (r=-0.40, p=0.04) but not NART FSIQ.

Figure 5.12.3: Relationship between genetic liability to bipolar disorder and WASI full-scale IQ in unaffected subjects from mixed families



5.12.4 Genetic liability to bipolar disorder and memory

There was no evidence of a relationship between genetic liability to bipolar disorder and scores on the Rivermead behavioural memory test within any group.

5.13 Discussion

Two-hundred patients were successfully recruited for the current study, in accordance with the pre-stated aims. Fifty controls, 74 affected patients and 76 unaffected relatives were recruited in approximately the proportions required. Slightly fewer bipolar patients from 'mixed' families with histories of both schizophrenia and bipolar disorder were recruited (20). Most subjects provided complete neuropsychological data and no subjects failed to complete more than 2 tests.

Demographically, the groups were reasonably close in terms of age, gender, paternal social class and weekly alcohol consumption. Patients with schizophrenia and bipolar patients from mixed families were more often unmarried than the other groups and patients with schizophrenia had higher levels of cigarette use than all of the other groups. Past cannabis use was common in all groups, but was most common in unaffected people from schizophrenic families and lowest in unaffected families with a history of bipolar disorder only. Height, weight and body mass index were also reasonably similar across all groups. Unaffected people from schizophrenic families had a slightly smaller proportion of people with a right handed preference for writing. An educational history of compulsory education or less was more common both in patients with schizophrenia and their well relatives than in the other 5 groups.

Medication status differed across all 7 groups, although no controls were receiving medication at the time of the study. Antidepressant, benzodiazepine and antipsychotic use was recorded in all patient groups. A few relatives also received an antidepressant (4), benzodiazepines (1), or an antipsychotic (1). However, none suffered from a major affective disorder or schizophrenia. Two unaffected relatives had recent

bereavements, an additional unaffected relative was prescribed a low-dose antipsychotic as a hypnotic agent and one further subject was prescribed an antidepressant for symptoms of anxiety. Medicated relatives or controls were deliberately not excluded from the analysis since prescription of many of these medications is common in the general population and to exclude them would have limited the study's generalisability.

All groups generally had low scores in terms of the HDRS, Y-MRS and PANSS subscales. However, none of the groups were symptom free and many individuals from each group had partially or full psychotic symptoms on the Present State Examination. It is perhaps regrettable that control subjects were not also rated using the PSE. This would have led to a more meaningful comparison of the groups in terms of psychotic and other symptoms. Patients with schizophrenia had the largest median HDRS and PANSS scores compared to the other groups. However, bipolar patients from mixed families had higher scores on the YMRS than the other groups. Some unaffected relatives and controls also had several symptoms rated from the HDRS. Fewer symptoms were recorded using the other two scales (PANSS positive and Y-MRS). As anticipated, scores on the three symptom scales used differed between amongst the groups. In order to correct between group differences for the effects of symptoms, these measures were used as covariates in the subsequent analyses.

Studies have examined neuropsychological function in symptom free patients. However, positive and affective symptoms in bipolar and schizophrenic patients are both common and enduring in studies of discharged patients and their exclusion would have decreased the study's generalisability in terms of its overall characteristics. Symptoms detected using the PSE would often not be detected during a routine clinical examination

and may reflect the tendency of people with psychotic diagnosis to have chronic positive symptoms between episodes about which they do not complain.

Patients with Bipolar Disorder I only were included since Bipolar II disorder is a generally milder condition of less certain nosological status which may be more closely related to depression (Angst and Marneros 2001). If patients with Bipolar II disorder had been included in the current study then the groups may have differed more in terms of past psychiatric histories and illness severity and could have further confounded the results. The number of previous psychiatric admissions was not recorded on the basis that patients from several areas were recruited each of which differed widely in terms of community provision limiting the use of 'number/duration of inpatient admissions' as an index of severity. However, case note information was also insufficiently complete to make this calculation possible, as many patients were known to have been admitted to other hospitals, although no record of this could be found in the current case notes.

Patients with bipolar disorder from mixed families were intermediate between patients with schizophrenia and bipolar patients from bipolar families on several measures (e.g. memory, IQ, educational history, current socio-economic status). This is possibly consistent with a spectrum of continuous phenotypic variation from schizophrenia to bipolar disorder through intermediate forms. The finding is consistent with data from other sources that finds evidence of continuous variation in patients with functional psychosis (van Os et al. 1999;McIntosh et al. 2001).

5.13.1 Measurement of genetic liability

Genetic liability was measured using a continuous measure devised by Pak Sham at the Institute of Psychiatry in London (Lawrie et al. 2001). It provides a continuous score of genetic loading which increases according to the number and proximity of affected relatives in a family. It has been criticised on the grounds that everybody exceeding the threshold liability is assumed to develop the target disorder. Some have suggested a probit model would be more appropriate as it allows risk to increase with genetic loading, but not to a stage where disease is ever inevitable. Secondly, the calculation of the loading score is dependent upon the quality of family information available. In many cases, family members who were interviewed could remember several generations of extended family history. However, the families questioned are likely to differ in their openness towards mental illness, the area in which affected relatives were treated and the recommended classification system of the time. These differences in recall of familial data may be random, although it is possible that the diagnosis of the affected probands may be associated with possible bias. For example, patients with schizophrenia (and their relatives) may perceive more stigma and have greater memory impairments than patients with bipolar disorder. This may lead them to recall less family members with psychiatric disorder or, alternatively make false recollections about the nature of particular psychiatric symptoms. These difficulties might have been overcome if family data had been limited to first and second degree relatives only or if family data was only accepted as true where it could be confirmed in all cases by the corroborative oral account of close relatives *and* from written case-note information. However, although case note information on family background was

typically sparse, collaborative information from a relative *was* available in all patients. The diagnosis of relatively distant family members was not always possible to confirm from case records using operationalised criteria, although the diagnosis of at least one family member (other than the participant themselves) was conformed in *all* cases. Nevertheless, these methodological factors limit the validity of the continuous measure of genetic liability used.

5.13.2 Neuropsychological findings

5.13.3 General intellectual ability (IQ)

Schizophrenic patients had lower NART FSIQ, WASI FSIQ, performance and verbal IQ than control subjects. Bipolar patients from bipolar families differed from controls in terms of performance IQ only, having on average a lower performance IQ by about 10 points. Bipolar subjects from mixed families had significantly lower WASI FSIQ and performance IQs than controls, and NART IQ and verbal IQ impairments were greater than found in the bipolar subjects suggesting that the genetic liability to schizophrenia conferred an additional intellectual disadvantage to these patients.

Unaffected subjects with schizophrenic relatives only were also reduced in terms of NART IQ, WASI FSIQ, performance and verbal IQ compared to controls. Unaffected subjects with mixed family histories were also reduced in terms of NART IQ, WASI FSIQ, performance IQ but not verbal IQ, although the difference was suggestive of a non-significant reduction compared to controls. In contrast however, unaffected subjects with bipolar relatives only, showed no overall differences in any measure of intellectual ability compared to controls.

These results suggest that a broad pattern of intellectual impairments is characteristic of a genetic liability to schizophrenia only. A genetic liability to bipolar disorder appears to have no independent effect on any intellectual measure, with the exception of performance IQ in affected patients. It has been suggested that any pathological process affecting the brain will have a tendency to affect performance rather than verbal IQ, and the verbal-performance IQ deficit has been taken as a measure suggestive of organic brain dysfunction in some studies (Max et al. 1998). The measure of cognitive decline used in this study was the NART-FSIQ deficit, and this deficit was present (and positive) in all patient groups. However, only the well subjects with schizophrenic relatives only showed a difference in NART versus current IQ. These results also suggest that all patients and the well relatives of people with schizophrenia may have operated at a higher intellectual level previously than they did at interview. The reason for the difference in well relatives of schizophrenic patients was not clear, but the possibility that some relatives may become ill in the course of time is one which must be considered. Furthermore, in prospective studies of people at high risk of schizophrenia, intellectual disadvantage has been shown to be a risk factor which precedes the onset of symptoms.

5.13.4 Memory

Total Rivermead Memory scores (E-RBMT) were reduced in all patients and relatives compared to controls, whether or not these results were corrected for current IQ. The differences were greatest in affected patients, although unaffected subjects with

schizophrenic relatives only, showed larger impairments compared to the other unaffected groups.

Therefore there was little evidence for disease specificity for memory impairments in functional psychoses or in their well relatives. This is perhaps unsurprising since studies of schizophrenic patients (Aleman et al. 1999) and bipolars (Quraishi and Frangou 2002) have show a reduction in memory function compared to controls. However, this study found that these differences did not appear to differ in magnitude according to either diagnosis or family history, although relatives were generally less severely impaired than patients.

The RBMT measures primarily episodic memory and is designed so that its component tasks reflect everyday memory tasks. This study found that everyday memory tasks are impaired in both relatives and affected patients with psychosis and that these results persisted after correction for differences in current IQ and prescribed medication.

5.13.5 Executive function

The mean vector consisting of executive function test scores did not differ significantly between groups using MANOVA. Therefore the chosen hypothesis test did not reveal differences between the groups in terms of the pattern of executive function. However, mean vectors may fail to differentiate groups when differences are present between only one or two groups, or only on one measure of executive function, but not others. For this reason, mixed model ANOVAs were conducted to compare the mean score between groups on each measure of executive function individually.

For the HSCT, no differences were observed between any groups and controls for overall scaled score or error score, whether or not FSIQ was included on the model as a covariate. Therefore, although pair-wise differences have been presented for exploratory reasons, there appears to be a finding of 'no difference' for this measure. This finding is in contrast to several others, including one from the Edinburgh High Risk Study of (Byrne et al. 2003). Patients in the current study are on average about 15 years older than those in the EHRS, and other studies. The unaffected subjects may therefore include fewer people likely to develop psychosis in future and the older patients identified in this study may be those with better functional outcomes than identified in prospective studies. However, neither of these explanations are very satisfactory and the failure to find a difference may simply be due to insufficient sample sizes.

In contrast however, the Stockings of Cambridge (SOC) test scores clearly differed between the groups when the model did not include current IQ. All patient groups performed significantly worse than controls. However, only the unaffected relatives with at least one schizophrenic relative performed significantly worse than controls, whether or not other family members had a history of bipolar disorder. Once current FSIQ was taken into account, bipolar patients from bipolar and mixed families performed significantly worse than controls in post-hoc tests, and all other pair-wise differences disappeared.

Verbal fluency test scores also differed significantly between groups, with all patient groups showing impairments compared to controls. Unaffected relatives from all groups did not differ significantly in terms of performance from controls and to the appropriate unaffected relative group, although schizophrenic patients did significantly

worse than unaffected relatives with the same family history. Once the results had been corrected for current FSIQ, all of the between-groups differences became non-significant.

5.13.6 Attention and psychomotor performance

Psychomotor performance was reduced compared to controls in all patient groups compared to controls. Patients had lower digit-symbol substitution scores and longer simple and choice reaction times, although choice reaction in bipolars from mixed family was non-significantly reduced compared to controls, but was in the expected direction. Schizophrenic subjects performed relatively worse than other patient groups in terms of digit-symbol scores, although these differences were not statistically significant. Bipolars from mixed families performed significantly worse than bipolar subjects from bipolar families but were not significantly different from patients with schizophrenia. Unaffected relatives from each group showed no differences in either simple or choice reaction time compared to controls. However, unaffected subjects with schizophrenic relatives only had significantly lower scores on the DSST than controls.

These results suggest that psychomotor impairments are a consequence of illness, but not a genetic liability to illness. The exception to this is a finding of DSST impairments in relatives of patients with schizophrenia. Deficits in cognitive tasks with a high attentional component have been found before in the relatives of patients with schizophrenia (Pogue-Geile et al. 1991;Franke et al. 1993). In fact, these deficits have been measured in a number of ways, including using psychophysiological methods. Their presence has suggested to some that attentional deficits may be a mechanism by

which schizophrenia may develop although few have proposed a similar mechanism in bipolar disorder. The finding of an attentional deficit in unaffected subjects with schizophrenic relatives only supports the view that attentional disorders may reflect a vulnerability to schizophrenia. However, their presence in all affected subjects suggests that once the disease is apparent, attentional deficits show no diagnostic specificity and may possibly act to maintain psychiatric symptoms regardless of the factors which led to their development.

5.13.6 Relationship to genetic liability

Associations with genetic liability were examined by estimating the correlation coefficient between genetic liability for each disorder and measures of neuropsychological function. Only IQ (NART FSIQ, WASI FSIQ, PIQ, and VBIQ) and memory were considered as they differed across each group. A significant negative association was found between genetic liability for schizophrenia and WASI verbal IQ in patients affected by schizophrenia, but not those with bipolar disorder from mixed families. In contrast, unaffected subjects from schizophrenic families showed a positive association between genetic liability and performance IQ. This finding in schizophrenic subjects is consistent with a growing body of evidence showing that premorbid IQ is reduced many years before the onset of schizophrenia (see chapter 2). This relationship in relatives is in the opposite direction to that expected since the group as a whole performed worse on this measure than controls with no family history of mental disorder. The finding could be interpreted as evidence that genes for schizophrenia carry an advantage for those who do not express the full-blown syndrome. Although this

finding could be a false positive, it is possible that within the unaffected group with schizophrenic relatives, a subgroup of people with schizophrenia spectrum disorders accounted for the lower mean IQ, whereas in those patients without these spectrum disorders, the effect of genes for schizophrenia was to convey an intellectual advantage. This hypothesis is speculative, and since no measure of schizotypy was used in this study, we were unable to test this hypothesis. The finding is not without some support from studies of obligate carriers of schizophrenia who have been shown to have superior intellectual performance in one study (Steel et al. 2002), in spite of relatively high genetic liability. Others have also suggested that the ability of schizophrenia to persist, despite the fact that affected individuals typically reproduce less compared to the general population, suggests that the genes for schizophrenia must confer an advantage in at least some of those who carry them.

Genetic loading for bipolar disorder had no effect in patients where the disorder 'bred true'. However, in families where there was a mixed history of both schizophrenia and bipolar disorder and schizophrenia, three associations were found. In unaffected relatives, genetic liability was negatively associated with WASI full-scale, verbal and performance IQ, but not NART IQ. These differences were not expected since the group as a whole showed non significant reductions in these measures compared to controls. However, the presence of a subgroup of patients with schizophrenia or bipolar spectrum disorders might clarify or explain this finding, although data was not collected which would have allowed us to explore this further.

5.14 Strengths and limitations

Patients and controls participating in research projects may be atypical of the populations they are chosen to represent. Consenting patients are likely to have better neuropsychological, social and clinical function than those who decline the offer of participation and observed effect sizes from case-control studies may therefore be underestimated. The current study may also been subject to this general limitation, although the inclusion of some detained patients may have reduced this effect to a degree. Similar concerns could also be expressed about the sample of healthy controls. For example, controls may be unrepresentative of the general population when they are drawn from socially advantaged backgrounds, such as from the clinical staff of an associated research institution. The control subjects for the current study were drawn, where possible, from the non-genetic relatives and social networks of the patients themselves. This was in an attempt to draw controls from a similar population as the other groups, differing only in terms of genetic background and diagnosis. However, it is uncertain whether this can ever be accomplished in case-control studies. Furthermore, control subjects from the current study had higher intellectual functioning than that expected from a mean population IQ of 100. It is possible therefore that some pairwise comparisons with controls may have been overestimated in this study, although other comparisons are less likely to have been affected. Furthermore, many analyses were adjusted for current IQ so that differences in neuropsychological performance were probably not due to differences in general intellectual function alone.

The measurement of IQ using the WASI is well validated in normal populations and the level of agreement with the full WAIS-R is known to be high (see product manual). Similarly, the other neuropsychological measures used were chosen because of

previous use in psychiatric populations and because they have yielded differences between psychotic patients and controls in other studies (Byrne et al. 2003). However, although the NART is repeatedly used in studies of psychiatric patients, it maybe be more unreliable (Heinrichs and Zakzanis 1998) and show a tendency to overestimate premorbid IQ in affected patients (David et al. 1997).

The results of this study were corrected for current symptoms (PANSS positive, Y-MRS, HDRS) in all cases. However, the possibility of confounding by motivation or general health (amongst others) is possible. Sex and, where appropriate, age were also included as covariates. A role for age and sex in neuropsychological test performance has been suggested by several authors, necessitating their inclusion as covariates. Age of onset, number of previous episodes and duration of illness were not included as covariates, although it is possible that they too may affect neuropsychological test performance. Age of onset and duration of illness in years were relatively similar in the three patient groups which may have reduced any potential confounding. An interaction between number of episodes and diagnosis has been suggested by some authors, although this was not systematically investigated in the current study. It is however possible that neuropsychological impairment in bipolar subjects is associated with cumulative episodes of illness and hypercortisolaemia (Rush et al. 1996), whereas in schizophrenia this relationship may be absent. Other potential confounds were deliberately not-adjusted for in the analysis. For example, current intellectual performance and socio-economic status may deteriorate after the first episode of illness. By matching on these variables, it is possible that socially and intellectually disadvantaged controls would have been selected.

