The neuropsychology of affective disorders and schizophrenia

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DECLARATION

This thesis has been composed by myself and that the work herein presented is my own except where otherwise stated. No part of this thesis has been submitted for any other degree or professional qualification.

Emma E Drysdale

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ABSTRACT

The underlying causes of major mental illness are not understood and diagnoses are made largely on the basis of characteristic clinical symptoms described by the patient. A long-standing aim of biological psychiatry is to identify clinical measurements related to illness that may assist in diagnosis in the same way that the measurement of blood glucose level is used in the diagnosis of diabetes. In genetic studies such biological markers of disease have been termed "endophenotypes". Neuropsychological impairments are well described in schizophrenia and bipolar disorder. This study investigates a possible role of specific neuropsychological impairments as markers and "endophenotypes" of illness. The aims of the present study were to (a) confirm previous findings in schizophrenia and bipolar affective disorder of selected cognitive impairments and effects of clinical state and medication, and (b) to establish whether members of a large family multiply affected with bipolar and unipolar affective disorder showing linkage to a chromosome 4 locus, show changes similar to the population group of bipolar and unipolar patients.

Groups of forty-one unipolar affective disorder patients, thirty-seven bipolar affective disorder patients, twenty-six schizophrenic patients, fifteen high risk family members and thirty-one healthy controls were assessed with a neuropsychological test battery focussing mainly on the domains of memory and executive function. Bipolar and schizophrenic patients had similar impairments of verbal learning and memory relative to controls. Schizophrenic patients were also

impaired on executive function tasks. Performance was not due to symptom severity or medication. There were no significant differences between unipolar affective disorder patients and controls. The second major finding from this work is that cognitive deficits were measured in relatives in one family who were at high genetic risk of developing bipolar disorder but who had not developed symptoms of the disorder. It can be concluded that these cognitive deficits may be considered as 'endophenotypes' in genetic studies of bipolar disorder.

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1.0 GENERAL INTRODUCTION

The underlying causes of the major mental illnesses including affective disorders and schizophrenia remain largely unknown and their definition and classification is essentially descriptive. Major mental disorders are diagnosed on the basis of symptoms described by the patient and no established biological markers are available to contribute to diagnosis. Structured interviews and standardised diagnostic criteria such as ICD-10 (World Health Organization 1992) and DSM-IV (American Psychiatric Association, 1994) have improved reliability of diagnoses but their validity remains uncertain. These diagnoses are operational definitions and according to Mechanic (1999) are neither theoretically grounded nor biologically validated. An emerging feature of schizophrenia and bipolar affective disorder research is underlying cognitive dysfunction and a clearer understanding of cognitive impairment, and indeed other abnormalities, in these disorders could improve knowledge of their biological causes and provide a basis for classification.

Neuropsychology is important in studies of psychosis for a number of reasons. Firstly, correct definition of patients' cognitive deficits will aid interventions and rehabilitation, giving neuropsychological assessment a role in patient management. Furthermore, neuropsychology has a role in diagnosis, for example distinguishing dementia from depression or identifying subgroups of depression. Finally, neuropsychological studies can lead to further understanding of the pathology of psychosis and its genetic basis. This thesis focuses on the second two points. The

main questions it attempts to address are: (1) do the cognitive deficits found in schizophrenia, unipolar depression and bipolar affective disorder differ? (2) Can neuropsychological impairments be measured in high risk unaffected relatives of probands and will testing learning and memory be useful in unravelling the genetic basis of major mental illness?

2.0 SCHIZOPHRENIA

2.1 Definition of Schizophrenia

The diagnosis of schizophrenia is based on the presence or absence of a number of characteristic clinical symptoms that include disorders of thinking, beliefs, perceptions, mood, and movement. No symptoms are exclusive to schizophrenia and there is an overlap with psychotic states associated with affective illness, stimulant drugs and organic brain pathology. The aetiology of schizophrenia is poorly understood and there are no objective tests so the diagnosis of the disorder relies upon clinical symptoms and outcome. It may be the case that the current diagnosis of schizophrenia encompasses a group of disorders having a similar course of illness which includes a tendency towards onset in adolescence or early adulthood, recurrent psychotic episodes and deterioration in social and occupational functioning (Johnstone, 1998).

Schizophrenia is a devastating disorder affecting around one in a hundred people in the general population and diagnosis is usually based on one of two classification schemes, the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV, 1994) of the American Psychiatric Association or the International Classification of Diseases (ICD-10, 1992) of the World health Organisation.

Towards the end of the nineteenth century, Kraepelin (1896/1987) proposed a simplified classification scheme for psychoses. Schizophrenia, termed "dementia

praecox" was distinguished from two other kinds of psychosis manic depressive and organic psychoses. The organic psychosis best described at that time was Alzheimer's disease with its characteristic neuropathology. No such characteristic neuropathology had been demonstrated in dementia praecox so it was therefore deemed a 'functional' as opposed to an organic condition. Within the functional psychoses, Kraepelin demarcated dementia praecox from manic-depressive psychosis through symptoms and course of illness. Dementia praecox was marked by decline with no recovery, whereas manic-depressive psychosis was characterised by alternating periods of illness and normality.

Bleuler (1908/1987) devised a different classification scheme, which placed greater emphasis on the psychological bases for schizophrenic symptoms. It was Bleuler who coined the term 'schizophrenia' in an effort to encompass his concept of the splitting apart of different mental faculties. In this sense, 'incongruity of affect' implies that emotion and understanding are no longer properly linked.

It is important to note that we only know about patients' bizarre experiences and beliefs because the patients themselves speak of them, hence they are known as symptoms. There are also abnormalities in behaviour that can be observed, known as signs. These can be broadly classified into two groups, positive and negative symptoms and signs. Positive symptoms are delusions and hallucinations that are abnormal by their presence. Negative symptoms including loss of motivation, poverty of action or alogia are known as such because they represent an absence of behaviours present in normal people. As the illness progresses it is often the case

that the bizarre experiences and beliefs that initially lead to diagnosis become less evident and only so-called negative symptoms are present.

The DSM-IV criteria for schizophrenia are as follows:

The patient must have

A) characteristic psychotic symptoms for at least one week

B) social functioning below previous levels during the disturbance

C) no major changes in mood (depression or elation)

D) continuous signs of the disturbance for at least 6 months

E) no evidence of organic factors (e.g. drugs)

Characteristic psychotic symptoms must include

Two of the following

delusions

prominent hallucinations

incoherence

catatonic behaviour

flat or grossly inappropriate affect

OR 2) bizarre delusions (e.g. thought broadcasting)

OR 3) prominent hallucinations of a voice with content unrelated to mood

The risk of developing schizophrenia seems to be largely independent of culture or socio-economic status. In men, the mean age of onset is in the early to mid-twenties but the disorder can be apparent in children as young as eight and

schizophrenic symptoms can be observed for the first time in the elderly. Schizophrenia is equally common in women although with an average slightly later age at onset in the mid-thirties (Häfner *et al.* 1989). The cause of schizophrenia remains unknown but it is generally assumed to have an organic basis because of neuropathology and neuroimaging findings (Zipursky *et al.* 1994; Bruton *et al.* 1990). There is strong evidence for a genetic component in the aetiology in schizophrenia and also some evidence for increased risk though birth injury or prenatal viral infection. There is no evidence that psychosocial factors directly cause schizophrenia but these may be precipitating factors or lead to relapse in those individuals who are already at risk, either through genetic or environmental factors or a combination of both. (Johnstone 1998)

2.2 Genetic Aspects of Schizophrenia

There is overwhelming evidence that genetic factors play an important part in the aetiology of schizophrenia. The illness has long been observed to "run in families" (Nurnberger and Berrettini 1998). Gottesman and Shields (1982) have shown from pooled European family study data that the age-corrected morbid risk of developing schizophrenia is 5.6% in parents, 10.1% in siblings and 12.8% in children of schizophrenics. It is suggested that the lower risk in parents compared to offspring is related to a relative decrease in fertility among schizophrenic patients. The morbid risk for schizophrenia in the general population is around one percent, so these figures show that all classes of first-degree relatives have increased risk of developing the disorder. However, family studies do not distinguish between shared genes and shared environment. This can be done by twin and adoption studies.

Twin studies in schizophrenia have repeatedly shown that monozygotic (MZ) twin concordance is greater than dizygotic (DZ) twin concordance, which is consistent with a genetic susceptibility. Nurnberger and Berrettini (1998) have summarised twin studies and calculated total concordance rates of 33% for MZ twins and 8% for DZ twins for strictly defined schizophrenia and MZ concordance rates of 49% and DZ concordance rates of 9% in more broadly defined schizophrenia. Kendler and Robinette (1983) have argued that the heritability of schizophrenia is around 70%, meaning that 70% of the variance in incidence of schizophrenia in the population is accounted for by genetic factors. However, Nurnberger and

Berrettini (1998) calculate the heritability to be around 44%, although using a different statistical method. Overall, it would seem that the heritability is considerable, as are the influence of non-genetic factors.

Adoption studies were first used to investigate schizophrenia by Heston (1966) who found increased incidence of schizophrenia in the adopted-away offspring of women with schizophrenia compared to control adoptees. Kety *et al.* (1983) conducted a large systematic review of studies in which adoptees were separated from their biological parents at an early age and adopted by non-relatives. The review revealed that there were more cases of schizophrenia and schizophrenia spectrum disorders in the biological relatives of schizophrenic adoptees than in the biological relatives of psychiatrically normal adoptees.

Recently, genetic linkage studies have identified several chromosome regions of interest. For example a disrupted brain expressed gene DISC 1 on the long arm of chromosome 1 has been described as segregating in a large family with schizophrenia and other major psychiatric disorders and may be one of several or many genes implicated in this complex disorder (Blackwood 2001; Millar 2000).

2.3 Imaging in Schizophrenia

Beginning with Pinel (1801) and later Kretschmer (1925) (both cited in Shenton *et al.* 2001), there has been an interest in brain and cranium size in mental illness, based on a presumed association between this and mental illness, socio-economic status, IQ and cognitive deficits.

After more than one hundred years of research, the neuropathology of schizophrenia remains controversial. Both Kraepelin (1896/1987) and Bleuler (1908/1987) were convinced that it would ultimately be linked to an organic brain disorder. A great deal of progress has since been made in neuroimaging, especially since the advent of magnetic resonance imaging (MRI) techniques, which have confirmed the presence of brain abnormalities in schizophrenia. The major findings include ventricular enlargement and the preferential involvement of the medial temporal structures including the amygdala, hippocampus and frontal cortical regions including the dorso-lateral prefrontal cortex. Many brain areas have been implicated in schizophrenia, and this is evident from studies that have found abnormalities in the parietal lobes, subcortical structures including the basal ganglia, corpus callosum and thalamus, and also the cerebellum (summarised by Ebmeier 1995). What these MRI studies have not been able to ascertain is the timing of the onset of these abnormalities although many are evident when the patient first becomes symptomatic. There is also some evidence that brain abnormalities may change over time. The most parsimonious explanation is that some abnormalities are neurodevelopmental in origin but their clinical

consequences unfold later in development, producing schizophrenia symptoms. However, there may be other factors such as stress or neurotoxicity that occur during adolescence or early adulthood and are necessary for the development of schizophrenia and may be associated with neurodegenerative changes. As Shenton *et al.* (2001) have stated, new models are needed to explain neural circuitry abnormalities affecting brain regions, which are not necessarily structurally proximal to each other but are nonetheless functionally interrelated, since so many brain regions appear to be involved in schizophrenia.

2.4 Neuropsychology of Schizophrenia

2.4.1 Why study neuropsychological function?

There are several important reasons for studying neuropsychological function in patients with psychiatric disorders. It is contended that people who suffer from psychiatric illnesses interpret the information they receive from their sensory systems incorrectly and consequently their behaviour is affected by responding to this distorted reality. People with psychiatric illnesses do not generally appear to have had greatly dissimilar life experiences from those of psychiatrically 'normal' people, so there must be something different about the way in which they process this distorted reality that distinguishes them from unaffected people. Neuropsychological data can inform the diagnostic process by distinguishing between different psychiatric disorders. An explanation, when evidence based, that illness may affect cognitive functions such as memory can be reassuring to patients suffering anxiety and self-doubt. It has been demonstrated that defects in

motivation and in abilities to plan, organise and carry out activities along with problems of self-monitoring can severely compromise patients' capacities to live independently (Green 1996) and neuropsychological assessment may contribute to patient management.

Much of the literature investigating the neuropsychological consequences of psychiatric disorders is essentially atheoretical as so little is known about the connection between psychiatric symptoms and neuropsychological dysfunction. Crowe (1998) has stressed the importance of investigating neuropsychological function to find similarities or differences between psychiatric disorders as an aid to understand aetiology and in the attempt to investigate whether neuropsychological dysfunction may be a biological marker of illness.

2.4.2 Why memory and executive function?

Lezak (1995) states that behaviour can be conceptualised in terms of three functional systems: (1) cognition, which is the information-handling aspect of behaviour; (2) emotionality, concerning feelings and motivation; and (3) executive functions, concerning how behaviour is expressed. Psychiatric disorders usually affect all three systems. Memory and executive function are the focus of this work because these are central to all cognitive functions (Lezak 1995). Memory impairment has severe implications for social and intellectual functioning. Executive functions enable people to engage in independent, purposeful, self-serving behaviour. Impaired executive function reduces the capacity for self-care,

for independent work and maintaining normal social relationships regardless of the level of cognitive capacities. Executive dysfunction can be observed globally, affecting all aspects of behaviour, or can be demonstrated in impaired strategies in planning or carrying out cognitive tasks, or poor self-monitoring. Thus, investigations of these aspects of neuropsychological function can inform our understanding of the pathology of psychiatric illness and its genetic basis, and have implications for outcome and management.

The investigation of neuropsychological outcome in schizophrenia is not merely an academic pursuit as cognitive impairment can have severe real-life consequences. Green (1996) conducted a review of studies using cognitive measures as predictors or correlates of functional outcome and uncovered some interesting findings. Verbal memory functioning appeared to be associated with all types of functional outcome and sustained attention and vigilance also related to social problem-solving and skill acquisition. Interestingly, psychotic symptoms were not significantly associated with outcome measures. Green therefore concluded that verbal memory and vigilance deficiencies prevent optimal adaptation and are thus rate-limiting factors in rehabilitation terms. These may be the central and enduring features of the illness, rather than psychoticism. Addington and Addington (1999) demonstrated that in schizophrenic patients, better cognitive flexibility and verbal memory was positively associated with greater interpersonal problem-solving ability. This evidence does therefore suggest that cognitive impairment in schizophrenia is directly related to social deficits and functional outcome.

2.4.3 Background to the review

The aim of this work is not to attempt to localise function in the brain. Benton (1981) asserts that symptoms should be interpreted as expressions of disturbance in a system and not as a direct expression of focal loss of neuronal tissue. A number of lesions can produce disruption in functions such as memory or executive function. These lesions may be widely distributed throughout the brain. The neuropsychological impairment only indicates that the distributed network involved in that particular function has been disrupted and the symptom itself gives little information about specific localisation. Luria (1973) states that each neuropsychological function is effected by a complex functional system incorporating a number of factors dependent upon the combined working of a number of cortical zones and subcortical structures, each making its own contribution to the performance of the function. The review of the literature will focus on empirical findings, meaning that an attempt will be made to clarify whether neuropsychological impairments occur in schizophrenia or not, rather than attempting to review in detail any theoretical models linking symptoms or anatomy with deficits as these are premature due to the current level of knowledge. However, attempts will be made where possible to describe any impairment in terms of a disruption of normal cognitive processes (Halligan and David 2001).

The following review of the literature of cognitive impairment in schizophrenia places particular emphasis on the domains of memory and executive function, which are the focus of this thesis.

2.4.4 General cognitive function

In an early monograph, Bleuler (1913/1950) asserted that intelligence and general cognitive function remained intact in schizophrenia, a view which was still accepted until fairly recently. It was accepted that schizophrenia sufferers performed poorly on intelligence tests but it was assumed that this was because symptoms of the disorder made testing difficult. However, Johnstone *et al.* (1976) demonstrated through the use of computerised tomography that chronic schizophrenics often had abnormally large lateral ventricles, so cognitive deficits may be expected in conjunction with cerebral pathology. When the cognitive abilities of chronic schizophrenic patients were examined in more detail, evidence was found of widespread cognitive impairment (Crow and Stevens 1978).

It is now accepted that marked cognitive impairment in schizophrenia is the norm and also that it may predate illness. The task now is to establish the nature and degree of impairment. Blanchard and Neale (1994) assert that the lesion-based approach, (attempting to localise the deficits by using specific neuropsychological tests purporting to correspond to a specific brain area), may be responsible for the variability of results between studies of schizophrenia. O'Carroll (2000) suggested that lack of consensus may reflect the heterogeneity of schizophrenia and the poor localising ability of standard neuropsychological instruments.

There is still no real consensus on what the core cognitive dysfunctions in schizophrenia are. Some studies find changes in memory function generally (McKenna 1991, Saykin *et al.* 1994), other studies demonstrate selective executive function deficits (Weinberger *et al.* 1986) or widespread neuropsychological dysfunction (Buchsbaum 1990). Heinrichs and Zakzanis (1998) conducted large-scale quantitative meta-analysis comparing case-control studies. This meta-analysis showed that the largest single impairment was in global verbal memory. However, several studies with very small sample sizes and therefore limited power were included in the meta-analysis. Furthermore, as O'Carroll (2000) points out, there are a large number of impairments, so any specific impairment, such as those in memory or executive function, exists within a widespread decline in general cognitive function.

Palmer *et al.* (1997) subjected a large number of patients and controls to a comprehensive neuropsychological battery and found that only 27% of the schizophrenia sufferers were neuropsychologically "normal", thus highlighting that cognitive impairment in schizophrenia is the norm, but that some patients remain cognitively intact. This would suggest that the pathophysiology underlying the cognitive deficits associated with schizophrenia is possibly distinct from that causing the core clinical symptoms. This is supported by Tsuang (2000) who asserted that diagnostic categories and psychiatric symptoms may reflect relatively remote and variable effects of genes predisposing to mental illness. Goldberg *et al.* (1993a) found that antipsychotics lead to an improvement in clinical symptoms in schizophrenics but with no corresponding increase in neuropsychological function.

2.4.5 Timing of onset of cognitive impairment in schizophrenia

There are problems associated with systematically investigating whether cognitive impairment predates the onset of schizophrenia. Jones *et al.* (1994) used data from the MRC National Survey of Health and Development to select a random sample of more than 5000 births in England and Wales in 1946. From this sample, 30 cases of schizophrenia developed between the ages of 16 and 43. The entire sample was tested for non-verbal, verbal and reading abilities at the ages of 8, 11 and 15 and also arithmetic at 11 and 15 and vocabulary at 8 and 11. Analysis of these tests showed that those children who went on to develop schizophrenia were significantly impaired on non-verbal and verbal IQ tests from the age of 8 and on maths skills from 11. This one study detected cognitive abnormalities in childhood predating the onset of illness. This is suggestive of a possible neurodevelopmental abnormality. David *et al.* (1997) described two possible explanations for a link between cognitive impairment and the onset of schizophrenia. The first may be that it is directly causal, for example cognitive impairment such as semantic memory dysfunction producing false beliefs and perceptions where aberrant connections between 'nodes' in a semantic network could lead to delusions; another possibility is that of indirect action via any factor causing low IQ, such as abnormal brain development, which then increases the risk of developing schizophrenia later.

2.4.6 Cognitive decline over time?

Another important issue is whether cognitive ability declines over time. It has long been assumed that any cognitive impairment in schizophrenia is progressive. Indeed, Kraeplin's (1896/1987) term "dementia praecox", meaning premature dementia, implies continuing cognitive decline. It has also been proposed that acute episodes of schizophrenia are neurotoxic and that the longer the duration of the initial untreated illness, the poorer the prognosis. There is now, however, evidence that the cognitive impairment precedes the illness. Russell *et al.* (1997) refer to the "myth" of intellectual decline in schizophrenia. They conducted a follow-up study of patients who had taken an IQ test in childhood and then gone on to develop schizophrenia, having their IQs tested again nineteen years later. No differences were found between their childhood and adult IQs. However, O'Carroll (2000) criticised this study on the grounds that the sample was unrepresentative because the participants had presented to child psychiatry units and thus were more intellectually impaired than participants in other studies of children who later developed schizophrenia. Rund (1998) carried out a longitudinal review and found that cognitive deficits are relatively stable over time, a finding that is more consistent with a static encephalopathy rather than neurodegeneration. However, most clinicians are able to identify patients whose intellectual functioning declines over the course of their illness. This is suggestive of a possible subgroup of patients who suffer from a more malignant form of the disorder that leads to a poorer cognitive outcome.

2.4.7 Information processing

Another issue of note in evaluating neuropsychological impairment in schizophrenia is how deficiencies relate to clinical signs and symptoms. Most researchers agree on the heterogeneity of schizophrenia and it may be the case that there is no consistent neuropsychological "signature". The syndromes and symptoms may more closely relate to disordered patterns of information processing. Information processing or cognitive processes are hypothetical computational processes which underlie all our behaviour and mental experience and occur mostly outwith our conscious awareness. Cognitive neuropsychology attempts to explain the signs and symptoms of mental disorders in terms of cognitive processes, the theory being that understanding what the specific impairments are will then lead to an attempt to localise them within the brain which in turn will inform our grasp of the aetiology. Liddle and Morris (1991) conducted an important study using an extensive neuropsychological battery of assessments that were purported to be sensitive to frontal lobe function. They found that symptoms clustered into three syndromes; a) psychomotor poverty, associated with slowness in mental activity; b) disorganisation, possibly associated with a specific difficulty in suppressing irrelevant verbal responses and c) reality distortion. This is a very interesting approach as it attempts to integrate neuropsychology with the clinical features of schizophrenia and pursuing this approach may result in an attempt to explain specific symptoms in terms of information processing difficulties. Following this line of reasoning, McKenna (1991) proposed that delusions arise as a consequence of a dysfunctional semantic

memory. This theory feels intuitively correct, as delusions must represent false knowledge. However, as yet, no convincing causal relationships have been found. Frith (1992) has proposed an, as yet purely theoretical, model that attempts to relate specific signs and symptoms to particular information processing abnormalities. For example, the inability to monitor the beliefs and intentions of others leads to delusions of reference, paranoia and third person hallucinations. As there is no firm evidence as yet to support these theories, this review will concentrate on empirical findings.

2.4.8 Classical neuropsychology and cognitive processes

Classical neuropsychology attempts to identify sites of brain damage through tests that are allegedly specific to that site. This means that someone with a lesion in a particular area should be impaired when tested with an instrument that is supposed to be specific to that area, whereas a person with a lesion in another area should perform satisfactorily. However, very few, if any, tests are that specific. Any neuropsychological instrument involves perception, either auditory or visual, attentional and central executive processes for allocating cognitive resources, some working memory (for remembering instructions) and motor control for generating responses, regardless of what site of interest the instrument purports to test. Attempts have been made to extend this method to the investigation of schizophrenia, the results of which have been to implicate almost every brain region as being crucially involved (see O'Carroll 2000). Frith (1992) asserts that the problem with these studies is that they used large groups of patients with

different signs and symptoms at the time of testing. As his theory attempts to link different signs and symptoms with different cognitive deficits, he claims that the mean performance of a heterogeneous group of schizophrenia sufferers results in a very misleading picture. This is a persuasive argument, but needs supporting evidence.

One flaw in the classical neuropsychological approach is that mere associations can lead to false positive results. As mentioned above, any psychological test involves many cognitive processes, only some of which are relevant to localisation. These may be termed 'specific' and 'non-specific'. If impairment were restricted to a very small range of tests, it would imply that specific processes are impaired. This is because non-specific processes will be shared by many tests. Also, if performance is adequate on most tests, it is likely that non-specific processes underlying performance are intact. Conversely, if there were wide-ranging impairment (as is the case with many schizophrenic patients) it would suggest that there is a deficit, which affects non-specific processes.

2.4.9 Schizophrenia and medication

Much experimental work has been done in schizophrenia but there has been very little agreement as to the significance of the results and replications of studies have often produced conflicting results. Some of the problems associated with studying schizophrenia may arise simply as a result of disease management. Drug treatment may be a problem as the vast majority of schizophrenic patients are medicated,

often quite heavily. In investigating schizophrenia it is therefore necessary to consider whether the drug treatment itself may be a contributing factor to cognitive impairment. Many patients are given a cocktail of drugs in addition to standard neuroleptics, some of which can produce memory impairment. It would, however, be difficult to argue that all such cognitive impairments are caused by medication. For example, most of Kraepelin's patients never received drug treatment but he asserted that they suffered from a form of dementia. There are, however, problems involved in trying to surmount the problems of drug treatment. If patients were left drug-free during the acute stage of the illness, they would usually be unable to comply with testing. On the other hand, if a clinician were happy to leave a patient unmedicated and they were happy to undertake psychological testing, they may be unrepresentative of the sample. Therefore, it is important to control for medication effects when assessing cognitions.

