GENETIC DISSECTION OF THE MOOD-PSYCHOSIS INTERFACE

By

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Abstract

Since Kraepelin first dichotomised the functional psychoses into dementia praecox and manic-depressive insanity at the end of the 19th century, the validity of the distinction has been challenged. Phenomenological, neurobiological, family, and molecular-genetic studies suggest that there is no neat biological distinction between these entities which are now known as schizophrenia and bipolar disorder.

The aim of this thesis was to explore the familial correlation of clinical measures within a large harmonised clinical dataset comprising samples of (a) families enriched for bipolar disorder, and (b) families enriched for schizophrenia. Analyses were performed across traditional diagnostic boundaries.

I carried out systematic clinical ratings on 835 individuals previously collected as part of ongoing molecular genetic studies. After an intensive training period, which included reliability exercises, I rated each case on approximately 200 variables, including a new set of rating scales developed as part of the PhD project.

I performed mixed-effects regression analysis on the data to estimate the intra-class correlation coefficient (ICC) and significance for each variable. After controlling for sample-of-origin and gender, thirty-one variables were significantly correlated within families. Amongst the most significant were age at onset (ICC=0.287, p=0.0006), longest admission (ICC=0.287, p=0.0006) and cannabis abuse/dependence (ICC=0.639, p=0.0007). Such variables may be influenced by genetic factors and may therefore be used to identify subgroups of patients more likely to share common underlying genetic susceptibilities.

In an analysis of a subset of sibling-pairs that were enriched for schizoaffective disorder I found that genetic similarity at chromosome 1q42 was significantly associated with phenotypic similarity for the most severe depressive episode.

I also undertook clinical ratings on a sample of previously-collected patients with Velo-Cardio-Facial Syndrome (VCFS) and found high-rates of both mood-disturbance and psychosis.

My findings show that clinical ratings can be a useful adjunct to categorical diagnoses and identify specific phenotypes to consider in genetic studies.

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1 Introduction

1.1 Thesis Overview

The main aim of this thesis was to undertake a large number of systematic clinical ratings in a dataset comprising families enriched for psychotic and affective disorders. Analyses could then be performed across traditional diagnostic boundaries to identify clinical items which were significantly clustered within families and which were therefore more likely to be influenced by genetic factors. These clinical variables may be useful in refining the phenotype in future molecular genetic studies of these debilitating illnesses.

1.2 Literature Search

A systematic literature search was performed on topics relevant to this thesis (discussed below) using the online databases Embase (1980-2008), Ovid MEDLINE (1950-2008) and Ovid OLDMEDLINE (1948-1965). Searches were restricted to English-language journals. Literature searches were performed on a regular basis from October 2004 until September 2008. A list of search-terms included can be found in Appendix T. In addition I included any papers brought to my attention by my supervisor and by other members of the research team.

1.3 The functional psychoses: Major mood and psychotic disorders of adulthood.

The group of severe mood and psychotic disorders of adulthood are divided into two categories, the organic psychoses and the functional psychoses. In the former the psychiatric symptoms are judged to be due to a general medical condition. In the latter, the term "functional" is somewhat misleading as it implies that their pathogenesis is primarily influenced by psychological factors. It is now recognised that the aetiological processes underlying these disorders are complex and multi-factorial, involving biological, psychological and social factors.

Since Emil Kraepelin's original suggestion (Kraepelin 1919; see below), and continuing in current diagnostic practice, the functional psychoses are divided into two broad categories: the affective psychoses, which include bipolar disorder; and the schizophrenic psychoses. This distinction is formalised within diagnostic classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSMIV; APA 2000a), the ICD-10 Classification of Mental and Behavioural Disorders (WHO 1993) and the Research Diagnostic Criteria (RDC; Spitzer et al. 1978). Although the work of this thesis is motivated by the substantial data that suggest that the functional psychoses do not divide neatly into two disease entities, much work has been conducted on this basis. It is, therefore, useful to consider briefly what types of illness are included within the diagnostic categories.

1.3.1 A brief introduction to schizophrenia

Schizophrenia is a debilitating illness typically characterised by positive symptoms such as delusions and hallucinations, negative features such as restricted affect and psychomotor retardation, and severe functional impairment (Murray et al,

2008b). Schizophrenia is traditionally associated with a chronic and deteriorating course; however recent studies suggest that although schizophrenia is a chronic illness, the majority of patients show some improvement over time (Rabinowitz et al. 2007).

Although estimates vary, a recent review (Tandon et al. 2008) estimates that the annual incidence of schizophrenia is approximately 15 cases per 100,000 individuals, the point prevalence is approximately 4.5 per population of 1,000, and the lifetime morbid risk of developing the disorder is approximately 0.7%.

Schizophrenia typically presents in late adolescence or early adulthood, although it can manifest at any time from early childhood to late adult life (Murray et al. 2008a). Early epidemiological studies demonstrated approximately equal rates of schizophrenia in men and women; however this may be because the broad concept of the illness used in the past resulted in the inclusion of a disproportionate number of women with mood disorders. A recent systematic review confirmed that the incidence of schizophrenia is higher amongst males than females, with a mean rate ratio of 1.4 (McGrath et al. 2004). Onset is typically earlier in males than in females; the mean age at first admission in the UK is approximately 22 for men and 27 for women (Castle and Murray 1991);(Kirkbride et al. 2006).

The first line of treatment in both acute and chronic schizophrenia is anti-psychotic medications which are often successful in treating both acute and chronic illness. Their introduction in the 1950s led to individuals with schizophrenia being treated as outpatients for the first time (Murray et al. 2008a). Today, anti-psychotic drugs (often second generation so-called "atypical antipsychotics") are frequently used alongside psychosocial interventions and psychological therapies to maximise the therapeutic response (Murray et al. 2008b).

It is well documented that the aetiology of schizophrenia is influenced by both genetic and environmental factors. A wealth of family, twin and adoption studies support the role of genes in schizophrenia pathogenesis (Gottesman 1991). Studies report that the children and siblings of individuals with a diagnosis of schizophrenia are approximately 10 times more likely than the general population to develop the illness themselves (Craddock et al. 2005). In a review of twin-studies of schizophrenia, Cardno & Gottesman (2000) report concordance rates of approximately 41-65% in monozygotic twins and 0-28% in dizygotic twins. These studies suggest that heritability is high and genes are responsible for approximately 80% of liability for the illness (Cardno et al. 1999). Studies are consistent with the existence of multiple susceptibility genes of small to moderate effect (McGuffin et al. 1995).

Environmental factors which have been reported to influence risk include antenatal factors (e.g. pre-natal malnutrition and maternal infection), obstetric and peri-natal complications, childhood trauma and adolescent cannabis-abuse, as well as factors such as immigration and urbanicity (Tandon et al. 2008). However the exact effects of these factors remain unclear and evidence suggests that no single environmental effect is sufficient or necessary to result in the manifestation of schizophrenia.

1.3.2 A brief introduction to bipolar disorder

Bipolar disorder (also known as manic-depression) is characterised by severe mood disturbance. To receive a diagnosis of bipolar I disorder (BPI), an individual must have had at least one episode of highly elated or irritable mood known as mania. Depressive episodes may also have occurred but are not necessary for a BPI

diagnosis. Bipolar II disorder (BPII) is characterised by episodes of less severe high mood, known as hypomania, which do not meet the criteria for a full manic episode, and which are accompanied by episodes of depression.

As reviewed in Goodwin & Jamison (2007), findings of recent studies suggest an overall lifetime prevalence of approximately 1% for BPI, although this rises to approximately 3.0%-8.3% if a broader bipolar spectrum is considered, which includes diagnoses such as BPII. Illness-onset tends to occur in early adulthood; Goodwin & Jamison (2007) pooled data from 15 studies examining age at onset, and derived a weighted-average onset of 22.2 years, with no significant difference between males and females. They also report roughly equal rates of bipolar disorder in males and females.

Bipolar disorder is associated with an episodic, remitting course. The majority of patients will experience multiple episodes of illness over their lifetime; for example, Tohen et al (1990) reported that in their sample of 75 patients with a diagnosis of bipolar disorder, only 28% remained in remission over the four year period in which they were followed up. Further studies suggest that the length of remission between episodes decreases as the number of episodes experienced increases (for example, Roy-Byrne et al. 1985), although results have not been consistent – for example, Angst & Sellaro (2000) found this to be true for the first few episodes, but not in later episodes. Long-term studies suggest that up to one-third of patients achieve full-remission and a similar proportion achieve complete functional recovery; approximately 20% of patients continue to experience chronic symptoms (Goodwin and Jamison 2007).

The treatment of bipolar disorder was revolutionised by the discovery of the mood-stabilising properties of lithium carbonate (first published by Cade, 1949)

which has been shown to be effective during all phases of bipolar illness and may be particularly effective in suicide-prevention (reviewed in Fountoulakis et al. 2007). Both first and second generation anti-psychotic medications are also widely prescribed for the treatment of acute mania. Anti-depressants are sometimes prescribed alongside mood-stabilisers for episodes of depression, although caution is advised due to their association with switching polarity and cycle-acceleration (Salvi et al. 2008). Psychological therapies are also recommended as an adjunct to medication and have been shown to be effective in helping to prevent relapse in patients with bipolar disorder (Scott et al. 2007).

Like schizophrenia, bipolar disorder aggregates within families, suggesting that genetic factors influence susceptibility to illness. This is supported by family, twin and adoption studies (for example, reviewed in Jones 2004), although most studies have considered fairly small samples. The two largest twin-studies published to date suggest a heritability of approximately 80% for bipolar disorder and studies suggest that inherited susceptibility to the disorder is most likely explained by multiple genes of small effect (for example, Berrettini 1998).

Environmental factors have not been studied as extensively in bipolar disorder as they have in schizophrenia; however there is some evidence to suggest that individuals who were abused during childhood or who suffered from early maternal loss are more likely to develop the disorder. Studies also suggest that stressful life-events may be responsible for triggering episodes of illness in some people, as well as sleep disturbance, alcohol, anti-depressant use, stressful life events and hormonal alterations which occur as a result of childbirth or the menopause (Leboyer and Henry 2005);(Goodwin and Jamison 2007).

As mentioned above, the dichotomisation of the functional psychoses into schizophrenia and bipolar disorder is based on the pioneering work of Emil Kraepelin in the late 19th and early 20th centuries. This is discussed below.

1.4 Classification and nosology of the functional psychoses: Kraepelin's dichotomy

1.4.1 Introduction to Kraepelin's Dichotomy

Emil Kraepelin (1856-1926) was a prominent German psychiatrist whose pioneering work on the classification of psychiatric disorders led to him being described as "the founder of modern scientific psychiatry, psychopharmacology and psychiatric genetics." (Eysenck et al. 1972). Pre-Kraepelin, the wide spectrum of illness manifestations described collectively as the "functional psychoses" were conceptualised in numerous complicated systems, for example; Guislain, 1833; Kahlbaum, 1882 (reviewed in Angst and Selloro 2000) none of which were widely accepted in the psychiatric community.

Kraepelin sought to create a classification system based on systematic observations of his patients. Whereas the majority of previous nosologists (with the notable exception of Kahlbaum, 1882) categorised patients according to the presence of specific symptoms, Kraepelin also took into account the family-history and illness-course of his patients. In this way he aimed to create a system that would facilitate accurate prognosis, successful treatment and ultimately illness-prevention (Angst 2002).

It was Kraepelin's work that led to the dichotomisation of the functional psychoses into two distinct entities: dementia praecox, characterised by a chronic and

deteriorating course; and manic-depressive insanity, characterised by remitting episodes of illness and a more favourable prognosis.

1.4.2 Operational Diagnostic Systems

The classification of psychiatric illness is an extremely important issue. Clinically the definition of boundaries between distinct disease entities or diagnoses allows judgements to be made regarding the best course of treatment and the likely prognosis of a patient, as well as enabling effective communication between health professionals.

In research, these diagnostic categories can be used to define groups which form the basis on which hypotheses can be made and tested. The introduction of operational diagnostic systems in the latter half of the twentieth century benefited the field of psychiatry by enhancing the reliability of diagnostic categories. In the US/UK diagnostic project, (Cooper et al. 1972) demonstrated that diagnoses made by trained interviewers, using structured interviews and diagnostic criteria were more reliable than those made by untrained clinicians making a diagnosis on the basis of a clinical interview.

Kraepelin's distinction between dementia praecox and manic-depressive insanity is enshrined today within operational diagnostic classification systems such as DSMIV (APA 2000b), the ICD10 (WHO 1993) and the RDC (Spitzer et al. 1978) under the diagnostic categories schizophrenia and bipolar disorder which are described above. These systems aimed to standardize psychiatric language and increase reliability, thus enhancing communication within the field.

The tables below summarise the diagnostic criteria for schizophrenia and bipolar disorder, under each of these three operational diagnostic systems.

In research studies of patient populations, data are usually gathered from a number of different sources including a structured lifetime psychiatric interview with the patient, information from informants, and written material such as hospital casenotes or referral letters. The standard diagnostic procedure used by researchers is known as the "best estimate approach" (Leckman et al. 1982). This involves multiple researchers reviewing all the available information for each patient and subsequently coming to a consensus diagnosis that they agree upon.

The introduction of operational diagnostic systems led to an improvement in diagnostic reliability, which is further facilitated in research by the use of the best estimate approach to diagnosing patients. However, with no definitive diagnostic test to confirm the presence or absence of specific disorders, the validity of these diagnostic categories remains unknown.

As described above, evidence from family, twin and adoption studies suggests that aetiologically schizophrenia and bipolar disorder are influenced by both genetic and environmental factors (Smoller and Finn 2003). The recent advances in molecular genetic techniques have provided researchers with a powerful tool with which to investigate the biological contributions to disease and potentially provide biological validation to disease categories. However, research in this area has not progressed as quickly as was originally anticipated and results have, to date, been inconclusive, with even the most promising findings failing to be consistently replicated.

	DSMIV	ICD10	RDC
Symptom Criteria	Two (or more) of the following have been present for a significant proportion of time over a one-month period: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, negative symptoms NB: Only one symptom is necessary if delusions are bizarre or if auditory hallucinations are present which talk in the third person or give a running commentary. **Impairment**: For a significant proportion of time since illness-onset, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or failure to achieve expected level of achievement if illness-onset is in childhood or adolescence).	At least one from list (1) or two from list (2) are experienced during an episode of psychotic illness lasting for at least one month: (1) Thought echo, insertion, withdrawal, or broadcasting; delusions of control, influence or passivity clearly referred to body or limb movements or sensations; delusional perception; running commentary voices; third person auditory hallucinations or other types of hallucinatory voices coming from some part of the body; persistent delusions of other kinds that are culturally inappropriate or completely impossible. (2) Persistent hallucinations which occur every day for at least one month, when accompanied by delusions without clear affective content, or when accompanied by consistent over-valued ideas; neologisms, breaks or interpolations in train of thought resulting in incoherence or irrelevant speech; catatonic behaviour; negative symptoms.	At least two of the following have been present during the active phase of illness: Thought broadcasting, insertion or withdrawal; delusions of being controlled (or influenced), other bizarre delusions or multiple delusions; somatic, grandiose, religious, or other delusions without persecutory or jealous content lasting at least one week; running commentary voices or two or more voices conversing with each other; non-affective verbal auditory hallucinations spoken to the subject; hallucinations of any type which last throughout the day for several days or intermittently for at least one month; definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganised behaviour.
Duration Criteria	Continuous signs of the disturbance persist for at least 6 months. This period must include at least 1 month of symptoms (less if successfully treated) that meet the Symptom Criteria listed above, and may include prodromal or residual symptoms which may be characterised by only negative symptoms or two or more symptoms present in an attenuated form.	At least one month.	Signs of illness have lasted at least 2 weeks from onset of a noticeable change in the subject's usual condition.
Exclusion Criteria	Schizoaffective disorder and mood disorder with psychotic features have been ruled out. Disturbance is not due to a general medical condition. If there is a history of autistic disorder or pervasive developmental disorder, the additional diagnosis of SZP is only made if prominent delusions or hallucinations are present for at least one month.	If patient also meets the criteria for a manic or depressive episode, the symptom criteria listed above must have been met *before* the disturbance in mood developed. Disorder is not attributable to organic brain disease, or to alcohol or drug-related intoxication, dependence or withdrawal.	At no time during the active period of illness being considered did the individual meet criteria for either probable or definite manic or depressive syndrome to such a degree that it was a prominent part of the illness. Symptoms only occur during periods of alcohol or drug-use or withdrawal from them.

Table 1-1: Comparison of diagnostic criteria for schizophrenia using DSM-IV (APA 1994); ICD-10 (WHO 1992); RDC (Spitzer et al. 1975)

	DSMIV	ICD10	RDC
Symptom Criteria	Two (or more) of the following have been present for a significant proportion of time over a one-month period: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, negative symptoms NB: Only one symptom is necessary if delusions are bizarre or if auditory hallucinations are present which talk in the third person or give a running commentary. **Impairment**: For a significant proportion of time since illness-onset, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or failure to achieve expected level of achievement if illness-onset is in childhood or adolescence).	At least one from list (1) or two from list (2) are experienced during an episode of psychotic illness lasting for at least one month: (1) Thought echo, insertion, withdrawal, or broadcasting; delusions of control, influence or passivity clearly referred to body or limb movements or sensations; delusional perception; running commentary voices; third person auditory hallucinations or other types of hallucinatory voices coming from some part of the body; persistent delusions of other kinds that are culturally inappropriate or completely impossible. (2) Persistent hallucinations which occur every day for at least one month, when accompanied by delusions without clear affective content, or when accompanied by consistent over-valued ideas; neologisms, breaks or interpolations in train of thought resulting in incoherence or irrelevant speech; catatonic behaviour; negative symptoms.	At least two of the following have been present during the active phase of illness: Thought broadcasting, insertion or withdrawal; delusions of being controlled (or influenced), other bizarre delusions or multiple delusions; somatic, grandiose, religious, or other delusions without persecutory or jealous content lasting at least one week; running commentary voices or two or more voices conversing with each other; non-affective verbal auditory hallucinations spoken to the subject; hallucinations of any type which last throughout the day for several days or intermittently for at least one month; definite instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganised behaviour.
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Exclusion Criteria	Schizoaffective disorder and mood disorder with psychotic features have been ruled out. Disturbance is not due to a general medical condition. If there is a history of autistic disorder or pervasive developmental disorder, the additional diagnosis of SZP is only made if prominent delusions or hallucinations are present for at least one month.	If patient also meets the criteria for a manic or depressive episode, the symptom criteria listed above must have been met *before* the disturbance in mood developed. Disorder is not attributable to organic brain disease, or to alcohol or drug-related intoxication, dependence or withdrawal.	At no time during the active period of illness being considered did the individual meet criteria for either probable or definite manic or depressive syndrome to such a degree that it was a prominent part of the illness. Symptoms only occur during periods of alcohol or drug-use or withdrawal from them.

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1.4.3 Challenging the dichotomy

The validity of Kraepelin's dichotomisation of the functional psychoses into the syndromes we know today as schizophrenia and bipolar disorder has received some support from a number of family studies. Several studies have shown increased risk of schizophrenia but not bipolar disorder in families of probands with typical schizophrenia, and increased risk of bipolar disorder but not schizophrenia in probands with typical bipolar disorder (Frangos et al. 1985; Gershon et al. 1982). This evidence, along with the conceptual simplicity of Kraepelin's dichotomy - which is in stark contrast to its numerous complicated and chaotic predecessors - is perhaps the main reason that the dichotomy has withstood the test of time.

However, despite its widespread acceptance in the field of psychiatry, the validity of Kraepelin's dichotomy was questioned almost from its point of conception, most notably by Kraepelin himself who, towards the end of his life, stated, "It is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation of the problem may be incorrect." (Kraepelin 1920). Kraepelin's doubts about the validity of his dichotomy have been supported by a growing body of research suggesting overlap between schizophrenia and bipolar disorder. In this introduction I have chosen to focus on the three areas most relevant to the themes of this PhD: overlapping clinical presentations, evidence from family studies and evidence from molecular genetic studies. These are discussed below.

i. Overlapping clinical presentations

Many clinical features overlap the traditional Kraepelinian divide, occurring commonly in both illnesses labelled as schizophrenic and those labelled as affective in nature, and it is widely recognised that there are no pathognomic indicators of either

diagnostic category. Schizophrenic patients often present with prominent symptoms of affective disturbance, whereas patients with affective disorder frequently present with psychotic features. For example, in their review of phenomenological studies focussing on the specificity of "schizophrenic" symptoms, Pope & Lipinski (1978) found that psychotic features were present in 20%-50% of patients with an acute manic episode. More recently, Coryell et al (2001) found that 90 out of the 139 (64.7%) manic patients in their study had psychotic features.

Schneider (1959) described a set of "first rank symptoms" of schizophrenia which included thought interference, thought echo, auditory hallucinations in the 3rd person, running commentary voices, delusions of passivity and primary delusional perception. Schneider proposed that, providing there was no evidence of coarse brain disease, any one of these symptoms was diagnostic of schizophrenia. These symptoms show high inter-rater reliability and have had considerable influence in the field of psychiatry; they are also incorporated within diagnostic systems such as those mentioned above. However, studies have shown that these are not uncommon in affective-disorder, for example, Tanenberg-Karant (1995) found that 29% of psychotic bipolar patients had first-rank symptoms at their first admission.

Symptoms of affective disturbance are also frequently reported in patients with schizophrenia. For example, in their study examining retrospective depressive symptoms in patients diagnosed with schizophrenia at their first admission, Hafner et al (2005) reported the lifetime prevalence of depressed mood (lasting at least 2 weeks) to be 83%. Additionally they found that 71% of patients presented with clinically significant depressive symptoms during their first psychotic episode (with 23% fulfilling ICD-10 criteria for a depressive episode).

The identification of mood symptoms in schizophrenic illness is made more

difficult by diagnostic-specific labels given to certain clinical features, i.e. symptoms which are similar in clinical presentation are sometimes labeled differently depending on whether they occur in schizophrenic or affective illness. For example, in a schizophrenic illness, symptoms such as poor motivation, poor energy, psychomotor retardation, anhedonia and restricted affect would be described as negative symptoms, which are thought to reflect a loss of normal functioning (as opposed to positive symptoms such as delusions and hallucinations which reflect an excess or distortion of functioning). However, the same clinical features experienced in a patient who does not have a typically schizophrenic illness are likely to be described as depressive symptoms. Similarly, symptoms such as incoherence and pressured speech are likely to be thought of as being indicative of positive formal thought disorder in schizophrenia and as symptoms characteristic of mania in affective illness. This is due to assumed-differences in the mechanisms underlying these clinical features, although there is little evidence to confirm that these differences are present in reality and this may well result in the under-reporting of affective-disturbance in schizophrenic illness.

In an attempt to demonstrate a dichotomy between schizophrenia and bipolar disorder patients, Brockington et al (1979) performed discriminant function analysis using 24 clinical variables covering phenotypic characteristics (e.g. family history, manic syndrome, schizophrenic psychotic symptoms, etc). They failed to find convincing evidence that the functional psychoses fall neatly into these two diagnostic categories.

This overlap in clinical presentation is best demonstrated by patients demonstrating prominent schizophrenic symptoms and prominent affective disturbance simultaneously, leading to diagnostic dilemmas. In fact, some of the first

criticisms of the dichotomy were based on the observation that many individuals did not fit easily into either diagnostic category.

In a study looking at 468 of Kraepelin's patients originally diagnosed with dementia praecox, Zendig (1909) found that 30% had a good prognosis, inconsistent with their original diagnoses (reviewed in Angst 2007). At the time, Zendig attributed this to mis-diagnosis, although later Kraepelin saw it as evidence of a weakness in his dichotomy, stating that, "The cases which are not classifiable are unfortunately very frequent."

The fact that Kraepelin's dichotomy failed to describe all cases of illness constituting the functional psychoses led to the development of a third diagnostic category, schizoaffective disorder (SAD). Some diagnostic traditions have also continued to recognise other specific diagnostic categories which have a particular mix of mood and psychotic features, including cycloid psychosis in Germany (Leonhard 1961) boufee delirante in France (Pichot 1986) and atypical psychosis in Japan (Mitsuda 1965).

The term schizoaffective was first proposed by Kasanin (1994) who described "acute schizoaffective psychosis", it could be used to categorise these "difficult-to-diagnose" patients who had prominent symptoms of both schizophrenia and affective disturbance. Since this time, researchers have debated whether schizoaffective disorder is a subtype of schizophrenia, a subtype of affective disorder, or an entity in its own right. Others have suggested that schizoaffective disorder does not exist at all and is merely a form of psychotic mood disorder (Lake and Hurwitz 2007a).

In clinical practise schizoaffective disorder has been a useful tool with which to diagnose difficult-to-classify patients, facilitating communication between medical

practitioners. However, no unequivocal definition of schizoaffective disorder exists, as demonstrated by the variations in diagnostic criteria between DSMIV, ICD10 and RDC (see chapter 3). Studies have also shown inter-rater reliability to be extremely low in diagnosing schizoaffective disorder; for example Maj et al (2000) reported a Cohen's kappa of 0.22 for the diagnosis of schizoaffective disorder, compared to 0.71 for a manic episode and 0.82 for a major depressive episode.

Studies have shown schizoaffective disorder to occupy an intermediate position between schizophrenia and affective disorder in terms of illness course, family morbidity, symptomatology and other clinical variables such as age at onset, comorbidity with substance abuse and response to drug treatment (reviewed in Cheniaux et al. 2008a). However, schizoaffective disorder is not clearly distinct from either schizophrenia or bipolar disorder and the boundaries between all three diagnostic entities are ambiguous.

In diagnostic systems, the difficulties caused by these overlaps are overcome due to the implementation of the diagnostic hierarchy (Spitzer and Williams 1990). This states that diagnoses "higher up" in the hierarchy take precedence over co-occurring diagnoses which are further down (illustrated in figure 1.1 below).

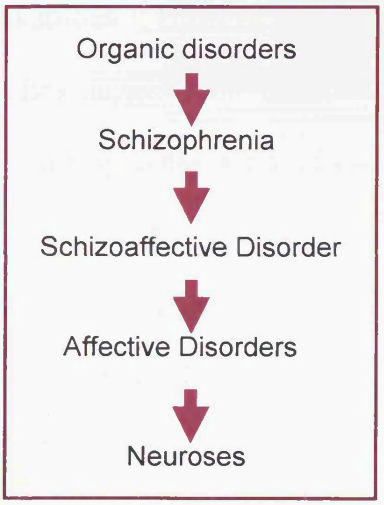

Figure 1-1: Representation of the diagnostic hierarchy in which higher-level diagnoses "trump" diagnoses further down the hierarchy (Foulds 1965).

This is enshrined within diagnostic criteria, for example an exclusion criteria for bipolar disorder states that the illness must not be better accounted for by "schizo-affective disorder, schizophrenia or other psychotic disorder". Therefore, if an individual had chronic schizophrenia but had also had a manic episode at some point during their illness, unless the mood symptoms were prominent enough to warrant a diagnosis of schizoaffective disorder, they would not be considered in the diagnosis.

The diagnostic hierarchy and the introduction of schizoaffective disorder have helped solve diagnostic-dilemmas and facilitated communication in the field of psychiatry. However the evidence for the clinical overlap which occurs between schizophrenia, schizoaffective disorder and bipolar disorder, along with the fact that no points of rarity have been identified between them, does not support the hypothesis that these separate diagnostic categories represent biologically distinct entities.

ii. Family studies

Family studies investigate how phenotypically similar genetically related individuals are for a specific trait or disease. If a disease is shown to aggregate within families, this suggests that shared genetic and/or environmental factors play an aetiological role. As stated above, both bipolar disorder and schizophrenia have been shown to "breed true" within families. However, these findings have not been consistent and other family-studies suggest that there is a non-trivial degree of familial co-aggregation between schizophrenia, schizoaffective disorder, and bipolar disorder.

One line of evidence supporting genetic overlap between diagnostic entities is the description of families in which multiple diagnoses are represented. For example, Pope & Yurgelun-Todd (1990) described two pedigrees in which schizophrenic individuals had first-degree relatives with bipolar disorder. Further, St Clair et al

(1990) described a large Scottish pedigree in which a chromosomal translocation co-segregated with a wide-spectrum of psychotic and affective illness, including schizophrenia, bipolar disorder and major recurrent depression.

McGuffin et al (1982) described a set of monozygotic triplets, two of whom met the Research Diagnostic Criteria (RDC) for schizophrenia, whilst the third met RDC criteria for bipolar disorder. This provides evidence in support of a genetic contribution to the functional psychoses in general, but against the hypothesis that schizophrenia and bipolar disorder are biologically distinct entities.

Recent research carried out on larger samples of patients has also found significant familial co-aggregation of these disorders. For example, Valles et al (2000) examined the prevalence of psychiatric disorders in an inpatient-sample of 103 patients with bipolar disorder and found that the morbid risk of both bipolar disorder (4.9%) and schizophrenia (2.8%) were higher in relatives of these patients compared with relatives of a control group of psychiatrically-well inpatients of a general hospital.

Similarly, Tsuang et al (1980) found elevated risk of both bipolar disorder and schizophrenia in relatives of probands with schizophrenia and relatives of probands with mania. Further, Kendler et al (1995) found increased risk of schizoaffective illness in relatives of probands with schizophrenic illness and probands with bipolar illness.

A limitation of the majority of previous research into the functional psychoses is that the majority of studies have been carried out under the assumptions of the diagnostic hierarchy, described above. If symptoms of affective disorder have occurred in schizophrenia, unless they are particularly prominent over the course of the illness they will be considered non-specific and not considered in analysis. Under

the alternative hypothesis that manic episodes which occur within the context of a schizophrenia diagnosis may be due to the existence of common risk factors, Cardno et al (2002) performed analysis unconstrained by the hierarchy, allowing a single individual to meet the criteria for more than one syndrome in their sample of monozygotic and same-sex dizygotic twin-pairs. They found evidence of both common and syndrome-specific genetic contributions to the schizophrenic and manic-syndrome.

Evidence from family studies suggests that there is a more complex relationship between the functional psychoses than is suggested by Kraepelin's dichotomy.

iii. Challenges from molecular genetic studies

Recent advances in molecular genetic techniques have provided researchers with a powerful tool with which to investigate genetic contributions to psychiatric illness. Family samples can be used to identify chromosomal regions likely to harbour susceptibility genes by investigating associations between variation in DNA markers covering the entire genome and the presence or absence of a specific trait/disease. This is known as linkage analysis. Genetic linkage is said to be present when the alleles of a marker and trait locus are observed to co-segregate within families. Because the location of the marker is known, the approximate location of the disease-gene can also be deduced.

Linkage analyses have been undertaken in samples of both schizophrenia and bipolar disorder families and numerous linkage regions have been identified for each disorder (for example, Ivleva et al. 2008; Lewis et al. 2003; Segurado et al. 2003). However, with the increasing number of linkage studies being undertaken, it soon

became apparent that several regions were being implicated in both disorders, suggesting that common genes within these regions may be involved in the susceptibility of both schizophrenia and bipolar disorder.

Overlapping regions identified include 13q, 22q, 18 and 6q (reviewed in Owen et al. 2007). However, results have not been consistent. For example, in the two meta-analyses performed on linkage analyses, Badner & Gershon (2002) found the most robustly replicated evidence for schizophrenia on 22q, 13q and 8p; and for 22q and 13q for bipolar disorder, suggesting that 22q and 13q are likely locations of common susceptibility genes. However, a second meta-analysis (Lewis et al. 2003) using a different technique found no significant linkage for bipolar disorder (although the strongest evidence was identified for 9p, 10q and 14q – (Segurado et al. 2003)), and evidence for genome-wide significant linkage in 12 regions in schizophrenia. Kelsoe (2007) suggests that the reason for the inconsistent findings in these two studies is most likely to be due to the large number of genes involved in the disorders and due to sampling effects.

Linkage regions have also been identified for intermediate phenotypes incorporating both features typically associated with affective illness and those typically associated with schizophrenia. For example Hamshere et al (2005) demonstrated genome-wide significant linkage at 1q42 and suggestive linkage at 22q11, in a sample of pedigrees enriched for schizoaffective disorder. These families were taken from two separate samples of patients, one enriched for bipolar disorder and the other enriched for schizophrenia. Analysis suggested that evidence for linkage was contributed from both samples equally.

The evidence from linkage analyses are consistent with the existence of common genes which are involved in susceptibility to both schizophrenia and bipolar

disorder. However, an alternative explanation for these overlapping regions is that they may contain both genes influencing susceptibility to schizophrenia and genes influencing susceptibility to bipolar disorder. A third possibility is that there is a gene within this region that influences susceptibility to a range of disorders or symptoms Evidence that the first explanation is the more probable in certain cases is provided by association studies, in which genetic variation in a sample of cases is compared with that in a sample of controls. These have succeeded in identifying genes which appear to influence susceptibility across the traditional Kraepelinian divide, including those summarised in Table 1-1 below. However, it must be noted that findings have been inconsistent and that negative, as well as positive, results have been reported for each of these genes.

Gene	Chromosome	Evidence in SZP	Evidence in BPD
COMT	22q	Li et al (1996)	Papolos et al (1998) – rapid cycling subtype
DISC1	1q	Blackwood et al (2001)	Hodgkinson et al (2004)
Dysbindin	6p	Straub et al (2002)	Kohn et al (2004-psychotic bipolar disorder)
DAOA	13q	Chumakov et al (2002)	Hattori et al (2003)
Neuregulin 1	8p	Stefansson et al (2002)	Thomson et al (2007)

Table 1-3: A summary of some of the overlapping susceptibility genes identified for schizophrenia and bipolar disorder

Evidence from molecular genetic studies suggests at least a partial overlap between genes involved in schizophrenia and those involved in bipolar disorder. Kelsoe (2007) proposes four possible models of genetic overlap to explain how common genes could result in different disorders: 1. Different mutations within the same gene might predispose to different disorders; 2. Common genes operate in both disorders and different environmental factors result in different disorders; 3. The same genes are involved in both, but different combinations of genes result in different

disorders; 4. Common genes are involved in both disorders and their effects add together along a single risk continuum – above a certain threshold results in bipolar disorder, above a higher threshold results in schizophrenia (this is known as the quantitative multiple threshold model).

Molecular genetic studies have provided researchers with an extremely powerful tool with which to investigate the genetic relationship between affective and psychotic disorders. This research, along with evidence produced from family, twin and adoption studies, supports the existence of overlapping genes. However, no overwhelmingly conclusive results have yet been produced.

1.4.4 Refining the phenotype

The majority of previous studies have been undertaken using samples of cases selected according to their lifetime diagnoses. However, as described above, studies have demonstrated that these diagnostic categories are highly heterogeneous and have many overlapping features. The identification of more phenotypically homogeneous subgroups, that may reflect underlying biological/genetic homogeneity, may facilitate molecular genetic studies in the future (e.g. by increasing power to detect linkage).

Such sub-groups can be identified by refining the phenotype, a process which aims to reduce clinical variability whilst maintaining or increasing heritability (or, in a more general sense, biological validity). Clinical variables that aggregate within families may be influenced genetically (although common environmental influences must also be considered) therefore familiality can be used with caution as a proxy for heritability. The identification of such variables is an important first step in the refinement of the phenotype, and has been the focus of numerous studies.

For example, O'Mahoney et al (2002) looked at a set of clinical variables in a sample of sibling-pairs with bipolar disorder. They found significant intra-pair correlations for age at onset, a dimensional score of psychosis and proportion of manic to depressive episodes, all of which remained significant after corrections were made for multiple testing. They also found significant intra-pair correlations for mania, a dimensional measure of incongruence, and frequency of manic and depressive episodes, although these did not remain significant after correcting for multiple comparisons.

In a family-based sample of individuals with bipolar disorder, Schulze et al (2006a) investigated the familiality of 40 diverse phenotypic variables. They found that substance abuse, alcoholism, psychosis, history of attempted suicide and level of social functioning were all highly familial. They also found suggestive evidence for familiality of age at onset and co-morbid panic disorder.

Numerous other studies have been undertaken to help identify other such variables which aggregate within families with bipolar disorder; these findings are summarised in table 1-2 below and represent phenotypic features which are likely to help reduce heterogeneity in future molecular genetic studies.

Similar studies have been undertaken in samples of schizophrenia families. For example Kendler et al (1997) examined the familiality of clinical variables within a sample of 457 sibling pairs with schizophrenia. They found significant intra-pair correlations for global course, outcome, depressive symptoms, manic symptoms, positive and negative thought disorder, affective deterioration, catatonic symptoms and delusions.

Further variables which have been shown to aggregate within families affected by schizophrenia are summarised in Table 1-3 below.

Clinical variables showing familiality in bipolar disorder samples
Age of onset [a,c,f]
Lifetime ever occurrence of mood-incongruent psychotic symptoms [c,g]
Lifetime ever occurrence of psychotic symptoms [c,f,j]
Severity of mania [c]
Rapid cycling [j]
Rapid mood switching [j]
Lifetime presence of panic disorder [f,h,j]
Lifetime occurrence of puerperal psychosis [i]
Alcohol abuse [b,j]
Episode frequency [c,d]
Polarity at onset of illness [e]
Substance abuse [f]
Suicide attempt [f]
Suicidal thoughts [j]
Level of social functioning [f]
Marital status [f]

Table 1-4: Clinical variables showing intra-familial aggregation in bipolar disorder.
a. Leboyer et al (1998); b. Potash et al (2000); c. O'Mahony et al (2002); d. Fisfalen et al (2005); e. Kassem et al (2006); f. Schulze et al (2006b); g. Goes et al (2007); h. MacKinnon et al (2002); i. Jones & Craddock (2001); j. Saunders et al (2008).

Clinical variable showing familiality in schizophrenia samples
Age of onset [a,d]
Negative symptom dimension [a,h]
Disorganisation dimension [a,e,i]
Depressive symptoms [c,j]
Manic symptoms [c]
Lifetime course of illness [c, k]
Outcome [c, k]
Anhedonia [f]
Positive formal thought disorder [c]
Negative formal thought disorder [c]
Catatonic symptoms [c,d]
Auditory hallucinations [b]
Visual hallucinations [j]
Hallucinations [c]
Delusions [c]
First rank symptoms [c]
Reality distortion factor [a]
Delusional proneness [f]

Table 1-5: Clinical variables showing intra-familial aggregation in schizophrenia.

a. Burke et al (1996); b. Choi et al (2007); c. Kendler et al (1997) ; d. Tsuang et al (1967); e. Loftus et al (1998); f. Schurhoff et al (2003a); g. Ristner et al (2005); h. Peralta & Cuesta (2007b); i. Cardno et al (1999); j. DeLisi et al (1987); k. Blueler (1978).

As described above, the ultimate aim of studies attempting to identify clinical variables which cluster within families is to inform sample-selection in molecular genetic studies. This is based on the theory that such variables are more likely to have a distinct genetic basis. The implementation of clinical variables showing familiality in molecular genetic studies has already demonstrated promising results.

For example, as presented in Table 1-2, a number of studies have identified psychotic symptoms to aggregate within families in samples of bipolar patients. Based on the hypothesis that patients with psychotic bipolar disorder may represent a genetically distinct subgroup, Potash et al (2003) performed linkage analysis in a sample of bipolar disorder patients who were labelled as "affected" only if they had a psychotic mood disorder. They detected two linkage regions, 13q and 22q, both of which had been previously implicated in schizophrenia and bipolar disorder.

Park et al (2004) also classed the bipolar cases in their sample according to the presence or absence of psychotic symptoms. They found evidence for significant linkage at 9p31 and 8p21, regions that had not previously been implicated in bipolar disorder but which had been implicated in schizophrenia (for example, reviewed in Baron 2001). They also found suggestive evidence for linkage on 9 further regions including 13q32.

In an attempt to detect loci which influence women's susceptibility to episodes of illness after childbirth, Jones et al (2007) performed a genome-wide linkage scan in a sub-sample of 35 bipolar disorder pedigrees enriched for puerperal psychosis. They found genome-wide significant linkage on 16p13 and suggestive linkage at 8p24;

neither region had been implicated in their original sample of pedigrees with bipolar disorder.

As stated above, one clinical feature that has been shown to aggregate within families affected by schizophrenia is the occurrence of depressive features (DeLisi et al. 1987; Kendler et al. 1997). This prompted Hamshere et al (2006) to include the presence or absence of depression as a covariate within their genome-wide linkage scan in a sample of schizophrenia pedigrees. They detected a genome-wide significant linkage signal on chromosome 4q28 (LOD=4.59 representing a significantly higher linkage peak than that found in their univariate analysis). They also report suggestive evidence for linkage on 20q11.21.

As stated above, these results may be interpreted as support for genetically distinct subgroups of patients with specific phenotypic presentations. Alternatively, there may be genes within these regions that increase risk across a broad range of symptoms that cut across traditional diagnostic boundaries.

Association studies also provide evidence that "refined" phenotypes can facilitate the detection of genes increasing susceptibility across the Kraepelinian divide. For example, D-amino-acid-oxidase activator (DAOA, formerly known as G72) is involved in modulating glutamate signalling by activating D-amino-acid oxidase. It is often referred to as DAOA/G30 due to the fact that it overlaps with the gene G30; the two are transcribed on opposite DNA strands. DAOA/G30 was originally implicated in schizophrenia susceptibility (Chumakov et al. 2002) and has since been reported as showing association in studies of bipolar disorder (Craddock et al. 2005; DePaulo 2004). Williams et al (2006) undertook a large systematic study of polymorphisms across the DAOA/G30 locus in a large well-characterised sample of schizophrenia and bipolar disorder cases. They found evidence for association in the

bipolar disorder sample but failed to detect such evidence in the schizophrenia sample. However, including only the schizophrenia patients who had experienced at least one episode of mood disturbance in the analysis, they found that their results were similar to those produced for the bipolar disorder sample.

Neuregulin 1 (NRG1) has previously been implicated in both schizophrenia (for example, Stefansson et al. 2002) and bipolar disorder (for example, Thomson et al. 2007). Green et al (2005a) performed case-control analysis on a sample of patients with bipolar disorder and a sample with schizophrenia and found similar effect sizes in both. However, they found a greater effect size in bipolar patients who had experienced mood-incongruent psychotic symptoms and in schizophrenic patients who had experienced manic features, suggesting that NRG1 may exert a specific influence on cases characterised by a mixture of psychotic and affective features. This is consistent with the linkage study by Hamshere et al (2005, described earlier) that suggests a relatively specific genetic contribution to schizoaffective illness.

The studies summarised above provide evidence for the existence of genes which influence susceptibility to psychiatric illness across the traditional boundaries imposed by diagnostic classification systems. The identification of such genes should help to increase our understanding of the relationship between mood disturbance and psychosis and about the biological and environmental processes involved in the pathogenesis of these debilitating conditions.

1.5 Measurement of psychopathology

As stated above, molecular genetic studies are likely to be facilitated by the identification of areas of the phenotype which aggregate within families. These may

be identified using statistical techniques; however, the use of such methods first requires the areas of the phenotype to be measured, i.e. they must be defined and described precisely in a way that allows them to be utilised in the necessary statistical analyses.

The introduction of operational definitions of psychiatric disorders led to the development of numerous structured and semi-structured standardised interviews, in which questions relating to each criterion can be asked. The aim of standardised interviews is to ensure that each individual is presented with exactly the same questions in a standard way, thus providing a, "comprehensive, accurate and technically specifiable means of describing and classifying phenomena in order to make comparisons" (WHO 1992). Such interviews include a standard, detailed definition for each symptom and guide questions can be added or modified in order to determine whether or not each symptom is present.

One such interview is the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), which is designed as "a set of schedules for the assessment, measurement and classification of psychopathology and behaviour associated with adult psychiatric disorders" (Wing et al. 1990). SCAN is a semi-structured interview based on the Present State Examination (Wing et al. 1974). It was designed for use within clinical populations and covers domains such as mania, depression, anxiety and alcohol and substance abuse.

A major advantage of SCAN is its glossary which contains detailed definitions of the symptoms and signs which are rated as part of the interview. Questions relating to each symptom are asked in order to determine both their presence and also their degree of severity. In this way a detailed and reliable picture of the clinical illness

can be established. This can be used alongside other sources of information to make clinical ratings which further describe the data.

The literature contains numerous descriptions of different rating scales and categorical approaches which can be used to measure various aspects of the clinical phenotype in patients with severe psychiatric illness. For example, the Operational Criteria (OPCRIT) (McGuffin et al. 1991), a symptom checklist designed to be used along with a computer program to generate diagnoses; the Bipolar Affective Disorder Dimension Scales (BADDS) (Craddock et al. 2004a) and the Global Assessment Scale (GAS) (Endicott et al. 1976) – these are all described in detail in Chapter 2. The value of such measures can be defined in terms of their reliability and validity (reviewed in Farmer et al. 2002).

Reliability analyses can be used to test the consistency of the measure. A measure which has good reliability will result in the same outcome/rating when used under the same circumstances. There are several ways to test reliability. Inter-rater reliability can be tested when two or more individuals examine the same information and make ratings on the measure independently. The degree of agreement between the two can be assessed. Other types of reliability include test-retest reliability, in which the same measure is used on the same information at two different time points; and intra-rater reliability in which the same measure is used on the same information by the same individual at two different time points – the consistency of the ratings can subsequently be assessed.

It is essential that measures selected for use in research show high levels of reliability. Unreliable measures will introduce varying degrees of random variation which are likely to make it substantially more difficult to detect significant effects.

In general, a reliable measure will be well-constructed, the instructions for their application must be explicit, and there needs to be clear guidance regarding the differences between ratings (Wittenborn, 1972, cited in Farmer et al. 2002). Although there is no absolute cut-off point above which reliability is considered acceptable, it is generally accepted that to be considered reliable a measure should produce a reliability coefficient of about 0.8.

There are a number of statistical tests which can be used to assess reliability; the nature of the data determines the test used. For example, Cohen's Kappa is often used to report inter-rater reliability statistics for dichotomous variables. The test is thought to be more useful than simply reporting percentage-agreement, because it also takes into account agreement that is likely to occur by chance (Cohen 1960).

For continuous data, intra-class correlations can be used to measure the level of agreement for a particular variable between two members within a group (e.g. two siblings within a larger family-based sample). In this method, the mean and standard deviation of the measure are calculated from the pooled data, across all members of the group. The intra-class correlation gives the proportion of variance that is attributable to between-group differences (Hinton 2004).

Validity refers to whether or not the measure succeeds in assessing the psychopathological construct it intends to. A number of terms are used to describe the different aspects of validity, such as face validity (does the measure appear to assess the construct of interest?), content validity (does the measure provide good coverage of the relevant domain(s)?), predictive validity (does the measure agree with a "gold standard" of accuracy?) and construct validity (does the measure correlate with external validators?).

For a test to be valid it must be reliable. However, it is possible for a test to be reliable but not valid, for example even though a measure gives consistent ratings, these ratings may not be measuring the target variable. In psychiatric research, some evidence for construct validity of a measure is suggested by the aggregation of scores on the measure within families, as this suggests that the measure may relate to underlying biological variability.

Robins & Guze (1970) proposed five criteria which, if fulfilled, indicate validity: clear and consistent clinical features; uniform aetiology or pathogenesis; uniform clinical course; increased prevalence in close relatives; an investigatory marker of the disorder, such as a laboratory test. Their emphasis on the role of family history in validating diagnostic groups is particularly relevant to the focus of this thesis, which aims to use clinical measures to identify variables which aggregate within families.

1.6 Summary

Emil Kraepelin's dichotomisation of the functional psychoses into the clinical entities today known as schizophrenia and bipolar disorder has had substantial influence over the field of psychiatry for over a century, due to the clinical utility and reliability of these diagnoses, and their tendency to "breed true" within families.

However, the evidence summarised above suggests that there is no neat biological distinction between the two, and that using diagnostic categories alone in the selection of cases for use in molecular genetics studies is likely to obscure biologically meaningful findings.

Research studies focussing on the discovery of phenotypic variables which aggregate within families, and which are therefore more likely to be genetically

influenced, will facilitate the definition of subgroups of patients more likely to reflect underlying genetic homogeneity.

When used in molecular genetic studies, such groups should help facilitate the identification of genetic pathways involved in the pathogenesis of these debilitating illnesses, and provide clues about the underlying biology which will help researchers develop new treatments to act specifically on the known biological pathways involved in illness.

This highlights the need for large family-based samples in which the phenotype is well characterised. Such samples would enable analyses to be performed on a wide-spectrum of phenotypic characteristics, with the aim of identifying areas of the phenotype that are familial and therefore more likely to be influenced by genetic factors.

1.7 Thesis Aims

The aim of this thesis was to contribute to this area of research by identifying clinical items that show familial aggregation in families affected by mood-psychosis illness and which may, therefore, be useful as covariates in genetic studies. This was achieved by:

1. Developing a set of tools which could be used across the Kraepelinian dichotomy in patients with psychotic features and/or affective disturbance. Existing phenotypic measures were utilised along with a novel set of measures which were developed specifically for this purpose.

2. Using these measures to make new ratings and investigate the phenotype within a sample of patients with Velo-Cardio-Facial Syndrome (VCFS) and within a family-sample enriched for schizoaffective disorder.

3. Using these measures to make new ratings within a sample of families enriched for bipolar disorder and within an independent sample of families enriched for schizophrenia.

4. Combining the samples to form a single large, well-characterised dataset comprising cases representing a spectrum of affective and psychotic illness.

5. Performing mixed-effects regression analysis within this dataset to investigate which clinical items showed familial aggregation.

2 General Methods: Detailed Characterisation of the Phenotype

As discussed in chapter one, studies have consistently demonstrated clinical overlap between schizophrenia and bipolar disorder, the diagnostic categories based on Kraepelin's dichotomisation of the functional psychoses. Despite this, the majority of studies into the causes of these debilitating illnesses have been carried out under the assumptions of the dichotomy. Previous research has demonstrated that using clinical measures alongside diagnostic categories can be useful in refining molecular genetic studies. To identify the clinical variables most likely to be useful in such studies, analyses can be performed to identify which of these aggregate within families, and are therefore more likely to be influenced by genetic factors. The identification of such variables was the primary focus of this thesis, and this could not be undertaken without first carrying out systematic ratings within the samples of interest. This enabled the formation of a large, richly described sample in which analyses could be undertaken. The methods involved in this process are discussed below.