Finally, many of the neuropsychological differences observed between groups may have affected recall of episodic and autobiographical events. This may have led to a biased assessment of genetic liability between groups making any adjustment for genetic liability between groups difficult. For example, differences between schizophrenic patients and their relatives could be taken as an index of neuropsychological impairment contingent upon phenotypic expression of illness. However, the calculation of genetic liability assumes that subjects become ill primarily because they are at increased genetic liability and affected subjects always have higher genetic loading scores that their unaffected relatives. However, there is some evidence (covered in more detail in the next chapter) that genetic liability is not the major determinant of phenotypic expression in multiply affected families, and that affected and unaffected family members are probably more closely matched on this measure that the results shown earlier in this chapter would suggest.

Although several differences were observed between the groups used in this study, it is impossible to be certain whether they preceded or followed the expression of illness in affected subjects. It is also likely that those impairments also found in close relatives (e.g. memory impairments) were present before illness onset. However, the possibility that these differences are magnified or confounded by the brain's adaptation to the effects of medication, psychotic symptoms or other aspect of the disease process cannot be excluded. The meaning of these differences in terms of the neurotransmitter or physiological pathways affected is also unclear. Although memory performance (for example) is associated with changes in the hippocampus in healthy subjects, the mechanism of impairments in those affected by psychosis or at increased genetic

liability may not necessarily involve the same mechanism. The interpretation of IQ in terms of brain physiology or structure is particularly difficult and may involve the coordination of several interconnected regions (Posthuma et al. 2003).

Future studies of neuropsychological performance in subjects with, or at increased liability to, psychosis could make several improvements in terms of study methodology. Firstly, unaffected subjects could be followed prospectively, preferably before illness onset such that performance could be ascertained before any physiological adaptation to illness or medication had the potential to confound the results. Once some subjects had become unwell, repeated assessments could continue in order to measure any progressive features of the illness. Large study numbers would be required, even if the study included only those at very high risk. Brain physiology could also be examined during test performance, to further elucidate the mechanisms underlying cognitive impairments.

Although the current study examined groups of people with 'functional psychosis' it is unclear whether the differences observed relate only to diagnosis, or whether they relate to psychotic symptoms (hallucinations or delusions). Most people included in the current study had psychotic symptoms, although the numbers involved do not allow enough statistical power to perform sensitivity analyses. It has also been suggested that dimensions of psychotic symptoms found in affected subjects represent the extremes of a range of variation within the population as a whole. Brian anatomy and physiology may be more closely related to these dimensions than to diagnosis. A future study could usefully re-examine symptom dimensions a broad spectrum of functional

psychotic illness and relate these findings to neuropsychological test performance, brain structure and perhaps function.

Chapter 6: Imaging Results

6.1 Summary of patient groups and contrasts performed

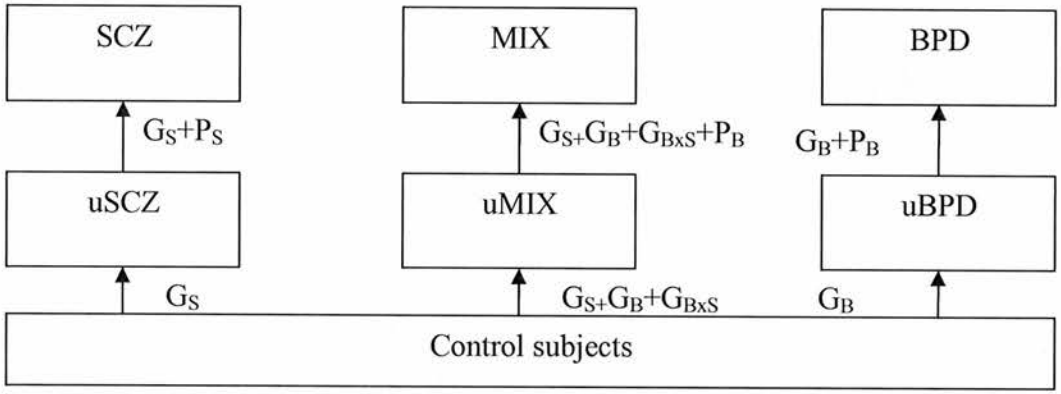
The purpose of collecting neuropsychological and imaging data on patients with psychosis and their well relatives was so that the role of genetic liability alone could be separated from environmental effects and effects which are dependent upon disease expression. Since environmental effects were not actually measured in this study, effects contingent upon disease expression or environmental exposure could not be separated.

Figure 6.1 summarises the main genetic and phenotypic effects in each group. G_S refers to a genetic liability to schizophrenia, G_B refers to a genetic liability to bipolar disorder and P_S and P_B refer to the phenotypic associations of schizophrenia and bipolar disorder respectively. G_{SxB} refers to a possible interaction between genetic liability for schizophrenia and bipolar disorder. Genetic and phenotypic/environmental effects are assumed to be additive in the diagram and lead to the brain structure observed in affected patients. The effects observed in relatives are assumed to reflect only the changes contingent upon genetic liability alone. Assuming a standard threshold-liability model, these assumptions may not be valid as differences between affected family members and their well relatives are likely to represent differences in genetic liability as well as environmental/phenotypic effects. However evidence from the Edinburgh High Risk Study (Johnstone et al. 2004) and from studies of identical twins (Cardno and Gottesman 2000;Sullivan et al. 2003) suggests that this may not be the case. In the EHRS, high-risk subjects who became unwell were similar to those who remained healthy in terms of the continuous measure of genetic liability used. Evidence from a meta-analysis of twin studies suggests that *shared* environmental factors are important for the development of schizophrenia in people matched in terms of their genetic

liability further suggesting that, at least in schizophrenic twins matched in terms of liability, that environmental influences may determine who becomes unwell. In general terms, these data are consistent with a two hit model with genes determining the presence of an extended schizophrenic phenotype (including schizotypal and other disorders) and environmental influences determining in the majority of cases who becomes unwell. This model could be criticised on a number of grounds including the fact that many people with psychosis show no personality or social impairments before they become unwell. However, it is not clear that a more suitable model is available and this relatively simple model is convenient for the purposes of the current study as long as its limitations are borne in mind. The figure is meant to act as a visual aid to the contrasts described on the following page and as an aid to the interpretation of results.

Figure 6.1: Summary of patient groups and effects on brain grey/white matter density

Abbreviations
SCZ: schizophrenic subjects from families affected by schizophrenia only
MIX: bipolar subjects from families affected by schizophrenia and bipolar disorder
BPD: bipolar subjects from families affected by bipolar disorder only
'u' prefix refers to unaffected members of the above three groups



The aim of the current study is chiefly to estimate the genotypic and phenotypic/environmental effects shown on the above figure. The contrasts chosen are listed on the following page along with a brief explanation of each.

Contrasts performed (grey matter)
(2-tailed unless otherwise stated)

Group 1: Patients versus controls

Two-tailed contrasts in this group were performed between each patient group and controls. This was in order to ascertain the additive genetic and environmental/phenotypic effects acting upon the subjects within each group. Differences between schizophrenics (SCZ) and controls are assumed to reflect the additive genetic and environmental/phenotypic influences acting in that group. The control versus bipolars from mixed families (MIX) contrast is assumed to represent the phenotypic/environmental effects of a bipolar phenotype plus the genetic liability to both bipolar disorder and schizophrenia. Finally, the differences between bipolars from bipolar families (BPD) and controls are assumed to reflect the phenotypic/environmental effects of having bipolar disorder plus the genetic liability to that disorder.

Contrasts performed in group 1
1a: SCZ versus controls: $(G_S + P_S - 0)$
1b: MIX versus controls: $G_S+G_B+G_{BxS}+P_B$
1c: BPD versus controls: G_B+P_B

Group 2: Between patient group contrasts

Contrasts were performed between patient groups to assess the magnitude and specificity of control versus patient differences found previously. Schizophrenic patients were compared with bipolar patients from both mixed and bipolar pedigrees in order to ascertain which control versus SCZ findings was specific to this contrast. Differences between schizophrenic subjects and bipolars from mixed families may also reflect

environmental/phenotypic effects contingent upon having bipolar disorder. Differences between bipolar subjects from mixed families and bipolars from bipolar families may also reflect differences contingent upon a genetic liability to schizophrenia.

Contrasts performed in group 2
2a: SCZ versus MIX: $(G_S+P_S)-(G_S+G_B+G_{BxS}+P_B)$
2b: SCZ versus BPD: $(G_S+P_S)-(G_B+P_B)$
2c: MIX versus BPD: $(G_S+G_B+G_{BxS}+P_B)-(G_B+P_B)$

Group 3: Masked contrasts

On the basis of the results of contrasts from group 3, two further masked contrasts were performed. Both were used to address the specificity of grey matter reductions in schizophrenic subjects compared to controls. The first contrast examined which reductions did not occur in the MIX versus control contrast (1b).The second examined which reductions did not occur in the BPD versus control contrast (1c).

Contrasts performed in group 3
3a: Contrast 1a masked by contrast 1b: (G_S+P_S) NOT $(G_S+G_B+G_{BxS}+P_B)$
3b: Contrast 1a masked by contrast 1c: (G_S+P_S) NOT (G_B+P_B)

Group 4: Patient versus unaffected relative contrasts

In order to assess the specific environmental/phenotypic effects in affected patients, three contrasts were made between affected patients and unaffected family members from the same family background. The first contrast compared schizophrenic patients to well family members and is assumed to reflect grey matter changes contingent upon the phenotypic effects of schizophrenia only. This may reflect the additional environmental or phenotypic effects in that group. The two bipolar groups

were also compared to family members from the same pedigrees. In both of these contrasts the environmental/phenotypic influences upon people with bipolar disorder were estimated. Differences between the results of these contrasts may also reflect the interaction of phenotypic/environmental effects with the effects of a genetic liability to schizophrenia.

Contrasts performed in group 4
4a: SCZ versus uSCZ: $(G_S+P_S)-(G_S)$
4b: MIX versus uMIX: $(G_S+G_B+G_{BxS}+P_B)-(G_S+G_B+G_{BxS})$
4c: BPD versus uBPD: $(G_B+P_B)-(G_B)$

Group 5: Unaffected subjects versus controls

Unaffected relatives of affected subjects from all groups were compared to controls. These contrasts were assumed to reflect the effect of genes for either schizophrenia or bipolar disorder or their sum. The actual contrasts computed are shown below.

Contrasts performed in group 5
5a: uSCZ versus controls: G_S
5b: uMIXversus controls: $G_S+G_B+G_{BxS}$
5c: uMIX versus controls: G_B

Group 6: Exploratory contrasts

Finally six exploratory contrasts were performed. The first calculated the schizophrenic versus relatives of schizophrenic patients contrast (SCZ vs. uSCZ, 1-tailed), masking it with the bipolar versus unaffected relatives of bipolar patients contras (BPDvs. uBPD, 1-tailed). This contrast may be taken to infer the effect of a phenotypic expression of schizophrenia that is not present in bipolar disorder. Secondly, the SCZ vs.

uSCZ contrast was masked with the MIX-uMIX contrast providing information on changes contingent upon phenotypic but not genotypic effects in patients affected by schizophrenia. Thirdly and fourthly, patients versus relatives contrasts were calculated for both bipolar groups and were masked by the schizophrenic versus unaffected family members form schizophrenic families contrast (SCZ vs. uSCZ, 1-tailed). These contrasts enabled grey matter differences contingent upon a phenotype of bipolar disorder to be calculated in both cases. In bipolar patients from bipolar families, this was assumed to reflect differences which were not present in schizophrenic patients. The second analysis was assumed to reflect phenotypic but not environmental influences upon a diagnosis of bipolar disorder.

Contrasts/analyses performed in group 6
6a: uSCZ-SCZ masked by uBPD-BPD: (PS) NOT (PB)
6b: uSCZ-SCZ (~PS) masked by uMIX-MIX (~GS): (PS) NOT (GS)
6c: uMIX-MIX(~PB) masked by uSCZ-SCZ (~PS): PB NOT PS
6d: uBPD-BPD (~PB) masked by uSCZ-SCZ (~PS): PB NOT PS
6e: uMIX-MIX (~PB) masked by control-uBPD (~GB): PB NOT GB

Contrasts performed (white matter)

Only contrasts from group 1, 3 and 5 were conducted based upon the results of the grey matter analyse, for the reasons which are outlined in the forthcoming pages. Further explanation for this choice of contrasts is given in the text alongside the appropriate section.

6.2 Images acquired

Seven people out of 200 (3.5%) declined to have an MRI scan of the brain. Of the remaining 193 scans, one further scan was lost from the 'bipolar from bipolar families' group at the reporting stage when a 'large cyst of presumed neurodevelopmental origin' was found on the scan by the reporting neuroradiologist. Therefore 192 people (96%) provided useable data and no scans were lost due to movement artefact. The proportion of each group providing useable data is summarised in table 6.1.

Table 6.1: Proportion from each group who received an MRI scan

Group	Had a scan? (n/%)		Total
	No	Yes	n
Control	1 (2)	49 (98)	50
Scz from Scz family	1 (3.7)	26 (96.3)	27
OK from Scz family	1 (4)	24 (96)	25
BPD from BPD family*	0	27 (100)	27
OK from BPD family	2 (8.3)	22 (91.7)	24
BPD from mixed family	1 (5)	19 (95)	20
OK from mixed family	1 (3.7)	26 (96.3)	27
Total	**7 (3.5)**	**193 (96.5)**	**200**

*A scan was lost at the reporting stage because of a large undiagnosed temporal lobe cyst

6.3 Characteristics of patients receiving an MRI scan

The proportions of people from each group expressing a right-handed preference for writing were similar. Patients with schizophrenia and their close unaffected relatives had the lowest proportions (88.5% and 83.3% respectively). The proportion of males from each group was less balanced between groups, ranging from a minimum of 14/26 (36.8%) in bipolar patients from mixed families to 14/26 (53.9%) in their close relatives

and in bipolar patients from bipolar families. Mean height was similar across all groups (maximum 1.72m in controls, minimum 1.67m in the relatives of schizophrenic subjects) with approximately equal variance. Mean age showed less balance across the groups ranging from a maximum of 40.5 years in bipolar subjects from bipolar families to a minimum of 34.2 years in unaffected people from mixed families. Since handedness, sex, height and age may all potentially confound between group differences in regional brain volumes, they were included as nuisance covariates in the VBM analyses.

Table 6.3: Demographic characteristics of subjects providing useable MRI data

Group	N	R Hand Pref n (%)	Male n (%)	Height mean (sd)	Age mean (sd)
Control	49	46 (93.9)	23 (46.9)	1.72 (0.10)	35.27 (11.12)
SCZ from SCZ	26	23 (88.5)	13 (50)	1.70 (0.08)	36.85 (13.70)
OK from SCZ	24	20 (83.3)	11 (45.8)	1.67 (0.07)	38.92 (12.87)
BPD from BPD	26	24 (92.3)	14 (53.9)	1.70 (0.11)	40.5 (12.07)
OK from BPD	22	21 (95.5)	9 (40.9)	1.70 (0.10)	34.73 (12.60)
BPD from MIX	19	19 (100)	7 (36.8)	1.69 (0.08)	39.74 (9.22)
OK from MIX	26	24 (92.3)	14 (53.9)	1.71 (0.11)	34.12 (12.98)
Total	**192**	**177 (92.2)**	**91 (47.4)**	**1.70 (0.10)**	**36.87 (12.15)**

Voxel based tests were conducted in three broad categories stated previously in the methods chapter. Each analysis used the same covariates stated above. Grey matter analyses included the number of grey matter voxels extracted from each scan as a covariate, extracted using the get_globals.m MATLAB script. Similarly total white

matter voxel number was used as a covariate in the white matter analyses. In both cases, voxels were extracted from brains in native (untransformed) space.

6.4 Differences between patients and controls

Pairwise differences between patients and controls were computed using t-contrasts. Results are presented in the form of tables and in the form of statistical parametric maps overlaid on transverse slices through the study specific T1 template. Parametric maps were *thresholded* at a significance of p=0.01. Differences with a *voxel-wise* significance level of p<0.1 (corrected) are reported in the tables at the voxel of maximum difference.