2.4.10 Schizophrenia and clinical state

There has been some debate in the literature over the years as to whether the cognitive impairment in schizophrenia is 'real' or merely a consequence of psychiatric symptoms and lack of motivation. Goldberg *et al.* (1993a) examined the relationship between psychotic symptoms and cognition in a group of patients with schizophrenia treated with neuroleptics over a fifteen-month period. The authors observed an improvement in psychotic symptomatology as assessed by the Brief Psychiatric Rating Scale (BPRS) but cognitive function remained impaired. In a further study, Goldberg *et al.* (1993b) contrasted the performance on a battery

of neuropsychological tests of groups of patients with different psychiatric diagnoses. As no normal control group was included, it is difficult to draw conclusions on the degree of impairment, however the group found that symptomatology had a larger impact on test performance in patients with affective disorder than in patients with schizophrenia. These findings suggest that certain neuropsychological impairments are relatively independent of psychotic symptoms, especially in schizophrenia, and that they are likely to be central and enduring features of the disease process and observable in stable patients. Furthermore, studies of children at high risk of developing schizophrenia have demonstrated that such impairments are often evident before the onset of clinical illness (Wolf and Cornblatt 1996).

As mentioned above, there is a large body of research that confirms that patients suffering from schizophrenia perform more poorly than normal controls on a wide variety of cognitive tasks. The literature also suggests that these deficits emerge at (or before) the onset of diagnosable schizophrenic symptoms and remain fairly stable throughout the course of the disorder (Heaton and Drexler 1987, Hyde *et al.* 1994). Controversy again arises as to whether there is a 'generalised' deficit, which is reflective of cognitive inefficiency, imprecision and psychomotor slowing, or whether there are specific deficits, which seem differentially severe and central to the disease process. Current neuropsychological methodology has as yet failed to find a specific profile of deficits from standardised measurement tools for any psychiatric disorder (Randolph *et al* 1993). However, four areas of

cognitive impairment have been consistently implicated in schizophrenia studies, these being attention, executive function, memory and language.

2.4.11 Attention in schizophrenia

Gourovitch and Goldberg (1996) state that attentional dysfunction is characteristic of clinical descriptions of schizophrenia as well as being prominent in patients' own accounts of their experiences. Reaction time experiments have shown that schizophrenia sufferers have difficulties relating to the speed at which they can allocate attention to relevant cognitive activities due to their limited processing resources. In their review, they describe abnormalities throughout the various components of attention including simple vigilance, the ability to benefit from regular or preparatory warning intervals, serial scanning and the ability to sustain attention over time. This therefore suggests that attention is an important area of deficit. Like so many processes impaired in schizophrenia, Mesulam (1985) has suggested that neural structures implicated in the control of attention are widely distributed rather than focal. However, there is a considerable overlap between attention and other cognitive functions, as most if not all neuropsychological tests require some degree of attentional effort.

2.4.12 Executive function

Kraepelin (1921) suggested that dysfunction of the frontal cortex and 'executive functions' may be responsible for the loss of integrative function in schizophrenia.

Such deficits can have a substantial impact on everyday functioning, but as Luria (1980) observed, they can be difficult to determine using standard psychometric techniques. Shallice (1982) has argued that the frontal lobes play a crucial role in planning, organising and controlling action and more recently suggests that frontal lobe dysfunction produces deficits in the Supervisory Attentional System (SAS). The SAS derives from the Norman and Shallice (1986) model of control of action, a broad and quite general model. This model assumes that ongoing actions can be controlled in two ways. The first occurs with well-learned skills, when prior learning allows the activity to proceed relatively automatically. When two activities come into conflict, it may become necessary to give one priority. In the model "contention scheduling" is a process whereby simple rules as to relative importance are built-in and are operated automatically. The SAS is hypothesised to have access to a representation of the environment and of the individual's intentions and cognitive capacities. It is held to operate not by directly controlling behaviour but by modulating the lower level contention scheduling system by activating or inhibiting particular schemata. It would be involved in willed actions and in situations where the routine selection of actions is unsatisfactory, such as novel situations, decision-making or overcoming temptation. Executive functions can involve problem solving, set shifting and response to feedback. The Wisconsin Card Sorting Test (WCST) has been widely used in schizophrenia to investigate executive function and it has been shown that schizophrenia sufferers have difficulty attaining concepts and may perseverate on an incorrect response even in the face of feedback to the contrary (Stuss *et al.* 1983). The patients are able to perform the task if they are provided with a structure, but if this is removed they

tend to return to their previous poor level of performance. Shallice (1988) explains perseverative errors or difficulty to initiate activity by assuming that there is an impairment in the functioning of the SAS, so that when a strategy has been adopted it will continue to run because the capacity to interrupt and change ongoing activity has been lost. If there is no well-established current activity the system will remain inert in the absence of the SAS, or tend to be stimulated by environmental stimuli, giving rise to distractibility. Studies have also shown that schizophrenics have difficulties with the formation of concepts and hypotheses. Furthermore, patients tend to exhibit poorer performance than control groups on tasks that measure guided lexical search such as word fluency (Kolb and Wishaw 1983, Goldberg *et al.* 1988). Again referring to Norman and Shallice's model, the fluency task is presumably difficult for the patient as there is no standard overlearned program for generating responses. Therefore, the individual must set up and run their own retrieval strategies whilst also monitoring that the items fit the correct category and are not repetitions. However, Baddeley (1990) asserts that category generation is within the capabilities of densely amnesic patients, suggesting that the principle problem is not with memory in general but with controlling retrieval strategies. Consistent deficits on executive function tasks combined with behavioural deficits in schizophrenia such as poor planning, impaired social judgement and insight and lack of initiative provided the impetus for describing a frontal lobe dysfunction in schizophrenia.

2.4.13 Executive function and reactive flexibility

Liddle and Morris (1991) investigated left frontal function in schizophrenia using a number of tests including the Wisconsin Card Sort Test (WCST) and found that on the whole, performance was impaired. These impairments were correlated with the severity of psychomotor poverty and disorganisation, but not with the severity of reality distortion. Weickert *et al.* (2000) found subtle deficits on the WCST relative to controls in patients who displayed otherwise intact intellect, suggesting that impaired performance is not simply a factor of impaired general cognitive ability.

Much of the research conducted into executive function in schizophrenia has used the WCST (Corcoran and Frith 1993). Weinberger and colleagues have consistently reported deficits in perfusion in the dorso-lateral prefrontal cortex (DLPFC) in schizophrenic patients when performing this task (Berman *et al.* 1986, Weinberger *et al.* 1988, Weinberger *et al.* 1986), leading the group to suggest that the DLPFC has a major role in the pathophysiology of schizophrenia. Other researchers, however, have suggested that either the medial frontal areas or the left inferior temporal region rather than the DLPFC are involved in failure to perform the task (Drewe 1974, Sagawa *et al.* 1990). As Crowe (1998) points out, these conflicting results may be explained by suggesting that the schizophrenic patient places too much reliance on the frontal lobes to carry out this task. However, as Miller (1983) has commented, poor performance on cognitive tests can be caused by a number of factors. This may be particularly true in patient groups where

performance can be affected by medication, compliance and motivation. Summerfeldt *et al.* (1991) reported that financial reward could improve performance to some extent in schizophrenia, suggesting that poor performance is a consequence of poor motivation. However, Shallice (1988) claims that motivation is not really plausible as a reason for poor performance as performance is often comparable to control data in other more complex tasks, such as the WAIS.

It has been claimed that poor performance on tasks such as the WCST occur because of a breakdown of executive function meaning that the patient is unable to 'abstract', to grasp similarities or essential features. This often results in persistence of response and failure to shift set. The patient has difficulty dealing with information from the environment to discover rules, attain concepts and change behaviour when required to do so (Faglioni 1999).

2.4.14 Executive function and spontaneous flexibility

Another task widely used in studies of schizophrenia to assess executive function is verbal fluency. Kelly *et al.* (2000), in a study of cognitive dysfunction in a community-based population of patients with schizophrenia, found that 49% of all patients with schizophrenia in an area of southwest Scotland demonstrated frontal dysfunction as measured by verbal fluency. Vinogradov *et al.* (2002), in examining predictors of verbal fluency performance, concluded that the restricted verbal output of schizophrenic patients was related to both impaired lexical retrieval and to variation in semantic memory organisation, which partly reflects

general intelligence. Deficits in verbal fluency tasks often reflect poor spontaneous flexibility in that the task requires the spontaneous production of a solution or strategy. The letter condition of the verbal fluency task is considered to be hard because one must explore the content of semantic memory just by initial letter and ignore the actual meaning, rather than using semantic cues which are how things are normally retrieved. Poor performance in the category condition may reflect a disorganised semantic store, or degradation of that store.

Byrne *et al.* (1999) assessed neuropsychological function in young people at high genetic risk of developing schizophrenia and found no significant differences between the high-risk group and normal controls in terms of verbal fluency. However, as the high-risk group was a young, well population tested on a wide-ranging neuropsychological battery, one would not necessarily expect significant differences between groups on all tasks. However, after controlling for differences in IQ, group differences remained for aspects of another test of executive function, the Hayling Sentence Completion Test. This test measures basic initiation speed and response suppression. High-risk subjects made significantly more errors and took longer to complete the task. This type of task reflects the inhibitory and regulatory activity of executive function (and putatively the frontal lobes). This is critical in allowing freedom of choice with regard to what information to accept and operations to carry out. The inability to plan actions and anticipate consequences is found with a tendency to produce the most obvious response even if it is inappropriate (Faglioni 1999).

The literature suggests that many of the cognitive deficits observed in schizophrenia are found in patients with negative rather than positive symptoms. Pantellis and Nelson (1994) claim that these are suggestive of a subcortical dementing process. The deficits observed include poor attention, concentration, memory, planning and activation. Crowe (1998) asserts that the pattern of executive dysfunction in schizophrenia is more in keeping with erosion of levels of drive and activation rather than the disinhibited basal forebrain style of executive disorder, and therefore consistent with a compromised dorso-lateral prefrontal cortex and connections to the brain stem, producing a marked avolitional state and overall diminution of drive and direction.

2.4.15 Memory

As Baddeley (1990) has pointed out, 'memory' as such is not a homogeneous and unified function but has many different aspects, each of which is characterised by a specific profile and involving different neurobiological systems. A more fundamental distinction is that between long-term memory (LTM) and short-term memory (STM). Long-term memory seems to have limitless capacity and involves handling information from over thirty seconds to many years. Short-term memory seems to have only a very limited capacity for only a few seconds. Long-term memory can be further divided into episodic memory (for personal experience), semantic memory (for general knowledge) and procedural memory (for skills). These different aspects can be affected to different extents in different illnesses. Chen and McKenna (1996) assert that from a clinical viewpoint, the relationship

between memory dysfunction and the emergence of psychiatric symptoms is an important issue. Memory is an important component in many everyday cognitive processes that underlie conscious experience. Chen and McKenna claim that it is possible that memory problems could lead to distortions and aberrations in ordinary experiences and that some of these may be related to the symptoms and disability observed in schizophrenia although this needs further investigation.

Memory dysfunction in schizophrenia was not considered an important feature of the disorder until fairly recently. Both Kraepelin (1921) and Bleuler (1913/1950) considered memory in schizophrenia to be largely unaffected. In his review, Cutting (1990) held that memory impairment was not observed except in severely disabled chronic patients with widespread cognitive dysfunction. However, recent systematic studies, which have taken account of factors such as premorbid IQ and current overall cognitive performance, have reported a disproportionate degree of memory impairment in a number of patients with both chronic and acute schizophrenia.

Memory dysfunction is one of the most reliable findings in cognitive studies of schizophrenia (Levin *et al* 1989). Deficits have been reported in a variety of paradigms implicating all stages of memory function from initial encoding to consolidation through to retrieval and recognition (Saykin *et al.* 1991, Calev *et al.* 1983,1987). There has been some controversy as to whether the memory deficits observed in schizophrenia are primary or whether they are secondary to other deficits such as in attention or executive function. However, various studies have

demonstrated consistent memory deficits. It has been shown that generally, the learning rate begins and ends more slowly in schizophrenia sufferers relative to controls (Goldberg *et al.* 1989). Kolb and Wishaw (1983) further demonstrated that schizophrenics' ability to recall stories and abstract designs is impaired compared to normal control groups. Gold *et al.* (1992a) found that schizophrenic patients' exhibited poorer performance on the Weschler Memory Scale-Revised (WMS-R) than on the Weschler Adult Intelligence Scale-Revised (WAIS-R). Thirty percent of the patients investigated in the study had a general memory index (both visual and verbal) fifteen or more points below their full-scale IQ. It is not however clear whether specific aspects of the memory system are differentially affected. McKenna *et al.* (1990) studied 60 patients with schizophrenia with varying degrees of illness severity. The authors found a pattern of memory performance, which was similar to that of classical amnesia, in that short-term memory remained intact but long-term memory and recognition were impaired. Another study conducted by Gold *et al.* (1992b) compared groups of schizophrenics and normal controls. A wide variety of memory deficits were demonstrated by the schizophrenic group, including recall ability, failure to utilise semantic cues aiding recall, recognition, attenuated sensitivity to frequency information and a tendency to make prior list and non-list intrusions. These impairments were shown in both effortful and more automatic memory functions, so the authors concluded that these results supported the notion of dysfunction of encoding of semantic information, frequency estimation and temporal order cues. The above evidence supports a hypothesised memory disorder involving functional

compromise of neural systems involved in the acquisition of new information associated with frontal and temporal lobes.

2.4.16 Short term memory in schizophrenia

Baddeley (1986) has extended the concept of a short-term memory store into a working memory system involving at least two "slave" subsystems (verbal phonological and visuospatial) and a "central executive system". Studies of working memory in schizophrenia have tended to focus on digit span. Gruzelier *et al.* (1988) investigated digit span in groups of schizophrenics, affective disorder patients and controls and found that compared to controls, patient groups were found to have slightly shorter spans for both digits and Corsi blocks. Tamlyn *et al.* (1992) found that of groups of both acute and chronic schizophrenic patients, 86% had digit spans of at least five, the remainder having spans of four. Duffy and O'Carroll (1994) demonstrated that patients with schizophrenia and Korsakoff's both had forward digit spans within normal limits. Goldberg *et al.* (1993c) investigated digit span in monozygotic twin pairs discordant for schizophrenia. Forward digit span was found to be equal in affected and unaffected twins, whereas backward digit span showed a non-significant trend towards poorer performance in affected co-twins. It seems from these verbal working memory studies that most schizophrenics have a forward digit span within the normal range. There are however some suggestions that mean digit span may be marginally impaired. The difference may be more pronounced in backward digit span, although this is often not reported. Tamlyn *et al.* (1992) have suggested that if there is a subtle working

memory deficit, it does not appear to be correlated with other memory deficits. They found that the schizophrenics involved in their study had specific and substantial degree of overall impairment in long term memory rather than short term memory, with relatively preserved Short Term Memory. Chen and McKenna (1996) also point out that this preservation is also shown by preservation of the recency effect in recall.

2.4.17 Long term memory in schizophrenia – retrograde studies

Investigations into long-term memory in schizophrenia can be fractionated into the memory subsystems outlined above. Retrograde studies of episodic memory assess memory for remote events acquired over long periods and determine the presence of a temporal gradient in episodic memory impairment (Butters and Cermak 1986). However, Chen and McKenna (1996) assert that this approach is vulnerable to methodological problems. For example, it is difficult with a list of famous events or personalities to assess whether any failure is due to memory impairment or to a longstanding lack of awareness. Calev *et al.* (1987) tested chronic schizophrenics and normal controls on the Famous Events Questionnaire and found that remote episodic memory was impaired in the schizophrenia group and also that there was no apparent temporal gradient. Tamlyn *et al.* (1992) with the same group of schizophrenics mentioned above found that all of them demonstrated poor performance compared to normal controls on the famous personalities test. There are very few studies to consider in this area but they do suggest that episodic

memory is impaired in schizophrenia but unlike classical amnesiac disorder, there is no clear temporal gradient.

2.4.18 Long term memory in schizophrenia – anterograde studies

Anterograde studies of episodic memory are tasks involving memorising items and subsequently testing retention of material either by recall or recognition. They involve a short time span and experimentally controlled presentation of items. Again, Chen and McKenna (1996) express concerns over possible methodological problems with tasks requiring the acquisition of new material, such as motivation and "input" factors such as attention. The objective of such tasks is to produce memory traces that are distinct from other traces. These traces are better examined through recognition rather than recall because the latter requires additional cognitive activity to access the items. Baddeley (1990) claims that similarity between the items will interfere with recognition but have variable effects on recall – it may assist access but interfere with discrimination. This underlies the observation that high frequency words tend to be recalled more easily whereas low frequency words tend to be recognised more easily. The assessment of memory by recognition is also complicated by the readiness of subjects to guess and answer when they cannot remember with certainty but have a vague sense of the answer. Calev *et al.* (1983), in a study involving groups of chronic and acute schizophrenic patients, tried to facilitate encoding with the introduction of an orienting task. This was achieved by getting the participants to sort the stimuli into semantic categories prior to learning and recall tests. Deficits were found at both the encoding stage in

the chronic and mild groups and in the post-encoding stage in the chronic group. Calev (1984) investigated the performance of chronic schizophrenics and normal controls on recall and recognition tasks matched for difficulty level. He found deficits in both in the schizophrenic group with recall being differentially more impaired. This suggests retrieval deficits with problems accessing stored material. Tamlyn *et al.* (1992) tested groups of acute and chronic schizophrenic patients on the Rivermead Behavioural Memory Test and found them to be impaired on most measures of long-term memory. A further study of five patients who were very impaired with the Recognition Memory Test found variable impairment for both word and face recognition. The authors concluded that both recall and recognition are impaired in schizophrenia. These are, however, tiny numbers from which to conclude anything. Goldberg *et al.* (1993c) in a study of discordant monozygotic twin pairs on paired associate learning found that the affected twins demonstrated poorer performance than the unaffected twins who were more similar to normal controls. No differences between the groups were found for delayed recall. However, the twins with schizophrenia failed to take advantage of semantic regularities as was observed in the other groups. These studies, although very small scale, show that there may be at least some evidence for impairment of Long Term Memory in schizophrenia, but the presence of a learning curve over trials argues against the notion that schizophrenics are similar to patients with amnesic syndrome.

2.4.19 Semantic memory in schizophrenia

Semantic memory refers to memory for facts, ideas and concepts that are not personal in nature. These are organised conceptually and with little temporal coding. As Baddeley (1990) states, this system is typically spared in classical amnesic syndrome. Category specific deficits have been found in some patients with brain lesions (Warrington and Shallice 1984), which is suggestive of topographical organisation. Tamlyn *et al.* (1992) in their study of acute and chronic schizophrenic patients tested them on the Silly Sentences test. They found that reaction time was increased in the schizophrenic groups with two thirds of them outside the normal range. Normal controls rarely make errors on this task, but 14 out of 60 schizophrenics made three or more mistakes, with five of them making more than ten errors. The tendency was for the patients to misclassify the statements as true and when questioned to give irrational reasons for their responses. McKenna *et al.* (1994) tested 41 schizophrenic patients ranging from chronic to mild with the Hodges Semantic Memory Test. This assesses different aspects of semantic memory including category fluency, naming, sorting and definition. The patients as a whole demonstrated impaired performance on many aspects. These studies suggest a specific anomaly in semantic memory function in schizophrenia. Chen *et al.* (1994) devised a categorisation task requiring a yes/no response, for example whether the exemplar 'chair' belongs to the category 'furniture'. The internal category structures appear to be intact in schizophrenia but items clearly outside the category boundary but related in some attributes – for example 'aeroplane' and the category 'birds' – seem to be treated as though they

were on the category boundary. Reaction time analysis shows that normal controls take longest to respond when an item is on the boundary but for schizophrenics the longest reaction times are for items outside the boundary but related. This is suggestive of disorganisation of semantic store.

2.4.20 Verbal versus nonverbal memory in schizophrenia

Some theories have suggested lateralisation in schizophrenia, which has led to the comparison of verbal and spatial memory. So far, the results have proved inconclusive. Chen and McKenna (1996) suggest this is due to serious methodological problems in that studies, which have reported laterality differences, have not employed verbal and non-verbal tasks, which are matched for difficulty level.

Deficits in both visual and verbal recall have been reported with some consistency in the literature, suggestive of disruption in cortical networks (Corcoran and Frith 1993).

Spatial memory tasks have also distinguished between schizophrenia sufferers and other patient groups (Park and Holtzman 1992). They claim that this suggests a failure in representational processing independent of modality. Archer *et al.* (1992) demonstrated that schizophrenic patients were less accurate than either depressed patients or healthy controls in recognising familiar faces, naming emotions shown in photographs or in distinguishing previously seen faces from an

array of distracters. This suggests a generalised failure of recognition of visual items.

2.4.21 Specific memory impairment in schizophrenia?

It appears that the pattern of memory impairment in schizophrenia has unique and specific features, which may eventually be related to the involvement of a specific set of neural subsystems. It is, however, well recognised that a number of schizophrenic patients have global cognitive impairment. This gives rise to the question of whether memory dysfunction in schizophrenia occurs entirely in the context of global impairment or whether it can be considered as a distinct psychological deficit. Braff *et al.* (1991) took an outpatient sample and found that schizophrenics have a non-specific and heterogeneous pattern of neuropsychological deficits. However, as Chen and McKenna (1996) point out, the study did not employ an extensive memory test battery. However, Tamlyn *et al.* (1992) found that the distribution of scores in their study suggested that the memory impairment is disproportionate to any generalised cognitive impairment. Duffy and O'Carroll (1994) confirmed this.

The specificity and extent of memory deficits in schizophrenia remains an area of contention (Calev *et al.* 1991). Aleman *et al.* (1999) conducted a meta-analytic review of memory impairment in schizophrenia and found evidence for a significant memory impairment that was stable, wide-ranging and not substantially affected by potential moderator variables such as symptom severity or duration of

illness. The composite effect size for recall performance (both verbal and non-verbal) was large, and recognition memory showed less but still significant impairment. Impairments in encoding and consolidation have been associated with hippocampal and temporal lobe dysfunction (Squire 1992, Hjiman 1996). Furthermore, frontal lobe systems, which may also be affected in schizophrenia have been to be involved in free recall of declarative memory (Wheeler *et al.* 1995, Ungerleider 1995).

2.4.22 Memory deficits in different illness stages in schizophrenia

The effect of length and severity of illness upon memory performance has produced variable results. However, studies have shown that memory impairment is prevalent in schizophrenia. McKenna *et al.* (1990) established that, using a test of 'everyday' memory, the performance of schizophrenic patients was no better than that of a sample of moderate or severe brain injured patients, and that this was not restricted to chronic patients, but seen in acute and remitted patients as well.

Byrne *et al.* (1999) further demonstrated that individuals at high genetic risk for developing the disorder recalled fewer words than age and sex matched normal controls on all trials of the Rey Auditory Verbal Learning Test, suggesting that this is a stable trait deficit, possibly neurodevelopmental in origin. However, these results could be accounted for by the difference in IQ between the groups.

Levin *et al.* (1989) claim that mildly disturbed schizophrenic patients show more deficits in encoding and organisation of material, whereas severely disturbed patients show something akin to retrograde amnesia. This, however, is at odds with the findings of Hoff *et al.*'s (1992) study, comparing first-episode schizophreniform patients and chronic schizophrenic patients in verbal and visual memory performance. No differences were found between the patient groups although both performed worse than healthy controls.

2.4.23 Recall versus recognition in schizophrenia

Gold *et al.* (1992b) theorise that memory deficits in schizophrenia are due to a disruption in the encoding of material, producing a lack of distinctiveness and specificity of verbal items. However, Paulsen *et al.* (1995) found evidence for a prominent retrieval deficit in schizophrenia, characterised by moderate to severe impaired total recall across all trials of the California Verbal Learning Test in the context of only mildly impaired recognition impairment. The schizophrenic patients in Paulsen *et al.*'s (1995) study further demonstrated a tendency to make phonologically related false positive errors in recognition, suggestive of superficial rather than semantic encoding, which is consistent with the Gold *et al.* (1992b) study findings.

Wood and Flowers (1990) examined cerebral blood flow in schizophrenia over repeated trials of a verbal recognition task. Both schizophrenic and bipolar groups could be distinguished from the unipolar depressed and healthy control groups on

the narrative prose task. However, they claimed that schizophrenia is "uniquely associated" with hypofrontal blood flow, failure of the frontal lobe to appropriately supervise decision processes in memory retrieval and recognition.

The evidence pertaining to memory function in schizophrenia does consistently report deficits in verbal and visual recall, especially in severely disturbed schizophrenia sufferers, similar to those found in classical amnesic syndrome, which suggests bilateral hippocampal involvement as the hippocampal complexes are involved in the acquisition of new factual knowledge, and specialised for different types of knowledge in a manner paralleling the usual functional arrangement of the brain (Tranel and Damasio 1996). In more mildly disturbed patients, and in patients with bipolar affective disorder, memory deficits are associated with poor organisation of material, producing disrupted encoding, and leading to disruption of attentional and organisational functions (Crowe 1998).