2.1 Samples

This thesis focussed on three samples of interest: a sample of patients with Velo-Cardio-Facial Syndrome (VCFS) and a major psychiatric diagnosis; a sample of sibling-pairs enriched for schizoaffective disorder-bipolar type, recently used within a genome-wide linkage study by Hamshere et al (2005); a large dataset formed by combining the large schizophrenia and bipolar disorder family-based samples,

recruited within the Department of Psychological Medicine, Cardiff University, as a result of ongoing molecular genetic studies. The two former samples are discussed in detail in chapters 2 and 5 of this thesis. The schizophrenia and bipolar disorder samples used to form the dataset which was used in the primary analyses of this thesis (described in chapter 5) are described below.

2.1.1 Description of the schizophrenia family sample

The Schizophrenia family sample comprised 196 sibling-pairs from 154 nuclear-families. It was originally described by Williams et al (1999) as part of a two-stage genome scan for schizophrenia susceptibility genes, in a study led by Professor Mike Owen and Professor Peter McGuffin. Families were ascertained through mental health services and mental health support groups in Wales, England, Scotland and Southern Ireland. The sample consisted of 216 males and 111 females, all of whom were Caucasian and had been born in the UK or in the Republic of Ireland. Each family was composed of a proband who met DSM-IV (APA 1994) criteria for schizophrenia, along with at least one sibling with a DSMIV-diagnosis of either schizophrenia or schizoaffective disorder. Where possible information was also collected on further affected family members.

Each individual was interviewed using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990) a semi-structured interview aimed at assessing, measuring and classifying psychopathology and behaviour associated with psychiatric illness. Each interview was conducted by a member of the Schizophrenia Research Team, including trained psychologists (Dr Lisa Jones and Dr Rob Sanders) and trained psychiatrists (Dr Alistair Cardno, Dr Marion Gray, Dr Geraldine McCarthy and Professor Kieran Murphy). Case notes were reviewed and a vignette was compiled from the clinical data available.

Clinical ratings were also made by the interviewer using several rating scales including the Operational Criteria (OPCRIT) (McGuffin et al. 1991), the Scales for Assessment of Positive and Negative Symptoms (SAPS/SANS) (Andreasen 1984a, 1984b) and the Global Assessment Scale (GAS) (Endicott et al. 1976).

During the recruitment process, regular reliability meetings were held in which cases were discussed and each case was diagnosed according to best estimate procedures (as described in chapter 1).

2.1.2 Description of the Bipolar-Disorder Family Sample

The Bipolar-Disorder family sample consisted of 395 sibling-pairs from 286 nuclear-families, ascertained as part of the Wellcome Trust UK-Irish bipolar affective disorder sibling-pair genome screen, in a study led by Professor Nick Craddock and Professor Michael Gill (Bennett et al. 2002b; Lambert et al. 2005b). Patients were recruited through mental health services, patient support groups and articles in the national media. The sample consisted of 402 males and 587 females and all but three families were of European Caucasian origin. Again, where possible, information was collected on further affected family members.

Each family consisted of a proband who met DSMIV criteria for bipolar I disorder (BPI) and at least one sibling with either BPI, schizoaffective disorder – bipolar type (SABP), bipolar II disorder (BPII) or bipolar disorder – not otherwise specified (BP-NOS).

Data for each case was collected using similar methods to those used in the schizophrenia sample. Each individual was interviewed by a fully trained member of the Bipolar Disorder Research Team, again using the SCAN (Wing et al. 1990). Case

notes were reviewed and a vignette was compiled from the clinical data available. Again, regular reliability meetings were held during the recruitment process, and diagnoses for each case were agreed upon using the best estimate method (see chapter 1).

Both the schizophrenia and the bipolar disorder samples were collected prior to the commencement of this PhD and have been used extensively within the department as part of numerous published molecular genetic studies (Green et al. 2005a; Green et al. 2006; Williams et al. 2006) and clinical studies (Forty et al. 2008; Jones et al. 2005).

Typical data for each case included:

- An interview vignette summarising the information collected as a result of interviewing each patient using the SCAN.
- Copies of hospital case-notes or a case-note vignette summarising this information.
- Copies of referral letters.

In the majority of cases an Operational Criteria (OPCRIT) symptom checklist had been completed (described below), and in the schizophrenia sample ratings had been made on the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS).

2.2 The Creation of a Single Harmonised Dataset

The research described in this thesis aimed to perform analyses across traditional diagnostic boundaries, and this could be achieved by combining the schizophrenia and bipolar disorder family-based samples, described above. The strengths and limitations of this method are discussed in Chapter 5.

However, although similar information was collected for both samples, using similar methodologies, it was not possible to simply combine them. Despite the use of detailed rating guidelines and the demonstration of acceptable levels of reliability, clinical rating scales involve an element of subjectivity. When used by different research teams, who may adopt slightly different approaches to the ratings, it is possible that systematic differences may occur, superimposed over noise introduced as a result of the subjective nature of these ratings.

To ensure that the schizophrenia and bipolar disorder samples were compatible, it was important to develop a common set of phenotype measures covering a wide range of clinical characteristics which showed variability across diagnostic boundaries. These could then be used to rate each case within the samples, using identical techniques and well-defined methods. The schizophrenia and bipolar disorder samples could then be combined to form a single large harmonised dataset.

2.3 Developing a Common Set of Phenotype Measures

In selecting a set of phenotype measures that could be used across the samples there were several factors to be taken into consideration. It was important to cover a wide range of clinical variables thus providing a rich description of each case. My

study built upon the measures that had been used extensively by the Mood Disorders Research Team over a period of more than 10 years. A set of detailed rating guidelines had been developed, ensuring ease of use and excellent reliability. These established tools of measurement used to record clinical details on each case are described in Part I below.

2.4 Measuring the Phenotype Part I – Established Tools of Measurement

For all measures previously used within the team, a set of detailed rating guidelines had been developed. These ensured ease of use and excellent reliability.

Prior to rating any cases that would be used in analysis, I undertook a rigorous training period. This was particularly important given that I had received no clinical training prior to the commencement of this PhD. This issue is discussed further in Chapter 5.

Initially my training period involved observing interviews carried out by trained members of the research team in order to gain a better understanding of how information was collected from participants. During this early stage I also read a large number of case notes and interview vignettes from the schizophrenia and bipolar disorder samples, in order to increase my knowledge of these illnesses particularly in terms of the type and range of symptoms experienced. This also gave me the opportunity to learn about symptom definitions and classifications.

The second stage of my training period involved rating a large number of cases (approximately 150) on these established measures and discussing these in detail with experienced members of the research team. I also attended regular

meetings in which a case that had been rated independently by members of the research team was discussed in detail, and consensus ratings were agreed upon for each measure. Attending these meetings during the year prior to the rating of these large datasets enabled me to develop a level of expertise.

Ratings were made on more than 200 clinical variables for each case contributing to the large harmonised dataset. Previously described rating-scales used as part of this thesis are described below. A full list of these along with the additional variables recorded for each case can be found in Appendix A.

2.5 Rating Scales Used

2.5.1 The Global Assessment Scale

The Global Assessment Scale (Endicott et al. 1976) was developed to measure the overall severity of psychiatric disturbance over a specific time period (usually the week prior to evaluation). The GAS was based on the Health-Sickness Rating Scale, originally developed by Luborksy in 1971, and sought to improve it by adding further anchor points which described more behaviourally-orientated systems, and by abolishing the diagnostic constraints described in the original scale.

The GAS is a 1-100 scale ranging from severe impairment to superior functioning. A score of 1 would be given to the hypothetically sickest individual whilst a score of 100 would be used to describe the hypothetically healthiest (see Appendix B).

The scale consists of ten clearly defined anchor points (1-10, 11-20, etc). A rating is made by selecting the lowest interval at which an individual's functioning can be described during the time-period specified. The rater must then decide where this individual lies within this range, by considering the descriptions of the intervals below and above that selected, and deciding whether one description describes their level of impairment more closely than the other.

The authors report good levels of inter-rater reliability, with intra-class correlation coefficients ranging from 0.69 to 0.91 and standard error measurements of between 5 and 6.

Since it was derived the GAS has been used extensively in research. Pillmann & Marneros (2005) carried out a study comparing the long-term course of individuals with acute and transient psychotic disorders and a control group of individuals with positive schizophrenia, using the GAS to measure level of functioning at three time-points, covering a period of seven years following the index episode. They found a significant difference between the GAS scores of the two groups at the third follow up; scores in the positive schizophrenia sample significantly decreased, whereas scores in the acute and transient psychotic group remained unchanged.

The GAS is also frequently used to assess treatment efficacy. For example, using GAS scores to measure level of functioning, Temple & Ho (2005) used the GAS to compare the level of functioning in schizophrenic patients who had received cognitive therapy for persistent psychosis, with a "treatment-as-usual" group, who had received no such therapy. They found significantly greater improvement in patients receiving the cognitive therapy as an adjunct to their regular treatment.

In the current research, the GAS was used to record the lowest level of functioning during the following periods: i) during the most severe episode of mania, ii) during the most severe episode of depression, iii) during the most severe psychotic episode, iv) during the most severe post-natal episode, v) during the most severe non-post-natal episode, vi) during the most severe episode overall, vii) during the week prior to interview. A score of 1-100 was assigned to each period, where applicable. In the vast majority of cases, only a subset of the above periods were rated, the remainder being recorded as either "Unknown" (where there was insufficient information to make a confident rating) or "Not Applicable" (where an individual had not experienced the state being rated).

2.5.2 Operational Criteria

The Operational Criteria (OPCRIT) were originally designed by McGuffin et al. (1991) as a diagnostic system consisting of a checklist of items of psychopathology and background information (defined by a brief glossary, see Appendix C) along with a suite of computer programs able to use this data to generate diagnoses according to multiple diagnostic systems (e.g. ICD-10, RDC).

The original paper reported good reliability in general with the majority of kappa scores ranging from 0.4-1.0 for items of psychopathology rated, and ranging from 0.57-0.87 for diagnoses generated. Craddock et al (1996) utilised the OPCRIT on a sample of 100 cases – 50 individuals from families enriched for bipolar disorder and 50 from families enriched for schizophrenia. They compared the diagnoses generated via the OPCRIT system with those made according to lifetime best-estimate consensus procedures (described in chapter 1). Good to excellent agreement between

the two different methods was generated, with Cohen's kappa statistics ranging from 0.67-0.97, providing support for the validity of the scale on samples of patients with bipolar and schizophrenic illness.

As well as using symptomatic data to produce multiple diagnoses, many studies have used OPCRIT simply to record the presence or absence of specific items of psychopathology during periods of illness. For example, Schulze et al (2005) carried out genotype-phenotype analysis looking at association between the DAOA/G30 locus (previously implicated in both schizophrenia and bipolar disorder) and psychotic features in a sample of bipolar affective disorder patients. They collected information on 21 psychotic symptoms using the OPCRIT checklist and performed logistic regression analysis, entering these symptoms into the model as explanatory variables. This analysis identified "lifetime history of persecutory delusions" as the only significant explanatory variable for the DAOA/G30 risk genotype, suggesting that bipolar disorder with persecutory delusions may be a distinct subgroup of bipolar disorder which overlaps with schizophrenia.

One limitation of the OPCRIT symptom definitions is that they are not independent of diagnostic concepts – the traditional assumptions regarding the dichotomisation of the affective disorders and schizophrenia are enshrined within the rating guidelines (as discussed by Craddock et al. 2007). For example, symptoms typically associated with affective disorder (such as anhedonia, irritability, impaired concentration, psychomotor retardation/agitation) are only rated if they are experienced within the context of an episode of disturbed mood. This meant that if, during a psychotic episode, an individual experienced several symptoms indicative of mood disturbance, but not enough to constitute an episode, these symptoms would not

have been recorded. Similarly, certain features rated in the Psychosis section of OPCRIT, would only have been rated positively if they occurred outside of a mood episode, due to assumptions made about the underlying causes. For example, "speech difficult to understand" and "inappropriate affect" would not have been rated positively if they occurred within the context of a manic episode as it was assumed that the underlying mechanisms involved in the manifestation of these symptoms during mania were different than those involved when mood was considered euthymic.

The aim of the current research was to examine the phenotype without being constrained by such assumptions. Therefore, as well as recording symptoms which occurred during affective episodes, I also completed "context-independent" ratings, i.e. if a symptom described met the OPCRIT glossary-defined definition, it was recorded independently of whether or not it was experienced during an episode of mania, depression, or euthymia. So, for example, if an individual was dysphoric during a psychotic episode but did not meet the criteria for a depressive episode, whereas in the past this symptom would have been ignored, using this method it was recorded as present, therefore providing a richer description of the phenotype.

2.5.3 Bipolar Affective Disorder Dimension Scales

Inspired by the limitations of diagnostic categories in defining illness, the Bipolar Affective Disorder Dimension Scales (BADDS) (Craddock et al. 2004b) use a dimensional approach to provide a rich description of psychopathology in the functional psychoses.

These scales were developed by the research teams in the Department of Psychological Medicine in Cardiff University and the Department of Psychiatry in the University of Birmingham, as part of the ongoing collaboration between these two centres. Although published in 2004, these scales had been extensively used within the research teams for over 5 years prior to their publication.

The BADDS comprise four 0-100 scales which pick up on the lifetime-ever occurrence of mood disturbance, psychosis, and the relationship between psychotic symptoms and mood (see Appendix D). The dimensions are defined as follows:

BADDS Mania (BADDSM) – Rated according to the presence, severity and frequency of manic symptoms or episodes ranging from no evidence of mania to many incapacitating episodes.

BADDS Depression (BADDSD) – Rated according to the presence, severity and frequency of depressive symptoms or episodes, ranging from no evidence of depression to many incapacitating episodes.

BADDS Psychosis (BADDSP) – Rated according to the presence and predominance of psychotic disturbance throughout the illness, ranging from no psychotic or near-psychotic features, through to prominent psychotic symptoms present throughout the illness.

BADDS Incongruence (BADDSI) – Defines the relationship between psychotic and affective disturbance and is only rated in individuals who have experienced psychosis at some point during the illness. The bottom of the scale reflects an illness in which psychotic symptoms have been experienced only in the context of an affective-episode and are completely congruent with mood state (for example,

delusions of grandiosity in the context of mania); scores at the top of the scale reflect an illness characterised by prominent psychotic symptoms which occur chronically outside, or in the absence of, mood disturbance.

Each scale is rated according to a set of clearly defined anchor-points which enable excellent inter-rater reliability. Craddock et al (2004b) report mean agreements of between 0.86 (for the Psychosis dimension) and 0.96 (for the mania dimension). Further, on a sample of "diagnostically challenging" cases, they report intra-class correlations of 0.91 for the mania dimension, 0.80 for the depression dimension, 0.96 for the psychosis dimension and 0.78 for the incongruence dimension.

The BADDS have been used widely both within the department and externally and have been important in a number of studies which provide further support for the advantages of using a richer description of lifetime psychopathology in both molecular genetic studies and studies of familiality. For example, in their study investigating the role of Neuregulin 1 (NRG1), traditionally considered to be a schizophrenia susceptibility gene, in bipolar disorder Green et al (2005b) found a greater effect in the bipolar cases with predominantly mood-incongruent psychotic features and in the schizophrenia cases with mania (both measured using BADDS), than in either the full schizophrenia family sample or the full bipolar disorder sample. This suggested that NRG1 may exert a specific effect on a subset of functional psychosis which includes features of mania and mood-incongruent psychosis.

2.6 Measuring the Phenotype Part II – Developing new ways in which to measure the phenotype in the functional psychoses.

A primary aim of this thesis was to make optimal use of the vast amount of information available in the family-samples described above, with the intention of identifying features of illness that cluster within families. Established tools of measurement, such as those described above, provide a useful way of describing the phenotype, reflecting the high degree of heterogeneity which occurs within diagnostic categories. The value of including this extra information in analysis is supported by a growing body of research, as discussed in chapter 1.

During my training period I rated a large number of cases using the established measures described above (approximately N=200). During this time it became apparent that there were several features of illness which occurred commonly within the samples but were not picked up on by the rating scales and measures already in use. I therefore became involved in designing a new set of measures, known as the Extended Rating Scales, developed to pick up on this extra detail.

2.7 Designing the Extended Rating Scales

These scales were developed as a result of an interactive and iterative process involving myself and Professor Nick Craddock. Scale definitions were agreed upon after detailed discussion. We focussed on clinical features of illness that varied across samples involving mood disturbance and/or psychotic features, appeared to be potentially important in distinguishing between cases, and were not picked up on adequately by established measures.

After scale definitions had been agreed upon, I developed an initial draft of the new scales. Scales were each discussed during regular meetings between myself and Professor Craddock. Drafts were refined according to issues arising from these discussions. When a detailed first complete-draft of the scales was complete, it was distributed amongst members of the Mood Disorders Research Team for comment, along with several practise vignettes which were rated and subsequently discussed in several Joint Field Team Meetings. Modifications were subsequently made to improve reliability and ease of utility. This work resulted in 9 new clinical rating scales, summarised below. Full rating guidelines for each scale can be found in Appendix E.

2.7.1 Extended Rating Scale 1: Predominance of manic episodes

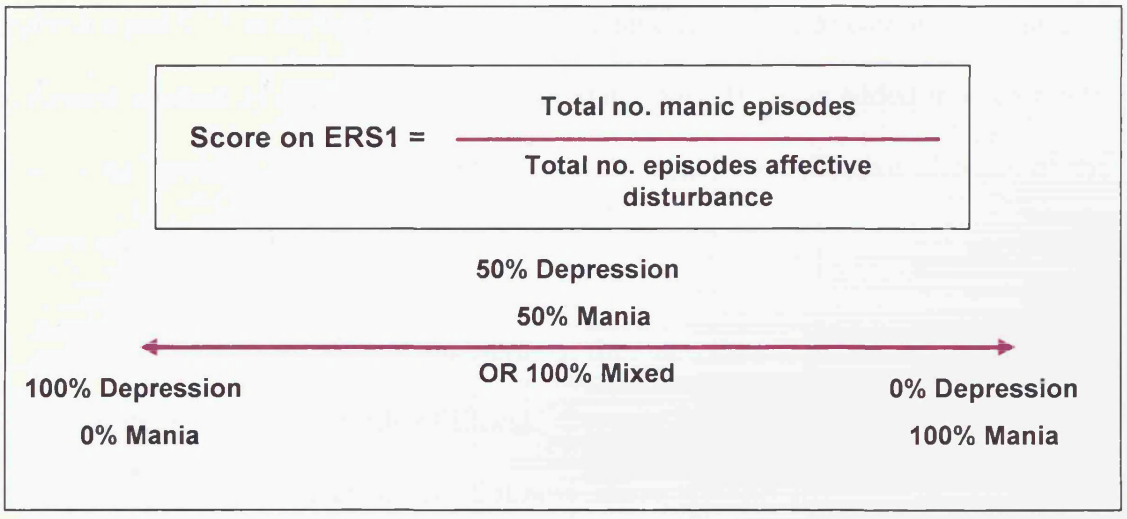

Figure 2-1: Summary of rating guidelines for ERS1: predominance of mixed affective episodes

The aim of Extended Rating Scale 1 (ERS1) was to measure the proportion of high mood relative to the total mood disturbance over the lifetime course of the illness. ERS1 is a 0-100 scale, with a score of "100" indicating a clinical picture in which affective disturbance was characterised entirely by mania, without the occurrence of mixed or depressive episodes. Conversely, a score of "0" indicates that

no manic episodes have occurred and that the occurrence of affective disturbance is entirely mixed or depressive in nature. If an individual has experienced no affective episodes, they should not be scored on ERS1.

As demonstrated in Figure 2-1, an individual's score on ERS1 is calculated by dividing the total number of manic episodes experienced over the entire duration of illness, by the total number of affective episodes (manic and depressive in nature) experienced over the lifetime duration, and multiplying this value by 100. Mixed episodes were treated differently according to whether they were predominantly manic in nature, e.g. dysphoric mania (in which case 0.75 was added to the total number of manic episodes and 0.25 to the total number of depressive episodes), predominantly depressive in nature (0.25 was added to the total number of manic episodes and 0.75 to the total number of depressive episodes), or comprised a roughly balanced mixture of depressive and manic symptoms (0.5 was added to each total). The scale therefore gave a measure of to what extent the affective element of the illness was characterised by high mood.

One limitation of this measure is the fact that it relies on the detailed documentation of each episode of illness. Because individuals are less likely to seek treatment during milder episodes of illness, these are less likely to be recorded in case-notes. Mild episodes of depression in particular are at risk of being excluded from the calculation. However, in general participants were asked in detail about the number and nature of episodes of mood disturbance they had experienced over the lifetime course of their illness at interview (see Chapter 6).

This scale was developed under the hypothesis that variation in the predominance of high mood relative to depressed mood corresponds with underlying genetic variation.

2.7.2 *Extended Rating Scale 2: Relationship between psychotic and affective features*

Score	Rating Criteria
-20	Episodes of clinically significant mood disturbance. No psychotic or near psychotic features occur
-19	Illness is predominantly affective but includes near psychotic features - occasional at low end of range, frequent at high end of range
0	Psychotic symptoms occur only during affective episodes and are entirely mood-congruent
20	Psychotic symptoms occur only during affective episodes. There is an approx. balance between congruent and incongruent symptoms
40	Psychotic symptoms occur only during affective episodes and are entirely mood-incongruent
43/47	Psychotic symptoms occur only during affective episodes and include one or more first rank symptoms
50	Psychotic symptoms are probably present outside of an episode of mood-disturbance
60	Psychotic symptoms are definitely present in the absence of an affective episode on at least one occasion
80	Psychotic symptoms are definitely present in the absence of an affective episode on many occasions
100	Psychotic symptoms dominate illness and occur chronically outside affective episodes. Affective episodes occur but are not a major feature of illness.
110	Psychotic symptoms dominate illness. Affective symptoms occur which do not meet criteria for an episode of mood-disturbance.
120	Illness is characterised by psychotic features in the absence of any disturbance in mood.

Table 2-1: Summary of rating guidelines for ERS2, which measures the relationship between affective and psychotic symptoms over the lifetime course of the illness.

As an extended version of the BADDS Incongruence dimension (BADDSI, see above), Extended Rating Scale 2 (ERS2) measures the relationship between affective and psychotic symptoms over the lifetime course of the illness. The BADDS Incongruence Dimension is a 0-100 scale, which can be used on any individual who has experienced psychotic symptoms, with or without symptoms or episodes of affective disturbance. A score of "0" on the BADDSI dimension indicates that, psychotic symptoms have occurred only during affective episodes, did not

include "first rank" symptoms (Schneider 1959)(see chapter 1) and were entirely congruent with the affective state in which they were experienced (such as grandiose delusions in the context of mania). A score of 100 indicates that psychotic features have dominated the clinical features and have occurred chronically outside of, or in the absence of, any episodes of affective disturbance. Ratings on the BADDSI dimension can therefore be used only on individuals who have experienced clear-cut psychotic symptoms, and it does not differentiate between those who have a predominantly psychotic illness but have also experienced minor symptoms of mood disturbance and those who have not experienced any symptoms indicative of mood disturbance.

ERS2 therefore extends the bottom end of the scale from "0" to "-20" - which can be used to describe an illness characterised entirely by episodes of mood disturbance, with no psychotic or near psychotic features. Scores between -19 and -2 can be used to indicate the increasing frequency of near-psychotic features (as defined by DSMIV, which includes features such as odd beliefs, magical thinking that influences behaviour and is inconsistent with sub-cultural norms, unusual perceptual experiences, suspiciousness or paranoid ideation, etc). At the opposite extreme, the top end of the scale has been extended from "100" to "120", with scores between 101 and 120 indicating increasing confidence that no symptoms indicative of mood disturbance have been experienced during the lifetime course of the illness.

Scores within the range 0-100 remain identical to those in the BADDS Incongruence dimension, with intermediate scores increasing firstly with the increasing incongruence of psychotic features, and then with the simultaneous

decreasing prominence of affective features and increasing prominence of psychotic features.

ERS2 was developed under the hypothesis that variability in the predominance of psychotic and affective features, and the relationship between these two symptom domains reflects underlying genetic variability.

2.7.3 Extended Rating Scale 3: Fluctuations in mood.

Score	Rating Criteria
100	Fluctuations in mood occur over 1 day
90	Fluctuations in mood occur over 4 days
80	Fluctuations in mood occur over 1 week
70	Fluctuations in mood occur over 10 days
60	Fluctuations in mood occur over 2 weeks
50	Fluctuations in mood occur over 4 weeks
40	Fluctuations in mood occur over 8 weeks
30	Fluctuations in mood occur over 12 weeks
20	Fluctuations in mood occur over 26 weeks
10	Fluctuations in mood occur over 52 weeks
0	No fluctuations in mood occur

Table 2-2: Summary of rating guidelines for ERS3 which measures the rapidity of mood

The aim of Extended Rating Scale 3 (ERS3) was to indicate the presence and rapidity of mood fluctuations within periods of affective disturbance. Scores on ERS3 were calculated by measuring the shortest time-period over which a fluctuation had occurred. In the case of ERS3, "fluctuation" refers to an acute phase of illness in which at least two switches in mood polarity (e.g. from depression to mania to depression, or vice versa) have occurred, with fewer than 8 weeks separating episodes. Ratings are then assigned according to the guidelines summarised in Table 2.2.

For example, Figure 2.2 below illustrates an illness in which an individual has experienced a manic episode, followed by an episode of major depression, which has

then switched to hypomania, before more minor depressed mood is experienced. In this example, the shortest period of time over which mood has fluctuated from one state, to another, and then back again is 2 weeks; this would be assigned a score of "60" on ERS3.

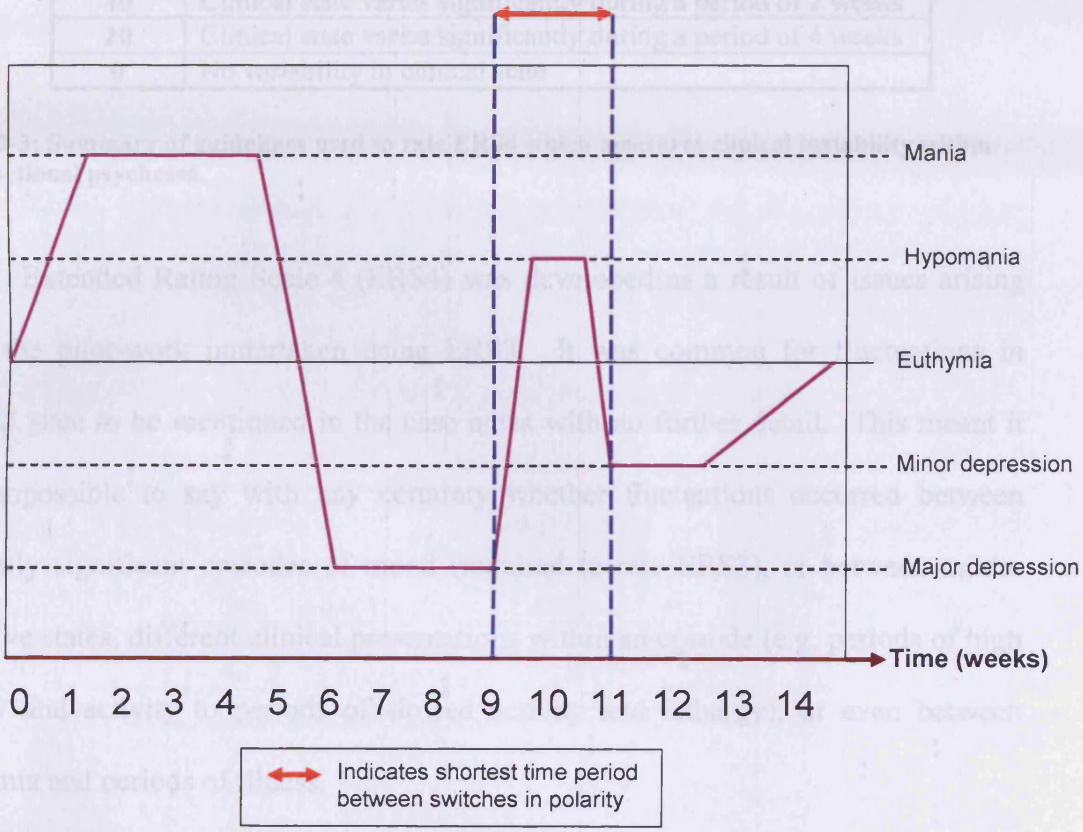

Figure 2-2: Example to demonstrate how fluctuations in mood are measured using ERS3.

To be considered when calculating an individual's score on this scale, the episode of mood disturbance must meet the DSMIV criteria for a manic, mixed or depressive episode.

ERS3 was developed under the hypothesis that variability in the occurrence and rapidity of fluctuating mood represents underlying genetic variability.

2.7.4 *Extended Rating Scale 4: Instability of clinical state*

Score	Rating Criteria (refers to most variable month of illness)
100	Clinical state varies significantly during a period of 10 mins
80	Clinical state varies significantly during a period of 1 day
60	Clinical state varies significantly during a period of 1 week
40	Clinical state varies significantly during a period of 2 weeks
20	Clinical state varies significantly during a period of 4 weeks
0	No variability in clinical state

Table 2-3: Summary of guidelines used to rate ERS4 which measures clinical instability within the functional psychoses.

Extended Rating Scale 4 (ERS4) was developed as a result of issues arising from the pilot-work undertaken using ERS3. It was common for fluctuations in clinical state to be mentioned in the case notes with no further detail. This meant it was impossible to say with any certainty whether fluctuations occurred between clinically significant episodes of mood (required to rate ERS3), or between milder affective states, different clinical presentations within an episode (e.g. periods of high energy and activity to periods of slowed activity and lethargy), or even between euthymia and periods of illness.

ERS4 therefore looks at "clinical instability" which refers to substantial changes in the psychopathological state and includes the domains of mood (both episodes of mood and more subtle fluctuations), perception, cognition and behaviour. Each individual is scored from 0-100 and scores are based on the most variable month of illness recorded. As presented in Table 2-3, a score of 0 would indicate that no clinical instability has occurred; a score of 100 suggests that clinical state varies significantly over a period of ten minutes or less.

Anchor points were also specified for ERS4, to deal with cases in which instability was referred to without specific reference either to the time period over

which variations occurred, or to the nature of the fluctuations in clinical state. For example, references to "lability" were commonly found in the notes, without further detail. These were given a score of 90*. References to for example, "fluctuating mood" or "mood up and down" were given a score of 80*. In both cases, a "*" was used to indicate that an anchor point had been used thus differentiating these scores from those made using more detailed clinical information.

ERS4 was developed under the hypothesis that the occurrence of, and variation in clinical instability reflects underlying genetic variation.

2.7.5 Extended Rating Scale 5: Periodicity of acute phases of illness

Score	Rating Criteria
100	5 acute phases of illness in 1 year
90	2 acute phases of illness in 1 year
70	2 acute phases of illness in 2 years
50	2 acute phases of illness in 5 years
30	2 acute phases of illness in 8 years
20	2 acute phases of illness in 10 years
10	2 acute phases of illness in 50 years
1	2 acute phases of illness in 50 years
0	Only 1 acute phase of illness

Table 2-4: Summary of rating guidelines for ERS5, which measures periodicity of acute phases of illness.

Extended Rating Scale 5 (ERS5) measures the tendency to recurrence of acute phases of illness during the lifetime course. "Acute phase of illness" was used as opposed to "episode of illness" due to the potential confusion caused by differences in the way the term "episode" may be interpreted. For example, if an individual had an episode of depression, immediately followed by an episode of mania, some would consider this to be a single episode of illness, as there was no recovery before the switch in mood polarity, whereas others would consider it to be two episodes of

illness, as both a manic and a depressive episode occurred within this time. "Acute phase of illness" therefore refers to a continuous period of time during which an individual has functional impairment (which is in contrast to their usual level of functioning). A period of at least 8 weeks of normal functioning was required to distinguish between these acute phases.

ERS5 is, again, a 0-100 scale, with 0 indicating "only one acute phase of illness" and a maximum of 100 indicating "5 acute phases of illness in one year". Scores between these extremes increase with increasing frequency of episodes within a shorter period of time, as demonstrated in Table 2.4.

ERS5 was developed under the hypothesis that variability in the frequency with which acute phases of illness occur, reflects underlying genetic variability.

2.7.6 *Extended Rating Scale 6: Predominance of a mixed affective state.*

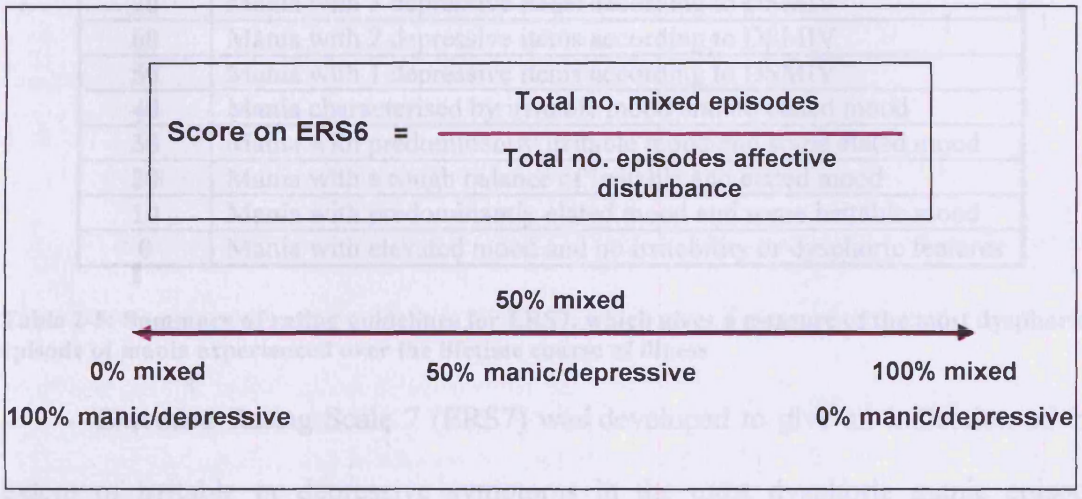

Figure 2-3: Summary of rating guidelines for ERS6, which measure the predominance of a mixed affective state.

In the same way that ERS1 measures the proportion of manic episodes to depressive episodes during the illness course, Extended Rating Scale 6 (ERS6) was developed to measure the proportion of mixed episodes over the lifetime course of

illness. As demonstrated in Figure 2.3, an individual's score on this scale is calculated by dividing the total number of mixed episodes (as defined by DSMIV) by the total number of episodes of mood disturbance overall, and then multiplying this value by 100. As the proportion of mixed episodes increases, so too does the score on ERS6 with a maximum score of 100 indicating that the individual has only experienced mixed affective episodes, with no episodes of mania or depression.

This scale was developed under the hypothesis that variation in the predominance of a mixed affective state over the lifetime course of illness reflects underlying genetic variability.

2.7.7 Extended Rating Scale 7: A measure of dysphoric mania

Score	Rating Criteria
100	Mania with 6 depressive items according to DSMIV
90	Mania with 5 depressive items according to DSMIV
80	Mania with 4 depressive items according to DSMIV
70	Mania with 3 depressive items according to DSMIV
60	Mania with 2 depressive items according to DSMIV
50	Mania with 1 depressive items according to DSMIV
40	Mania characterised by irritable mood and no elated mood
30	Mania with predominantly irritable mood and some elated mood
20	Mania with a rough balance of irritable and elated mood
10	Mania with predominantly elated mood and some irritable mood
0	Mania with elevated mood and no irritability or dysphoric features

Table 2-5: Summary of rating guidelines for ERS7, which gives a measure of the most dysphoric episode of mania experienced over the lifetime course of illness

Extended Rating Scale 7 (ERS7) was developed to give an indication of the extent of irritable or depressive symptoms in the most dysphoric manic episode experienced by the participant. Scores on this scale would only be made for individuals who have had at least one manic (or mixed) episode. As demonstrated in Table 2.5, a score of 0 indicates that any manic episodes experienced were characterised entirely by elevated mood, with no signs of irritability or depressive

symptomatology. An assumption made by the design of this scale, is that irritability within a manic episode is related to dysphoric mania, therefore scores increase firstly with the balance of elated to irritable mood and then with the increasing number of depressive symptoms experienced during this episode. A score of 100 indicates an episode of mania with at least 6 depressive items according to DSMIV.

ERS7 was developed under the hypothesis that variation in the extent to which manic episodes are dysphoric in nature is reflective of underlying genetic variability.

2.7.8 *Extended Rating Scale 8: Extent to which illness reflects "prototypical schizophrenia" vs. "prototypical affective disorder".*

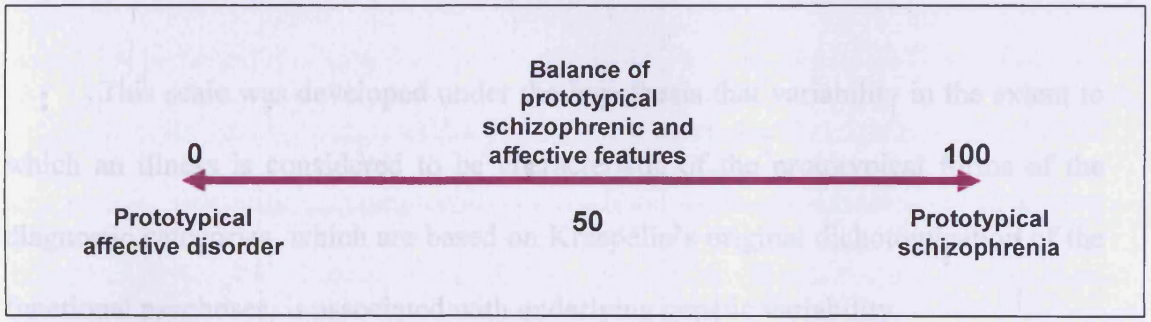

Figure 2-4: Summary of rating guidelines for ERS8, which measures the extent to which the lifetime illness reflects prototypical schizophrenia vs. prototypical affective disorder.

Unlike the other novel scales described here, Extended Rating Scale 8 (ERS8) specifies no anchor points and is based entirely on the rater's judgement. The rater must use all the information available for each case to assess how "schizophrenic" or "affective" they judge the illness to be. As demonstrated in Figure 2.4, a score of 0 would indicate that the rater considers this illness to be totally characteristic of pure affective illness (bipolar disorder or depressive disorder) with no symptoms indicative or suggestive of their perception of prototypical schizophrenic illness. A score of 100 would indicate that the rater considers the illness to be characteristic of prototypical

schizophrenia. Scores between these two extremes increase as the illness goes from being considered prototypically affective in nature, to being increasingly "schizophrenic".

Prototypical affective disorder in this scale is considered to be an episodic illness characterised by one or more manic or depressive episodes with a remitting course and no evidence of psychotic or near psychotic symptoms. Prototypical schizophrenia is defined as a chronic illness characterised by an insidious onset, positive and negative symptoms, and no evidence of mood disturbance. Other than the definitions of these two extremes, raters are given no guidelines as to how to rate intermediate forms of illness, but must make a judgement as to what point on the scale they feel an individual would be best represented.

This scale was developed under the hypothesis that variability in the extent to which an illness is considered to be characteristic of the prototypical forms of the diagnostic categories, which are based on Kraepelin's original dichotomisation of the functional psychoses, is associated with underlying genetic variability.

2.7.9 Extended Rating Scale 9: Predominance of a chronic defect state.

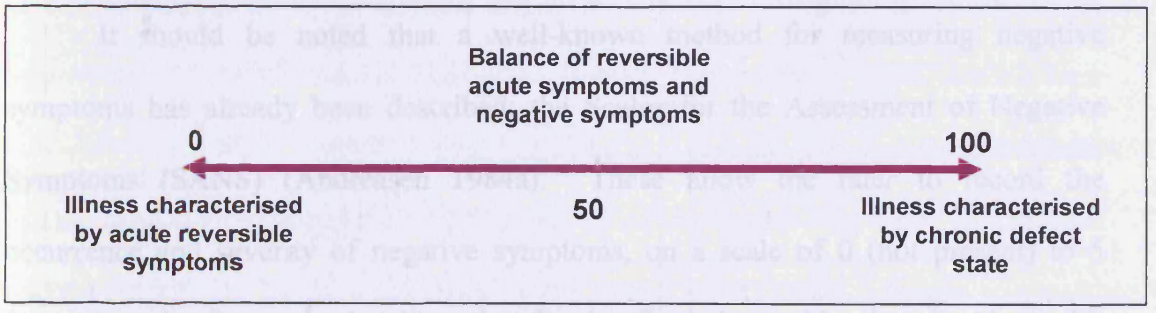

Figure 2-5: Summary of rating guidelines for ERS9, which measures the predominance of a chronic defect state over the lifetime course of illness.

The aim of Extended Rating Scale 9 (ERS9) was to give an indication of whether positive or negative features predominate the clinical picture. In this scale, a "chronic defect state" refers to negative, non-reversible symptoms such as affective flattening, alogia, anhedonia, etc. As demonstrated in Figure 2.5, a score of 0 would be used to indicate an individual with an illness characterised by acute, reversible symptoms, including positive symptoms such as affective symptoms, psychotic symptoms, bizarre behaviour and formal thought disorder.

At the extreme end of this scale, a score of 100 would reflect a case in which a chronic defect state persisted throughout the lifetime course of the illness, with no occurrence of positive features such as mood disturbance or psychotic symptoms. It was as a result of such a case that this scale was developed. During my training period I encountered a case characterised purely by chronic negative symptoms. Despite the debilitating nature of the illness, because no positive symptoms had been encountered, few positive ratings could be made on existing measures, and there was no way to indicate the nature of the illness. This scale both allows the nature of the illness to be recorded, and picks up on the predominance of negative symptoms over the lifetime course of the illness.

It should be noted that a well-known method for measuring negative symptoms has already been described; the Scales for the Assessment of Negative Symptoms (SANS) (Andreasen 1984a). These allow the rater to record the occurrence and severity of negative symptoms, on a scale of 0 (not present) to 5 (severe), under five major headings: i. Affective flattening or blunting; ii. Alogia; iii. Avolition-apathy; iv. Anhedonia-asociality; v. Attention. The SANS were designed to measure negative symptomatology at a specific time-point, usually when

examining the patient, and is therefore difficult to rate in the samples used in this thesis. ERS9 on the other hand is designed to be used on previously-collected cases, providing that they are richly described, and gives an overall measure of negative symptoms experienced over the life-time course of the illness.

In this way ERS 9 can also be used to identify individuals with the deficit syndrome of schizophrenia (e.g. Carpenter et al, 1988). This describes a group of patients who have clinically significant negative symptoms that have persisted for at least 12 months during periods of clinical stability and which are not secondary to factors (e.g. drug-effects, anxiety, mental-retardation) other than the disease process. Individuals with the deficit syndrome would score at the top end of this scale and in this way could be differentiated from individuals without the syndrome.

ERS9 was developed under the hypothesis that variation in the extent to which an illness is characterised by positive vs. negative symptoms reflects underlying genetic variability.

Extended Rating Scales 10 and 11

Unlike the Extended Rating Scales 1 to 9, Extended Rating Scales 10 and 11 were developed prior to the commencement of this PhD by Dr George Kirov in the Department of Psychological Medicine, Cardiff University. These scales were included within the Extended Rating Scales as they measured symptom dimensions which varied both within and across samples and it was hypothesised that they may be useful in distinguishing between cases. These scales are described below.

2.7.10 *Extended Rating Scale 10: Catatonic Symptoms*

Symptom	
Waxy flexibility	One point is awarded for the presence of any of the following symptoms (unless otherwise stated) up to a maximum of 4 points
Stupor (clear description of catatonic stupor = 2 points)	
Physiological pillow	
Excessive purposeless over-activity	
Mannerisms	
Grimacing	
Echolalia, echopraxia, automatic obedience	
Negativism (clear description needed)	

Figure 2-6: Summary of rating guidelines for ERS10, which gives a measure of catatonic symptoms, experienced over the lifetime course of illness.

Extended Rating Scale 10 (ERS10) measures the occurrence of catatonic symptoms experienced over the life-time course of the illness, on a 5-point scale from 0-4, as demonstrated in Figure 2-6 above. It was measured in two ways, firstly excluding symptoms that were "explicable by affective change", and secondly on a context-independent basis, which included symptoms experienced within affective disturbance, provided they were adequately described by the symptom definitions of ERS10. For example, within the context of a manic episode, "excessive activity" would not be scored on this scale unless it was excessive, purposeless, and sufficiently extreme for the rater to differentiate it from the conventional descriptions of over-activity described in mania. This is discussed further in chapter 5.

2.7.11 Extended Rating Scale 11: Disorganised Behaviour

Symptom
Patient talks him/herself
Laughing for no reason
Hoarding rubbish
Odd, inappropriate behaviour
Acts of senseless violence
Extremely poor personal hygiene

One point is awarded for the presence of any of the following symptoms up to a maximum of 2 points

Figure 2-7: Summary of rating guidelines for ERS11, which gives a measure of disorganised behaviour, experienced over the lifetime course of illness.

Extended Rating Scale 11 (ERS11) gave a measure of the occurrence of catatonic symptoms experienced over the life-time course of the illness, on a 3-point scale from 0-2, as summarised in Figure 2.7 above. Like ERS10, scores on ERS11 were measured in two ways, firstly excluding symptoms that were "explicable by affective change", and secondly on a context-independent basis, in which symptoms experienced within episodes of affective disturbance were rated, provided they were adequately severe and could be differentiated from typical symptoms of affective disturbance on account of the severity or nature of the symptom described. Again, this is discussed further in chapter 5.

2.8 Reliability

To test reliability of these scales, a sample of 20 cases was rated by at least two members of the research team (including myself and Professor Nick Craddock, Dr Danny Smith, Dr James Walters, Ms Liz Forty and Ms Christine Fraser). These included cases representing a range of diagnoses, including schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder. Meetings

were held in which ratings for each new scale were discussed for each case and consensus ratings were reached.

Reliability calculations were performed by comparing my own ratings with the consensus agreed on after discussing the case. All 11 scales were shown to have good to excellent reliability, with intra-class correlation coefficients ranging from 0.786-1.000 as presented in the table below:

Rating Scale	ICC
Predominance Mania (ERS1)	0.987
Affective vs. Psychotic Illness (ERS2)	0.979
Fluctuations in Mood (ERS3)	1.000
Instability of Clinical State (ERS4)	0.998
Periodicity of Acute Illness Phases (ERS5)	0.941
Predominance Mixed Episodes (ERS6)	0.999
Most Dysphoric Manic Episode (ERS7)	0.872
Prototypical Affective Illness vs. SZP (ERS8)	0.853
Predominance Chronic Defect State (ERS9)	0.806
Rating Scale	**Cohen's Kappa**
Catatonic Symptoms (ERS10)	0.955
Disorganised Behaviour (ERS11)	0.786

Table 2-6: Results of inter-rater reliability analyses performed on the Extended Rating Scales (ICC – Intra-class correlation).

2.8.1 Further novel measures included within the OPCRIT symptom checklist

As well as developing new rating scales, two other items of psychopathology were developed as part of my PhD work.

At an early stage of the rating process it became evident that there were certain features of illness that occurred relatively frequently in the samples and appeared potentially important for distinguishing between cases, but were not captured adequately by the current OPCRIT checklist. The two which occurred most

frequently were increased or inappropriate sexual behaviour and aggressive behaviour.

Previously, increased sexual activity was likely to be rated within the definition of "Excessive Activity" item in the section of OPCRIT describing manic symptoms. Inappropriate sexual behaviour would generally be rated under "Increased Sociability". Although there is an argument for continuing to categorise it in this way, related to assumptions made about the origins of the symptom, this method meant that an individual who, for example, was over familiar with strangers would not be differentiated from someone who engaged in aggressive, non-consensual sexual behaviour when ill. I therefore added an additional item to the OPCRIT symptom checklist, "28a: Increased sexual activity." This comprised a 0-2 scale which allows the occurrence of the symptom to be recorded and gives an indication of severity.

Aggressive behaviour, in its milder form, would generally have been rated under irritability in the past. Again, this does not distinguish between people who are short-tempered when ill and those who become extremely aggressive and physically violent. I therefore added a further measure to the OPCRIT symptom checklist: "54a. Aggressive behaviour". Ratings were made on a four-point scale ranging from behaviour perceived as threatening and out of proportion with the circumstances, to multiple acts of severe aggression resulting in physical injury to others or police involvement.

The main objective in the development of these additional ratings was to enable behaviours to be recorded, without making assumptions about their underlying

causes, or the context in which they were experienced. Rating guidelines can be found in Appendix C.

2.9 Summary

This chapter describes a set of clinical measures that were selected and developed to measure clinical variability across the traditional diagnostic boundaries dictated by Kraepelin's dichotomisation of the functional psychoses. These measures were subsequently implemented on three samples of interest:

1. A large, harmonised dataset comprising families enriched for schizophrenia and families enriched for bipolar disorder; the creation and characteristics of this sample are described in detail in chapter 5.

2. A sample of patients with Velo-Cardio-Facial Syndrome (VCFS) and a major psychiatric disorder, as described in chapter 3.

3. A sub-set of individuals from the large-harmonised dataset comprising sibling-pairs enriched for schizoaffective disorder, as described in chapter 4.

3 Phenotype assessment in a sample of patients with Velo-Cardio-Facial Syndrome and a psychiatric disorder

3.1 Introduction

Velo-cardio-facial syndrome (VCFS) is a genetic disorder associated with hemizygous interstitial micro-deletions on chromosome 22. It is one of the most common genetic disorders with a minimum prevalence of approximately 1 in 5000 live births (Botto et al. 2003). VCFS is characterised by a range of phenotypic characteristics, the most common of which include cleft palate, cardiac defects and characteristic facial features, e.g. long face, retruded lower jaw, broad nasal root and tip, malar flatness and narrow palpebral fissures (Goldberg et al. 1993). It is also associated with speech and language impairments, developmental delays and learning disabilities.