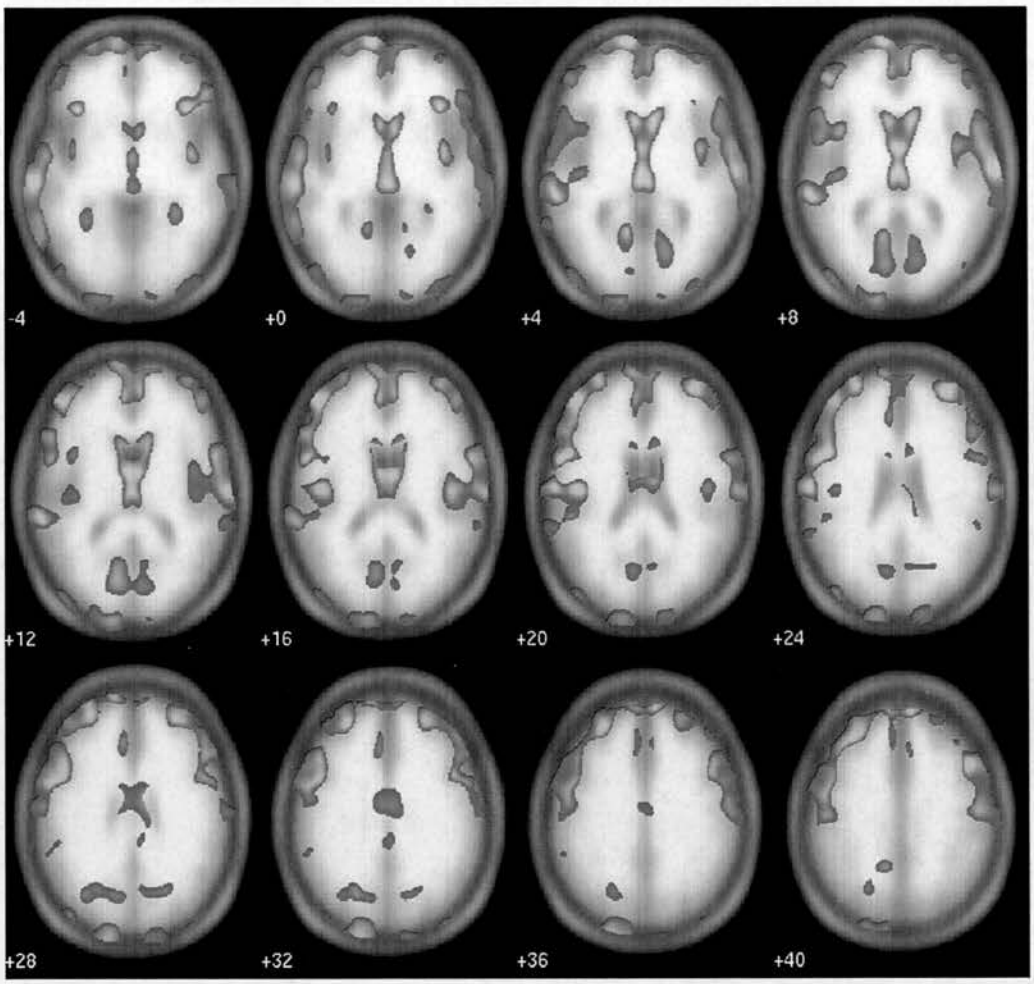
Differences between schizophrenic subjects and controls were found in several areas, particularly the left middle and inferior frontal gyri and also in Broca's area (BA 44). A trend was also found for reductions in left parahippocampal grey matter density in schizophrenic patients compared to controls. Significant differences were also found in the medial-dorsal and anterior thalamus using the small volume correction (SVC) image. Although the differences in cortical volumes are right-sided, the contrast image suggests that corresponding areas of left-sided reduction may also be present which failed to reach voxel-wise significance.

Patients with bipolar disorder from mixed families showed reductions in grey matter density in the right inferior frontal gyrus, right insula and right pre-central gyrus (non-significant trend). The qualitative appearance of the contrast image is similar to that for the schizophrenic versus control comparison (thresholded at p<0.01) and the significant right sided critical differences found appear to also have left sided

counterparts which did not reach voxel-wise significance. However, no differences were found in thalamus, amygdala or hippocampal grey matter density using the SVC, although areas of possible difference can be seen on the contrast image at the anterior pole of the thalamus which failed to reach voxel-wise significance.

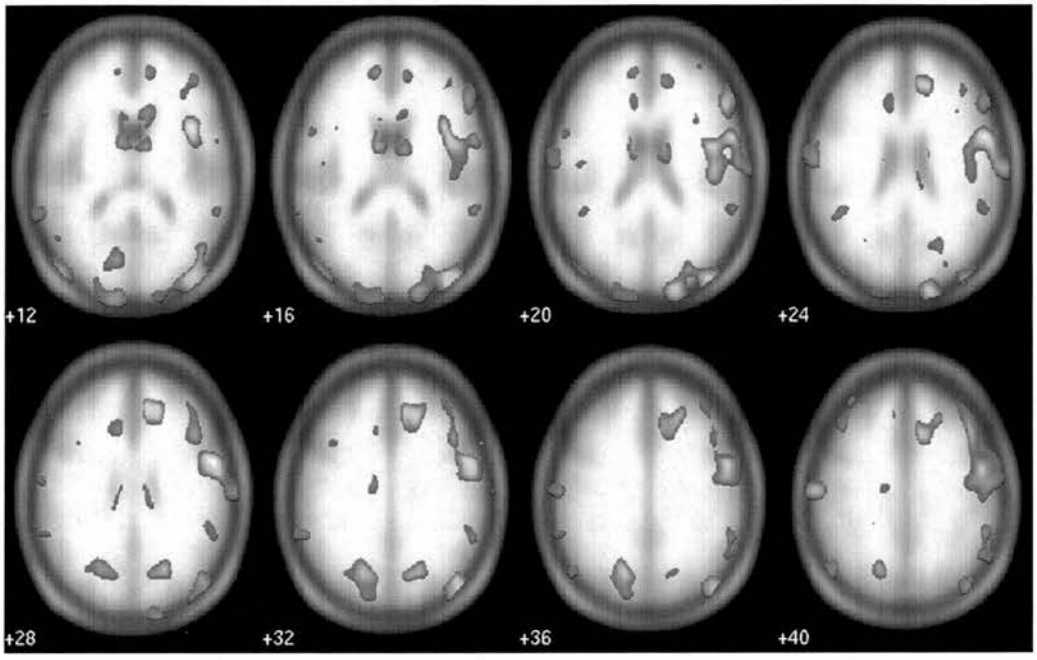
Bipolar patients from bipolar families showed none of the frontal grey matter reductions found in schizophrenic patients or bipolar patients from mixed families. Even frontal grey matter differences thresholded at $p<0.01$ (uncorrected) were sparse and did not appear to form confluent areas. However, bipolar patients from bipolar families differed significantly in terms of anterior thalamic density bilaterally compared to controls. The voxel of maximal difference was situated immediately anterior to the anterior thalamus and the map of uncorrected voxels with which it was contiguous clearly included the anterior thalamus. However, a small part of the caudate nucleus was also included in the region of difference (overlaid on the contrast image and thresholded at $p<0.01$).

Figure 6.4.1 and Table 6.4.1: Differences in grey matter density between schizophrenic subjects and controls



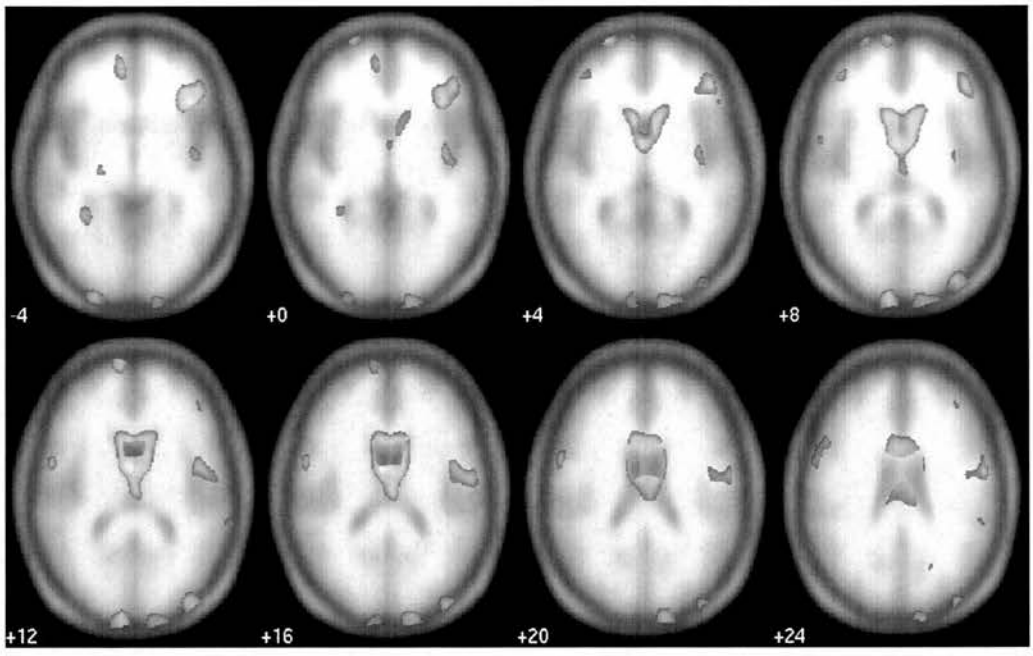
Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain				
0.002	-41	12	48	Middle frontal gyrus, BA6
0.004	-34	31	40	Middle frontal gyrus, BA 8
0.046	-50	11	21	Inferior frontal gyrus, BA 44
0.075	-31	-48	-5	Parahippocampal gyrus, BA 19
Small volume correction thalamus and amygdala-hippocampus				
0.004	1	-16	7	Thalamus (medial dorsal nucleus)
0.006	0	-1	9	Thalamus (anterior nucleus)
0.017	5	-21	6	Thalamus (medial dorsal nucleus)

Figure 6.4.2 and Table 6.4.2: Differences in grey matter density between bipolar subjects from mixed families and controls



Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain				
0.004	55	5	25	Inferior frontal gyrus, BA 9
0.021	41	11	12	Insula, BA 13
0.089	50	-1	44	Pre-central gyrus, BA 4
Small volume correction thalamus and amygdala-hippocampus: No differences				

Figure 6.4.3 and Table 6.4.3: Differences in grey matter density between bipolar subjects from bipolar families and controls



Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain				
0.075	51	-7	46	Pre-central gyrus (BA 4)
Small volume correction thalamus and amygdala-hippocampus				
0.005	-4	-1	11	Thalamus (anterior nucleus) and body of caudate nucleus
0.01	2	-3	13	Thalamus (anterior nucleus) and body of caudate nucleus

6.5 Pairwise differences between patients with psychosis

Pairwise contrasts between each affected patient group were conducted. No significant differences were found for any region. A single trend to significance was found between schizophrenic subjects and bipolars from mixed families. Schizophrenic subjects had a single area of decreased density in the left superior temporal gyrus compared to bipolars from mixed families (Talairach coordinates -53, -31, 11; $p_{corrected}$=0.059) although the voxel of maximum difference was approximately 3mm from the superior temporal gyrus itself. No other significant differences were found.

Since considerable differences were found for each control-patient comparison, between patient differences required further clarification. Since most subjects were in the control group, contrasts including this group will have had the greatest statistical power. Furthermore, within patients with a given diagnosis there may be considerable heterogeneity in terms of symptoms, cognitive deficits and previous risk factor exposures (e.g. obstetric, drug and alcohol, stressful life events). A given diagnosis may therefore reflect a single endpoint of a number of different aetiological pathways each of which may have different effects on brain structure. Therefore, grey and white matter density may show greater variance within affected patients than within control subjects, further reducing the power to detect any real differences between groups. For these practical and theoretical reasons, pairwise differences between patient groups were investigated by computing the contrast image between schizophrenic subjects and controls and masking the differences with each bipolar versus control contrast images. Each mask was thresholded at $p<0.05$ (uncorrected) so that any differences between bipolar subjects and controls significant at this level would be removed from the

schizophrenic versus control comparison. This analysis effectively yields differences in grey matter density between schizophrenics and controls (for example) which are not found between bipolars and controls (the masking images).

Table 6.4: VBM analysis of schizophrenia versus bipolar patients from mixed families

Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain				
0.059	-53	-31	11	Superior temporal gyrus, BA 41
Small volume correction thalamus and amygdala-hippocampus: No differences				

6.6 Masked contrasts

In order to overcome these potential problems of direct patient group comparisons, two further analyses were conducted. Firstly, the control versus schizophrenia contrast was masked with the control versus bipolars from mixed families contrast. This contrast removed any significant regions of differences in both groups from further consideration and therefore tested whether any reductions were exclusive to schizophrenia, or were also found in bipolar patients with a family history of schizophrenia. Secondly, the control versus schizophrenia contrast was masked with the controls versus bipolar from bipolar families contrast. Again, this removed any regions of common difference from further consideration, and tested for differences which were not present in bipolars from bipolar families.

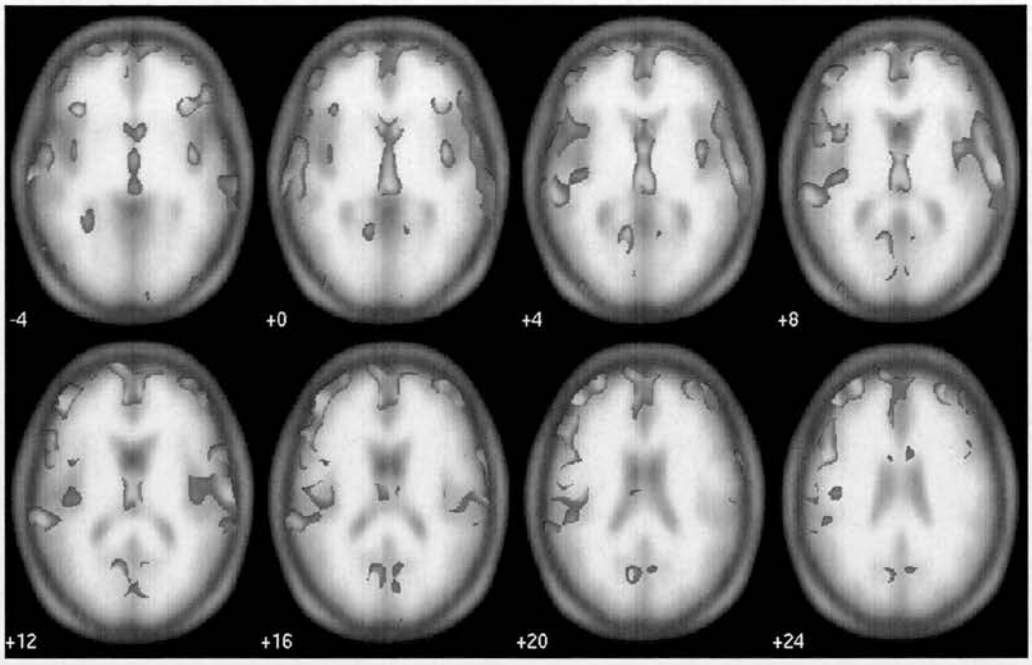
Masked contrast 1: schizophrenia versus controls contrast masked with bipolars from mixed families versus controls contrast

The first contrast examined which reductions in grey matter density found between schizophrenics and controls were not found in bipolars from mixed families compared to controls. The resulting analysis found that reductions in middle and inferior frontal gyrus and dorsomedial thalamus remained after masking with the control-bipolar from mixed families contrast image. This suggests that these reductions are greater in schizophrenia and are possibly specific to this group. An area close to the anterior thalamus also emerged as significant. However, by inspecting the contrast image itself, this voxel appears to be contiguous with an area of medial and midline difference suggesting medial rather than anterior thalamic differences.

Masked contrast 2: schizophrenia versus controls contrast masked with bipolars from bipolar families versus controls contrast

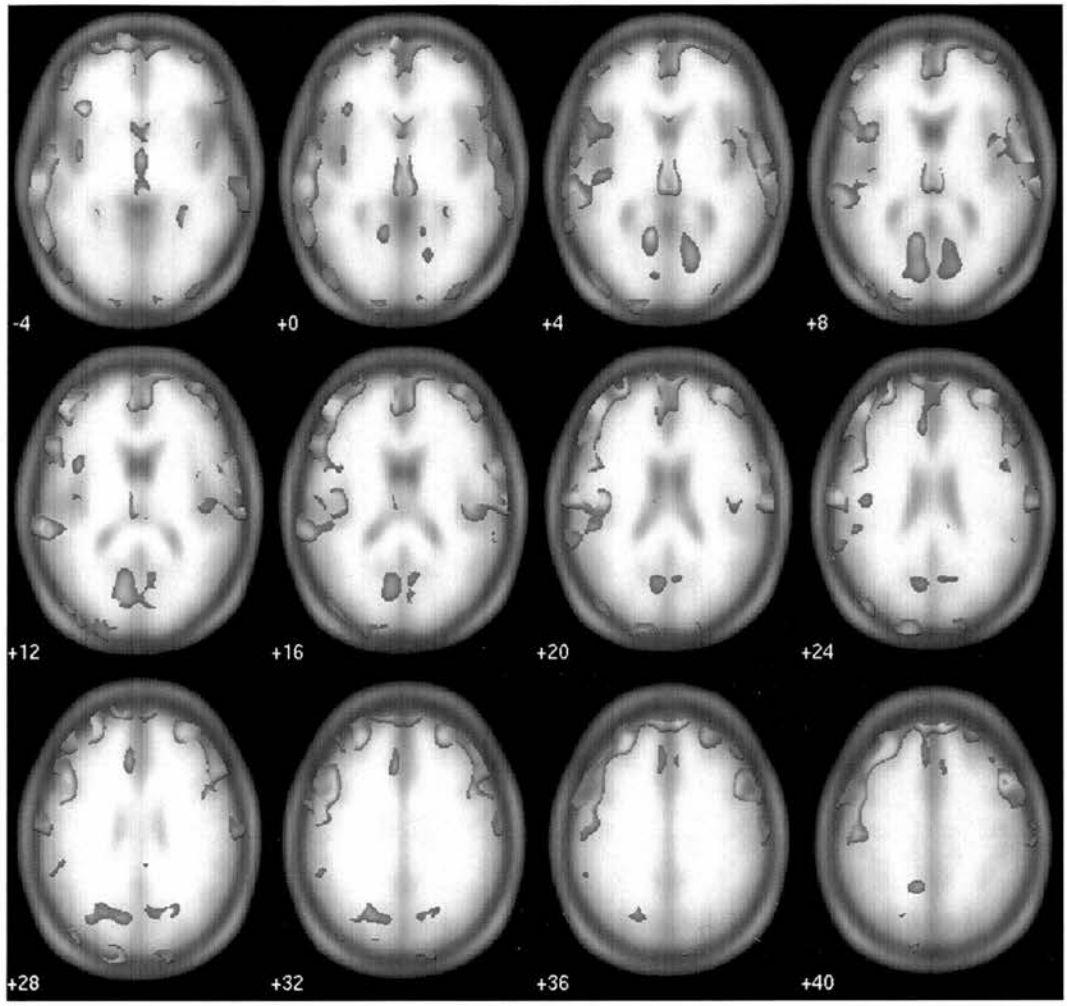
The second contrast examined which reductions in grey matter density found between schizophrenics and controls were not found in bipolars from bipolar families compared to controls. Middle frontal gyrus grey matter density reductions were found which were not removed by the masking image. However, all inferior frontal gyral reductions were removed after the mask was applied (BA 9 and 44). Dorsomedial thalamic grey matter reductions remained significant suggesting they were either greater in schizophrenic subjects or specific to them.