2.4.24 Association of memory and executive function

A relationship has been found between memory impairment and executive function. Some authors have noted that the memory impairment in schizophrenia appears to affect recall over recognition and have suggested that this may reflect an executive pattern of impairment (Goldberg *et al.* 1989). However, as Tamlyn *et al.* (1992) have shown, intact recognition is not a universal finding. The frontal lobes have a role to play in executive function but it is not clear whether frontal lobe lesioned patients always show a pattern of impaired recall with relatively intact

recognition. For example, Delbecq-Derousene *et al.* (1990) report a patient with frontal lobe syndrome who showed selectively impaired recognition memory and Hirst (1982) report a disparity between recall and recognition in classical amnesic syndrome without frontal lobe involvement. Another important question is whether executive function deficits as reported in schizophrenia are disproportionate to the overall level of poor intellectual functioning. Conclusions cannot yet be drawn with any confidence on this issue. Saykin *et al.* (1991) employed an extensive battery of tests and found that when scores were compared across tests, patients were no more impaired on executive function tasks than on anything else. Indeed learning and memory deficits were significantly more prominent than any executive dysfunction. However, Shallice *et al.* (1991) employed a similarly wide battery and found a more or less consistent pattern of severe executive impairment. The authors argue that executive dysfunction is the common denominator of neuropsychological impairment and when it is present in relative isolation, it could plausibly account for poor performance on some memory tasks, for example compromised frontal lobe systems have been shown to be involved in the active retrieval of declarative memories (Ungerleider 1995).

2.4.25 Language in schizophrenia

A further area of cognitive impairment implicated in schizophrenia is that of language. One component of thought-disordered language is the lack of executive planning and editing of discourse together with the inability to inhibit inappropriate associations. Barr *et al.* (1990) showed that the majority of errors in language

functioning as exhibited by schizophrenic patients such as perseveration of words and perseveration of prior semantic and phonemic properties of words are related to executive dysfunction.

Gourovitch and Goldberg (1996) suggest that errors in schizophrenic speech have more to do with the inability to inhibit irrelevant or facilitate relevant activated units of language rather than a breakdown of the semantic system per se.

2.5 Endophenotypes in Schizophrenia

Diagnosis of schizophrenia relies on clinical symptoms reported by the patient. The picture might change if we had reliable biological markers of risk to assist in determining who is a "case". Much research has been directed towards the identification of biological variables that could act as trait markers of risk of disease. Endophenotypes are heritable traits associated with the expression of an illness. For example cognitive deficits discussed in Section 2.4 may be considered as possible endophenotypes for schizophrenia and abnormal neurophysiological, biochemical, endocrinological and neuroanatomical findings have all been proposed. Leboyer *et al.* (1998) state that in order to meet the criteria for a marker trait, an endophenotype must occur before the onset of illness and must be heritable. Specific physiological responses such as eye movements and the auditory P300 event related potential. (Blackwood *et al.* 1990) are deemed to be endophenotypes. Roxborough *et al.* (1993) investigated neuropsychological and P300 abnormalities in schizophrenic patients and in relatives of schizophrenics and

found that patients performed less well than controls on neuropsychological tasks believed to be sensitive to frontal and temporal lobe impairment. Furthermore, the patients showed prolonged P300 latency. The relatives of schizophrenic patients fell into two groups. Those with abnormal P300 showed similar deficits to the schizophrenic patients, but those with normal P300 performed at the level of the normal comparison group. Shajahan *et al.* (1997), in a relatively small-scale study, found lower amplitude and longer latency of P300 in schizophrenics when compared with age- and gender-matched normal controls. Correlations were also found between P300 amplitude and latency and neuropsychological performance in the patient group. Blackwood *et al.* (1999) found that, in patients with schizophrenia and their relatives, altered cerebral perfusion as measured by single photon emission computed tomography (SPECT) was correlated with verbal memory and P300 abnormalities.

Findings from the Edinburgh High Risk Study confirm that neuropsychological impairment may be a risk indicator. In a recent paper, Byrne *et al.* (1999) showed that high-risk subjects performed more poorly than controls on test of intellectual function and on aspects of executive function and memory. However, to be useful as an aid to diagnosis, a disease endophenotype must fulfil the following criteria:

1. Be related to disease at the population level.
2. Segregate with illness in families.
3. Clearly differentiate "affected" from "unaffected" individuals. In practice that requires a mean level in "affecteds" more than three standard deviations from the control mean.

To date, no biological variable has been shown to fit these criteria in schizophrenia.

3.0 UNIPOLAR AFFECTIVE DISORDER

3.1 General Description

The aetiology of affective disorders is not fully understood and like schizophrenia, definitions are based on the presence of specific signs and symptoms. The fundamental feature of an affective disorder is a severe and prolonged disturbance of mood which may be depression and anxiety if a patient is diagnosed with a depressive illness, of elation and excitement if a patient is diagnosed as being in a manic or hypomanic state. Unipolar depression will be described first.

Kraepelin's original concept of manic-depressive illness was a catch-all for all illnesses with manic or depressive symptoms or a mixture of the two regardless of duration or specific symptomatology. It was not until Angst (1966, cited in Nurnberger and Berrettini 1998) and Perris (1966) drew attention to the differences between patients suffering from periods of mania and periods of depression and those patients who only suffered from depressive episodes that the original concept was seriously challenged.

Evidence from family studies suggests that unipolar and bipolar disorders should be considered as two disorders rather than a unitary one. Perris (1966) found an increased risk of bipolar illness and unipolar depression in first-degree relatives of bipolar patients, and a high risk of unipolar illness and no increase in bipolar illness in the relatives of unipolar probands. Angst (1966) found that relatives of

bipolar patients had a high risk of both unipolar and bipolar disorder, while the relatives of unipolar probands had a high risk only of unipolar disorder.

In DSM-IV the major affective disorders are sub classified as bipolar and unipolar disorders. The essential feature of a bipolar illness is the presence of one or more episodes of mania or hypomania usually, but not exclusively, occurring with a history of major depressive episodes. The diagnosis of unipolar depressive disorder requires one or more episodes of depression with no history of either mania or hypomania.

The DSM-IV (APA, 1994) diagnostic criteria state that for a diagnosis of Major Depressive Disorder the patient must have:

At least one of the following three abnormal moods which significantly interfered with the person's life:

Abnormal depressed mood most of the day, nearly every day, for at least two weeks.

Abnormal loss of all interest and pleasure most of the day, nearly every day, for at least two weeks.

At least five of the following symptoms have been present during the same two week depressed period:

Abnormal depressed mood.

Abnormal loss of all interest and pleasure.

Appetite or weight disturbance, either:

Abnormal weight loss (when not dieting) or decrease in appetite or

Abnormal weight gain or increase in appetite.

Sleep disturbance, either abnormal insomnia or abnormal hypersomnia.

Activity disturbance, either abnormal agitation or abnormal slowing (observable by others).

Abnormal fatigue or loss of energy.

Abnormal self-reproach or inappropriate guilt.

Abnormal poor concentration or indecisiveness.

Abnormal morbid thoughts of death (not just fear of dying) or suicide.

The following are exclusion criteria:

The symptoms are not due to schizophrenia.

There has never been a manic episode, a mixed episode or a hypomanic episode.

The symptoms are not due to physical illness, alcohol, medication or street drugs.

The symptoms are not due to normal bereavement.

Appetite disturbance can be manifested as either increased or decreased desire for food which leads in turn to a corresponding loss or gain in weight. Similarly, sleep

disturbance can take the form of either insomnia or hypersomnia. Lack of sleep may result from being unable to fall asleep on first going to bed, restlessness and waking during the night and waking very early in the morning and being unable to fall back to sleep. Alternatively the patient may find that he is sleeping far more than usual and spending most of the day in bed. The depressive patient may experience psychomotor agitation, being unable to sit still, or psychomotor retardation in which he feels very much 'slowed down'. The patient often expresses feelings of worthlessness and guilt and also slowness of thinking.

Other characteristic signs of depression are tearfulness, anxiety, irritability, obsessive ruminations, excessive concern with physical health, panic attacks and phobias. If delusions and hallucinations are experienced they tend to be mood-congruent. Commonly, delusions take the form being punished or persecuted due to some moral transgression or personal inadequacy. The patient may present with nihilistic delusions of the world or personal destruction, somatic delusions of serious illness or delusions of poverty. Hallucinations, if they occur, are usually transient, involving accusatory or condemnatory voices.

The onset of a major depressive episode can be variable. Symptoms tend to develop over a period of days or weeks, although in some cases the onset can be relatively sudden, for example as a reaction to stress. In a number of cases there are prodromal symptoms such as generalised anxiety, panic attacks phobias or mild depressive symptoms (Goodwin 1998).

The duration of a major depressive episode is also very variable. If left untreated, the episode will generally resolve itself in six months or longer. Usually, there is a complete remission of symptoms and general functioning returns to the premorbid level. Some patients experience episodes of depression separated by several years of normal functioning. Other patients suffer clusters of episodes; others still have increasingly frequent episodes as they grow older (Kendell 1987).

3.2 Epidemiological Findings

Studies of the prevalence of Major Depressive Disorder in the USA and Europe have reported values of between 4.9% to 8.7% for females and 2.3% to 4.4% for males (Weissman *et al.* 1996)

In unipolar disorder the mean age at onset shows little variation, being between 24.8 and 34.8 years (Weissman *et al.* 1996) and the rates of major depression are usually higher for women than men (Angold and Worthman 1993).

3.3 Cognitive Impairment in unipolar depression

3.3.1 Memory

Until relatively recently it was believed that even severe depression was associated with only minor impairment in cognitive function. However, more recent research has clearly established that memory functioning appears to be impaired in major

depression and this is not simply due to reduction in motivation (Richards and Ruff 1989). Ilsley *et al.* (1995) compared patients suffering from major depression with controls marched for age, sex and IQ on a battery of tests aimed at fractionating memory dysfunction in depression. Patients were unimpaired relative to controls on measures of short-term memory, recognition, semantic memory and implicit memory. No correlation was found between depression severity and level of memory impairment. It was found, however, that the depressed patients demonstrated deficits in psychomotor speed and in immediate and delayed free recall. This would suggest that material is satisfactorily encoded but that the patients are particularly impaired with regard to search and retrieval processes.

Austin *et al.* (2001) carried out a review of the literature examining cognitive deficits in depression and their brain correlates. Cognitive deficits are often viewed as epiphenomena of the disorder. The review concluded that depression is associated with a number of deficits in episodic memory and learning and appears to involve both explicit verbal and visual memory. Implicit memory tasks appear to be spared. Sheline *et al.* (1996) found reductions in volume of the hippocampus in patients with major depression and this ties in with these findings as temporal lobe lesions typically disrupt episodic memory.

3.3.2 Executive function

Studies investigating executive function in depression have produced conflicting results but in general significant impairment was found in patients with severe

depression. The review suggests that executive deficits may be selective for set-shifting tasks. Several studies suggest that these impairments occur independently of age, depression severity and subtype, task difficulty, motivation and response bias. A few studies suggest that cognitive deficits may persist upon recovery and that these findings are reported in all age groups, although more frequently in older patients. The presence of neuropsychological deficits is important evidence that enduring brain abnormalities are implicated in the aetiology of depression because if cognitive impairment were simply secondary to the severity of depressed mood, it would be expected to fully recover with the remission of the acute episode.

Purcell *et al.* (1997) investigated cognitive function in younger out-patients with moderate depression, and found no impairment in working memory, but impaired motor speed and attentional set shifting, with around half the depression group failing to complete the task. Impairment was associated with the number of admissions, suggesting that patients with greater illness severity are more impaired on set shifting tasks.

Channon and Green (1999) further investigated executive function in depression, working on the notion that depressed patients fail to generate or implement adequate performance strategies. This followed on from an earlier study (Channon, 1996) investigating the performance of dysphoric undergraduates on the WSCT, the findings of which were consistent with models of depression which conceptualise it in terms of impaired executive functioning on effortful tasks with intact automatic processing. Unipolar patients were compared with matched

healthy controls on tasks sensitive to executive function and were found to be impaired relative to controls and to use appropriate strategies spontaneously less often, although their strategies were similar. The findings of this study are consistent with cognitive models predicting impairment in controlled processes in depression resulting from reduced or diverted attentional processing resources.

As there is evidence for reduced prefrontal cortical blood flow and metabolism in both depression and schizophrenia, Merriam *et al* (1999) conducted a study to directly compare these two groups along with a healthy comparison group on the Wisconsin Card Sort Test as it is sensitive to such dysfunctions. The findings showed that depressed patients were significantly impaired on the task relative to the healthy controls, although unsurprisingly these deficits were less severe than those exhibited by the schizophrenic patients. The authors suggest that the difference in performance deficits between the patient groups may be due to the greater severity of illness in the schizophrenics. However, it may rather be due to disorder-specific effects on prefrontal cortex function. The authors do conclude that as there was an association between cognitive impairment and depressive symptoms, these findings may be state-dependent.

3.3.3 Cognitive performance and clinical state

Much of the literature relating to cognitive impairments in depression suggests that these abnormalities are more pronounced in elderly patients or midlife patients with psychotic features. Little work has been conducted in younger patients. This

is an important area of study because early onset depression may be a distinct subgroup of the disorder. Grant *et al.* (2001) conducted a large scale study with the express intention of addressing this issue, including 123 nonbipolar, nonchronic, unmedicated patients with major depressive disorder and an age- and gender-matched healthy comparison group. The authors were struck by the absence of significant cognitive impairment in this group of depressed patients. There were mild impairments in executive function as measured by the Wisconsin Card Sort Test but attention, memory and motor functioning appeared to be intact.

Sweeney *et al.* (2000) directly compared the performances of bipolar and unipolar patients on the Cambridge Neuropsychological Test Automated Battery (CANTAB). Manic and mixed affective state bipolar patients demonstrated deficits in episodic and working memory, spatial attention and problem solving. However, depressed bipolar and nonbipolar patients demonstrated only impairments in episodic memory. These findings suggest that neuropsychological deficits are significantly more pronounced in mixed/manic phases than during the depressed phase of bipolar disorder, and indeed that the pattern of neuropsychological deficits is similar in bipolar and nonbipolar depression. The authors suggest that such deficits may be related primarily to the state of illness at the time of testing rather than persistent stable cognitive deficits. This, however, warrants further investigation.

Thus depression results in a disruption of orderly information processing, characterised by relatively poor performance on memory and higher level problem

solving tasks. It may be that these deficits are more indicative of a loss of effortful processing rather than intrinsic problems with information processing *per se* and it may be that these deficits are state rather than trait dependent.

4.0 BIPOLAR AFFECTIVE DISORDER

4.1 General Description

Similar to schizophrenia and unipolar affective disorder, the aetiology of bipolar disorder is not entirely clear, and diagnosis is made on the basis of signs and symptoms.

Originally Kraepelin (1921) combined unipolar and bipolar illnesses within his category of manic-depressive psychosis. It was not until Leonhard (1957) separated unipolar and bipolar affective disorders that they came to be investigated as discrete illnesses for research purposes. However, the distinction between the two is not always so clear-cut. It is well established that between ten and twenty percent of patients whose first episodes of illness are all depressive in nature and are therefore initially classified as suffering from a unipolar depressive illness will go on to develop manic episodes and consequently be reclassified as bipolar (Kendell 1987). Akiskal (1983) states that there are a number of features which a unipolar patient who is subsequently diagnosed as bipolar tends to exhibit. These include early onset (before the age of 25), especially acute onset, psychotic depression, postnatal depression, a hypersomnic retarded clinical picture, hypomania triggered by antidepressant drugs or ECT and a family history of bipolar disorder.

Leonhard's (1957) distinction between unipolar and bipolar disorders has been supported by a number of findings. These include investigations of familial distribution, natural history and response to treatment. The rate of illness found in first-degree relatives varies to a significant extent between unipolar and bipolar probands. Perris (1966, cited in Nurnberger and Berrettini 1998) found that the risk of affective illness is increased in relatives of bipolar patients. In a study of 138 bipolars and 139 unipolars, bipolar family history was found in 16% of the cases and a family history of unipolar disorder in 0.8% of the bipolar probands. In the unipolar probands, a family history of bipolar disorder occurred in 0.5% of cases and family history of unipolar disorder in 10.6% of cases. Twin studies have revealed increased concordance between bipolar monozygotic twins than between unipolar monozygotic twins, suggesting a greater genetic contribution.

Bipolar illnesses are usually classified according to the predominant mood of the current episode. Thus the patient may be described as being in a manic or depressed or separately a mixed state if elation and depression are exhibited at the same time.

The DSM-IV (APA, 1994) diagnostic criteria for bipolar I disorder are as follows:

For a manic episode:

A distinct period of abnormally and persistently elevated, expansive or irritable mood, lasting at least one week (or any duration if hospitalisation is necessary).

During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

Inflated self-esteem or grandiosity.

Decreased need for sleep (e.g. feels rested after only three hours of sleep).

More talkative than usual or pressure to keep talking.

Insomnia or hypersomnia nearly every day.

Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

Flight of ideas or subjective experience that thoughts are racing.

Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli).

Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.

Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions or foolish business investments).

The symptoms do not meet criteria for a mixed episode.

The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or

to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features.

The symptoms are not due to the direct physiological effects of a substance (drug of abuse or medication) or a general medical condition.

For a depressed episode:

The patient must fulfil the same criteria given for unipolar affective disorder.

Associated symptoms may include inflated self-esteem, grandiosity and decreased need for sleep, pressure of speech, flight of ideas, distractibility, excessive and impracticable planning, psychomotor agitation and unwarranted involvement in activities the desirability or feasibility of which the sufferer may not examine. Inflated self-esteem can range from uncritical self-confidence to marked grandiosity which is often delusional. The patient may feel that he is very important and have special powers, plans and abilities. The patient feels less need for sleep but still feels full of energy. If the sleep disturbance is especially severe the patient may go for several days without feeling the need for sleep or feeling that he is too busy to waste time in sleeping. Manic patients often talk more than is usual or feel the pressure to keep on talking. Manic speech is characterised by increased volume, rapidity and difficulty of interpretation. It may be full of jokes, puns, plays on words and irrelevancies. The patient may experience flight of ideas which is exhibited in a flow of accelerated speech with abrupt changes from topic

to topic. These rapid changes in topic are typically based on understandable associations, distracting stimuli or plays on words. In very severe cases speech may be disorganised and incoherent.

A manic patient can be distractible in that he may have difficulty concentrating on events round about him because his attention switches to unimportant items. This is apparent through rapid changes in speech or activity due to responding to irrelevant external stimuli. The patient can also exhibit increased goal-directed activity which may mean excessive planning of and participation in multiple activities. These can include social, employment, sexual and physical activities. The patient's social interactions can often become intrusive, demanding and domineering although this is usually not recognised by the sufferer. These activities tend to have a disorganised, flamboyant or bizarre quality. The manic patient also has a tendency to indulge in imprudent activities which have a high risk component, often of a sexual or financial nature (Goodwin 1998). If the patient's mood swings towards irritability rather than elation, he may exhibit aggressive or even violent behaviour.

A patient suffering from a manic episode often does not recognise that he is ill and will strenuously resist any efforts made to treat him. He will exhibit lability of mood with rapid shifts between elation and expansiveness and anger and depression. Occasionally the depressive and manic symptoms occur simultaneously or alternate rapidly within a period of a few days.

The patient may experience delusions and hallucinations during the period of primary mood disturbance. The content of these is congruent with the predominant mood.

4.2 Epidemiological Findings

DSM-IV reviews the prevalence of bipolar affective disorder and estimates it as 0.4% to 1.2 % of the adult population.

In bipolar disorder the sex incidence is roughly equivalent or shows a slight excess of females. The peak age of onset is between 25 and 29 years of age with no sex difference. Onset is rare before puberty, although symptoms may occur during the teenage years when the diagnosis may be missed. It has been claimed that the stability of its demographic characteristics favour primarily biological causes (Goodwin 1998).

4.3 Genetics of Affective Disorders

Segman & Lerer (2000) suggest on the basis of twin studies that bipolar disorder receives a greater genetic contribution than unipolar disorder. This suggestion supports the pathogenic distinction between unipolar and bipolar disorder made on the basis of neuropsychological data. Where twin probands had bipolar illness the MZ concordance was found to be 72% and the DZ concordance 14%, whereas for unipolar disorder the MZ concordance was 40% and the DZ 11%. Bertelsen *et*

al.'s (1977) study based on the Danish National Twin Register found that the MZ/DZ concordance rate is higher (almost 4:1) when the proband has bipolar disorder than when the proband has unipolar disorder (just over 2:1).

Linkage analysis has been useful in identifying the chromosomal location of genes for disorders such as cystic fibrosis and Huntingdon's disease and has also produced encouraging results in genetically complex disorders such as bipolar disorder (Potash and DePaulo 2000). Blackwood *et al.* (2001) in a review of linkage studies of bipolar disorder in large families proposed that genes of a relatively major effect can cause illness in single multiply affected pedigrees. Bipolar disorder is likely to be genetically heterogeneous with mutations in one of several independent genes producing a similar clinical phenotype. An alternative, or perhaps additional, model is that clinical symptoms can be seen as continuous variables, known as quantitative traits. These are produced by the additive or interactive effects of mutations in two or more genes (Risch and Botstein 1996). The notion is that each quantitative trait locus (QTL) only has a small effect on the trait and symptoms develop due to the cumulative effects of mutations in several genes, most probably combined with other environmental risk factors. Advantages of studying a single large family include the fact that the influence of one or a few genes will be dominant and detectable. However, a single family may express an uncommon form of a disease and may not be applicable to the general population. Blackwood *et al.* (1996) identified a locus for bipolar disorder on chromosome 4p in one large bipolar pedigree and the phenotype will be examined in members of that family in more detail in the present study.

4.4 Cognitive change in Affective Disorders

4.4.1 Why study neuropsychology in affective disorders?

Until fairly recently, investigation of cognitive function in psychiatric illness focussed mainly on schizophrenia and unipolar depression. One possible reason for this may be that professionals are still influenced by the work of Kraepelin (1913/1950) who felt that cognitive decline was associated with schizophrenia and not bipolar disorder. However, Goodwin and Jamison (1990) estimate that between 30 and 50% of bipolar patients fail to attain premorbid levels of psychosocial functioning after remittance of illness, and that this may be due to persistent cognitive impairment. Comparison of neuropsychological function in bipolar disorder and other major mental illnesses may help to establish whether any cognitive deficits are specific to bipolar disorder, and go some way towards shedding light on the aetiology of the illness. Persistent cognitive dysfunction outwith episodes of illness may then be considered to be trait rather then state deficits.

4.4.2 Cognitive deficits in symptomatic patients

The major findings of cognitive impairment in depression have been covered in the previous chapter. There are fewer studies which have attempted to address the nature of impairments in mania. In their review of the neuropsychology of bipolar disorder, Murphy and Sahakian (2001) suggest this may be due to the practical difficulties of assessing patients with mania. However, patients with mania have

been studied using tasks which assess aspects of learning and memory, visuospatial ability and executive function. Taylor and Abrams (1986) conducted a study of manic patients on tests of attention, visuospatial function and memory. Approximately half of the sample demonstrated moderate or severe global cognitive dysfunction. A more recent finding from Murphy *et al* (1999) showed that bipolar patients in a manic state are impaired on tests of pattern and spatial recognition memory and delayed visual recognition. The authors of the review state that the notion that mania is associated with a dysexecutive syndrome seems reasonable as patients generally exhibit disrupted social behaviour and decision-making similar to that seen in patients with lesions to the frontal cortex (Bechara *et al*. 1994). There has been little work investigating these types of abilities in mania. Morice (1990) and Clark *et al* (2002) have investigated attentional set-shifting, Murphy *et al* (1999) have looked at planning ability and Clark *et al.* (2002) and Murphy *et al*. (2001) have investigated decision-making. Impairments have been observed in all these areas.

Much of the literature that has directly compared mania with depression suggests that on tasks of attention, memory and executive function, patients with mania and patients with depression are virtually indistinguishable. Bulbena and Berrios (1993) investigated patients during acute episodes of mania and depression using tests of attention, memory, visuospatial function and choice reaction time. When compared with a healthy control group the patients were generally impaired but no differences between mania and depression were found. Indeed, Goldberg *et al* (1993b) found that bipolar patients who were either depressed or manic did not

differ on the WAIS-R, WCST, or on neuropsychological tests of reading, line orientation or facial recognition.