The term VCFS was first coined in 1978 by Robert Shprintzen, a speech pathologist, who described a familial syndrome associated with cleft palate, velopharyngeal incompetence (resulting in hypernasal speech), heart defects, learning disabilities and characteristic facial features. The VCFS phenotype was later expanded to include over 180 characteristic features (with each patient displaying a selection of these).

As the VCFS phenotype expanded, it was noted that there was a symptomatic overlap between VCFS and the previously described DiGeorge syndrome (Pinsky and Digeorge 1965), known to be associated with deletions at chromosome 22q11. It was this overlap that prompted Driscoll et al (1992) to carry out molecular genetic tests on their sample of VCFS patients, under the hypothesis that VCFS and DiGeorge syndrome may share a common pathogenesis. Fourteen out of their sample of fifteen

patients with VCFS had deletions at chromosome 22q11, supporting the association. This finding has since been replicated in numerous studies (Amati et al. 1999).

Strikingly VCFS is also strongly associated with high levels of psychiatric disturbance. In 1992 Shprintzen reported that of the approximately 90 VCFS cases seen by both himself and his colleagues at the Centre for Craniofacial Disorders, over 10% had developed psychiatric disorders. When they looked only at those individuals aged 16 or above, this rose to nearly 38%. Shprintzen reported that these psychiatric disorders most commonly resembled "chronic schizophrenia with paranoid delusions".

Since this time, the psychiatric phenotype associated with VCFS has been the focus of much research, although reported findings have varied. The most common psychiatric disorder associated with VCFS in the literature is schizophrenia (e.g. Bassett et al. 1998; Driscoll et al. 1992; Gothelf et al. 1999; Shprintzen et al. 1992, Murphy et al. 1999). However, other studies report high rates of mood disorders. For example, a study carried out by Papolos et al (1996) aimed to examine the behavioural phenotype of 25 children and adolescents with VCFS, in order to further investigate the suggested association between VCFS and schizophrenia. The analysis was later expanded to include adults, as findings were not consistent with this expected association. Instead, they reported high rates of bipolar-spectrum conditions (64% of their sample) including BPI (12%), BPII (40%), Cyclothymia (4%) and Schizoaffective Disorder-Manic type (8%). Of these, four (25%) had experienced psychotic symptoms (both schizoaffective patients and two BPI patients).

Arnold et al (2001) found that twelve out of their sample of twenty VCFS patients (60%) met the Diagnostic and Statistical Manual of Mental Disorders IV (DSMIV) criteria for a psychiatric disorder. Of these, eight (67%) had mood

disorders (dysthymia and major depressive disorder). Although no true psychotic symptoms were reported, three also had schizotypal traits.

One potential explanation for these disparate results is the age differences in ascertainment groups used in the various studies. It is of note that the two studies mentioned above, which report high rates of mood disturbance and not schizophrenia, have studied samples largely consisting of children and adolescents. The age-range of the sample collected by Papolos et al was 5 to 34 with a mean age of 15.6 years. In the sample collected by Arnold and colleagues, age at ascertainment ranged from 6 to 20, with a mean age of 11 years.

In contrast, studies reporting high rates of schizophrenia generally used samples drawn from adult populations (Murphy et al. 1999 - mean age 34 years); (Gothelf et al. 1999 - mean age 26.5 years); (Bassett et al. 2003 - mean age 31.5 years), suggesting the possibility of a clinical course in which affective disturbance occurs in the early stages of the illness, whereas features more typically associated with schizophrenia manifest at a later stage.

Under the diagnostic hierarchy (see chapter 1), unless they are a prominent feature of the illness and have overlapped at some point with schizophrenic features, episodes of mood disturbance will not generally have been considered in studies focussing solely on diagnostic categories. If mood symptoms have occurred at a relatively early stage of the psychiatric disturbance, they are less likely to be picked up in studies of adult populations.

A further explanation for the differences in the psychiatric phenotypes associated with VCFS reported by various studies may be diagnostic disagreement – different clinicians or researchers applying diagnostic criteria in slightly different ways, or interpreting symptoms observed or reported differently. An example of this

is given by Papolos et al (1996), who reassessed a patient who had originally participated in a study by Pulver et al (1994). Whereas, in Pulver's study, this individual was diagnosed with schizophrenia, Papolos and colleagues diagnosed them as BPI (rapid cycling) and described an illness course "far more consistent with mood-congruent psychotic depression followed by irritable manic episodes".

Despite the fact that the exact psychiatric phenotype associated with VCFS remains somewhat ambiguous, the relevance of the syndrome in the search for genes increasing susceptibility to psychiatric illness cannot be denied. The association of VCFS with known deletions at 22q11 have made this chromosomal region the target of numerous molecular genetic studies.

Suggestive evidence for linkage at chromosome 22q11 has been reported in family-samples of both bipolar disorder (Edenberg et al. 1997; Kelsoe 2003; Lachman et al. 1997), and schizophrenia (Coon et al. 1994; Shaw et al. 1998; Williams et al. 2003). In a meta-analysis of published whole-genome linkage scans of both bipolar disorder and schizophrenia, Badner and Gershon (2002) found that the strongest evidence for regions harbouring susceptibility loci for both bipolar disorder and schizophrenia was produced for regions 13q and 22q.

Recent studies, focussing on phenotypes which incorporate features of mood-disturbance and psychosis, have yielded further interesting results. Potash et al (2003) performed linkage analysis on a sample of 65 bipolar disorder pedigrees in order to test the hypothesis that those families enriched for psychotic symptoms would show increased evidence for linkage to regions previously implicated in both schizophrenia and bipolar disorder samples. Their findings were consistent with this; the ten bipolar families enriched for psychotic regions showed linkage to 13q31 and 22q12 (with

respective LOD scores of 2.52 and 3.06), whereas little or no evidence at these regions was produced in analysis performed on the full sample of 65 families.

Suggestive evidence for linkage at 22q11 was produced in a genome-wide linkage scan performed by Hamshere et al (2005) in a sample enriched for schizoaffective disorder (LOD score = 1.96). Again, this supports the hypothesis that this region may harbour genes that influence susceptibility to psychiatric illness incorporating features characteristic of both mood disturbance and schizophrenia. This sample is described further in chapter 4).

The region of chromosome 22 which is deleted in VCFS contains approximately 48 genes. Of these, several have been identified as promising candidate genes for psychiatric illness (Murphy 2005; Shprintzen et al. 2005; Williams et al. 2008) and work is ongoing to identify specific genetic variations which influence susceptibility.

Findings from both molecular genetic studies, implicating 22q11 in schizophrenia, bipolar disorder, and intermediate-phenotypes, along with the reportedly high rates of psychiatric disturbance incorporating both psychosis and mood disturbance in patients deleted at this region, support the hypothesis that this region of chromosome 22 may harbour a gene or genes which increases susceptibility to psychiatric illness across the traditional Kraepelinian divide.

It could be argued that the main limitation of many previous studies which have focussed on the characterisation of the psychiatric phenotype in VCFS, or the search for chromosomal regions and genes implicated in psychiatric illness, is their tendency to focus solely on diagnostic categories. As discussed in chapters 1 and 2, using these categories alone can lead to heterogeneous samples. This is likely to be particularly problematic in clinical samples associated with multiple diagnoses, as is

the case in VCFS, as these are likely to reflect a more variable clinical picture which is more difficult to classify.

It is of note that one of the most promising linkage findings on chromosome 22 was reported in a study using a more homogeneous sample – bipolar patients who had also experienced psychotic symptoms (Potash et al. 2003). This supports the hypothesis that this region is associated with a psychiatric phenotype involving both disturbances in mood and psychosis, and highlights the benefits of looking more closely at the clinical picture in patients with VCFS. It is on this reasoning that my work is based.

Clinical information was available in the department for 21 individuals with VCFS from a sample previously collected by Professor Kieran Murphy and colleagues in the late 1990s. In the largest study of adult patients to date, Murphy et al (1999) evaluated 50 patients with VCFS in order to characterise the psychiatric-phenotype. They found that 21 individuals (42%) met criteria for a major psychiatric disorder, although the authors note that this may be partially due to ascertainment bias as 6 individuals from the sample were recruited through psychiatric services (see discussion). Of these, 12 (57%) met DSMIV-criteria for schizophrenia. The remainder were given diagnoses of major depression (N=6), bipolar disorder (N=1), schizoaffective disorder - bipolar type (N=1) and psychosis – not otherwise specified (N=1).

The study also compared schizophrenic patients in the VCFS sample ("SZ/VCFS group") with a matched control group of patients with schizophrenia who did not have a chromosome 22q11 deletion ("SZ group"). Murphy et al reported that the SZ/VCFS group had significantly fewer negative symptoms and a significantly later age of onset than the SZ group.

My research aimed to extend the work of Murphy et al by rating the sample of 21 individuals who met criteria for a major psychiatric disorder, on the large number of phenotypic characteristics described in chapter 2, paying particular attention to the prevalence of and relationship between mood symptoms and psychotic symptoms, under the hypothesis that affective-disturbance may be more prevalent in the sample than the DSMIV-diagnoses suggest.

3.2 Methods

3.2.1 Subjects

The sample comprised twenty-one individuals with a diagnosis of VCFS and major psychiatric disorder. This was a subset of fifty individuals originally collected by Professor Kieran Murphy and colleagues, with the intention of characterising the psychiatric phenotype in a comparatively large sample (as described above). The sample consisted of five males and sixteen females, with age at ascertainment ranging from seventeen to fifty-two years (mean 35.9 years, standard deviation 11.8 years).

The majority of these individuals (N=34) were recruited through departments of medical genetics throughout England and Wales. Others were recruited from psychiatric services (N=6), the UK VCFS support group (N=5), the local cardiology department (N=4), and one individual self-referred.

Each participant had been interviewed by Murphy and colleagues, using either the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990) or the Psychiatric Assessment Schedule for Adults with Developmental Disability. Using this information an interview vignette had been constructed for each case. Where applicable, summaries from other sources of information such as casenotes

were also provided. As mentioned, DSMIV-diagnoses were made using all available information and 21 cases were found to meet criteria for a major psychiatric disorder (schizophrenia - 12; major depressive disorder – 6; schizoaffective disorder, bipolar type - 1; bipolar I disorder, rapid cycling – 1; psychosis-not otherwise specified - 1).

The most up-to-date genetic data available confirmed deletions at 22q11 in all 21 cases with VCFS and major psychiatric disorder.

3.2.2 Assessment of the Phenotype

In order to explore the phenotype of this sample further, each case needed to be rated on the large number of variables, detailed in the previous chapter. The rating of these cases took place in the relatively early stages of my research, and because of this, the items rated differed slightly from those used when rating the combined schizophrenia and bipolar disorder datasets (see Chapter 5); this was due to the identification of areas of the phenotype that could be better captured by altering existing rating guidelines, or by adding further items, during the rating of this large combined sample (this process is described in detail in chapters 2 and 5) A copy of the rating sheet used to rate the VCFS cases can be found in Appendix F. Ratings were made blind to Professor Murphy's original diagnoses of these cases.

Each case was rated on approximately 150 items of psychopathology, including the occurrence of specific symptoms (using the Operational Criteria symptom checklist (Modified OPCRIT – version 6 – 01.12.05), ages of onset, number of episodes, and scores on the Bipolar Affective Disorder Dimension Scales (BADDS)(Craddock et al. 2004b) and the Global Assessment Scale (GAS)(Endicott et al. 1976) (see chapter 2). Diagnoses were also made according to DSMIV, the

ICD-10 Classification of Mental and Behavioural Disorders (WHO 1993) and the Research Diagnostic Criteria (RDC) (Spitzer et al. 1975).

Each case was examined in detail and ratings were made by three individuals independently – two psychiatrists (Professor Nick Craddock and Dr James Walters) and one psychologist (myself). All individuals had been fully trained in the use of these methods. As part of my training, a series of meetings were held in which each case was discussed in detail, and a consensus rating was reached for each item.

3.2.3 Examination of the data

Comparison of Diagnoses

DSMIV-diagnoses made by KM and colleagues were compared on a case-by-case basis with RDC-diagnoses made as part of the current research. RDC uses less restrictive criteria in the diagnosis of schizoaffective disorder and is more sensitive in picking up on cases with a mixture of affective and psychotic symptomatology. For the same reason I also allowed a single individual to receive more than one diagnosis.

Prevalence of Mood Disturbance

The prevalence of mood disturbance was defined in two ways: firstly as the occurrence of one or more episodes of mood disturbance over the course of the illness; secondly as the definite presence of affective symptoms which did not necessarily meet the criteria for an episode of mood disturbance.

To identify cases in which episodes of mood disturbance had occurred, scores on the Bipolar Affective Disorder Dimension Scales (BADDS; previously discussed in chapter 2) were used. A score of 40 or above on the BADDS Mania dimension indicates that an individual has had at least one episode of hypomania. Scores above

60 indicate at least one manic episode. On the BADDS Depression scale, scores over 40 indicate at least one major depressive episode.

Cases in which mood-symptoms had definitely occurred were identified using BADDS scores of greater than 18. In the BADDS rating guidelines, a range of 1-19 is used to identify cases in which "mild sub-hypomanic" or "sub-minor depression" has occurred. A rating of 19 was used to indicate that there was evidence for mood disturbance, but not enough information was available (e.g. regarding duration or number of symptoms) to make a higher rating with the certainty required by the guidelines. For example, references to "lability of mood", or "depressive symptomatology" were not rated higher than 19, even though they are statements suggestive of more prominent mood disturbance.

3.3 Results

3.3.1 Comparison of Diagnoses

When DSMIV diagnoses made by Professor Kieran Murphy and colleagues were compared with RDC diagnoses made as part of the current research, diagnoses "differed" in 11 (52.3%) cases (see table 3-1 below for summary).

Of the original twelve cases diagnosed as Schizophrenic using DSMIV criteria, diagnoses made using RDC remained the same in four cases. In a further single case, KM's diagnosis of schizophrenia remained unchanged but the individual also met RDC criteria for Major Recurrent Depressive Disorder. This second diagnosis would not have been recognised under the diagnostic hierarchy, which states that a diagnosis of schizophrenia "trumps" that of affective disorders.

ID	DSMIV (KM)	RDC (ER)
V01/04	Schizophrenia	Schizophrenia
V03/03	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V06/02	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V08/02	Major Depressive Disorder	Major Depressive Disorder (Recurrent)
V09/03	**Bipolar Disorder**	**Schizoaffective Disorder – Bipolar Type**
V11/04	Major Depressive Disorder	Major Depressive Disorder (Recurrent)
V12/04	**Schizophrenia**	**Schizophrenia and Major Depressive Disorder (Recurrent)**
V14/02	**Major Depressive Disorder**	**Minor Depressive Disorder**
V15/01	Schizophrenia	Schizophrenia
V18/05	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V19/03	**Schizophrenia**	**Schizoaffective Disorder – Bipolar Type**
V22/02	Major Depressive Disorder	Major Depressive Disorder (Recurrent)
V23/02	Major Depressive Disorder	Major Depressive Disorder (Single Episode)
V24/02	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V25/04	Major Depressive Disorder	Major Depressive Disorder (Single Episode)
V31/03	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V33/06	**Other Psychotic Disorder**	**Schizoaffective Disorder – Depressed Type**
V34/02	Schizophrenia	Schizophrenia
V35/01	**Schizophrenia**	**Schizoaffective Disorder – Depressed Type**
V43/10	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Bipolar Type
V44/03	Schizophrenia	Schizophrenia

Table 3-1: Comparison of diagnoses made by KM and colleagues using DSMIV, with diagnoses made by ER and colleagues using RDC.

Of the remaining seven cases, six met RDC-criteria for Schizoaffective Disorder – Depressed Type and the remaining case met RDC-criteria for Schizoaffective Disorder – Bipolar Type.

These, along with the three other cases in which diagnoses "differed" when using different criteria, are summarised in Table 3-2 below, which compares the DSMIV diagnoses made by KM et al, with the RDC diagnoses made by ER et al.

DSMIV Diagnoses (KM et al)	RDC Diagnoses (ER et al)					
	Diagnosis	BPI	SABP	MDD	SADep	SZP
	BPI	0	**1**	0	0	0
	SABP	0	**1**	0	0	0
	MDD	0	0	**6**	0	0
	SADep	0	0	0	0	0
	SZP	0	**1**	0	**6**	**5**
	OPD	0	0	0	**1**	0

Table 3-2: Summary of diagnoses when different diagnostic criteria were implemented within the sample.

BPI – bipolar I disorder; SABP – schizoaffective disorder, bipolar type; MDD – major depressive disorder; SADep – schizoaffective disorder, depressed type; SZP – schizophrenia; OPD – other psychotic disorder.

3.3.2 Prevalence of mood symptoms

Out of the sample of 21 patients with VCFS and a psychiatric disorder, 17 (81%) had experienced at least one depressive, manic or hypomanic episode. The majority of these (11/17) also experienced psychotic symptoms. Only four individuals had experienced psychotic symptoms without definite episodes of mood disturbance.

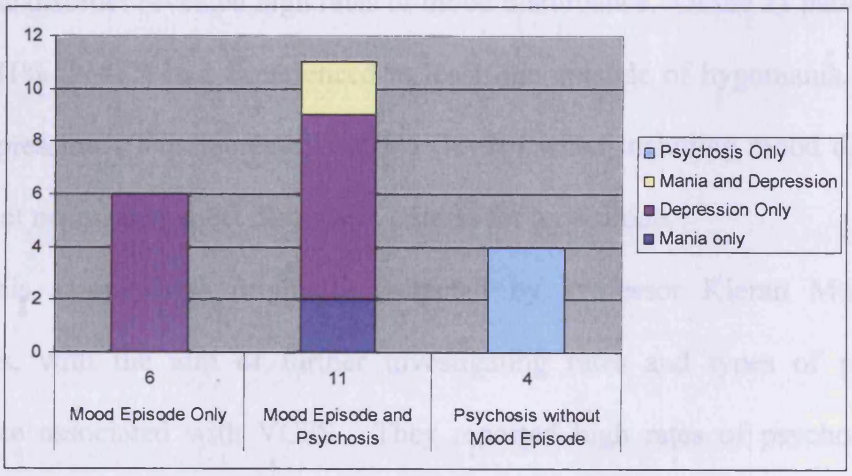

Figure 3-1: Prevalence of and relationship between affective episodes and psychotic symptoms within a sample of VCFS patients with a major psychiatric diagnosis.

When looking at the prevalence of mood symptoms in the sample (i.e. BADDS Scores $\geq$ 19), rather than the more narrowly defined-mood episodes, the number of individuals experiencing mood disturbance increases to twenty out of

twenty-one (95%). Only a single individual had a pure psychotic illness with no evidence of symptoms indicative of affective disturbance.

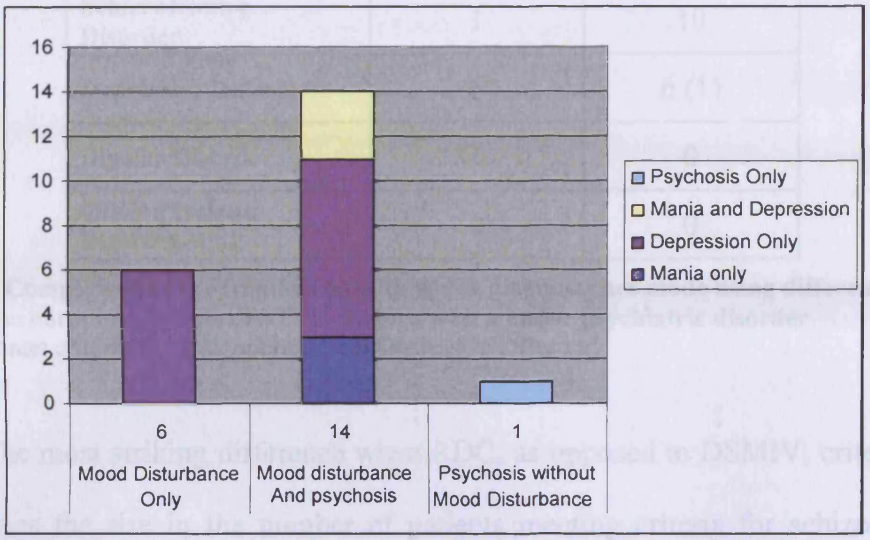

Figure 3-2: Prevalence and relationship between affective disturbance and psychotic symptoms within a sample of VCFS patients with a major psychiatric diagnosis.

3.4 Discussion

Detailed phenotype examination of a sample of patients with VCFS and a major psychiatric disorder revealed high rates of mood disturbance. Of the 21 patients in the sample, 81% (N=17) had experienced at least one episode of hypomania, mania or major depression. This increases to 95% (N=20) when including mood disturbance that did not necessarily meet diagnostic criteria for an episode.

This sample was originally collected by Professor Kieran Murphy and colleagues, with the aim of further investigating rates and types of psychiatric disturbance associated with VCFS. They reported high rates of psychosis in the sample (15/21), most commonly fitting diagnostic criteria for DSMIV defined schizophrenia (12/21). However, when RDC, rather than DSMIV, criteria were used to diagnose these patients, diagnoses differed in 52.3% of cases. The table below shows the frequency in which each diagnostic category was assigned to cases in this sample under DSMIV criteria (KM) and RDC criteria (ER).

Diagnostic Category	DSMIV (KM)	RDC (ER)
Schizophrenia	12	4 (1)
Schizoaffective Disorder	1	10
Depressive Disorder	6	6 (1)
Bipolar Disorder	1	0
Other Psychotic Disorder	1	0

Table 3-3: Comparison of the frequencies with which diagnoses are made using different diagnostic criteria in a sample of VCFS patients with a major psychiatric disorder
[(1) patient met criteria for Schizophrenia and Depressive Disorder]

The most striking difference when RDC, as opposed to DSMIV, criteria were applied was the rise in the number of patients meeting criteria for schizoaffective disorder, and the concurrent fall in those diagnosed with schizophrenia. RDC uses less restrictive criteria for the diagnosis of schizoaffective disorder (see chapter 4), for example, in terms of the required prominence of the affective disturbance. A diagnosis of schizoaffective disorder according to RDC requires the occurrence of only a single episode of mood disturbance, which has at some point overlapped with symptoms suggestive of schizophrenia for a schizoaffective diagnosis. In DSMIV a diagnosis of schizoaffective disorder requires that symptoms which meet the criteria for an episode of mood-disturbance are present for a substantial proportion of the total duration of illness.

In the current study, RDC diagnoses better reflect the high incidence of mood disturbance within the VCFS sample, suggesting that this sample is associated with a clinical picture involving both psychotic features and mood disturbance. The narrower definition of schizoaffective disorder under DSMIV means that this level of detail is lost, with features of mood disorder being disregarded under the diagnostic hierarchy, unless they are present for a substantial proportion of the total illness.

However, although the RDC definition of schizoaffective disorder better recognises the occurrence of manic and depressive symptoms, it does not distinguish between patients who have had a single episode of mood disturbance and those who experience many episodes of affective illness concurrent with a schizophrenic syndrome.

As outlined in the introduction above, results of previous studies which have attempted to characterise the psychiatric phenotype associated with this syndrome, have been mixed, with some reporting high rates of schizophrenia (e.g. Shprintzen et al. 1992) and others high rates of mood disorder (e.g. Arnold et al. 2001). The results summarised in the tables above demonstrate how, even when investigating the same sample of patients, different ways of measuring the phenotype can lead researchers to different conclusions.

Another possible explanation for the discrepant findings between previous studies could be related to the age range of the samples studied. Investigations studying the psychiatric phenotype associated with VCFS which report high rates of mood disturbance have involved samples consisting largely of children and adolescents (Papolos et al. 1996), whereas those reporting higher rates of schizophrenia tend to be based on adult samples. This may suggest a characteristic clinical course of illness involving early disturbance of mood, with features typically associated with schizophrenia only occurring at a later stage of the illness. Mood symptoms which occur at a relatively early stage of the illness are less likely to be picked up in studies of adult populations.

In the current sample, a comparison of ages at onset of mood and psychosis revealed that the average age at first psychotic symptom was lower than the average age at first mood disturbance (average age at first psychosis = 23.29, average age at

first mood disturbance = 26.38), which does not support the hypothesis of a characteristic course involving early mood disturbance and later psychotic features. However, as stated in the introduction to this chapter this may be because if mood symptoms have occurred at a relatively early stage of the psychiatric disturbance they are less likely to be picked up in studies of adult populations such as this. Due to the sample size no formal statistical tests were performed on this sample.

The possibility of a characteristic course of illness involving early mood disturbance and the later development of symptoms characteristic of schizophrenia could be investigated further using a longitudinal study design which included detailed characterisation of the psychiatric phenotype in individuals with VCFS at regular intervals, ideally starting in early childhood.

A further explanation for the differences in previous findings could be that the initial reports suggesting that VCFS was associated with schizophrenia may, to some extent, have resulted in systematic differences in studies seeking to further investigate this association. It is possible that the symptoms indicative of mood-disturbance were explored less rigorously than those suggestive of schizophrenic illness. This may have led to subjects being given a diagnosis of schizophrenia when, if the clinical picture was examined more closely, a diagnosis of schizoaffective disorder, or even major depression with psychotic features or bipolar disorder (as described above in the case originally collected by Pulver and re-examined by Papolos et al, 1996), may have been appropriate.

Similarly, despite efforts made to prevent it, systematic differences may have been introduced in the current study which was carried out under the hypothesis that symptoms of affective disturbance were more prevalent in the sample than Professor Murphy's original DSMIV diagnoses suggested. This can be examined further by

comparing the original DSMIV diagnoses made by Murphy et al (1999) with DSMIV diagnoses my Russell et al, described in this chapter.

ID	DSMIV (KM)	DSMIV (ER)	*RDC (ER)*
V01/04	Schizophrenia	Schizophrenia	*Schizophrenia*
V03/03	Schizophrenia	Schizoaffective Disorder – Depressed Type	*Schizoaffective Disorder – Depressed Type*
V06/02	Schizophrenia	Schizoaffective Disorder – Depressed Type	*Schizoaffective Disorder – Depressed Type*
V08/02	Major Depressive Disorder	Major Depressive Disorder (Recurrent)	*Major Depressive Disorder (Recurrent)*
V09/03	Bipolar Disorder	Bipolar Disorder	*Schizoaffective Disorder – Bipolar Type*
V11/04	Major Depressive Disorder	Major Depressive Disorder (Recurrent)	*Major Depressive Disorder (Recurrent)*
V12/04	Schizophrenia	Schizophrenia and Major Depressive Disorder (Recurrent)	*Schizophrenia and Major Depressive Disorder (Recurrent)*
V14/02	Major Depressive Disorder	Depressive Disorder – Not Otherwise Specified	*Minor Depressive Disorder*
V15/01	Schizophrenia	Schizophrenia	*Schizophrenia*
V18/05	Schizophrenia	Schizoaffective Disorder – Depressed Type	*Schizoaffective Disorder – Depressed Type*
V19/03	Schizophrenia	Schizoaffective Disorder – Bipolar Type	*Schizoaffective Disorder – Bipolar Type*
V22/02	Major Depressive Disorder	Major Depressive Disorder	*Major Depressive Disorder (Recurrent)*
V23/02	Major Depressive Disorder	Depressive Disorder – Not Otherwise Specified	*Major Depressive Disorder (Single Episode)*
V24/02	Schizophrenia	Schizoaffective Disorder – Depressed Type	*Schizoaffective Disorder – Depressed Type*
V25/04	Major Depressive Disorder	Major Depressive Disorder (Single Episode)	*Major Depressive Disorder (Single Episode)*
V31/03	Schizophrenia	Schizoaffective Disorder – Depressed Type	*Schizoaffective Disorder – Depressed Type*
V33/06	Other Psychotic Disorder	Other Psychotic Disorder	*Schizoaffective Disorder – Depressed Type*
V34/02	Schizophrenia	Schizophrenia	*Schizophrenia*
V35/01	Schizophrenia	Schizophrenia	*Schizoaffective Disorder – Depressed Type*
V43/10	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Bipolar Type	Schizoaffective Disorder – Bipolar Type
V44/03	Schizophrenia	Schizophrenia	*Schizophrenia*

Table 3-2: Comparison of diagnoses made by KM and colleagues using DSMIV, with diagnoses made by ER and colleagues using DSMIV.

As shown in the table above, even when using the same diagnostic criteria, diagnostic differences still occurred between the two research-groups. Six of the eight individuals diagnosed with schizophrenia by Murphy et al (1999) were diagnosed with schizoaffective disorder when the same diagnostic criteria were

applied by Russell et al, suggesting some element of bias by one or both groups. To meet the criteria for schizoaffective disorder as defined by DSMIV an individual must experience symptoms that meet the criteria for a mood episode for a "substantial portion of the total duration of the active and residual periods of the illness". What constitutes a "substantial portion" of the total duration of illness is open to a degree of interpretation and therefore may result in diagnostic differences in cases which comprise a mixture of psychotic and affective symptoms.

The fact that these diagnostic differences occurred when using the same diagnostic criteria further demonstrates the limitations of diagnostic classification systems and the importance of using clinical variables as an adjunct to diagnosis to give a fuller description of the clinical picture.

VCFS is of particular interest to molecular genetic researchers because it involves the association of a known chromosomal abnormality with high rates of psychiatric disturbance. This suggests that there may be a gene or genes in this area which influence susceptibility to this disturbance in the general population. Murphy et al (2005) suggested that if a disease is truly associated with a gene: i) there should be increased incidence of the disease in a population of individuals with a specific chromosomal abnormality; ii) there should be an increased incidence of the chromosomal abnormality in a population of individuals with the disease and; iii) molecular genetic studies should suggest that a susceptibility locus for the disease may be located at the region associated with the chromosomal abnormality.

In the case of VCFS, points i) and iii) have already been discussed; there is an increased incidence of psychiatric illness in populations with deletions at chromosome 22q11 and this region has been implicated in molecular genetic studies. Studies have also been carried out to investigate point ii) and have provided support for the

hypothesis that deletions in the VCFS region are more common in populations with schizophrenia than in the general population.

The effects of the deletion will vary according to the mechanism by which a risk allele influences illness. For example, the effects of a loss of function allele will be made more obvious by the presence of a deletion, whereas gain of function alleles will be relatively unaffected by the deletion.

The reported prevalence rates of 22q11 deletions in samples of patients with schizophrenia vary from 2% (Wiehahn et al. 2004) to 53% (Bassett et al. 1998). The highest prevalence reported was in a sample of patients selected on the basis that they had a DSMIV diagnosis of schizophrenia (N=7) or schizoaffective disorder (N=1) along with at least two physical features associated with VCFS (e.g. palatal abnormalities, cardiac abnormalities, dysmorphic facies or other physical congenital abnormalities).

In a random sample of schizophrenic patients (N=100) Karayiorgou and colleagues (1995) found that 2% were deleted at chromosome 22q11. Usiskin et al (1999) reported deletions at chromosome 22q11 in 6% of their sample of childhood-onset schizophrenia cases (N=43, onset of psychosis below the age of 12). Both are well above the estimated prevalence of 22q11 deletions in the general population (approx. 0.02%, Botto et al. 2003).

It is of note that higher rates of deletions at the VCFS region are reported in samples in which the phenotype has been refined (e.g. only including patients with early onset schizophrenia). Further characterisation of the psychiatric phenotype associated with the syndrome will enable the selection of samples which are more representative of psychiatric disturbance in VCFS – for example, it may be that a sample of patients with a DSMIV diagnosis of schizophrenia who have also had at

least one episode of mood disturbance would show increased numbers of deletions at chromosome 22q11.

In the case of molecular genetic studies, the identification of a more precise psychiatric phenotype associated with VCFS would be beneficial because, as it is associated with a specific chromosomal abnormality, it is likely to describe a genetically meaningful subgroup of patients. The use of samples that are more reflective of this better-defined phenotype is more likely to yield more interesting and significant results in both linkage and association studies.

There are several limitations to this study. Firstly it was retrospective, i.e. the VCFS sample had been recruited prior to the start of my PhD. This meant that participants could not be asked directly about specific items of psychopathology that were rated during this study. The advantages and disadvantages of retrospective studies are discussed further in chapter 6.

A major limitation of the work described in this chapter is sample size. The small number of individuals (N=21) with VCFS and a psychiatric disorder meant that formal statistical tests were unfeasible as there would be insufficient power to detect true effects. Such a small sample is also less likely to be representative of the larger population of individuals with VCFS and a psychiatric disorder. Large, well-characterised samples of patients with VCFS and psychiatric disorder would facilitate future work in this area.

There may also be an ascertainment bias within the sample. As discussed by Murphy et al (1999), the majority of individuals in the sample were ascertained because they had a child with VCFS. It is therefore possible that the patients collected in this way may represent a higher functioning group (as individuals with more debilitating illnesses are less likely to have children).

Further ascertainment bias may have been introduced by the fact that 6 individuals within the sample were recruited through psychiatric services. As well as inflating the levels of psychiatric illness reported in this sample of VCFS patients (as acknowledged by Professor Murphy and colleagues) it would also have had an impact on the types of illness represented within the sample. Individuals who have had contact with psychiatric services are more likely to have experienced a more severe clinical picture which has had a greater impact on their everyday levels of functioning.

A more representative sample could be ascertained through systematic recruitment. As discussed above, longitudinal studies which include detailed examination of the psychiatric phenotype at various stages throughout the lives of individuals with VCFS would allow more robust conclusions to be drawn regarding the psychiatric phenotype of individuals with this syndrome.

The result from this study suggests that depression is particularly prevalent in the VCFS sample. However, high rates of depression are also reported in schizophrenia samples that are not specifically associated with deletions on chromosome 22q11 (for example, reviewed in Hausmann and Fleischhacker 2000). More detailed examination of the phenotype in studies focussing on general schizophrenia samples would facilitate the identification of genetically-meaningful subtypes.

3.5 Conclusions

Detailed phenotype examination revealed high rates of mood-disturbance (depression in particular) in a sample of VCFS patients with a major psychiatric disorder. These results must be interpreted with caution due to the limitations discussed above. However, they are consistent with the hypothesis that a gene or

genes located in the deleted region of chromosome 22q11 may be associated with a psychiatric phenotype characterised by a mixture of psychotic symptoms and affective disturbance.

4 Phenotype Analysis in a Sample of Pedigrees Enriched for Schizoaffective Disorder

4.1 Introduction

The disadvantages of conducting molecular genetic studies into the functional psychoses based on the assumptions of the Kraepelinian dichotomy have already been covered extensively in this thesis. The concept of schizophrenia and bipolar disorder as separate disease entities suggests separate underlying aetiologies. In fact there is a degree of overlap in both the clinical features of these illnesses, and in the genes and chromosomal regions implicated in genetic analyses (as reviewed in Chapter 1).

The concept of schizoaffective disorder was developed to facilitate the classification of these "difficult-to-diagnose" cases, characterised by substantial overlap between features indicative of schizophrenia, and those typical of mood disorder. Kasanin (1994) first conceptualised schizoaffective disorder as "acute schizoaffective psychosis" in 1933. Since this time it has been operationalised and included in diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSMIV) (APA 1994), the ICD-10 Classification of Mental and Behavioural Disorders (WHO 1992) and the Research Diagnostic Criteria (RDC) (Spitzer et al. 1975).

Although useful in resolving diagnostic-dilemmas, schizoaffective disorder remains a poorly-defined category. Differences in the criteria for schizoaffective disorder specified by the individual diagnostic systems exist, and are summarised in table 4-1.

DSMIV-defined schizoaffective disorder is further complicated by the duration criterion for mood disturbance. What constitutes a "substantial proportion"

Table 4-1: Summary of diagnostic criteria for schizoaffective disorder for DSM-IV (APA 1994); ICD-10 (WHO 1992); RDC (Spitzer et al. 1975)

of the overall illness is subjective and therefore susceptible to diagnostic-bias. It also creates diagnostic instability, in that the proportion of affective disturbance over the total duration of illness is subject to change over time. An individual with prominent mood features in the first few years of illness, which then diminish may have an initial diagnosis of schizoaffective disorder which is later changed to schizophrenia.

Studies investigating the diagnostic stability of schizoaffective disorder have emphasised this issue. A study by Nardi et al (2005) reassessed a sample of 61 patients five-years after they had received a diagnosis of schizoaffective disorder. They found that less than half of these patients sustained their original diagnoses, with the majority (61%) subsequently meeting diagnostic-criteria for bipolar disorder. Another study found high rates of schizophrenia diagnoses in those originally diagnosed with schizoaffective disorder (Schwartz et al. 2000).

The nature of schizoaffective disorder has been an issue of debate since it was first described in the literature. One possibility is that schizoaffective disorder reflects the coincidental co-occurrence of schizophrenia and a mood disorder, both of which are relatively common illnesses. As discussed by Abrams and colleagues (2008) if this is the case then schizoaffective disorder would not merit unique identification in psychiatric nosology. Alternatively it may be a relatively specific disorder in its own right.

Several further nosological concepts have been suggested. These include: 1. That schizoaffective disorder is a variant of affective disorder (Pope et al. 1980); 2. That it is a variant of schizophrenia (Evans et al. 1999); 3. That it is an intermediate entity between schizophrenia and affective disorders (Tsuang and Dempsey 1979); 4. That is the mid-point of a continuum of the functional psychoses, with schizophrenia at one end and bipolar disorder at the other (Angst et al. 1983).

In their systematic review of the literature, Cheniaux et al (Cheniaux et al. 2008b) conclude that schizoaffective disorder is best conceptualised as a mid-point along a continuum of psychotic-affective illness, or as a heterogeneous group comprising patients with a mixture of affective disorders and schizophrenia. In another recent review (Lake and Hurwitz 2007b) the authors suggest that patients diagnosed as schizoaffective are more likely to have a psychotic mood disorder. They go as far as to suggest that schizoaffective disorder should be eliminated from the nomenclature, suggesting that patients with a schizoaffective diagnosis are more likely to receive sub-standard treatment.

Despite concerns regarding the validity of the schizoaffective diagnosis, it has proved useful both clinically (e.g. in allowing predictions to be made about illness course and treatment response) and in research. In terms of molecular genetic studies, cases involving intermediate forms of illness which involve features typical of both mood disorders and schizophrenia have been shown to be familial (Schulze et al. 2006b; Schurhoff et al. 2003b). Picking out cases involving mixed symptomatology would also help to "purify" samples by reducing heterogeneity. This would result in more homogeneous groups, more reflective of "prototypical" forms of schizophrenia and affective disorder, which may be more useful in molecular genetic studies.

To date, few molecular genetic studies have focussed on schizoaffective disorder as a diagnostic category, although as reviewed in chapter 1 there are numerous chromosomal regions that have been implicated in both schizophrenia, bipolar disorder, and in intermediate forms of the disorders (e.g. bipolar disorder with mood incongruent psychotic features) (O'Mahony et al. 2002). As with studies of schizophrenia and bipolar disorder, the heterogeneity of the schizoaffective diagnosis is likely to hinder genetic analyses.

Hamshere et al (2005) performed the first systematic genome-wide linkage scan to search for loci influencing susceptibility to schizoaffective disorder. They found a genome-wide significant signal on chromosome 1q42 (LOD = 3.54) – a region previously implicated in both schizophrenia and bipolar disorder. Suggestive evidence for linkage was also produced at regions 22q11 (LOD = 1.96) (see Chapter 3) and 19p13 (LOD = 1.85). This study provides evidence to support the hypothesis that there is genetic susceptibility which is specific to schizoaffective illness. Alternatively there may be a gene or genes within this region that have relatively broad effects, increasing risk for a range of disorders or symptoms.

The significant finding at chromosome 1q42 is particularly interesting as it is close to the gene Disrupted in Schizophrenia 1 (DISC1). DISC1 was originally discovered in a large Scottish pedigree, in which a balanced translocation between chromosomes 1q42 and 11q14 was found to segregate with a broad range of psychiatric illness manifestations, including schizophrenia, bipolar disorder, major recurrent depressive disorder, adolescent conduct disorder and emotional disorders (St-Clair et al. 1990). A maximum LOD score of 7.1 was produced using a broad diagnostic model including schizophrenia, bipolar disorder and major recurrent depression (Blackwood et al. 2001).

As mentioned previously, the chromosomal region 1q42 has been implicated in both schizophrenia and bipolar disorder (Porteous et al. 2006). Analyses focussing on the DISC1 gene have also shown significant association between numerous diagnoses including bipolar disorder, schizophrenia and schizoaffective disorder (Hodgkinson et al. 2004).

The implication of the chromosomal region containing a gene associated with such a range of psychiatric diagnoses, comprising both psychotic illness and affective

disturbance, makes it an attractive candidate for phenotype refinement, particularly in light of the study described above, which provides evidence for linkage in a sample enriched for schizoaffective disorder. This research, conducted by Dr Hamshere and colleagues, was conducted in the Department of Psychological Medicine in Cardiff University and it was possible to access hard copies of the data contributing to this study. This included detailed clinical information on each case in the sample.

In keeping with the theme of this thesis, my research aimed to further investigate the phenotype associated with the increased allele sharing identified at the linkage peaks in the sample described by Hamshere et al. Conducting research on this sample also allowed me to pilot methods to be used in the primary analyses of this PhD, described in Chapter 5.

4.1.1

4.2 Method

4.2.1 Sample

The sample used in this study comprised a subset of cases taken from the family-based samples originally collected as part of two independent linkage studies, one investigating bipolar disorder and the other schizophrenia (Bennett et al. 2002a; Lambert et al. 2005b; Williams et al. 1999). These samples formed the basis of my primary analyses, and detailed descriptions can be found in chapters 2 and 5.

From these samples, Hamshere and colleagues (Hamshere et al. 2005) selected pedigrees in which at least one family-member had a DSMIV-defined diagnosis of schizoaffective disorder, bipolar type and an additional member had a diagnosis of schizoaffective disorder bipolar type, schizophrenia or bipolar disorder (also according to DSMIV criteria).

The total sample consisted of 53 individuals from 24 pedigrees (11 from the schizophrenia family sample and 13 from the bipolar disorder family sample), which comprised 35 affected sibling-pairs. There were a total number of 24 females and 29 males, forming 9 male-male pairs, 10 female-female pairs and 16 mixed-sex pairs.

Each participant was interviewed by a trained psychologist or psychiatrist, using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990), a semi-structured interview aimed at assessing, measuring and classifying psychopathology and behaviour associated with psychiatric illness. Where possible, copies of the patients' case-notes had been reviewed, and a vignette was compiled summarising this information in detail.

4.2.2 Data available for a typical case

A typical case in this sample would consist of the following information:

- An interview vignette detailing information on episodes of illness ascertained using the SCAN semi-structured interview.
- Case-notes, usually in the form of a case-note vignette describing the illness on an episode-by-episode basis.
- Referral letters.
- Completed rating scales including an Operational Criteria symptom checklist (version 3.31; OPCRIT) (McGuffin et al. 1991), the Scales for Assessment of Positive and Negative Symptoms (Andreasen 1984a, 1984b) and the Global Assessment Scale (GAS) (Endicott et al. 1976).

4.2.3 Genetic Data Available

Estimations of the maximum-likelihood identical-by-descent (IBD) allele-sharing probabilities were available for each sibling-pair in the sample at the chromosomal

locations in which significant and suggestive linkage had been shown by Hamshere et al (2005), i.e. 1q42.2, 22q11.1 and 19p13.2.

4.2.4 Phenotype Assessment

All relevant data were examined in detail for each case, and ratings were made on 23 continuous variables, including the Bipolar Affective Disorder Dimension Scales (BADDS) the Global Assessment Scale (GAS): A full list of variables rated can be found in Appendix G.

Because this was a pilot for the methods used in creating the large harmonised dataset described (LHD) in Chapter 5, ratings made for this sample were identical to those made for the LHD with two exceptions: at this point, the additional OPCRIT items (28a – increased sexual behaviour and 54a – aggressive behaviour) had not yet been included. These ratings were added as a result of observations made during the rating of the pilot phase (which included work described in this chapter and the initial stages of the work undertaken in chapter 5).

Reliability

Each case in this sample was rated on the set of variables shown in Appendix G by both myself and Professor Nick Craddock. Ratings were made independently and meetings were held in which each case was discussed in detail and a consensus rating was agreed upon for each measure. Where no agreement could be reached, a third fully-trained individual was consulted (Dr Ian Jones) and a consensus was reached in this way. Excellent reliability was demonstrated for the majority of variables, as shown in Appendix H.

Analysis

Analysis was performed on a set of continuous variables (N=23). These were a subset of the ratings made for this sample, and were selected because it had been

possible to rate them on a substantial number of cases, there was sufficient variability within the data, and it was thought that they may reflect measures that are biologically relevant. For each sibling-pair, the between-sibling difference in the scores for each variable was squared to give a value used as the dependent variable in this analysis (i.e. (sib1 score (variableX) – sib2 score (variableX)) ^{2}). Using SPSS (Statistical Package for the Social Sciences), Spearman's Rho correlations were then performed on these data, correlating the dependent variables with the IBD scores for the linkage peaks at 1q42, 22q11 and 19p13. This is consistent with a method originally described by Haseman and Elston (1972), in which linkage was investigated by regressing the squared difference in trait values with the estimated proportion of IBD alleles shared. Corrections were then made for multiple testing (by multiplying the original p-value by the number of statistical tests performed – N=23).

The Spearman's Rho analyses were used to measure the strength and direction of associations between genetic similarity and phenotypic similarity (as measured by individual clinical variables) in a sample comprising related pairs. One-tailed tests were used as only significant negative correlations could be interpreted as being biologically meaningful (negative correlations indicate that increased allele sharing is associated with increased sibling-similarity on the variable being tested, whereas the reverse is true for positive correlations). For this reason all positive correlations were considered to be non-significant (see tables below).

A disadvantage of using the Spearman's Rho analysis is that it assumes that the pairs included in the sample are independent. If a single family contributes more than one pair to the sample, these pairs cannot be considered independent, therefore this assumption was violated in the SABP sample. However, only using a single pair

from each family reduces the sample size and therefore the power to detect significant effects.

To address this issue, data were first analysed using the full sample, which included all pairs. Where significant results were found, the analysis for that variable was then performed in a sub-sample of case which comprised a single pair from each family.

In the creation of the sub-sample of patients, a single pair was randomly selected from each family using an online computer program, in which data entered in list-form is randomised (www.random.org/lists). The identification numbers for each pedigree were entered into the program as a list and then randomised. The two individuals which were at the top of the list for each pedigree after randomisation were selected for inclusion within the smaller sample of independent pairs.

Because the region of 1q42 had been shown to be associated with schizoaffective disorder, one possible prediction was that IBD at this region would be associated with clinical variables which take into account both mood and psychotic symptoms. For example, the BADDS Incongruence dimension, which measures the relationship between mood and psychosis, or Extended Rating Scale 8 which rates each individual according to how "prototypically" affective vs. schizophrenic their overall clinical picture is considered (see chapter 5).

However, because this region had previously been implicated with schizophrenia, bipolar disorder and major recurrent depressive disorder (as reviewed in Porteous et al, 2006), and therefore may be considered a more general genetic risk factor for a broad range of psychiatric illnesses, it was difficult to make firm predictions.

4.3 Results

Results for chromosome 1q42

The results from the Spearman's-rho analyses for the IBD-data at 1q42 are presented in the table below.

Variable	Chromosome 1q42	
	Rs	**p**
BADDS Mania	-.136	.222
BADDS Depression	.079	NS
BADDS Psychosis	.111	NS
BADDS Incongruence	-.076	.345
GAS Depression	**-.737**	**.00021**
GAS Mania	-.013	.949
GAS Psychosis	-.275	.083
GAS Worst Ever	-.173	.169
GAS Past Week	-.276	.082
No. Manic Episodes	-.179	.078
No. Dep. Episodes	-.166	.143
AOO Impairment	**-.322**	**.044**
Age of first mania	.030	NS
Age of first depression	-.304	.055
Age of first psychosis	-.137	.141
ERS1	.236	NS
ERS2	.090	NS
ERS4	-.100	.310
ERS5	-.048	.397
ERS7	.207	NS
ERS8	-.028	.438
ERS9	-.116	.268
Course of Disorder	-.113	.132

Table 4-2: Results of Spearman's-rho analyses correlating genetic similarity at 1q42 with phenotypic similarity in a sample of sibling pairs. NS = Non-significant.

As shown in table 4-2, the genetic similarity of sibling-pairs at 1q42 is significantly correlated with the phenotypic-similarity in impairment, as measured using the GAS, during the worst episode of depression; a significant negative correlation was also found between the IBD-scores at 1q42 and sibling-similarity of onset-age. The two variables for which significant results were produced were then

analysed in the smaller dataset, comprising a single pair from each family. Results are presented in the table below, which compares results produced in the full sample, with the results produced in the sample of independent pairs. A significant result was maintained for GAS-depression but not for Age of onset.

Variable	Sample	N pairs	Rs	p
GAS-Depression	Full Sample	20	-0.737	0.00021
	Independent pairs only	18	-0.696	0.0029
Age of Onset	Full Sample	28	-0.322	0.044
	Independent pairs only	19	-0.273	$p > 0.05$

Table 4-3: Results of Spearman's-rho analyses correlating genetic similarity at 1q42 with phenotypic similarity, in the full sample and a reduced sample of independent pairs

The table below presents the results after corrections have been made for multiple testing (using the Bonferroni method). As shown, only the GAS-Depression scores in the full dataset remain significant, although a trend towards significance was found in the smaller dataset comprising independent pairs.

Variable	Sample	N pairs	Rs	p
GAS-Depression	Full Sample	20	-0.737	0.00483
	Independent pairs only	18	-0.696	0.0667
Age of Onset	Full Sample	28	-0.322	$p > 0.05$
	Independent pairs only	19	-0.273	$p > 0.05$

Table 4-4: Results of Spearman's-rho analyses correlating genetic similarity at 1q42 with phenotypic similarity, in the full sample and a reduced sample of independent pairs after corrections were made for multiple testing.

Results for 19p13 and 22q13

These analyses were also undertaken using IBD scores at the regions which showed suggestive linkage in the sample enriched for schizoaffective disorder, 19p13 and 22q11. These results are presented in the table below.