Figure and table 6.6.1: Differences in grey matter density between schizophrenic subjects and controls (exclusively masked by control versus bipolars from mixed families contrast)



Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain				
0.004	-34	31	40	Middle frontal gyrus, BA 8
0.040	-40	13	46	Middle frontal gyrus, BA 6
0.046	-50	11	22	Inferior frontal gyrus, BA 44
0.08	-31	-48	-6	Parahippocampal gyrus, BA 19
Small volume correction thalamus and amygdala-hippocampus				
0.004	0	-16	7	Thalamus (medial dorsal nucleus)
0.013	-1	-2	7	Thalamus
0.016	5	-21	6	Thalamus (medical dorsal nucleus)

Figure and table 6.6.2: Differences in grey matter density between schizophrenic subjects and controls (exclusively masked by control-bipolar from bipolar families contrast)



Voxel P corrected	x, y, z (mm) Talairach coordinates			Region of difference
				Results for whole brain
0.003	-40	13	50	Middle frontal gyrus, BA 6
0.004	-34	31	40	Middle frontal gyrus, BA 8
				Small volume correction thalamus and amygdala-hippocampus
0.02	-4	-19	6	Thalamus, mediodorsal nucleus

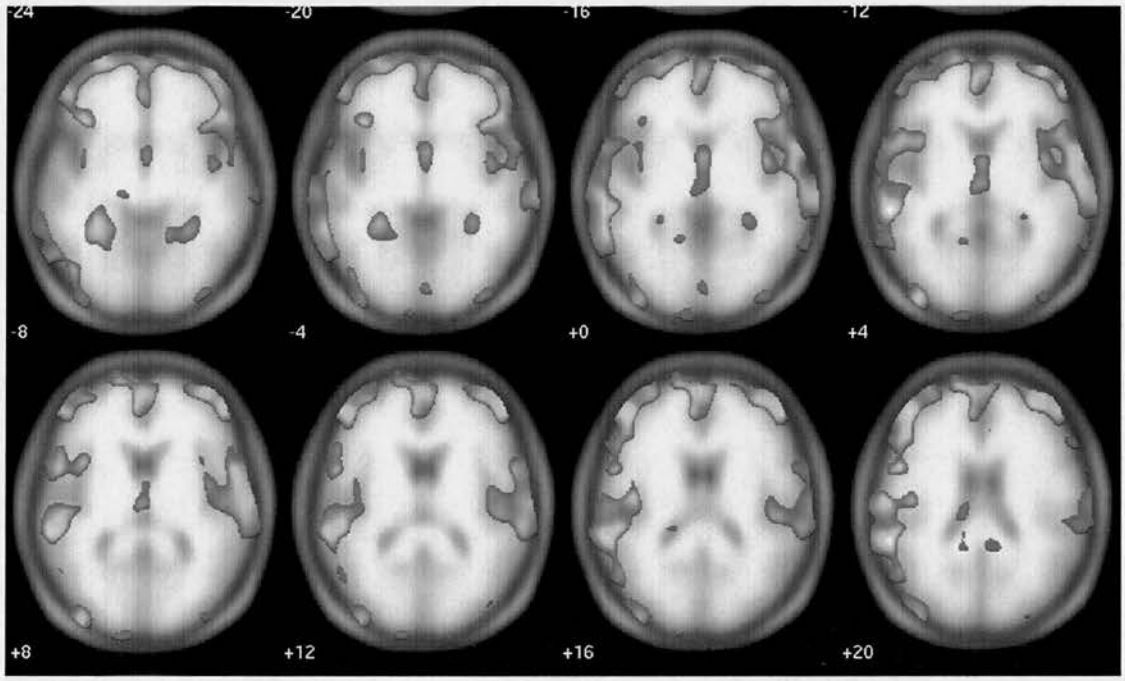
6.7 Differences between patients and unaffected relatives

To detect differences contingent upon the expression of illness, pairwise comparisons were made between patients and unaffected subjects from the same types of family.

Differences between schizophrenic subjects and their well relatives were the most extensive, and qualitatively similar in many regards to the differences between schizophrenic subjects and controls. Significant differences in grey matter density were found in the left superior and middle temporal gyri and left pre-central gyrus. Using the small volume correction, reductions were also found in right amygdala. Examination of the contrast image itself, with differences of significance $p<0.01$ uncorrected superimposed, did not suggest the presence of lateralised differences.

No significant differences were found between bipolar subjects from bipolar families and their well relatives or between bipolars from mixed families and their well relatives.

Figure and Table 6.7.1: VBM analysis of schizophrenics versus healthy subjects from schizophrenic families



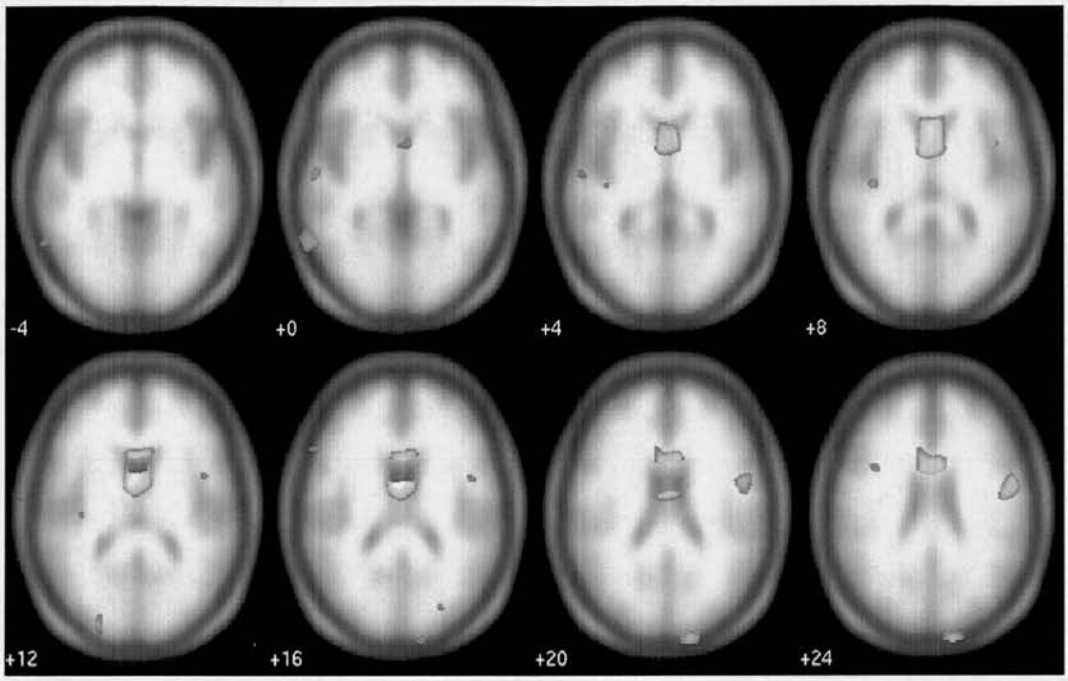
Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
				Results for whole brain
0.006	-58	-39	20	Superior temporal gyrus, BA 22
0.009	-58	-33	5	Middle temporal gyrus, BA 22
0.012	-53	-15	36	Pre-central gyrus, BA 4
				Small volume correction thalamus and amygdala-hippocampus
0.033	30	1	-20	Amygdala

6.8 Differences between unaffected relatives and controls

No significant differences were found between unaffected subjects from schizophrenic families and controls. Unaffected relatives from bipolar families had reduced grey matter density maximal immediately anterior to the thalamus and posterior to the caudate nucleus. The area of contiguous voxels (thresholded at $p<0.01$ uncorrected) extended into both caudate and anterior thalamus, although were much more extensively distributed in the latter structure. A trend to significance was also found in a similar region, but in the right hemisphere. The area of contiguous voxels (thresholded at $p<0.01$ uncorrected) also extended into both caudate and anterior thalamus.

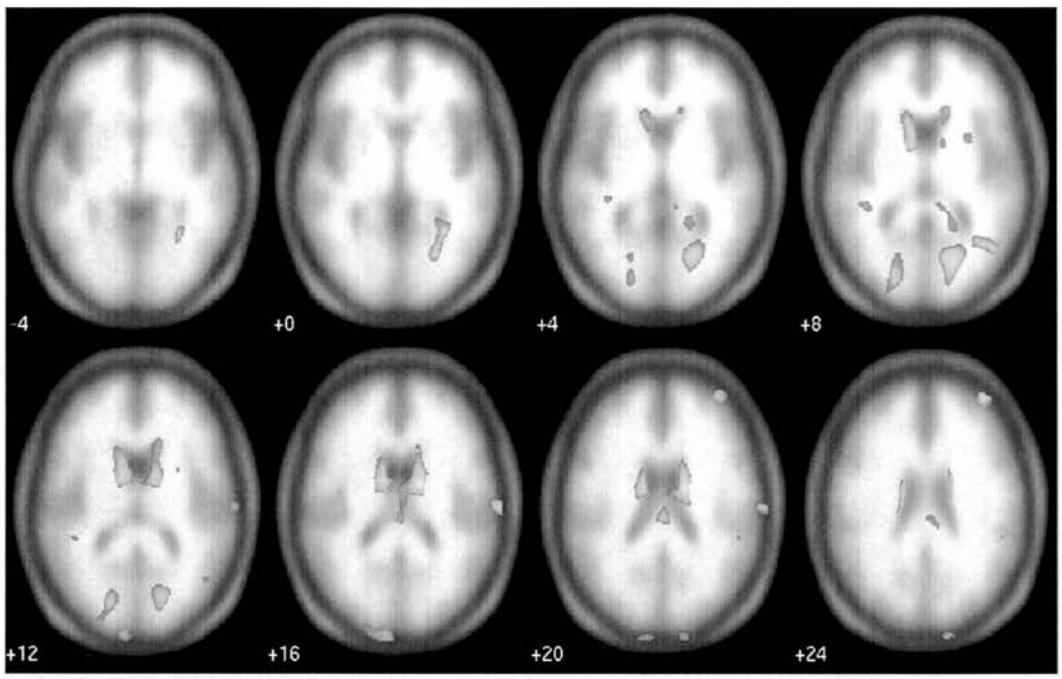
Unaffected relatives from mixed families differed from healthy controls in left and right anterior thalamic nuclear density. The region of contiguous voxels extended into the body of the caudate bilaterally, although the anterior thalamus was more closely associated with this region of significant difference.

Figure and table 6.8.1: Differences in grey matter density between unaffected subjects from bipolar families and controls



Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain: No differences				
Small volume correction thalamus and amygdala-hippocampus				
0.026	-5	-1	12	Thalamus (anterior nucleus) and body of caudate
0.092	3	-1	13	Thalamus (anterior nucleus)

Figure and table 6.8.2: Differences in grey matter density between unaffected subjects from mixed families and controls



Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results for whole brain: No differences				
Small volume correction thalamus and amygdala-hippocampus				
0.026	15	-4	16	Thalamus (anterior nucleus) and body of caudate
0.092	-10	1	13	Thalamus (anterior nucleus) and body of caudate

6.9 Thalamic densities across groups

Evidence for a reduction in anterior thalamic grey matter density was found in schizophrenic and bipolar subjects compared to controls, regardless of the family history. Reductions in bipolars from mixed families compared to controls were indirectly inferred from the contrast image, which showed reductions in anterior nucleus grey matter ($p<0.01$ uncorrected) and from the masking contrasts. In addition, significant differences were also found between unaffected relatives from bipolar families and controls and between unaffected subjects from mixed families and controls. Therefore, anterior thalamic grey matter density was reduced significantly for control versus patient and control versus relative comparisons apart from the 'unaffected relatives from schizophrenic families versus controls' comparison.

Schizophrenic patients had an additional region of dorsomedial thalamic grey matter reduction compared to controls, which was not evident in other comparisons. This area of dorsomedial thalamic reduction remained after the contrast was masked with the control versus bipolar contrast but was removed when masked by the control versus bipolars from mixed families contrast. No significant differences were found between unaffected people from schizophrenic families and controls in terms of anterior or dorsomedial thalamic grey matter density.

Anterior thalamic density reductions appeared to show no disease specificity, and were present in two of the three relatives groups compared to controls. Since the groups sizes were relatively small, it was not safe to conclude that there was no difference in anterior thalamic density between controls and unaffected people from schizophrenic families without first examining the effect size in that group. Three

further post-hoc contrasts were performed comparing 1) controls to all groups 2) controls to all patients and 3) controls to all relatives. In each case, reductions in anterior thalamic density were found in all contrasts. The maximum difference was found at a voxel anterior to the anterior thalamus in all cases, but the region of difference (contiguous voxels thresholded at $p<0.01$ uncorrected) extended into the body of the anterior nucleus in all cases, and was present bilaterally. The controls versus all groups contrast also showed significant differences in anterior thalamic grey matter density. Two further seeds were placed at the anterior pole of the anterior thalamic nuclei using the study-specific template [MNI ±7, -5, 12]. The grey matter density at each voxel are plotted in the two following figures and reveal differences in grey matter density across all groups, with the smallest difference in density being between controls and unaffected relatives of schizophrenic patients. Although the 95% confidence intervals for all patients and controls showed considerable overlap with one another, none of the patient or relative groups' confidence intervals overlapped with that of the control group suggesting that the differences in grey matter density were likely to be present across all patient and control groups, and were not disease specific.

Figure 6.8.1: Grey matter density in left anterior thalamus

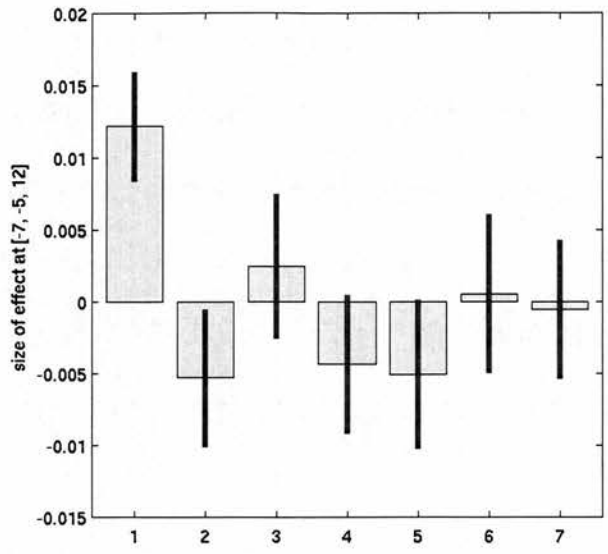
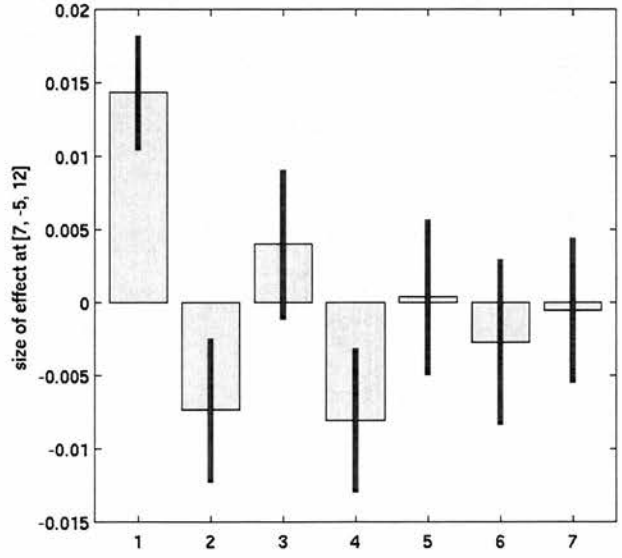


Figure 6.8.2: Grey matter density in right anterior thalamus



6.10 Exploratory contrasts

Analyses 6a-f were conducted as planned. Analyses 6a and 6b were the only ones to yield differences which were significant at $p<0.1$ (corrected). The negative

contrasts were all intended as 4 separate tests of the specificity of changes occurring in those with bipolar disorder or as a consequence of a genetic liability to the disorder. Contrasts 6c (uMIX-MX masked by uSCZ-SCZ) and 6d (uBPD-BPD masked by uSCZ-SCZ) were both measures of grey matter reduction occurring as a consequence of the bipolar phenotype that were not present as a consequence of a the schizophrenic phenotype. Analysis 6e (UMIX-MIX masked by control-uBPD) was intended as a measure of the phenotypic consequences of bipolar disorder which could not be attributed to genetic liability to bipolar disorder. This result was also non-significant.