4.5 Cognitive deficits during remission

Previous work investigating cognitive functioning in bipolar disorder showed that during periods of illness, patients experienced some cognitive difficulties but after the clinical symptoms disappeared, many patients returned to their normal levels of functioning. However, there is a body of evidence that reports that some bipolar patients have cognitive difficulties after the remission of an acute episode, which points to the existence of a subgroup of bipolar disorder patients who have a more malignant form of the disorder. Savard *et al.* (1980) reported in a study with limited numbers that acutely depressed bipolar patients have a marked cognitive deficit on the Halstead-Reitan categories test, in which subjects must arrive at the organising principle differentiating one visual stimulus from another three over a number of trials, part of a battery of tests originally developed to distinguish brain-damaged from non-brain-damaged subjects. On retest in the improved state, some bipolar patients continued to experience fundamental cognitive impairment outwith periods of illness. A study by Tham *et al.* (1997) of twenty-six patients with recurrent mood disorders found a remarkably lowered cognitive function in a number of euthymic patients. A significant positive relationship between a number of neuropsychological domains, including visual-constructive reasoning, general intelligence and the Trailmaking Test for visuospatial scanning and flexibility, and the number of hospitalisation episodes was found in remitted bipolar patients. The

patients generally had an overall lowered performance compared to control data, but patients with impaired cognitive functioning had experienced significantly more hospitalisations than those with normal cognitive functioning. It is, however, worth mentioning that no definition of 'euthymic' was given and mention made of measurement of residual symptoms, and also that a matched control group was not constructed for this study but rather data was drawn from a database of normal controls.

Further support for persistent deficits in affective disorders comes from a study by Addington and Addington (1997) who found that stable outpatient bipolars' visual attention was not significantly different from controls, but neither was it significantly different from schizophrenia patients. This suggests that there may be some attentional impairment on tests which are considered to be vulnerability indicators in schizophrenia, in that impairments are evident in high risk groups, actively psychotic and remitted schizophrenic patients. It further suggests that where there is an abnormal reduction in the availability of cognitive resources when there is a high processing load resulting in difficulties remembering a target whilst monitoring a stream of potential targets, deficits in information processing are not specific to schizophrenia.

McKay *et al.* (1995) screened unipolar and bipolar patients during remission on a battery of neuropsychological tests and found five bipolar patients with chronic, severe illness were impaired on one or more measures. A more detailed investigation showed a variable pattern of impairment ranging from verbal memory

and executive function to widespread poor performance. These five patients were from what the authors termed the chronic, severe group so it is unclear whether these deficits occur as a direct consequence of long-term illness or whether they could precede the onset of clinical illness. However, any conclusions drawn from a sample size of five must be very tentative indeed. It must be noted, furthermore, that a clinical judgement of euthymia was only backed up with ratings of depression and not mania, and some rapid cycling patients were tested between mood swings "when they were (sometimes only briefly) euthymic" (p52).

van Gorp *et al.* (1998) investigated cognitive impairment in twenty-five bipolar disorder patients with and without prior alcohol dependence (whilst euthymic for at least three months and not suffering from the effects of alcohol abuse). No significant differences in visuospatial, nonverbal memory or psychomotor speed abilities were found between the bipolar groups and controls, which suggests that there is not a diffuse cognitive deficit, and also is not in keeping with previous notions of a relative right hemisphere dysfunction in bipolar disorder (Flor-Henry and Yeudall, 1979). However, both bipolars with and without a history of alcohol abuse performed more poorly than controls on both long, short, free and cued recall conditions and total number of words acquired on a test of verbal memory (the California Verbal Learning Test). This suggests both acquisition and storage difficulties. Patients with an alcoholic history achieved fewer categories on the Wisconsin Card Sorting Test, an executive function task, which suggests that some capacity has been lost to interrupt and change ongoing activity and adapt to new rules. The authors found that for both bipolar groups, lifetime months of mania

and depression were negatively correlated with performance on verbal memory and executive function tasks. The conclusion that the authors drew from this relatively small-scale study was that these deficits were due to disease process. It should be noted that although medication effects could not entirely be ruled out, the authors found no significant correlations between current lithium level and cognitive test performance.

Ferrier *et al.* (1999) found that both 'good' and 'poor' outcome bipolar patients (based on the number of affective episodes over the previous five years) performed more poorly than controls on a number of neuropsychological tests, indicating impairment of new learning and recall in both verbal and non-verbal domains, impaired executive function and visuomotor speed and sustained attention. When age, premorbid IQ and low level depressive symptoms were controlled for, the results showed impaired executive function, specifically in tasks with a working memory component and also involving set shifting and strategy generation, suggesting difficulties with both reactive and spontaneous flexibility similar to that described in schizophrenia. No differences were found between the 'good' and 'poor' outcome groups, but as these groups were arbitrary, it is difficult to draw any conclusions about the relationship of neuropsychological functioning to outcome. As with other studies of euthymic bipolar patients, the possibility of the impairments being due to medication effects cannot be entirely ruled out. However, the fact that this well-defined group of euthymic bipolar patients demonstrated specific deficits even after controlling for residual symptoms provides good evidence for a persistent deficit in the disorder, which the authors

suggest may reflect frontal lobe damage or disruption of frontal circuits, although this remains unclear, as does whether any neuroanatomic abnormalities are a consequence of disease process or present before the onset of illness.

Kessing (1998) concluded from a controlled cohort study that neuropsychological deficits in outpatients with unipolar and bipolar disorder seem to be associated with the number of acute episodes of depression. However, there was a large difference in sample size between the two affective disorder groups, with unipolar patients outnumbering bipolar patients. Furthermore, all the bipolar patients had had more than one episode, whereas almost half the unipolar patients had experienced only one episode. However, no differences were found between the affective disorder groups on cognitive function.

Cavanagh *et al.* (2002) tested the hypothesis that euthymic bipolar patients would exhibit impairment in verbal learning and memory and executive function compared to healthy controls matched for age, gender and premorbid IQ. Impairments were found in cases compared with controls in aspects of the California Verbal Learning Test, most notable in immediate recall, a measure of global learning, and recognition. Verbal learning and memory were found to be negatively correlated with the number of manic episodes. These results suggest that impaired verbal learning and memory may be a trait variable in bipolar affective disorder. However, it may be that these deficits are due to disease process effects, and little work has been done investigating neuropsychological performance in first episode bipolar affective disorder patients which would be

informative in this matter. The inclusion in the present study of biological relatives of bipolar probands at high genetic risk of developing the disorder will attempt to differentiate trait versus disease process effects.

It has been a criticism levelled at several of these studies investigating bipolar patients in remission that their clinical status is not well defined. This led Rubinsztein *et al.* (2000) to carry out a case-control study with stringent clinical criteria, with patients having to have been in remission for at least four months. The results demonstrated that euthymic bipolar patients showed a relatively specific impairment in visuospatial recognition memory. The study also included tests of executive function on which accuracy was not impaired in the patients, although response latency was abnormal. This study failed to resolve the discrepancies in the literature about whether euthymic bipolar patients have deficits in executive function, memory or both. A study by El-Badri *et al.* (2001) found that young euthymic patients with bipolar affective disorder have significant EEG abnormalities and cognitive impairments compared with control subjects of similar age and premorbid IQ. Interestingly, there were no correlations between EEG and neurocognitive results but significant differences between patients and controls were more frequent in cognitive tests depending on manipulation of visuospatial stimuli. The EEG abnormalities were marked in right temporoparietal area, important for visuospatial processing. No relation to illness duration or age of onset was found but the number of affective episodes was significantly related to the degree of cognitive impairment. These results suggest that cognitive impairments may be present throughout the disease process.

Krabbendam *et al.* (2000) compared cognitive functioning in relation to white matter lesions in bipolar disorder in remission and in schizophrenia. The results indicated that euthymic patients with bipolar disorder have persistent cognitive deficits which involve several domains, including memory (immediate and delayed recall, but not recognition), speed and cognitive flexibility, and which were similar to the deficits seen in the schizophrenic group. No relationship was found between cognitive deficits and white matter lesions in either of the patient groups. However, because of the estimated power of the analyses, the results must be tentatively interpreted. These findings are in conflict with those of Fazekas (1989) and DeCarli *et al.* (1995) who did find a relation between white matter lesions and cognitive functioning.

Summing up recent work investigating the specific domains of memory and executive function in remitted bipolar disorder patients, studies of verbal memory in bipolar disorder have used different versions of word lists, such as the California Verbal Learning Test (CVLT), the Auditory Verbal Learning Test (AVLT) and the Rey Auditory Verbal Learning Test (RAVLT). Recent studies finding impairment in remitted bipolar disorder compared to controls include van Gorp *et al.* (1998) who found that patients performed poorly on the CVLT and that this impairment was associated with the number and duration of illness episodes. Patients with a prior history of alcohol abuse performed more poorly still. Ferrier *et al.* (1999) also found impairment in verbal memory compared to controls using a similar task, the RAVLT. Interestingly, impairment was more pronounced in patients with

fewer episodes and good inter-episode recovery. Krabbendam (2000) also found poorer verbal memory in remitted bipolar patients compared to a healthy comparison group when tested on the AVLT. There is therefore some evidence for verbal memory problems and cognitive flexibility deficits on executive function tasks. Evidence for nonverbal memory problems is less clear-cut.

As with schizophrenia, executive function in bipolar disorder has often been measured using the WCST and verbal fluency, measures of reactive and spontaneous cognitive flexibility and to some extent, organisation of the semantic store. Ferrier *et al.* (1999) reported reduced verbal fluency performance compared to controls in a group of remitted bipolar patients with residual depressive symptoms, a finding which persisted even after controlling for group differences in depressive symptomatology. Atre-Vaidya *et al.* (1998) found that their sample of stable bipolar patients demonstrated verbal fluency scores below the normative age corrected mean for this test.

On the basis of their recent review Quraishi and Frangou (2002) conclude that deficits in executive function in bipolar disorder appear to be closely associated with the presence of residual symptoms. Low level manic and depressive symptoms seem to produce an increase in perseverative errors (Coffman *et al.* 1990, McGrath *et al.* 1997), verbal fluency (Ferrier *et al.*1999) and planning ability (Ferrier *et al.*1999, Rubinsztein *et al.* 2000). Quraishi and Frangou (2002) also conclude that whilst symptomatic, bipolar patients exhibit deficits on the WCST comparable to those of schizophrenic patients, but when remitted they may

outperform schizophrenics. They conclude that symptomatic bipolar patients have widespread cognitive deficits, and that verbal memory may be a trait deficit. Executive function may also be affected in at least some remitted bipolar patients.

Investigating the cognitive performance of MZ twins discordant for a neuropsychiatric disorder allows for the examination of both clinical disease-specific impairments (in the comparison of affected to unaffected twins) and clinical risk factors (in the comparison of unaffected twins to normal twins). Gourovitch *et al.* (1999) investigated intelligence, attention, visuospatial skills, language, learning and memory and problem solving in MZ twin pairs discordant for bipolar illness and normal MZ twins. The results showed that the affected twins were significantly impaired in some visuospatial and verbal memory measures compared with unaffected and normal twins. However, the unaffected twins performed significantly worse than normal twins on a memory task and verbal list learning. This suggests that while some deficits may be features of bipolar disorder associated with the clinically apparent disease process, mild deficits in overall verbal learning and retrieval function may be a genetic marker of risk for the disorder. Although the results should be interpreted somewhat tentatively due to the fact that only seven pairs of twins were included in the study (although this may be due to the difficulties inherent in finding MZ twins discordant for bipolar disorder), the presence of cognitive deficits in asymptomatic individuals, as with patients at the onset of illness, may agree with other studies showing that, as in schizophrenia, neurodevelopmental factors play a role in the aetiology of bipolar disorder.

A clearer picture is needed to attempt to establish whether any persistent deficits displayed by bipolar patients are a function of the disease process or are trait variables. If persistent cognitive deficits can be observed in remitted or euthymic bipolar affective disorder patients, this suggests that such deficits could be considered to be trait rather than state dependent, especially if it can be shown that they are not due to symptomatology or medication. Investigation of cognitive function would be useful in defining the phenotype and in the search for endophenotypes in healthy biological relatives of patients.

4.6 Comparison of unipolar and bipolar disorder

A study comparing the neuropsychological performance of patients with bipolar and unipolar disorder during an acute depressive episode was conducted by Borkowska and Rybakowski (2001) who found greater cognitive impairment (measured by tests of executive function including the WCST, verbal fluency, Stroop and Trails A and B) during an acute depressive episode in bipolar compared with unipolar patients. The differences between bipolar and unipolar patients were not explained by symptom severity or duration of the illness and the pattern and extent of abnormalities connected with frontal lobe function pointed to differences in pathology between bipolar and unipolar affective disorder. The authors further concluded that pronounced deficits in working memory and executive function suggest similarities between bipolar disorder and schizophrenia, particularly as there is evidence that in bipolar illness, as in schizophrenia, cognitive disturbance

may already be present during the first episode of the illness (Yurgellun-Todd *et al.* 2000, Murphy *et al.* 2000). There are some limitations to this particular study, in that a relatively small bipolar group was recruited and there was an unequal distribution of gender in both groups. However, no differences were found between males and females in either group. It is also difficult to conclude whether the patient groups were performing at an abnormal level as no control data was provided.

Paradiso *et al.* (1997) compared the cognitive performance of chronic unipolar depression and bipolar disorder patients in remission with a normal comparison group. Results indicated that unipolar depressive patients demonstrated cognitive deficits on measures of visuo-motor sequencing, executive function and immediate memory and attention. These deficits are consistent with a prefrontal-type syndrome. Remitted bipolar patients, however, showed mild deficits in some cognitive measures relative to controls but these did not reach statistical significance. This may be due to the small sample size (eleven patients). The authors suggested that in the light of these findings patients with unipolar and bipolar disorder should not be considered as have a unitary disorder.

4.7 Neuropsychological deficits in bipolar disorder compared with schizophrenia

It has been assumed previously that deficits such as those described in the preceding chapter are specific to schizophrenia. However, this may not be the

case. Hoff *et al.* (1990) investigated 35 patients with a diagnosis of bipolar affective disorder, manic type, and 30 patients with schizophrenia tested on a comprehensive neuropsychological test battery including tests on verbal learning and memory, executive function, visuo-spatial memory and psychomotor speed. This study failed to differentiate between schizophrenic and bipolar patients on measures of verbal, spatial and speed variables with age, sex, education, duration of illness, number of hospitalisations and medication at the time of testing controlled for. This then refutes previous notions that schizophrenia and bipolar disorder have lateralised deficits in the left and right hemispheres respectively. Hoff *et al.* concluded that this failure to discriminate between the two patient groups may relate to indications that bipolar patients also have abnormalities in brain morphology. Morice (1990), from a study of 60 schizophrenic patients, 20 bipolar (manic) patients and 34 non-patient controls tested on the Wisconsin Card Sort Test, concluded that cognitive inflexibility and/or prefrontal dysfunction may not be specific to schizophrenia as bipolar patients who were both recovering from an acute episode and those in remission had an equivalent level of performance to schizophrenics. Morice concluded that problems with cognitive inflexibility suggest some level of dysfunction of the prefrontal cortex in both schizophrenia and bipolar disorder.

Berrettini (2000) has suggested that on the basis of recent genetic studies showing a degree of overlap in familial risk, in that relatives of bipolar probands are at increased risk for recurrent unipolar, bipolar and schizoaffective disorders and that relatives of probands with schizophrenia are at increased risk for schizophrenia,

schizoaffective and recurrent unipolar disorders, there may be some shared genetic susceptibility and that consequently the disorders may not be as distinct as current diagnostic systems suggest. Kéri *et al.* (2001), working on the basis of this evidence, investigated performance on cognitive measures often found to be affected in patients with bipolar disorder and schizophrenia in biological relatives of probands with these disorders. Although dysfunction in sensory-perceptual analysis (revealed by a visual backward masking task) and spatial working memory distinguished relatives of schizophrenic patients from relatives of patients with bipolar disorder, both groups displayed deficits in verbal recall, suggesting a common impairment of the fronto-hippocampal system. The cognitive battery employed in this study was fairly limited, and utilized a relatively small sample size, but this was however determined by strict selection criteria, using high-functioning individuals to minimize confounding factors. This does then make the finding of cognitive abnormalities in high-functioning well relatives of probands very interesting.

Murphy and Sahakian (2001) have reviewed several studies that have compared neuropsychological performance in mania and schizophrenia. Findings from these studies show that on tests of selective attention (Oltmanns, 1978), perceptual span (Strauss *et al.* 1984) and shifting attentional set as measured by the WCST (Morice 1990), patients with mania and those with schizophrenia are virtually indistinguishable. A study by Otteson and Holzman (1976) compared schizophrenics, non-schizophrenic psychotic patients and non-psychotic patients with each other and with a healthy comparison group on a variety of

neuropsychological tests. Group differences were apparent between psychiatric patients and controls and between patients with and without psychosis. However, there were no differences between the schizophrenic and manic groups. Differences appeared to be related to degree rather than type of disorganisation.

Differences between manics and schizophrenics have also been reported, however. Andreasen and Powers (1974) found overinclusive thinking to be more prominent in mania than schizophrenia and Goldberg *et al.* (1993b) reported that schizophrenic patients performed more poorly than patients with affective disorder (unipolar depression, bipolar depression and bipolar mania) on tests of psychomotor speed, attention, memory and attentional set-shifting. However the schizophrenic group showed greater intellectual deterioration. It should be noted that the bipolar disorder group included in this study was quite small, so there may be power implications. Murphy and Sahakian (2001) have further suggested that the cognitive deficits observed in bipolar depression could be unrelated to similar impairments in unipolar depression.

Bearden *et al.* (2001), in their review of the neuropsychology and neuroanatomy of bipolar disorder, state that generally, when symptomatic, cognitive abilities in bipolar patients appear to more closely resemble those of schizophrenic patients. The question is, given the recent findings of enduring deficits in bipolar disorder; do the similarities between the disorders persist?

4.8 Neuroimaging findings in affective disorders

There has been considerable number of both structural and functional imaging investigations in affective disorder. Soares and Mann (1997a) reported in their review reported that structural abnormalities in basal ganglia, frontal lobe, temporal lobe and cerebellum. They claim that this suggests the presence of regional atrophy. It is further reported that the pattern of abnormalities distinguishes between unipolar and bipolar disorders, as unipolar patients smaller frontal lobes and bipolar patients additionally have abnormalities in the temporal lobe. The possibility that different brain structures are involved in unipolar and bipolar disorder is consistent with a biological distinction in the pathophysiology of these disorders. An increased frequency of signal hyperintensities has also been reported in the brains of both unipolar and bipolar patients, although in unipolar depression these seem to be more apparent in elderly patients (Coffey *et al.* 1989). A recent meta-analyses of MRI findings in patients with affective disorders reported that these signal hyperintensities are often localised in the frontal lobes and basal ganglia, which is suggestive of a basal ganglia/frontal circuit impairment. It has also been reported that these abnormalities are correlated with the cognitive impairment observed in unipolar and bipolar disorder (Videbech, 1997). Videbech's recent meta-analysis further concluded that age of onset seems to be less significant in bipolar patients displaying signal hyperintensities, as there is evidence of them in younger and first episode patients (Strakowski *et al.* 1993; Botteron *et al.* 1995), whereas normally they are associated with ageing. He

further speculated that this may be due to the relatively greater importance of genetic factors in bipolar disorder.

The prefrontal cortex has been implicated in control of willed action, working memory, inhibition, motivation and mood regulation (Soares and Mann 1997b). The findings of decreased blood flow and metabolism would suggest that it is important in the development of affective disorders.

Another main area of structural and functional abnormality is that of the basal ganglia. There is evidence of functional abnormalities in unipolar disorder, and perhaps also for bipolar disorder. Soares and Mann (1997b) outline a hypothetical neural circuit connecting basal ganglia structures with medial temporal structures such as the amygdala and hippocampus, which in turn have connections with the prefrontal cortex, whereby damage to the circuit may result in depression.

The temporal lobe may also be dysfunctional in bipolar disorder and possibly also in unipolar disorder, and the importance of this in affective disorder may be related to abnormalities in the limbic structures found in the temporal lobes. It is not clear what the cause of this dysfunction is, but as Soares and Mann (1997b) suggest, it may be that genetic and environmental factors interact with the structures implicated in bipolar disorder in ways which are not yet clear.

Bearden *et al.* (2001), undertaking an extensive review of the neuroimaging literature, in an attempt to delineate the most consistently reported structural brain

abnormalities and to determine whether any were specific to bipolar disorder, concluded that significant cognitive impairment may be present and that these may correlate with signal hyperintensities in the frontal lobes and basal ganglia, associated with executive function, attention, learning and memory and affect regulation. Little evidence was found for a selective right hemisphere dysfunction as had previously been supposed on the basis of earlier reports of relatively greater impairment of visuospatial function, literalised abnormalities and mania secondary to right hemisphere lesions. They further conjectured that the overlap in abnormalities in brain structure and function in schizophrenia and bipolar disorder could be caused by similar anomalies in gene expression affecting development in both patient groups. This suggests the need for neuroimaging studies in high-risk populations.

There are problems inherent in reviewing neuroimaging data, principally in selection and definition of patient groups and controls, but also with different methodologies employed in the imaging studies themselves. However, the data would suggest that there are some consistently reported structural and functional abnormalities, and that they seem to be correlated with findings of cognitive impairment in affective disorder.

4.9 Neurophysiological changes in affective disorders

There has been less investigation of auditory P300 in affective disorders than there has in schizophrenia. Auditory P300 amplitude has been found to be reduced in depression (Diner *et al.* 1985). Some studies have indicated that the amplitude of event-related potentials in depression are related to clinical state (Blackwood *et al.* 1987; Gangadhar *et al.* 1993). A large-scale study of auditory P300 in affective disorders was conducted by Muir *et al.* (1991) comparing patients with bipolar depression and unipolar depression with psychiatric in-patient and normal controls. The results showed that the latency of P300 was significantly greater in schizophrenic and bipolar patients than in any of the other groups. The differences were not due to age, state or medication and support the distinction between unipolar and bipolar depression as P300 did not distinguish between unipolars and controls. This finding of prolonged P300 latency in bipolar depression compared with controls was replicated by Souza *et al.* (1995).

Eye movement disorder has been suggested to be such a biological risk factor in bipolar disorder and schizophrenia. When a slow moving object is visually tracked, the neurological control of eye movements involves both the smooth-pursuit eye tracking system and higher frequency saccadic movements. It has been established that some schizophrenics have impaired smooth-pursuit and similar impairments have been reported in affective illness. However, the eye-movement abnormalities found in bipolar disorder patients differ from those found in schizophrenia (Abel *et al.* 1992) and there is some evidence to suggest that

although it is seen in relatives of schizophrenic probands it is less common in relatives of bipolar patients (Holzman *et al.* 1984).

Although not conclusive, these data are suggestive of a possible stronger relationship between bipolar disorder and schizophrenia, rather than between bipolar disorder and unipolar disorder.

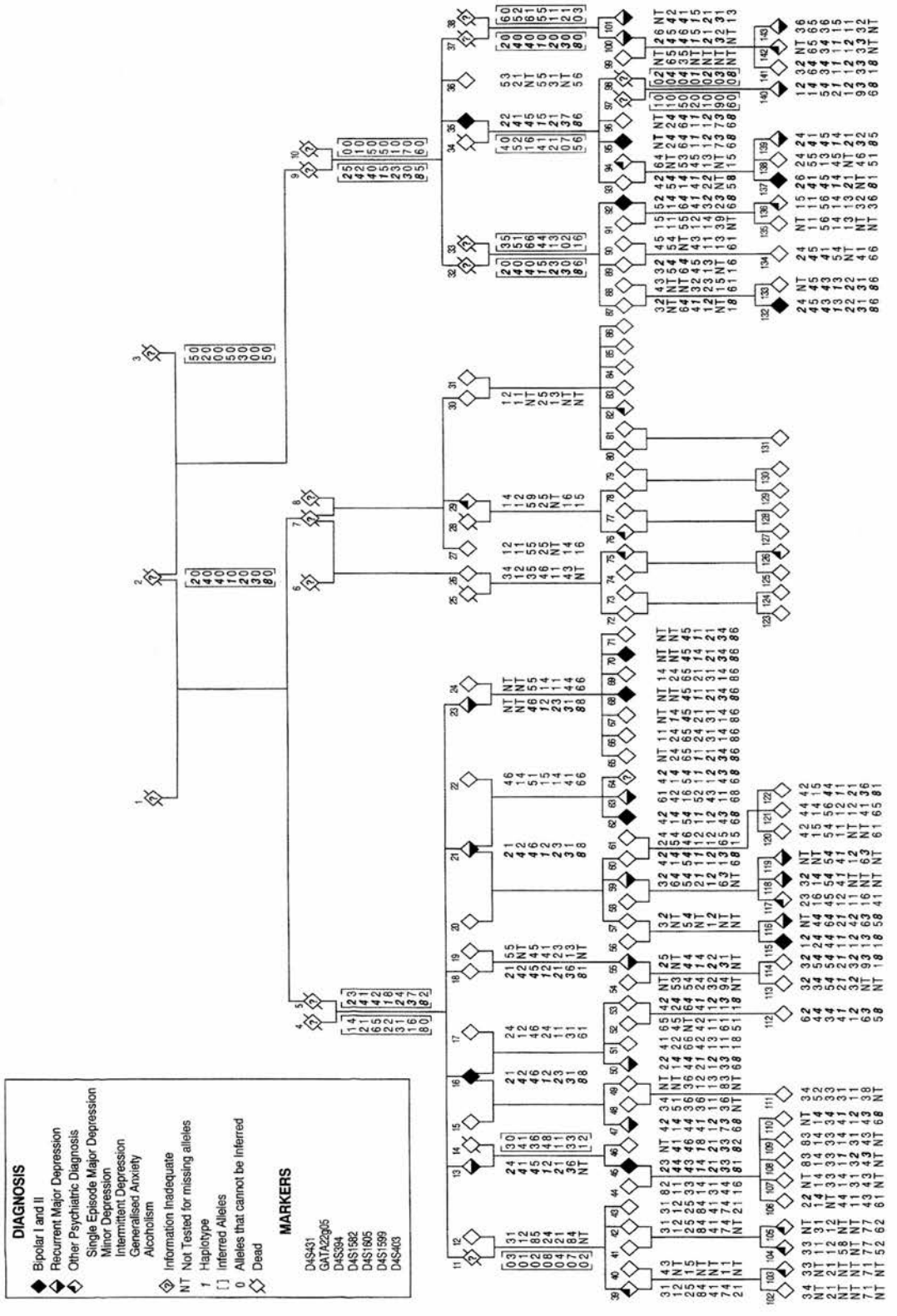
4.10 Description of a pedigree showing evidence of linkage of bipolar disorder to a locus on chromosome 4

Blackwood *et al.* (1996) identified a large extended family multiply affected by bipolar and unipolar disorder in which linkage between markers and disease was reported on the short arm of chromosome 4. In this pedigree, Family 22, clinical and genotype data have been obtained from 120 individuals, including eleven with bipolar disorder and sixteen with recurrent major depression. This analysis identified a haplotype, a set of closely linked genetic markers, present on chromosome 4 which is inherited by all bipolar family members and fourteen of the sixteen unipolar relatives. The resulting LOD score (greater than 4) confirmed significant linkage between these markers and affective illness. In Figure 1, the alleles of the chromosome 4 markers D4S431, GATA22g05, D4S1582, D4S1605, D4S1599 and D4S403 are shown. The chromosomes represented by alleles 2441238 are inherited from their parents by all relatives with bipolar disorder and by 14 of 16 with unipolar depression. In this family, some relatives are "high risk"

with no symptoms. Relatives with the disease-related haplotype have a forty-fold increased risk of developing an affective disorder (Visscher *et al.* 2001).