Variable	19p13 (1-tailed)		22q11 (1-tailed)	
	rs	p	rs	p
BADDS Mania	.211	NS	-.193	.138
BADDS Depression	.026	NS	-.058	.373
BADDS Psychosis	.084	NS	.305	NS
BADDS Incongruence	.298	NS	.141	NS
GAS Depression	-.178	.227	-.205	.193
GAS Mania	.355	NS	.097	NS
GAS Psychosis	.003	NS	-.269	.088
GAS Worst Ever	.051	NS	**-.418**	**.008**
GAS Past Week	.068	NS	.289	NS
No. Manic Episodes	-.074	.339	-.200	.129
No. Dep. Episodes	.065	NS	-.061	.372
AOO Impairment	-.162	.201	.080	NS
Age of first mania	.041	NS	-.083	.357
Age of first depression	-.296	.117	.355	NS
Age of first psychosis	.018	NS	.199	NS
ERS1	-.055	.354	.003	NS
ERS2	-.157	.189	-.216	.110
ERS4	.106	NS	-.173	.195
ERS5	.086	NS	.392	NS
ERS7	.040	NS	.004	NS
ERS8	-.045	.400	-.011	.476
ERS9	.012	NS	.186	NS
Course of Disorder	-.050	.389	-.225	.101

Table 4-5: Results of Spearman's-rho analyses correlating genetic similarity at 19p13 and 22q11 with phenotypic similarity in a sample of sibling pairs. NS = Non-significant.

As shown in table 4-5, a significant negative correlation was found between the genetic similarity of the siblings at 22q11 and the phenotypic-similarity for GAS scores during their worst ever episodes of illness. The analysis was then performed in the smaller sample, comprising a single pair from each family. As shown in table 4-6, a significant negative correlation was also found in the smaller sample of independent pairs. However, neither result withstood corrections for multiple testing.

Variable	Sample	N pairs	Rs	p
GAS-Worst Ever Episode	Full Sample	33	-0.418	.008
	Independent pairs only	21	-0.432	0.025

Table 4-6: Results of Spearman's-rho analyses correlating genetic similarity at 22q11 with phenotypic similarity in the full sample and a reduced sample of independent pairs

4.3.1 Review of Pilot Work

As well as the statistical analyses performed in the sample, this study also served as a means of piloting methods to be used in the bipolar disorder and schizophrenia family-based samples. There were three key issues that it was important to assess: utility of methods planned, length of time taken to complete a typical case, and reliability of ratings made.

Methods involved in rating each case were found to be straightforward, facilitated by an extensive training period undertaken prior to the rating of these cases (see Chapter 2) and by detailed, project-specific rating guidelines (see Chapter 5). This is supported by the generally excellent inter-rater reliability demonstrated, as discussed earlier.

The time-taken to complete each case was an important issue, as this would influence time-planning when completing the ratings for the large harmonised dataset. It was found that the time needed to complete each case, i.e. complete initial ratings, agree on consensus ratings and enter the data, was approximately two hours.

In terms of the Extended Rating Scales, Scales 3 (fluctuations in mood) and 6 (predominance of mixed affective illness) were not included in analyses due to the small number of participants who could be scored on these scales. This was most frequently due to the lack of scale-specific information in the cases (e.g. not enough information on specific symptoms to be able to state with confidence that an episode

of affective illness was mixed). A second reason was that neither scale could be used in individuals who had not experienced mood disturbance. However, due to the small sample size and the success of using these scales in previous samples (e.g. the VCFS sample) this did not cause particular concern. See Chapter 6 for further discussion regarding the utility of these scales.

4.4 Discussion

A set of clinical ratings were applied to a sample enriched for schizoaffective disorder-bipolar type, in which a genome-wide linkage scan had previously reported genome-wide significant linkage on chromosome 1q42, and suggestive evidence for linkage on chromosomes 19p13 and 22q11. Spearman's-rho analyses were used to test for associations between the IBD allele-sharing probabilities and the squared difference in sibling pair scores (DISPS; which gave an indication of how similar the pair was with respect to each variable). The only result that withstood corrections for multiple testing was that produced when IBD data at 1q42 were correlated with DISPS for level of impairment (as measured using the GAS) during the worst episode of depression (N=20, rs=-0.737, p=0.00483). A significant result was also found when this variable was analysed in the smaller sample comprising independent pairs, (N=18, rs=-0.696, p=0.0029), although this did not withstand corrections for multiple testing. The scatter plots below demonstrate the relationship between genetic-similarity (IBD scores) and phenotypic similarity for impairment during depression (squared difference of sibs' scores on the GAS scale rated for worst episode of depression). Graph 4-1 presents the data from the full sample and Graph 4-2 presents the data from the sample comprising a single pair from each family.

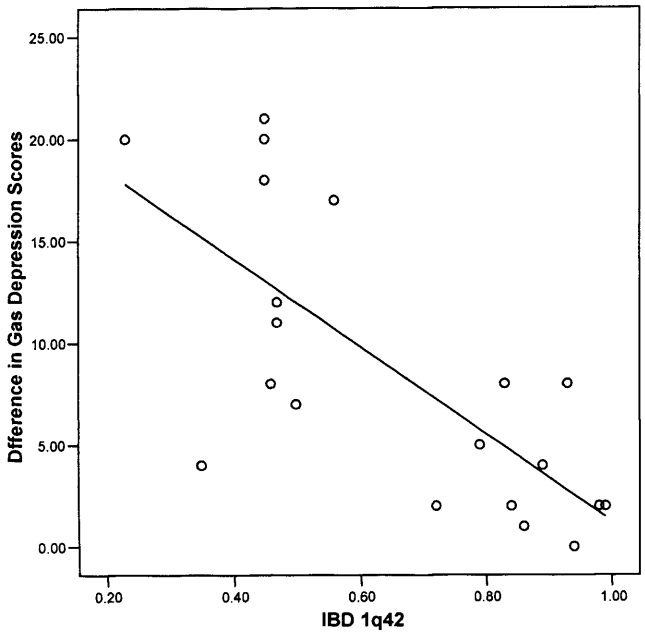

Figure 4-1: Scatter-plot to demonstrate the relationship between allele-sharing at 1q42 and sibling-similarity during their worst episode of depression (as measured using the GAS). All pairs included.

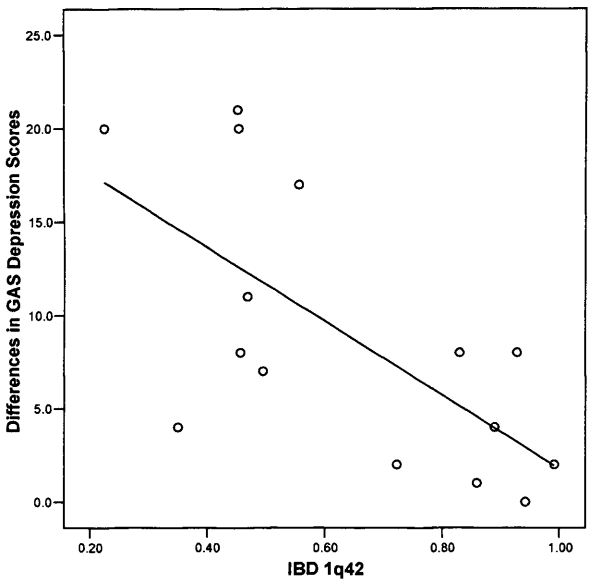

Figure 4-2: Scatter-plot to demonstrate the relationship between allele-sharing at 1q42 and sibling-similarity during their worst episode of depression (as measured using the GAS). Sample comprising independent sibling-pairs.

Significant negative correlations were also found when IBD sharing was correlated with age at onset (N=22, rs=-0.322, p=0.044). However, this significant result was not maintained after corrections were made for multiple testing, and was

not significant in the sample of independent sibling pairs. The fact that no significant result was found in the sample comprising independent pairs may be due to the decreased sample size (from N=29 to N=18), resulting in loss of power. An alternative explanation may be that the sibling-pairs excluded from this second analysis contributed to the initial significant result.

The analyses were also performed using the genetic data for the regions which showed suggestive evidence of linkage in the study by Hamshere et al (2005). No significant correlations were found for the data on 19p13. However, a significant negative correlation was produced when the estimated maximum IBD allele sharing probabilities were correlated with the similarity of siblings' scores on the Global Assessment Scale, measured during their worst ever episodes of illness (N=33, rs=-0.418, p=0.008). A significant result was also found when the data were analysed in the smaller sample of independent sibling pairs (N=21, rs=-0.432, p=0.025. However neither of these results withstood corrections made for multiple testing.

The fact that the two most significant results for these analyses related to scores on the Global Assessment Scale is of interest particularly because the significant results were found using the genetic data on different chromosomal regions. The results provide tentative support for the hypothesis that impairment caused by illness is influenced by genetic factors.

As well as significant negative correlations, significant positive correlations were also found using the Spearman's-rho correlations (i.e. for the BADDS Psychosis dimension and scores on Extended Rating Scale 5 measures the periodicity of illness episodes). As stated above, if IBD scores increase as the difference between sibs' scores on a particular variable decrease, this indicates that genetic similarity is associated with similarity for the variable being tested (e.g. the GAS-Depression

scores on 1q42). In contrast, a positive correlation suggests that the less genetically similar a related pair are, the more similar they are with respect to the variable being tested. Because this research aimed to identify variables which may be genetically influenced (which would be inferred by significant negative correlations), one-tailed tests were performed on the data and the positive correlations found were attributed to chance.

One strength of this study was the level of detail which had been collected when the patients were originally recruited. This facilitated the rating process and enabled ratings to be made on the majority of cases. As mentioned above, excellent reliability was also demonstrated for the majority of variables tested.

One of the main limitations of this study was the number of tests performed, leading to an increased risk of false positives. These multiple-testing issues came about due to the exploratory nature of this analysis, i.e. the aim was to identify hypotheses worth testing in future studies. Further work attempting to replicate these findings is important.

The Bonferonni method was used to correct for multiple testing. However, this approach assumes that all tests performed are independent; this was not the case for all of the measures tested in this study. For example, the Global Assessment Scale (GAS) was scored for 5 different states (GAS-Depression, GAS-Mania, GAS-Psychosis, GAS-Worst Ever, and GAS-Past Week) and scores for these would not always have been independent. If an individual's worst ever level of functioning occurred during an episode of psychotic depression, their scores on the GAS-Depression, GAS-Psychosis and GAS-Worst Ever measures would be the same. For this reason, it is likely that the corrections made for multiple testing were somewhat over-conservative.

A second limitation of the study was the relatively small sample-size. This was exacerbated in variables which were more difficult to rate or which could only be rated on a proportion of the sample (e.g. ERS7 could only be rated for individuals who had experienced an episode of mania). A larger sample would have increased power to detect smaller effects. However, this study was exploratory in nature and the significant results identified can be used to formulate and test hypotheses in future studies.

Despite the limitations discussed above, a significant negative correlation was produced which suggested that increased allele sharing was significantly correlated with greater similarity between siblings' scores on a measure of impairment in functioning experienced during their worst depressive episode.

4.5 Summary and Conclusions

In the first known study of its kind, Hamshere et al (2005) undertook genome-wide linkage analysis in a sample enriched for schizoaffective disorder, and provided evidence to support the existence of loci which influence susceptibility to schizoaffective illness. Further investigation of clinical characteristics associated with increased allele-sharing at these loci revealed a significant negative correlation between IBD score and the similarity of between-sibling scores on the GAS-Depression which measures impairment in functioning during the worst episode of depressive illness. This suggests that the impairment caused by the illness, particularly in relation to depressive episodes, may reflect underlying genetic variability in patients with schizoaffective illness, and therefore may be useful in future molecular genetic studies.

Future work involving large well-defined samples of patients with schizoaffective illness will help to further investigate the relationship between genetic factors and clinical measures in these illnesses.

5 Assessment of the Familiality of Phenotypic Variables in a Large Harmonised Dataset Comprising Families Enriched for Bipolar Disorder and Schizophrenia

5.1 Introduction

The work described in this chapter was undertaken with the aim of creating a large, richly-described dataset consisting of families enriched for schizophrenia and families enriched for bipolar disorder. This was made possible by implementing the methods described in chapter 2 on two large family samples which had been previously collected as part of ongoing molecular genetic studies within the Department of Psychological Medicine, Cardiff University. These samples were then combined to form a single Large Harmonised Dataset. Using the methods described below, it was subsequently possible to perform analysis to identify clinical variables which correlate within families.

5.2 Method

5.2.1 Participants

As stated above, the participants involved in this research were taken from the schizophrenia and bipolar disorder family-based samples, which are both described in detail in chapter 2. The samples were originally recruited as part of two separate linkage studies; one attempting to locate chromosomal regions implicated in schizophrenia and the other in bipolar disorder (Bennett et al. 2002b; Lambert et al. 2005a; Williams et al. 1999). Both samples were recruited in the 1990s, prior to the

commencement of the current research. Participants were recruited via mental health services, mental health support groups and articles in the national media. After applying the methods described below, the total sample comprised 835 individuals from 373 families. Further details of these samples are presented in the table below, as well as in the results section of this chapter

	Individuals from SZP family sample	Individuals from BPD family sample	Full Sample
Individuals (N)	399	436	835
Families (N)	198	175	373
Family Size (mean (sd))	2.02 (0.858)	2.49 (1.04)	2.24 (.978)
Males (N)	261	173	434
Females (N)	138	263	401
Age at recruitment (mean (sd))	41.67 (12.91)	46.31 (14.67)	44.10 (14.04)

Table 5-1: Summary of sample characteristics in the large harmonised dataset (LHD), and in the schizophrenia and bipolar disorder sub-samples from which the LHD was comprised.

5.2.2 The Rating Process

As described in detail in chapter 2, a common set of clinical measures were developed to be used in an identical way across each of the cases in the bipolar disorder and schizophrenia family-based samples. Ratings were made on approximately 200 variables for each case. These included:

- Ages of onset (years)
- Items from the Operational Criteria (OPCRIT) symptom checklist (McGuffin et al. 1991).
- Variables relating to illness course and onset.
- Dimensional ratings using the Bipolar Affective Disorder Dimension Scales (Craddock et al. 2004a).
- Global Assessment Scale (GAS) scores (Endicott et al. 1976) which give a measure of impairment caused by the illness.

- Measures of the number and length of illness episodes.
- Ratings made on the novel measures developed during this PhD (see chapter 2), the Extended Rating Scales (ERS).

A full list of items rated can be found in an example rating-sheet, found in Appendix I. A sheet such as this was completed for each case in the sample. Data were then entered into a Microsoft Excel spreadsheet.

5.2.3 Checks performed on the data

Data checks were carried out on this sample prior to conducting any analyses in the following ways:

- The minimum and maximum data-values for each variable were checked to ensure that they were consistent with those in the rating guidelines.
- Approximately 1 in 20 cases were subject to a detailed checking procedure in which the hard data (i.e. the data on the original rating-sheet) were checked against the data contained within the electronic data-file.
- Both gender and age of onset were rated twice, firstly in the "general information" section rated at the beginning of the case, and secondly in the "extra OPCRIT items", rated at the end of the case. Ratings made could be compared to check for consistency.

The Identification numbers for each case within the sample were checked against the "sample-of-origin" (SOO) rating. Cases originating from the schizophrenia family sample were rated "1" on the SOO rating; cases originating from the bipolar disorder sub-sample were rated as "2". Checks were made to ensure that the IDs allocated to schizophrenia-families and those allocated to bipolar disorder-families

were correctly identified prior to analyses. It was extremely important that this information was accurate because SOO was included as a covariate in the primary analyses, as discussed below. The SOO variable was also used to dichotomise the LHD into the two sub-samples so analyses could be performed on the schizophrenia and bipolar disorder data individually.

5.2.4 OPCRIT Item 84: A measure of data quality

The information contained in cases varied both in quantity and quality. In the majority of instances the data were detailed and informative, and it was therefore possible to be confident that ratings made were as accurate as possible.

However, the sample also contained cases for which the quantity or quality of information was such that the ratings made were likely to be less valid and reliable. For example, sometimes it had not been possible to acquire case-note information, despite the fact that numerous inpatient admissions had been mentioned in other sources of data (usually in the patient's interview vignette). Because it is common for people not to remember episodes of illness clearly, particularly those that happened many years prior to their participation in the research, the impression given of an individual's clinical picture based on the interview alone is almost inevitably going to be less accurate and detailed than if multiple sources of information were available for this case. This point is supported by Brockington et al (1992) who carried out a study examining the relative strength of data collected via patient interviews, informant interviews and casenotes. They found that, in general, the weakest source of information was that collected via patient-interview, whereas the strongest was the information collected from casenotes.

Sometimes multiple sources of information were available for only a relatively brief proportion of the illness. For example, an individual may have had a total illness-duration of 20 years, but detailed information was only available for 5 of these. Because many ratings are made over the lifetime course of the illness, this missing information is likely to have an effect on results. It was therefore important to be able to pick out such cases and exclude them from the primary analyses.

This issue was addressed by adapting a rating from the OPCRIT – OPCRIT 84: Information not credible. Originally this was a 0/1 rating used to indicate where the participant had given "misleading answers to questions" and/or had provided a "jumbled, incoherent or inconsistent account". I expanded this definition to include cases in which the quality or quantity of data could be called into question. A three-point scale was used: 0 = no major concerns with quality or quantity of data; 1 = some concerns with quality or quantity of data; 2 = significant concerns with quantity or quality of data. Anonymised examples of cases which would meet criteria 0, 1 and 2 are included in Appendix L.

Three major points were considered when scoring an individual on this variable: Firstly the level of detail contained within the case; secondly the number of sources of information considered in total; thirdly the proportion of the overall illness described within the case. Analyses could then be performed on either the whole sample, or on a sample comprising solely of cases in which the quality and quantity of data caused little or no concern. Test-retest reliability analyses were performed for OPCRIT Item 84 on a sub-set of 25 cases from the LHD. Excellent reliability was demonstrated (Kappa=0.903; $p<0.001$).

5.2.5 Selecting Samples for Analysis

In selecting the cases to be used in the primary analyses I aimed to maximise the validity of the data whilst maintaining as large a sample-size as possible. OPCRIT item 84 was used to indicate cases in which the quality or quantity of the data was considered insufficient to make ratings with confidence. Cases which scored a "1" or "2" on this item were excluded from the sample when certain variables were analysed. These variables included ratings made using the OPCRIT symptom checklist.

The OPCRIT symptom checklist allows the rater to indicate whether or not a symptom has been present during the illness. In the analyses described in this thesis, "context independent lifetime ever" ratings were used. A positive rating was used to indicate that the symptom had definitely been present at some point over the illness course, independently of the context in which it was experienced. A rating of "1", indicating that a symptom had definitely occurred, could be made with confidence because, to achieve this rating, a clear description of the symptom must have been present within the information available for the case. A rating of "0" was used where there was no evidence to indicate that the symptom had occurred. However, a score of "0" does not necessarily mean that this symptom had *not* occurred at some point during the lifetime course of the illness (or, of course, that it would not occur at a later stage of the illness). This introduced a rating-bias more likely to occur where data was considered "not credible" according to OPCRIT 84 (i.e. cases containing less information were less likely to include the descriptive detail necessary to rate these specific symptoms). To address this issue, when data from the OPCRIT symptom checklist were analysed, only cases which had been scored "0" on OPCRIT item 84 -

indicating that there were no major concerns regarding the quality or quantity of the information available for the case - were included within the sample.

Other variables for which uncertainty about the rating made could be indicated, were the Bipolar Affective Disorder Dimension Scales (BADDS). For these scales, uncertainty was indicated either by using a score of "-99" (unknown/uncertain) or by marking the rating made with a "*". The latter method was used where, given the evidence available, at least two trained researchers agreed that this rating was the most appropriate, although the evidence was not sufficient to assign this rating to the case with total certainty. For example, an instance in which this rating may be used would be where not enough symptoms had been described to constitute an episode of mood disturbance, although the overall evidence included within the case suggested that an episode had occurred. Because of the element of uncertainty indicated by a BADDS "*" rating, these data were excluded from the analyses.

For other rating scales, uncertainty was indicated by a score of "-99", which was given where the information available was not sufficient to make a confident rating; these were automatically excluded from any analyses.

5.2.6 Reliability of Ratings Made

As discussed in chapter 2, good to excellent reliability has been demonstrated for each of the measures selected for use within this research, both in the papers in which they were originally described (for example, Craddock et al. 2004b) and within the Mood Disorders Research Team (See Appendix K). However, it was crucial that my own ratings were consistent as it was these ratings that formed the dataset on which the primary analyses were undertaken. The extensive training period

undertaken during the early stages of my PhD provided me with the expertise required to carry out these procedures with confidence. Excellent inter-rater reliability has already been demonstrated in Chapter 4, for the pilot study on sibling-pairs enriched for schizoaffective disorder, in which ratings were made on a subset of cases from this sample. During the extensive period over which the ratings were made, I also participated in regular reliability meetings with the Mood Disorders Research team, thus minimising rater-drift.

Good reliability in the current large sample was maintained and assessed in the following ways:

Inter-rater reliability

Consensus meetings

This procedure is identical to that described in chapter 3. Over the duration of the period in which ratings were made, 20 cases were selected and rated by two fully-trained raters independently (myself and Professor Nick Craddock). Meetings were then held in which each case was discussed in detail, any discrepant ratings were examined and a consensus rating was agreed upon for each variable.

Reliability of cases rated in this way was assessed and good to excellent reliability was demonstrated for the majority of variables (ICCs range from 0.517-1.00; kappa scores from 0.455-1.00, see Appendix M), with only two variables scoring less then 0.6 (considered to represent good inter-rater agreement). These variables were "longest duration of mania" (k=0.517) and the OPCRIT item "delusions of passivity" (k=0.455).

One factor that differentiated this method from those described below was the fact that cases were not selected at random. In fact, several cases were selected because they were considered to be more difficult to rate. The detailed discussion

between several members of the team was therefore beneficial in highlighting these issues and coming to an agreement regarding the most appropriate rating.

It is possible that it was issues relating to the two variables for which only moderate agreement was demonstrated that resulted in these cases being selected for consensus rating in this way. This would account for the lower kappa scores. However, given that the cases selected for consensus-rating in this way were enriched for more "tricky" cases, it is reassuring that moderate to excellent agreement was demonstrated for all variables.

Consensus review of ratings

This was a shorter procedure which was utilised on the majority of cases in the sample. I undertook ratings on the full set of cases. These were often annotated with notes about how I had reached a particular score. Cases were then reviewed by Professor Nick Craddock, who examined each case, along with the ratings I had made and indicated any ratings with which he disagreed. Following this, I reviewed any changes suggested by Professor Craddock. Any significant disagreements could then be discussed, although in reality this occurred rarely, as where changes were made they tended to be slight. In this way a consensus rating was reached for each item.

To assess inter-rater reliability using method ii a sample of 20 cases were selected at random (10 from the schizophrenia dataset and 10 from the bipolar disorder dataset). This was achieved by entering a complete list of case ID-numbers for each sample into an online program, which randomises list-order (www.random.org). For each sample the top-ten cases in the list generated by the program were initially selected. Cases that had been consensus rated using method i) above were excluded and an additional case was added to the bottom of the list where this occurred. If more than one individual from the same family had been included on

the list, the family member who appeared lower down would have been excluded and a case would have been added to the bottom of the list (in reality this did not occur).

Inter-rater reliability was then assessed using ratings made by myself vs. ratings made by Professor Craddock. Excellent reliability was shown (ICCs range from 0.975-1.00; kappa scores from 0.902-1.00, as shown in Appendix N).

Test - Re-test Reliability

Because a single individual was largely responsible for rating this large sample over a period of almost two years, it was important to check for rater-drift. Rater drift occurs when an individual's rating techniques change gradually over time. Rater-drift can be assessed by re-rating a series of cases that were rated at an earlier stage of the research.

Twenty cases were selected at random using the list-randomisation method described above (again, 10 were selected from the schizophrenia sample and 10 from the bipolar disorder sample) each of which I rated for a second time (without referring to the ratings made previously). Reliability analyses were then performed to compare the ratings made for each measure at the two different time-points.

Good or excellent reliability was demonstrated for all variables tested (ICCs range from 0.734-1.00; kappa scores from 0.64-1.00, see Appendix O) thus providing reassurance that no significant rater-drift had occurred over the time-period in which ratings had been made.

5.2.7 The Creation of a Large Harmonised Dataset

As described in chapter 2 and in the introduction above, the main aim of this research was the formation of a large harmonised dataset comprising families enriched for illnesses representing a spectrum of the functional psychoses. To do this,

cases from the bipolar disorder and schizophrenia family-based samples were rated using identical methods on the same set of clinical measures. On completion of the methods described above, the individual samples could be combined to form a large sample of 835 individuals representing 373 families, on which analyses could be performed.

5.2.8 Statistical Methods

Prior to undertaking any statistical analyses, advice was sought from experts in the area who are based in the Department of Psychological Medicine: Professor Peter Holmans, Professor of Biostatistics and Genetic Epidemiology; and Dr Marian Hamshere, Research Fellow in Statistical Genetics. There were several issues to take into consideration when selecting a method of analysing familiality in this dataset. Firstly, data did not follow the normal distribution for any variable tested, despite attempts to transform the data; therefore the assumptions of many parametric statistical tests were violated.

A second issue involved the use of methods which utilised paired-data (i.e. sib1 vs. sib2). Because many families consisted of more than 2 individuals, using these methods a single family would often contribute multiple, non-independent pairs to the sample. To create a sample consisting solely of independent pairs, one pair from each family could be used. However, this would result in a large loss of data and therefore loss of power.

Thirdly, the option of including covariates within the statistical model was desirable (for reasons discussed later on in this chapter).

The statistical methods considered were: i) Spearman's Rho correlations (Statistical Package for the Social Sciences, Version 12.0.2, 2004); ii. Tetrachoric and polychoric correlations (performed using Mx) (Neale et al. 2003); iii) Mixed-effects regression analysis (performed using The FORTRAN programs MIXOR for ordinal data, and MIXREG for continuous data; (Hedeker and Gibbons 1996a).

After considering all three main options, mixed-effects regression was selected for the primary analyses. This is described below, along with the advantages and disadvantages of all three methods considered.

Mixed Effects Regression Analysis

The mixed-effects regression methods used in the primary analysis of this thesis employed a logistic regression approach to test data-likelihood under different models (Hosmer & Lemeshow, 1989).

Logistic regression aims to obtain the best-fitting model to describe the relationship between a dependent variable and a set of predictor variables by seeking to maximise the likelihood of observing sample values. Binary logistic regression seeks to predict membership of two categories, using logit transformations. The methods described here further extend this process to consider multiple ordinal categories.

Mixed-effects regression can be used to analyse clustered data - in this study clusters represented families. Analyses could be performed using the FORTRAN programs MIXOR (for binary and ordinal outcome variables) and MIXREG (for continuous outcome variables) (Hedeker & Gibbons, 1996a). However, MIXREG analyses data on the assumption that they are normally distributed. As stated above

this was not the case for any variable considered here, therefore the assumption of normality would be consistently violated. This posed a major problem in the analysis of continuous data which was overcome by creating ordinal categories from continuous variables and analysing these data using MIXOR

The analysis was carried out under two different models: 1. All data were assumed to be independent; 2. Data within clusters (families) were assumed to be dependent. The degree of dependency was estimated by the program and an intra-class correlation was produced for each outcome variable.

These methods have a number of advantages. Unlike the other methods considered, both programs allow for the consideration of differing numbers of individuals per cluster/family. This meant that the entire dataset could be included in analysis, thus making optimal use of the data. Further, because data weren't paired, order effects were avoided as was the issue of non-independent pairs (this is discussed below).

MIXOR and MIXREG also allow for the inclusion of covariates within the model, allowing for variables which may influence the phenotype, such as gender, to be controlled for. This is discussed more fully later in this chapter.

Both MIXOR and MIXREG have been used successfully in previous studies, including that by Schulze et al. (2006a) which used both programs to look at the familiality of phenotypic variables in a sample of bipolar disorder-pedigrees.

Other Statistical Methods Considered

Spearman's Rho – non-parametric correlations performed using SPSS.

Spearman's Rho correlations can be performed on non-parametric data, to assess the magnitude and direction of an association between two variables (in this case it is the association of scores between two related individuals for each variable considered). One of the main advantages of Spearman's Rho correlations is that, once the data are in the correct format, analyses are easy and quick to perform, with the SPSS output producing a correlation coefficient and a p-value. A second advantage is that the same method can be used on both continuous and ordinal data, meaning that the raw data for each variable can be used.

In terms of disadvantages, results produced using this method are influenced by the order of the siblings in the pairs, i.e. sibling 1 vs. sibling 2; switching the order of these may give different results. Secondly, because this analysis utilises paired-data, there are problems caused by non-independent pairs from the same family. In using this method, a decision would have had to be made as to whether to include all pairs within the analyses, accepting that many of them are non-independent, or whether to use a single pair from each family which would result in decreased power and wasted data.

Tetrachoric and polychoric correlations

Tetrachoric and polychoric correlations can be used where dichotomous and ordinal variables are assumed to represent underlying continuous bivariate normal distributions. These have been commonly used in twin and sibling-pair studies (e.g. Cannon et al, 1998; Sullivan et al, 2003). They could be performed on this sample using Mx (Neale et al. 2003) (www.vcu.edu/mx) in conjunction with scripts written by Dr Stuart McGregor in the Department of Psychological Medicine at Cardiff University.

Because this method of analysis utilises paired-data, the issues regarding non-independent pairs, discussed above, are also relevant here. Mx also requires the use of scripts which require increased knowledge of computer-programming when compared with the other methods considered in this chapter. This method was therefore disregarded for the primary analyses in favour of MIXOR, which uses a mixed-effects regression model to analyse data.

5.2.9 The Primary Analyses

Because it was the only method described which was consistent with using the entire dataset, did not require normally distributed data and allowed for variation in family-size, MIXOR (Hedeker and Gibbons 1996a) was used in the primary analyses. This required the transformation of continuous data into ordinal categories, as described at a later point in this chapter.

MIXOR can be used to perform mixed-effects ordinal regression. In this study, participants were clustered within families. The mixed-effects model assumes that data within clusters (i.e. families) are dependent and variance between families is used to estimate the degree of dependency.

Before the analyses could be performed, the data-file containing the information to be analysed had to be set up in a very precise way. Data-files were prepared in spreadsheet-form using Microsoft Excel. To ensure that MIXOR would run properly the data had to be in standard-text format, each field had to be separated by at least one blank and only numerical data could be included in the file. This was achieved by preparing the files in Microsoft Excel and saving them in "Text (tab-delimited)" format. Letters (e.g. "m" indicated that only mixed episodes had occurred in the BADDS Mania dimension), and symbols (e.g. "+"s and "*"s – see Chapter 2) were replaced with numerical indicators (e.g. ".1" replaced each "+"). Blanks within

the data prevented the program from running so a value of "-99" was used to indicate missing data. Careful records were kept specifying which column of data contained each variable (column headings could not be included in the files).

Data-checks could then be made by comparing data within the input file used in the analysis with the data in the original raw-data file, using Excel formulae. Examples of input-data and the output produced by MIXOR can be found in Appendices P-Q.

5.2.10 The inclusion of "sample-of-origin" and gender as covariates

A major advantage of using MIXOR as opposed to the other methods of analysis considered is that it allows for the inclusion of covariates within the model. Doing so controls for any familiality which may be caused by these effects. Because previous studies have identified gender-effects in both schizophrenia and bipolar disorder samples (for example, Benedetti et al. 2007; Tang et al. 2007), gender was included as a covariate within the model.

A second variable which was included as a covariate was sample-of-origin. This relates to whether a family was originally collected as part of the bipolar disorder sample or as part of the schizophrenia sample. Although there are many clinical overlaps between bipolar disorder and schizophrenia, there are also features that are more distinctive of one syndrome than the other. Further, certain rating scales (for example the BADDS Incongruence dimension) were designed with these more diagnosis-specific characteristics in mind (for example, one anchor point is dictated by the presence of the "S set" of symptoms, traditionally associated with a more schizophrenic clinical-picture, as discussed in chapter 1). If sample-of-origin was not controlled for, in a number of cases significant correlations produced could be attributed to differences between the two separate samples which make up the large

harmonised dataset – schizophrenia families vs. bipolar disorder families. The aim of this thesis was to look for correlations over and above this simple dichotomy.

MIXOR: Set-up prior to analysis

To set the MIXOR program up prior to performing analysis in this sample the following had to be specified for each file of data: the electronic location of the definition, input and output files; the field containing Level-2 Units (family ID numbers); value used to indicate missing data (in this case, "-99"); and fields containing covariates.

Before running the analysis, the field containing the outcome-variable of interest had to be specified along with the number of ordinal outcome variable categories, and the number associated with each category (e.g. 3 categories defined using number 0, 1 or 2).

For each variable, the analysis was run twice, using two different models – the first included clustering (including family membership as a random effect), the second ignored clustering. An estimated intra-class correlation was produced, representing the proportion of the variance that is accounted for by family membership. To obtain a p-value, a likelihood-ratio test was performed for each variable, comparing the log-likelihood values for each model.

The Formation of Ordinal Categories from Continuous Variables

The continuous variables considered in this study were as follows: Scores on the BADDS; GAS scores; number and duration of episodes of illness; ages of onset; number of hospital admissions and length of the longest admission; proportion of time admitted over the duration of illness; proportion of time individual had been well since illness onset; and the Extended Rating Scales. Continuous measures were taken

one at a time, considered carefully, and ordinal categories were created for each. The following points were taken into consideration during this process:

Technical Issues

The distribution of the data. Histograms were produced for each measure and natural breaks in the data were noted. It was considered to be more appropriate to divide data into separate categories at points of rarity.

The number of individuals included in each ordinal category. MIXOR is most likely to produce stable parameter estimates when the number of individuals per category is fairly balanced. This was not possible for all variables (see discussion). Where categories contain relatively few individuals, the program will not produce an output. In general, as long as categories contained at least ten individuals the program would run correctly.

Issues Relating to Phenotype

Anchor points included in scale definitions. These could be used to differentiate adjacent scores which were more similar from adjacent scores which were less similar. For example, on the BADDS Mania dimension, scores 78 and 79 are more similar than scores 79 and 80. The former both indicate that at least one manic episode has occurred; the difference in scores is due to the number and severity of additional episodes. In the latter example, the higher score reflects that the individual has had a single incapacitating episode of illness (for example, the episode may have included psychotic features, or may have resulted in the individual being sectioned under the Mental Health Act). Therefore, although quantitatively identical, the difference between scores 79 and 80 is qualitatively greater than the difference

between 78 and 79. It was considered more appropriate to divide data into separate categories at adjacent scores that were less similar.

The number of ordinal categories for each measure. MIXOR allowed a maximum of 16 ordinal categories to be specified for each measure. To better reflect the continuous nature of the data, as many ordinal categories as was appropriate were defined for each continuous variable.

A summary of the ordinal-categories along with details of the data-points in the raw-data they correspond to can be found in Appendix R.

As discussed below, the analysis was performed firstly on the large harmonised dataset (LHD). Where significant intra-familial correlations were found in the LHD, the sample was dichotomised and the analyses were performed on the bipolar disorder and schizophrenia sub-samples separately. On a number of occasions it was not possible to use identical ordinal categories specified for the LHD. Splitting the large dataset into the two sub-samples meant that the distribution of data differed from the LHD. It was common for certain categories not to be represented at all in a single sub-sample. An example of this is shown below.

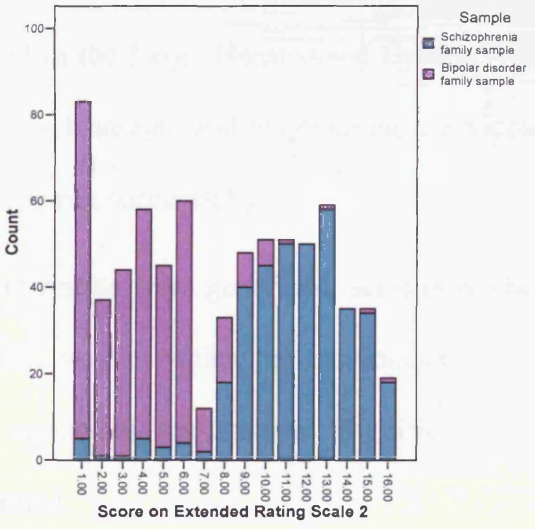

Figure 5-1: The distribution of ordinal categories for Extended Rating Scale 2 showing the relative contributions from the SZP and BPD sub-samples for each ordinal category.

In the case of Extended Rating Scale 2, ordinal category "14" did not contain any individuals at all in the bipolar disorder sample, therefore MIXOR did not run and no output was produced. To deal with this problem, for each sub-sample the distribution of scores within ordinal categories was examined. Where possible, the ordinal categories were kept the same. Where there were fewer than 10 individuals within a specific category, the categories either side were examined (e.g. if looking at ERS2 "14", ERS2 "13" and ERS2 "15" would be examined). Taking into consideration the number of individuals in the adjacent categories, along with points discussed above, categories with few numbers would either be combined with adjacent categories, split between adjacent categories or removed altogether (in cases where a specific category was "empty, e.g. ERS2 "14" above).

The opposite problem also occurred, in that a large proportion of the subgroup would fit into a single ordinal category. For example, ERS2 "1" above contains a large proportion of the Bipolar Disorder Sample. In this case, again examining the data and taking into consideration the points discussed above, data may be split to better reflect the distribution within the sub-sample.

This method ensured that ordinal categories remained as similar as possible to those originally specified in the Large Harmonised Dataset, whilst still representing the variation within each sub-sample and maintaining the necessary criteria required for the MIXOR program to run successfully.

Where significant results were generated, sensitivity checks were performed. This involved altering the way in which the continuous variables were reduced to ordinal categories, and re-running the analyses. Significant results were maintained for all of the variables tested.

Program-Performance Checks (MIXOR)

It was possible to check that the MIXOR program had run correctly for each variable. Maximum and minimum values were produced for each variable considered in the analysis, which could then be checked against the minimum and maximum values in the raw data file. For each variable, MIXOR produces means and standard deviations. When the program has run correctly, these are identical to those produced using SPSS in the raw data file. These checks provided reassurance that the program was running properly and producing meaningful results.

5.2.11 Performing the Primary Analyses

The mixed-effects logistic regression analysis performed using MIXOR was undertaken firstly on the data contained in the Large Harmonised Dataset. P-values were then calculated for the intra-class correlation produced for each variable (using likelihood-ratio tests). Where a significant intra-familial effect was demonstrated, after controlling for sample-of-origin and gender, the data from the LHD was dichotomised into the individual subsets, i.e. the schizophrenia and bipolar disorder sub-samples. After carrying out the procedure described in the "creation of ordinal categories from continuous variables" section above, the analysis was then performed in each individual subset, and p-values were produced for each variable. Output was discussed with Professor Peter Holmans.

5.3 Results

As stated above, the final sample comprised 835 individuals, of which 436 originated from the bipolar disorder family sample and 399 from the schizophrenia sample. The table below gives some general phenotype information on the sample:

Variable	Large Harmonised Dataset	Schizophrenia Sub-sample	Bipolar Disorder Sub-sample
Duration of illness (years) Mean (sd)	18.34 (11.949)	17.2 (11.384)	19.37 (12.362)
Age of onset (years) Mean (sd)	25.18 (9.474)	23.90 (8.078)	26.37 (10.467)
LE Psychosis %	81.0	96.9	64.0
LE (Hypo)Manic Episode (BADDS>39) %	55.9	25.5	83.0
LE Depressive Episode (BADDS>39) %	71.1	50.9	89.2
LE Manic Symptoms (BADDS>19) %	62.0	33.8	86.0
LE Depressive Symptoms (BADDS>19) %	81.0	66.6	93.9

Table 5-2: General information on the large harmonised dataset and the two sub-samples from which it was created.

The newly developed Extended Rating Scales, designed to be used on sets of data comprising features of both psychotic and affective illness, formed an important part of this work; the medians and ranges for each scale are presented in the table below. Number of individuals included in the analysis are also included to provide information on the number of cases for which it was possible to make a positive rating (as opposed to a missing data value) thereby giving an indication of scale-utility.

Extended Rating Scale	Range of scale	Large harmonised dataset	Schizophrenia sub-sample	Bipolar disorder sub-sample
ERS1: Predominance Mania - N, median (range)	0-100	N=669 38 (100)	N=254 0 (100)	N=412 50 (100)
ERS2: Relationship between psychosis and mood disturbance - N, median (range)	-20-120	N=725 55 (140)	N=371 85 (140)	N=357 10 (139)
ERS3: Fluctuations in mood - N, median (range)	0-100	N=576 0 (100)	N=324 0 (99)	N=250 0 (100)
ERS4: Instability of clinical state - N, median (range)	0-100	N=616 20 (100)	N=285 20 (100)	N=319 20 (98)
ERS5: Periodicity of acute phases of illness - N, median (range)	0-100	N=696 90 (97)	N=318 90 (97)	N=377 90 (96)
ERS6: Predominance mixed episodes - N, median (range)	0-100	N=718 0 (100)	N=350 0 (100)	N=367 0 (100)
ERS7: Most dysphoric manic episode - N, median (range)	1-100	N=398 30 (100)	N=92 40 (100)	N=306 30 (100)
ERS8: Prototypical SZP vs prototypical affective disorder - N, median (range)	1-100	N=778 27 (100)	N=367 70 (100)	N=410 7 (94)

Extended Rating Scale	Range of scale	Large harmonised dataset	Schizophrenia sub-sample	Bipolar disorder sub-sample
ERS9: Predominance negative defect state - N, median (range)	1-100	N=755 0 (100)	N=348 10 (100)	N=406 0 (70)
ERS10: Catatonic symptoms - N, median (range)	0-4	N=779 0 (4)	N=366 0 (4)	N=412 0 (3)
ERS11: Disorganised behaviour - N, median (range)	0-2	N=647 1 (2)	N=347 2 (2)	N=297 0 (2)

Table 5-3: Table showing N, median and range for each extended rating scale in the large harmonised datasets

The tables below summarise the results from the primary analyses. All variables in which significant familiality was found in the large harmonised dataset are presented, along with results for analyses performed in the sub-samples. Results are presented in the following 4 tables:

1. *Variables showing significant familiality in the large harmonised dataset (LHD) and both sub-samples.*
2. *Variables showing significant familiality in the LHD and the schizophrenia sub-sample only.*
3. *Variables showing significant familiality in the LHD and the bipolar disorder sub-sample only.*
4. *Variables showing significant familiality in the LHD only.*

Variable	Large Harmonised Dataset N=835			Schizophrenia Sub-sample N=399			Bipolar Disorder Sub-sample N=436		
	N*	ICC	p-val**	N*	ICC	p-val**	N*	ICC	p-val**
Length of Longest ADM	622 (355)	0.287	**.000575**	320 (178)	0.295	**.014185**	302 (157)	0.252	**0.018417**
Age at first admission	660 (349)	0.257	**0.000592**	345 (188)	0.289	**0.004483**	315 (161)	0.227	**0.043807**
Age at first impairment	752 (362)	0.223	**0.00108**	362 (193)	0.249	**0.007335**	390 (169)	0.200	**0.049972**
Course of Disorder	803 (371)	0.163	**0.003936**	377 (197)	0.233	**0.046044**	426 (174)	0.176	**0.022756**
ERS8	774 (362)	0.127	**0.028229**	366 (192)	0.201	**0.027985**	408 (170)	0.158	**0.023367**

Table 5-4: Variables which showed significant familiality in the large harmonised dataset (LHD) and both the schizophrenia and the bipolar disorder sub-samples.
N*= Number of individuals (number of families). NA = Variable not analysed due to lack of variability within the sample or floor/ceiling effects. ** 1-tailed.

Variable	Large Harmonised Dataset N=835			Schizophrenia Sub-sample N=399			Bipolar Disorder Sub-sample N=436		
	N*	ICC	p-val**	N*	ICC	p-val**	N*	ICC	p-val**
LE Cannabis Abuse	632 (328)	0.689	**0.000692**	328 (186)	0.777	**0.0000561**	NA	NA	NA
Aggressive Behaviour	655 (326)	0.273	**0.000754**	324 (177)	0.332	**0.003238**	331 (145)	0.144	0.175538
GAS Psychosis	598 (329)	0.258	**0.000967**	370 (195)	0.264	**0.004366**	228 (134)	0.297	0.057433
BADDSI	586 (324)	0.224	**0.004835**	362 (192)	0.285	**0.003978**	224 (132)	0.181	0.190856
ERS2 (extended BADDSI)	720 (352)	0.171	**0.008974**	369 (193)	0.265	**0.004919**	351 (159)	0.119	0.174016
Age at first contact	698 (353)	0.154	**0.010922**	357 (190)	0.241	**0.008363**	341 (163)	0.160	0.072433
AOO Psychosis	476 (289)	0.221	**0.014121**	303 (180)	0.334	**0.00341**	168 (110)	0.039	0.821332
Chronic Defect State (0/1)	757 (367)	0.351	**.040519**	348 (194)	0.363	**.039412**	NA	NA	NA
Other Substance abuse	572 (315)	0.587	**0.015648**	283 (172)	0.537	**0.046044**	289 (143)	0.66	0.219751
Deterioration since onset	715 (362)	.251	**0.046044**	362 (196)	0.391	**0.032309**	353 (166)	0.069	0.711282

Table 5-4: Variables which showed significant familiality in the large harmonised dataset (LHD) and the schizophrenia sub-sample only. N*= Number of individuals (number of families). NA = Variable not analysed due to lack of variability within the sample or floor/ceiling effects. ** 1-tailed.

Variable	Large Harmonised Dataset N=835			Schizophrenia Sub-sample N=399			Bipolar Disorder Sub-sample N=436		
	N*	ICC	p-val**	N*	ICC	p-val**	N*	ICC	p-val**
GASM	466 (270)	0.257	**0.001819**	109 (81)	0.079	0.756684	357 (171)	0.201	**0.034881**
Psychomotor retardation	720 (355)	0.268	**0.003573**	345 (188)	0.089	0.559253	375 (167)	0.367	**0.002146**
GASWE	811 (370)	0.156	**0.004466**	385 (197)	0.164	0.059474	426 (173)	0.167	**0.02302**
Diminished Libido	723 (356)	0.309	**0.005054**	346 (189)	0.095	0.621332	377 (167)	0.43	**0.002343**
Age at first mania	295 (190)	0.355	**0.010842**	66 (52)	0.361	0.303444	229 (138)	0.341	**0.023206**
Negative FTD	705 (348)	0.355	**0.014177**	321 (180)	0.268	0.093096	385 (168)	0.601	**0.021758**
Marital Status	710 (351)	0.273	**0.020486**	344 (188)	0.222	0.210498	366 (163)	0.336	**0.038157**
Anhedonia	717 (356)	0.190	**0.048**	348 (189)	0.008	0.950	369 (167)	0.367	**0.009**
ERS10	749 (364)	0.229	**0.016**	356 (192)	0.112	0.380	393 (141)	0.366	**0.010**
ERS11	625 (330)	0.358	**0.024**	339 (189)	0.093	0.650	286 (141)	0.716	**0.002**
ERS7	398 (231)	0.216	**0.030712**	92 (71)	0.139	0.65634	306 (160)	0.253	**0.024203**
BADDSP	729 (355)	0.147	**0.032996**	363 (193)	0.089	0.425527	352 (160)	0.223	**0.024527**
Excessive Self Reproach	720 (356)	0.187	**0.033034**	348 (189)	0.013	0.91647	372 (167)	0.337	**0.007146**

Variable	Large Harmonised Dataset N=835			Schizophrenia Sub-sample N=399			Bipolar Disorder Sub-sample N=436		
	N*	ICC	p-val**	N*	ICC	p-val**	N*	ICC	p-val**
DelsofInfl/Persecution01	677 (345)	0.223	**0.039066**	NA	NA	NA	339 (159)	0.316	**0.018407**

Table 5-5: Variables which showed significant familiality in the large harmonised dataset (LHD) and the bipolar disorder sub-sample only. N*= Number of individuals (number of families). NA = Variable not analysed due to lack of variability within the sample or floor/ceiling effects. ** 1-tailed.

Variable	Large Harmonised Dataset N=835			Schizophrenia Sub-sample N=399			Bipolar Disorder Sub-sample N=436		
	N*	ICC	p-val**	N*	ICC	p-val**	N*	ICC	p-val**
OP49 Positive FTD	681 (345)	0.448	**0.012617**	301 (177)	0.328	0.097254	382 (168)	0.659	0.075094
No Admissions	806 (367)	0.171	**0.014692**	381 (194)	0.164	0.053156	425 (173)	0.123	0.148169
Age at first depression	296 (200)	0.313	**0.027217**	108 (84)	0.369	0.183258	118 (116)	0.317	0.065752
ERS9 Chronic Defect state	751 (364)	0.184	**0.034616**	347 (194)	0.185	0.058797	404 (170)	0.172	0.422987

Table 5-6: Variables which showed significant familiality in the large harmonised dataset (LHD) only. N*= Number of individuals (number of families). NA = Variable not analysed due to lack of variability within the sample or floor/ceiling effects. ** 1-tailed.

5.4 Discussion

5.4.1 Summary of Results

Performing systematic clinical ratings in both a sample comprising families enriched for schizophrenia and a sample comprising families enriched for bipolar disorder, enabled these two samples to be combined to form a single, well-characterised, large harmonised dataset, representing a spectrum of psychotic-affective illness. Exploratory analysis, using a mixed-effects regression model in which sample-of-origin and gender were included as covariates, identified significant intra-familial correlations for 31 variables. Subsequent analyses performed separately in the schizophrenia and bipolar disorder sub-samples revealed that 4 of these variables were also significant in both the schizophrenia and bipolar disorder sub-samples (see table 5-4); 9 were also significant in the schizophrenia sub-sample, but not in the bipolar disorder sub-sample; see table 5-5); and 14 were also significant in

the bipolar disorder sub-sample (but not in the schizophrenia sub-sample; see table 5-6).