Analyses 6a (uSCZ-SCZ masked by uBPD-BPD) and 6b (uSCZ-SCZ masked by uMIX-MIX) were intended as a measure of the consequences of the schizophrenic phenotype, that were not also common to the bipolar phenotype. The results of both analyses are identical to those given in the comparison between schizophrenic subjects and their well relatives. These results both indicate a grey matter density loss in superior temporal gyrus, pre-central gyrus and, using the thalamus/amygdala-hippocampal SVC, amygdala.

6.9 White matter analysis

White matter density was contrasted between each patient and relative group and controls. This was not originally part of the analysis plan and so hypotheses were generated on the basis of the other imaging results and were deliberately limited in number. Analyses were restricted to two specific regions chosen on the basis of the grey matter analysis. Firstly, two spherical volumes of subgyral prefrontal white matter were chosen on the basis they were likely to contain white matter tracts from

many regions of the brain to several prefrontal cortical areas. These spheres were located at (±22, 40, 6) and were both of 11mm radius. Secondly, two spheres of tissue were also placed in the left and right limb of the anterior internal capsule. The spheres were located at (±18, 12, 6) [MNI] and were also of 11mm radius. This was chosen because the anterior limb of the internal capsule contains thalamo-prefrontal fibres originating from the anterior thalamic nucleus. This area has been shown to have reduced white matter density in schizophrenic subjects compared to controls (Suzuki et al. 2002), although no study has yet examined this region in bipolar patients. Since the results suggested reductions in anterior thalamic density across all patient and relative groups, the efferent projections from this area to the prefrontal cortex appeared worthy of further investigation. Secondly, projections from the anterior thalamus are thought to project principally to the anterior cingulate cortex. Since this area has been implicated in both schizophrenia and bipolar affective disorder, white matter density reductions and/or increases might form a physical substrate for functional deficits observed in several other studies. All spheres were added to a single SVC image and used in all subsequent analyses. Together, the SVC image consisted of 6.7 RESELS. All analyses were conducted using the SVC since these regions of interest were the only ones suggested by the previous analyses, with the possible exception of projections from dorsomedial thalamus to amygdala. However, although frontal grey matter and thalamus (anterior and dorsomedial nuclei) were reduced in density, this study found no evidence of amygdala grey matter density reduction in any of the patient or relative groups compared to controls, although some evidence of reduced density was found in schizophrenic subjects compared to their unaffected relatives. Hence only those white matter pathways

connecting regions shown to be reduced in grey matter density in *this* sample were examined.

6.9.1 Contrasts between patients and controls

Patients with schizophrenia showed reductions in subgyral white-matter (bilaterally) and also in left anterior internal capsule white matter. Additionally, a region of white matter density reduction was found in the left anterior cingulate. Although significant reductions in anterior internal capsule white matter were found only in the left hemisphere, inspection of the contrast image (thresholded at $p<0.01$ uncorrected) suggested the presence of a non-significant white matter reduction in the right anterior internal capsule also.

Patients with bipolar disorder from mixed families showed no significant differences in white matter density compared to controls. Examination of the contrast image (thresholded at $p<0.01$ uncorrected) suggested no trends to statistical significance. Patients with bipolar disorder from bipolar families showed white matter density reductions in left anterior internal capsule but not in subgyral white matter, although there was a suggestion of a non-significant trend in left subgyral white matter. The significant reduction in left-sided anterior internal capsule white matter was matched by a non-significant right-sided reduction on the contrast image, suggesting that this deficit was not lateralised.

Patient groups were compared by masking the control-patients contrast with another patient-control contrast image. This method of analysis was chosen because of the grey matter findings and because white matter densities have greater variances than grey matter. Power issues are therefore likely to be at least as pertinent for white

matter as they are for grey. Therefore by keeping the control group in each analysis the number of subjects included in each comparison was maximised.

Masked contrast 1: schizophrenia versus controls contrast masked with bipolars from mixed families versus controls contrast

Once control versus schizophrenic white matter differences were masked with the control versus bipolars from mixed families contrast image, no significant differences remained. This suggests that similar white matter reductions may be found in bipolars from mixed families that did not reach voxel-wise significance.

Masked contrast 2: schizophrenia versus controls contrast masked with bipolars from mixed families versus controls contrast

Once control versus schizophrenic white matter differences were masked with the control versus bipolars from mixed families contrast image, significant differences in prefrontal subgyral white matter density remained (bilaterally). This suggests that the anterior internal capsule white matter reductions are also found in bipolars from bipolar families, but that frontal subgyral differences are either much greater in schizophrenia or absent in bipolar patients without schizophrenic relatives.

Figure 6.9.1: Differences in white matter density between schizophrenic subjects and controls

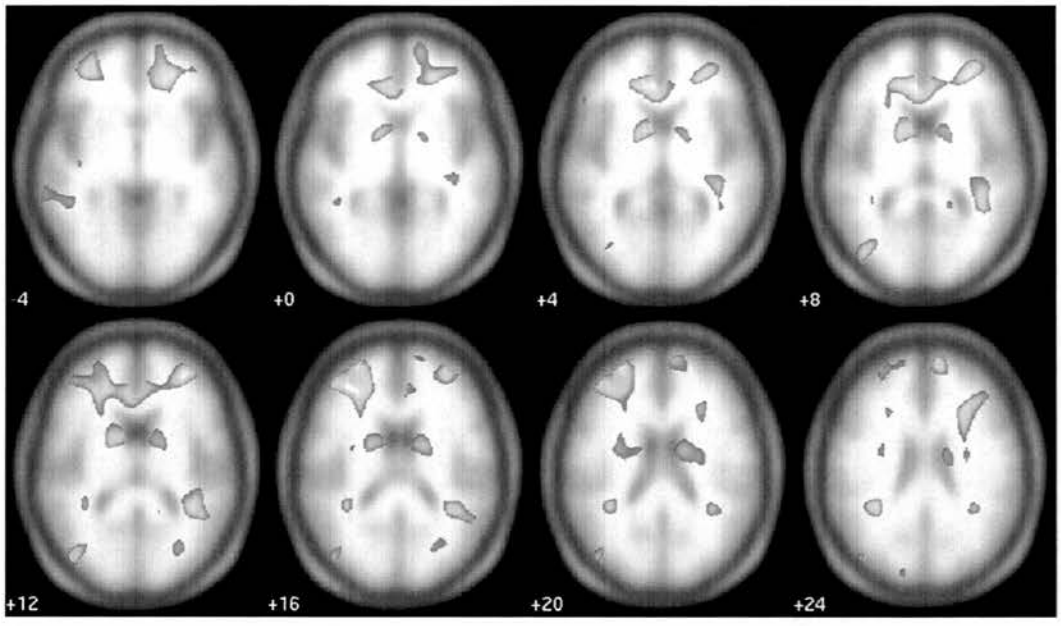
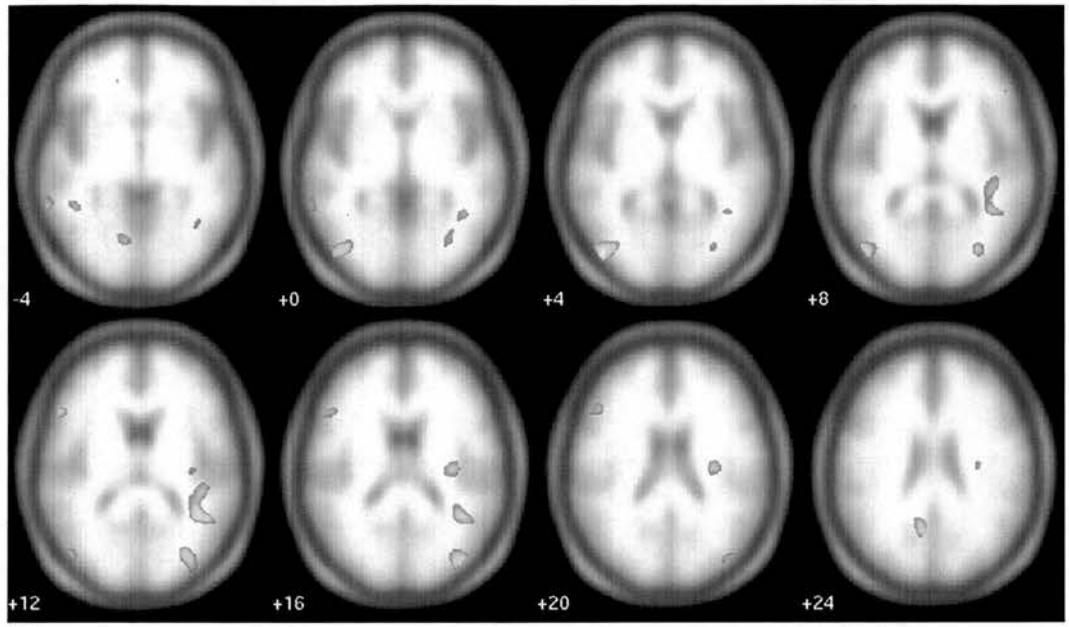


Table : White matter differences between schizophrenics and controls

Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results after frontal white matter small volume correction				
0.01	-25	35	15	Left subgyral frontal white matter[1]
0.011	-12	37	4	Left anterior cingulate
0.012	31	44	6	Right subgyral frontal white matter[2]
0.045	-15	4	7	Left anterior internal capsule

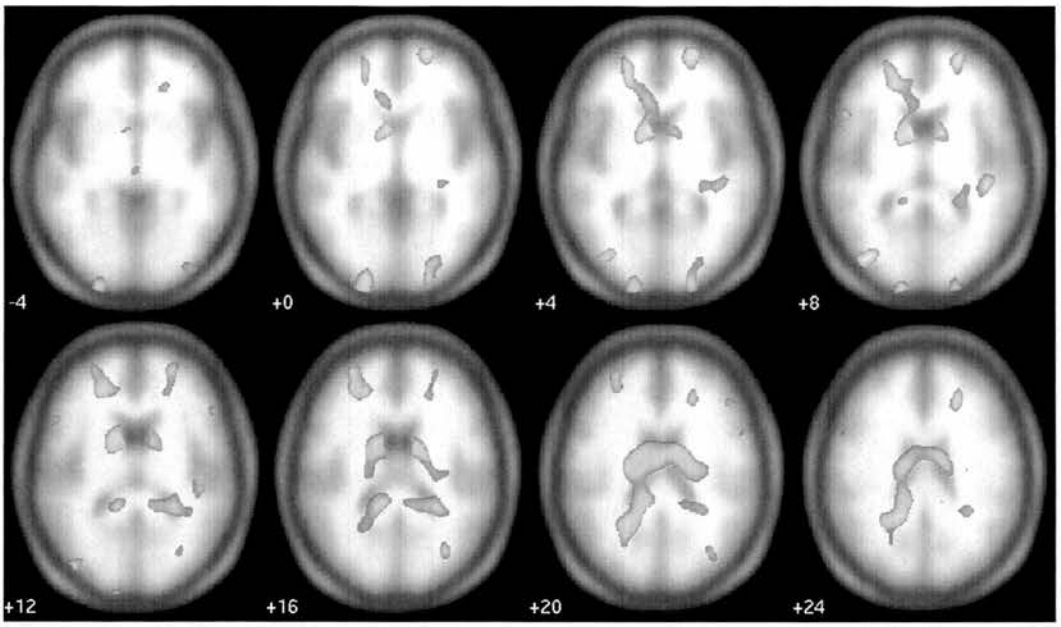
[1]Nearest grey matter BA 9, [2]nearest grey matter BA 10

Figure 6.9.2: Differences in white matter density between bipolar subjects from mixed families and controls



Voxel P corrected	X, y, z (mm) Talairach coordinates	Region of difference
Results after frontal white matter small volume correction		
No significant differences		

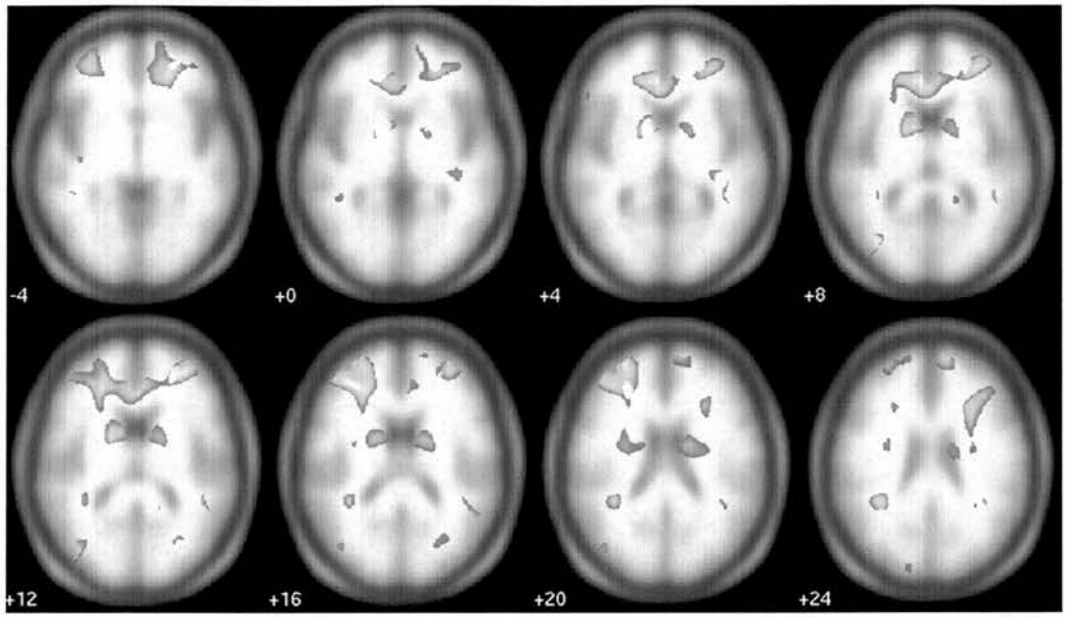
Figure 6.9.3: Differences in white matter density between bipolar subjects from bipolar families and controls



Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results after frontal white matter small volume correction				
0.036	-8	8	5.1	Left anterior internal capsule
0.069	-22	38	9	Left subgyral frontal white matter

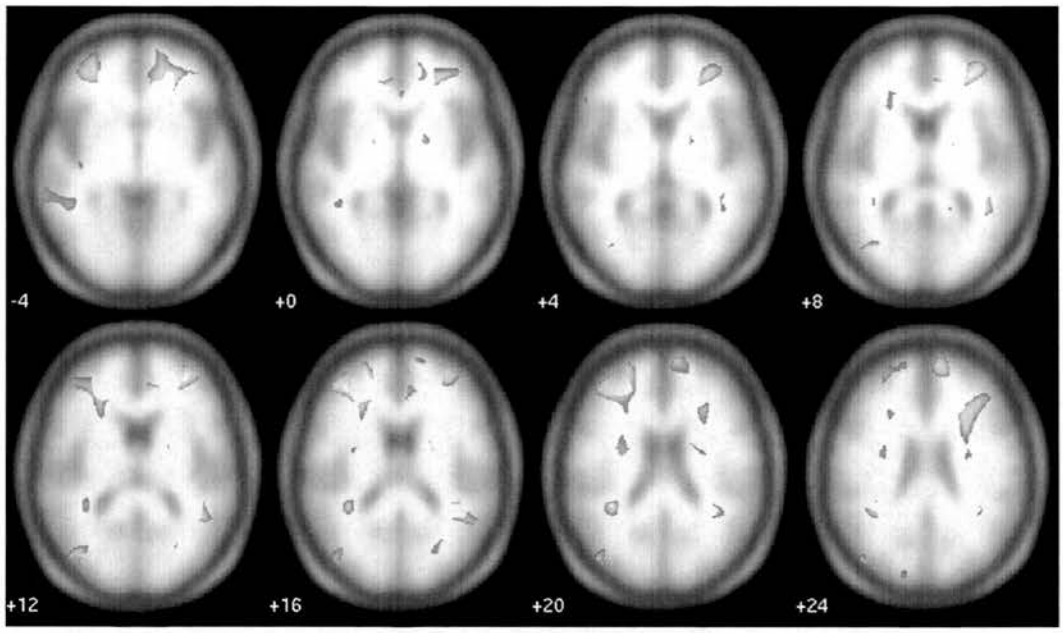
[1]Nearest grey matter BA 32

Figure 6.9.4: Differences in white matter density between schizophrenic subjects and controls (masked exclusively with controls versus bipolars from mixed families contrast)



Voxel P corrected	X, y, z (mm) Talairach coordinates	Region of difference
Results after frontal white matter small volume correction		
No significant differences		

Figure and table 6.9.5: Differences in white matter density between schizophrenic subjects and controls (masked exclusively with control versus bipolars from bipolar families contrast)



Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results after frontal white matter small volume correction				
0.012	31	4	6	Right middle frontal gyral white matter
0.033	25	42	-5	Right middle frontal gyral white matter

6.9.2 Contrasts between unaffected relatives and controls

No significant differences were found between unaffected subjects from either schizophrenic or bipolar families and controls. Unaffected relatives from mixed families showed two areas of significant difference compared to controls. The first region of difference was found in right superior frontal gyrus white matter and the second in right medial frontal gyrus white matter. These were unexpected being present in neither relatives of schizophrenics nor relatives of bipolars subjects compared to controls.