This family offers a unique opportunity to study the relation between neuropsychological deficits, clinical symptoms and genetic risk in bipolar illness. By studying members of a single family it is expected that genetic heterogeneity will be minimised and variation in environmental influences will be reduced. Genetic risk can be accurately measured and high risk individuals detected by their genotype. Therefore comparison of three groups will permit a separation of effects of genetic risk and effects of symptoms. The three groups are 1) relatives with symptoms and disease haplotype, 2) relatives without symptoms and with disease haplotype and 3) relatives without disease haplotype.

Figure 1. Family 22 pedigree – reprinted from Blackwood *et al* (1996) with permission of the author



5.0 ETHICAL CONTEXT

Recent dramatic advances in molecular genetics and the completion of the sequencing of the human genome have highlighted the need for ethical guidelines for research with a genetic component related to mental disorders. This need was recognised by the Nuffield Council on Bioethics which published a report (1998) with a major aim of identifying and defining ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern.

The areas of bioethics that have most practical relevance and are important to the projects described in this thesis are those relating to informed consent, the role of ethics committees, the role of the individual researcher, and confidentiality of information about individuals taking part in genetic research projects (Meslin 1997).

Farmer *et al.* (2000) stress that participants in all types of genetic research should be fully informed and need to understand the likely benefits, risks and alternatives to participation in a study. One ethical concern is that the research may cause non-physical harm. Several types of possible misconceptions about research may require clarification. Participants may fail to recognise the difference between testing that may inform treatment and non-therapeutic testing done for research purposes only. Furthermore, relatives of patients may expect that by participating in such research, they will learn more about their own susceptibility for developing

mental illness. The presence of 'susceptibility' genes does not necessarily mean that an individual will develop the disorder. Consent forms must therefore be very clear in stating whether or not participants can expect any benefits from the study and if not the consent form must state clearly that participation is only for the benefit of scientific and medical knowledge.

A particular issue is how to gain informed consent from people with major mental disorders, who are a vulnerable group who may have reduced capacity to understand the purposes of research. The Nuffield Council on Bioethics Report (1998) states that an important principle in ethics is respect for human beings and their autonomy and dignity, and that this principle underlies the legal requirement to seek consent. Even at its worst, mental disorder rarely results in comprehensive incapacity, and most people suffering from a mental illness can continue, throughout the duration of their disorder, to take decisions for themselves. Therefore individuals with mental illness have capacity (as legally defined) to give informed and genuine consent to participate in research, unless it can be shown otherwise, and are not any different in their capacity to understand and agree to participate in research from people suffering from other types of illness. In determining whether someone has the necessary capacity to decide whether or not to participate in a research study, it must be established that the person possess the capacity to make a choice; understands what the study aims to do and why it is being done; understands what participation will involve; understands any benefits or risks, or in the case of non-therapeutic research, that there are no direct benefits; and understands the consequences of not participating, or it is made clear that non-

participation will not affect any treatment that they , or in the case of unaffected family member their relative, may receive, as is the case in this study. In Scotland this issue has recently been clarified by the Scottish Executive, one of whose first actions was to draft the "Adults with Incapacity Act" laying down the legal rules for research on patients including the mentally ill and those with dementia who may have limited capacity to understand the technical details of a research project.

When seeking consent, respect should be given to an individual's capacity for understanding and time should be allowed for them to ask questions. In this study, a written information sheet was provided and consent forms and information sheets conformed to the guidelines proposed by the Scottish Executive.

The principles by which research proposals are scrutinised are enshrined in the Nuremberg Code (1949). This states that participants in research should give voluntary consent, not be subjected to suffering and that the work will produce "fruitful results for the good of society, unprocurable by other methods or means of study". The implication is that in order to be ethical, research must also be methodologically sound. Farmer *et al.* (2000) pertinently comment that a major problem for ethics committees is to be able to judge the merits of a study given the rapidly changing nature of the field, so expert opinion should be obtained.

The nature of genetic research means that information is often required from unaffected family members. It is a given that relatives should not be approached if the proband refuses permission. In this study, contact was made with relatives

only after consent was given by the proband. Key family members then contacted other family members who were then approached by the research team after consultation with their General Practitioner. This family has previously given their consent to be involved in a genetic linkage study and many relatives had indicated willingness to participate in further studies including neuropsychological testing.

Another issue that arises when working with unaffected family members in genetic research is that of how their perception of the illness can be changed by participation in a study. It may be the case that family members are unaware that illnesses such as depression may have a genetic basis and researchers have to accept the role of educators. Confidentiality is also a major concern. Participants may reveal information to researchers that they would not wish the rest of the family to know, so confidentiality must be strictly preserved. A general area of concern when considering genetics and mental health is the use that may be made of and individual's genetic information. A unique aspect about genetic information is that it is likely to be common to, and therefore of relevance to, other family members. This raises a peculiar issue about confidentiality, concerning who should have access to genetic information derived from one person if it is relevant to another family member, if the person does not want it to be disclosed. As the Nuffield Council on Bioethics Report (1998) states, it must be a matter for the individual concerned to agree to the disclosure of their genetic information, unless very strong public interest justifications exist. If such confidentiality is not assured, people will no longer consent to be involved in such studies. One further issue concerning confidentiality which is of particular importance to the current

study is that when using the genetic information in research, it is of paramount importance that inadvertent disclosure is guarded against and no identifying information is published (Parker 2002).

Genetic information about people with mental disorders may affect how others view people suffering from mental illness, and in particular raises issues about stigma. Stigma often originates from ignorance and misconceptions about mental illness. Jorm *et al.* (1997) found that over half the respondents in a large survey were inclined to blame people with mental disorders for their condition. Stigma also affects the families of people with mental illness, in that they may be viewed as 'tainted' or be blamed for the illness. Stigmatisation can make mental illness an object of fear and thus deter people from seeking help when they suffer from it. Farmer *et al.* (2000) suggest that increased understanding of the genetics of mental illness may lead to a reduction in stigmatisation. They cite examples of parents whose offspring suffer from schizophrenia who are reassured that the illness has a substantial genetic component and is not the result of poor parenting, and the fact that the stigma associated with Alzheimer's disease has reduced as understanding of the biological basis of the illness has increased. However, the Nuffield Council on Bioethics report (1998) argues that linking mental illness with genetic differences might reinforce the notion of fundamental differences between people with mental illness and 'normal' people.

Genetic research on complex conditions with genetic and environmental components such as bipolar disorder present special ethical issues. However, as

scientific advances are made, the debate is still some way from reaching a final conclusion.

In this study these ethical concerns were dealt with as follows:

1. First contact with relatives of probands was made by the proband and not by a researcher.
2. All prospective participants were given a detailed information sheet and had time to ask questions about the project before signing the consent form.
3. The consent form included a statement that information was confidential, that no clinical or genetic information would be fed back to participants and that participation in the study would not affect treatment in any way.
4. The study was reviewed and approved by the local Ethics of Medical Research Committee (Psychiatry and Clinical Psychology Research Ethics Sub-Committee of Lothian Health Research Ethics Committee).

6.0 AIMS OF THE STUDY AND HYPOTHESES

6.1 Aims

The first part of the study was designed to measure memory and executive function in groups of patients with schizophrenia, bipolar disorder and unipolar depression and healthy controls to measure the extent and nature of impairment in each of these subject groups and to compare results between groups, as previous work has produced conflicting results. There is clear evidence for impaired memory, both verbal and to some extent nonverbal, and executive function deficits of the reactive and spontaneous flexibility type in schizophrenia. There is now growing evidence for a similar pattern of impairment in symptomatic and perhaps euthymic bipolar patients also. The effects of medication and symptom severity on cognitive performance were analysed. The purpose of this was principally to determine whether impairments previously described in bipolar disorder patients during remission could be replicated. If so, this would suggest that such deficits are trait rather than state dependent and may therefore be useful in defining the phenotype in the disorder. In comparing bipolar patients with schizophrenic patients, the aim was to assess whether the deficits that can make the two groups indistinguishable during episodes of illness persisted upon recovery. Comparing remitted unipolar patients with remitted bipolar patients aimed to assess whether the bipolar group exhibited impairment where the unipolar group did not. Based on the review of the literature showing that bipolar patients may show similar deficits to those exhibited

by schizophrenia sufferers, it was hypothesised that the schizophrenic group would be impaired relative to controls and the bipolar group would exhibit similar impairments to the schizophrenic group. The evidence for a distinction between unipolar and bipolar disorder in addition to the literature showing that cognitive impairment in unipolar affective disorder may be more state than trait dependent leads to the hypothesis that the unipolar group would not show the pattern of deficits found in bipolar and schizophrenic patient groups but would be similar to controls.

The second part of the study was an analysis of memory and executive function in the single large family (Family 22) that showed linkage of affective disorder to chromosome 4. Within–family comparisons were made between relatives carrying high and low genetic risk. If the population group of bipolar disorder patients show deficits in memory and executive function unrelated to clinical state or medication status, it may be that these are trait changes and related to genetic aetiology of the illness, rather than an effect of disease process. Therefore it was a hypothesis that family members carrying high genetic risk will demonstrate similar, perhaps milder, deficits even though they have never shown symptoms of bipolar illness. This would then suggest that neuropsychological impairment could be useful in investigating the relationship between the observable phenotype and the genetic background. The identification of such endophenotypes may facilitate molecular genetic research to find genes responsible for the transmission of vulnerability to bipolar affective disorder.

6.2 Hypotheses

The hypotheses proposed and tested were that:

1. Significant between group differences in memory and executive function will be observed between the schizophrenia and control groups and between the bipolar and control groups, and not between the unipolar and control groups.
2. The degree of neuropsychological impairment in schizophrenia and bipolar disorder will not correlate with medication, age, sex or symptom severity at time of testing.
3. Members of the Family 22 kindred with illness linked to a locus on chromosome 4p will manifest deficits in memory and executive function similar to those observed in the unrelated bipolar disorder group.
4. In Family 22, deficits in memory and executive function will be measured in "high risk" relatives who carry the disease-related haplotype but have no symptoms compared to "low risk" relatives without the disease-related haplotype and controls.

7.0 METHODS

7.1 Rationale and Aims

The aims of the study were (1.) to examine the effects of major psychiatric illness on the psychological responses of schizophrenic, bipolar and unipolar affective disorder patients in comparison with a group of population control participants and (2.) to examine neuropsychological performances of members of Family 22, a large family with several members affected with major mental illness. The study of a single large pedigree whose members could be classified as "high risk" or controls on the basis of genetic markers has several advantages for dissecting the influences of symptoms and medication from genetics. From our knowledge such an approach has never before been feasible or attempted.

Neuropsychological tests were selected for their ability to measure a specific psychological function, primarily in the domains of memory and executive function as highlighted by existing research.

7.2 Design

Neuropsychological data were generally collected within one session lasting between one and two hours. In a few cases, patients became tired, inattentive or uncooperative before testing had been completed, and testing had to be carried over for another day. Participants were interviewed at various locations including

the Royal Edinburgh Hospital, day units around the city and in participants' own homes. Participants were assessed with the Hamilton Rating Scale for Depression (Hamilton, 1960), the Beck Depression Inventory (1961), the Modified Manic Rating Scale (Blackburn *et al.* 1977) and Brief Psychiatric Rating Scale (Overall 1983) for psychosis in schizophrenia to measure symptom severity at the time of testing.

7.3 Participants

Twenty-six patients with schizophrenia, thirty-six with bipolar affective disorder, forty one with unipolar affective disorder and thirty-one controls formed the study groups. From the single large family with several members affected by major psychiatric illness (see Blackwood *et al.* 1996), fifteen were identified as having the haplotype and six did not. Five family members who were approached declined to participate. The patient groups were recruited from inpatients and outpatient clinics and day hospitals around Edinburgh. The control group was recruited from hospital staff and members of the general public.

Criteria for Selection

The patients were selected to be approached for inclusion in the study after examination of their case notes and after consultation with members of the medical team involved in their care. The patients met DSM-IV criteria for a diagnosis of affective disorder or schizophrenia and had no history of drug or alcohol abuse,

head injury with loss of consciousness, epilepsy or stroke. Family members were already part of an ongoing study of the genetics of bipolar disorder. The control participants had no history of psychiatric disorder and no physical or neurological illness reported by screening questions at interviews. All participants were aged between 18 and 70. Diagnoses were made by a trained psychiatrist according to DSM-IV criteria and were based on casenote reviews, discussion with medical staff and completion of the semi-structured interview The Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L, Spitzer and Endicott 1978). All participants gave informed consent. Ethical approval for the study was sought from and granted by the local area research ethics sub-committee.

7.4 Measures and Rating Scales Used

The measures used for severity rating and psychological tests were established and validated tests which have been previously used in research and clinical practice. This enables comparisons to be made with other studies and replication of this study.

7.4.1 Severity Rating Scales

7.4.1.1 Hamilton Rating Scale for Depression (HRSD)

The HRSD (Hamilton 1960) is based on a factor-analytic study based on 272 depressed in-patients. It was revised in 1967. Its main purpose is to provide a simple way of assessing the severity of a patient's depression quantitively and

showing changes in the condition. The HRSD is an observer rating scale and has become a standard instrument for depression ratings. It is completed after a clinical interview and takes account of information from all sources concerning the patient's behaviour during the previous week.

The full scale consists of 21 items. The scores are added to give a total score measuring severity of depression. Each of the items is scored on a 3 (0-2) or 5 (0-4) point scale for its intensity or frequency.

The reliability has been found to range from 0.81 (Prusoff *et al.* 1972) to 0.90 (Hamilton 1972) between raters at the same interview. The validity of the scale as assessed by its correlation with other instruments for measuring depression ranges from 0.79 to 0.82 (Brown and Zung 1972). The scale is sufficiently brief to allow easy completion but yet is reasonably thorough.

7.4.1.2 The Beck Depression Inventory (BDI)

The original version of the BDI was introduced by Beck *et al.* (1961) and revised in 1971. The Beck Depression Inventory is a 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. The depression rating is obtained by adding the scores for each of the twenty-one questions. The highest score on each question is three, and the highest possible for the whole test is sixty-three. The lowest possible score for the whole test is zero. The BDI takes approximately ten minutes to complete and the content was obtained by consensus from clinicians regarding the symptoms of depressed patients. The inventory is

prone to halo effects in that subjects' general attitude can influence responses to many of the items and there is uncertainty as to what is actually measured (Dennis *et al.* 1992).

Internal consistency for the BDI ranges from 0.73 to 0.92 with a mean of 0.86 (Beck *et al.* 1988), and a split-half reliability co-efficient of 0.93. Beck *et al.* (1961) did not recommend conventional test-retest reliability for the original measures for the inventory. Beck suggested that if the BDI was re-administered within a short interval the scores could be spuriously inflated due to memory effects. If the test was re-administered after a long interval then consistency would be lower due to the intensity of the depression. Alternate test-retest reliability methods by Beck *et al.* (1961) found that regardless of the test was reissued at two or six week intervals, the scores on the inventory tended to reflect changes in the clinical depth of depression. Groth-Marnat (1990) reported moderate correlations between the BDI and other scales measuring depression such as the HDRS (0.73).

7.4.1.3 The Modified Manic State Rating Scale (MMRS)

The MMRS (Blackburn *et al.* 1977) is a version of the Manic State Rating Scale which was developed by Beigel and Murphy (1971). The MMRS was developed to meet the lack of specific rating scales of mania relative to those measuring depression and to provide information about the diversity of manifestations of mania, the relative remission rate of different symptoms or the relationship of mania to depressive illness and other psychiatric states. An observer rated scale

was necessary because of the inability of patients to rate themselves due to lack of insight.

Shortcomings of the Manic State Rating Scale included lack of agreement on definitions of symptoms, and confusion between related but separately scored items. It also omitted certain important aspects of manic behaviour such as sleep disturbance. The MMRS condensed related items and added other symptoms and signs to produce a scale of 28 items. Each item is scored from 0 (absent) to 5 (continuous and gross). Information for scoring each item is obtained by interviewing the patient, asking ward staff for information and by observing the patient. Reliability and validity measures were provided by the authors who conducted a study on sixteen manic in-patients. Ratings of the patients using the MMRS were administered every two weeks, as were analogue ratings of mania by staff. Each patient was rated independently by three raters, after an interview by one of the raters using the Present State Examination. The overall correlations between each pair of raters was 0.85, 0.79 and 0.81. All the individual items except 'looks depressed' significantly correlated with the total score. Validity, as estimated by comparing the MMRS ratings with the analogue ratings of the medical staff was computed as r=0.654 to 0.801 for all ratings.

7.4.1.4 The Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale provides clinicians with a method for the quick assessment of major dimensions of psychopathology. The original measure was interview-based and consisted of sixteen items, although it has since been

expanded to its present eighteen-item form (Overall 1983). The scale items were designed to cover a broad range of symptoms and were based on factor analytic studies and clinical expertise (Overall 1983, Overall and Gorman 1962). The scale is commonly used for the diagnosis of and evaluation of treatment for severe psychopathology and is most widely used with schizophrenic patients (Schutte and Malouff 1995). The scale is administered by the mental health professional during interview with the patient, with each of the eighteen items being scored on a 7-point scale of severity. A rating of zero on any item indicates an absence of that symptom.

Hedlund and Vieweg (1980) reviewed a number of studies investigating the reliability of the BPRS and found that the median interrater reliability for the total psychopathology score was .85. Flemenbaum and Zimmerman (1973) investigated the test-retest reliability and found that for each of the eighteen items, three- to six-month test-retest reliability ranged from near zero to .91.

Schutte and Malouff (1995) report that numerous studies have confirmed the validity of the BPRS and that it has become a standard rating instrument for diagnoses and treatment assessment against which new instruments have been compared.

7.4.2 Psychological Measures

7.4.2.1 Premorbid IQ

The National Adult Reading Test (NART) (Nelson and Willison 1991) was developed to assess impairment in intellectual functioning in dementia. Until its development, the method of estimating deterioration in functioning was to compare 'hold' and 'non-hold' tests. However, this was rather unsatisfactory due to the widespread abilities which different individuals demonstrate.

Nelson and McKenna (1975) showed that word reading ability and general intelligence were highly correlated (r=0.75) in a group of 98 normal adults using the WAIS full scale IQ and the Schonell Graded Word Reading Test (GWRT) score. A regressive equation was extracted from the normative data to enable a WAIS full scale IQ to be predicted from the GWRT score. Testing a group of dementing patients showed that word reading ability was well maintained.

Nelson found that the GWRT did not contain enough difficult items to produce a reliable estimate of the higher IQ levels. On the basis of this, the NART was constructed and standardised. The NART aims to provide an estimate of premorbid IQ levels by providing a sensitive measure of previous familiarity with words. All the words contained in the NART are irregular and therefore their pronunciation cannot be inferred from phonetic knowledge but only from

familiarity. The NART consists of fifty words presented in order of increasing difficulty.

The words are selected from an initial list of one hundred and forty irregular words used in a pilot study with 25 non-dementing patients with extra-cerebral disorders and ten relatives of out-patients. The NART was standardised using 120 in-patients with extra-cerebral disorders. Seven WAIS subtests and the GWRT were also administered. The reliability of the NART was assessed by a split-half technique (Cronbach alpha) which gave a reliability coefficient of 0.93.

Nelson and O'Connell (1978) administered the NART and the GWRT to forty patients with bilateral cortical atrophy. The atrophy group had a lower mean WAIS score than the 120 patients used in the standardisation study. The two groups scored closer in the NART than in the GWRT, suggesting that the NART is more resistant to the effects of the dementing process.

The NART is a relatively quick test to administer and does not demand close and prolonged attention or motivation. Nelson reported that it is suitable for depressed and other psychiatric patients. Although the data are not available for NART scores with different psychiatric illnesses, Nelson stated that "there is no reason to suppose that word reading ability would be impaired by psychiatric disorders".

7.4.2.2 Current IQ

The Weschler Adult Intelligence Scale – Revised (WAIS-R) (Weschler 1981) has become a widely used measure of intellectual abilities and impairment and is made up of eleven subtests. Due to time constraints in testing it was not possible to administer the complete scale and so selected subtests were used. Crawford *et al.* (1992) evaluated a variety of short forms of the WAIS-R in terms of their validity in predicting full-length IQ and in terms of their clinical utility. The authors used a representative sample of the UK adult population to whom they administered the full-length WAIS-R. They then built regression equations to predict full-length IQ from the short forms. They concluded that short forms have a valid role in the initial screening of subjects to provide a broad estimate of current intellectual abilities. As Crawford *et al.* (1992) state, choosing between the different short forms available is generally a matter of personal preference. However, a two-subtest short form is unlikely to prove sufficient. The authors found that six- and seven-item versions provided the best predictors of full-length IQ. However, given the length of the test battery employed in the present study, it was felt that Crawford's own four-item version comprising Block Design, Similarities, Object Assembly and Comprehension, gave a satisfactory estimate of full-length IQ and superior factorial validity. A measure of current IQ in addition to premorbid IQ was included to assess any intellectual deterioration, especially in schizophrenia sufferers.

7.4.2.3 Memory

7.4.2.3.1 The California Verbal Learning Test

The California Verbal Learning Test (CVLT) (Delis *et al.* 1987) measures both recall and recognition of word lists over a number of trials. It first assesses the individual's ability to recall a list of 16 words (four words each from each of four semantic categories) over five trials. An interference list of sixteen words is then presented for one trial, immediately followed by free and category-cued recall of the first list. The two lists are presented as items on shopping lists (the "Monday" and "Tuesday" lists) in an attempt to make the task more relevant to the individual. After a delay of around twenty minutes during which unrelated testing occurs, free recall, cued recall and recognition of the first list is assessed. This allows assessment of such variables as levels of total recall and recognition on all trials, learning rate across trials, consistency of item recall across trials, retention of information over short and longer delays and enhancement of recall performance by category cueing and recognition testing. The ability to learn and retain verbal information is disrupted in a wide range of psychiatric disorders. This underscores the importance of learning and memory assessment in any neuropsychological evaluation. Learning and memory tests have been criticised (see Lezak 1995) mainly because they involve calculating memory performance on the basis of a single score made up of the total amount of material learned. However, as the authors of this test point out, patients with memory impairment differ amongst themselves on factors like encoding strategies, learning rates, consistency of recall, degree of vulnerability to interference, retention of information over time, error

types and improvement with cued and recognition testing. It is argued that other existing assessments of verbal learning and memory have not addressed this complexity.