Discussion of methods used in analysis

Mixed-effects ordinal regression analyses were performed on the data, using the Fortran program MIXOR (Hedeker and Gibbons 1996a). For each variable, an intra-class correlation coefficient was generated, representing the proportion of the variance accounted for by family membership. One of the main advantages of this method was that it allowed for variation in family size. In the final dataset, the number of individuals per family ranged from one to seven (with a mean family size of 2.23). Other methods considered used paired-data and assumed that all pairs were independent; because a single family would frequently have contributed multiple pairs to the dataset, this assumption would have been violated. Using a single pair from each family would have addressed this issue, but would also have lead to a dramatic loss of data.

A second and extremely important advantage of using MIXOR was that it allowed for the inclusion of covariates within the model, and thus controlled for any familiality which may be caused by these variables. Sex-differences in clinical variables have previously been demonstrated in both studies of schizophrenia (Tang et al. 2007) and bipolar disorder (Benedetti et al. 2007), therefore gender was included as a covariate.

A second covariate included in the model was sample-of-origin. This referred to whether an individual was originally recruited to the study in the sample enriched for bipolar disorder, or in the sample enriched for schizophrenia. As stated previously, although there are many overlapping clinical features which occur in both disorders, there are also certain features of illness that are more characteristic of one

or the other. For example, by definition, manic symptoms such as elation and irritability will occur more frequently in families enriched for bipolar disorder. If "irritable mood" is analysed in the large harmonised dataset, without controlling for sample-of-origin, an intra-class correlation coefficient of 0.372 is produced ($p<0.001$). However, if sample-of-origin is included as a covariate within the model, the intra-class correlation is dramatically reduced to 0.057 ($p>0.05$), suggesting that the strong correlation produced in the first analysis was largely due to differences between the samples. The aim of this research was to identify variables that showed familiality over and above that caused by inter-sample differences; controlling for sample-of-origin made this possible.

Because none of the data passed tests for normality (despite attempts made to transform the data), MIXREG – the Fortran program designed for use in continuous data, which assumes that data are normally distributed (Hedeker and Gibbons 1996a) – could not be used. It was therefore necessary to convert continuous variables into ordinal categories before they could be analysed in MIXOR. It is inevitable that whenever continuous data are converted into fewer, more general categories, some fine-detail of the data will be lost. As described in the methods section, a considerable amount of care was taken when converting the continuous data into ordinal categories; for example, high numbers of categories were created to keep loss-of-information to a minimum. Even so, it is important to consider this when interpreting results as it is possible that significant correlations may be seen as a spurious result of the way the categories were created. In the current research, reassurance that this was not the case and that the results reflected a genuine relationship in the data, was provided via two means. Firstly sensitivity testing, in

which significant correlations were re-tested using a different arrangement of categories (see methods) – all variables tested remained significant.

Secondly, variables in which significant results were produced using the mixed-effects ordinal regression analysis were also analysed using Spearman's Rho correlations, as performed in SPSS (Statistical Package for the Social Sciences, Version 12.0.2, 2004). To overcome the issue of non-independent pairs, a randomly-selected single pair was used from each family (see methods). Spearman's Rho analyses were performed on the variables which were found to be significant when analysed using the mixed-effects regression method, firstly in the LHD, and subsequently in the individual schizophrenia and bipolar disorder sub-samples. Because sample-of-origin was not controlled for using this method, care must be taken in interpreting results for variables analysed in the large harmonised dataset. Results for the sub-samples are more directly comparable to those generated using the mixed effects regression analysis. A significant result produced using these methods on the raw continuous data supports the suggestion that there is a genuine familial effect in the sample. A non-significant result produced using these methods suggests that the significant result reported in the primary analysis may be due to an artefact produced by the reduction of continuous data into ordinal categories. For each variable discussed below, the Spearman's-rho correlations are presented alongside the results found in the primary analyses.

As stated in the methods section, due to time constraints only variables that were significant in the large harmonised dataset were followed up in the individual subsamples. This meant that there was a risk of missing significant correlations in either the schizophrenia or the bipolar disorder sub-set of cases. This is discussed further in chapter 6.

Discussion of Results

The aim of this research was to identify clinical variables more likely to be under genetic influence, which therefore may be useful in the advancement of molecular genetic studies. However, members of the same family are more likely to share environmental risk factors which studies have consistently shown to be important in the pathogenesis of both schizophrenia (for example, reveiwed in Tsuang et al. 2001) and bipolar disorder (for example, reviewed in Leboyer and Henry 2005). It was not possible to investigate the relative contributions of genetic factors and environmental influences on the familiality of these variables; this could be investigated using twin or adoption studies. However, of the 157 variables included in the analyses, the 31 for which significant intra-familial correlations were produced are most likely to be genetically influenced, and therefore may be useful in future molecular genetic studies.

Due to the large number of variables for which significant intra-familial correlations were generated, I have chosen to focus in on those which are particularly relevant to the focus of this thesis. The variables that are discussed in more detail below are those for which significant results were found in the large harmonised dataset and in one or both sub-samples. A significant result produced in at least one of the sub-samples provides strong, contextual support for the robustness of the familial findings for that variable. Variables are discussed below in the following order:

1. **Variables which are significant in the large harmonised dataset and in both the schizophrenia and the bipolar disorder sub-samples.**
2. **Discussion of variables which are significant in the large harmonised dataset ($p<0.01$) and in one of the sub-samples.**

3. **Brief discussion of variables which are significant in the large harmonised dataset (p>0.01) and in one of the sub-samples.**

4. **Brief discussion of variables which are significant in the large harmonised dataset only.**

5.4.2 A note about the risk of false positives

As stated at a number of points throughout this thesis, my primary analysis was exploratory in nature. One hundred and fifty seven variables were tested, covering a broad range of clinical characteristics. Although thirty-one variables were found to be significantly correlated within families in the large harmonised dataset, the large number of tests performed introduces a high risk of false positives.

Although each significant result is discussed in detail below, it should be remembered that no significant result withstood corrections made for multiple-testing. It is entirely possible that the majority of significant results reported here are false-positives and this must be considered when reading the discussion of significant findings below.

Conversely it is entirely possible that the majority of significant results represent true findings. As is the nature of all exploratory analyses, the main of this research was to facilitate future hypothesis-driven studies which aim to replicate these findings. This is discussed further in this chapter and in chapter 6.

Variables significant in the large harmonised dataset and across both sub-samples

In relation to the aim of this work, i.e. to identify variables that show familiality across traditional diagnostic boundaries, the variables that show significant intra-familial correlations across the large harmonised dataset and both sub-samples are of particular interest. The fact that significant results were produced in both the

schizophrenia and bipolar disorder sub-samples indicates that the variable could be measured commonly enough in both, and that enough variability had occurred within the data to produce such results. These overlapping clinical features are more likely to reflect overlapping genetic aetiologies that influence the functional psychoses across the Kraepelinian divide between schizophrenia and bipolar disorder.

Results from the Spearman's Rho analyses are presented along with the results from the primary analyses (i.e. the mixed-effects regression analyses) for each variable. Results using this alternative method were consistent with those reported in the primary analyses for all four variables. This provides reassurance that there was a genuine familial effect in the data, and that the significant results produced were not merely caused by the conversion of the continuous measures into ordinal categories.

Results are discussed individually below.

Age at onset

Measure: Age at onset (years) was measured in four different ways: age at first symptom, age at first impairment, age at first contact with psychiatric-services and age at first admission to a psychiatric hospital.

Results: Significant intra-familial correlations were identified for ages at first impairment, first contact and first admission. Age at first admission and age at first impairment were significant in the large harmonised dataset (LHD) and both the schizophrenia and the bipolar disorder sub-samples; age at first contact was significant in the LHD and the schizophrenia sub-sample only. Results from the mixed-effects regression analyses (MERA) are presented in Tables 5-8 – 5-9 below, along with the results produced using the Spearman's Rho analyses (SRA), performed on the sub-set of randomly selected, independent sibling-pairs.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.257	0.00059	0.289	0.0045	0.227	0.044
SRA (r, p)	**0.350**	**0.000001**	**0.325**	**0.00032**	**0.364**	**0.00039**

Table 5-7: Age at first admission - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.223	0.00108	0.249	0.007335	0.200	0.050
SRA (r, p)	**0.342**	**0.000001**	**0.333**	**0.00014**	**0.333**	**0.00045**

Table 5-8: Age at first impairment - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion:

The significant result for age at illness-onset found in the large harmonised dataset, as well as in the individual schizophrenia and bipolar disorder sub-samples, is consistent with previous studies which have shown age at onset to be familial in both schizophrenia (Burke et al. 1996; Kendler et al. 1987; Tsuang 1967) and bipolar disorder (Leboyer et al. 1998; O'Mahony et al. 2002). A significant intra-familial correlation was also reported in a sample of bipolar pedigrees described by Schulze et al (2006a), who used very similar methods to those described in this chapter, although their results for age at onset did not remain significant after corrections were made for multiple testing.

Further evidence implicating age at illness onset as a clinical marker of underlying genetic variability has been suggested by molecular genetic studies. For example, Lin et al (2005) performed linkage analysis on their sample of patients with bipolar disorder and included age at onset as a covariate. They identified two regions

of interest: 21q22.13, which showed increased linkage in patients with early onset bipolar disorder (onset before 21 years); and 18p11.2, which showed increased linkage in patients with later onset bipolar disorder (onset after 21 years). In their genome-wide linkage study of age of onset in schizophrenia, Cardno et al (2001) found suggestive evidence for linkage at chromosome 17q, although none of the LOD (Logarithm of Odds) scores produced in their analyses reached genome-wide statistical significance.

Association studies have also addressed the possible role of genes in influencing age at onset. For example, Chao et al (2008) found the Val66Met variant of the BDNF gene to be associated with age at first psychiatric admission and age at first schizophrenic symptoms in a sample of African American patients diagnosed with schizophrenia; this was consistent with Numata et al (2006) who originally reported the association in a Japanese sample. However, negative results for this gene have also been published (Gourion et al. 2005; Naoe et al. 2007).

One limitation of this analysis is that age at onset is a censored variable, i.e. siblings within the sample are correlated in chronological age, and are therefore also likely to be similar in their ages at onset. LeBoyer et al (1998) encountered a similar problem in their study which aimed to investigate age at onset and gender resemblance in siblings with bipolar disorder. They tried to overcome it by performing their analysis in a sub-set of siblings over the age of 35. However, this resulted in a loss of data.

In their study into the familiality of various clinical variables in siblings with bipolar disorder which used similar methods to those described in this thesis, Schulze et al (2006) included age at interview as a covariate in the model. This was not done in the primary analysis described here as this information was not available for all

individuals, therefore including it as a covariate would have lead to a reduction in the sample-size. However, because it is particularly relevant for age at onset, the analysis was performed again including age at interview as a covariate. A significant result was maintained (ICC=0.230, p=0.00164). As Schulze and colleagues (2006) point out, although this approach does not fully compensate for the censoring present within the data, it should eliminate large biases due to age.

Further work looking to investigate the familiality of age at onset should include systematic ascertainment and long-term follow up of unaffected siblings.

As shown in the tables above, the most significant results were produced for age at first admission. One possible reason for this is that, in general, the most detailed information available was for cases involving at least one hospital admission. It was also more likely that these cases contained multiple sources of data, i.e. casenotes and discharge letters as well as information collected at interview. Previous studies have shown case-notes to be the best individual source of such data (Brockington et al. 1992) and have stressed the importance of having multiple sources of data (Brockington and Meltzer 1982). Therefore, age at first admission is likely to be the most reliable measure. In contrast, age at first symptom relies largely on patient-recollection and is more likely to be subject to random variation and/or bias.

Alternatively, it may be because age at first admission is more likely to be influenced by environmental factors than age at first impairment. For example, because members of the same family are more likely to live in closer proximity to each other and are therefore more likely to be under the care of the same psychiatric services. The availability and quality of such services is likely to influence whether or not an individual is admitted to hospital (e.g. availability of home-treatment teams, number of beds on psychiatric wards, etc). Siblings are also more likely to have a

similar level of support from individuals within their family, particularly from shared parents. The willingness and ability of a family-member to care for an individual when they become unwell is likely to influence their need for admission.

In summary, the significant intra-familial correlations produced in the mixed effects regression analysis of age at onset are consistent with numerous lines of research which suggest that variation in onset-age may be related to underlying aetiological variation. Age at onset may therefore be useful in identifying more biologically homogeneous subgroups of patients amongst those suffering from psychotic-affective illness.

Course of disorder

Measure: The Operational Criteria (OPCRIT) (McGuffin et al. 1991) definition of course of disorder was used. As demonstrated in the table below, the scale comprised a 0-5 scale which aimed to measure the extent to which the illness was remitting vs. chronic and deteriorating in course.

Rating	Criteria
1	**Patient has only experienced a single episode of illness from which they have made a full recovery**
2	**Patient has experienced multiple episodes, with good recovery between episodes.**
3	**Patient has experienced multiple episodes with partial recovery between episodes**
4	**Patient has a continuous chronic illness**
5	**Patient has a continuous chronic illness with deterioration**

Table 5-9: Summary of Operational Criteria for course of disorder.

Results: Results from the mixed-effects regression analyses (MERA) are presented in Table 5-10 below, along with the results produced using the Spearman's

Rho analyses (SRA), performed on the sub-set of randomly selected, independent sibling-pairs.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.163	0.0039	0.233	0.046	0.176	0.023
SRA (r, p)	**0.665**	**0.0000005**	**0.325**	**0.000005**	**0.244**	**0.001**

Table 5-10: Course of disorder - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: Course of disorder was first shown to be significantly correlated within families with psychotic illness by Slater et al (1953). This finding has since been replicated in a number of studies involving samples of patients with schizophrenia and non-affective psychosis (Bleuler 1978; Burke et al. 1996; Kendler et al. 1997; Wickham et al. 2002). Fewer studies have investigated the familial aggregation of illness course in bipolar disorder. However, Duffy et al (2002) found a strong association between the quality of remission between parents with bipolar disorder and their affected children. Further, familiality of episode frequency has been reported in samples of patients with bipolar disorder (Fisfalen et al. 2005; O'Mahony et al. 2002).

In bipolar disorder, course of illness has also been significantly associated with other variables that show familiality such as mood-incongruent psychotic symptoms, age at onset and severity of disorder (for example, Strakowski et al. 2000). In schizophrenia, negative symptoms, associated with a more chronic illness course, have also been found to show familiality (Burke et al. 1996), as has the deficit syndrome of schizophrenia, which describes individuals with chronic negative symptoms which persist during periods of clinical stability (Ross et al, 2000).

The evidence summarised above suggests that illness course may help identify individuals who are more genetically homogeneous.

Length of longest admission

Measure: The length of the patient's longest admission was measured in weeks.

Results: Results from the mixed-effects regression analyses (MERA) are presented in Table 5-11 below, along with the results produced using the Spearman's Rho analyses (SRA), performed on the sub-set of randomly selected, independent sibling-pairs.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**p**
MERA (ICC, p)	0.287	0.000058	0.295	0.014	0.252	0.018
SRA (r, p)	**0.323**	**0.0000025**	**0.281**	**0.002**	**0.325**	**0.001**

Table 5-11: Longest admission - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: As far as the author is aware, the length of a patient's longest hospital admission has not been included in previous studies investigating the familiality of clinical variables within psychotic-affective illness. However, it follows that the number of weeks for which a patient requires hospitalisation is related to the course of the illness, discussed above, with a more chronic illness requiring more extensive periods of hospitalisation.

However, as with age at first hospital admission, duration of admission is also likely to be influenced by environmental factors more likely to be shared by members of the same family. Examples include availability of appropriate housing, ability of

shared family-members to care for individuals when ill and the availability and quality of local services (see discussion above).

Extended Rating Scale 8: Prototypical schizophrenia vs. prototypical affective disorder

Measure: Extended Rating Scale 8 (ERS8) is a novel measure, the development of which is discussed in chapter 2. ERS8 gives a lifetime measure of how prototypically "affective" or "schizophrenic" an individual's illness is (see chapters 2 and 6).

Results: Results from the mixed-effects regression analyses (MERA) are presented in Table 5-12 below, along with the results produced using the Spearman's Rho analyses (SRA), performed on the sub-set of randomly selected, independent sibling-pairs.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**p**
MERA (ICC, p)	0.127	0.028	0.201	0.028	0.158	0.023
SRA (r, p)	**0.746**	**0.000001**	**0.272**	**0.001**	**0.155**	**0.031**

Table 5-12: Extended Rating Scale 8 - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: This scale had no fixed anchor points and was far more subjective than the other measures used in this research. Prototypical schizophrenia was defined in the rating guidelines as, "a chronic illness characterised by insidious onset, positive and negative symptoms and no evidence of affective disturbance," whilst in contrast prototypical affective disorder was defined as, "episodic illness characterised by one or more manic or depressive episodes with good recovery in

between multiple episodes and with no evidence of psychotic or near psychotic symptoms." Raters were required to use these definitions along with their overall impression of the illness to place an individual at the most appropriate point on this 0-100 scale, based on all of the available information. Again, ERS8 is related to chronicity of illness, although less specifically as the numerous other factors associated with prototypical forms of illness are also considered.

It is of relevance that three of the four variables identified as showing significant intra-familial correlations in the LHD and across both sub-samples focus on an overlapping area of the phenotype. These are measures which delineate more typical schizophrenic illness from more typical affective disturbance and therefore relate directly to the foundation of Kraepelin's dichotomy which differentiated dementia praecox - a chronic deteriorating illness; from manic-depressive insanity - an episodic, remitting illness with a good prognosis.

These results provide support for Kraepelin's hypothesis that course of illness is an important aetiological factor. However, they do not support the hypothesis that the dichotomy is the best approach to the classification of the functional psychoses. The fact that these results show familiality over and above that resulting from the differences between the schizophrenia and bipolar disorder samples suggests that these variables are important both across traditional boundaries and within diagnostic categories, and may be used to differentiate groups of patients more likely to share a common genetic pathogenesis.

5.4.3 Discussion of variables which are significant in the large harmonised dataset ($p<0.01$) and in one of the sub-samples.

When analysed using the mixed-effects regression analysis, the variables discussed below showed significant intra-familial correlation in the large harmonised

dataset (LHD) and either the schizophrenia sub-sample or the bipolar disorder sub-sample. There are several possible reasons as to why significant results were found in one sub-sample but not the other. It may be that genetic and/or environmental factors which influence the variable are more specific to one diagnostic group than the other. Alternatively it may be that, within one of the sub-samples, there is insufficient power to detect familiality, due to the sample size. Variability within the sub-samples is also an important issue. If a variable is present in the majority of cases, or in very few cases (i.e. floor/ceiling effects), there may not be enough variability to detect a familial effect. For example, the vast majority of patients with schizophrenia will have experienced psychotic symptoms at some point during their illness, therefore there is unlikely to be sufficient variability within the schizophrenia sub-sample to produce significant results.

As presented in table 5-5 in the results section, 9 variables were significant in the LHD and the schizophrenia sub-sample, of which 5 had a $p<0.01$; and 14 variables were significant in the LHD and the bipolar-disorder sample, of which 4 had $p<0.01$ (table 5-6). The nine most significant variables, which are discussed in detail in this section are: Cannabis abuse/dependence; aggressive behaviour; level of impairment (as measured using the Global Assessment Scale) during worst psychotic episode, worst manic episode and worst ever episode; psychomotor retardation; scores on the BADDS Incongruence dimension; scores on Extended Rating Scale 2, which measures the relationship between psychotic and affective symptoms; and diminished libido.

Cannabis abuse/dependence

Measure: The item from the OPCRIT symptom checklist was used to record the lifetime-occurrence of cannabis use or abuse.

Results: Significant intra-familial correlations were found in the large harmonised dataset (LHD) and in the schizophrenia sub-sample, using the mixed effects regression analyses. These results were supported by the Spearman's-rho analyses performed on the smaller dataset in which each family was represented by a single pair of individuals. Mixed-effects regression analysis was not performed in the bipolar disorder sample because cannabis abuse/dependence was only reported in 12 cases (less than 2%). Of the 157 variables considered overall in these analyses, results produced for cannabis abuse/dependence in the LHD and the schizophrenia sub-sample were the most strongly correlated and highly significant. Results are presented in the table below.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.689	0.0006	0.777	0.000056	NA	NA
SRA (r, p)	**0.510**	**0.000**	**0.610**	**0.000001**	**-0.047**	**0.326**

Table 5-13: Cannabis abuse/dependence - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: The significant intra-familial correlation produced for cannabis abuse/dependence is consistent with previous studies which have shown that substance abuse in general, and cannabis abuse in particular, correlates within families (Mirin et al. 1991), suggesting a possible genetic effect. Interestingly, "substance misuse" was the most significant finding in a study by Schulze et al (2006a) which looked at the familiality of various phenotypic variables in a sample of families enriched for bipolar disorder, using methods very similar to those described

in this chapter (ICC=0.304, $p<0.001$). This suggests that genetic effects may also influence substance abuse in bipolar disorder.

Although there is evidence to suggest that cannabis abuse is clustered within families, this does not necessarily indicate a common genetic cause. There are many environmental factors that have been shown to increase an individual's susceptibility to drug-abuse and which are likely to be shared amongst family-members. These include increased environmental exposure to drugs, impaired parenting behaviour, negative life-events, disrupted family structure and social deprivation (Merikangas et al. 1998).

It is beyond the scope of this thesis to investigate the relative contributions of genetic factors and environmental influences on the strong intra-familial effect of cannabis abuse seen within the sample described in this chapter. However, genetic influences have been shown to play a role in the development of cannabis abuse, with heritability estimates ranging from 0.30 – 0.70 (Agrawal and Lynskey 2008). Kendler & Prescott (1998) looked at cannabis use, abuse and dependence in a sample of female monozygotic and dizygotic twin-pairs. They found evidence to suggest that heritability of cannabis *use* was moderate with genetic risk-factors accounting for less than half of the overall liability. In contrast when they studied cannabis *heavy use* (using cannabis more than 10 times in a month), and cannabis *abuse* (defined using DSMIV criteria), their results suggested that genetic factors were responsible for 60-80% of the variance in liability. This may be because cannabis use is more likely to be associated with the availability of the drug, whereas abuse is a behavioural trait more likely to be related to underlying biological factors.

This evidence suggests that, although common environmental risk-factors such as those described above, increase susceptibility to substance abuse within

families, genetic factors also have a role to play. These genetic factors may be independent of risk factors for schizophrenia or bipolar disorder, i.e. they may modify the course of illness rather than influence the risk of the illness itself.

Studies have consistently shown that cannabis use in populations with psychotic disorders is higher than that in the general population (Regier et al. 1990). The main psychoactive compound within cannabis (delta-9-tetrahydrocannabinol) acts through the cannabinoid receptor CRN1 which is located on 6q14-15 – a region of replicated linkage for schizophrenia (Lewis et al. 2003). Although findings have been inconsistent, several studies have provided evidence suggesting association between variation at CRN1 and schizophrenia (Ujike et al. 2002).

Another gene that has been hypothesised to interact with cannabis abuse is catechol-o-methyl transferase (COMT) – a gene involved in the degradation of dopamine in the brain which has previously been implicated in both schizophrenia and bipolar disorder (Li et al. 1996; Papolos et al. 1998). A common polymorphism in COMT results in a valine/methionine substitution which has been shown to associate with corresponding high-activity and low-activity enzyme variants (Lachman et al. 1996). Increased mesolimbic dopamine transmission has been implicated in the pathogenesis of psychotic symptoms – because of this, Caspi et al (2005) hypothesised that the high-activity (158Val) allele would confer increased risk of psychosis in individuals using cannabis. Their results supported this hypothesis, with carriers of the COMT valine^{158} allele who first smoked cannabis before the age of 18 being at the highest risk of developing psychotic symptoms and of going on to develop schizophreniform disorder. No such effect was found in individuals homozygous for the COMT methionine^{158} allele. However, results have been inconsistent and no such findings were reported in a larger sample of schizophrenic

patients (Zammit et al. 2007), even when using the same cut-off period of cannabis-use prior to the age of 18.

Given this evidence and despite the somewhat inconsistent results, it is reasonable to suggest that groups of patients with psychotic illness and comorbid cannabis abuse may represent a more genetically homogeneous sub-sample of patients, and that the identification of such groups may facilitate future molecular genetic studies.

Aggressive Behaviour

Measure: Aggressive behaviour was measured using a 4-point scale as shown in table 5-14 below.

Rating	Criteria
1	**Behaviour which is perceived as threatening and is out of proportion to the circumstances. Includes verbal aggression. Rated with a low threshold.**
2	**Acts of physical aggression which do not meet the criteria for "3". Includes damage to property and mild acts of unprovoked violence towards others.**
3	**Severe acts of aggression which result in physical injury to others, police involvement or in the individual being restrained.**
4	**Multiple act of severe aggression which meet the criteria for "3".**

Table 5-14: Summary of rating guidelines for novel measure of aggressive behaviour.

Results: Significant intra-familial correlations were found in the large harmonised dataset and in the schizophrenia sub-sample, using the mixed effects regression analyses. These results were consistent with the Spearman's Rho analyses performed on the smaller dataset in which each family was represented by a single pair of individuals. Results are presented in the table below.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.273	0.00754	0.332	0.003238	0.144	0.175538
SRA (r, p)	**0.319**	**0.000001**	**0.285**	**0.001**	**0.081**	**0.200**

Table 5-15: aggressive behaviour - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: Aggressive behaviour is an important issue in psychiatry, particularly as it is a major factor contributing to the stigma surrounding mental illness in general and schizophrenia in particular. As is the case with cannabis abuse, aggressive behaviour is associated with a number of environmental factors such as abuse in childhood (Sappington 2000). Another factor that has been consistently associated with aggressive behaviour is substance abuse (Grunebaum et al. 2006). To ensure that the significant result produced here for aggressive behaviour was not merely due to its association with substance abuse, the analysis was performed again in the large harmonised dataset, with the inclusion of substance-abuse (a binary variable denoting the presence or absence of alcohol and/or illicit drug abuse/dependence) as a covariate. A significant result was maintained (ICC= 0.269, p=0.0097), suggesting that the significant result produced for aggressive behaviour was not due to its association with substance abuse.

As far as the author is aware, aggressive behaviour has not previously been studied by researchers attempting to identify familial variables in samples of patients with affective or psychotic illness. However, twin and adoption studies support the hypothesis that antisocial behaviour such as aggression is influenced by both genetic and environmental factors (Gustavsson et al. 1996) and it is estimated that genetic factors account for 40-50% of variance in risk in the general population (Rhee and Waldman 2002).

Molecular genetic studies have also investigated the possibility that aggressive behaviour may be genetically influenced. For example, recent studies suggest that genes involving the degradation of catecholamines, such as MAOA (Monoamine Oxidase A) (Fresan et al. 2007) and COMT (Catechol-O-Methyl Transferase, see Chapter 3) may be involved. Both genes have been implicated in both schizophrenia (Li et al. 1996) and bipolar disorder (Muller et al. 2007; Papolos et al. 1998) although findings have not been consistent (Norton et al. 2002).

It has been suggested that aggression is a heterogeneous construct, for example, Volavka et al (2008) list three subtypes of aggressive behaviour: 1. Aggression directly related to positive symptoms, e.g. persecutory delusions; 2. Impulsive aggression, which may be based on response inhibition; 3. Aggression stemming from co-morbidity with psychopathy. These subtypes are likely to be aetiologically different, therefore genetic studies may be facilitated by differentiating between them.

The significant results produced in the large harmonised dataset and the schizophrenia sub-sample are consistent with the hypothesis that aggressive behaviour is a clinical marker of underlying genetic heterogeneity. However, no such significant result was produced in the bipolar disorder sub-sample. This may be due to the fact that aggressive behaviour occurred less frequently in the bipolar disorder sub-sample (12% of the bipolar disorder sample had been physically aggressive at some point during their illness compared to 40% of the schizophrenia sample), therefore the negative result may be due to insufficient sample-size. Although aggression does occur in increased rates in bipolar disorder, particularly during manic and mixed states (Maj et al. 2003), this phenomenon has not been investigated in bipolar disorder

to the extent that it has in schizophrenia. Further research is needed to investigate this further.

The significant result observed in the large harmonised dataset along with the research summarised above suggests that aggressive behaviour is influenced by genetic as well as environmental factors. This variable may therefore be useful when defining subgroups of patients who are more likely to share a common genetic pathogenesis. However, because aggression itself is a heterogeneous concept, this research may be further facilitated by refining the definition of aggressive behaviour into subtypes of aggression such as those described above.

Scores on the Global Assessment Scale

Measure: The Global Assessment Scale (GAS)(Endicott et al. 1976) is a 0-100 variable which can be used to measure an individual's level of functioning during a specific period of time, thus giving an indication of illness severity (see Appendix B).

The GAS was used to measure impairment at five different points during the illness, where possible. These were: i) during the worst episode of psychosis (GAS-P); ii) during the worst manic episode (GAS-M); iii) during the worst episode of depression (GAS-D); iv) during the worst ever episode of illness (GAS-WE), and; v) during the week prior to their participation in the research (i.e. the week prior to interview; GAS-PW). Of these, significant results were found for GAS-P, GAS-WE and GAS-M. These results are discussed below.

Results: When data for GAS-P were analysed using the mixed-effects regression method, significant intra-familial correlations were found in the large harmonised dataset (LHD) and the schizophrenia sub-sample; the result for the

bipolar disorder sub-sample approached significance, as presented in table 5-16. When the data were analysed using Spearman's Rho correlations, significant results were produced for the large harmonised dataset and both sub-samples.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.258	0.00097	0.264	0.0044	0.297	0.057
SRA (r, p)	**0.270**	**0.000**	**0.279**	**0.00050**	**0.115**	0.013

Table 5-16: GAS scores for worst ever psychotic episode - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs. MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

When scores for GAS-WE were analysed using the mixed-effects regression method, a significant familial effect was identified in the LHD and in the bipolar disorder sub-sample; and results approached significance in the schizophrenia sub-sample. When the smaller, paired dataset was analysed using Spearman analyses, significant correlations were found across all three samples. These results are summarised in Table 5-17.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**P**	**ICC/r**	**P**
MERA (ICC, p)	0.156	0.0045	0.164	0.059	0.167	0.023
SRA (r, p)	**0.403**	**0.000**	**0.321**	0.000046	**0.231**	**0.002**

Table 5-17: GAS scores for worst ever episode of illness - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs. MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

When the primary analyses were performed on the GAS-M data, significant results were produced in the LHD and the bipolar-disorder sub-sample, and the results of the Spearman analyses were consistent with this. Results are presented in Table 5-18.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**P**	**ICC/r**	**P**
MERA (ICC, p)	0.257	0.0018	0.079	0.76	0.201	0.035
SRA (r, p)	**0.277**	**0.001**	**0.126**	**0.304**	**0.220**	**0.009**

Table 5-18: GAS scores for worst ever manic episode - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs. MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: The fact that both GAS-P and GAS-WE are significant or approaching significance across all three samples when analysed using the mixed-effects regression analysis, and that they are significant across all three samples when analysed using Spearman's-rho correlations suggests that variation in illness-severity may reflect variation in underlying genetic mechanisms which act across traditional diagnostic boundaries. The fact that GAS-M scores are not significantly correlated within families in the schizophrenia sub-sample may be because of the smaller sample-size (as mania occurred less frequently within the schizophrenia sample).

These results, which suggest that illness severity aggregates within families, are consistent with findings from previous studies which have shown the overall severity of illness to be familial. For example, Wickham et al (2002), found impairment in functioning to be highly familial in their sample of patients with schizophrenia. Familiality has also been demonstrated for variables which have been shown to be associated with illness-severity such as incongruent psychotic features (Goes et al. 2007) and course of illness (see above).

Molecular genetic studies have also sought to investigate further the possibility that severity of illness is genetically influenced. For example, Zandi et al (2008) found a significant association between scores on the GAS and variation

within the gene PPARD (peroxisome proliferators activated receptor delta) located on chromosome 6p21, a region previously implicated in schizophrenia (Lewis et al. 2003).

The significant intra-familial correlations found when analyses were performed on Global Assessment Scale scores during the worst psychotic episode, worst manic episode, and worst over-all episode, support the hypothesis that this clinical variable may be genetically influenced. These finding are consistent with previous studies, which provide further evidence to suggest that future molecular genetic studies may be facilitated by taking variation in impairment during specific periods of illness into account.

Bipolar Affective Disorder Dimension Scale, Incongruence Dimension (BADDS-I) and Extended Rating Scale 2 (ERS2).

Measure: The BADDS Incongruence dimension (BADDS-I) gives a measure of the relationship between psychotic and affective symptoms. The bottom of the scale (0) represents affective illness in which the psychotic symptoms which have occurred are entirely congruent with the mood state in which they were experienced. Scores then increase as the balance shifts from mood-congruent to mood-incongruent psychosis and then with the presence of first-rank symptoms. Scores at the top end of the scale increase with the greater predominance of psychotic symptoms, and the decreasing prominence of affective disturbance.

Extended Rating Scale 2 (ERS2) was created as an extension of the BADDS Incongruence dimension (see chapters 2 and 6). The BADDS-I can only be rated for individuals who have experienced psychosis, ERS2 was created to allow ratings to be made across the entire spectrum of illness, from mood-disorder without psychotic

symptoms to schizophrenia with no symptoms of mood-disturbance. The results produced for each variable are presented in Table 5-19 and Table 5-20 below.

Results: Both variables were significantly correlated within families in both the large harmonised dataset (LHD) and the schizophrenia sub-sample when analysed using the mixed-effects regression method and when analysed using Spearman correlations.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.224	0.0048	0.285	0.0040	0.181	0.19
SRA (r, p)	**0.688**	**0.000**	**0.344**	**0.000028**	**0.203**	**0.078**

Table 5-19: BADDS-Incongruence dimension - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.171	0.0090	0.265	0.0049	0.119	0.17
SRA (r, p)	**0.724**	**0.000**	**0.333**	**0.000036**	**0.092**	**0.161**

Table 5-20: Extended Rating Scale 2 - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: DSMIV (APA, 1994) defines mood-incongruent psychotic symptoms as those with "content...inconsistent with depressive themes such as guilt, illness, personal inadequacy or catastrophe," or, "inconsistent with manic themes such as inflated worth, power, knowledge, identity or special relationship to a deity or famous person." Previous studies have found that incongruent psychotic symptoms are correlated within families with affective disorder. A recent study by Goes et al (2007) found that relatives of individuals with bipolar disorder who had experienced mood-incongruent psychosis were significantly more likely to have had mood-

incongruent psychotic symptoms themselves. They went on to perform a genome-wide linkage scan incorporating incongruent psychosis as a covariate. This revealed evidence for linkage on chromosome 13q21-33, a region previously implicated in both schizophrenia and bipolar disorder, and 2p11-q14, previously implicated in schizophrenia.

Hamshere et al (in press) also found evidence that incongruent-psychotic features aggregate within families; when covariate linkage analysis was performed in a large sample of bipolar pedigrees, which included individuals from the sample described in this chapter, genome-wide suggestive linkage signals were found at chromosomes 1q32.3, 7p13 and 20q13.31 – none of which were identified when incongruent psychosis was not included as a covariate. This provides further evidence to suggest that the nature of the psychotic symptoms in affective disturbance may reflect underlying genetic heterogeneity.

However, not all findings have been consistent, for example O'Mahony et al (2002) found that the BADDS Incongruence dimension was associated with moderate intra-familial correlation in their sample of sibling-pairs with bipolar disorder but this was not significant after corrections were made for multiple testing.

Despite these positive findings, no significant familiality was demonstrated in the bipolar disorder sub-sample. This may be due to differences in the way incongruence was measured. The studies which have reported familiality for this variable (Goes et al. 2007; Hamshere et al, In Press) used a binary-variable, indicating the lifetime presence or absence of mood-incongruent psychosis; this is in contrast to the continuous measures described here.

The congruence of psychotic symptoms within schizophrenic illness has not been considered in previous research; this is probably because unless affective

disturbance is prominent enough to warrant a diagnosis of schizoaffective disorder, it is usually discounted under the diagnostic hierarchy (see chapter 1). It is therefore particularly interesting that scores on the BADDS Incongruence dimension, and on ERS2, were significantly correlated within families in the schizophrenia sample. This, alongside previous research suggesting the relationship between psychotic and affective symptoms is important in affective disorder, suggests that the relationship between psychotic and affective disturbance is a potential indicator of underlying biological heterogeneity.

Slowed activity

Measure: The OPCRIT symptom checklist was used to define slowed activity. To be scored positively on this measure an individual must have experienced a feeling of being slowed-up or unable to move. This is a symptom typically associated with depression.

Results: Using both methods of analysis, significant results were produced within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-21.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.268	0.0036	0.089	0.56	0.367	0.0021
SRA (r, p)	**0.225**	**0.000001**	**0.042**	**0.251**	**0.305**	**0.000001**

Table 5-21: slowed activity - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: Of all the binary variables analysed during this research, the most significant results were produced for slowed activity. This variable is related to psychomotor retardation and is a symptom associated with depression. Studies have

shown that psychomotor retardation is a clinical feature that is more likely to occur in bipolar-depression, than unipolar-depression (Mitchell et al. 2008).

Pychomotor poverty is one of five independent symptom dimensions associated with schizophrenia (Liddle 1987), which includes poverty of speech, a reduction in spontaneous movement and restricted affect. Wickham et al (2001) found this psychomotor poverty dimension to be familial. Additionally, they found that psychomotor poverty was associated with a more chronic and deteriorating course of illness and single marital status, both of which were found to correlate within families in this research.

In their twin-study of older adults, Gatz et al (1992) found that, of the 20 depressive symptoms they studied, genetic factors were most influential for symptoms of psychomotor retardation and somatic complaints. Further support for the biological significance of this symptom is its association with decreased presynaptic dopamine function in the left caudate of depressed patients (Martinot et al. 2001).

In summary, the significant intra-familial correlations produced using the methods described in this chapter, along with evidence from the previous research such as that summarised above, support the hypothesis that defining groups according to the presence or absence of psychomotor retardation may facilitate molecular genetic research.

Diminished Libido

Measure: Diminished libido was defined according to the OPCRIT symptom checklist (McGuffin et al. 1991) as "a definite and persistent reduction in sexual drive or interest as compared with before the onset of the disorder."

Results: Using both methods of analysis, significant results were produced within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-22.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.309	0.0051	0.095	0.62	0.430	0.0023
SRA (r, p)	**0.182**	**0.002**	**0.065**	**0.240**	**0.255**	**0.002**

Table 5-22: Diminished libido - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Discussion: As far as the author is aware, diminished libido has not been investigated within previous studies which have sought to identify clinical variables which aggregate within families. The significant result found within this sample suggests that this variable warrants further investigation in future studies.

Brief discussion of variables which are significant in the large harmonised dataset (p>0.01), and in one of the sub-samples

Age at first psychosis

Measure: The measure reported here was the age at which the individual first experienced psychotic symptoms. Significant results were also produced when measuring age at first impairment due to psychosis.

Results: Significant intra-familial correlations were demonstrated in the large harmonised dataset (LHD) and in the schizophrenia sub-sample using the mixed-effects regression analyses. When Spearman correlations were used, significant results were found across all three samples. These results are presented in the table below:

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.211	0.014	0.334	0.0034	0.039	0.82
SRA (r, p)	**0.339**	**0.000**	**0.330**	**0.001**	**0.400**	0.016

Table 5-23: Age at first psychosis - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: The fact that the results found in the bipolar disorder sub-sample using the two methods differed to such an extent suggests that the way in which the continuous data for this variable were converted to ordinal categories may have obscured a genuine familial effect in the families enriched for bipolar disorder. However, no significant intra-familial correlation was found when the continuous data were categorised differently during sensitivity analyses (see methods). An alternative explanation is that the smaller, paired dataset did not contain a representative sample of patients. The result may also be influenced by gender effects which were not controlled for when using this alternative method. However, when the mixed effects regression analysis was run without gender as a covariate, the result remained non-significant (ICC=0.066; p=0.731). The points relating to age at onset in general, which are also relevant to this variable, are discussed in section 1 above.

Chronic defect state

Measure: This was rated using a binary measure, formed by dichotomising the results from Extended Rating Scale 9 (ERS9) into individuals who had experienced features characteristic of a chronic defect state, and those who did not.

Results: Using the mixed effects regression method, significant results were found in the large harmonised dataset (LHD) and in the schizophrenia sub-sample (analyses were not performed in the bipolar disorder sub-sample due to the small

number of individuals who scored positively on this measure). However, when the smaller, paired datasets were analysed using Spearman's Rho correlations, the significant results seen in the schizophrenia sub-sample were not maintained. This may be due to a decreased power to detect familial effects, caused by the smaller sample size. It may also be that gender effects which are not controlled for may be obscuring a significant effect within the data.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.351	0.041	0.363	0.039	NA	NA
SRA (r, p)	**0.335**	**0.000**	**0.031**	**0.370**	**-0.048**	**0.285**

Table 5-24: Presence/absence of a chronic defect state - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: Negative features have previously shown familiality using alternative methods. This is discussed in chapter 6, along with Extended Rating Scale 9 (ERS9). The deficit syndrome of schizophrenia, which is characterised by chronic negative features which persist for at least 12 month during periods of clinical stability, has also been shown to correlate significantly within families (Ross et al, 2000).

Other substance abuse/dependence

Measure: "Other substance abuse" refers to any illicit substance other than cannabis, which is dealt with using a separate measure (as described above)

Results: Significant intra-familial correlations were found in the large harmonised dataset (LHD) and in the schizophrenia sub-sample using the mixed-effects regression analyses on the full datasets and using the Spearman's Rho analyses performed on the smaller, paired samples.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.587	0.016	0.537	0.046	0.660	0.22
SRA (r, p)	**0.321**	**0.000**	**0.411**	**0.0000054**	**0.051**	**0.300**

Table 5-25: Other substance abuse - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: Substance abuse has been shown to be familial in previous studies. This is discussed in section 2 under "cannabis abuse/dependence".

Deterioration since onset

Measure: The OPCRIT definition of deterioration was used to measure deterioration. An individual was scored positively on this item if they did not regain their premorbid social, occupational or emotional functioning after an acute phase of illness (McGuffin et al. 1991).

Results: Significant intra-familial correlations were found in the large harmonised dataset (LHD) and in the schizophrenia sub-sample using the mixed-effects regression analyses. When using the Spearman's Rho analyses, which were performed on the smaller, paired samples, significant results were found in the LHD only, although results approached significance in the schizophrenia sub-sample. These results are presented in table 5-26.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.251	0.046	0.391	0.032	0.069	0.71
SRA (r, p)	**0.529**	**0.000**	**0.136**	**0.063**	**0.087**	**0.19**

Table 5-26: Deterioration since onset - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: Although significant results were produced for this variable, the fact that this variable is only just significant suggests that when identifying more homogeneous subgroups of patients by illness course, the continuous measure (i.e. course of disorder, discussed above) is likely to be more useful than this binary measure.

Extended Rating Scale 10: Catatonic features

Measure: Extended Rating Scale 10 (ERS10) was one of the novel measures used within this thesis. Originally developed by Dr George Kirov, it comprised a 0-4 scale in which a point was added for each feature of catatonia experienced, over the lifetime course of the illness. This scale is discussed in more detail in chapter 6.

Results: Using both methods to analyse the data, significant results were produced within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-27.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.229	0.016	0.112	0.380	0.366	0.010
SRA (r, p)	**0.331**	**0.0000010**	**0.056**	**0.216**	**0.223**	**0.00017**

Table 5-27: Extended Rating Scale 10, catatonic symptoms - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: The strong correlation found within the bipolar disorder sub-sample is particularly interesting, as the familiality of catatonic features has not previously been studied within samples of patients with affective illness. However, previous familiality studies of schizophrenia samples have reported catatonia to correlate significantly within families (Kendler et al. 1997; Tsuang 1967). Negative

results have also been reported in schizophrenia family-samples for catatonic symptoms (Kyeong-Sook Choi et al, 2007). ERS10 is discussed in more detail in chapter 6.

Extended Rating Scale 11 - Disorganised behaviour

Measure: Like ERS10, Extended Rating Scale 11 (ERS11) was one of the novel measures used within this thesis and was originally developed by Dr George Kirov. It comprised a 0-2 scale in which a point was added for each feature of disorganised behaviour experienced over the lifetime course of the illness. This scale is discussed in more detail in chapter 6.

Results: Using both methods to analyse the data, significant results were found within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-28.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.358	0.024	0.093	0.650	0.716	0.002
SRA (r, p)	**0.171**	**0.000010**	**0.055**	**0.205**	**0.264**	**0.0000010**

Table 5-28: Extended Rating Scale 11, disorganised behaviour - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's-rho Analyses.

Comment: Previous studies have not focussed on disorganisation using this measure. However, the disorganisation dimension derived from factor analyses performed in samples of patients with schizophrenia, has been shown to aggregate within families (e.g. Cardno et al, 1999), although negative findings have also been reported (Choi et al, 2007). This is discussed further in chapter 6.

Anhedonia

Measure: The OPCRIT symptom checklist definition was used to determine whether this symptom was present/absent. This defines anhedonia as, "the pervasive inability to enjoy any activity" (McGuffin et al. 1991).

Results: Using both methods to analyse the data, significant results were produced within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-29.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.190	0.048	0.008	0.950	0.367	0.009
SRA (r, p)	**0.207**	**0.0000010**	**0.000**	**0.500**	**0.224**	**0.0000070**

Table 5-29: Anhedonia - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: There have been no previous reports of anhedonia correlating within families of patients with bipolar disorder. However, anhedonia has been shown to be significantly correlated within families in a sample of schizophrenia patients (Schurhoff et al. 2003a). In contrast to this finding, the intra-class correlation coefficient approached zero when the schizophrenia sub-sample was analysed using the mixed-effects regression method. It would be useful to include this symptom within future studies investigating the familiality of clinical variables in both samples of families enriched for schizophrenia and in family-samples enriched for bipolar disorder.

Negative formal thought disorder

Measure: The OPCRIT definition of negative formal thought disorder (NFTD) was used which requires the presence of one of the following features for a

positive rating to be made: paucity of thought, frequent thought blocking, poverty of speech, or poverty of content of speech.

Results: Using both methods to analyse the data, significant results were found within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-30.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.355	0.014	0.268	0.093	0.601	0.022
SRA (r, p)	**0.333**	**0.000**	**0.161**	**0.051**	**0.315**	**0.00009**

Table 5-30: Negative formal thought disorder - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: In the majority of previous studies, negative formal thought disorder (NFTD) would not have been rated unless it occurred outside of the context of mood, due to assumptions made about its underlying causes. It is therefore particularly interesting that this variable has shown significant familiality in the bipolar disorder sub-sample, as well as showing a trend towards significance in the schizophrenia sample. A previous study investigating the familiality of clinical variables within a sample of schizophrenia patients found NFTD to be significantly correlated within families (Kendler et al. 1997), further supporting the hypothesis that this variable may be influenced by genetic factors, and may therefore be useful in defining more homogeneous subgroups of patients in future molecular genetic studies. However, negative findings have also been reported in the literature. For example Choi and colleagues (2007) investigated the familiality of a related variable (poverty of speech) and found it to be non-significant in their sample of schizophrenia pedigrees.

Marital Status

Measure: Marital status was a binary measure in which a rating of "1" indicated that the individual had never been married and had never lived as married at any point during their life.

Results: In the primary analyses, significant intra-familial correlations were found in the LHD and the bipolar disorder sub-sample. When Spearman's-rho analyses were used, results for the LHD and bipolar disorder sub-sample were consistent with the mixed effects regression analyses, and a significant result was also found in the schizophrenia sub-sample, as shown in table 5-31.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**P**	**ICC/r**	**P**
MERA (ICC, p)	0.273	0.020	0.222	0.21	0.336	0.038
SRA (r, p)	**0.325**	**0.000**	**0.180**	0.026	**0.351**	**0.00003**

Table 5-31: Marital status - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: These results are consistent with a recent study by Potash et al (2007) in which marital status was found to be significantly correlated within their large family-based sample enriched for bipolar disorder.

Extended Rating Scale 7: Dysphoric mania

Measure: Extended Rating Scale 7 (ERS7) measures the extent to which the individual's most dysphoric manic episode was dysphoric in nature. It comprises a 0-100 scale in which scores range from a purely elated manic state (0), through irritability; scores then increase with the number of depressive features experienced during the episode. ERS7 is discussed further in the general discussion (chapter 6).

Results: Using both methods to analyse the data, significant results were found within the large harmonised dataset (LHD) and the bipolar disorder sub-sample, as presented in Table 5-32.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.216	0.031	0.139	0.66	0.253	0.024
SRA (r, p)	**0.272**	**0.002**	**-0.215**	**0.22**	**0.291**	**0.003**

Table 5-32: Extended Rating Scale 7 , most dysphoric mania - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: The significant intra-familial correlations found when analysing this novel measure within the LHD and the bipolar disorder sub-sample, suggest that the extent to which an individuals "most dysphoric" manic episode is characterised by irritable or depressive symptoms as opposed to pure elation, may be influenced by genetic or environmental factors.

Delusions of influence/persecution

Measure: A binary measure was used in which an individual was rated as "1" if they had experienced delusions of influence and/or persecutory delusions.

Results: Results using both methods were significant in the LHD and the bipolar disorder. The analysis was not run in the primary analysis on the schizophrenia sample, due to lack of variability within the data.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.233	0.039	NA	NA	0.316	0.018
SRA (r, p)	**0.299**	**0.000**	**NA**	**NA**	**0.176**	**0.034**

Table 5-33: Delusions of influence/persecution - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.

MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

Comment: This measure has not previously been analysed in studies investigating the familiality of clinical variables. The significant result found in this research suggests that it may be worth including this measure in future studies, particularly as, when analysed individually, persecutory delusions and delusions of influence were not shown to be significantly correlated within families.