Table 6.9.2: Differences in white matter density between bipolar subjects from mixed families and controls

Voxel P corrected	X, y, z (mm) Talairach coordinates			Region of difference
Results after frontal white matter small volume correction				
0.02	30	43	9	Right superior frontal gyral white matter
0.049	16	47	0	Right medial frontal gyral white matter

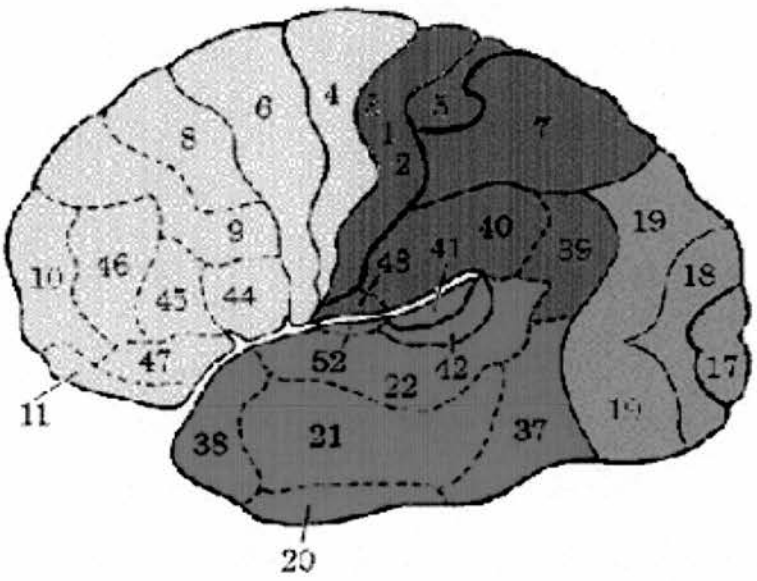
6.10 Discussion

6.10.1 Main findings: prefrontal cortex

Prefrontal cortical grey matter reductions were most extensive in the schizophrenic group with reductions in Brodmann's areas 6, 8 and 44. Differences were also found in bipolar subjects from mixed families in BA 9 (dorsolateral prefrontal cortex). However, when patient groups were compared directly, no significant pairwise differences in frontal lobe grey matter density remained. Similarly, when reductions in schizophrenics compared to controls were 'masked' by the other patient-control contrasts, only the reduction in middle frontal gyrus (BA 6 and 8) in schizophrenic subjects remained. These results show that there are widespread reductions in prefrontal grey matter density in schizophrenic subjects compared to controls, which are greater than in either bipolar group. There is insufficient evidence to conclude that such differences are *absent* in bipolar disorder, since the mixed group were smallest in number of all groups. The smaller number of subjects in this group is likely to have left fewer significant voxels (thresholded at $p<0.05$ uncorrected) in the masking image and therefore more control versus schizophrenic differences will have remained. Furthermore, two differences between schizophrenics and controls were removed by the application of the bipolar from bipolar families versus controls mask suggesting that a trend to significant difference between bipolars and controls in BA 9 and 44 is likely.

The frontal lobe regions implicated in this study include BA 6, 8, 9 and 44 (see figure 6.10.1). All of these areas form a contiguous region situated mostly on the dorsal and lateral aspect of the prefrontal cortex.

Figure 6.10.1: Brodmann's areas. Reproduced from www.clarkson.edu/~rcarlson with the permission of the author



Brodmann's area's 9 and 44 are sometimes both included in the definition of dorsolateral prefrontal cortex (DLPFC). Reductions were found in both schizophrenic subjects and bipolar subjects from mixed families compared to controls but not between unaffected relatives and controls. This suggests either that these differences are the expression of quantitative trait (e.g. mood incongruent features), the expression of a certain threshold of liability to schizophrenia or a *general* liability to schizophrenia. However, for the third possibility to be tenable, the failure to find differences between unaffected relatives of schizophrenic subjects and controls would need to be explained (e.g. perhaps by low statistical power). The possibility that the similarity between schizophrenics and bipolars from mixed families is a quantitative trait has support from several strands of evidence. Firstly, some evidence suggests that the presence of a personal or family history of affective disorder conveys a prognostic advantage to people with schizophrenia (Vaillant 1964). Secondly, there is evidence from several factor analysis studies that

continuous variation in symptoms and course can be observed in a broad spectrum of people with unselected functional psychotic illness (van Os et al. 1999) and that these may be associated with patterns of brain volume reduction (McIntosh et al. 2001). Broca's area is also located in BA 44. The finding of reduced grey matter density in this area in schizophrenic patients compared to controls is of interest since this area has been implicated previously in functional imaging studies of hallucinating patients (McGuire et al. 1993;Cleghorn et al. 1990).

Brodmann's areas 6 and 8 were reduced in grey matter density in schizophrenic subjects compared to controls, but were not reduced in the other groups compared to controls. Area 6 is often activated during working memory tasks, especially where the stimulus is verbal or numeric (Coull et al. 1996). Area 8 is thought to be involved in eye movements and in attention for visual stimuli. Perfusion of area 8 has also been related to the perception of hedonic odours (Fulbright et al. 1998) and the severity of delusional ideation in subjects with Alzheimer's Disease (Sultzer et al. 2003). The precise functional role of both structures is as yet unclear.

6.10.2 Main findings: thalamus

Anterior thalamic density reductions were apparent across all patient and relative groups, although relatives from schizophrenic families only demonstrated this reduction on a post-hoc comparison. In addition, the schizophrenic patients, but not their relatives demonstrated reductions in dorsomedial thalamic grey matter density that were not found in any of the other groups. These results suggest that the anterior thalamic reductions may be one expression of a general liability to

psychosis, irrespective of the phenotype. In contrast, dorsomedial thalamic reductions appear specific to schizophrenia being absent in all other control versus patient or relative contrasts.

Thalamic reductions in schizophrenic patients are well described in several region-of-interest studies and have led some investigators (e.g. the Iowa group, Andreasen et al. 1999) to propose a central role for this structure in schizophrenia. The role of the thalamus as a filter of sensory information has also been proposed to account for the symptoms of schizophrenia (Vollenweider and Geyer 2001). The thalamus is a diverse collection of nuclei each having a unique pattern of cortical and subcortical projections. Since most studies combine these nuclei in a single volumetric measure, few will be able to attribute overall differences to a specific region or function.

A few ROI studies have examined specific nuclei. Two MRI studies from the same research group have found results suggestive of anterior thalamic nucleus volume reductions in one study of schizophrenic subjects (Kemether et al. 2003) and mediodorsal nuclear volume reductions in another two (Byne et al. 2001;Kemether et al. 2003). The former study also found evidence of thalamic shape differences and dorsomedial under perfusion in schizophrenic subjects. Further support for these findings can be found in several post-mortem studies from several groups which have found evidence of reduced mediodorsal (Dom et al. 1981;Pakkenberg 1990;1992;1993a;Popken et al. 2000;Byne et al. 2002;Danos et al. 2003) and anterior nuclear volumes (Danos et al. 1998;Young et al. 2000).

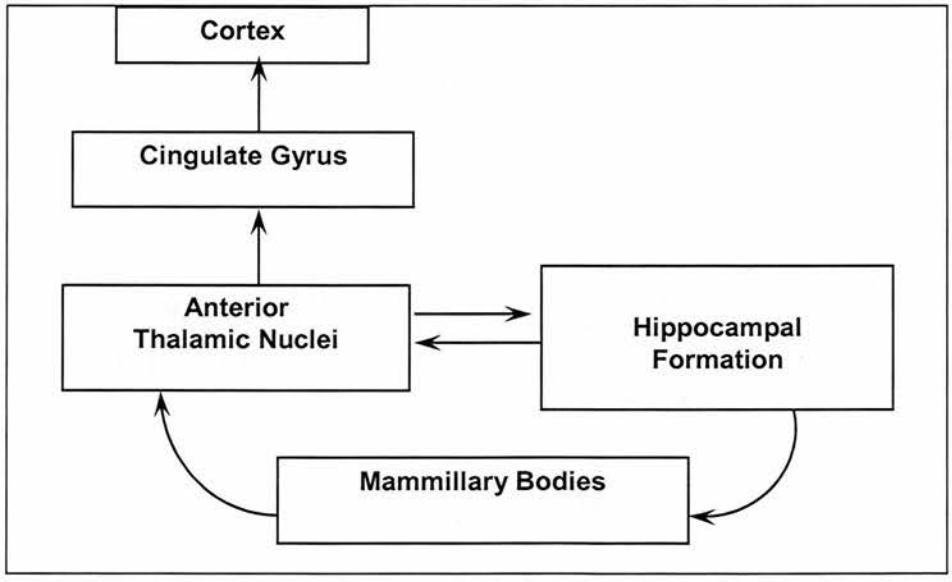
Studies of total thalamic volume in bipolar disorder tend to suggest that thalamic volume is neither increased nor decreased compared to controls or subjects

with schizophrenia (see chapter 3). However, there is considerable between study heterogeneity and studies exist which find effects in both directions (Strakowski et al. 1999;Getz et al. 2002). MRI studies of specific nuclei in bipolar patients are yet to be performed and no post-mortem studies of the thalamus could be found. Reductions of anterior thalamic density in schizophrenia and bipolar disorder are however of some interest because of its connection with the anterior cingulate cortex. Abnormalities of the anterior cingulate have been implicated in many neuropathological (see Knable et al. 2002;Eastwood and Harrison 2001 for a review), structural (Lopez-Larson et al. 2002) and functional neuroimaging (Blumberg et al. 2000;Rubinsztein et al. 2001) studies of bipolar disorder. Studies of schizophrenic subjects versus controls also implicate this region (Goldstein et al. 1999;Job et al. 2002). Since the anterior thalamic nucleus is a major afferent input to this structure, its structure and function are also likely to be important to the aetiology of bipolar disorder and schizophrenia.

The anterior thalamic nucleus is situated at the anterior pole of the thalamic nuclear complex. It sends efferent connections to anterior cingulate cortex and hippocampus and receives its major input from the hippocampal complex and mammillary bodies. It was initially thought that the anterior thalamus was part of a circuit ('Papez Circuit') thought to serve emotional experience and expression (Papez 1937). More recently the Papez Circuit has been implicated in mnemonic functions, the theta rhythm of electrical activity found on EEG tracings and is also associated with fear and avoidance conditioning in rats (Vertes et al. 2001). It is thought that the anterior thalamus may also have a role in working memory function and with motivation via its connections with anterior cingulate. For instance there is

some evidence from fMRI that the anterior thalamus and cingulate become activated when alcoholics are exposed to alcohol related cues (George et al. 2001). There is also some unpublished evidence (personal communication with Professor W Deakin at 2004 Schizophrenia Winter Workshop) that the anterior thalamus and Papez circuit may be activated during emotionally salient tasks (e.g. hearing a child cry). Such tasks are likely to clarify a role for this nucleus in normal subjects and explain why volumetric reductions in psychosis may be a risk factor or consequence of illness. However, functional studies of the thalamus are rare and a precise function role for this area has yet to be found. Future functional imaging studies might design or discover tasks which activate this region and help clarify its connectivity and role.

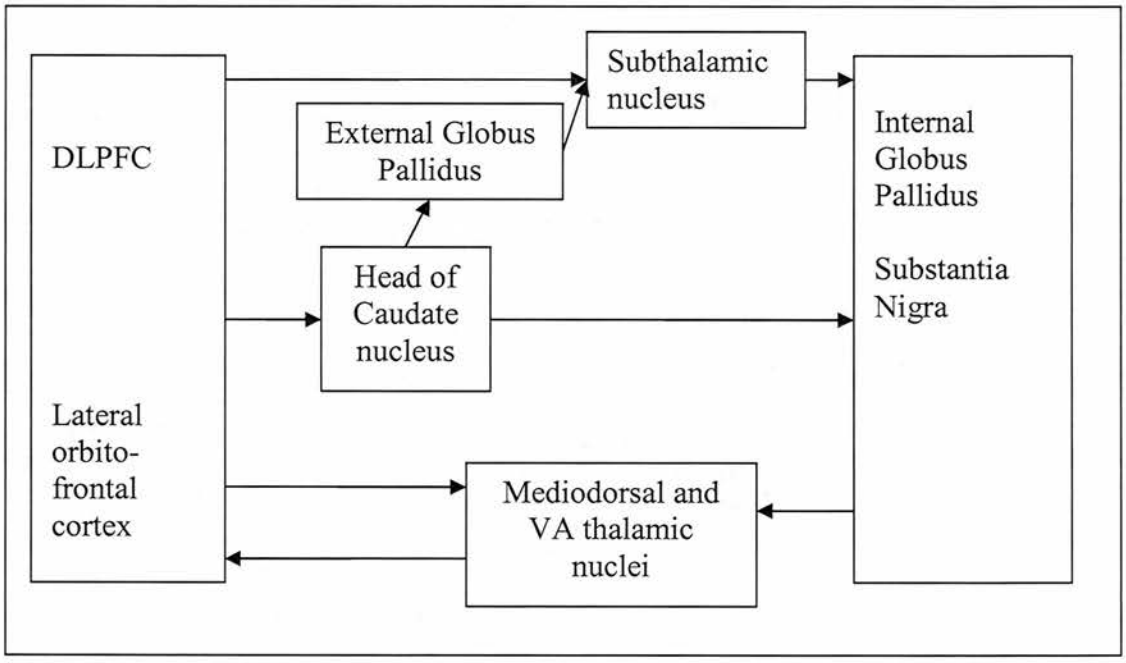
Figure 6.10.2.1: Connections of anterior thalamic nucleus



The mediodorsal nucleus of the thalamus has extensive efferent projections to prefrontal cortex, and has reciprocal connections with amygdala and other medial temporal areas (Nolte 1988). It is thought to control emotional and motivational

responses to sensory stimuli perhaps mediated by its connections with orbitofrontal cortex. It is also involved in two fronto-subcortical loops linking areas of the prefrontal cortex and basal ganglia (Alexander et al. 1990). The first loop links the dorsolateral and lateral orbitofrontal cortex with the internal globus pallidus and substantial nigra. Since dorsolateral prefrontal cortex is thought to be involved in both animal and human working memory, this loop is also thought to play a role in the manipulation of several items in memory. Lesions of the dorsomedial thalamus are associated with global amnesia and with Korskoff's syndrome (Joseph 1996).

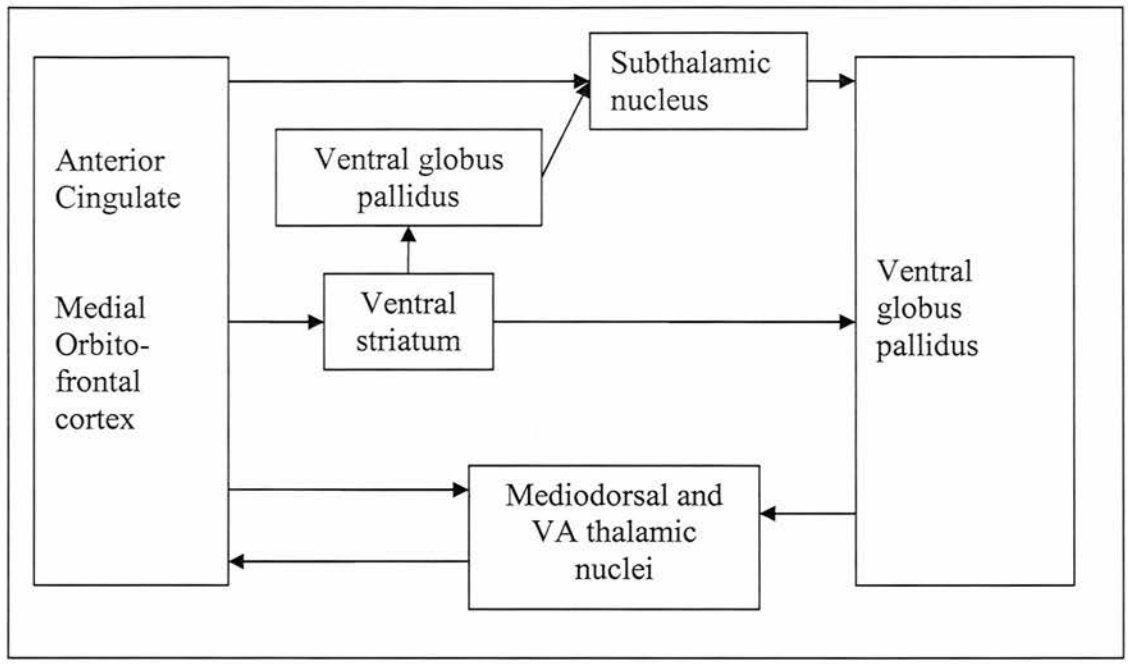
Figure 6.10.2.2: Alexander's prefrontal circuit



Mediodorsal thalamus is also implicated in Alexander's limbic loop. This loop involves orbitofrontal cortex, anterior cingulate, ventral pallidum and ventral striatum. This circuit is thought to be over-activated during pain, depression and in patients with obsessive compulsive disorder. There is some functional imaging

literature to support these hypotheses (see Ebmeier and Reid 1998 for a review) and also to implicate this circuit in the aetiology of abnormal emotion and social function found in schizophrenic patients (Taylor et al. 2002;Chemerinski et al. 2002).