The basic format of the CVLT was modelled on the Rey Auditory Verbal Learning Test. Rey's test involved five presentations of a list of fifteen unrelated words, one presentation of a new list of fifteen unrelated words and recall and recognition testing of the first list. The CVLT, however, entails the learning of categorised words instead of unrelated ones. The presentation of the words ensures that a given word is never followed by one from the same category. Consecutive recall of words from the same category, known as semantic clustering (Bousfield 1953) reflects the extent to which the participant has actively imposed an organisation on the list based on shared semantic features. This learning strategy typically results in the most effective encoding into long-term memory. The CVLT word lists were constructed to include high frequency well-established categories such as "clothing" to avoid floor effects in brain-damaged patients; and also lower frequency categories such as "spices and herbs" to minimise ceiling effects in normal controls. The most common alternative strategy to semantic clustering is serial-order clustering. This is the recall of items in the order in which they were presented. Generally, serial-order clustering is a less effective learning strategy than semantic clustering and according to Delis *et al.* (1987) it correlates with poor performance on many other of the CVLT parameters.

7.4.2.3.2 The Doors and People Test

Deficits in learning and memory are common and disabling in psychiatric illness. These deficits, whether transitory or long-term, can be devastating as they impact on everyday life and also can affect the capacity to benefit from therapy. The Doors and People Test (Baddeley *et al.* 1994) offers a broad estimate of both visual and verbal memory, combined with scores of learning and forgetting, recall and recognition. The Doors and People test is useful in that it provides comparable measures for visual and verbal memory whilst avoiding floor and ceiling effects and including checks that deficits are not due to perceptual as opposed to mnemonic problems, and also that measures are based on two sets of observations to ensure reliable conclusions whilst also being relatively unstressful. The existing tools measuring visual long-term memory all had certain drawbacks. The Rey Osterreith figure has been widely used but gives a single measure based on a single complex pattern which involves great perceptual and copying skills as well as memory. The Weschler Memory Scale-Revised includes visual subtests but the authors of the current test feel that they may encourage verbal encoding.

The test is made up of four separate subtests:

The Doors test is a test of visual recognition. The stimuli are coloured photographs of doors from different types of buildings. Participants are presented with a target sequence of twelve doors presented individually. This is then followed by the recognition set in which the target doors are presented in 2x2 matrices with three distracters, the participant being required to pick out the door he has previously seen. The targets are presented in a random order and tested in a different order.

Visual recall is tested by the Shapes test. Participants are shown four different line drawings of crosses which they are asked to copy (to allow for the possibility that distortions may be due to difficulty in drawing rather than memory). The original crosses and the copy are then removed and participants asked to draw them again from memory. The drawings are rated on three dimensions; overall shape (elongated or square); presence of features at the ends of the arms and presence of a feature at the intersection of the arms. This is repeated after a short delay to give an indication of forgetting.

The Names test assesses verbal recognition. The target stimuli are twelve forename/surname pairs which are presented singly, followed by the recognition set consisting of the target items presented in vertical lists with three distracters, all of which share the same forename. Names are a good choice of stimulus for a general estimate of verbal memory as they are ecologically meaningful but do not really allow for encoding in terms of meaning or visualisation as standard, unrelated items do. Pilot studies were run to eliminate names associated with well-known persons or companies. Again, presentation was randomised.

The People test assesses verbal recall. Participants are presented with colour photographs of four people with a name and job written underneath. The photographs are removed and participants then asked what, for example, the doctor's name is. Participants are also asked to recall the four names after a short delay.

Performance norms for the Doors and People test were collected from a stratified sample of 238 subjects with roughly equal numbers from each of the social class categories and balanced for equal numbers of men and women from each of five age bands ranging from 16 to 97. During development of the test, the authors showed that it has a wide range of applicability and is sensitive to the effects of Alzheimer's disease, stroke, normal ageing and schizophrenia. The test gives a robust and sensitive overall memory score. The development process also showed that the detailed pattern of performance varies from one patient group to another in ways which suggest that different aetiologies produce different patterns of impairment. However, due to lack of replication to date, the authors emphasise the overall score as the most robust feature of the test.

7.4.2.4 Executive Function

7.4.2.4.1 The Hayling Sentence Completion Test

The Hayling Sentence Completion Test (Burgess and Shallice 1997) assesses abilities associated with frontal lobe dysfunction and dysexecutive symptoms in everyday life. It consists of two sections, providing a measure of basic task initiation speed as well as performance on a response suppression task. Each section consists of fifteen sentences which each have the last word missing. The sentences are read aloud by the examiner to the participant who is then required to make a verbal response. In section one, they are asked to complete the sentence sensibly as quickly as possible, for example "he posted a letter without a…stamp".

In section two the participant is required to give a word which is unconnected to the sentences in every way, for example "the captain wanted to stay with the sinking...banana". Section one measures simple response initiation through the sum of response latencies, while section two gives two measures of response suppression (error score and time taken to respond). Errors on section two are words which straightforwardly complete the sentence or are closely semantically related. Comparison of the error score and the time taken to respond in section two may allow for some judgements to be made about the style of failure – for example an impulsive individual may be quick to respond but make errors, but someone who has difficulty disengaging from the expected response but can suppress it may show the opposite pattern.

Four groups of subjects were used as an initial standardisation sample for the Hayling test. One of the groups was made up of healthy volunteers and who were drawn from a wide variety of educational backgrounds. The other three groups were made up of neurological lesion patients who fell into three ultimate categories. They were classified according to site of lesion based on a radiologist's report of a CT scan. Any patient who had involvement of the frontal lobes was classified as 'anterior'. Patients with lesions elsewhere in the cortex not involving the frontal lobes were classified as 'posterior'. Patients with bilateral frontal lobe lesions with no posterior involvement were considered as a separate 'bifrontal' group. In a comparison of lesion and control groups' performance no laterality effects were found on any measure of the Hayling test. The unilateral anterior group were significantly poorer than controls on all measures. The posterior group

however were not significantly poorer than controls on any of the Hayling test measures.

7.4.2.4.2 The Brixton Spatial Anticipation Test

The Brixton Spatial Anticipation Test (Burgess and Shallice 1997) is a rule attainment task similar to the Wisconsin Card Sort Test and again measures deficits in frontal lobe function. It consists of a stimulus book in which each page shows the same array of ten circles in two rows of five. Each circle is numbered from one to ten. On each page, one of the circles is filled in blue. The position of the coloured circle differs from page to page on most presentations. The participant is shown one page at a time and asked to indicate where the next coloured circle will be by trying to see a pattern or rule based on what they have seen on the previous pages. This then assesses cognitive flexibility and rule detection and following. There are three broad classes of error on this task: repeating one's response; misapplication of a strategy; or 'guessing' or 'bizarre response'. These latter errors are most likely in frontal lobe dysfunction. The Brixton test is designed to be a straightforward test which is more pleasant and quicker for the volunteer to perform than some others and which is quick to score and interpret.

The Brixton test was standardised in a similar fashion to the Hayling test described above. The unilateral anterior group were significantly poorer than the posteriors or the controls, with the posterior group not differing significantly from the

controls. The bifrontal group were the poorest of all, but the contrast with the unilateral anteriors just failed to reach significance.

Correlations between the two executive function tasks show significant relationships between all the Hayling measures and the Brixton test. However, the authors performed partial correlations removing the effects of age and IQ and found that the resultant correlations were not significantly different from zero. They therefore contend that the correlations between the two tests probably reflect shared IQ and age effects rather than suggesting a common executive resource for each test. Indeed, Burgess and Shallice (1997) reported individual cases with frontal lobe lesions who showed double dissociations on the Hayling and Brixton tests. These findings therefore suggest that the Hayling and Brixton tests probably measure different cognitive processes or resources.

7.4.2.4.3 Verbal Fluency

In Verbal Fluency (Benton and Hamsher 1978) letter, participants are required to say as many words as they can think of beginning with a given letter of the alphabet (in this case, F, A and then S) excluding proper nouns and numbers over a one minute trial. In the category or semantic condition, they are required to generate as many words as they can which fit into a certain category (here, animals, fruits and flowers). The score is the sum of acceptable words over the trials. This measures a combination of efficiency of semantic processing (search strategies) and integrity of semantic store (organisation of semantic memory) and

could therefore be described as measuring both executive function and memory. Lezak (1995) states that word fluency provides an excellent means of finding out how well and whether subjects organise their thinking. Fluency tests requiring word generation according to an initial letter give the greatest scope to subjects seeking a strategy for guiding the search for words and are most difficult for subjects who cannot develop strategies of their own. Fluency tests calling for items in a category provide the structure which is lacking in tests of initial letter word generation. Lezak (1995) states that in the category test, those subjects with good strategies develop sub-categories, for example in the category 'animals', they produce clusters of wild animals, farm animals and so on. Other types of clustering which have been observed include 'conceptual clustering', phonological clustering such as 'salute', 'salvage'; 'baboon', 'beaver' and semantic clusters which can be associated, such as 'soldier', 'salute', or shared ('salt', 'sugar').

Impaired verbal fluency is associated with frontal lobe damage producing cognitive inflexibility. It may be that differences in the hierarchical organisation of the two categories (letters and categories) may account for performance differences, as retrieval by letter requires exploration of more category subsets than does retrieval by category. Frontal lobe damage produces reduced ability to develop semantic strategies.

7.5 Procedure

All participants were asked to attempt the same test battery. The participant was seated in a comfortable situation with a table at hand to place materials on. The purpose of the study was explained to participants and a brief history was taken. Participants then undertook the neuropsychological test battery. Most of the assessments included in the battery are self-paced so the time taken to complete them varied. However, administration of the tests generally took around an hour and a half.

Participants initially undertook the short form of the WAIS-R. The subtests were completed in the following order: block design; similarities; object completion and comprehension. This was then followed by the NART, then the CVLT. During the interval before long-delay memory testing on the CVLT the Hayling and Brixton tests were administered. Following completion of the CVLT participants then attempted Verbal Fluency letter and category. The Doors and People test concluded the neuropsychological test battery. The order of the tests was fixed in order that any decline in motivation or fatigue could be controlled for. The majority of tests required verbal responses. The tester recorded all the participant's responses. Following the completion of the neuropsychological test battery, the symptom severity rating scales were filled out. The SADS-L was subsequently completed using the patient's case notes.

Not all patients were able to complete testing in one session. If this was the case, the patient was seen again as soon as possible to finish the battery. However, not all patients did undertake all the assessments due to refusal or time constraints. Their incomplete scores have however been included in the analyses.

8.0 RESULTS

8.1 Clinical Sample

The control group comprised 31 healthy controls and 6 married-in non-ill members of Family 22. The unipolar affective disorder group (UPs) consisted of 41 depressed participants and the bipolar affective disorder group (BPs) was made up of 37 patients. Twenty-six patients made up the schizophrenic group. The Family 22 group comprised fifteen members of the family carrying the haplotype, seven of whom were unaffected by psychiatric illness and eight of whom had a diagnosis of either recurrent unipolar or bipolar affective disorder.

8.2 Demographic data for all groups

Table 1 shows the results of all the groups (controls, unipolar depressed patients, bipolar disorder patients, schizophrenic patients and Family 22 haplotype carriers) for age, IQ and sex. For continuous variables, groups were compared by one way analysis of variance (ANOVA) and for dichotomous traits (sex) by chi-square. No significant differences were apparent on age, sex, estimated premorbid intelligence level and current intelligence level (measured by NART and WAIS-R respectively). These variables were therefore not included in further between group analyses.

Table 1 Age, IQ and Sex for all groups showing means (standard deviations)

	Controls n=37	Unipolars n=41	Bipolars n=37	Schizophrenics n=26	Family 22 n=15	F	p
Age	35.2 (11.4)	36.0 (16.1)	40.5 (14.6)	42.4 (8.7)	42.8 (12.0)	2.12	0.08
NART IQ	111.1 (6.4)	111.0 (9.8)	109.9 (12.3)	105.8 (12.4)	105.3 (5.7)	2.06	0.09
WAIS-R IQ	110.6 (10.1)	109.7 (11.8)	103.3 (13.2)	103.6 (11.8)	101.8 (10.3)	2.09	0.09
Sex M / F	17/20	19/22	16/21	20/6	7/8		All p>0.05

8.3 Performance of control and patient groups on cognitive tests

Between group differences in the cognitive tests were assessed using one way analysis of variance. The significance of differences between means were further examined with Scheffé tests. Where the data were not normally distributed a Kruskall-Wallis non-parametric one-way analysis of variance was conducted with significant results further examined with Mann-Whitney tests. Tables 2 to 10 show the means and standard deviations of the performance of the control, unipolar disorder, bipolar disorder and schizophrenic groups and the comparisons between the means using Scheffé. For Mann-Whitney comparisons the mean and range are presented.

Distribution of data was examined using Kormolgorov-Smirnoff tests of normality. The following test results did not conform to normal distribution and were analysed by non-parametric tests: Hayling Sentence Completion Test (HSCT) time taken to complete sensible completion; HSCT time taken to complete unconnected completion; HSCT time taken for unconnected completion less time taken for sensible completion; HSCT type A errors and HSCT type B errors.

Table 2 ANOVA showing groups' performances on the California Verbal Learning Test (CVLT) showing means (standard deviations)

	Controls n=31	Unipolars n=41	Bipolars n=37	Schizophrenics n=26	F (p)	Scheffé
CVLT 1	8.0 (2.1)	7.0 (2.3)	6.0 (1.9)	5.2 (1.6)	8.69 (0.000)	C=U>B p=0.005 C=U>S p=0.000
CVLT 1-5	57.9 (11.1)	52.3 (15.2)	46.7 (13.6)	39.7 (13.5)	7.39 (0.000)	C=U>B p=0.02 C=U>S p=0.000
CVLT SD	12.1 (2.9)	10.3 (3.9)	8.9 (3.9)	7.9 (3.4)	5.46 (0.000)	C=U>B p=0.01 C=U>S p=0.000
CVLT LD	12.4 (2.6)	11.0 (3.9)	9.2 (3.9)	8.4 (3.7)	5.35 (0.000)	C=U>B p=0.01 C=U>S p=0.005
CVLT Rec	15.3 (0.9)	14.3 (2.1)	13.9 (2.6)	13.5 (2.3)	3.13 (0.02)	C=U>S p=0.03
CVLT Rec less FP	14.5 (1.7)	13.3 (2.7)	12.4 (4.0)	11.6 (3.6)	2.88 (0.03)	NS

CVLT 1=total words recalled Trial 1; CVLT 1-5=total words recalled Trials 1 to 5; CVLT SD=total number of words recalled after short delay; CVLT LD=total number of words recalled after long delay; CVLT Rec=total number of words correctly recognised; CVLT Rec less FP= total number of words correctly recognised less the number of false positives; C=controls; U=unipolars; B=bipolars; S=schizophrenics

Table 3 ANOVA showing groups' performances on the Doors and People Test (D & P) showing means (standard deviations)

	Controls n=30	Unipolars n=39	Bipolars n=30	Schizophrenics n=19	F (p)	Scheffé
D&P People	12.0 (2.9)	11.7 (3.1)	9.5 (3.9)	8.9 (4.5)	2.87 (0.03)	NS
D&P Doors	10.7 (2.3)	11.5 (3.6)	7.9 (3.0)	8.1 (4.0)	4.70 (0.002)	C=U>S=B p=0.008
D&P Shapes	11.0 (1.9)	11.1 (2.1)	10.4 (3.6)	10.8 (2.8)	1.00 (0.41)	NS
D&P Names	13.0 (2.8)	10.6 (3.7)	9.4 (3.6)	10.1 (2.9)	3.74 (0.007)	C=U=S>B p=0.01
D&P Total Age scale	46.6 (5.6)	44.9 (8.3)	37.2 (10.7)	39.0 (9.6)	5.00 (0.001)	C=U=S>B p=0.04
D&P VisVerb	8.3 (1.6)	8.4 (1.3)	8.8 (1.8)	8.6 (0.8)	0.64 (0.64)	NS
D&P RecallRec	9.1 (1.5)	9.4 (0.9)	9.7 (0.6)	9.3 (0.9)	0.79 (0.54)	NS
D&P Forget	10.6 (2.0)	9.8 (2.2)	8.9 (2.9)	10.4 (1.9)	1.74 (0.15)	NS

D&P People=People subtest age scale score;D&P Doors=Doors subtest age scale score; D&P Shapes=Shapes subtest age scale score; D&P Names=Names subtest age scale score; D&P Total Age Scale=sum of age scale scores for all subtests; D&P VisVerb=Visual versus Verbal memory discrepancy score; D&P RecallRec=Recall versus Recognition memory discrepancy score; D&P Forget=overall forgetting score

Table 4 Mann-Whitney comparisons of Hayling Sentence Completion Test (HSCT) Time to Complete Sensible Completion showing means (range)

	Mean (range)	Mann-Whitney U	
Controls vs Unipolars	11.6 (2-19) 17.5 (7-50)	438.5	P=0.003
Controls vs Bipolars	17.9 (8-42)	324.0	P=0.000
Controls vs Schizophrenics	17.5 (8-44)	253.0	NS
Unipolars vs Bipolars	17.5 (7-50) 17.9 (8-42))	652.0	NS
Unipolars vs Schizophrenics	17.5 (8-44)	452.0	NS
Bipolars vs Schizophrenics	17.9 (8-42) 17.5 (8-44)	363.0	NS

Table 5 Mann-Whitney comparisons of Hayling Sentence Completion Test (HSCT) Time to Complete Unconnected Completion showing means (range)

	Mean (range)	Mann-Whitney U	
Controls vs Unipolars	30.5 (7-99) 40.9 (13-138)	496.0	NS
Controls vs Bipolars	51.4 (11-113)	351.0	P=0.001
Controls vs Schizophrenics	50.3 (15-143)	243.5	P=0.008
Unipolars vs Bipolars	40.9 (13-138) 51.4 (11-113)	548.0	NS
Unipolars vs Schizophrenics	50.3 (15-143)	387.0	NS
Bipolars vs Schizophrenics	51.4 (11-113) 50.3 (15-143)	375.0	NS

Table 6 Mann-Whitney comparisons of Hayling Sentence Completion Test (HSCT) Time to Complete Unconnected Completion less time taken to complete sensible completion showing means (range)

	Mean (range)	Mann-Whitney U	
Controls vs Unipolars	18.8 (-4-87) 23.5 (-8-95)	632.0	NS
Controls vs Bipolars	33.6 (-6-89)	439.0	NS
Controls vs Schizophrenics	32.8 (-21-130)	297.0	NS
Unipolars vs Bipolars	23.5 (-8-95) 33.6 (-6-89)	559.0	NS
Unipolars vs Schizophrenics	32.8 (-21-130)	379.0	NS
Bipolars vs Schizophrenics	33.6 (-6-89) 32.8 (-21-130)	385.5	NS

Table 7 Mann-Whitney comparisons of number of Type A errors made in HSCT unconnected completion showing means (range)

	Mean (range)	Mann-Whitney U	
Controls vs Unipolars	0.8 (0-6) 0.5 (0-4)	657.5	NS
Controls vs Bipolars	1.6 (0-9)	520.0	NS
Controls vs Schizophrenics	2.4 (0-13)	284.0	NS
Unipolars vs Bipolars	0.5 (0-4 1.6 (0-9)	519.5	NS
Unipolars vs Schizophrenics	2.4 (0-13)	275.0	P=0.002
Bipolars vs Schizophrenics	1.6 (0-9) 2.4 (0-13)	347.5	NS

Table 8 Mann-Whitney comparisons of number of Type B errors made in HSCT unconnected completion showing means (range)

	Mean (range)	Mann-Whitney U	
Controls vs Unipolars	1.9 (0-12) 2.9 (0-9)	583.0	NS
Controls vs Bipolars	3.8 (0-10)	441.0	NS
Controls vs Schizophrenics	3.6 (0-8)	256.5	NS
Unipolars vs Bipolars	2.9 (0-9) 3.8 (0-10)	641.5	NS
Unipolars vs Schizophrenics	3.6 (0-8)	387.5	NS
Bipolars vs Schizophrenics	3.8 (0-10) 3.6 (0-8)	388.5	NS

Table 9 ANOVA showing groups' performances on the Brixton Spatial Anticipation Test showing means (standard deviations)

	Controls n=31	Unipolars n=38	Bipolars n=34	Schizophrenics n=24	F (p)	Scheffé
Brixton Raw	14.4 (6.8)	16.4 (7.9)	17.1 (10.5)	25.4 (13.2)	5.54 (0.000)	C=U=B>S p=0.001
Brixton Scale	6.4 (2.2)	5.9 (2.6)	5.9 (2.8)	4.0 (2.3)	3.95 (0.005)	C=U=B>S p=0.008

Table 10 ANOVA showing groups' performances on Verbal Fluency showing means (standard deviations)

	Controls n=31	Unipolars n=39	Bipolars n=31	Schizophrenics n=21	F (p)	Scheffé
Verbal Fluency Letters	48.5 (13.5)	45.4 (13.9)	40.5 (12.9)	38.5 (12.9)	3.09 (0.02)	NS
Verbal Fluency Categories	51.3 (10.6)	46.1 (12.9)	41.1 (13.5)	40.9 (10.0)	4.48 (0.002)	C=U>B=S p=0.03
Verbal Fluency All	99.8 (21.6)	90.6 (24.9)	81.5 (22.1)	80.0 (20.9)	4.34 (0.002)	C=U>B p=0.02 C=U>S p=0.03

Table 11 Summary of results where patient groups differ from controls showing Scheffé p values

Cognitive Measure	Unipolars	Bipolars	Schizophrenics
CVLT 1	-	**P=0.005**	**P=0.000**
CVLT 1-5	-	**P=0.02**	**P=0.000**
CVLT SD	-	**P=0.01**	**P=0.000**
CVLT LD	-	**P=0.01**	**P=0.005**
CVLT Rec	-	-	**P=0.03**
CVLT Rec less FP	-	-	-
D&P People	-	-	-
D&P Doors	-	**P=0.008**	**P=0.008**
D&P Shapes	-	-	-
D&P Names	-	**P=0.01**	-
D&P Total Age Scale	-	**P=0.04**	-
D&P VisVerb	-	-	-
D&P RecallRec	-	-	-
D&P Forget	-	-	-
HSCT Time 1	**P=0.003**	**P=0.000**	-
HSCT Time 2	-	**P=0.001**	**P=0.008**
HSCT Time 2 less 1	-	-	-
HSCT Type A Errors	-	-	-
HSCT Type B Errors	-	-	-
Brixton Raw	-	-	**P=0.001**
Brixton Scale	-	-	**P=0.008**
VF Letters	-	-	-
VF Categories	-	**P=0.03**	**P=0.03**
VF All	-	**P=0.02**	**P=0.03**

These results show that the bipolar and schizophrenic group are similar in their cognitive deficits but that the schizophrenic group is more impaired in executive function tasks. The relative normality of the unipolar group should also be noted.

8.4 Multiple Testing

A large number of comparisons are being made and some apparently significant differences between groups could arise by chance. This can be addressed in two ways:

1. Applying a Bonferroni Correction (Miller 1981). If a null hypothesis which is in fact true is tested taking 0.05 as the critical significance level, there is a probability of 0.95 of coming to a 'not significant' (correct) conclusion. If twenty such hypotheses are tested, the expected number of spurious significant results is 20x0.05=1. If the alpha level is made small enough, the probability that none of the separate tests is significant can be made equal to 0.95. This means that if any of the comparisons has a p value less than alpha, the difference is significant at the 0.05 level. If the alpha level is divided by n, where alpha = 0.05 and n = the number of comparisons, which in this instance is 72, this would mean taking a p level of 0.0007 to be significant at the 0.05 level. This is conservative and may lead to rejection of real findings because it could be argued that for some tests there are *a priori* reasons for expecting a change.
2. Only considering results to be significant at the p=0.01 level or less, as there are 72 comparisons so at the 0.05 level one would expect less than four spuriously significant results, whereas at the 0.01 level, less than one spurious result would be expected. This was the approach taken.

8.5 Effect of symptom severity on cognitive performance in the patient groups

All the patient groups were assessed on the severity of their symptoms with diagnosis-specific rating scales. In order to assess whether their clinical state at the time of testing was adversely affecting their cognitive performance, performance on cognitive test was correlated with scores on the severity rating scales.

The unipolar disorder group was assessed using the Hamilton Depression Rating Scale (mean 14.2, SD 6.9) and the Beck Depression Inventory (mean 25.7, SD 10.7). Correlations between these scales and key cognitive measures are presented in Tables 12 and 13.

Table 12 Correlational Analyses for symptom severity and cognitive performance Unipolar Group

Hamilton Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.127 (0.448)
CVLT 1-5	0.108 (0.578)
CVLT Long Delay	0.172 (0.303)
CVLT Total Recognition less False Positives	0.138 (0.409)
HSCT Time 1	0.001 (0.996)
HSCT Time 2	-0.016 (0.923)
HSCT Time 2 less 1	0.012 (0.945)
Brixton Scale Score	0.014 (0.937)
Verbal Fluency Total Score	-0.168 (0.319)
Doors and People Total Age Scale Score	0.156 (0.447)

Table 13 Correlational Analyses for symptom severity and cognitive performance Unipolar Group

Beck Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.143 (0.420)
CVLT 1-5	0.145 (0.412)
CVLT Total Recognition less False Positives	0.021 (0.906)
HSCT Time 1	-0.534 (0.001)**
HSCT Time 2	-0.299 (0.086)
HSCT Time 2 less 1	-0.387 (0.044)
Brixton Scale Score	0.299 (0.091)
Verbal Fluency Total Score	0.020 (0.911)
Doors and People Total Age Scale Score	0.172 (0.433)

The bipolar disorder group were assessed on the same depression rating measures (HDRS mean 5.6, SD 7.1; BDI mean 12.9, SD 12.2) and also on the Modified Manic Rating Scale (mean 1.7, SD 3.8). Correlations between these scales and key cognitive measures are presented in Tables 14 and 15.