5.4.4 Variables significant in the large harmonised dataset only

The variables discussed briefly below were significant in the large harmonised dataset only when analysed using the mixed-effects regression analysis. Of these four variables, positive formal thought disorder has previously identified as a familial variable in a sample of patients with schizophrenia and a sample with non-affective psychosis (Kendler et al. 1997), although negative findings for formal thought disorder have also been published (e.g. DeLisi et al, 1987); Extended Rating Scale 9 (ERS9) has not been studied previously, but is associated with the negative syndrome for which familiality has been previously identified (Burke et al. 1996; Peralta and Cuesta 2007a) although again, negative findings have also been published (e.g. Loftus et al, 1998); and age at first depression is related to age at onset which is discussed above.

Number of admissions has not been identified as a familial variable in the past, although it is related to the course and severity of illness which have been identified as familial within this sample and which are discussed above. However, the number of times an individual has been admitted into hospital over the course of their illness is likely to be associated with the duration of their illness, i.e. individuals who were recruited after or during their first episode of illness may go on to have numerous

hospital admissions over time. Further, as discussed above for the variables "age at first admission" and "duration of admission", the number of times an individual has been admitted to hospital is likely to be particularly susceptible to environmental factors which are more likely to be shared by individuals from the same family (e.g. social situation, availability of local services, etc. See above).

The tables below present the results from the mixed effects regression analysis for each of these variables, along with results from the Spearman's Rho analysis. The latter provide further evidence that positive formal thought disorder and number of admissions may be useful in identifying more homogeneous groups of patients across diagnostic boundaries. However, the significant results produced in the sub-samples may be due to a non-representative selection of cases within this smaller sample, or gender effects which have not been controlled for.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**P**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.448	0.013	0.328	0.097	0.659	0.075
SRA (r, p)	**0.338**	**0.000**	**0.257**	0.007	**0.418**	0.000001

Table 5-34: Positive formal thought disorder - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.171	0.015	0.164	0.053	0.123	0.15
SRA (r, p)	**0.283**	**0.000**	**0.287**	0.0003	**0.255**	0.001

Table 5-35: Number of admissions - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.313	0.027	0.369	0.18	0.317	0.066
SRA (r, p)	**0.417**	**0.001**	**0.473**	0.032	**0.390**	0.01

Table 5-36: Age at first depression - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

	Large Harmonised Dataset		Schizophrenia Sub-Sample		Bipolar Disorder Sub-Sample	
	ICC/r	**p**	**ICC/r**	**p**	**ICC/r**	**P**
MERA (ICC, p)	0.184	0.035	0.185	0.059	0.172	0.42
SRA (r, p)	**0.406**	**0.000**	**0.031**	**0.371**	**0.124**	**0.069**

Table 5-37: Extended Rating Scale 9, chronic defect state - comparison of results from primary analyses with results from Spearman's-rho analyses in a sub-sample of independent sibling pairs.
MERA - Mixed-Effects Regression Analyses (primary analyses); SRA – Spearman's Rho Analyses.

5.4.5 Strengths and Limitations of the study design

Strengths

1. The sample.

The primary analyses were undertaken on a large, well-characterised sample of patients, comprising families enriched for schizophrenia and families enriched for bipolar disorder. This meant that analyses could be performed across traditional diagnostic boundaries, to investigate the familiality of clinical variables in prototypical functional psychoses.

It was also possible to dichotomise the large harmonised dataset back into the two samples from which it was comprised: the schizophrenia family-sample and the bipolar disorder family-sample. This meant that analyses could also be performed on

these sub-samples individually. These results were more comparable to those produced in previous studies, which have predominantly focussed on samples enriched for a single diagnostic category (i.e. bipolar disorder *or* schizophrenia).

Power analysis can be used to investigate the probability of detecting a true effect within a sample of interest, in this case the large harmonised dataset (LHD). However, due to the structure of the sample (i.e. families of varying size) and method of analysis (logistic regression allowing for covariates), it was not possible to perform power analyses that directly reflected the study design, as this would require a simulation approach which would be computationally intensive.

One method that could be used to give a rough "ball park" estimate of power within the sample was the Pearson product-moment coefficient (r). To calculate power, a test-statistic of $p<0.05$ was used, and effect sizes were defined according to Cohen (1988), i.e. small effect size: r=0.10; medium effect size: r=0.30; large effect size: r=0.50.

Power tables were used to investigate the statistical power (Cohen 1988). These were first applied to the entire paired-dataset (N pairs = 668), which included non-independent pairs; and in the dataset comprising independent pairs (i.e. each family is represented by a single related pair; N pairs = 310). The true power using the Pearson product-moment coefficient should lie somewhere between results reported for these methods. Whilst not being directly comparable with the power of the logistic regression method used, none-the-less, this estimate will provide a general guide to the power of my analysis. The results for these sample-sizes are presented in the table below:

Sample	Number of pairs	Power to detect small effect r=0.10 (approx %)	Power to detect a medium effect r=0.30 (approx %)	Power to detect a large effect r=0.50 (approx %)
All pairs	N = 668	55	99	99
Independent pairs only	N = 310	28	99	99

Table 5-38: Power to detect small, medium and large effect sizes in the dataset comprising all related-pairs and in the dataset comprising one pair from each family.

For the majority of variables, data were not available for all individuals leading to a reduction in sample size. For example, it was possible to rate Extended Rating Scale 8, which gives a measure of whether the illness is "prototypically" schizophrenia or affective in nature, in the majority of cases within the sample, therefore the number of pairs for this variable were approaching those reported above (N=660 when all pairs were included; N=277 in the sample of independent pairs. In contrast, Extended Rating Scale 7, which gives a measure of dysphoric mania, could not be rated in such a large proportion of the sample and the number of pairs included in the analyses were greatly reduced (N=294 in the full sample and N=95). Power to detect significant effects would be greatly reduced as demonstrated in table 5-39.

Sample	Number of pairs	Power to detect small effect r=0.10 (approx %)	Power to detect a medium effect r=0.30 (approx %)	Power to detect a large effect r=0.50 (approx %)
All pairs	N = 294	23	81	99
Independent pairs only	N = 95	8	73	95

Table 5-39: Power to detect small, medium and large effect sizes in the dataset comprising all related-pairs and in the dataset comprising one pair from each family, when using the data for Extended Rating Scale 7.

The power for the other variables considered in these analyses would lie somewhere in between those reported for the variable which could be rated in the fewest cases (ERS7) and for those that could be rated in the highest proportion of cases (ERS8).

In summary, these estimates provide a general indication that my analysis was well powered to detect effects of large or medium size (at $p<0.05$) but that power was likely to be modest or poor to detect small effect sizes, particularly for those variables where data was incomplete.

2. Statistical methods

The main advantages of using the Fortran program MIXOR (Hedeker and Gibbons 1996b) to perform mixed effects regression analyses were that: i) it allowed for variations in family-size and; ii) covariates could be included within the model and thus controlled for. By controlling for sample-of-origin effects it was possible to look for variables which showed significant intra-familial correlations above and beyond the familiality that would arise as a result of the natural differences between the schizophrenia and bipolar disorder sub-samples. Gender-effects could also be controlled for in this way.

3. A single rater was responsible for rating the entire sample of patients

After an extensive training period and participation in numerous reliability exercises, I was responsible for rating the entire sample of 835 patients, over a period of almost two years. This intensive procedure allowed me to become extremely familiar with the sample and eliminated the possibility of systematic errors which may be introduced by inter-rater differences. This issue is discussed further below.

4. Tools of measurement selected and developed

Both the established tools of measurement and the novel methods developed for use within this thesis demonstrated excellent reliability and utility. This is discussed further in chapters 2 and 6.

5. Non-independent measures used to measure certain clinical features

Many of the measures used in which familiality was demonstrated were non-independent. This allowed major themes to be identified such as: ages at onset (as measures in overall illness, mania, depression and psychosis); illness course (e.g. related to course of disorder, ERS8, number and duration of admissions); and severity of illness (Global Assessment Scale measures for worst ever period of illness, worst manic episode, worst depressive episode and worst psychosis).

6. The schizophrenia and bipolar disorder family samples

The schizophrenia and bipolar samples, referred to as "sub-samples" within this thesis, as they are combined to form the large harmonised dataset, were originally collected as part of ongoing molecular genetic studies within the Department of Psychological Medicine in Cardiff University and the Department of Psychiatry in the University of Birmingham. Because the research teams have historically recognised the importance of phenotype definition, when these samples were originally recruited it was ensured that detailed information was collected on the clinical phenotype, from numerous sources of information. It was the quality and quantity of the data collected that made the research described in this thesis possible.

Limitations

1. Retrospective study design

As is true for all retrospective studies, the quality of the data used in this research was reliant on the quality and quantity of previously-collected data. To make positive ratings using the tools selected, detailed descriptions of the relevant items of psychopathology were essential. As stated above, in general each case was extremely

well described, using numerous sources (e.g. interview vignettes, background information vignettes, case-notes, etc). However, there were items for which it was more difficult to make positive ratings, such as the novel measure Extended Rating Scale 3 which measured fluctuations in mood. To make a positive rating on this scale, the rater had to be convinced that at least two switches in mood had occurred during an acute phase of illness. It was often difficult to be sure whether fluctuations described were between mood states (e.g. mania to depression to mania), between affective disturbance and euthymia, or between different states within the same affective episode (e.g. irritability to elation within mania). In a prospective study, information required to make a specific rating could be collected specifically (i.e. questions could be asked directly relating to the rating criteria), thus facilitating the rating process.

However, although a prospective study would have allowed more project-specific data to be collected, it would have been an expensive and time-consuming procedure. Taking into account the size of the previously recruited samples, and given the amount of detail collected for each case, it would have been a considerable waste of resources to disregard these samples and to recruit further patients for this purpose. Given the time-scale of this thesis, it would also have resulted in the final dataset being substantially smaller in size. The study-design used allowed hypotheses to be generated, which can be tested prospectively (as discussed in chapter 6).

2. Multiple testing

Performing analyses on such a large number of variables within the sample (N=157) introduced multiple-testing issues that reduced power to detect significant

effects. After corrections were made for multiple testing using the Bonferroni methd, no significant results were maintained.

Due to the large number of tests performed the risk of false positives is high. As stated previously, it is entirely possible that the majority of significant findings reported in this chapter are false positives. Future work is needed to replicate these findings.

However, this was very much an exploratory analysis, and the variables identified using these methods can be used to form hypotheses which can be tested in future studies. This is discussed further in chapter 6.

3. A single rater was responsible for rating the entire sample of patients

This methodological issue has also been discussed above, in relation to the advantages of using this method. However, there are also potential disadvantages which must be acknowledged. The fact that a single rater was involved in rating the entire sample over a considerable period of time, introduces the risk of rater-drift, in which an individual's method of rating alters gradually over time. However, given the time-scale this was the only study-design feasible in creating such a large and richly described sample. The limitations of this method were recognised prior to the implementation of the methods, and were dealt with in the following ways. Firstly, before rating this sample, I underwent a rigorous training program, as described in chapter 2. This involved regular meetings with experienced members of the research team in both Cardiff University and the University of Birmingham, in which methods were discussed. I also participated in regular reliability exercises in which cases were rated by trained members of the research teams individually, and then discussed until a consensus rating was agreed upon for each measure.

During the rating of cases comprising the large harmonised dataset, I carried out reliability analyses using the following methods: i) inter-rater reliability, in which my ratings were compared to the ratings of other members of the research team for each measure; ii) analyses in which cases rated in full by myself were then checked by Professor Nick Craddock, who highlighted any ratings with which he disagreed; iii) Rater-drift analyses, in which I re-rated cases which I had rated at an earlier stage of the research, and compared ratings made during the two different time-points. Excellent reliability was demonstrated using all methods, providing reassurance that my ratings were consistent both over-time and with ratings made by other members of the research team (see methods).

4. Possible bias caused by rating members of the same family together

Another possible risk was that rating members of the same family together would bias ratings made, i.e. characteristics that occurred between family-members would be considered more similar than those occurring between unrelated individuals. Because of this, where possible, family-groups were not rated consecutively, for example cases from the schizophrenia sub-sample and cases from the bipolar disorder sub-sample were rated alternately. The order in which the ratings were made was also influenced by the preparation of data for cases used in the Wellcome Trust Case Control Consortium (WTCCC 2007). Cases included in this study were prioritised. Because the WTCCC was an association study, only a single individual from each family was included, and their family-members were rated at a different and usually much later date. A list of individuals included in this study, which were also used within the WTCCC can be found in Appendix S.

5. The sample is enriched for "prototypical" forms of the disorders

The samples used to create the large harmonised dataset (LHD) were collected on the basis of a proband with the "core diagnosis" (i.e. bipolar disorder or schizophrenia) and at least one sibling who met diagnostic criteria for a "broad diagnosis" (as described in Chapter 2). This meant that the combined sample was enriched for prototypical forms of the disorder, rather than for the more intermediate forms characterised by mixed features of both illnesses. It also meant that certain pairs were not included within the LHD – for example there were no siblings within the sample who both had a diagnosis of DSMIV defined schizoaffective disorder.

The inclusion of families enriched for schizoaffective disorder would have resulted in a broader representation of the functional psychoses. This could be achieved by recruiting a sample of patients based on a proband with a diagnosis of schizoaffective disorder.

In addition to schizoaffective disorder, other diagnoses characterised by mood disturbance and/or psychotic features are not included within this sample, for example delusional disorder, brief psychotic disorder, dysthymic disorder, cyclothymic disorder, etc. Including these in future work would result in a sample more representative of a broad spectrum of functional psychoses.

The inclusion of families enriched for diagnoses such as schizoaffective disorder would facilitate phenotypic analyses across diagnostic boundaries. This was not possible during this research, which was focussed on samples previously collected, but would be an important consideration for future studies.

6. Lack of clinical training

As stated in Chapter 2, the fact that I had received no clinical training prior to the onset of my PhD made the training period I underwent prior to beginning my

work on the schizophrenia and bipolar disorder datasets extremely important. A lack of clinical experience meant that my knowledge of the clinical features involved in these illnesses was limited to academic study of relevant articles and textbooks.

This is likely to have had some influence on the way in which I rated these cases. For example, when reviewing patient case-notes, a trained clinician would be more able to "read between the lines" and make judgements based on their own clinical experience. Raters with clinical training would also be more able to recognise the presence of symptoms based on descriptions of behaviour described in the case-notes; this would be a lot more difficult for an individual with no clinical training and in this way certain symptoms may have been missed.

However, despite these limitations, it could be argued that there are some potential advantages to a lack of clinical experience when undertaking methods described in this thesis. My training in the recognition of these symptoms was directly related to the rating guidelines used in my primary analyses. For example, the Operational Criteria (OPRCIT, McGuffin et al, 1991) was used to record the presence of specific symptoms and the glossary provides detailed definitions which must be fulfilled before a symptom can be deemed to be present. A rater with clinical training would be more likely to make a positive rating based on their prior understanding of what constitutes this particular clinical feature, rather than rating it positively only if it meets the specific criteria defined by the OPCRIT rating guidelines for this item of psychopathology. Rating according to the standard definition given by the rating guidelines is likely to increase reliability as it may reduce a degree of subjectivity introduced as a result of clinical experience. Such an effect has been observed during the research study (Professor Nick Craddock, personal communication).

7. Non-systematic recruitment

Non-systematic recruitment may have resulted in ascertainment bias within the sample. Systematic ascertainment would have led to the samples being more representative.

8. No follow-up of participants

Participants were not followed up over time, therefore clinical information was only available up to the point they were recruited to the study. The majority of participants would be likely to experience more episodes of illness post-participation which would be likely to alter to some degree their ratings on various rating scales which cover the lifetime course of the illness.

9. Possibility of missing less severe episodes of illness

The clinical ratings which were made on the sample relied on detailed and accurate documentation of the individual's illness. This information was obtained at interview (during which previous episodes of illness were asked about) and from psychiatric case-notes. General Practioner notes were also available for some, but not all cases. This meant that it was likely that some episodes of illness, particularly those that were insufficiently severe to require treatment, were not recorded and therefore not considered when clinical ratings were made.

5.4.6 General discussion of findings

The primary analyses performed on the large harmonised dataset identified 31 variables that were significantly correlated within families. Due to the exploratory

nature of this study, no individual result withstood corrections for multiple testing using the Bonferonni method. However, because many of the variables were non-independent, corrections made are likely to be over-conservative. Further, when testing 157 variables using a 5% significance level, 7.85 variables would be expected to show significant results by chance, assuming that these variables were independent. Although, as discussed above, not all the measures tested were independent in this research, the fact that 31 variables were identified suggests that many of these are likely to reflect a genuine effect within the sample, rather than chance-findings.

It is encouraging that many of the variables that were significantly aggregated within families in this sample are consistent with previous studies investigating familiality in clinical variables. As well as providing further evidence to support the hypothesis that there is a genuine familial effect, it also provides reassurance regarding the validity of the ratings made for this research. This is discussed further in chapter 6.

In the majority of cases, the Spearman's-rho analyses performed on the paired-sample comprising a single pair from each family supported the results produced in the primary analyses. Where differences did occur, in the majority of cases the findings from the Spearman's analyses were more significant than those found using the mixed effects regression analyses, and resulted in the variable reaching significance in the sub-sample in which no significant effect was found originally. This supports the hypothesis that the significant results reported in the primary analyses reflect a genuine familial effect within the data, and were not false-positives produced as a result of the way the continuous data were converted into ordinal categories.

However, caution must be taken when interpreting the results from the Spearman's analyses. Unlike in the primary analyses, gender and sample-of-origin were not controlled for, which could account for the differences observed in the results. Further, Spearman's-rho correlations are influenced by the way the siblings are ordered, i.e. sibling 1 vs. sibling 2. If the order of some of the siblings were switched, results may be different. It may also be the case that, despite selecting pairs at random to form the smaller dataset, it may be unrepresentative of the larger sample from which it was formed.

It is particularly interesting that three of the four variables that were significant in the large harmonised dataset and both sub-samples were related to course of illness which Kraepelin (1919) used to differentiate patients with dementia praecox from patients with manic-depressive insanity. These results support Kraepelin's hypothesis that course of illness is an important aetiological factor in the functional psychoses. However, the fact that significant familiality was demonstrated in the schizophrenia and bipolar disorder samples individually, as well as in the LHD after controlling for sample-of-origin effects, suggests that course of illness may be useful in defining more homogeneous subgroups of patients both within and across the traditional diagnostic boundary enforced by the dichotomy.

It is also interesting to note that several variables for which significant familiality was found in the LHD and in the bipolar disorder sub-sample have previously been thought of as more typically associated with schizophrenic illness. These include catatonic symptoms (ERS10), disorganised behaviour (ERS11) and negative formal thought disorder. It may be that these measures are more generally related to severity of illness, which would be consistent with the findings for GAS-M (which measured impairment during the worst ever episode of mania). For example,

for the symptoms included in the rating criteria for ERS10 and ERS11 to be rated, they had to be distinguishable from features more typical of affective disturbance, in terms of their nature or severity.

Although it is likely that shared environmental effects are involved in the pathogenesis of many of the variables identified in this study, of the 157 variables tested the variables for which a familial effect was demonstrated in this sample are the most likely to be genetically influenced, and therefore are the most likely to be of use on future molecular genetic studies. Future research studies into psychotic-affective illness should be informed by phenotypic analyses such as these. It is important that information allowing these measures to be rated are collected in the large samples needed to elucidate the genetic mechanisms involved in the functional psychoses. This is discussed further in chapter 6.

5.5 Conclusion

In conclusion the successful implementation of the methods described within this chapter resulted in the identification of 31 clinical variables which showed familiality in a mixed sample comprising families enriched for schizophrenia and families enriched for bipolar disorder (although due to the number of variables tested the risk of false positives is high). These may be useful in future studies to help identify subgroups of patients more likely to share a common genetic pathogenesis. It is hoped that in the future, increased understanding of the biological mechanisms involved in these debilitating disorders will lead to more successful treatments which are more tailored to the underlying biology of the illness, ultimately leading to improved quality of life for patients and their families.

6 General Discussion

The aim of this thesis was to develop a set of measures that could be used across traditional boundaries on patients with psychotic-affective illness; to assess the familiality of these variables in a large sample of patients representing a spectrum of the functional psychoses; to perform phenotype assessment in a sample of patients with Velo-Cardio-Facial Syndrome (VCFS); and to perform analyses in a sample enriched for schizoaffective disorder. The results of these analyses are summarised below.

6.1 Summary of results

6.1.1 Primary Analysis

The primary analysis was carried out on a large harmonised dataset comprising families enriched for psychotic and affective illness. Each case was rated on a set of approximately 200 clinical variables, which covered a wide-spectrum of clinical characteristics. Mixed-effects regression analysis was performed on the final dataset, which consisted of 835 individuals from 373 families, to investigate which of the clinical variables measured were significantly correlated within families. Thirty-one such variables were identified; these are presented in table 6-1 below.

At a 5% significance level, approximately 8 variables would be expected to show significant intra-familial correlations by chance. The fact that 31 variables were identified is therefore particularly encouraging and suggests that a number of these significant results are likely to be indicators of a genuine effect, rather than false-positives. However, none of these individual significant results withstood corrections for multiple testing, which is unsurprising given the large number of variables that were tested (N=157).

However, few variables tested were likely to be completely independent. For example, age at onset was measured in a number of different ways (e.g. age at first symptom, age at first admission, age at first psychosis, etc). Level of impairment was also measured in a number of different ways using the Global Assessment Scales (GAS, Endicott et al, 1976), for example during worst depression, worst psychosis, etc. Further, many of the rating scales overlap to a degree. For example, ratings made using the GAS, the Bipolar Affective Disorder Dimension Scales (BADDS, Craddock et al, 2004), and Extended Rating Scale 8 (prototypical schizophrenia vs. prototypical affective disorder) are all influenced by the overall severity of an individual's illness.

Because not all variables tested were independent, the corrections made for multiple-testing are likely to be over-conservative. However, due to the large number of tests performed there is still a high risk of false positives, as discussed previously.

Clinical variables which showed significant IFC in the LHD and both sub-samples	**Clinical variables which showed significant IFC in the LHD and the SZP sub-sample**	**Clinical variables which showed significant IFC in the LHD and the BPD sub-sample**	**Clinical variables which showed significant IFC in the LHD only**
Length of longest admission**	LE Cannabis abuse**	Impairment during worst mania*	Positive formal thought disorder
Age at onset**	Aggressive behaviour**	Psychomotor retardation*	Number of admissions
Course of disorder*	Impairment during worst psychosis**	Impairment during worst illness*	Age at first depression
ERS8: prototypical affective disorder vs prototypical SZP	Dimensional measure of incongruence*	Diminished libido*	ERS9: Extent to which illness is characterised by a chronic defect state
	ERS2: Relationship between psychotic and affective symptoms*	Age at first mania	
	Age at first psychotic symptoms	Negative formal thought disorder	
	Presence/absence of chronic defect state	Marital status	
	Other substance abuse	ERS7: Most dysphoric manic episode	
	Deterioration since illness onset	Excessive self-reproach	
		Delusions of influence and/or persecution	
		ERS10: Catatonica	
		ERS11: Disorganised behaviour	
		Anhedonia	

Table 6-1: Summary of variables for which a significant intra-familial correlation was produced in the large harmonised dataset (LHD) using mixed effects regression analysis.
*p<0.01 in the LHD, **pp<0.001 in the LHD. ERS – "Extended Rating Scale"; LE – "Lifetime Ever". IFC – intra-familial correlation

ii. Velo-Cardio-Facial Syndrome Sample

To investigate the phenotype in a sample of 21 patients with Velo-Cardio-Facial Syndrome (VCFS) and a major psychiatric disorder I rated each case on a subset of the ratings used in the primary analyses. I also diagnosed each patient using the Research Diagnostic Criteria (RDC) (Spitzer, Endicott & Robins, 1975). The sample was characterised by high rates of schizoaffective disorder; 47.6% of the sample met RDC criteria for this diagnosis. Of the remainder, 23.8% were diagnosed with schizophrenia and 28.6% with major depressive disorder.

Using the Bipolar Affective Disorder Dimension Scales (BADDS, see chapter 2), it was possible to further examine the rates of affective and psychotic disturbance within the sample. Psychotic symptoms were present in 71% of the sample (N=15). Rates of affective disturbance were high, with 81% of the sample (N=17) having experienced at least one episode of mania, hypomania or major depression. When the criteria were relaxed to include sub-clinical episodes of affective-disturbance, this rose to 95% (N=20). The relationship between psychotic features and affective disturbance is summarised in the graph overleaf.

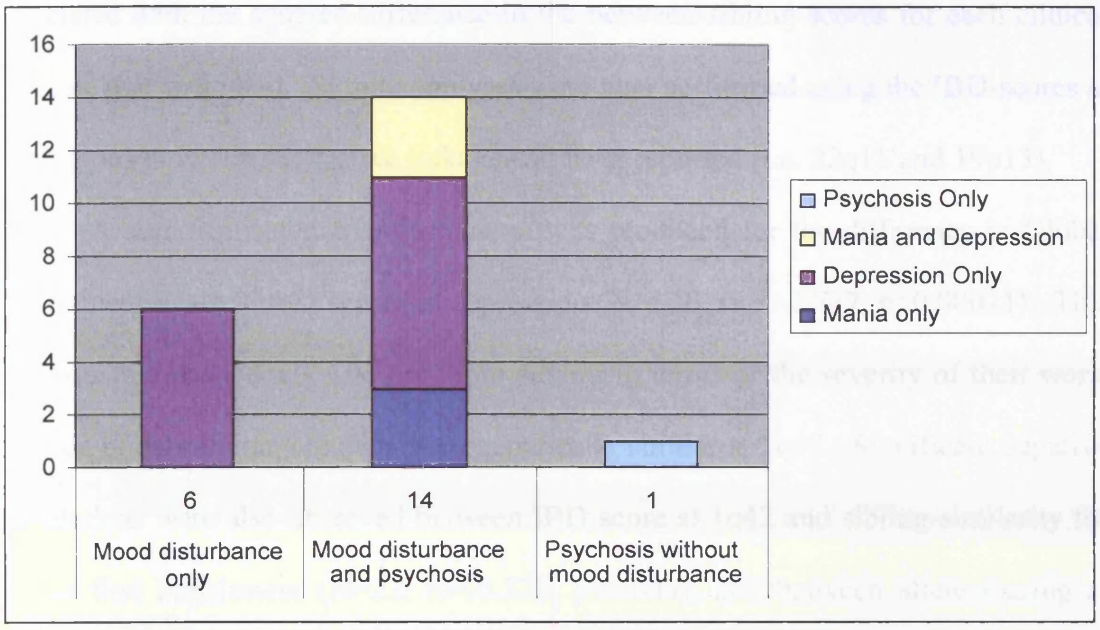

Figure 6-1: Prevalence and relationship between affective disturbance and psychotic symptoms within a sample of VCFS patients with a major psychiatric diagnosis.

Depression was found to be particularly prevalent in the sample, with 62% (N=13) having experienced at least one episode of major depression, rising to 67% (N=14) if minor episodes of depression were also included. These results suggest that VCFS may be associated with a phenotype characterised by high rates of psychosis and mood disturbance, most frequently characterised by depressive episodes.

iii. Schizoaffective sub-sample

Clinical ratings were also undertaken on a subset of patients from the LHD in which a genome-wide linkage scan had previously been undertaken (Hamshere *et al*, 2005). These comprised 35 sibling-pairs enriched for schizoaffective disorder, for which significant genome-wide linkage had been reported on 1q42, and suggestive linkage on 22q11 and 19p13. Estimations of the maximum-likelihood identical-by-descent (IBD) allele-sharing probabilities were available for each sibling-pair in the sample at these three chromosomal locations. IBD-scores on chromosome 1q42 were

correlated with the squared-difference in the between-sibling scores for each clinical variable that was rated. Similar analyses were also performed using the IBD-scores at the regions in which suggestive linkage had been reported (i.e. 22q11 and 19p13).

A significant negative correlation was produced for the difference in Global Assessment Scale (GAS) scores in depression (N = 20, rs = -0.737, p=0.00021). This suggests that individuals who are more similar in terms of the severity of their worst episode of depression, are also more genetically similar at 1q42. Significant negative correlations were also observed between IBD score at 1q42 and sibling-similarity for age at first impairment (N=22, rs=-0.322, p=0.044), and between allele-sharing at chromosome 22q11 and sibling-similarity for worst level of functional impairment experienced over the entire duration of illness (as measured by the GAS; N=33, rs=-0.418, p=0.015).

These results suggest, when using genetic linkage signals as biological validators, taking into account the severity of depressive illness, age at onset and the severity of illness during the worst overall episode may be useful in defining more homogeneous subgroups of patients with schizoaffective illness.

The two smaller samples of patients described in chapters 3 and 4 are of interest because both have phenotypes which have some biological validation; the VCFS sample because each case was deleted at chromosome 22q11, and the schizoaffective disorder sample because significant genome-wide linkage had been demonstrated at chromosomes 1q42, and suggestive evidence for linkage was reported at 19p13 and 22q11. Further definition of the phenotype in samples such as these is particularly important due to the fact that findings can be related to underlying biological mechanisms. The fact that significant negative correlations were produced

for three clinical variables in the schizoaffective sample provides further evidence to support the hypothesis that using such clinical measures as an adjunct to diagnostic categories may be useful in molecular genetic research.

It is interesting that depression was picked out as an important factor in both the VCFS sample, which was characterised by high rates of depressive illness, and in the sample enriched for schizoaffective disorder (bipolar type), in which between-sibling similarity on GAS scores during their worst episode of depressive illness were significantly correlated with their similarity at a genetic level. This provides further evidence to suggest that depression may be useful in defining more genetically homogeneous subgroups of patients, as suggested in previous studies. For example, as described in chapter 1, Hamshere et al (2006) performed genome-wide linkage analysis on a sample of patients with schizophrenia, conditioning on the occurrence of depressive episodes and found genome-wide significant linkage at 4q28.3 and suggestive evidence at 20q11.21. These regions did not meet the criteria for genome-wide significant or suggestive linkage when depressive episodes were not included within the model as a covariate.

It is interesting that age at illness-onset and GAS scores for the worst ever episode of illness were shown both to significantly aggregate within families in the LHD and to be significantly correlated with genetic similarity in analyses performed in the sub-sample of cases enriched for schizoaffective disorder. This provides further evidence to suggest that these variables are influenced by genetic factors and that they therefore may be useful in future studies, for example in refining linkage analyses (as discussed later in this chapter).

6.2 Discussion of novel rating scales

The Extended Rating Scales (ERS) were developed to be used across diagnostic categories on cases involving affective disturbance and/or psychotic symptoms. Having now applied these scales to the 835 cases comprising the large harmonised dataset, it is possible to draw conclusions about the utility of these novel rating scales. Each measure is discussed below in relation to the following points: its reliability, ease of use within the samples of interest and whether significant results were obtained using the mixed-effects regression analyses to assess intra-familial correlation.

Extended Rating Scale 1 – Proportion of affective episodes manic in nature.

The aim of Extended Rating Scale 1 (ERS1) was to assess the proportion of episodes of affective-disturbance that were manic in nature. As shown in figure 6-2, this was calculated by dividing the total number of manic episodes, by the overall number of episodes of affective-disturbance.

Mixed episodes were treated differently according to whether they were predominantly manic in nature, e.g. dysphoric mania (in which case 0.75 was added to the total number of manic episodes and 0.25 to the total number of depressive episodes), predominantly depressive in nature (0.25 was added to the total number of manic episodes and 0.75 to the total number of depressive episodes), or comprised a roughly balanced mixture of depressive and manic symptoms (0.5 was added to each total).

The scale therefore gave a measure of the extent to which the affective element of the illness was characterised by high mood.

As discussed in the introduction, a limitation of this scale was that it relied on detailed and accurate documentation of illness-episodes. Although less severe

episodes were less likely to be documented in the case-notes, the majority of participants were asked in detail about these at interview. Where it was felt that there was not sufficient information to make an accurate rating, a score of "999" (unknown/uncertain) was given and the case was excluded from the analysis.

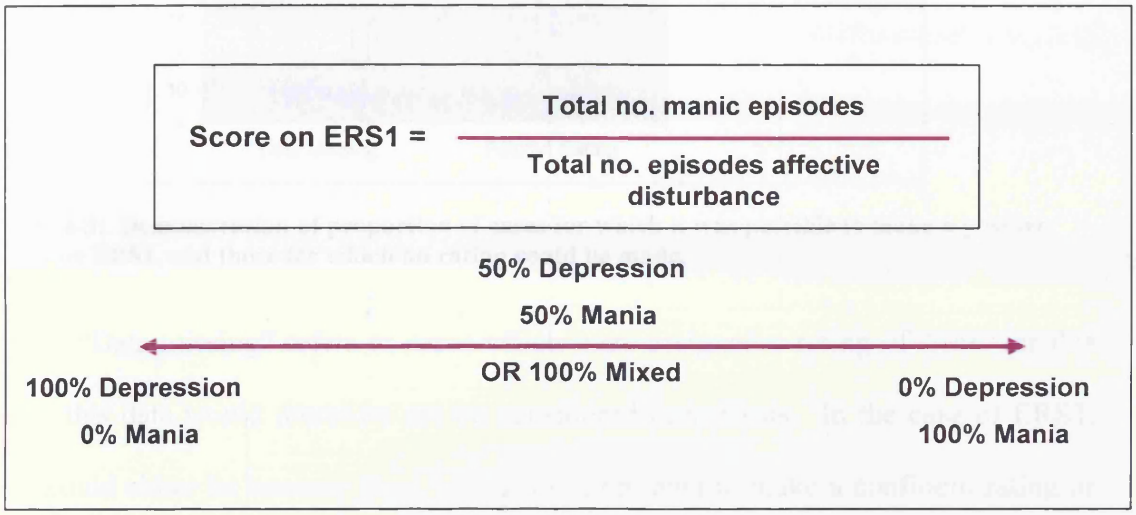

Figure 6-2: Summary of rating guidelines for ERS1.

Reliability

Excellent inter-rater reliability was demonstrated for ERS1 (ICC=0.987).

Utility

The detailed information available for these cases, usually from multiple sources, made the calculation of the number and nature of affective-episodes relatively simple in the majority of cases. It was possible to rate 80.1% of cases overall on ERS1. When considering the two sub-samples individually, it was possible to rate ERS1 in 63.7% of the schizophrenia cases and 95.2% of the bipolar disorder cases. This is demonstrated in the graph below.

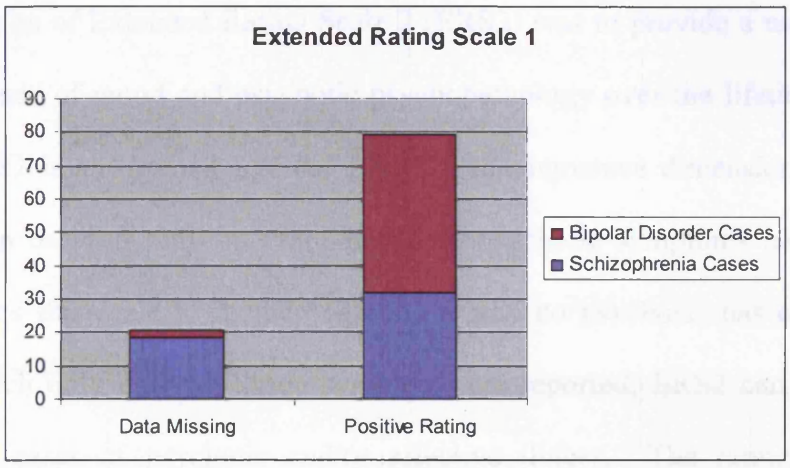

Figure 6-3: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS1, and those for which no rating could be made.

"Data missing" refers to cases which were assigned a rating of "-99" for this scale; this data would therefore not be considered in analysis. In the case of ERS1, this would either be because there was insufficient data to make a confident rating or because no affective episodes had occurred over the lifetime course of the illness. The fact that a large proportion of cases were rated in the schizophrenia sub-sample is an indication that high levels of affective disturbance were present in this sample.

Results from the mixed-effects regression analysis

Although ERS 1 succeeded in terms of its ease of utility and reliability, results produced using the mixed-effects regression analysis did not demonstrate that this measure was significantly correlated within families, as demonstrated in the table below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS1	0.085	0.22	0.245	0.14	0.061	0.35

Table 6-2: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 2 – Relationship between psychotic and affective symptoms

The aim of Extended Rating Scale 2 (ERS2) was to provide a measure of the relative balance of mood and psychotic psychopathology over the lifetime course of illness. ERS2 is an extension of the BADDS Incongruence dimension (BADDSI). BADDSI can be used only on cases in which psychotic symptoms have occurred. ERS2 extends this scale to include cases in which no psychosis has occurred, and cases in which only near-psychotic symptoms are reported; ERS2 can therefore be used on all cases of psychotic and/or affective illness. The rating criteria are summarised in the table below, and can be found in full in Appendix E.

Score	Rating Criteria
-20	Episodes of clinically significant mood disturbance. No psychotic or near psychotic features occur
-19	Illness is predominantly affective but includes near psychotic features - occasional at low end of range, frequent at high end of range
0	Psychotic symptoms occur only during affective episodes and are entirely mood-congruent
20	Psychotic symptoms occur only during affective episodes. There is an approximate balance between congruent and incongruent symptoms
40	Psychotic symptoms occur only during affective episodes and are entirely mood-incongruent
43/47	Psychotic symptoms occur only during affective episodes and include one or more first rank symptoms
50	Psychotic symptoms are probably present outside of an episode of mood-disturbance
60	Psychotic symptoms are definitely present in the absence of an affective episode on at least one occasion
80	Psychotic symptoms are definitely present in the absence of an affective episode on many occasions
100	Psychotic symptoms dominate illness and occur chronically outside of affective episodes. Affective episodes occur but are not a major feature of illness.
110	Psychotic symptoms dominate illness. Affective symptoms occur which do not meet criteria for an episode of mood-disturbance.
120	Illness is characterised by psychotic features in the absence of any disturbance in mood.

Table 6-3: Summary of rating criteria for ERS2.

Reliability

Excellent inter-rater reliability was demonstrated for ERS2 (ICC=0.979).

Utility

It was possible to rate 87.65% of the total sample, which when broken down into the sub-samples included 92.7% of the schizophrenia sub-sample and 82.6% of the bipolar disorder sub-sample, as demonstrated in the graph below.

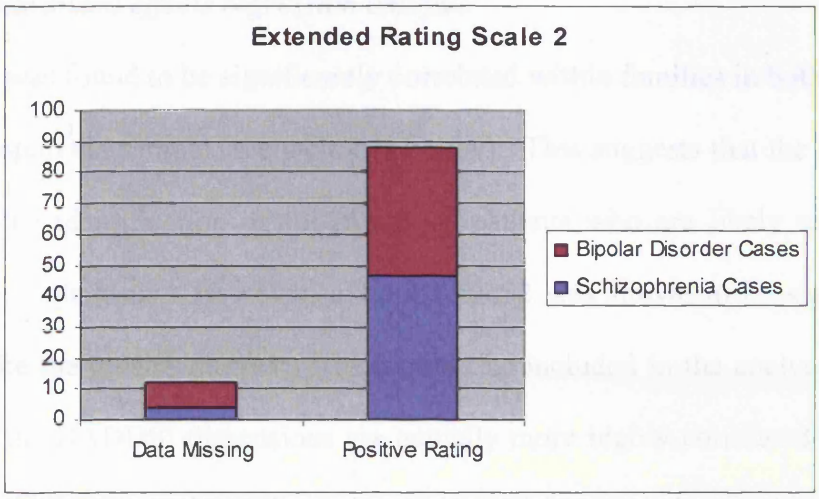

Figure 6-4: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS2, and those for which no rating could be made.

In ERS2, "data missing" refers to cases in which it was not possible to make a confident rating, due to the descriptions within the data, e.g. it was not clear whether psychosis had definitely occurred. In contrast, when BADDSI is used to make ratings, "data missing" refers to cases in which it was not possible to make a confident rating due to the data but also cases in which no psychotic symptoms had occurred at all. For this reason, it was possible to rate a far greater number of cases using ERS2, as demonstrated in the graph below.

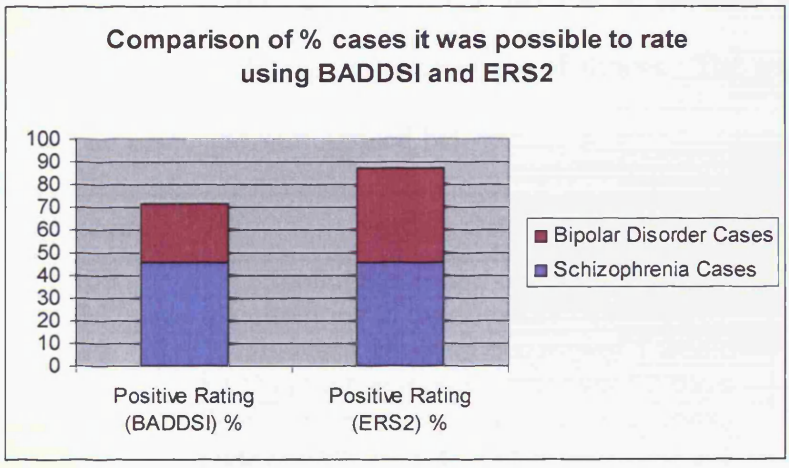

Figure 6-5: Comparison of positive ratings made using BADDSI with positive ratings made using ERS2.

Results from the mixed-effects regression analysis

ERS2 was found to be significantly correlated within families in both the LHD and the schizophrenia sample (see table 6-4 below). This suggests that the scale may be useful in the identification of subgroups of patients who are likely to be more genetically homogeneous. However, although ERS2 was shown to be significantly familial despite the greater numbers which could be included in the analyses, results produced for the BADDSI dimensions are actually more highly correlated and more significant in the LHD and the SZP sub-sample (see Table 6-4 below), which suggests that extending the BADDSI scale to include cases in which no clear psychotic symptoms occur may not be beneficial.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS2	0.171	0.0080	0.265	0.0049	0.119	0.17
BADDSI	*0.224*	*0.0048*	*0.285*	*0.0040*	*0.181*	*0.19*

Table 6-4: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples for ERS2 and BADDSI.

Extended Rating Scale 3: Fluctuations in mood

The aim of Extended Rating Scale 3 (ERS3) was to measure the maximum rapidity of mood fluctuations during an acute phase of illness. The guidelines used when rating a case on ERS3 are summarised below:

Score	Rating Criteria
100	Fluctuations in mood occur over 1 day
90	Fluctuations in mood occur over 4 days
80	Fluctuations in mood occur over 1 week
70	Fluctuations in mood occur over 10 days
60	Fluctuations in mood occur over 2 weeks
50	Fluctuations in mood occur over 4 weeks
40	Fluctuations in mood occur over 8 weeks
30	Fluctuations in mood occur over 12 weeks
20	Fluctuations in mood occur over 26 weeks
10	Fluctuations in mood occur over 52 weeks
0	No fluctuations in mood occur

Table 6-5: Summary of rating criteria for ERS3.

Reliability

Excellent inter-rater reliability for ERS3 was demonstrated (ICC=0.99). However, it must be noted that in the cases used to measure reliability, only three individuals were rated as being greater than 0 - the remainder being scored as "unknown/uncertain" or "0" which indicates that no fluctuations had occurred.

Utility

It was possible to rate 69.5% of cases on this rating scale in the LHD, which when broken down into the sub-samples, included 81.2% of the schizophrenia cases and 57.8% of the bipolar disorder cases. This is demonstrated in the graph below.

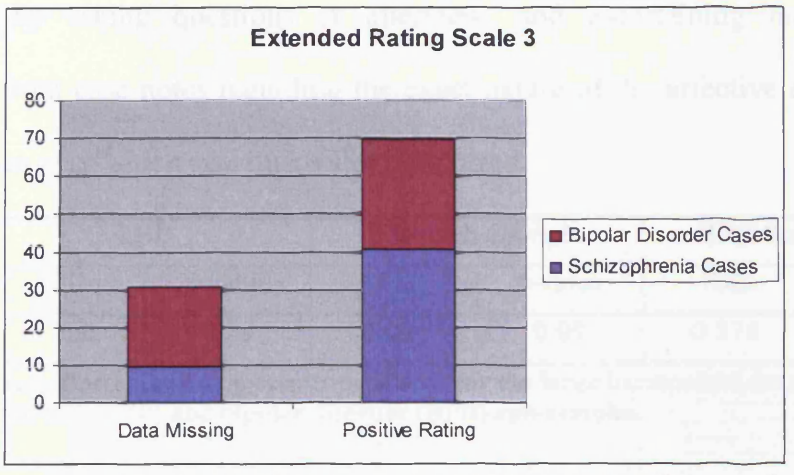

Figure 6-6: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS2, and those for which no rating could be made.

As mentioned above, a score of "0" is a positive rating, indicating that although episodes of mood disturbance have occurred, there have been no fluctuations in affect. Although a relatively large number of cases could be rated using this scale, a large proportion of these were rated "0" (64% of the LHD, 79.9% of the SZP sub-sample and 47.9% of the BPD sub-sample). Fluctuating mood could only be measured in 9.3% of the schizophrenia cases and 9.9% of the bipolar disorder cases.

In general, the clinical information available for each case was extremely detailed. However, the rating guidelines state that enough information must be present to allow the rater to conclude both that these fluctuations involved definite

swings from high/mixed mood to depression or vice versa, and to make a judgement of the time-scale over which these fluctuations occurred. Because of the specific nature of these requirements, it was often not possible to make a confident rating.

Results of the mixed-effects regression analysis

Due to the lack of variability within the sample, it is unsurprising that the mixed-effects regression analysis did not produce significant results (see Table 6-6 below). However, this does not necessarily mean that ERS3 should be dismissed altogether and it may be useful to implement this scale on a sample of patients in which more detailed and specific information was collected regarding fluctuations in mood, e.g. by asking questions at interview, and ascertaining more specific information from case-notes regarding the exact nature of the affective episodes and the time-scales over which any fluctuations occurred.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS3	0.256	0.29	0.054	0.99	0.274	0.27

Table 6-6: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 4: Instability of clinical state.

The aim of Extended Rating Scale 4 (ERS4) was to give an indication of the maximum instability in clinical state during the most variable month of illness. Unlike ERS3, ERS4 allowed ratings to be made on instability even when the exact nature of the clinical state was unknown. For example, broad statements such as "rapid fluctuations in mood" which appeared frequently in hospital case-notes could be rated using anchor points on ERS4, whereas a score of "uncertain" would be made on ERS3 because: i. It would not be possible to be sure that the fluctuations involved switches in polarity or more subtle variations in clinical state and; ii. It would not be

possible from this information to be certain of the time period in which variation occurred. The rating guidelines are summarised below; details of anchor points can be found in Appendix E.

Score	Rating Criteria (refers to most variable month of illness)
100	Clinical state varies significantly during a period of 10 mins
80	Clinical state varies significantly during a period of 1 day
60	Clinical state varies significantly during a period of 1 week
40	Clinical state varies significantly during a period of 2 weeks
20	Clinical state varies significantly during a period of 4 weeks
0	No variability in clinical state

Table 6-7: Summary of rating criteria for ERS4.

Reliability

Excellent inter-rater reliability was demonstrated for ERS4 (ICC=0.997)

Utility

Rating clinical variability using this measure was possible in 73.9% of cases in total – 71.9% of the schizophrenia cases and 75.5% of the bipolar disorder cases, as demonstrated in figure 6-7 below.

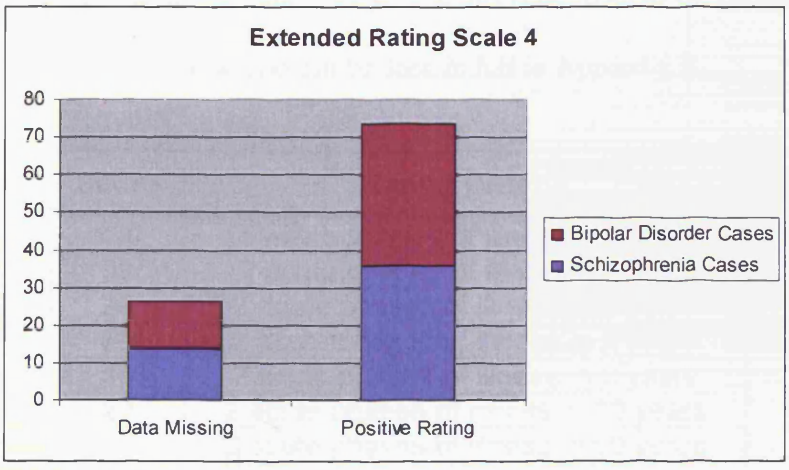

Figure 6-7: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS4, and those for which no rating could be made.

Further, only 18.3% of the schizophrenia cases and 19% of the bipolar disorder cases were given a rating of "0" indicating that no variation in clinical state had occurred over a period of 4 weeks or less. It was therefore possible to make measurements of clinical variability in 55.1% of cases (compared to 9.6% when using ERS3).

Results of the mixed-effects regression analysis

Although ERS 4 succeeded in terms of its ease of utility and reliability, results produced using the mixed-effects regression analysis, which showed almost zero correlation, did not demonstrate that this measure was significantly correlated within families, as demonstrated in the table below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS4	0.00	0.99	0.001	0.99	0.001	1.0

Table 6-8: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 5: Periodicity of acute phases of illness

The aim of Extended Rating Scale 5 (ERS5) was to measure the tendency to recurrence of acute phases of illness over the lifetime course of illness. The rating guidelines are summarised below, and can be seen in full in Appendix E.

Score	Rating Criteria
100	5 acute phases of illness in 1 year
90	2 acute phases of illness in 1 year
70	2 acute phases of illness in 2 years
50	2 acute phases of illness in 5 years
30	2 acute phases of illness in 8 years
20	2 acute phases of illness in 10 years
10	2 acute phases of illness in 50 years
1	< 2 acute phases of illness in 50 years
0	Only 1 acute phase of illness

Table 6-9 Summary of rating criteria for ERS5.

Reliability

Excellent inter-rater reliability was demonstrated for ERS5 (ICC=0.941).

Utility

ERS5 was easy to use within the sample and could be rated in 83.3% of cases (79.7% of the schizophrenia sample and 86.9% of the bipolar disorder sample), as demonstrated in figure 6-8 below.