Figure 6.10.2.3: Alexander's limbic circuit



6.10.3 Other findings

Parahippocampal volumes were also decreased in schizophrenics compared to both controls and unaffected relatives, although the masked control versus schizophrenia differences were not statistically significant. This region is almost certainly reduced in volume in schizophrenia (Wright et al. 2000). Reduced volume has also been associated with poor memory performance on some tasks (e.g. verbal fluency- recall task). However, the precise role of this brain area is probably unknown although it receives afferent inputs from the cingulate gyrus with which it is in anatomical continuity with around the splenium of the corpus callosum (Crossman and Neary 1988).

Grey matter density reductions in the body of the caudate nucleus were found in the unaffected relatives of both bipolar groups and in bipolar subjects from bipolar families compared to controls. These changes were not found in bipolar patients from

mixed families, but since this group was smaller in number than any of the other groups, this may simply reflect a lower statistical power for this contrast. In each case the region of difference extended into anterior thalamus and was in fact more closely associated with this structure than the caudate nucleus. The failure to distinguish these structures may reflect their close anatomical proximity and the use of an 8mm smoothing kernel. This would have smeared grey matter voxels from the edges of both structures and may have made their delineation more difficult. No ROI or VBM studies reporting volumetric reductions in caudate volume and/or density could be located (see chapter 3). Functional studies reporting a state-dependent hyper-perfusion of the caudate nucleus have been reported previously (Blumberg et al. 2000;Caligiuri et al. 2003) and may point to an underlying dysfunction of this nucleus. Lesion studies, usually following vascular accidents, also suggest that the caudate nucleus has a role in the production of manic symptoms, apathy and catatonia (Joseph 1996). The caudate nucleus is continuous with the putamen and these two structures are sometimes collectively referred to as neostriatum. This region is important in the control of movement and is rich in dopamine containing neurones. Functional and effective connectivity between caudate, dorsolateral prefrontal cortex and thalamus is also enhanced by the dopamine antagonist sulpiride (Honey et al. 2003). This provides a possible mechanism to explain the efficacy of antipsychotic medication in mania and is further evidence of its potential importance in bipolar disorder.

The white matter findings were complimentary to those for grey matter in affected patients. Schizophrenic patients had reductions in frontal subgyral white matter which were complementary to the results for grey matter in that they included

association and projection fibres to those areas. Bipolar patients from bipolar families and schizophrenic subjects also had reductions in anterior internal capsule white matter, carrying white matter tracts from anterior thalamus to cingulate cortex. No differences were found between bipolar subjects from mixed families and controls. Relatives of schizophrenic and bipolar subjects showed no white matter differences compared to controls. Unaffected subjects from mixed families showed reductions in subgyral white matter which were unexpected. This may be attributable to a gene-gene interaction in this group, a greater propensity to develop mental illness at a later age, a false positive finding or an additive effect of genes for both disorders.

The finding of amygdala density reduction in schizophrenic patients compared to their relatives also has some support from previous studies. It is perhaps surprising that this difference was unobserved in the schizophrenia versus controls comparison. By observing the differences between schizophrenic patients and controls overlaid on coronal sections of the study-specific template, evidence of reduced areas of amygdala density can be found. The fact that these are non-significant might reflect sampling error or reduced variance in either the relative or schizophrenics group (although this seams unlikely). A further possibility is that amygdala grey matter density was increased in relatives of schizophrenic subjects, although I am aware of no supportive studies to substantiate that possibility.

6.11 Methodological limitations

The current study included 192 subjects (49 controls and 143 patients/relatives) making it comparatively large and therefore able to estimate the

error (sampling) variation comparatively accurately. The issues of whether the patients, relatives and controls were representative of the populations from which they drawn has been addressed in the previous chapter, as has the potential confounding effects of medication. Several people declined the offer of an MRI scan and this may have led to patients who were less severely ill remaining in the experiment, if the numbers had been large and unbalanced. The fact that only 8 from 200 failed to complete the imaging stage is not likely to have introduced any further bias.

Relatives of affected subjects were chosen because of their common genetic liability to schizophrenia. By studying relatives it was hope that brain changes contingent upon either disease expression or genetic variation could be separated. However, the threshold-liability model adopted in the calculation of genetic liability used earlier assumes that it is those subjects with greatest liability who will become unwell. Therefore, relatives and affected subjects were probably unequal in terms of genetic liability which probably confounded any comparisons made. The methodological difficulties involved in the calculation of genetic liability were outlined in the previous chapter. These made any attempt to correct analyses for genetic liability difficult and dependent of several assumptions. For example, the calculation of genetic liability in mixed pedigrees would have to quantify the extra genetic liability contingent upon having a family member with schizophrenia (and vice versa). I am aware of no methods by which this calculation can be made.

Voxel based morphometry (VBM) as implemented in SPM99 is also a relatively new technique for the study of grey matter differences between groups. Although it shows a large degree of agreement with conventional ROI studies,

differences remain and until these are better understood, region of interest studies will probably be regarded as providing more robust data than those reliant solely on VBM (Kubicki et al. 2002b). In contrast to ROI analysis, VBM can measure grey matter density in an objective manner and find differences in very small structures. It is much less time consuming and practical problems (such as employing several image analysers over the time course of a study) are effectively avoided.

The validity of VBM is dependent on accurate image registration and normalisation both of which were performed using established methods employed by other researchers in Edinburgh (Job et al. 2002) and elsewhere (Maguire et al. 2000). This study used the grey and white matter optimised techniques employed by other researchers which might have led to better image normalisation (Good et al. 2001). However, further refinements have been made to SPM recently which might have provided for a better fit between source images and template. For instance, SPM2 now performs normalisation by Bayesian methods which it claims, on its website, achieves better a match for individual cortical gyri. Other software, designed specifically for structural image analysis, is also available (Suckling et al. 1999) but it is unclear whether this software would have led to the same results being obtained. At the current time, there appears to be no image analysis software which can take into account the non-independence of observations from members of the same family.

The template generation was based on an MNI template based on 152 normal brain scans (Evans et al. 1993). Although a custom template was subsequently used, unusual or outlying voxel densities in any of the MNI scans might have led to an inaccurate template. In fact the MNI template is known to differ structurally from the

Talairach brain atlas and 3D transformations have had to be developed in order to make the 'brains' more compatible. An alternative method of brain analysis might have taken into account variation in normal brain structure and used this in the statistical models fitted. However, normal brain structure appears to have been characterised too poorly for an analysis of this sort to take place and in fact no software is currently available which provides this sort of analysis, so far as I am aware. VBM also makes the additional assumption that errors are normally distributed. Whilst this may have been the case, it is difficult to check. Even in analyses where error terms are non-normally distributed, violation of normality is often not very important unless the data are very skewed and the number of observations relatively small. White matter density however, has a large variance with most values around 0 (not white) or 1 (white). This generates a bimodal distribution which is markedly non-normal. Using a small volume correction meant that these results could not be confirmed using a permutation test and should therefore be interpreted cautiously.

Finally, areas of peak difference between groups sometimes occurred outwith the region with which they were contiguous. This may be explained by the fact that differences in brain structures occurring across groups are most likely at the edges (where presumably variation in grey matter density/volume is the greatest). The region of maximum difference may then be displaced from its location in native space by the smoothing process. A related phenomenon may occur when two separate regions situated closely together show reductions in grey matter volume (e.g. caudate and anterior thalamus). Because the grey matter voxel values are smoothed, the point of maximum difference between groups may occur at a point

intermediate between the two structures, particularly when those areas are separated by a distance less than the width of the smoothing kernel at half maximum.

All analyses in the current study were checked and the areas of difference (thresholded at $p<0.01$) were overlaid on the custom template constructed from the study's source images. By checking the analysis in this way, in addition to using the Talairach Daemon, areas of difference were inspected to ensure that they lay within the regions of interest quoted. Problems with the registration of normalised images also have the potential to give misleading results. These registration errors can occur as a consequence of an abnormal brain structure in affected patients and the attempt to normalise these images to a template constructed from 'healthy' brains. Non-linear functions have the ability to compress or stretch regions from abnormal brain images so that the images contours more closely fit the template image. Around brain areas of abnormal shape or structure, such as the third ventricle, differences in grey matter density found between groups may reflect abnormal shape or volume of the third ventricle. Whilst the thalamic reductions found in the current study could be due to mis-registration of images, the use of a grey matter optimised template makes this less likely since CSF and white matter voxels are not used in the normalisation process. Furthermore, whilst anterior thalamic density differed across all groups, third ventricular enlargement has been demonstrated convincingly only in schizophrenia and in some (but not all) studies of close relatives (Wright 2000;Sharma 1998). Bipolar patients and their relatives *do not* consistently show ventricular enlargement compared to controls (see chapter 3).

6.12 Summary

One hundred and ninety-two patients completed the scanning stage of the study. Image analysis revealed grey matter differences between schizophrenic subjects and controls which may be relatively specific to schizophrenia. Principally these areas included BA 6 and 8, BA9 (dorsolateral prefrontal cortex) and BA44 (Broca's area and dorsolateral prefrontal cortex) and dorsomedial thalamus. All patients and relatives, regardless of diagnosis, showed evidence of a reduction in anterior thalamic grey matter density compared to controls. This suggests that the reduction is either a marker of genetic liability to psychosis in general, or an adaptation to it. Bipolar patients from mixed families showed a single area of frontal grey matter reduction suggesting that affected patients from that group may be intermediate between the other two patient groups. Unaffected relatives of each patient group showed no differences in addition to their anterior thalamic grey matter reductions. These observations are consistent with variation in prefrontal grey matter across a continuous phenotype.

White matter reductions generally complimented grey matter findings in affected patients. Groups with frontal grey matter reductions had complimentary frontal subgyral white matter reductions in addition. Anterior thalamic grey matter reductions were complimented by reductions in anterior internal capsule white matter, although these were not present in unaffected relatives. Unaffected relatives of mixed families, in contrast, showed reductions in frontal white matter compared to controls. This may have been because white matter analyses are more difficult to model in SPM, or because genes raising the likelihood of both disorders interact to give rise to these areas of difference.

The current study was relatively complex in terms of the number of groups examined, although the total number of participants was relatively large. However, repeating the current study with larger numbers would be a useful development which would improve the power of the study and reduce the possibility of false positive findings. Because the current study was a case-control design and could not determine whether grey/white matter density reductions were risk factor or a consequence of illness or its treatment, this study should be followed-up using a prospective study of schizophrenic and bipolar subjects from before the illness has become manifest. The practical difficulties involved in such research are likely to mean that any prospective study will follow a cohort of unaffected people at enhanced risk for the disorder. Information collected on life events and early development could also potentially clarify the role of environmental influences.

The current study examined white matter density using Voxel Based Morphometry of white matter from T1-weighted images. This technique has largely been superseded by diffusion-weighted imaging (DWI) which can examine white matter integrity *and* directionality. It is possible that DWI would have shown differences in white matter integrity which were not apparent using analysis of T1 weighted images. There remains some controversy surrounding the use of VBM (Bookstein 2001) and it is possible that the combination of VBM and ROI analysis will help resolve the areas of disagreement.

Whilst structural analysis can yield volumetric differences associated with broadly defined phenotypes and genetic liability, it does not necessarily bridge the gap between abnormal structure and clinical symptoms or course. A future study might usefully combine functional and structural imaging to demonstrate altered

cerebral physiology during a suitable task. In the current study, memory performance and executive tasks would have been of some interest because memory showed no disease specificity whilst executive function appeared to be reduced in the schizophrenic patients.

Chapter 7: Brain Mapping and the Future of Attempts to Separate 'Functional' Psychotic Disorders

7.1 Introduction

Although schizophrenia and bipolar disorder have remained 'legitimate' diagnoses for almost a century, they are relatively poor predictors of treatment response and outcome. This has led some to question the division of 'functional psychoses' into schizophrenia, depression, bipolar disorder and intermediate forms. There is no concrete evidence to either confirm or refute these entities on biological grounds. Nevertheless, these diagnoses continue to be used in day to day practice presumably because they provide some, if rather limited, useful information for both patients and clinicians.

Diagnoses based on aetiology are likely to be the most useful, as in other medical disorders prognosis and rational treatments generally follow from an understanding of the biological basis for the disorder. Unfortunately, psychiatric disorders have been slow to reveal their aetiology and schizophrenia and bipolar disorder continue to be syndromes rather than diagnoses which may be confirmed or refuted by laboratory or radiological investigation.

At the present time, the confirmation, refutation or reformulation of existing diagnostic categories is best based on evidence of strong causal factors. Where this is not possible, a division based on experimental function, structural imaging or pathology is probably better than relying on the symptoms alone. A sine qua non of this approach is that patients with both disorders should be optimally studied within the same experiment, otherwise observed differences inferred from indirect comparisons may be due to methodological differences between studies which have nothing to do with true differences in phenotype. Until now bipolar disorder has been rarely directly compared to schizophrenia and subsequently research in bipolar disorder has proceeded at a very

slow pace in comparison (Clement et al. 2003b), despite the fact that it affects about as many people.

7.2 Causation and psychosis

The causation of psychosis could be investigated using several methods. Epidemiological research of large representative samples has provided many positive results and obstetric complications, maternal influenza and, more recently, urbanicity have all been linked to a later diagnosis of schizophrenia. Epidemiological research often uses routinely collected data which was not collected for the purpose of research, and the quality of such data is sometimes uncertain. However, the recruitment of large, representative cohorts of people make this a particularly useful form of research which may suggest public health level interventions aimed at reducing disease incidence. Although evidence based on epidemiological studies has provided several possible risk factors, some of which have been replicated, the proportion of cases in a population attributable to these environmental factors is small (Murray et al. 2003) and most risk factors for schizophrenia also confer additional risk for bipolar disorder (Gattaz and Hafner 2004;van Os and Verdoux 2003).

Genetic factors have been shown to account for the majority of risk to psychosis and are probably the area of aetiological research which has the greatest possible potential in the longer term. However, as discussed in chapter 1, there is evidence that these factors also show little diagnostic specificity. Recently, replicated reports of individual gene loci thought to raise the probability of schizophrenia or bipolar disorder have begun to emerge. Although these may be non-specific, they provide an important

means by which individual gene effects on the risk of psychosis can be investigated. The discovery of genes of major and minor effect is certainly advancing but has still not accounted for the majority of genetic risk in the population as a whole, although the explained risk in specific populations may be somewhat higher.

The relative paucity of specific genes for schizophrenia or bipolar disorder has also contributed to a lack of animal models in this area. Several animal models exist for chronic diseases such as Parkinson's Disease and Alzheimer's Dementia (Lythgoe et al. 2003). These models have enhanced our understanding of these conditions and are beginning to suggest novel treatments (e.g. stem cell research, gene replacement). Animal models may also be based on a physiological mechanism, such as the reduced sensorimotor gating found in schizophrenia (Braff et al. 1995). Animal models have been developed which mimic this dysfunction by artificially inducing these gating abnormalities using psychostimulants (Ellenbroek 2003). However, although these models are helping to describe the brain pathways involved in sensorimotor gating and habituation, the proximity of these animal models to patients with positive psychotic or affective symptoms remains debateable.

In light of the shortcomings of epidemiological and genetic research, evidence from neuropathology, neuroanatomy, structural imaging and experimental function must be considered. Neuropathology has the potential to identify 'causes' by searching for macroscopic and molecular lesions, but may also lead to the discovery of a *chain* of events leading to the disease in question. However, there are many methodological limitations to this research (please refer to chapter 2) and the current political climate is making this type of research somewhat difficult. The fact that brain structure and

function may also be investigated *in vivo* using a variety of neurophysiologic, neuropsychological and imaging techniques is arguably the strongest method of assessing pathophysiology.

Prior to 1976, there was no accepted 'macroscopic pathology' of functional psychosis. Positive pneumoencephalographic and neuropathological studies had been conducted previously but were generally dismissed as the secondary effects of institutionalisation or treatment. Following Johnstone's 1976 study, it was gradually accepted that structural abnormalities were to be found in the brains of patients with schizophrenia. Subsequent studies showed that these changes were present at first-episode and could not be attributed to medication or institutionalisation. It was hoped that with better imaging techniques the neuropathology of schizophrenia might be elucidated but, in spite of numerous methodological advances, brain imaging has not yet led to the discovery of a cause and rarely provides information which guides the clinical care of affected patients.

The apparent failure of imaging and related methods to provide a cause could be attributed to several factors. There are certainly a number of methodological problems with current research (see following section), but this may not be the only or even the main reason for an apparent lack of success in this area. For other neurological diseases (e.g. multiple sclerosis, Parkinson's disease, stroke, certain dementias) in which imaging has been important in the understanding of causation/pathology, the lesions are much less subtle than anything found so far in schizophrenia or bipolar disorder. Although it is possible that a given set of brain/functional measures will account for each case of schizophrenia or bipolar disorder in time, there is no reason to guarantee that this will be

the case. The contribution of neuroimaging and studies of experimental function to knowledge of causation is, in my view, likely to be through the discovery of the mechanisms by which genetic and environmental factors lead to brain changes, neuropsychological deficits and finally the clinical syndrome.

7.3 Issues of study design and analysis in imaging research

Subjects willing to participate in research tend to have less severe illnesses than those who do not and controls have a tendency to be recruited from relatively advantaged backgrounds or be members of health professions. Even, where differences between cases and controls are minimised, the groups are likely to differ in many respects limiting the number of inferences which can reliably be made from this type of research. These differences can be tackled by matching on important confounds which are associated with both disease and exposure, but by definition do not lie on the causal pathway. Age and height may be examples of confounds, but limited knowledge of the precise mechanisms leading to psychosis means that true confounds are somewhat difficult to identify.