Table 14 Correlational Analyses for symptom severity and cognitive performance Bipolar Group

Hamilton Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.051 (0.776)
CVLT 1-5	0.045 (0.805)
CVLT Long Delay	0.104 (0.577)
CVLT Total Recognition less False Positives	0.121 (0.517)
HSCT Time 1	0.144 (0.433)
HSCT Time 2	-0.208 (0.262)
HSCT Time 2 less 1	-0.284 (0.121)
Brixton Scale Score	0.130 (0.494)
Verbal Fluency Total Score	-0.042 (0.829)
Doors and People Total Age Scale Score	-.0083 (0.698)

Table 15 Correlational Analyses for symptom severity and cognitive performance

Bipolar Group

Beck Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.090 (0.625)
CVLT 1-5	-0.148 (0.418)
CVLT Total Recognition less False Positives	-0.055 (0.773)
HSCT Time 1	-0.016 (0.933)
HSCT Time 2	-0.159 (0.402)
HSCT Time 2 less 1	-0.213 (0.258)
Brixton Scale Score	0.085 (0.655)
Verbal Fluency Total Score	-0.202 (0.313)
Doors and People Total Age Scale Score	-0.230 (0.292)

MMRS Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.224 (0.189)
CVLT 1-5	-0.277 (0.102)
CVLT Long Delay	-0.042 (0.812)
CVLT Total Recognition less False Positives	-0.034 (0.848)
HSCT Time 1	0.220 (0.207)
HSCT Time 2	0.127 (0.475)
HSCT Time 2 less 1	0.115 (0.518)
Brixton Scale Score	-0.197 (0.454)
Verbal Fluency Total Score	-0.035 (0.854)
Doors and People Total Age Scale Score	-0.071 (0.734)

The schizophrenic group's symptom severity was measured with the Brief Psychiatric Rating Scale (mean 6.5, SD 3.7). Correlations between this scale and key cognitive measures are presented in Table 16.

Table 16 Correlational Analyses for symptom severity and cognitive performance
Schizophrenic Group
BPRS Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.081 (0.687)
CVLT 1-5	-0.130 (0.526)
CVLT Total Recognition less False Positives	-0.182 (0.384)
HSCT Time 1	0.024 (0.913)
HSCT Time 2	-0.112 (0.601)
HSCT Time 2 less 1	-0.053 (0.807)
Brixton Scale Score	0.033 (0.874)
Verbal Fluency Total Score	-0.198 (0.390)
Doors and People Total Age Scale Score	-0.122 (0.754)

Scores on the cognitive tests did not correlate significantly with symptom severity measures in any of the patient groups.

8.6 Performance of Family 22 "high risk" on cognitive tests compared with the control group

Analysis of the family data was hypothesis-driven. The hypotheses were that both affected and unaffected haplotype carriers would be similar to the bipolar patient group on the cognitive measures. Family 22 has a high incidence of bipolar and unipolar affective disorder. Therefore the Family 22 haplotype carriers (the "high risk" group) were compared with the control group on only those tests where between group differences had been observed for the bipolar disorder group. The F22 family members not at risk were included in the control group for this analysis after establishing the equivalence of their performances. Group differences were examined with Mann-Whitney U tests and independent t tests. Means and ranges are presented in Tables 17 to 20.

Table 17 Comparisons of controls' and Family 22 family members' performances on the California Verbal Learning Test (CVLT) showing means (range)

	Controls n=37	Family 22 n=15	Mann-Whitney U	p	t	p
CVLT 1	7.9 (5-12)	5.9 (4-9)	121.0	0.002	3.31	0.001
CVLT 1-5	57.2 (36-75)	49.8 (22-68)	170.0	0.04	2.48	0.02
CVLT SD	11.9 (5-16)	10.4 (7-15)	180.0	0.06	1.87	0.05
CVLT LD	12.1 (6-16)	10.7 (4-15)	185.0	0.08	1.83	0.08

Table 18 Mann-Whitney comparisons of controls' and Family 22 family members' performances on the Doors and People (D & P) test showing means (range)

	Controls n=35	Family 22 n=13	Mann-Whitney U	p	t	p
D&P Doors	10.4 (5-14)	8.8 (3-13)	80.5	0.26	1.39	0.17
D&P Names	12.9 (7-16)	10.0 (3-14)	49.5	0.02	2.48	0.02
D&P Ttl Age Scale	46.7 (34-57)	38.6 (29-53)	48.0	0.02	3.07	0.004

Table 19 Mann-Whitney comparisons of controls' and Family 22 members' performances on Hayling Sentence Completion Test (HSCT) time to complete sensible and unconnected completion showing means (range)

	Controls n=36	Family 22 n=13	Mann-Whitney U	p
HSCT Sensible Completion	11.7 (2-19)	15.8 (10-31)	161.5	0.03
HSCT Unconnected Completion	30.5 (7-99)	46.7 (13-146)	195.0	0.12

Table 20 Mann-Whitney comparisons of controls' and Family 22 members' performances on Verbal Fluency measures showing means (range)

	Controls n=36	Family 22 n=15	Mann-Whitney U	p	t	p
Verbal Fluency Categories	50.5 (34-90)	39.8 (26-46)	89.5	0.000	4.55	0.000
Verbal Fluency Total	99.9 (62-161)	82.4 (34-105)	146.0	0.01	3.14	0.004

8.7 Comparison of affected and unaffected Family 22 "high risk" group's cognitive performance with controls

The Family 22 group was partitioned into unaffected and affected groups and their scores on key cognitive measured were analysed in relation to the control group. The results of the Mann-Whitney comparisons with means and range are presented in Tables 21 to 28

Table 21 Mann-Whitney comparisons of unaffected and affected haplotype carrier family members on key cognitive measures showing means (range)

	Family 22 Unaffected n=7	Family 22 Affected n=8	Mann-Whitney U	p	T	p
CVLT 1	6.3 (5-9)	5.8 (4-8)	24.0	0.63	0.69	0.505
CVLT 1-5	50.4 (22-68)	49.1 (41-60)	20.0	0.35	0.221	0.83
CVLT Tot less FP	10.4 (-12-16)	13.5 (10-15)	24.5	0.67	-0.79	0.46
HSCT Time 1	15.2 (10.5-31.3)	16.3 (9.8-23.9)	20.0	0.36		
HSCT Time 2	31.6 (12.8-56.4)	53.1 (14.8-145.8)	16.0	0.17		
HSCT Time 2 less 1	16.4 (-9.5-44.9)	38.1 (1.7-121.9)	17.0	0.20		
Brixton Scale	5.4 (2-8)	5.1 (1-10)	23.5	0.60	0.22	0.83
VF All	82.9 (65-105)	82.0 (34-99)	22.0	0.49	0.09	0.93
D&P Ttl Age Scale	40.5 (33-53)	37.0 (29-48)	6.0	0.33	0.58	0.58

Table 22 Mann-Whitney comparisons of controls and unaffected Family 22 haplotype carriers on key cognitive measures showing means (range)

	Controls	Family 22 Unaffected n=7	Mann-Whitney U	p	t	p
CVLT 1	8.07 (5-12)	6.3 (5-9)	49.5	0.03	-2.08	0.05
CVLT 1-5	57.9 (36-75)	50.4 (22-68)	73.0	0.21	-1.52	0.14
CVLT Tot less FP	14.5 (10-16)	10.4 (-12-16)	82.0	0.35	-2.19	0.04
HSCT Time 1	11.9 (2.0-19.1)	15.2 (10.5-31.3)	78.5	0.30		
HSCT Time 2	29.6 (8.8-98.9)	31.6 (12.8-56.4)	93.0	0.64		
HSCT Time 2 less 1	17.7 (-3.6-86.9)	16.4 (-9.5-44.9)	100.0	0.85		
Brixton Scale	6.4 (1-10)	5.4 (2-8)	84.0	0.40	-1.09	0.286
VF All	99.8 (62-161)	82.8 (65-105)	59.0	0.07	-1.95	0.04
D&P Ttl Age Scale	46.6 (34-54)	40.5 (33-53)	20.0	0.17	-1.77	0.09

Table 23 Mann-Whitney comparisons of controls and affected Family 22 haplotype carriers on key cognitive measures showing means (range)

	Controls	Family 22 Affected n=8	Mann-Whitney U	p	t	p
CVLT 1	8.07 (5-12)	5.8 (4-8)	44.5	0.006	2.92	0.006
CVLT 1-5	57.9 (36-75)	49.1 (41-60)	62.0	0.04	3.01	0.007
CVLT Tot less FP	14.5 (10-16)	13.5 (10-15)	74.0	0.09	1.50	0.14
HSCT Time 1	11.9 (2.0-19.1)	16.3 (9.8-23.9)	66.0	0.05		
HSCT Time 2	29.6 (8.8-98.9)	53.1 (14.8-145.8)	60.0	0.03		
HSCT Time 2 less 1	17.7 (-3.6-86.9)	38.1 (1.7-121.9)	74.0	0.10		
Brixton Scale	6.4 (1-10)	5.1 (1-10)	75.0	0.10	1.42	0.17
VF All	99.8 (62-161)	82.0 (34-99)	68.0	0.06	2.09	0.05
D&P Ttl Age Scale	46.6 (34-54)	37.0 (29-48)	17.0	0.04	2.92	0.008

No significant differences were found between the affected and unaffected F22 "at risk" group on any of the key cognitive measures. When comparisons were made between the control group and the unaffected F22 group, number of words recalled on CVLT trial 1 showed a trend towards significance between the groups and there was also a significant difference in the total number of words generated in Verbal Fluency.

In comparisons between the control group and the affected F22 group, several significant differences were found, namely CVLT trial 1 and trials 1 to 5. There was a trend towards significance on the HSCT sensible completion and a

significant difference on the unconnected completion. A further trend was noted in the Verbal Fluency total, and the F22 affected group's Doors and People total age scale score was significantly lower than the control group.

8.8 Effect of symptom severity on cognitive performance in Family 22 haplotype carriers

The Family 22 haplotype carriers were assessed on the severity of their symptoms, if any, with depression and mania rating scales. In order to assess whether their state at the time of testing was adversely affecting their cognitive performance, performance on cognitive test was correlated with scores on the severity rating scales.

The Family 22 group's mean score on the HDRS was 4.1 (SD 5.6), 5.8 (SD 7.3) on the BDI and 0.3 (SD 0.8) on the MMRS. Correlations between these scales and key cognitive measures are presented in Table 24.

Table 24 Correlational analyses for symptom severity and cognitive performance Family 22 haplotype carrier group

Hamilton Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.051 (0.776)
CVLT 1-5	0.045 (0.805)
CVLT Long Delay	0.104 (0.577)
CVLT Total Recognition less False Positives	0.121 (0.517)
HSCT Time 1	0.144 (0.433)
HSCT Time 2	-0.208 (0.260)
HSCT Time 2 less 1	-0.284 (0.121)
Brixton Scale Score	0.130 (0.494)
Verbal Fluency Total Score	-0.042 (0.829)
Doors and People Total Age Scale Score	-0.083 (0.698)

Beck Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.498 (0.119)
CVLT 1-5	-.592 (0.055)
CVLT Total Recognition less False Positives	-0.202 (0.551)
HSCT Time 1	0.248 (0.462)
HSCT Time 2	0.418 (0.200)
HSCT Time 2 less 1	0.414 (0.206)
Brixton Scale Score	-0.466 (0.148)
Verbal Fluency Total Score	-0.300 (0.371)
Doors and People Total Age Scale Score	-0.214 (0.645)

MMRS Score

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.244 (0.189)
CVLT 1-5	-0.277 (0.102)
CVLT Long Delay	-0.042 (0.812)
CVLT Total Recognition less False Positives	-0.034 (0.848)
HSCT Time 1	0.220 (0.204)
HSCT Time 2	0.127 (0.475)
HSCT Time 2 less 1	0.115 (0.518)
Brixton Scale Score	-0.135 (0.454)
Verbal Fluency Total Score	-0.035 (0.884)
Doors and People Total Age Scale Score	0.071 (0.734)

Scores on the cognitive tests did not correlate significantly with symptom severity measures in this group.

8.9 Effects of sex on cognitive performance in patient groups and Family 22 haplotype carriers

Sex differences within the groups on key cognitive measures were examined with Mann-Whitney tests. The results are presented in Tables 25 to 28.

Table 25 Mann-Whitney comparisons of males versus females in the unipolar disorder group on key cognitive measures showing means (standard deviations)

		Mean (SD)	Mann-Whitney U	
CVLT 1	Males vs Females	6.6 (2.2) 7.5 (2.4)	157.0	NS
CVLT 1-5	Males vs Females	50.7 (16.8) 53.7 (13.8)	185.5	NS
CVLT Rec less FP	Males vs Females	13.3 (3.1) 13.2 (2.4)	190.0	NS
HSCT 1	Males vs Females	17.4 (9.1) 17.5 (10.8)	182.0	NS
HSCT 2	Males vs Females	48.2 (32.2) 34.4 (17.2)	149.0	NS
HSCT 2 less 1	Males vs Females	30.7 (26.6) 16.9 (17.6)	130.0	NS
Brixton Scale	Males vs Females	5.1 (2.8) 6.6 (2.2)	119.5	NS
Verbal Fluency total	Males vs Females	88.4 (18.4) 92.5 (29.8)	162.0	NS
Door & People total score	Males vs Females	43.0 (9.8) 46.9 (5.9)	72.5	NS

Table 26 Mann-Whitney comparisons of males versus females in the bipolar disorder group on key cognitive measures showing means (standard deviations)

		Mean (SD)	Mann-Whitney U	
CVLT 1	Males vs Females	5.6 (1.9) 6.4 (1.9)	122.0	NS
CVLT 1-5	Males vs Females	42.3 (15.6) 50.0 (11.2)	112.0	NS
CVLT Rec less FP	Males vs Females	11.8 (3.3) 12.9 (4.5)	107.0	NS
HSCT 1	Males vs Females	18.5 (8.6) 17.4 (8.3)	136.0	NS
HSCT 2	Males vs Females	55.1 (32.1) 48.7 (27.7)	135.0	NS
HSCT 2 less 1	Males vs Females	36.7 (29.8) 31.3 (26.4)	130.0	NS
Brixton Scale	Males vs Females	6.1 (2.9) 5.8 (2.8)	134.0	NS
Verbal Fluency total	Males vs Females	78.7 (26.5) 84.1 (17.7)	95.5	NS
Door & People total score	Males vs Females	35.7 (12.8) 38.8 (8.1)	65.0	NS

Table 27 Mann-Whitney comparisons of males versus females in the schizophrenic group on key cognitive measures showing means (standard deviations)

		Mean (SD)	Mann-Whitney U	
CVLT 1	Males vs Females	5.2 (1.7) 5.2 (1.6)	56.5	NS
CVLT 1-5	Males vs Females	39.3 (13.5) 41.2 (14.7)	58.5	NS
CVLT Rec less FP	Males vs Females	11.9 (3.6) 10.5 (3.9)	42.5	NS
HSCT 1	Males vs Females	15.3 (8.2) 25.4 (13.0)	22.0	NS
HSCT 2	Males vs Females	44.0 (32.8) 73.1 (34.5)	17.0	NS
HSCT 2 less 1	Males vs Females	28.7 (33.5) 47.7 (33.4)	29.0	NS
Brixton Scale	Males vs Females	4.1 (2.3) 3.6 (2.6)	41.0	NS
Verbal Fluency total	Males vs Females	82.6 (18.7) 72.2 (27.5)	21.0	NS
Door & People total score	Males vs Females	37.3 (10.7) 44.0 (1.4)	4.5	NS

Table 28 Mann-Whitney comparisons of males versus females in the Family 22 haplotype carrier group on key cognitive measures showing means (standard deviations)

		Mean (SD)	Mann-Whitney U	
CVLT 1	Males vs. Females	6.1 (1.8) 5.9 (1.3)	27.0	NS
CVLT 1-5	Males vs. Females	49.4 (14.3) 50.0 (6.6)	25.0	NS
CVLT Rec less FP	Males vs. Females	10.7 (10.1) 13.3 (2.4)	25.0	NS
HSCT 1	Males vs. Females	14.2 (7.6) 17.1 (4.3)	22.0	NS
HSCT 2	Males vs. Females	36.5 (17.4) 48.8 (42.9)	11.0	NS
HSCT 2 less 1	Males vs. Females	223. (21.1) 32.9 (40.8)	27.0	NS
Brixton Scale	Males vs. Females	5.6 (2.6) 5.0 (2.6)	26.0	NS
Verbal Fluency total	Males vs. Females	85.4 (14.4) 79.8 (21.1)	25.5	NS
Door & People total score	Males vs. Females	39.6 (9.8) 37.3 (8.1)	25.5	NS

No significant effects of sex were found within any of the groups.

8.10 Effects of medication on cognitive performance in the patient and Family 22 haplotype carrier group

The numbers of patients taking medication at the time of testing are listed in Appendix 1 along with the type of medication.

Within the bipolar disorder group, the effects of lithium on cognitive performance was examined by comparing the performance of patients taking lithium with those patients not on the drug with Mann-Whitney tests. The results are presented in Table 29.

Table 29 Mann-Whitney comparisons of cognitive performance in bipolar disorder patients taking lithium with those not taking lithium showing means (standard deviations)

		Mean (SD)	Mann-Whitney U	
CVLT 1	Lithium vs No Lithium	6.2 (1.6) 5.9 (1.3)	138.0	NS
CVLT 1-5	Lithium vs No Lithium	44.6 (12.1) 48.8 (14.8)	107.0	NS
CVLT Rec less FP	Lithium vs No Lithium	12.4 (3.1) 12.4 (4.8)	108.5	NS
HSCT 1	Lithium vs No Lithium	18.5 (9.5) 16.3 (6.1)	124.5	NS
HSCT 2	Lithium vs No Lithium	49.6 (33.1) 53.3 (23.2)	112.0	NS
HSCT 2 less 1	Lithium vs No Lithium	31.8 (32.1) 36.6 (22.8)	102.0	NS
Brixton Scale	Lithium vs No Lithium	4.6 (3.2) 6.8 (2.2)	67.0	NS
Verbal Fluency total	Lithium vs No Lithium	74.4 (21.7) 85.5 (19.9)	65.0	NS
Door & People total score	Lithium vs No Lithium	36.7 (5.7) 38.7 (11.3)	41.0	NS

No significant differences were found between bipolar disorder patients taking lithium and those not in any of the key cognitive measures.

8.11 Effect of age of onset of illness on cognitive performance in patient groups and Family 22 haplotype carriers

Correlational analyses on age of onset effects within the groups on key cognitive measures were carried out. The results are presented in Tables 30 to 33.

Table 30 Correlational analyses of age of onset and key cognitive measures unipolar disorder group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.499 (0.002)*
CVLT 1-5	-0.448 (0.007)*
CVLT Total Recognition less False Positives	-0.498 (0.002)*
HSCT Time 1	0.141 (0.428)
HSCT Time 2	-0.146 (0.411)
HSCT Time 2 less 1	-0.209 (0.236)
Brixton Scale Score	-0.354 (0.043)
Verbal Fluency Total Score	-0.405 (0.019)
Doors and People Total Age Scale Score	-0.236 (0.267)

*.Correlation is significant at the 0.01 level

Table 31 Correlational analyses of age of onset and key cognitive measures bipolar disorder group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.029 (0.892)
CVLT 1-5	0.213 (0.307)
CVLT Total Recognition less False Positives	-0.034 (0.873)
HSCT Time 1	-0.123 (0.557)
HSCT Time 2	-0.084 (0.689)
HSCT Time 2 less 1	-0.097 (0.645)
Brixton Scale Score	0.105 (0.617)
Verbal Fluency Total Score	0.104 (0.637)
Doors and People Total Age Scale Score	-0.291 (0.200)

Table 32 Correlational analyses of age of onset and key cognitive measures schizophrenic group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.667 (0.219)
CVLT 1-5	0.900 (0.037)
CVLT Total Recognition less False Positives	0.400 (0.600)
HSCT Time 1	-0.700 (0.188)
HSCT Time 2	0.600 (0.285)
HSCT Time 2 less 1	0.600 (0.285)
Brixton Scale Score	0.100 (0.873)
Verbal Fluency Total Score	-0.400 (0.600)
Doors and People Total Age Scale Score	-1.000 (1.000)

Table 33 Correlational analyses of age of onset and key cognitive measures Family 22 haplotype carriers

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.266 (0.525)
CVLT 1-5	-0.036 (0.933)
CVLT Total Recognition less False Positives	-0.797 (0.018)
HSCT Time 1	0.407 (0.317)
HSCT Time 2	-0.228 (0.588)
HSCT Time 2 less 1	-0.252 (0.548)
Brixton Scale Score	-0.428 (0.290)
Verbal Fluency Total Score	-0.180 (0.670)
Doors and People Total Age Scale Score	0.154 (0.805)

There were significant negative correlations in the unipolar disorder group between age of onset of illness and the CVLT measures number of words recalled in trial 1 and trials 1 to 5, and total number of words recognised less the number of false positives.

There were no significant correlations between age of onset and key cognitive measures in any of the other groups.

8.12 Effect of duration of illness on cognitive performance in patient groups and Family 22 haplotype carriers

Correlational analyses on duration of illness effects within the groups on key cognitive measures were carried out. The results are presented in Tables 34 to 37.

Table 34 Correlational analyses of duration of illness and key cognitive measures unipolar disorder group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.35 (0.04)*
CVLT 1-5	-0.24 (0.17)
CVLT Total Recognition less False Positives	-0.29 (0.09)
HSCT Time 1	0.15 (0.40)
HSCT Time 2	0.41 (0.02)
HSCT Time 2 less 1	0.47 (0.005)**
Brixton Scale Score	-0.29 (0.09)
Verbal Fluency Total Score	-0.09 (0.62)
Doors and People Total Age Scale Score	-0.08 (0.70)

*.Correlation is significant at the 0.05 level **.Correlation is significant at the 0.01 level

Table 35 Correlational analyses of duration of illness and key cognitive measures bipolar disorder group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.24 (0.25)
CVLT 1-5	-0.03 (0.89)
CVLT Total Recognition less False Positives	-0.14 (0.53)
HSCT Time 1	0.17 (0.43)
HSCT Time 2	-0.03 (0.88)
HSCT Time 2 less 1	-0.06 (0.78)
Brixton Scale Score	-0.58 (0.002)**
Verbal Fluency Total Score	-0.20 (0.36)
Doors and People Total Age Scale Score	-0.17 (0.47)

**.Correlation is significant at the 0.01 level

Table 36 Correlational analyses of duration of illness and key cognitive measures schizophrenia group

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	-0.15 (0.81)
CVLT 1-5	-0.60 (0.29)
CVLT Total Recognition less False Positives	-0.40 (0.60)
HSCT Time 1	0.20 (0.75)
HSCT Time 2	-0.90 (0.04)*
HSCT Time 2 less 1	-0.90 (0.04)*
Brixton Scale Score	-0.10 (0.87)
Verbal Fluency Total Score	-0.20 (0.80)
Doors and People Total Age Scale Score	1.00 **

*.Correlation is significant at the 0.05 level **.Correlation is significant at the 0.01 level

Table 37 Correlational analyses of duration of illness and key cognitive measures Family 22 haplotype carriers

Neuropsychological Test Score	Spearman's r_s (p value)
CVLT 1	0.01 (0.98)
CVLT 1-5	-0.67 (0.07)
CVLT Total Recognition less False Positives	0.06 (0.88)
HSCT Time 1	0.69 (0.06)
HSCT Time 2	0.02 (0.96)
HSCT Time 2 less 1	0.14 (0.74)
Brixton Scale Score	0.08 (0.84)
Verbal Fluency Total Score	-0.48 (0.23)
Doors and People Total Age Scale Score	0.20 (0.75)

There were significant positive correlations in the unipolar disorder group between duration of illness and HSCT time for unconnected completion and unconnected completion less time for sensible completion. A significant negative correlation was found between duration of illness and CVLT number of words recalled in trial 1.

A significant negative correlation between duration of illness and Brixton scale score was found in the bipolar disorder group.

Significant negative correlations between duration of illness and HSCT time for unconnected completion and unconnected completion less time for sensible completion were shown in the schizophrenia group.

No significant correlations were found between duration of illness and key cognitive measures in the F22 "at risk" group, perhaps due to size limitations.

9.0 DISCUSSION

9.1 Summary of main findings

This study has shown that patients with schizophrenia and bipolar disorder have impaired performance in several domains of cognitive function and the unipolar depressed patients show no differences from controls. These results confirm and extend the findings of a number of published studies. The second major finding from this work is that cognitive deficits were measured in relatives in one family, who were at high genetic risk of developing bipolar disorder but who had not developed symptoms of the disorder. It can be concluded that these cognitive deficits associated with increased genetic risk may be considered as 'endophenotypes' in genetic studies of bipolar disorder.