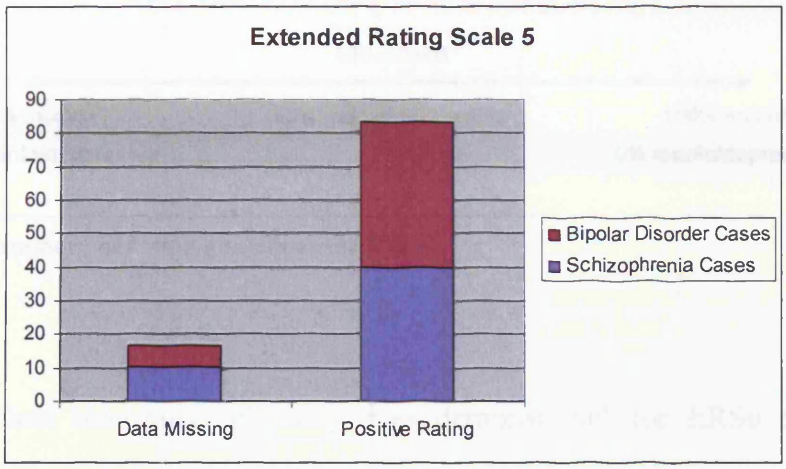

Figure 6-8: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS5, and those for which no rating could be made.

Results of the mixed-effects regression analysis

Although the implementation of ERS5 on the current sample was successful, no significant intra-familial correlation was produced, as demonstrated in Table 6-10 below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS5	0.046	0.443	0.075	0.499	0.031	0.681

Table 6-10: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 6: Proportion of affective episodes of mixed polarity.

The aim of Extended Rating Scale 6 (ERS6) was to assess the proportion of episodes of affective-disturbance that were mixed in nature, i.e. symptoms indicative

of both mania and depression were present simultaneously. As shown in the diagram below, ratings on this scale were calculated by dividing the total number of manic episodes, by the overall number of episodes of affective-disturbance.

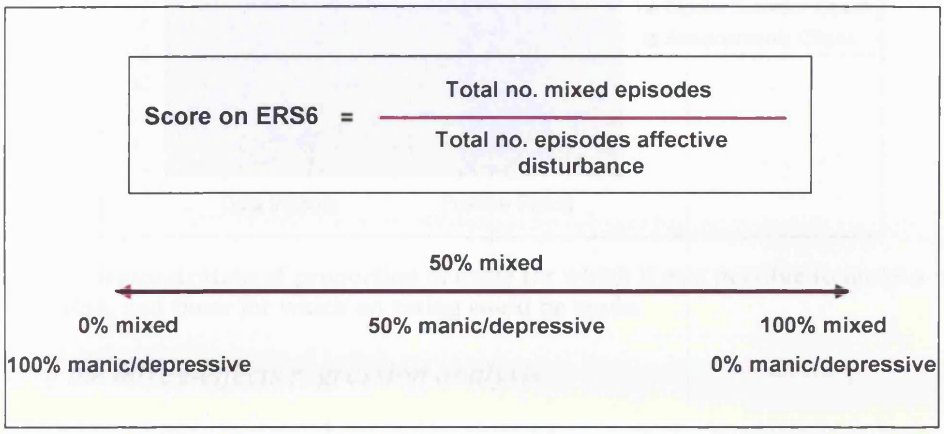

Figure 6-9: Summary of rating guidelines for ERS6.

Reliability

Excellent inter-rater reliability was demonstrated for ERS6 (ICC=0.999). However, as for ERS3, it must be noted here that of the 20 cases considered in the reliability analysis, only two had been scored above "0" for this measure.

Utility

Generally ERS6 was easy to use within the sample, and it was possible to make positive ratings on 86.3% of cases (87.7% of the schizophrenia sub-sample and 84.9% of the bipolar disorder sub-sample), as demonstrated in figure 6-10 below. The main reason that cases could not be rated was that there was not quite enough evidence to state whether the criteria for a mixed-episode had been reached. For example, a mention of "mixed episode" in the case-notes was not considered sufficient evidence that an episode of mixed mood had definitely occurred, according to DSMIV criteria.

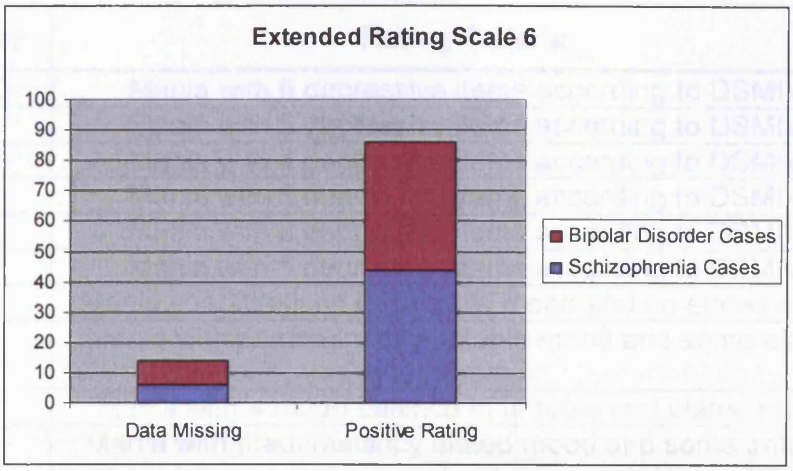

Figure 6-10: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS6, and those for which no rating could be made.

Results of the mixed-effects regression analysis

Although ERS 6 succeeded in terms of its ease of utility and reliability, results produced using the mixed-effects regression analysis did not demonstrate that this measure was significantly correlated within families, as demonstrated in the table below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS6	0.309	0.075	0.256	0.60	0.318	0.086

Table 6-11: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 7: Most dysphoric manic episode

Extended Rating Scale 7 (ERS7) was developed to measure the extent to which a manic episode is dysphoric in nature. ERS7 was used to rate the "most dysphoric" manic episode, i.e. the episode that was characterised by the highest number of dysphoric symptoms or, in the absence of these, the highest proportion of irritable mood. Rating guidelines are summarised in Table 6-12 below.

Score	Rating Criteria
100	Mania with 6 depressive items according to DSMIV
90	Mania with 5 depressive items according to DSMIV
80	Mania with 4 depressive items according to DSMIV
70	Mania with 3 depressive items according to DSMIV
60	Mania with 2 depressive items according to DSMIV
50	Mania with 1 depressive items according to DSMIV
40	Mania characterised by irritable mood and no elated mood
30	Mania with predominantly irritable mood and some elated mood
20	Mania with a rough balance of irritable and elated mood
10	Mania with predominantly elated mood and some irritable mood
0	Mania with elevated mood and no irritability or dysphoric features

Table 6-12: Summary of rating criteria for ERS7.

Reliability

Excellent inter-rater reliability was demonstrated for ERS7 (ICC=0.872).

Utility

ERS7 could only be measured in individuals who had experienced a manic or hypomanic episode, therefore a large proportion of individuals, particularly in the schizophrenia sample could not be rated. However, in cases in which mania had occurred, this scale could be applied easily to the data. In total, a positive rating could be made for 47.2% of the cases in the total sample (23.3% of the schizophrenia cases and 71.1% of the bipolar disorder cases), as demonstrated in figure 6-11 below.

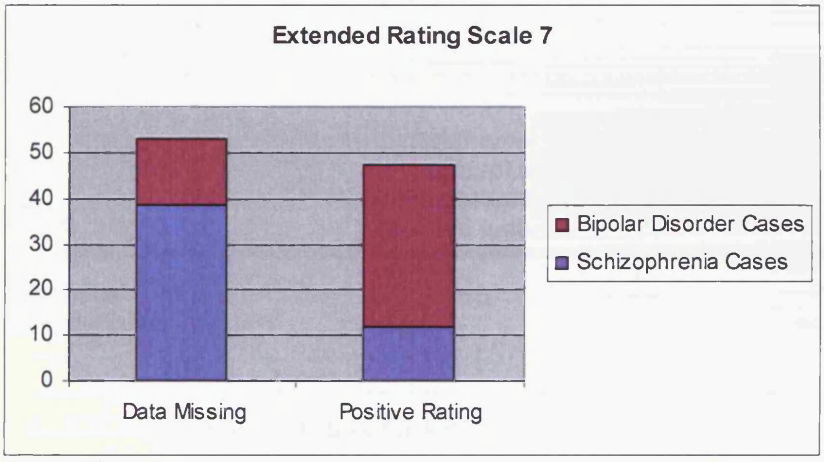

Figure 6-11: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS7, and those for which no rating could be made.

Results from the mixed-effects regression analysis

As presented in Table 6-13 below, significant results were produced in the large harmonised dataset and in the bipolar disorder sample, suggesting that scores on this measure aggregate within families.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS7	0.216	0.031	0.139	0.66	0.253	0.024

Table 6-13: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 8: Extent to which illness is characteristic of prototypical affective disorder vs. prototypical schizophrenia

Extended Rating Scale 8 (ERS8) was developed to allow raters to subjectively score each case on a scale of 0-100, from "prototypical affective disorder" to "prototypical schizophrenia". Unlike for the other Extended Rating Scales, there are no anchor points or specific rating guidelines for ERS8, apart from the general guide demonstrated in figure 6-12 below. The rater must therefore make a judgement after considering all of the available information, and score each case according to their overall impression of the nature of the illness.

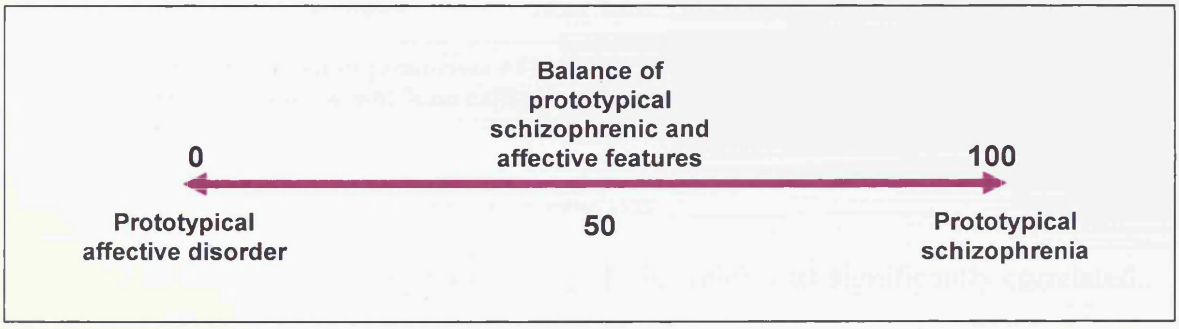

Figure 6-12: Summary of rating guidelines for ERS8.

Reliability

Despite the lack of stringent rating criteria, excellent inter-rater reliability was demonstrated for ERS8 (ICC=0.853).

Utility

The detailed information available for cases within the sample meant that ERS8 could be easily-utilised within the sample. Of all the Extended Rating Scales, ERS8 could be rated in the greatest proportion of cases. The lack of specific rating criteria meant that the rater did not have to rely on the presence of a detailed description of a specific item of psychopathology, which may or may not be present within the notes, but instead could use the data that was available to give an overall impression of the clinical picture for each individual. Positive ratings could be made in 93.4% of cases (92% of the schizophrenia cases and 94.7% of the bipolar disorder cases).

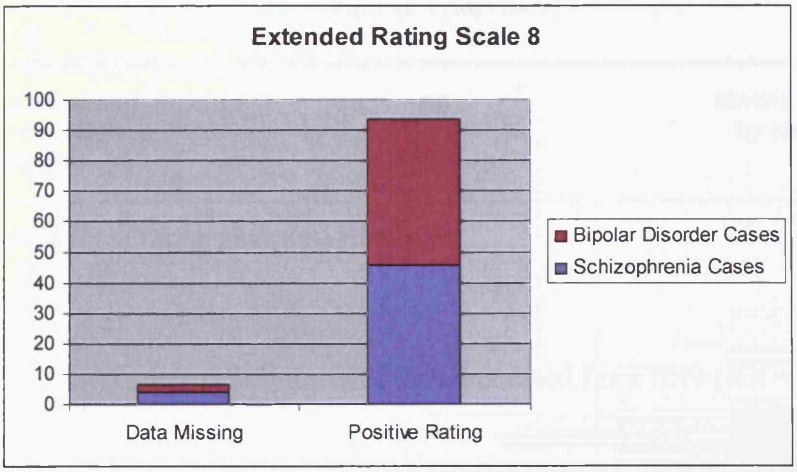

Figure 6-13: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS8, and those for which no rating could be made.

Results from the mixed-effects regression analysis

ERS8 was the only Extended Rating Scale which was significantly correlated in the large harmonised dataset and both sub-samples. Results are demonstrated in Table 6-14 below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS8	0.127	0.028	0.201	0.028	0.158	0.023

Table 6-14: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 9: Predominance of chronic defect state

Extended Rating Scale 9 (ERS9) was developed to measure the proportion of the illness characterised by a chronic defect state – which included negative symptoms (e.g. restricted affect, apathy, poor motivation and asociality) which appeared to be irreversible and were a longstanding feature of the overall clinical picture. Rating guidelines are summarised in the diagram below and can be found in full in Appendix E.

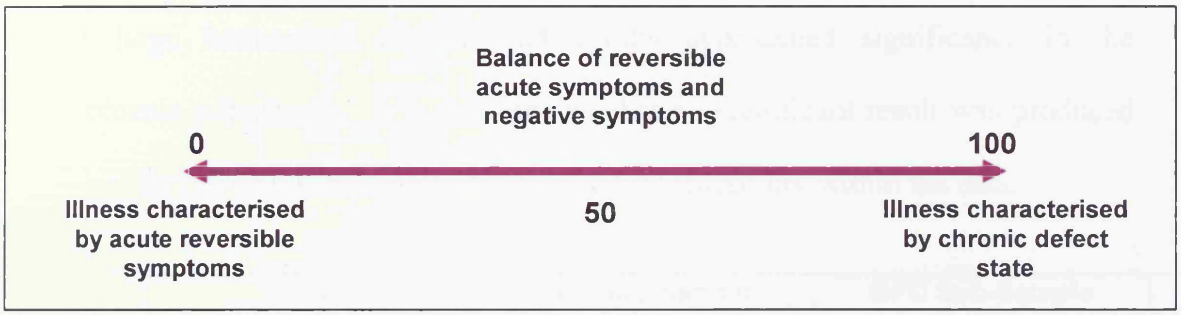

Figure 6-14: Summary of rating guidelines for ERS9.

Reliability

Excellent inter-rater reliability was demonstrated for ERS9 (ICC=0.806).

Utility

ERS9 was utilised with ease within the sample. A high proportion of the cases could be rated positively, as demonstrated in figure 6-15 below (90.5% of the sample overall; 87.2% of the schizophrenia sub-sample and 93.8% of the bipolar disorder sample). However, in the bipolar disorder sub-sample, a high proportion of these

(84.2%) were scored "0" – indicating that the illness was characterised entirely by reversible, acute symptoms.

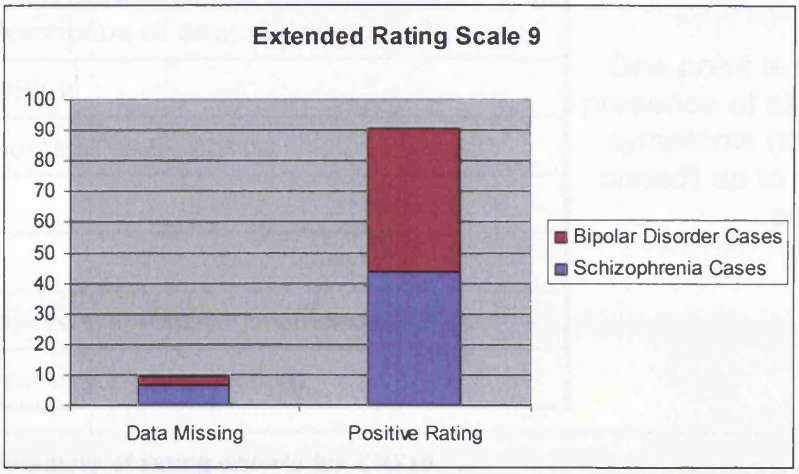

Figure 6-15: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS9, and those for which no rating could be made.

Results from the mixed-effects regression analysis

As presented in Table 6-15, ERS9 was significantly correlated within families in the large harmonised dataset, and results approached significance in the schizophrenia sub-sample. It is unsurprising that no significant result was produced in the bipolar disorder sub-sample, due to a lack of variability within the data.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS9	0.184	0.035	0.185	0.059	0.172	0.42

Table 6-15: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 10: Measure of catatonic symptoms

Extended Rating Scale 10 (ERS10) was originally developed by Dr George Kirov. The aim of the scale was to give a measure of catatonic symptoms during the lifetime course of the illness. Catatonic symptoms are rated on a 0-4 scale, as demonstrated below.

Symptom	
Waxy flexibility	One point is awarded for the presence of any of the following symptoms (unless otherwise stated) up to a maximum of 4 points
Stupor (clear description of catatonic stupor = 2 points)	
Physiological pillow	
Excessive purposeless over-activity	
Mannerisms	
Grimacing	
Echolalia, echopraxia, automatic obedience	
Negativism (clear description needed)	

Figure 6-16: Summary of rating criteria for ERS10.

Reliability

Excellent inter-rater reliability was demonstrated for ERS10 (ICC=0.955)

Utility

ERS10 was easily utilised within the sample. Originally the scale excluded symptoms that were "explicable by affective change". This is because symptoms such as "excessive purposeless over-activity" cannot easily be distinguished from "excessive-activity" – a symptom of mania – if there is a distinction to be made at all. The same is true of "stupor" and "psychomotor retardation" – a symptom of depression. Because this thesis aimed to perform analyses without making assumptions about the underlying causes of illness – descriptions of excessive purposeless over-activity or stupor within episodes of affective illness were not necessarily dismissed. However, to be included in the ERS10-rating, symptoms would have to meet the symptom definitions specified within the scale (e.g. excessive activity within the context of mania would have to be considered "purposeless", and the rater should be able to differentiate them, in terms of their nature and/or severity, from symptoms typically described within the context of mania or depression.

Descriptions of the catatonic symptoms therefore had to be well-described for a confident rating to be made. Despite these rigorous criteria it was generally easy to apply this rating scale to the data and ratings could be made on 93.6% of the LHD (91.7% of the schizophrenia cases and 95.6% of the bipolar disorder cases). Catatonic symptoms were relatively rare within the sample, therefore the majority of cases were rated "0" (76.7% of the schizophrenia cases and 89.2% of the bipolar disorder cases). The low incidence of catatonic features within the sample increases the risk of false positives.

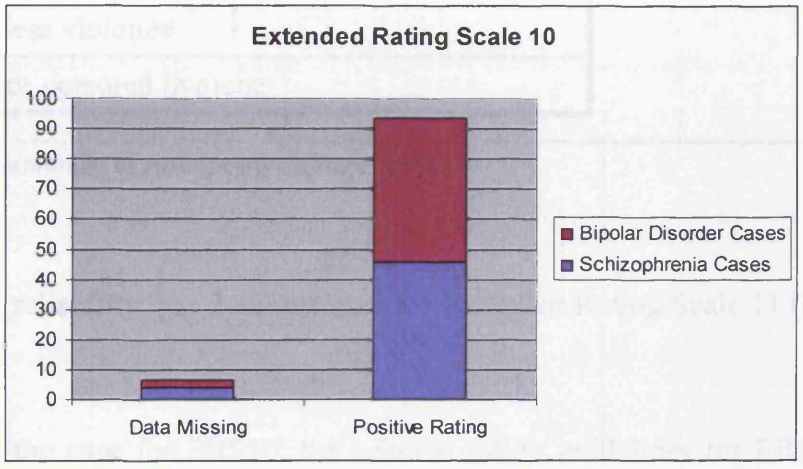

Figure 6-17: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS10, and those for which no rating could be made.

Results from the mixed-effects regression analysis

Significant intra-familial correlations were produced in the large harmonised dataset and in the bipolar disorder sample, as presented in the table below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS10	0.358	0.024	0.093	0.65	0.716	0.0019

Table 6-16: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scale 11: Measure of disorganised behaviour

Extended Rating Scale 11 (ERS11) was developed by Dr George Kirov to measure disorganised behaviour over the lifetime course of the illness. The rating guidelines are summarised in Table 6-18 below.

Symptom	
Patient talks him/herself	One point is awarded for the presence of any of the following symptoms up to a maximum of 2 points
Laughing for no reason	
Hoarding rubbish	
Odd, inappropriate behaviour	
Acts of senseless violence	
Extremely poor personal hygiene	

Figure 6-18: Summary of rating criteria for ERS11.

Reliability

Good reliability was demonstrated for Extended Rating Scale 11 (ICC=0.786)

Utility

As is the case for ERS10, the original rating guidelines for ERS11 stipulate that symptoms are only counted towards the rating if they are not explicable by affective state. Again, because this research aimed to perform analyses without making assumptions about the underlying causes, symptoms experienced within the context of an affective episode were not necessarily dismissed. However, several symptoms, such as "odd, inappropriate behaviour" and "laughing for no reason" are frequently observed in episodes of mania. Again, symptoms were not counted towards the rating unless they were extreme, beyond the typical manic presentation. However, it was occasionally difficult to make a confident judgement about the exact nature of these symptoms from the descriptions within the cases whether this was the case, which resulted in a rating of "unknown/uncertain". Despite this, positive ratings

could be made in 77.9% of the LHD (87% of the schizophrenia cases and 68.7% of the bipolar cases), as demonstrated in figure 6-19 below.

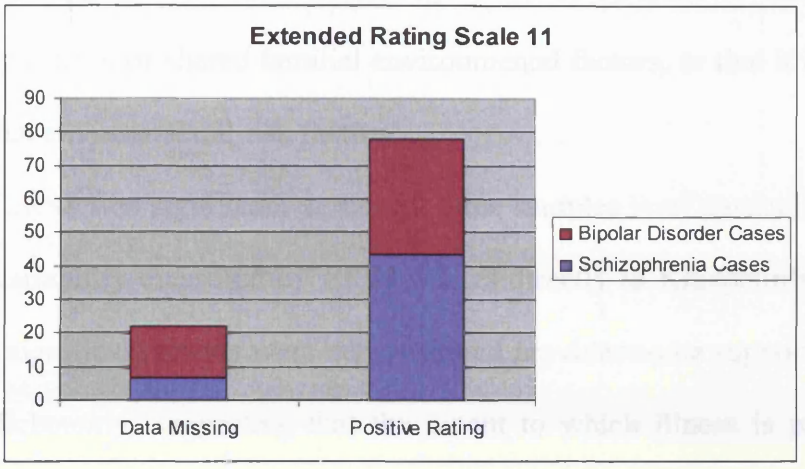

Figure 6-19: Demonstration of proportion of cases for which it was possible to make a positive rating on ERS11, and those for which no rating could be made.

Results from the mixed-effects regression analysis

Significant results were produced for ERS11 in both the LHD and in the bipolar disorder sub-sample, as demonstrated in table 6-17 below.

	LHD		SZP Sub-Sample		BPD Sub-Sample	
	ICC	p-value	ICC	p-value	ICC	p-value
ERS11	0.229	0.016	0.112	0.38	0.366	0.0098

Table 6-17: Mixed-effects regression results produced for the large harmonised dataset (LHD), and the schizophrenia (SZP) and bipolar disorder (BPD) sub-samples.

Extended Rating Scales – Overall Conclusions

In general the extended rating scales showed ease of utility and excellent reliability, and can therefore be considered a success in terms of their use within this sample. It is particularly encouraging that, when analysed using the mixed-effects regression method to assess familiality, six out of the eleven scales developed produced significant results.

It is of note that significant intra-familial correlations were not produced for either ERS3 or ERS4, both of which assessed variability within acute phases of illness. This suggests that such variability is either random in nature and not influenced by genetic or shared familial environmental factors, or that it is influenced by non-familial environmental risk factors.

That ERS8 was significant across all three samples is of particular interest as the clinical variability measured by ERS8 relates directly to Kraepelin's dichotomy. The fact that significant results were demonstrated provides some support for the idea behind the dichotomy, suggesting that the extent to which illness is prototypically schizophrenic or affective in nature aggregates within families, and therefore may be influenced by genes.

In terms of utility, the main limitation of using the scales within this sample was that the cases had already been collected so it was not possible to ask specific questions relating to the scales, or to include extra details relevant to the rating criteria in the case-note vignettes. For this reason, it would be useful to continue to use all of these measures in future studies. This is discussed further in the "Future Work" section below.

6.3 Comparison of results of primary analyses with results from previous studies

As stated previously, the results reported in chapter 5 could be compared with previous findings by dividing the large, harmonised dataset into the individual bipolar disorder and schizophrenia family samples and performing the analysis separately on each. In the primary analysis only variables that were significantly familial in the large harmonised dataset were followed up in the sub-samples. As discussed

previously, this meant that there was a risk of missing significant correlations that were only significant in one dataset.

To enable comparisons to be made between my work and previous findings, I undertook analysis on both the schizophrenia and bipolar disorder sub-samples for variables which had previously been found to be familial.

As discussed in detail in the previous chapter, several of the significant findings from the primary analysis were consistent with results from previous studies; these are summarised in the table below. It is of note that, with the exception of marital status, each of these variables has been reported to be significantly familial in more than one previous study. This, along with the fact that my results also replicate these findings, makes these variables the most promising candidates of those tested here for future phenotype refinement.

Variable studied in the literature	Previously reported to be familial in:	Measure used in the current research	Large Harmonised dataset		SZP sub-sample		BPD sub-sample	
			ICC	p-value	ICC	p-value	ICC	p-value
Age at onset [1,2,3,4,5]	SZP and BP	Age at first admission	.287	.001	.295	.014	.252	.018
Psychotic symptoms [2,3,7]	BP	BADDS Psychosis	.147	.033	.087	.426	.223	.025
Marital Status [3]	BP	Binary measure Yes/No	.273	.020	.222	.210	.336	.038
Lifetime course of illness [14,15, 19, 20]	SZP and BP	Course of Disorder	.163	.004	.233	.046	.176	.023
		Extended Rating Scale 8	.127	.028	.201	.028	.158	.023
Negative symptom dimension [4,16]	SZP	Negative symptoms Y/N	.351	.041	.363	.039	NA	NA

Table 6-18: Summary of variables found to be familial in previous studies which were replicated in the primary analysis

LHD – "large harmonised dataset"; SZP – "schizophrenia"; BPD – "bipolar disorder"; PFTD – "positive formal thought disorder"; NFTD – "negative formal thought disorder". +, familiality reported within previous samples; -, familiality not reported within previous samples. NA – Analysis was not run because there was not enough variability within the sub-sample.

References: 1. Leboyer et al (1998); 2. O'Mahoney et al (2002); 3. Schulze et al (2006); 4. Burke et al (1996); 5. Tsuang et al (1967); 7. Jones & Craddock (1987); 14. Kendler et al (1997); 15. Blueler (1978); 16. Peralta & Cuesta (2007); 19. Ross et al (2000); 20. Duffy et al (2002).

Contrary to expectations, certain variables previously reported as showing familiality in schizophrenia family-samples, were found to be significantly correlated within families in the bipolar disorder sub-sample but not the schizophrenia sub-sample. Similarly, variables previously reported as showing familiality within bipolar disorder family samples, were found to be significantly correlated within the schizophrenia families but not the bipolar disorder families. These results are presented in the table below.

Variable studied in the literature	Previously reported to be familial in:	Measure used in the current research	Large Harmonised dataset		SZP sub-sample		BPD sub-sample	
			ICC	p-value	ICC	p-value	ICC	p-value
Substance Abuse [3]	BP	Cannabis abuse	.639	.001	.332	.003	NA	NA
		Other substance abuse	.587	.016	.537	.046	.660	.220
LE mood-incongruent psychotic symptoms [3,6]	BP	BADDS Incongruence	.224	.005	.285	.004	.181	.191
Anhedonia [11]	SZP	OPCRIT2: Anhedonia	.190	.048	.008	.950	.367	.009
Negative formal thought disorder [14]	SZP	OPCRIT50: NFTD	.355	.014	.268	.093	.601	.022
Catatonic symptoms [14,5]	SZP	Extended Rating Scale 10	.358	.024	.093	.650	.716	.002
Disorganisation dimension [4,17,18]	SZP	Extended Rating Scale 11	.229	.016	.112	.380	.366	.010

Table 6-19: Summary of variables found to be familial in previous studies which were partially consistent with previous findings

LHD – "large harmonised dataset"; SZP – "schizophrenia"; BPD – "bipolar disorder"; PFTD – "positive formal thought disorder"; NFTD – "negative formal thought disorder". +, familiality reported within previous samples; -, familiality not reported within previous samples. NA – Analysis was not run because there was not enough variability within the sub-sample.

References: 3. Schulze et al (2006); 5. Tsuang et al (1967); 6. Goes et al (2007); 11. Schurhoff et al (2003); 14. Kendler et al (1997); 17. Loftus et al (1998); 18. Cardno et al (1999).

As shown above, three variables found to be significantly familial but not in the sub-sample for which previous familiality had been reported, were "Negative Formal Thought Disorder", "Catatonic Symptoms" (as measured using ERS10), and "Disorganisation" (as measured using ERS11). All three had been previously reported as being significantly familial within samples of patients with schizophrenia

(although negative findings have also been reported for all three; Choi et al, 2007); in the current analysis, all three were found to show significant intra-familial correlations in the LHD and the bipolar disorder sub-sample but not in the schizophrenia sub-sample. One possible explanation for these apparently discrepant results is sample-variability. For example, studies which have reported significant familiality for these variables in schizophrenia samples may have been characterised by higher levels of affective disturbance than other studies, and would therefore be more comparable to the large harmonised dataset described here.

What is particularly interesting about these variables is that, in the past, rating guidelines for all three dictated extreme caution when rating these items within the context of affective disturbance. It is therefore unlikely that they would have been considered in previous studies involving samples of patients with mood-disorders. The fact that significant results were produced within such a sample provides support for the hypothesis that measuring items independently of the context in which they were experienced, and therefore without making assumptions about their underlying causes, may enhance research.

Another item which falls under this heading is "substance abuse". Previous studies have reported this to show familiality within samples of patients with bipolar disorder. In the current study, substance abuse, as measured using the OPCRIT items "cannabis abuse" and "other substance abuse" (the latter referring to the abuse of any illicit substance other than cannabis), was found to show a strong intra-familial correlation within the schizophrenia sub-sample, along with the LHD, but not in the bipolar disorder sub-sample.

Results for incongruent psychotic symptoms were also inconsistent with the majority of previous studies, which have shown this variable to be correlated within

families enriched for bipolar disorder (e.g. Hamshere et al, in press). Using a binary variable indicating whether incongruent psychotic symptoms were present/absent over the lifetime course of the illness did not yield significant results in any of the samples. However, when a dimensional measure of incongruence was used (using the BADDS Incongruence dimension), significant results were produced in the LHD and the schizophrenia sample but not in the bipolar disorder sample.

The final item which falls under this heading is "anhedonia". A previous study demonstrated familiality of anhedonia in a family-based schizophrenia sample (Schurhoff, Szoke, Bellivier, *et al*, 2003). Schulze et al (2006) included loss of interest in their analysis and did not find this variable to be significantly correlated within their sample of families with bipolar disorder. When anhedonia was included in the mixed-effects regression analysis, significant intra-familial correlations were found in the LHD and the bipolar disorder sample, but not in the schizophrenia sample.

As stated above, one explanation for these findings is that (with the exception of anhedonia) these variables have not previously been tested in the sub-samples in which significant familiality was demonstrated here (e.g. negative formal thought disorder has not previously been investigated in family samples of patients with bipolar disorder.

However, due to the substantial number of tests performed in this work, the high risk of Type I errors must be acknowledged. It is likely that some, if not all, these discrepant results represent false positives rather than true findings. However, it would be interesting to follow up these variables in further samples.

Variable studied in the literature	Previously reported to be familial in:	Measure used in the current research	Large Harmonised dataset		SZP sub-sample		BPD sub-sample	
			ICC	p-value	ICC	p-value	ICC	p-value
Manic symptoms [2]	BP	Binary Variable Y/N	.187	.061	.256	.097	.136	.212
		BADDS Mania	.025	.724	.115	.224	.034	.298
Rapid Cycling [8]	BP	Present/Absent	.252	.310	.275	.271	.397	.137
Rapid switches in mood [8]	BP	Present/Absent	.257	.293	NA	NA	.275	.274
		Extended Rating Scale 3	.256	.290	.054	.990	.274	.270
Puerperal Psychosis [7]	BP	Present/Absent	.272	.293	.587	.714	.262	.287
Alcohol abuse [8,9]	BP	Present/Absent	.176	.163	.185	.238	.162	.454
Episode frequency [2,10]	BP	Extended Rating Scale 5	.046	.443	.075	.499	.031	.681
Suicidal Ideation [3]	BP	Present/Absent	.100	.274	.053	.721	.054	.658
Suicide Attempt [3]	BP	Present/Absent	.149	.115	.129	.273	.257	.070
Auditory Hallucinations [12]	SZP	Present/Absent	.063	.516	NA	NA	.131	.325
Hallucinations [13]	SZP	Present/Absent	.075	.403	NA	NA	.137	.243
Delusions [14]	SZP	Present/Absent	.161	.093	.084	.671	.189	.095
Positive formal thought disorder [14]	SZP	OPCRIT49: PFTD	.448	.013	.328	.097	.659	.075

Table: Summary of variables found to be familial in previous studies which were not supported by results from the primary analysis

LHD – "large harmonised dataset"; SZP – "schizophrenia"; BPD – "bipolar disorder"; PFTD – "positive formal thought disorder"; NFTD – "negative formal thought disorder". +, familiality reported within previous samples; -, familiality not reported within previous samples. NA – Analysis was not run because there was not enough variability within the sub-sample.

References: 2. O'Mahoney et al (2002); 3. Schulze et al (2006); 7. Jones & Craddock (2001); 8. Saunders et al (2008); 9. Potash et al (2000); 10. Fisfalen et al (2005); 12. Choi et al (2007); 13. DeLisi et al (1987); 14. Kendler et al (1997).

The variables listed in the table above were found to show significant familiality within previous schizophrenia or bipolar disorder family samples, but not within the sub-samples used in the current study. Possible reasons for these discrepant findings include sample differences and differences in the ways in which items of psychopathology were measured. The fact that no significant results were found for these variables in the current work may also be due to a lack of power within the samples.

6.4 Methodological Strengths and Limitations

The strengths and limitations of the methods utilised within this thesis have been discussed in detail in previous chapters, and the main points are summarised below:

Strengths

- Analyses were undertaken in a large dataset - in the primary analyses, combining the schizophrenia and bipolar disorder family samples resulted in a total sample of 835 cases from 373 families.
- A spectrum of psychotic and affective illness was represented, allowing analyses to be performed across traditional diagnostic boundaries.
- A new set of measures were developed specifically for use within this sample.
- After extensive training and participation in numerous reliability exercises, a single rater (myself) was responsible for rating the entire sample. This allowed me to become familiar with the sample and eliminated the risk of any variability caused by inter-rater differences.
- The mixed-effects regression method implemented in the primary analyses allowed for the inclusion of covariates which controlled for any familiality caused by these.

Limitations

- Data had been collected prior to the commencement of this PhD. This meant that the information collected for each case was not done so with this specific set of measures in mind. A prospective study design would have ensured adequate information was collected for this specific set of measures, facilitating the rating process.
- Participants were not followed up over time.

- The ratings made relied on detailed and accurate documentation of the participant's previous episodes of illness, therefore there was a risk of missing less severe episodes of particular that did not require the participant to seek treatment.
- Because the cases were collected on the basis of a proband with a diagnosis of bipolar disorder or schizophrenia, the sample was enriched for prototypical forms of the disorders. The inclusion of families enriched for schizoaffective disorder would have introduced more of a spectrum of illness, in which the intermediate phenotypes were better represented.
- In the primary analyses, continuous variables had to be converted to ordinal categories to allow the data to be analysed using the mixed-effects regression method. Reassuringly, significant results were supported by sensitivity analysis (see chapter 5) and the Spearman's Rho analyses, which were used on the raw continuous variables.
- A single rater was responsible for rating the entire sample, introducing the risk of rater-drift. Reassurance that this had not occurred was provided by results produced in the reliability analysis, reported in Chapter 5.
- Investigating the familiality of such a large number of variables (N=157) introduced multiple-testing problems that reduced power to detect significant effects. It is therefore likely that some (or even a majority) of the variables for which significant results were found in this study are false positives. However, this was very much an exploratory analysis, and the variables identified using these methods can be used to form hypotheses which can be tested in future studies.

6.5 Future Work

The main aim of this research was to perform analysis in a sample enriched for a spectrum of affective and psychotic disorders in order to identify clinical variables which aggregate within families. Although, due to the exploratory nature of this analysis, no significant results withstood corrections for multiple testing, it is the thirty-one variables identified that are most likely to be of use in refining the phenotype, the best candidates for future work being those that were consistent with previous findings (i.e. age at onset, psychotic symptoms, marital status, negative symptoms and lifetime course of illness). It is therefore important to ensure that information on these variables is collected where possible in future studies which aim to investigate the genotype or phenotype of the functional psychoses.

Ideally, a prospective study could be undertaken, involving the recruitment of a similar family-based sample representing a spectrum of diagnoses. This would have several major advantages; as well as allowing researchers to investigate whether these results generalise to other samples, the study could be designed specifically to focus in on these variables, allowing more detailed and specific information to be collected which would facilitate the rating process. Focussing in on a smaller number of variables (i.e. those for which significant results were produced in this thesis, and particularly those which were consistent with previously published work) would also reduce the impact of corrections made for multiple testing. However, to conduct such a study would be extremely expensive. A more cost-effective means of investigating whether or not these results generalise to other samples would be to collaborate with other research teams who have already recruited such samples.

As discussed in the previous chapter, although the results of the mixed-effects regression analyses suggest that those variables for which a significant familial affect

was shown may be influenced by genes, it could be argued that this familiality may be due to shared environmental factors. Twin and adoption studies could be used to investigate the genetic and environmental influences on the clinical variables identified in this thesis (reviewed in Gottesman, 1991). Adoption studies compare adoptees with their biological parents under the hypothesis that similarities observed are more likely to be due to genetic rather than environmental effects. Under the equal environments assumption, twin studies aim to investigate the role of genetic influences by comparing concordance rates between monozygotic and dizygotic twin-pairs. Comparisons between affected and unaffected monozygotic twins may be used to study the role of environmental factors.

Again, although ideally carrying out a prospective study, as described above, would mean that specific information regarding the variables-of-interest could be collected, facilitating the rating process, in reality the more cost-effective approach of collaborating with other research teams who have been involved in recruiting samples is a more feasible way of conducting such future studies.

Clearly the ultimate test of whether the variables identified in the analyses described in Chapter 5 would be to utilise them within molecular genetic analyses. The recent technological advances in molecular genetic research, along with substantial reductions in the cost of implementing these methods (McCarthy, Abecasis & Cardon, 2008) make this a viable and cost-effective option. Further, because the family-samples described within this thesis were originally collected as part of ongoing molecular genetic studies in the Department of Psychological Medicine, Cardiff University, genetic data are available for these cases and can be used in future studies to investigate the genetic basis of the variables which showed familiality.

One method by which clinical measures can be used to refine genetic analyses is by including them as covariates within linkage studies (Rice, Rochberg, Neuman, *et al*, 1999). Taking account of such variables within analyses may facilitate the identification of chromosomal regions which may be involved in influencing susceptibility to, or modifying the course of illness. For example, Hamshere et al (in press) performed multipoint model-free affected relative pair covariate linkage analysis on a sample of patients with bipolar disorder, in which the presence or absence of mood-incongruent psychotic features was included in the model as a covariate. This method involved the modelling of allele-sharing probabilities using logistic regression analysis, which allowed for the inclusion of covariates. They identified three regions showing suggestive linkage (1q32.3, 7p13 and 20q13.31), none of which were identified within the sample when univariate analyses were performed, in which bipolar disorder was considered a homogeneous entity.

Association analyses may be used to examine specific genetic variation that contributes to these clinical measures. For example, functional psychoses cases which include a specific clinical feature which has been shown to aggregate within families, such as incongruent psychotic symptoms, could be compared to unaffected controls, or to affected controls who have not experienced this particular clinical symptom in an attempt to identify genetic variation contributing to susceptibility to, or modifying the course of illness. For continuous variables, cases could be defined by their genotype (e.g. 00, 01, 11) and one-way analysis-of-variance (ANOVA) analysis could be performed to compare the means of the groups.

The variables identified in this thesis can therefore be used to form hypotheses which can be tested in future studies, using methodologies such as those discussed above.

The methods described in this thesis focus on specific clinical variables that can be obtained from interview, case-notes etc and which are looked at individually. Rather than focus on these individual items, an alternative approach is to consider factor analysis, a method which has been applied to psychiatric measures since the 1960s (Jablensky, 2006), and examines whether correlations occur between specific items. In this way, factors can be extracted from the correlation matrix in the form of dimensions, which account for the relationship amongst the variables of interest and explain a proportion of their variance. Methods aim to maximise the similarity between items loading on one factor, whilst simultaneously maximising the difference between factors (Farmer, McGuffin & Williams, 2002).

A number of studies have performed factor analysis within samples of patients with schizophrenia (reviewed in Jablensky, 2006). For example, a three-factor structure was proposed by Liddle (1987), who performed factor analysis on items from the Scales for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and Scales for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a). In this model, negative symptoms load on a single factor, "psychomotor poverty", whilst positive symptoms load on two separate factors, "reality distortion" (delusions and hallucinations), and "disorganisation" (disorganised speech, thought disorder).

Cardno et al (1996) performed factor analysis on a sample of schizophrenia patients, using items from the Operational Criteria symptom checklist (OPCRIT) (McGuffin, AE & Harvey, 1991). Their initial analyses produced a three-factor structure featuring positive, negative and disorganised dimensions. However, when they applied the scree test to the data – which involves plotting the eigenvalues in descending order of magnitude against their factor numbers and determining where

they level off (D'agostina & Russell, 2005) – five factors were suggested, with the positive factor separating into three-factors characterised by paranoid symptoms, first rank delusions and first rank hallucinations.

A recent study by McGrath et al (2004) also identified five factors in their large sample of schizophrenia patients, which were associated with risk of psychoses and affective disorders in relatives: positive symptoms, negative symptoms, disorganisation, affective disturbance and early onset/development. Cuesta & Peralta (2001) suggested that a hierarchical 10-dimensional model was most appropriate on both statistical and clinical grounds.

Studies have also been performed to investigate whether dimensions identified via factor analysis aggregate within families. For example, Burke et al (1996) found the negative dimension, disorganisation dimension and reality distortion dimension to be significantly correlated within sibling-pairs in their sample of schizophrenia patients.

Performing factor analysis within the large harmonised dataset described in this thesis could be used to both reduce the number of variables and to detect the structure of relationships between them. Analyses could subsequently be performed to assess the familiality of these factors.

6.6 Final Conclusions

The research described in this thesis was undertaken under the hypothesis that looking beyond diagnostic categories to perform familiality analysis on a set of clinical measures that vary both within and across diagnostic categories, may facilitate the identification of sub-groups of patients who are more likely to be genetically

homogeneous. The identification of such samples is likely to increase power in future molecular genetic studies.

Previous research has demonstrated the advantages of looking beyond diagnostic categories, and the hierarchy rooted in diagnostic tradition, to consider variables which cluster within families or which have some biological validation, e.g. 22q11 deletion in VCFS and genome-wide significant linkage at 1q42 in SABP (see chapter 4).

The research described in this thesis aimed to explore the familial correlation of clinical measures within a large harmonised clinical dataset comprising samples of (a) families enriched for bipolar disorder, and (b) families enriched for schizophrenia. Cases were rated on a set of variables which included a new set of clinical ratings. These were designed specifically to be used within this sample and covered eleven clinical characteristics that varied across samples, that were not picked up on adequately by established measures, and which appeared to be potentially important in distinguishing between cases.

Analyses were performed across traditional diagnostic boundaries, and thirty-one clinical measures were found to be significantly correlated within families, after controlling for sample-of-origin and gender. However, due to the exploratory nature of this thesis the risk of false positives is high and this must be acknowledged when considering these findings.

Variables which correlate within families may be influenced by genetic factors and may therefore be used to identify subgroups of patients more likely to share common underlying genetic susceptibilities.

In an analysis of a subset of cases from the large harmonised dataset, which comprised sibling-pairs that were enriched for schizoaffective disorder, it was found

that genetic similarity at chromosome 1q42 was significantly associated with phenotypic similarity during the most severe depressive episode, as measured by the Global Assessment Scale (GAS) which measures functional impairment; and with age at onset. Genetic similarity at chromosome 22q11 was significantly associated with phenotypic similarity during the most severe period of illness, again measured using the GAS.

I also undertook clinical ratings on a sample of previously-collected patients with Velo-Cardio-Facial Syndrome (VCFS) and found high-rates of both mood-disturbance and psychosis.

The findings reported in this thesis support the hypothesis that clinical ratings can be a useful adjunct to categorical diagnoses, and can be used to identify specific phenotypes which may be worth considering in future genetic studies. It is hoped that this will facilitate the identification of genes involved in the functional psychoses, leading to increased understanding of the aetiological processes underlying such disorders. This should allow researchers to develop new, more specific treatments which target the underlying biological mechanisms involved in these debilitating illnesses, leading to improved quality of life for patients and their families.

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Appendices

Appendix A

List of variables rated in the large harmonised dataset

- DSMIV diagnosis
- ICD10 diagnosis
- RDC diagnosis
- BADDS Mania
- BADDS Depression
- BADDS Psychosis
- BADDS Incongruence
- GAS – impairment during worst ever depression
- GAS – impairment during worst ever mania
- GAS – impairment during worst ever psychosis
- GAS – impairment during worst ever episode of illness
- Occurrence of section 2 symptoms over the lifetime course of illness
- Mood congruence of psychotic symptoms over the lifetime course of illness
- Occurrence of near-section 2 symptoms over the lifetime course of illness
- Predominant manic affect
- Occurrence of dysphoric mania over the lifetime course of illness
- Number of manic episodes
- Number of depressive episodes
- Number of non-affective episodes
- Number of post-natal episodes
- Duration of longest episode of mania
- Duration of longest episode of depression
- Duration of longest episode of non-affective psychosis
- Duration of longest post-natal episode
- Age at first symptom
- Age at first impairment
- Age at first contact
- Age at first admission
- Age at first mania
- Age at first depression
- Age at first psychosis
- Age at first post natal episode
- Number of admissions
- Length of longest admission
- Proportion of time admitted
- Proportion of time well since onset
- First episode of illness post-natal (yes/no/unknown)
- Occurrence of a post-natal episode over the lifetime course of illness
- Occurrence of rapid cycling over the lifetime course of illness
- Suicidal ideation
- Occurrence of switches in mood over the lifetime course of illness.
- Medication response
- Psychiatric sequelae after each full-term delivery
- Extended Rating Scale 1: Predominance mania
- Extended Rating Scale 2: Relationship between psychotic and affective symptoms
- Extended Rating Scale 3: Fluctuations in mood
- Extended Rating Scale 4: Instability of clinical state
- Extended Rating Scale 5: Periodicity of acute phases of illness
- Extended Rating Scale 6: Predominance of mixed affective state
- Extended Rating Scale 7: Most dysphoric mania
- Extended Rating Scale 8: Extent to which illness reflects prototypical affective disorder vs. prototypical schizophrenia

- Extended Rating Scale 9: Predominance chronic defect state
- Extended Rating Scale 10: Catatonic symptoms
- Extended Rating Scale 11: Disorganised behaviour
- The following items of psychopathology were recorded using the OPCRIT symptom checklist:

1) Dysphoria
2) Anhedonia
3) Diurnal mood variation
4) Suicidal ideation
5) Excessive self reproach
6) Poor concentration
7) Slowed activity
8) Loss of energy/tiredness
9) Poor appetite
10) Weight loss
11) Increased appetite
12) Weight gain
13) Initial insomnia
14) Middle insomnia
15) Early morning waking
16) Excessive sleep
17) Diminished libido
18) Agitated activity
19) Elevated mood
20) Irritable mood
21) Thoughts racing
22) Pressured speech
23) Distractibility
24) Excessive activity
25) Increased self-esteem
26) Reckless activity
27) Reduced need for sleep
28) Increased sociability
29) Third person auditory hallucinations
30) Running commentary voices
31) Abusive/accusatory/persecutory voices
32) Other non-affective auditory hallucinations
33) Non-affective visual hallucinations
34) Non-affective hallucinations in any other modality
35) Thought echo
36) Thought insertion
37) Thought broadcast
38) Thought withdrawal
39) Delusions of passivity
40) Delusions of influence
41) Primary delusional perception
42) Persecutory delusions
43) Bizarre delusions
44) Other primary delusions
45) Bizarre behaviour
46) Catatonia
47) Speech difficult to understand
48) Incoherent
49) Positive formal thought disorder
50) Negative formal thought disorder
51) Restricted affect
52) Blunted affect
53) Inappropriate affect
54) Perplexity
55) Aggressive behaviour

56) Grandiose delusions
57) Delusions of guilt
58) Nihilistic delusions
59) Mood congruent third person auditory hallucinations
60) Mood congruent second person auditory hallucinations
61) Mood congruent visual hallucinations
62) Mood congruent hallucinations in any other modality
63) Other secondary delusions

- Increase sexual activity (novel rating)
- Aggressive behaviour (novel rating)
- Details and history recorded using the OPCRIT checklist:
    - Source of rating
    - Time frame
    - Sex
    - Age of onset
    - Mode of onset
    - Single
    - Unemployed at onset
    - Duration of illness in weeks
    - Poor work adjustment
    - Poor pre-morbid social adjustment
    - Premorbid personality disorder
    - Alcohol/drug abuse within one year of onset
    - Family history of schizophrenia
    - Family history of other psychiatric disorder
    - Coarse brain disease prior to onset
    - Definite psychosocial stressor prior to onset
    - Lifetime diagnosis of alcohol/cannabis/other substance abuse/dependence
    - Information not credible
    - Lack of insight
    - Rapport difficult
    - Impairment/incapacity during disorder
    - Deterioration from premorbid level of functioning
    - Psychotic symptoms respond to neuroleptics
    - Course of disorder

Appendix B

The Global Assessment Scale (GAS)

(Endicott et al, 1976)

100 – 91	No symptoms, superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his warmth and integrity.
90 – 81	Transient symptoms may occur, but good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, "everyday" worries that only occasionally get out of hand.
80 – 71	Minimal symptoms may be present but no more that slight impairment in functioning, varying degrees of "everyday" worries and problems that sometimes get out of hand.
70 – 61	Some mild symptoms (e.g. depressive mood and mild insomnia) OR some difficulty in several areas of functioning, but generally functioning pretty well, has some meaningful interpersonal relationships and most untrained people would not consider him "sick".
60 – 51	Moderate symptoms OR generally functioning with some difficulty (e.g. few friends and flat affect, depressed mood and pathological self-doubt; euphoric mood and pressure of speech, moderately severe antisocial behaviour).
50 – 41	Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (e.g. suicidal preoccupation or gesture, severe obsessional rituals, frequent anxiety attacks, serious antisocial behaviour, compulsive drinking).
40 – 31	Major impairment in several areas, such as work, family relations, judgement, thinking or mood (e.g. depressed woman avoids friends, neglects family, unable to do housework), OR some impairment in reality testing or communication (e.g. speech is at times obscure, illogical or irrelevant), OR single serious suicide attempt.
30 – 21	Unable to function in almost all areas (e.g. stays in bed all day), OR behaviour is considerably influenced by either delusions or hallucinations, OR serious impairment in communication (e.g. sometimes incoherent or unresponsive) or judgement (e.g. acts grossly inappropriately).
20 – 11	Needs some supervision to prevent hurting self or others, or to maintain minimal personal hygiene (e.g. repeated suicide attempts, frequently violent, manic excitement, smears faeces), OR gross impairment in communication (e.g. largely incoherent or mute).
10 – 1	Needs constant supervision for several days to prevent hurting self or others, or makes no attempt to maintain minimal personal hygiene.