Random sampling from a geographically defined population might lead to more representative cohorts being obtained. However, such an approach is unlikely to receive ethical permission and because subjects would still have to 'opt-in', socioeconomic differences between patients and controls may still emerge. Even if representative cohorts were recruited, it would be difficult to distinguish those biological factors (e.g. brain anatomy, neuropsychology) which are risk factors from those which are an adaptation to the illness or its treatment.

The relatively low lifetime risk for psychosis means that prospective study of healthy individuals before they become unwell is virtually impossible for practical reasons alone. However, the paradox is that without it, it will be impossible to distinguish changes which are 'causal' from those which reflect adaptive/tertiary processes or the effects of medication. Technological advances occurring during the execution of the study are also likely to render the methods obsolete many years before it can be completed. For these reasons, studies of unaffected cohorts at increased risk of the disorder seem to be the only realistic alternative. Several high risk studies of schizophrenia are underway and one has been completed (Mednick 1966). Only a few have obtained prospective imaging data and one of these, the Edinburgh High Risk Study, will shortly begin publishing the final results for those subjects who have developed schizophrenia. No study has yet been published which has followed patients at high risk of bipolar disorder. Few areas of the country have sufficiently stable populations to make this practical and, using conventional criteria, a high risk individual who develops depression could not yet be considered to have bipolar disorder until a second manic episode of illness had occurred, perhaps many years later. There are also uncertainties within the concept of bipolar disorders as to whether Bipolar Disorder I and II should be separated from one another and whether bipolar disorder should be separated from unipolar affective disorders. However, providing sufficient numbers could be recruited, most of these practical problems could be overcome.

Much of the neuroimaging literature is internally inconsistent. This is due in part to clinical heterogeneity and to the relatively small sample sizes typical of imaging research. A possible solution to the problem is to combine the results of several studies

together in a meta-analysis. However, the summary effect sizes of such analyses are often heterogeneous and the overall result is often misleading unless the causes for statistical heterogeneity are explained in some detail. A meta-analysis of the results from several studies are a relatively inefficient way of examining the role of effect modifiers or confounders which are often better examined within the subjects of an individual study, or using individual patient data from several studies combined. However, investigators are likely to restrict their analyses to a limited number of hypotheses and outcome measures and studies frequently cannot be combined because compatible data from several studies are not comprehensively published, even if they were actually collected at the time. Collaborative re-analysis and meta-analysis using individual patient data are alternative approaches to the problem but require the presence of large data repositories with detailed meta-data available across wide geographical networks.

7.4 Developments in image acquisition

Studying the neuropsychology of a disorder can be justified on the basis that it provides additional clinical information helpful to patients or clinicians, or provides data on aetiology. Neuropsychological data ideally provides an indirect examination of brain integrity, but is influenced by effort, motivation, the confounding effects of positive symptoms and general intelligence. Unfortunately, it is difficult to control for many of these factors. However, where neuropsychological functions can be localised to specific brain regions or networks, the findings in affected subjects may be closer to the fundamental biology of illness than symptoms alone, which are arguably influenced to a relatively greater extent by life events and personality.

Neuropsychological and psychophysiological associations of psychiatric disorders, single symptoms and symptom dimensions may reveal the mechanisms underlying symptom/syndrome generation more fruitfully than MRI imaging alone, acting as an intermediate level between the syndrome and the structure and function of individual neurones. Psychophysiological experiments have proved very popular in schizophrenia, and have the added advantage that robust animal models exist. This enables the pathways and mechanisms to be studied in animals in a way which would never be possible in human volunteers. Psychophysiological experiments in bipolar subjects are however particularly rare.

Functional MRI is a relatively recent development in imaging research designed to measure changes in cerebral blood flow/oxygenation. It is based on the property that the iron in deoxygenated haemoglobin has paramagnetic properties which cause local magnetic field gradients around blood vessels. The resultant gradient inhomogeneity interferes with the spin-spin relaxation properties in a concentration dependent manner and accelerates the dephasing of proton nuclei resulting in a shortening of the T2* relaxation constant. As neural activity in a brain region increases, the flow of diamagnetic oxygenated haemoglobin will increase and the ratio of deoxygenated to oxygenated haemoglobin will decrease, extending T2* relaxation times in the circumscribed area of increased activity. This change in T2* weighted signal is referred to as the blood oxygen level dependent (BOLD) signal. BOLD signal changes can be detected using sequences with short repetition times which are sensitive to short term changes in local signal strength (commonly FLASH or echo-planar imaging sequences). There are however, a large number of variations on experimental designs (Aguirre and

D'Esposito 2000) and an extensive list of methodological limitations (Kim and Ugurbil 1997).

A number of experimental designs can be combined with fMRI in order to observe specific neurovascular responses contingent upon a subject's experience or task performance. Commonly experiments are 'blocked', 'parametric' or 'event -related'. Block-design experiments typically involve the repeated presentation of an active and rest condition alternately over many identical trials. The difference in BOLD signal between tasks, represent a subtraction in the cognitive processes involved in both tasks, although this is an oversimplification.

Parametric designs are essentially similar but involve the variation of a single task over the course of an experiment by altering one of its parameters continuously between trials. The study design assumes that as a task becomes more difficult blood flow to a specific region will increase or decrease.

Event-related designs involve the presentation of a single stimulus during which the temporal pattern of BOLD response is determined in detail. Involving often only one stimulus presentation, they generally have less statistical power compared to other sorts of design, although the assumptions upon which the other study designs are based may be more frequently violated.

The major advantage of fMRI is that it is able to provide relatively high-resolution data on neural function whilst subjects perform a specific task or are presented with a specific stimulus. This technique has been useful in determining the neural consequences of neuropsychological test performance, providing more direct

evidence of the differences in neural activation which underlie differences in task performance.

Functional MRI has also enabled a reformulation of many of the problems of contemporary psychiatry. For instance, a study of auditory hallucinations using a novel sampling strategy (Silbersweig and Stern 1996;Shergill et al. 2000) has revealed differences in the hallucinating versus non-hallucinating state which do not appear to be specific to any given phenotype and suggest a defective monitoring of inner speech. It is also possible to meaningfully reformulate psychiatric problems in terms of disturbances in normal neurocognitive systems (Bullmore and Fletcher 2003) and to examine functional and effective fronto-temporal connectivity in schizophrenic subjects and controls. These studies have revealed a pattern of dysconnectivity in schizophrenic subjects which may be due to a defect in an existing neurocognitive mechanism.

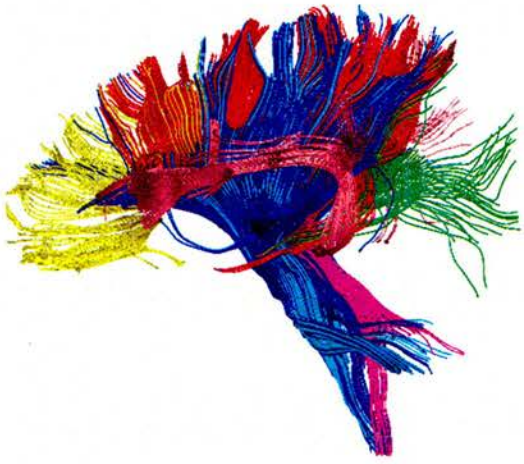
In spite of its obvious advantages, fMRI has not quite been able to bridge the gap between neural function and neuropsychological/psychophysiological performance or symptoms. This is partly due to the fact that the temporal resolution is poorer than, for example, the EEG and, the spatial resolution is unlikely to be sufficient to image individual cells. However, resolution is continuously improving and recently researchers at the University of Minnesota have used high-field MRI to provide functional imaging data on the visual cortex. This technique is able to image neuronal activity in individual populations of neurones in single ocular dominance columns on a sub-millimetre scale (Yacoub et al. 2003).

A newer form of imaging, diffusion tensor imaging (DTI) has also been developed which can view white matter integrity by examining the constrained motion

of free water molecules across membranes. This technique can provide a scalar measure of white matter integrity as well as a vector based measure enabling the directionality and integrity (see figure 7.4) of individual white matter tracts to be examined in vivo (Behrens et al. 2003). The techniques for assessing the directionality and connectivity of white matter tracts are still in their infancy (Behrens et al. 2003) but have the potential to provide a structural substrate for dysconnectivity found in functional imaging studies.

DTI has been used in schizophrenic patients to examine the integrity of fronto-temporal white matter tracts. Results have so far shown a 'structural dysconnectivity' in white matter integrity between frontal and temporal lobe which may represent a physical substrate for fronto-temporal dysconnectivity found in fMRI studies. However, this is only one example of how differing imaging modalities can be integrated to provide additional information about neural activity, pharmacology, connectivity and task performance. Concurrent DTI examination of subjects in the current study might have revealed which white matter tracts, if any, were compromised in terms of their integrity instead of the rather exploratory and indirect examination actually made.

Figure 7.4: Tractography of a single subject using DTI (image provided by Dr M Bastin, Edinburgh University)



Information provided by multiple structural (sMRI, DTI) and functional (e.g. fMRI, MRS, EEG) imaging techniques could be combined fruitfully with clinical data allowing the integration of information on clinical presentation, brain structure and function and neuropsychology/psychophysiology which may improve our understanding of how these 'fundamental' deficits translate into the clinical features.

7.5 Imaging analysis

Over the last 25 years there has been a large shift in the methods employed for the analysis of medical images. Studies initially measured ventricle to brain ratio, conflating two anatomical measures in one statistic. These studies were often positive and gradually, as better image acquisition methods became available, investigators began to measure individual structures firstly by hand, and subsequently using (semi) automated methods assisted by operationalised definitions and detailed brain atlases to define regions of interest (ROIs). However, even these methods may be subjective and/or unreliable for small structures, even when such structures are traced in three dimensions simultaneously. The results for many brain regions (e.g. thalamus, prefrontal cortex) often ignore the anatomical sub divisions of these structures and their diverse functional associations.

Over the last 10 years, fully automated methods have become available which involve no manual tracing of brain regions, are highly reliable, and involve few

subjective judgements. These techniques, exemplified by statistical parametric mapping (SPM), generally register all brains from an experiment in standard anatomical space, smooth the images to provide voxel intensities with randomly distributed errors, and compare average voxel intensities across each group. These analyses are a major advance over the preceding semi-automated techniques, although their results sometimes conflict with those of conventional ROI analyses and may be more difficult to interpret. Potential limitations of such analyses include the imperfect registration and normalisation of images and the assumption of normally-distributed random errors.

Conventional analysis of biometric data commonly involves the parametric assumptions of equality of variance, independence of observation and normally distributed errors. It is not clear whether these assumptions are met in all VBM or functional studies and there is uncertainty as to how such data should best be analysed. Often, non-parametric randomisation tests are conducted to confirm the results of a parametric analysis. These analyses involve the empirical estimation of a kernel density and examine the probability with which the actual data would have been observed by chance alone. They are based on conventional hypothesis testing and incorporate no prior information into the analysis, only the sample images themselves. They have the advantage of being distribution free tests but are likely to have a lower statistical power than the corresponding parametric analysis.

Methods for the analysis of non-normally distributed, autocorrelated data, without equality of variance, have been available for some time. Several programs allow distribution free tests to be conducted using rank transformed data or by repeated re-sampling or simulation (e.g. randomisation, bootstrapping and Monte Carlo analysis).

An exciting development, outwith the neuroimaging literature, is the ability to combine re-sampling techniques with prior information about the distribution and values of the parameters estimated. An example of such a program is BUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling). BUGS can incorporate prior distributional assumptions about population parameters and can resample the data to provide posterior distributions of each parameter involved using Markov chain Monte Carlo methods.

Although I am aware of no fully-Bayesian realisation of such a technique in the imaging analysis literature, a Bayesian framework is now used for the normalisation of images in SPM2 and some authors are clearly beginning to appreciate the potential of such techniques (Friston et al. 2002). Such models could incorporate information about the distribution of grey/write matter density in a normal population and model the role of confounds and potential biases (Spiegelhalter et al. 2004). It is of course desirable that normal brain structure be modelled using informative priors based on well characterised and representative populations. This would require a much greater characterisation of normal brain structure, and its correlates, than is currently available at the present time. Some advantages and disadvantages of Bayesian versus conventional (frequentist) are shown in table 7.5.

Table 7.5: Comparison of Bayesian and conventional analysis

Classical inference	Based on classical 'Popperian' hypothesis testing in which null hypotheses are tested and, in the absence of evidence, rejected. P-values represent the problem of obtaining the observed data in the absence of an effect, not he likelihood of the effect being present. Although the p-value reflects evidence against the null hypothesis, it is often arbitrarily interpreted as <0.05 significant, >0.05 significant The p-value can never reject the presence of an effect (H_A), just the provide evidence against H_0 Given enough observations, almost all differences or relationships (no matter how small) can become 'significant'. P-values are dependent on the number of comparisons/search volume. However, the likelihood that such an effect is present is independent of these considerations
Bayesian inference	Uses prior information about the distribution of the parameters/effects which can be found from previous studies or sample information. Priors can be uncertain/non-informative and assume no prior knowledge about the parameters studies or increasing degrees of knowledge. Sample information is then collected in order to provide a posterior probability distribution for the parameters/effects given the sample information. The posterior distribution of parameters can be stated in terms of a credible interval (usually 95%) which gives the most likely estimate and an upper and lower bound. Avoids many of the problems of multiple hypothesis testing and arbitrarily defined p-values Bayesian analyses are usually more computationally intensive and have been criticised widely in the past on the basis that the prior information provided is somewhat arbitrary, largely determines the results, and is subjective/unscientific

7.6 Clinical associations and exploratory factor analysis

Within the current diagnoses of schizophrenia and bipolar disorder there is a great deal of clinical heterogeneity. It is possible that certain clinical symptoms or historical variables (e.g. drug history) may themselves be associated with particular

patterns of brain structure and anatomical function and if, as suggested, the current categories are imperfectly defined, much clinical and historical information is being sacrificed at the expense of making a diagnostic decision.

Novel clusters of individual patients, defined on the basis of clinical difference (usually Euclidian or 'statistical' distance) could be extracted from clinical and historical data in an *atheoretical* way using multivariate techniques such as cluster and latent class analysis. Unfortunately, this might have the effect of replacing an arbitrary classification which most people 'understand' with another which is not. The problem of information loss would not be solved by this approach. However, investigating the clinical correlates of single clinical and historical variables might be somewhat more fruitful (e.g. symptoms, age of onset, course and prognosis) and has already yielded some positive results (e.g. though disorder and STG volumes in schizophrenia, Shenton et al. 1992;Rajarethinam et al. 2000). Investigation of co-occurring symptoms and clinical variables using the technique of factor analysis might also be useful since the effect of a single misreported symptom or variable might be minimised and the redundancy in the data caused by multi-colinearity would be avoided. This technique has also showed some promise in the neuroimaging and neuropsychological literature, both in schizophrenia alone (Liddle et al. 1992;Chua et al. 1997) and within a spectrum of individuals with a number of functional psychotic diagnoses (McIntosh et al. 2001).

Epidemiological research concerning dimensional representations of psychosis is also providing interesting results. The distribution of psychotic and quasi-symptoms in representative populations has the potential to clarify whether diagnoses represent the upper tail of a normal distribution of symptoms, whether such symptoms are bimodal, or

whether the distribution is half normal (i.e. most people have no symptoms). van Os and Verdoux (2003) have suggested the distribution of symptom dimensions in the general population has the potential to reveal whether risk factors are specific for one dimension or diagnosis and also whether they act alone (are of major effect) or co-participate with other factors. The combination of large scale epidemiological and neuroimaging research is an attractive prospect which would require considerable resources, but such research could be more generalisable and help to overcome the sampling difficulties inherent in many existing imaging studies.

7.7 Conclusions

Neuroimaging research in the 'functional' psychoses has made considerable progress over the last twenty-five years. Disorders once regarded as the consequence of bad parenting are now firmly within the remit of the 'cognitive neuroscientist and brain imager'. However, progress has been slower than expected and maybe due to inadequately powered and inappropriately designed experiments rather than a failure to acquire new technology.

With the advent of the internet and broadband data connectivity, the technical resources to share large quantities of data across multiple centres are now becoming possible. A recent publication in Nature suggests that centres in the USA are already sharing large amounts of neuroimaging data across networks (Chicurel 2000). A recent call for e-science proposals to the MRC in the UK suggests that at least some researchers have had the same idea this side of the Atlantic. However, there has so far been no decision on what to include in these databases and technical obstacles relating to data

collection and relational databases have still to be overcome. Even if such obstacles are overcome, it remains to be seen how well researchers will collaborate with other centres they may previously have viewed as competitors.

Recent innovations in imaging technology and statistical analysis and the possibility of multimodal imaging make the prospects for understanding the mechanism of mental disorder better than ever before. Although the international diagnostic concepts currently used clinically may be imperfectly defined, there is good reason to suppose that reformulation of the problems in terms of correlated symptoms or in terms of disrupted normal neurocognitive processes are likely to lead to rationally defined syndromes or dimensions which will confirm, modify or totally reformulate our current classification of functional psychotic illness.

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