The bipolar affective disorder group were impaired relative to controls on several measures of verbal learning and memory, namely California Verbal Learning Test immediate recall condition (CVLT trial 1), a global measure of learning performance (CVLT total score of immediate free recall trials 1 to 5), and short and long delay free recall. The bipolar group was also impaired compared to controls on measures of visual and verbal recognition (Doors and People subtests Doors and Names), reflected in their overall lower total age scale score on the Doors and People test. On executive function tasks, the bipolar group was slower to complete both the sensible and unconnected completion trials of the Hayling

Sentence Completion Test. The Verbal Fluency task of generating words fitting into particular categories was performed more poorly by the bipolar group than by controls, and the bipolar group generated fewer words overall in Verbal Fluency than controls.

The schizophrenic group's performance on the cognitive tests was similar to that of the bipolar group in general profile. The schizophrenic group differed from controls on all the measures of verbal learning and memory mentioned above, with the addition of impaired delayed recognition. The schizophrenic group was also impaired relative to controls on a measure of visual recognition (Doors and People subtest Doors). The schizophrenia group differed from the bipolar group in the degree of impairment and in tests of executive function, being slower to complete the unconnected trial of the Hayling Sentence Completion Test. This group also exhibited deficits on the Brixton Spatial Anticipation Test, making significantly more errors than the control group. The schizophrenic group's performance on measures of Verbal Fluency was equivalent to that of the bipolar affective disorder group and impaired relative to the control group.

The unipolar affective disorder group was relatively unimpaired when compared to the normal control group. The only significant difference between this group and the controls was in the time taken to complete the sensible completion trial of the Hayling Sentence Completion Test, a measure of basic initiation speed.

In the three patient groups, schizophrenic, bipolar and unipolar affective disorder, cognitive impairment was not related to severity of symptoms or medication at the time of testing, so cognitive impairments appear to be measures of 'trait' rather than 'state'.

These results show that bipolar affective disorder patients not experiencing an acute episode of illness are cognitively impaired when compared to healthy controls and that the deficits they experience are generally similar to those found in schizophrenic patients, the main difference between the bipolar and schizophrenic groups being in executive ability.

Analysis of the data from members of the extended bipolar pedigree (Family 22) showed that relatives with bipolar or unipolar disorder, in this family, had similar cognitive changes to the unrelated bipolar patient group. Strikingly, a group of relatives who had no symptoms of unipolar or bipolar disorder but who carried the genetic markers associated with increased risk of bipolar disorder also had significant cognitive deficits. The majority of tests that highlighted cognitive changes in the bipolar group also showed significant differences or trends towards significance in the Family 22 "high risk" group. No significant differences on performance of the cognitive tests were found between those haplotype carriers with a diagnosis of psychiatric illness and unaffected haplotype carriers.

Further investigation showed that cognitive changes noted in the patient and Family 22 groups were not due to the effects of medication or symptom severity at

the time of testing. Taken overall, these results show that these neuropsychological tests are trait markers of risk in this bipolar/unipolar family.

9.2 Cognitive changes in schizophrenia

The impairments apparent in the schizophrenia group, in verbal learning and memory and in executive function, support previous findings reported in the schizophrenia literature. Memory dysfunction is a reliable finding in schizophrenia (Levin *et al.* 1989), although there is some debate as to the nature of memory impairment in the disorder. The finding in this study of impaired global verbal learning performance across trials is suggestive of an acquisition deficit, although it is not possible to conclude from these results what the mechanism for this deficit may be, as difficulties with attention, encoding, motivation and organisation of the to-be-remembered information have all been implicated (Paulsen *et al.* 1995). However, as the schizophrenia group did not appear to exhibit rapid forgetting of the acquired information after a delay period (as the short and long delay recall performances are similar, although deficient compared to controls) this suggests that this group do not suffer from particular storage deficits. The finding of poor delayed verbal recognition when compared to controls suggests that there may be some degree of retrieval deficit as the recognition format allows for the demonstration of acquired knowledge without relying on the effortful initiation of search and retrieval mechanisms. However, as there is no significant difference between controls and the schizophrenia group on the measure of recognition performance after the removal of false positives, this is suggestive more of an

encoding deficit and may reflect disorganisation of the information. The findings generally are in line with the large-scale Heinrichs and Zakzanis (1998) meta-analysis of cognitive impairment in schizophrenia that identified impairment in global verbal memory as the single most severe impairment. More specifically, the findings support the study by Calev (1984) of chronic schizophrenic patients and controls on recall and recognition tasks, finding both aspects of memory impaired in the patient group. However, there was a significant impairment of visual recognition compared to controls as evidenced by poor performance on the Doors subtest of the Door and People task, the only subtest of this task that was impaired in the schizophrenic group. This again is suggestive of encoding deficits, or may simply reflect the increased difficulty of this recognition task as opposed to many others, as it was deliberately designed to compensate for the problem that recognition tasks are often easier than recall tasks, as photographs of doors were presented, stimuli which are similar anyway, and then target doors required to be recognised from three distracters in each case. However, as there was no corresponding deficit in the verbal recognition task, requiring the recognition of target names from three distracters, this may reflect a specific verbal recognition deficit. Alternatively, it may be that as names are more 'everyday' stimuli, it may be that patients are simply more practised in recognising them. These findings do not support previous theories of an amnesic syndrome in schizophrenia proposed by McKenna *et al.* (1990) because deficits would be found across modalities, whereas these results are more suggestive of a verbal deficit. There has been some controversy as to whether the memory deficits observed in schizophrenia are primary cognitive deficits or are secondary to other deficits, for example in

executive function. Current neuropsychological methodology is unable to tease apart these domains as any neuropsychological instrument involves a variety of cognitive resources. Goldberg *et al.* (1989) have suggested that the memory impairment in schizophrenia appears to affect recall over recognition, possibly indicative of an executive pattern of impairment with difficulties implementing effective search and retrieval strategies. These results are in line with a recent meta-analysis finding significant memory impairment largely for recall, but with some evidence for impaired recognition memory, associated with hippocampal and temporal lobe dysfunction, brain regions implicated in encoding and storage (Aleman *et al.* 1999).

Executive function deficits were observed in this sample, notably on the Brixton Spatial Anticipation Test and in Verbal Fluency. Deficits on the Brixton Test are in line with other findings in schizophrenia including poor performance on other 'rule' attainment tasks such as the Wisconsin Card Sort Test. It has been suggested that deficits on tasks such as these stem form an inability to 'abstract' or to grasp essential features. This usually produces persistence in adhering to one rule and a failure to shift responses from the previously irrelevant to the relevant, leading to an inability to detect rules (Faglioni, 1999). This reflects reactive inflexibility, a deficit in processing information gathered from the environment to discover rules and change behaviour. Stuss *et al.* (1983) showed with this task that patients with schizophrenia have difficulty attaining concepts and make incorrect perseverative errors even when given feedback. More recently, Weickert (2000) found subtle deficits in a similar task, the Wisconsin Card Sort Test, even in patients with

preserved intellect, similar to the sample here who did not display reduced IQ scores relative to the control group. Executive function tasks such as these have been associated with dysfunction in the frontal lobes, notably in reduced perfusion in the dorso-lateral prefrontal cortex (Weinberger *et al.* 1988).

Goldberg *et al.* (1988) have also shown that schizophrenic patients exhibit poor performance on tasks that measure guided lexical search such as Verbal Fluency. Lezak (1995) has asserted that word generation according to letter is the more difficult of the two conditions for subjects who have difficulty developing efficient search strategies of their own. It is noteworthy, although difficult to explain, that controls and schizophrenics did not differ on this task but on the allegedly less demanding category condition. One possible explanation could be that the fluency deficits in this group of schizophrenic patients are due to a disorganisation or degradation of the semantic store, rather than retrieval dysfunction. If the deficit were one of guided search or retrieval, the schizophrenia group would be expected to demonstrate equal deficits on both letter (phonologic) and category (semantic) tasks. However, if there is a problem with the semantic store, the category condition which requires access to and search within a network would be more impaired than phonologic search, which requires only phonemic or lexical cues to guide word production. Gourovitch *et al.* (1996) investigated the nature of fluency deficits in schizophrenia patients and found that although the schizophrenics were impaired on both phonologic and semantic fluency compared to normal controls, they demonstrated particular difficulty in the semantic category, producing the opposite pattern of results to that of the control group who consistently generated

more words in the category than the letter condition. They concluded that schizophrenia may be associated with a breakdown of semantic information processing beyond "executive" search and retrieval, and that this is suggestive of dysfunction of the frontal and temporoparietal areas of the brain. These findings are in line with those of the present study. As predicted, the schizophrenic group generated fewer words in total than the control group which is also in agreement with the Gourovitch *et al.* (1996) of impaired performance generally on this task.

This group of schizophrenia sufferers did not show impairment on the Hayling Sentence Completion Test apart from a slower time to complete the unconnected condition compared to controls. The lack of errors may be considered to be at odds with errors on the Brixton task, as it could be considered that if executive function generally is impaired, one may expect to see the most stereotyped or simplest reactions in response to surface cues in the environment, regardless of whether they are incorrect for the task at hand. However, these results suggest that the inhibitory aspects of executive function may be relatively unimpaired in this group, taking longer as they do to complete the more demanding condition but doing so successfully. This would tend to agree with Crowe's (1998) assertion that executive dysfunction in schizophrenia related more to the diminution of drive and direction rather than disinhibition, consistent with a compromised dorso-lateral prefrontal cortex. However, it may be that in this group of reasonably high-functioning individuals, the task is simply not sufficiently sensitive to pick up on dysfunctions of this type.

Generally, the findings for this sample of schizophrenic patients tend to support the findings of Buchsbaum (1990) of widespread neuropsychological dysfunction rather than of Weinberger *et al.* (1986) who proposed more selective executive function deficits. Neuropsychological tests are imperfect in localising deficits neuroanatomically but the pattern of impairments found in this study support the proposal of Gold *et al* (1992b) that neural systems associated with frontal and temporal lobes in schizophrenia are compromised.

Performance on cognitive testing did not correlate with measures of symptom severity, years of illness or medication, supporting previous findings of Goldberg *et al.* (1993a) who found that treatment with neuroleptics led to improvement in psychotic symptomatology without a corresponding improvement in cognitive function. This would suggest that neuropsychological impairments are relatively independent of psychotic symptoms and medication and are likely to be central and enduring features of the disease process.

9.3 Cognitive changes in unipolar affective disorder

The performance of the unipolar disorder group was not significantly different to that of the control group apart from a measure of basic initiation speed, Hayling Sentence Completion Test sensible completion. This suggests a deficit in psychomotor speed and is most likely to be a state-dependent deficit, correlating as it does with the Beck Depression Inventory score. Although memory and executive function deficits have been widely documented in unipolar affective

disorder as highlighted by Austin *et al.* (2001), there is little evidence for persistent deficits outwith periods of acute illness in unipolar depression, and what evidence there is tends to suggest that persistent deficits are found more in elderly patients with depression. Indeed Grant *et al.* (2001) concluded from a study investigating cognitive impairment in a large sample of unmedicated, nonbipolar, nonchronic younger adults that major depressive disorder in healthy younger outpatients does not cause appreciable impairments in cognitive functioning, findings supported by the present study.

Significant negative correlations between verbal memory and age of onset of depression is somewhat unexpected, suggesting as it does that an earlier age of onset produces better performance. This may be explained by the fact that much of the unipolar affective disorder group was made up of young people, with early onset but short duration of illness.

9.4 Cognitive changes in bipolar affective disorder

The findings of this study of persistent cognitive deficits in remitted bipolar disorder support recent findings of impaired cognitive function in euthymic patients who have recurrent bipolar affective disorder (Tham *et al.* 1998; van Gorp 1998; Ferrier *et al.* 1999). The bipolar group was significantly impaired on measures of verbal learning and recall compared to controls, in keeping with a study by Cavanagh *et al.* (2002) who reported deficits in immediate recall, global verbal learning, and short and long delay recall in a case-control study of euthymic

bipolar patients. These deficits were remarkably similar to those observed in the schizophrenia sample in this study, suggesting an acquisition difficulty, but no particular difficulties in storage of the to-be-remembered information, evidenced by the equivalence of short and long delay recall scores, even though these were poor compared to the controls' performance. Cavanagh *et al.* also found deficits in verbal recognition on the California Verbal Learning Test and this was not found in the present study. The performance on the recognition aspects of the California Verbal Learning Test suggest that this group of bipolar patients may have deficits in accessing the stored material, and perhaps in generating search and retrieval strategies. However, deficits in verbal recognition were observed on the Doors and People subtest Names, along with visual recognition as illustrated by deficits in the Doors and People subtest Doors. The pattern of deficits observed in the memory tasks in this study do not support older notions of a selective right hemisphere dysfunction in bipolar disorder (Goodwin and Jamison 1990), as complex verbal learning and memory functions are clearly impaired in this patient group. It may be that the recognition tasks in the Doors and People test are simply sufficiently sensitive to detect deficits in these domains, whereas the corresponding recall tasks are not. Quraishi and Frangou (2002) concluded that the evidence for a non-verbal memory deficit in bipolar patients in remission is rather contradictory and appears to be dependent on the tests employed in its investigation.

Deficits in executive function were less pronounced in the bipolar group than in the schizophrenia group, although slower performance on both trials of the Hayling Sentence Completion Test would indicate impairment of basic initiation speed.

However, the bipolar group did not differ from controls on the number of errors made, so patients were able to suppress incorrect responses, again performing in a similar fashion to that of the schizophrenia sample. The bipolar group did not appear to be impaired on the Brixton test relative to controls, which would suggest that this group of patients does not suffer from the reactive inflexibility seen in the schizophrenia group. However, it may be that with a larger sample, such deficits may have been apparent. Executive function deficits are not a universal finding in remitted bipolar disorder. The deficits observed by Rubinsztein *et al.* (2000) in a relatively small sample of stringently defined remitted bipolar patients, including a relatively specific memory impairment with some recovery of function on executive tasks, were similar to those described here.

The bipolar patients were impaired on aspects on Verbal Fluency, to a certain extent supporting previous findings from Ferrier *et al.* (1999) and also interestingly showing a similar pattern of deficits to the schizophrenia group in that they had more difficulty in generating words in the category as opposed to the letter condition, which again may suggest disorganisation of the semantic store rather than simple search and retrieval difficulties. However, Ferrier *et al.* suggested that residual impairments in bipolar affective disorder were specific to executive function, a suggestion not supported by the findings of this study. On the other hand, Clark *et al.* (2002) found intact performance in executive function tasks in euthymic bipolar disorder patients, instead finding deficits in sustained attention. One must be wary, however, of interpreting the pattern of impairments due to the overlap between cognitive functions assessed by different neuropsychological

tests. Executive function by definition involves the deployment and regulation of other cognitive functions, so specific tests rely on other functions being intact. Similarly, performance on neuropsychological tests generally relies on executive function to a greater or lesser degree. Indeed, conscious remembering (recall and recognition memory) engages some attentional resources, as some cognitive effort is required to recognised or recall specific items as being 'remembered'.

The similarity of deficits between the bipolar affective disorder and schizophrenic groups supports previous studies that fail to distinguish between these two types of patient groups. Hoff *et al.* (1990) showed that deficits in verbal, spatial and speed variables were not specific to schizophrenia but were also measured in patients with mania. Krabbendam *et* al. (2000) found that outpatients with bipolar disorder in remission had a similar pattern of impairments when directly compared with a schizophrenia group, one of the few studies to do so, including deficits in memory, speed of information processing and cognitive flexibility, although impairments in the bipolar group were generally less severe than those observed in the schizophrenia group. The schizophrenia and bipolar groups in this study were not really differentiated by the measures used apart from increased executive dysfunction in the schizophrenia group. This would suggest schizophrenia and bipolar affective disorder share many features and may involve similar dysfunctions. Nasrallah (1991) has argued that bipolar disorder is characterised by structural brain changes similar to those in schizophrenia, which in both disorders may have a neurodevelopmental origin.

Performance on cognitive measures did not significantly correlate with measures of symptom severity or years of illness. Although symptom severity scores were not statistically controlled for in this study, the mean scores are very low.

Previous studies of residual cognitive deficits in bipolar disorder have been criticised for failing to measure depressive or manic symptomatology and thus subclinical psychopathology may partially account for these persistent deficits (Murphy and Sahakian 2001). However, Rubensztein *et al.* (2000) conducted a study notable for its rigorous recruitment of asymptomatic patients with bipolar disorder and found deficits in tests of visuospatial recognition memory and relatively spared executive functioning, concluding that bipolar disorder is characterised by a trait abnormality in temporal lobe functioning.

The clear differences in performance of the unipolar and bipolar affective disorder groups suggests that depression is a heterogeneous condition and the distinction between unipolar and bipolar disorder may have a sound biological basis. However, some cases of unipolar depression may be part of the bipolar spectrum and this is well-illustrated in the study of the extended bipolar kindred (Family 22). "Bipolar spectrum" is a term used to define a subgroup of patients with unipolar depression who are likely to develop bipolar disorder (i.e. to have a manic episode) at some future stage in their illness. Patients classified as "bipolar spectrum" include 1) those with first or second degree relatives with bipolar illness, 2) unipolar patients who have brief (less than four days) episodes of hypomanic symptoms or these symptoms only in response to antidepressant medication. By

definition all patients with unipolar depression in Family 22 belong in the category "bipolar spectrum" and these did show impaired cognitions.

9.5 Effects of medication on cognitive performance

There is some debate in the literature as to the strength of any effect medication may have on cognitive performance. Lithium was the main area of concern in this study as large numbers of patients were maintained on it. Some studies have demonstrated cognitive impairment as a result of medication (Kocsis *et al.* 1993) whereas others have found no such impairment. Engelsmann *et al.* (1988) followed up a cohort of patients treated with lithium over a six-year period and found a stable cognitive performance among the sample. This is supported by the present study, finding no statistically significant differences between patients treated with lithium and those not.

9.6 Cognitive changes in Family 22 haplotype carriers

The results of this study support the hypothesis that family members who carry the haplotype linked to illness and are thus identified as being at very high risk of developing bipolar illness show cognitive deficits similar to those observed in the bipolar patient group. In practically all the measures showing differences between the bipolar and control groups the "high risk" Family 22 group showed significant differences or trends towards significance. The analysis of the family data when partitioned into affected and unaffected haplotype carriers shows that the unaffected group had the same range of deficits as those with symptoms. Importantly, no differences were observed in a direct comparison of the affected and unaffected haplotype carriers. This suggests that neuropsychological impairment may be a useful approach to studying the genetic basis of affective disorders and the segregation of illness in families. Cognitive changes could be termed "endophenotypes" in bipolar disorder. Almasy and Blangero (2001) have commented that the term "endophenotype" seems to be used only in the field of psychiatric genetics and is used to mean a trait that is hopefully more directly connected to the underlying neuropathology than the clinical symptoms. In order to be considered an endophenotype, the trait should be correlated with disease but not due to medication or degeneration due to the disease process. Furthermore, unaffected relatives of an affected individual should show a similar, but perhaps milder, profile. As Almasy and Blangero (2001) state, the next step is to validate these endophenotypes and their relationship to psychiatric illness by studying them in affected individuals and their relatives, as is the case in the present study. Once

the relationship between the endophenotype and the psychiatric illness is established, the next step is to attempt to localise the genes influencing the endophenotype and hopefully then to identify biological pathways involved in producing risk for developing psychiatric illness. Psychiatric diagnoses rely almost entirely on symptoms reported by the patient and therefore have limited reliability. An ideal endophenotype is an objective, biologically based marker for a disease such as bipolar disorder in the same way as blood glucose measurement detects diabetes.

Leboyer *et al.* (1998) remarked that the early enthusiasm for molecular genetic contributions to the understanding of psychiatric illness had waned somewhat when attempts to replicate linkage for major psychiatric disorders such as schizophrenia and bipolar disorder met with mixed success. This slow progress may be partly because advances in the technology of molecular biology and genetic epidemiology have not been matched by progress in accurate, reliable and valid phenotypic description. Psychiatrists rely on clinical symptoms and diagnostic schemes that have no clear biological validity. Leboyer *et al.* (1998) therefore posed the question: do modern definitions of clinical syndromes (phenotypes) accurately reflect underlying genetic substrates (genotypes)? The answer they came up with was no and one example is the lack of complete concordance for bipolar disorder in monozygotic twins. In this case cognitive impairment is a better way to diagnose illness than reliance on symptoms alone because a study by Gourovitch *et al.* (1999) of monozygotic twins discordant for bipolar disorder found deficits in verbal memory in the unaffected co-twins as well

as the bipolar probands. Neuropsychological impairment may make it possible to distinguish high and low risk relatives of bipolar individuals. The identification of phenotypes in unaffected relatives who carry vulnerability genes may be useful in identifying common alleles with non-specific and moderate effects on disease risk. It is clear that understanding the genetic basis of psychiatric illness requires accurate description of the inherited phenotype. This study was designed to determine whether or not "high risk" but asymptomatic relatives in Family 22 had cognitive deficits similar to those found in bipolar disorder. In other words, can neuropsychological impairment be considered a possible endophenotype for bipolar disorder? At this stage, the endophenotype would then be useful in attempts to localise the gene(s) implicated in bipolar affective disorder, rather than in specifically predicting which family members would go on to develop the disorder. To be valuable in bipolar research it is not essential that an endophenotype can be used in place of symptoms to reach a diagnosis. The data from this study show for the first time that totally asymptomatic high risk individuals have cognitive deficits and these are endophenotypes that deserve further investigation, as they are likely to generate new hypotheses about the pathogenesis of affective disorders. As there is overlap of results with controls, the cognitive test results from this study will not be useful "diagnostic" markers to distinguish cases from controls. For that one would need to identify a biological variable where the difference between cases and controls is much greater.

Phenotypes in bipolar disorder have been less studied than they have been in schizophrenia where neurophysiological and neuropsychological tests are well

established (Blackwood 2001). The findings of this study supported the report by Gourovitch *et al.* (1999) in showing that unaffected high risk relatives of bipolar patients performed worse than controls on measures of verbal learning and memory and word generation. This suggests that in bipolar disorder, some cognitive deficits are related to symptoms or course of illness, but deficits in verbal leaning and memory are independent of symptoms and may have a genetic basis.

9.7 Conclusions

The results of this study show that performance on cognitive tests differentiates between controls and unipolar depressed patients on the one hand and schizophrenic and bipolar affective disorder patients on the other. These changes were not due to age, sex, IQ, symptomatology at time of testing or medication. The results suggest that the relationship between schizophrenia and bipolar disorder may be closer than that between bipolar and unipolar affective disorders. The findings also agree with Ferrier and Thompson (2002) who suggest that the cognitive profile of bipolar disorder is characterised by deficits in memory, executive function or a combination of the two. The interpretation of these results must remain somewhat speculative, but they are in keeping with an impairment of the neuroanatomical connections between the prefrontal cortex and temporo-limbic circuit and the family "high risk" study suggests the cause has a genetic basis.

This work investigated cognitive abilities on neuropsychological tasks using neutral materials. The exclusion of material emotionally relevant to bipolar

affective disorder means that the possible relationship between mood and cognition in bipolar affective could not be investigated. Further work would benefit from incorporating affective material into the experimental design.

The fact that both affected and unaffected haplotype carriers from Family 22 were differentiated from the control group in measures of verbal learning and memory suggests that mild deficits in these domains may be a biological marker of risk for at least one genetic form of bipolar disorder. The finding that bipolar patients experience continuing problems with memory and to some extent executive function, and that a similar, although milder, deficits can be observed in "high risk" relative suggests that an approach utilising neuropsychological performance an as endophenotype may be useful for future genetic studies investigating the aetiology of this disorder, similar to the approach used in schizophrenia. Ferrier and Thompson (2002), in reviewing recent findings in bipolar disorder, state that cognitive dysfunction in bipolar disorder represents an important marker for future neurobiological and pharmacological research. More research should address the question of whether early diagnosis and treatment could reduce the cognitive dysfunction associated with the illness. Although unique, the family size in this study was relatively small and future work should be extended to investigate neuropsychological function in other large families multiply affected with major mental illness linked to a genetic marker in order to establish to replicability and applicability of these findings. A further interesting area of research would be to combine neuroimaging with cognitive assessment in families to establish whether

the cognitive deficits are associated with brain structural or functional abnormalities.

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APPENDICES

Appendix 1

Numbers of schizophrenic, bipolar and unipolar patients and Family 22 members taking antidepressant, antipsychotic, mood stabilising and sedative medication

	Schizophrenic patients	Bipolar patients	Unipolar patients	Family 22 members
Antidepressants	9	10	37	4
Antipsychotics	21	15	6	0
Anticonvulsants	1	2	0	0
Lithium	1	14	4	1
Sedatives	3	2	6	0
No medication	4	7	3	11