Notes: Rate the subject's lowest level of functioning in the last week by selecting the lowest range that describes his functioning on a hypothetical continuum of mental health illness. For example, a subject whose "behaviour is considerably influenced by delusions" (range 21-30) should be given a rating in that range even though he has "major impairment in several areas" (range 31-40). Use intermediary levels when appropriate (e.g. 35, 58, 63). Rate actual functioning independent of whether or not subject is receiving, and may be helped by, medication or some other form of treatment.

Appendix C

Modified OPCRIT Symptom Checklist

Item Definitions

McGuffin et al (1991)

DEPRESSIVE SYMPTOMS
Should be rated as present if present for at least 2 weeks.
Items marked * are not in the original OPCRIT.

All items are rated	0	No
	1	Yes
	9	Unknown/Missing

1. ***Dysphoria***
Persistently low or depressed mood, irritable and sad mood or pervasive loss of interest.

Note that this item includes irritability which does not occur in the context of a manic syndrome. Includes pervasive loss of interest as well as depressed mood.

2. ***Loss of pleasure***
Pervasive inability to enjoy any activity. Include marked loss of interest or loss of libido.

3. ***Diurnal variation (mood worse mornings)***
Dysphoria/low mood and/or associated depressive symptoms are at their worst soon after awakening with some improvement (even if only slight) as the day goes on.

4. ***Suicidal ideation***
Preoccupation with thoughts of death (not necessarily own). Thinking of suicide, wishing to be dead, attempts to kill self.

Include moderate and severe tedium vitae here.

5. ***Excessive self reproach***
Extreme feelings of guilt and unworthiness. May be of delusional intensity ('worse person in the whole world').

Primarily guilt, but also low self-esteem. Rated if out of proportion to the situation.

6. ***Poor concentration***
Subjective complaint of being unable to think clearly, make decisions etc.

7. ***Slowed activity***
Patient complains that he feels slowed up and unable to move. Others may report subjective feeling of retardation or retardation may be noted by examining clinician.

8. ***Loss of energy/tiredness***
Subjective complaint of being excessively tired with no energy.

9. ***Poor appetite***
Subjective complaint that patient has poor appetite. Not necessarily observed to be eating less.

10. ***Weight loss***

Rate as present for a loss of at least 2 lbs a week over several weeks. Do not score those who have reduced weight as a result of dieting.

11. Increased appetite
Patient reports increased appetite and/or 'comfort eating'.

12. Weight gain
Rate as present for a gain of at least 2 lbs a week over several weeks.

13. Initial insomnia
Patient complains that unable to get off to sleep and lies awake for at least one hour.

Rate positively if the patient has considerably more difficulty than usual in getting off to sleep, even if they cannot specify the time during which they lie awake

14. Middle insomnia (broken sleep)
Most nights sleep disturbed; subject awakes in the middle of sleep and experiences difficulty in getting back to sleep.

NB IF YOU ONLY HAVE INFORMATION ON 'INSOMNIA', SCORE ITEM 13 AND 14.

15. Early morning waking
Patient complains that persistently wakes up at least one hour earlier than usual waking time.

Rated positively if the patient wakes considerably earlier than usual, even if they are unable to specify the time of waking.

16. Excessive sleep
Patient complains that sleeping too much.

17. Diminished libido
Definite and persistent reduction in sexual drive or interest as compared with before onset of disorder.

18. Agitated activity
Patient shows excessive repetitive activity, such as fidgety restlessness, wringing of hands, pacing up and down, all usually accompanied by expression of mental anguish.

MANIC SYMPTOMS
Should be rated as present if present for at least 4 days.
Items marked * are not in the original OPCRIT.

All items are rated	0	No
	1	Yes
	9	Unknown/Missing

19. Elevated mood
Patient's predominant mood is one of elation. *(Can be co-rated with irritable mood).*

20. Irritable mood
Patient's mood is predominantly irritable. *(Can be co-rated with elevated mood).*

21. Thoughts racing
Patient experiences thoughts racing through his head or others observe flights of ideas and find difficulty in following what patient is saying or in interrupting because of the rapidity and quantity of speech.

22. Pressured speech

Patient much more talkative than usual or feels under pressure to continue talking. Include manic type of formal thought disorder with clang associations, punning and rhyming etc.

23. Distractibility

Patient experiences difficulties concentrating on what is going on around because attention is too easily drawn to irrelevant or extraneous factors.

24. Excessive activity

Patient is markedly over-active. This includes motor, social and sexual activity.

25. Increased self esteem

Patient believes that he is an exceptional person with special powers, plans, talents or abilities. Rate positively here if overvalued idea but if delusional in quality also score grandiose delusions.

26. Reckless activity

Patient is excessively involved in activities with high potential for painful consequences which is not recognised, e.g. excessive spending, sexual indiscretions, reckless driving, etc.

Include sexual recklessness leading to risk of pregnancy or venereal disease.

27. Reduced need for sleep

Patient sleeps less but there is no complaint of insomnia. Extra waking time is usually taken up with excessive activities.

28. Increased sociability

Rate as present for loss of social inhibitions resulting in behaviour which is inappropriate to the circumstances and out of character.

28a. Increased sexual activity (NOVEL MEASURE)

0 - Not known to be present despite adequate clinical information.
1 - Increased sexual interest and / or activity.
2 - Increased sexual behaviour that caused harm (including physical, psychological, social, legal) to self or others.

Ratings of '2' should also be co-rated at item 26 'reckless activity'.

PSYCHOTIC SYMPTOMS

Should be rated as present if present for at least a significant portion of time in a 1 month period or less if successfully treated

Items marked * are not in the original OPCRIT.

All items (except #) are rated	0	No
	1	Yes
	9	Unknown/Missing

29. Third person auditory hallucinations

Two or more voices discussing the patient in the third person. Score if either 'true' or 'pseudo' hallucinations, i.e. differentiation of the source of the voices is unimportant.

Two or more voices talking about the patient in the third person. May be rated without an example if a clear description is given that these occur. Rate if the notes say "third person auditory hallucinations".

30. Running commentary voices

Patient hears voice(s) describing his actions, sensations or emotions as they occur. Score whether these are possible 'pseudo' hallucinations or definite ('true') hallucinations.

Voice must be in the third person. May be rated without an example if a clear description is given that commentary occurs.

31. Abusive/accusatory/persecutory voices
Voices talking to the patient in an accusatory, abusive or persecutory manner.

Voices must be in the second person. If voices are congruent with mood state also rate item 60.

32. Other (non affective) auditory hallucinations
Any other kind of auditory hallucination. Includes pleasant or neutral voices and non verbal hallucinations.

Note that this includes non-verbal auditory hallucinations. If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

33.* Non-affective visual hallucinations
Visual hallucinations in which the content has no apparent relationship to elation or depression.

If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

34. Non-affective hallucination in any other modality
Hallucinations in which the content has no apparent relationship to elation or depression.

Rated positively if a clear description is given, even without a specific time period. If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

NB. WHEN SCORING DELUSIONS PLEASE SCORE EACH SEPARATE DELUSION UNDER ONE AND ONLY ONE CATEGORY DESCRIBING THE SPECIFIC TYPE OF THE DELUSION i.e. AS EITHER; PERSECUTORY, GRANDIOSE, INFLUENCE/REFERENCE, BIZARRE, PASSIVITY, PRIMARY DEL PERCEPTION, OTHER PRIMARY DEL, THOUGHT WITHDRAWAL, THOUGHT BROADCAST, THOUGHT INSERTION, GUILT, POVERTY OR NIHILISTIC.

35. Thought echo
Score if patient experiences thoughts repeated or echoed in his or her head or by a voice outside the head.

As with the other thought interference items, this is rated conservatively. Repeated thoughts must <u>not</u> be under the patient's control. Ruminative thoughts do not qualify. Note that this definition includes a voice repeating a person's thoughts.

36. Thought insertion
Patient recognises that thoughts are being put into his head which are not his own and which have probably or definitely been inserted by some external agency.

Definition from SCAN. Example required for positive rating. In particular, ideas taken on by the patient from influential people in their lives are <u>not</u> rated positively.

37. *Thought broadcast*
Patient experiences thoughts diffusing out of his head so that they may be shared by others or even heard by others.

Definition from SCAN. Example required for a positive rating. A belief that other people know what the patient is thinking and an elaboration of this belief that they can therefore read his/her mind does not qualify. Note that this definition includes thoughts being heard by others (loud thoughts).

38. *Thought withdrawal*
Patient experiences thoughts ceasing in his head which may be interpreted as thoughts being removed (or 'stolen') by some external agency.

Definition from SCAN. Example required for a positive rating.

39. *Delusions of passivity*
Include all 'made' sensations, emotions or actions. Includes all experiences of influence where patient knows that his own feelings, impulses, volitional acts or somatic sensations are controlled or imposed by an external agency.

The definition from SCAN is used. An example is required before a positive rating can be given. In particular, other people or hallucinatory voices telling the patient to perform a certain act and the patient acting under this pressure to do so is not rated positively.

40. *Delusions of influence*
Events, objects or other people in patient's immediate surroundings have a special significance, often of a persecutory nature. Include ideas of reference from the TV or radio, or newspapers, where patient believes that these are providing instructions or prescribing certain behaviour.

Require a definite delusion to rate this item. Delusion must refer to something outside of the body. Include delusional jealousy, delusional lover, and delusion of being spied upon.

41. *Primary delusional perception*
The patient perceives something in the outside world which triggers a special, significant relatively non understandable belief of which he is certain and which is in some way loosely linked to the triggering perception.

42. *Persecutory delusions*
Includes all delusions with persecutory ideation.

43. *Bizarre delusions*
Strange, absurd or fantastic delusions whose content may have a mystical, magical or 'science fiction' quality.

A particularly troublesome item. To be rated here, the delusion must be totally implausible in DSM IV terminology. The RDC definition adds that it must be patently absurd or fantastic. Most simple delusions of reference or persecution are not included. Great caution should be applied before rating delusions of a religious or supernatural nature or delusions which involve extra-sensory perception. Note that Capgras syndrome and other delusions of misidentification are rated here. If a delusion is bizarre, but can be rated elsewhere, rate it as bizarre (except for first rank symptoms).

44. *Other primary delusions*
Includes delusional mood and delusional ideas. Delusional mood is a strange mood in which the environment appears changed in a threatening way but the significance

of the change cannot be understood by the patient who is usually tense, anxious or bewildered. Can lead to a delusional belief. A delusional idea appears abruptly in the patient's mind fully developed and unheralded by any related thoughts.

Include other delusions not classified elsewhere which are not secondary to mood disturbance, alcohol, or any other phenomena, e.g., delusion of thoughts being read, dysmorphophobia, hypochondriacal delusions.

45. Bizarre behaviour #

Behaviour that is strange and incomprehensible to others. Includes behaviour which could be interpreted as response to auditory hallucinations or thought interference.

Rated as present with low threshold including, e.g., an entry in case-notes saying that the patient's behaviour was strange or bizarre for no apparent reason or possibly as a consequence of psychotic symptoms. Behaviour must not be explicable by affective change.

46. Catatonia #

Patient exhibits persistent mannerisms, stereotypies, posturing, catalepsy, stupor, command automatism or excitement which is not explicable by affective change.

Include automatic obedience.

47. Speech difficult to understand #

Speech which makes communication difficult because of lack of logical or understandable organisation. Does not include dysarthria or speech impediment.

May be rated '1' if, e.g., a case-note entry says the patient's speech was difficult to understand because it was disorganised, without a specific example of the nature of the disorganisation.

48. Incoherent #

Normal grammatical sentence construction has broken down. Includes "word salad" and should only be rated conservatively for extreme forms of formal thought disorder.

Note this is only rated in extreme cases in addition to items 47 & 49. Entry of 'incoherent' in notes is not sufficient, normally rated at item 47 unless there is more specific information about the nature of the speech disturbance.

49. Positive formal thought disorder #

The patient has fluent speech but tends to communicate poorly due to neologisms, bizarre use of words, derailments, loosening of associations.

This definition is similar to item 47. This item may be rated as well as item 47 if, in addition to an observation or description of disorganised speech, an example is given which allows it to be defined as positive formal thought disorder in Andreasen's terminology or a description of the nature of the disorganisation is given which similarly allows it to be classified as a form of positive formal thought disorder. Do not include circumstantiality or clanging. Care is required regarding the meaning of an entry of 'thought disorder' in case-notes, i.e., formal thought disorder must be differentiated from schizophrenic thought disorder (that is, thought insertion/broadcast/withdrawal/ control).

50. Negative formal thought disorder #

Includes paucity of thought, frequent thought blocking, poverty of speech or poverty of content of speech.

Excludes occurrence during a depressive episode. Note that this definition includes frequent thought blocking. Poverty of content of speech should be rated under item 49.

51. *Restricted affect #*
Patient's emotional responses are restricted in range and at interview there is an impression of bland indifference or 'lack of contact'.

Exclude flat affect during a depressive episode, i.e., care is required regarding the meaning of an entry of 'flattened affect' in case-notes. Care is required when flat affect is in the context of Parkinsonian side-effects.

52. *Blunted affect #*
Where the patient's emotional responses are persistently flat and show a complete failure to 'resonate' to external change. (NB. Differences between restricted and blunted affect should be regarded as one of degree, with 'blunted' only being rated in extreme cases).

If this item is rated positively, then so must item 51. Exclude flat affect during a depressive episode, i.e., care is required regarding the meaning of an entry of 'flattened affect' in case-notes. Care is required when flat affect is in the context of Parkinsonian side-effects.

53. *Inappropriate affect #*
Patient's emotional responses are inappropriate to the circumstance, e.g. laughter when discussing painful or sad occurrences, fatuous giggling without apparent reason.

This item includes fatuous giggling for no reason, as well as emotional responses inappropriate to the circumstances. Care is required if in the context of a manic episode.

54.* *Perplexity #*
Severe or marked confusion, bewilderment, perplexity or puzzlement. Proband is unable to judge correctly events in their surroundings. The proband may no longer understand the connections in the events around them and everything appears peculiar. The patient may keep on speaking about things not relevant to the theme but this is due to a failure to comprehend their environment rather than an abundance of flight of ideas. Proband may express feeling of being in a dream like state, being on another planet, or being like a zombie. Does not result from a lack of interest in surroundings (c.f. negative symptoms and depression). Not merely speech that is difficult to understand due to severe flight of ideas or formal thought disorder. Not due a change in the quality of perception of external space (c.f. de-realisation). Not the situation in which an individual can not make sense of a delusional system. Do not rate if obviously due to the effects of drugs (illicit or prescribed) or alcohol intoxication. NOTE: Very difficult to distinguish from a number of other symptoms including flight of ideas, negative symptoms, depression, marked delusional system, de-personalisation and de-realisation. Rate making the best estimate of whether symptom present based on all the available evidence.

54a: Aggressive Behaviour (NOVEL MEASURE)
1=Behaviour which is perceived as threatening and is out of proportion to the circumstances. Includes verbal aggression. Rate with a low threshold.
2=Act of physical aggression which does not meet the criteria for 3. Includes damage to property or minor acts of unprovoked violence towards others.
3=Severe acts of aggression which result in physical injury to others or police involvement or individual needs to be restrained.
4=Multiple acts of severe aggression which fulfil the criteria for 3.

PSYCHOTIC AFFECTIVE SYMPTOMS

Should be rated as present if present for at least a significant portion of time in a 1 month period or less if successfully treated

Items marked * are not in the original OPCRIT.

All items are rated

0	No
1	Yes
9	Unknown/Missing

55. Grandiose delusions

Patient has grossly exaggerated sense of own importance, has exceptional abilities or believes that he is rich or famous, titled or related to Royalty. Also included are delusions of identification with God, angels, the Messiah etc. (See also 'increased self-esteem').

Score as present if present for at least 4 days.

56. Delusions of guilt

Firm belief held by subject that they have committed some sin, crime or have caused harm to others despite absence of any evidence to support this.

Score as present if present for at least 2 weeks.

57. Delusions of poverty

Firm belief held by subject that they have lost all or much of their money or property and have become impoverished despite absence of any evidence to support this.

Score as present if present for at least 2 weeks.

58. Nihilistic delusions

Firmly held belief that some part of patient's body has disappeared or is rotting away or is affected by some devastating or malignant disorder despite a lack of any objective supporting evidence.

Score as present if present for at least 2 weeks. *Include patient's belief that he/she is dead.*

59.* Mood congruent third person auditory hallucinations

Two or more voices discussing the patient in the third person or patient hears voice(s) describing his actions, sensations or emotions as they occur. The content of the hallucinations has a clear relationship to a depressed/manic mood. Score if either 'true' or 'pseudo' hallucinations, i.e. differentiation of the source of the voices is unimportant.

May be rated without an example if a clear description is given that these occur. Rate if the notes say "third person auditory hallucinations". If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

60.* Mood congruent second person auditory hallucinations

Second person auditory hallucinations, where the content of the voices has a clear relationship to a depressed/manic mood.

Include here mood congruent non-verbal auditory hallucinations. If voices are abusive/accusatory/persecutory also rate item 31. If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

61.* Mood congruent visual hallucinations

Visual hallucinations in which the content has a clear relationship to a depressed/manic mood.

If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

62.* ***Mood congruent hallucinations in any other modality***
Hallucinations in which the content has a clear relationship to a depressed/manic mood.

Rated positively if a clear description is given, even without a specific time period. If hallucinations occur in the context of a mood episode and it is unclear whether they are congruent or incongruent, rate as congruent and rate'9' for the equivalent incongruent item.

63.* ***Other secondary delusions***
Delusions not rated elsewhere in which there is a clear relationship to a depressed/manic mood.

Appendix D

The Bipolar Affective Disorder Dimension Scale (BADDS)

Craddock et al (2004)

General information

The Bipolar Affective Disorder Dimension Scale (BADDS) has been developed in order to address some of the disadvantages of a purely categorical approach to diagnostic classification of Bipolar Spectrum Disorders.

BADDS is a dimensional rating scheme that retains and builds upon current categorical classifications. It is intended for use in clinical samples from populations over-represented by Bipolar Spectrum illness. It was not developed for use in general population samples.

BADDS has been under development since 1996 and has now been used by a variety of researchers within our group on more than 1100 cases. It has proved to be user friendly and has excellent reliability, even on sets of diagnostically challenging cases.

BADDS comprises 4 dimensions: M: Mania; D: Depression; P: Psychosis; I: Incongruence. Each dimension is rated using integer scores on a 0 – 100 scale. Ratings are made after review of all available clinical data on a subject (e.g. case records, semi-structured psychiatric interview and information from an informant) and can be performed as a simple addition to the conventional consensus lifetime psychiatric diagnostic procedures already in use by many research groups. Each rating reflects a mixture of severity and frequency of clinical features. Guidelines are provided that define anchor points in the rating scales and specify how ratings should be made.

BADDS: General rating guidelines

1) Do not rate a dimension if there is insufficient information - just leave the dimension blank.
2) Use all available information to make the best judgement for each rating.
3) It is expected that when used for research BADDS will be used within the accepted framework of the lifetime best-estimate consensus diagnostic procedure.
4) All ratings should be made using integers in the range 0 - 100.
5) Ratings for M and D are a mixture of severity and frequency. Generally the severity of the most severe episode identifies a range in which the rating will be made and the frequency determines the score assigned within the range. In assigning a rating, start at the lowest score in the range and then add points according to any relevant psychopathology over and above that of the most severe episode according to the following guidelines:

   a) In general each additional episode *of that level of severity* will add a score of 2 in a 20 point range and 1 in a 10 point range.

   b) Scores in the identified severity range can and should be modified according to severity and duration of total episodes – but with a substantial down-weighting for episodes of lower severity.

   c) For episodes that are one level of severity lower than the rating range, add 0.25 points for each episode of lower severity for a score in a 10 point range and 0.5 points for each episode of lower severity for a score in a 20 point range.

   d) For episodes that are more than one level of severity lower than the rating range the total adjustment should not normally exceed 1 or 2 points.

6) For the P and I dimensions anchor points are given in these guidelines. Judgment is used to assign scores between anchor points.
7) Under very exceptional circumstances a score can be rated outside the severity range. However, this should always be agreed by at least two raters and the rating should lie in the interval 0 - 100. Such a rating should be indicated by an asterisk (*) following the rating for that dimension. An example of the applicability of this rule is the rating up of an episode in which the balance of evidence clearly suggests a severe illness that is not adequately supported by the documented evidence *because of poor documentation.* Another example would be the rating down of an episode if the balance of evidence strongly suggests that the formal evidence clearly over-represents the clinical significance of the episode.

1) Mania dimension (M)

- The rating reflects severity and frequency.
- Use ICD10 to define symptom and duration criteria for hypomanic and manic syndromes.
- Sub-hypomanic features in the ranges 1 - 19 and 20 - 39 should be rated using judgement according to the balance of number and duration of symptoms.
- No impairment criterion is used for hypomania.
- The impairment criteria for mania are one or more of:

  Disrupts work or social life more or less completely
  Markedly inappropriate overspending that is reckless within the context of the subject's financial position
  Fights
  Lost job
  Police involvement
  Family split up
  Received specific treatment (including dose increase of mood stabilizer) *for acute mania*
  Psychotic features

- *Incapacitating mania* refers to a severe manic episode that includes the presence of one or more of the following features: incoherence, disorientation, loss of contact with reality (which includes psychotic features), frenzied or bizarre psychomotor activity. *NB: Being admitted on a Section is an example of incapacitating mania.*
- Mixed episodes are rated on the M dimension. If *all* manic episodes are mixed, add "m" to the rating (eg. 65m).

Key points and ranges on the M dimension

0	No manic features.
1 - 19	Mild sub-hypomanic features. Elation/irritability and less than 3 symptoms.
20 - 39	Sub-hypomanic features. Elation/irritability and 3+ symptoms for at least 1 day.
40 - 59	Hypomanic features. At least one hypomanic episode.
60 - 79	Manic features. At least one manic episode.
80 - 100	Severe manic features. At least one episode of incapacitating mania.

NB: *a) if * enter as .01, e.g., 65* = 65.01*
b) if m enter as .02, e.g., 65m = 65.02
*c) if both * and m enter as .03, e.g., 65*m = 65.03)*

2) Depression (D)

- Rating reflects severity and duration.
- Use ICD10 to define depressive syndromes. This includes 10 symptoms of depression that count for the purposes of diagnosis:

A
Depressed mood
Loss of interest/pleasure
Loss of energy

B
Suicidal ideation
Pathological guilt
Loss of confidence/self esteem
Loss of concentration
Slowed activity
Change of appetite or weight
Change in sleep pattern

- Depression severity: Mild - 4+ symptoms (2+ from A); moderate - 6+ symptoms (2+ from A); severe - 8+ symptoms (3 from A). Refer to ICD10 for full definition of syndromes and symptoms.
- Duration criterion for Major Depressive Episode is 2 + weeks. If 1- 2 weeks, classify as Minor Depression.
- Rate depression as severe if (a) ICD10 criteria fulfilled, or (b) criteria for major depression are fulfilled and there has been a serious suicide attempt, ECT treatment or hospital admission for depression.
- Minor depression refers to at least 1 week of low mood accompanied by 2 or more depression items or to brief episodes that would otherwise meet criteria for Major Depression.
- Incapacitating depression refers to severe major depression that includes presence of one or more of the following features: stupor; mutism; loss of contact with reality (including psychotic features). *NB: Being admitted on a Section is an example of incapacitating depression.*
- If psychotic features are present, a depressive episode can be rated as incapacitating if the minimum criteria for major depression are satisfied (ie. 4 items).

Key points and ranges on D dimension

0	No features of depression during lifetime. .
1 – 19	Sub-Minor depression.
20 - 39	Minor depression.
40 - 49	Mild major depression.
50 - 59	Moderate major depression.
60 - 79	Severe depression.
80 - 100	Incapacitating depression

*NB: if * enter as .01, e.g., 65* = 65.01*

3) Psychotic features (P)

- Psychotic features refers to delusions, hallucinations, positive formal thought disorder, catatonia or grossly disorganized behaviour (but see exclusions below).
- Ratings on this dimension exclude stupor or excitement during an affective episode or positive formal thought disorder during mania.
- Lifetime occurrence of psychotic features is rated.
- Near psychotic schizotypal features refers to the following DSMIV schizotypal items: ideas of reference; odd beliefs or magical thinking that influences behaviour and is inconsistent with sub-cultural norms; unusual perceptual experiences including bodily illusions; odd thinking and speech; suspiciousness or paranoid ideation; behaviour or appearance that is odd eccentric or peculiar. Depersonalization and derealization are not classified as near psychotic features.
- The period of illness considered refers to all affective and non-affective periods of psychopathology.
- Rating should take account of both number and duration of episodes with and without psychotic features. If in doubt, "rate up" the psychotic features. Examples:
    - If there have been two 1 week long affective psychotic episodes and a 1 year non-psychotic depressive episode, rate 60 (ie. approx. 2/3 of illness *episodes*).
    - If there have been nine 1 month non-psychotic affective episodes, one 1 month psychotic affective episode and 4 years of chronic hallucinations outside affective episodes, rate 80 (ie. approx. 80% of illness *duration*).
- The Uncertain category (P = 1) is used for situations in which insufficient information is available to determine if sign or symptom meets criteria for near psychotic feature.

Key points and ranges on P dimension

0	Absent.
1	Uncertain.
2 - 9	Near psychotic features: occasional at low end of range, frequent at High end of range. Occurrence of true psychotic symptoms should not be rated in this range.
10 - 20	Brief clear-cut psychotic symptom that are not a prominent feature of illness. 10 – Single. 20 – Multiple.
21 – 100	Psychotic symptoms that are a prominent feature in one of more episodes of illness. 25 - present for 25% of illness. 50 - present for 50% of illness. 75 - present for 75% of illness. 100 - prominent psychotic features present throughout illness.

NB: *a) If there is only one manic episode which is psychotic, then P=100.*
b) Experiences which are unusual but not definitely schizotypal or psychotic should be rated '1' (uncertain) here. Such experiences should be rated as '1' on the 'near section 2 features' variable.
c) When calculating the % of episodes that are psychotic, milder episodes of illness may be weighted down compared with more severe episodes (use clinical judgement). In general use the rule of counting a mild episode as equivalent to 1/4 of a more severe episode. For example, if there have been 2 episodes of psychotic mania and 3 episodes of mild depression which have not needed treatment this would be counted as equivalent to [2 + (3x0.25)] = 2.75 episodes of mood disturbance and rated P as 73, i.e., 2 /[2 + (3x0.25)] = 73.

4) Mood incongruence (I)

- DSMIV definitions of congruence and incongruence are used.
- Rate incongruence of lifetime occurrence of psychotic features.
- For convenience, the set of psychotic symptoms recognized as having special weight in the diagnosis of schizophrenia and schizoaffective disorder (thought echo, insertion, withdrawal or broadcasting; passivity experiences; hallucinatory voices giving running commentary, discussing subject in third person or originating in some part of the body; bizarre delusions; catatonia) are denoted in the guidelines as the "S set".
- If Psychosis Features dimension, P < 10, leave I blank.

Key points on I dimension

0 -40	Psychotic symptoms occur only during affective episodes and do not include any of the S set. Rating 0 – virtually completely mood congruent. Rating 20 – approximate balance between mood congruent and incongruent. Rating 40- virtually completely mood incongruent
43	Psychotic symptoms occur only during affective episodes and include one or more of the S set which have not definitely been present for 2 weeks.
47	Psychotic symptoms occur only during affective episodes and include one or more of the S set which have definitely been present for 2 weeks.
50 - 59	Psychotic symptoms probably present for at least 2 weeks either side of an affective episode. Rating 50 – on at least one occasion. Ratings of 51-59 used to reflect recurrence and/or certainty.
60 - 100	Psychotic symptoms definitely present for at least 2 weeks either side of an affective episode. Rating 60 – on at least one occasion. Rating 80- on many occasions. Rating 100 – Psychotic symptoms predominate illness and occur chronically outside (or in absence of) affective episodes.

NB: *a) a rating of 100 does not necessarily imply schizophrenia.*
b) when rating congruence rate psychotic symptoms occurring outside the affective states as incongruent.
c) if there is a delusional system – some can be congruent and others incongruent with the affective state. Rate as congruent if <u>all</u> the delusions are understandable in relation to the mood.
d) mixed episodes – if it is not possible to determine a temporal relationship between the affective states and psychotic symptoms rate 20 (approx. balance between congruence and incongruence). If it is possible to determine a temporal relationship, rate congruence in relation to the affective states.

Appendix E

The Extended Rating Scales

- Use all available information to make the best judgement for each rating.
- Ratings should only be made for cases which involve affective and/or psychotic features

Extended Scale 1: Predominance of Mania in lifetime mood disturbances

Aim: To measure the relative amount of depressive and manic episodes experienced during lifetime.

0.....50.....100

100% Depression	Balanced Mania/Depression	100% Mania

Rating Guidelines

- Rating is calculated as percentage of mood episodes which are manic in nature.

i.e. $\frac{\textbf{No. of episodes mania}}{\textbf{[No. of episodes depression] + [No. of episodes mania]}}$ **x100**

- Episodes of illness must meet criteria for major depression (at least mild), mania or hypomania, be clinically significant and cause impairment to be included in calculation

- Use best estimate of the number of episodes

- Mixed episodes should be rated on this dimension according to these rules:
  1. Approximate balance between mania and depression
     Mania = 0.5 Depression = 0.5
  2. Episode is predominantly manic
     Mania = 0.75 Depression = 0.25
  3. Episode is predominantly depressive
     Mania = 0.25 Depression = 0.75
     If in doubt, use rating 1

If no episodes of mood disturbance are described, leave blank (do not rate 0).

Extended Scale 2: Relationship between Mood and Psychotic Symptoms

Aim of scale: To measure the relative balance of mood and psychotic psychopathology over the lifetime experience of illness. This is an extension of the I dimension of BADDS.

-20	Episodes of clinically significant mood disturbance. No psychotic features.
-19	Illness is predominantly affective and includes near psychotic features: occasional at low end of range, frequent at high end of range. Occurrence of true psychotic symptoms should not be rated here.
-1	Unsure/uncertain as to whether or not psychosis has occurred
0	Psychotic symptoms occur but only during affective episodes and do not include any of the S set. Virtually completely mood congruent.
20	Psychotic symptoms occur but only during affective episodes and do not include any of the S set. Approximate balance between mood congruent and incongruent.
40	Psychotic symptoms occur but only during affective episodes and do not include any of the S set. Virtually completely mood incongruent.
43	Psychotic symptoms occur but only during affective episodes and include one or more of the S set which have not definitely been present for 2 weeks.
47	Psychotic symptoms occur but only during affective episodes and include one or more of the S set which have definitely been present for 2 weeks.
50	Psychotic symptoms probably present in the absence of an affective episode such that at least 2 weeks of normal mood occurs between the mood disturbance and the psychotic symptoms (Rating 50 – on at least one occasion. Ratings of 51-59 used to reflect recurrence and/or certainty).
60	Psychotic symptoms definitely present in the absence of an affective episode such that at least 2 weeks of normal mood occurs between the mood disturbance and the psychotic symptoms - on at least one occasion.
80	Psychotic symptoms definitely present present in the absence of an affective episode such that at least 2 weeks of normal mood occurs between the mood disturbance and the psychotic symptoms - on many occasions.
100	Psychotic symptoms predominate illness and occur chronically outside affective episodes. Affective episodes occur but are not a major feature of illness.
110	Illness is predominantly psychotic and includes some affective symptoms which do not meet the criteria for an episode.
120	Psychotic features in the absence of any clinically significant mood disturbance.

Rating guidelines

- DSMIV definitions of congruence and incongruence are used.
- Rate incongruence of lifetime occurrence of psychotic features.
- For convenience, the set of psychotic symptoms recognized as having special weight in the diagnosis of schizophrenia and schizoaffective disorder (thought echo, insertion, withdrawal or broadcasting; passivity experiences; hallucinatory voices giving running commentary, discussing subject in third person or originating in some part of the body; bizarre delusions; catatonia) are denoted in the guidelines as the "S set".
- Where no psychotic features are present, rate – 20.
- Where no mood features are present, rate + 120.

Extended Scale 3: Fluctuation of mood within acute phases of illness

Anchor points

100 Fluctuations in mood occur over 1 day during at least one acute phase of illness.

90 Fluctuations in mood occur over 4 days during at least one acute phase of illness.

80 Fluctuations in mood occur over 1 week during at least one acute phase of illness.

70 Fluctuations in mood occur over 10 days during at least one acute phase of illness.

60 Fluctuations in mood occur over 2 weeks during at least one acute phase of illness.

50 Fluctuations in mood occur over 4 weeks during at least one acute phase of illness.

40 Fluctuations in mood occur over 8 weeks during at least one acute phase of illness.

30 Fluctuations in mood occur over 12 weeks during at least one acute phase of illness.

20 Fluctuations in mood occur over 26 weeks during at least one acute phase of illness.

10 Fluctuations in mood occur over 52 weeks during at least one acute phase of illness.

0 No fluctuations in mood occur.

Rating Guidelines

- Aim of scale is to give an indication of the maximum rapidity of mood fluctuation during an acute phase of illness.
- "Acute phase of illness" is defined as a continuous interval of time during which the individual has impaired function, *compared with the usual functioning*. (Thus, if an individual has 3 months of depression with a switch to 2 months of mania and a return to normal functioning, this is an acute phase lasting 5 months. If an individual has a chronic impairment relating to illness, it is the *change* from this usual (but impaired) function that is used as a reference baseline for determining acute phases).
- **"Fluctuation" is defined as at least 2 changes of mood pole (ie. Depression – mania – depression or mania-depression-mania).**
- Ratings should be made using an integer on the 0 – 100 scale that best represents the maximum rapidity of fluctuation that has occurred during the lifetime experience of illness.
- If there is insufficient information to rate accurately, leave blank.

Extended Scale 4: Instability of clinical state within acute phases of illness

Anchor points

100 Clinical state varies significantly during a period of 10 minutes during the most variable one month of illness.

80 Clinical state varies significantly during a period of 1 day during the most variable one month of illness.

60 Clinical state varies significantly during a period of 1 week during the most variable one month of illness.

40 Clinical state varies significantly during a period of 2 weeks during the most variable one month of illness.

20 Clinical state varies significantly during a period of 4 weeks during the most variable one month of illness.

0 No variability in clinical state during the most variable one month of illness.

Rating Guidelines

- Aim of scale is to give an indication of the maximum instability in clinical state ever experienced during a one month phase of illness.
- "Clinical instability" refers to substantial changes in the psychopathological state and includes the domains of mood, perception, cognition and behaviour.
- Changes of mood that can be rated include mood states that meet full criteria for an episode and also more subtle variation of mood states that do not meet full criteria.
- Note that it is possible to have fluctuations in mood (scale 3) over a 12 week period with instability of clinical state occurring over a period of 1 day.
- Ratings should be made using an integer on the 0 – 100 scale that best represents the maximum level of instability that has occurred during a one month period in the individual's lifetime experience of illness.
- **Anchor points**: Where "rapid mood changes" are mentioned or where mood is described as "labile" with no additional information, rate as 90*; where mood is described as "variable" with no additional information, rate as 80*. This estimate can also be used for similar descriptions (e.g. "fluctuating affective state", "mood up and down", etc).
- If a switch in mood is described, rate 20 unless it is clear that the switch definitely occurred over period of less than 4 weeks.
- If it is clear that some degree of fluctuation occurs but there is insufficient information to make a definite rating on the scale, rate 10.
- If there is insufficient information to rate accurately, leave blank.

Extended Scale 5: Periodicity of acute phases of illness

Anchor points

100	5 acute phases of illness in one year.
90	2 acute phases of illness in one year.
70	2 acute phases of illness in 2 years
50	2 acute phases of illness in 5 years
30	2 acute phases of illness in 8 years
20	2 acute phases of illness in 10 years
10	2 acute phases of illness in 20 years
1	2 acute phases of illness in 50 years
0	Only one acute phase of illness.

Rating guidelines

- Aim of scale is to measure the tendency to recurrence of acute phases of illness during the lifetime course.
- "Acute phase of illness" is defined as a continuous interval of time during which the individual has impaired function, *compared with the usual functioning*. (Thus, if an individual has 3 months of depression with a switch to 2 months of mania and a return to normal functioning, this is an acute phase lasting 5 months. If an individual has a chronic impairment relating to illness, it is the *change* from this usual (but impaired) function that is used as a reference baseline for determining acute phases).
- A period of at least 2 months of usual functioning is required between adjacent acute phases of illness (which gives an upper limit of 5 such phases within one year).
- Ratings should be made based on knowledge of the lifetime course of illness experienced by the subject. Rate the *maximum* periodicity during the lifetime. Thus, if there were 2 acute phases of illness in the first 10 years since onset and then 2 acute phases in one year, rate 90.
- A single chronic phase lasting 20 years with no superposed acute phases should be rated as 0.

Extended Scale 6: Predominance of mixed episodes in episodes of mood disturbance

0.....50.....100

0% episodes of mood disturbance are mixed

100% episodes of mood disturbance are mixed

Rating Guidelines

- Aim of scale is to measure the relative amount of mood episodes that involve a mixed affective state.
- "Mixed episode" refers to an episode of mood disturbance in which both depressive and manic syndromes occur simultaneously. However, to recognize the difficulty of obtaining adequate retrospective information about the depressive aspects of mixed states, one less symptom is required for determining the presence of depression (ie. Depressed mood + 3 symptoms).
- Rating is calculated as proportion of affective episodes which are mixed in nature. i.e.

$$\frac{\textbf{No. of mixed episodes}}{\textbf{[No. of mixed episodes]+[No. of episodes depression]+[No. of episodes mania]}} \textbf{ x100}$$

- Episodes of illness must be clinically significant and cause impairment to be included in calculation
- If no episodes of affective illness are described, leave blank (do not rate 0).

Extended Scale 7: Most dysphoric manic episode experienced

Anchor points

100	Mania with 6 depressive items according to DSMIV.
90	Mania with 5 depressive items according to DSMIV.
80	Mania with 4 depressive items according to DSMIV.
70	Mania with 3 depressive items according to DSMIV.
60	Mania with 2 depressive items according to DSMIV.
50	Mania with one depressive item according to DSMIV.
40	Mania with irritable mood and no evidence of elated but no other depressive features.
30	Mania with predominantly irritable and some elated mood but no other depressive features.
20	Mania with rough balance of elevated and irritable mood but no other depressive features.
10	Mania with predominantly elevated mood and some evidence of irritability but no other depressive features.
0	Mania with elevated mood and no irritability or dysphoric features.

Rating Guidelines

- Mania refers to manic episode as defined by DSMIV criteria.
- Rate the manic episode in which the greatest number of depressive features occur.
- Depressive items refers to those used in the diagnosis of a major depressive episode according to DSMIV (i.e. depressed mood, anhedonia, disturbance in appetite and/or weight loss or gain, psychomotor agitation or retardation, fatigue/loss of energy, excessive self reproach, reduced concentration and suicidal ideation).
- If an episode is described as being "mixed" with no additional information, rate as 65*.

Extended Scale 8: Extent to which illness is "purely" psychotic or "purely" affective

0.....50.....100	
Prototypical affective disorder	Prototypical schizophrenia

- Judgement to be made based on whole clinical picture over entire duration of illness.
- "prototypical affective disorder" refers to episodic illness characterised by one or more manic or depressive episodes with good recovery in between multiple episodes and with no evidence of psychotic or near psychotic symptoms.
- prototypical schizophrenia refers to chronic illness characterised by insidious onset, positive and negative symptoms and no evidence of affective disturbance.

Extended Scale 9 – Relationship between Positive and Negative Symptoms

0.....50.....100	
Illness characterised by by reversible acute symptoms	Illness characterised chronic defect-state

- Judgement to be made based on whole clinical picture over entire duration of illness.
- Chronic defect state includes negative symptoms such as affective flattening or blunting, alogia, avolition/apathy, anhedonia/asociality and poor attention, which appear to be irreversible and are a longstanding characteristic of the clinical picture.
- Reversible acute symptoms include positive symptoms such as hallucinations, delusions, bizarre behaviour, positive formal thought disorder and affective symptoms/episodes.

Extended Scale 10: Catatonic Symptoms

One point should be given for the presence of any of the following symptoms, up to a maximum of 4 points.

Symptoms explicable by affective change should not be counted

- Waxy flexibility
- Stupor (clear description of catatonic stupor deserves 2 points, give 1 point for a condition described as sub-stupor. Do not rate here slowing down which is common in depressive episodes)
- Physiological pillow
- Excessive purposeless overactivity (not in a manic context)
- Mannerisms
- Grimacing
- Echolalia, echopraxia, automatic obedience (need clear descriptions)
- Negativism (need clear descriptions)

Extended Scale 10L: Catatonic Symptoms – Lifetime Ever

One point should be given for the presence of any of the following symptoms, up to a maximum of 4 points.

Includes symptoms which occur during affective episodes

- Waxy flexibility
- Stupor (clear description of catatonic stupor deserves 2 points, give 1 point for a condition described as sub-stupor. Do not rate here slowing down which is common in depressive episodes)
- Physiological pillow
- Excessive purposeless overactivity (not in a manic context)
- Mannerisms
- Grimacing
- Echolalia, echopraxia, automatic obedience (need clear descriptions)
- Negativism (need clear descriptions)

Extended Scale 11: Disorganised Behaviour

One point should be given if any the following symptoms that are present over the course of the illness. If an item is present repeatedly during the illness or if several items are present, a score of 2 should be given.

Symptoms explicable by affective change should not be counted

- Talking to themselves
- Laughing for no reason
- Hoarding rubbish
- Odd, inappropriate behaviour (e.g. undressing or urinating in public)
- Acts of senseless violence
- Extremely poor personal hygiene

Extended Scale 11L: Disorganised Behaviour

One point should be given if any the following symptoms that are present over the course of the illness. If an item is present repeatedly during the illness or if several items are present, a score of 2 should be given.

Includes symptoms which occur during an affective episode

- Talking to themselves
- Laughing for no reason
- Hoarding rubbish
- Odd, inappropriate behaviour (e.g. undressing or urinating in public)
- Acts of senseless violence
- Extremely poor personal hygiene

Appendix F

Sheet used to rate the Velo-Cardio-Facial Syndrome Cases

STUDY ID _____ **INITIALS** _____ **DOB** _____

RATER _____ **DATE** _____ **AGE AT INT.** _____

GENDER _____ **ETHNICITY** _____

DSM-IV	ICD-10	RDC	CYCLOID

Family History: Affective Disorders _____ Other _____

DIMENSION SCORES:

M ___ ___ ___
D ___ ___ ___
P ___ ___ ___
I ___ ___ ___

GAS SCORES:

LIFETIME WORST (IN DEP EPISODE) _____
LIFETIME WORST (IN NON-PN DEP EPISODE) _____
LIFETIME WORST (IN PN DEP EPISODE) _____
LIFETIME WORST (IN MANIC EPISODE) _____
LIFETIME WORST (IN NON-PN MANIC EPISODE) _____
LIFETIME WORST (IN PN MANIC EPISODE) _____
LIFETIME WORST (IN PSYCHOSIS) _____
LIFETIME WORST (IN NON-PN PSYCHOSIS) _____
LIFETIME WORST (IN PN PSYCHOSIS) _____
LIFETIME WORST EVER _____
PAST WEEK _____

SECTION 2 (LE)____ **MOOD CONGRUENCE (LE)** ____ **NEAR SECTION 2 (LE)** ____

SECTION 2 (PN) _____ MOOD CONGRUENCE (PN) _____
SECTION 2 (NON-PN) _____ MOOD CONGRUENCE (NON-PN) _____

PREDOMINANT MAN AFFECT (LE) ____ **DYSPHORIC MAN (LE)** ____

PRED MAN AFFECT (NON-PN MAN) ____ DYSPHORIC MAN (NON-PN MAN) ____
PRED MAN AFFECT (PN MAN) ____ DYSPHORIC MAN (PN MAN) ____

NO. EPISODES:	**MANIA**	____	**DEPRESSION**	____
	PN MANIA	____	PN DEPRESSION	____
	NON-PN MAN	____	NON-PN DEPRESSION	____

LONGEST DURATION:	**MANIA**	____	**DEPRESSION**
____			
	PN MANIA	____	PN DEP
____			
	NON-PN MAN	____	NON-PN DEP
____			

AGE ONSET:

SYMPTOM ____ IMPAIRMENT ____ CONTACT ____ ADMISSION ____

FIRST DEPRESSION	____
FIRST PN DEPRESSION	____
FIRST NON-PN DEP	____

FIRST SYMPTOMS	**MANIA** _____	**DEP** _____
FIRST IMPAIRMENT	**MANIA** _____	**DEP** _____
FIRST PSYCHIATRIC CONTACT	_____	
FIRST ADMISSION	**MANIA** _____	**DEP** _____
MOST RECENT ADMISSION	**MANIA** _____	**DEP** _____

FIRST SYMPTOMS	PN DEP _____	NON-PN DEP _____
FIRST IMPAIRMENT	PN DEP _____	NON-PN DEP _____
FIRST ADMISSION	PN DEP _____	NON-PN DEP _____
MOST RECENT ADMISSION	PN DEP _____	NON-PN DEP _____

NO. ADMISSIONS: _____
LONGEST ADMISSION _____

AGE OF FIRST PSYCHOSIS (HALLUCINATION OR DELUSION): _____

FIRST EPISODE POSTPARTUM? Y / N / UK / NA

PUERPERAL EPISODE ____ MENSTRUAL ____ RAPID CYCLING ____

SUICIDAL IDEATION (LE) ____

SUICIDAL IDEATION (PN) ____

SUICIDAL IDEATION (NON PN) ____

LITHIUM RESPONSE ____ **ANTI-DEPRESSANT RESPONSE (inc ECT)** ____

SWITCH OF POLARITY FOLLOWING ANTI-DEPRESSANTS ____

	PSYCHIATRIC SEQUELAE	ONSET (WKS AFTER DELIVERY)
FULL-TERM DELIVERY #1		
FULL-TERM DELIVERY #2		
FULL-TERM DELIVERY #3		
FULL-TERM DELIVERY #4		
FULL-TERM DELIVERY #5		
FULL-TERM DELIVERY #6		

Delivery # of Episode rated in OPCRIT _____

EXTENDED RATING SCALES:

Scale 1 _____ (predominance mania)

Scale 2 _____ (affective vs. psychotic features)

Scale 3 _____ (fluctuations in mood)

Scale 4 _____ (instability)

Scale 5 _____ (periodicity)

Scale 6 _____ (predominance mixed)

Scale 7 _____ (dysphoric mania)

Scale 8 _____ (affective disorder vs. SZP)

MOLECULAR PSYCHIATRY GROUP

SYMPTOM CHECKLIST (Modified OPCRIT version 6 – 01.12.05)

STUDY ID _____ **INITIALS** _____ **RATER** _____

DOB _____ **DATE** _____

NB: For women who have had puerperal illness please rate the worst puerperal episode (WE – PN) and indicate the polarity below – complete all sections of the form independent of polarity of episode. If the worst puerperal episode is depression please rate the worst non-puerperal episode of depression (WE-NON-PN, and complete all sections of the form). If the worst puerperal episode is mania/mixed please rate the worst non-puerperal episode of mania/mixed (WE-NON-PN, and complete all sections of the form). If the worst puerperal episode is psychosis only please rate the worst non-puerperal episode of psychosis only (but if there is not a non-PN episode of psychosis only, please rate the worst non-puerperal episode of mania/mixed).

The columns marked WE and LE should be rated in the usual way.

Polarity of worst puerperal episode

1 Depression
2 Mania
3 Mixed
4 Not applicable. Rate all males here.
5 Psychosis only

	DEPRESSIVE SYMPTOMS	**WE**	**LE**	**WE (PN)**	**WE (NON-PN)**
1.	Dysphoria	☐	☐	☐	☐
2.	Loss of pleasure	☐	☐	☐	☐
3.	Diurnal variation (mood worse mornings)	☐	☐	☐	☐
4.	Suicidal ideation	☐	☐	☐	☐
5.	Excessive self reproach	☐	☐	☐	☐
6.	Poor concentration	☐	☐	☐	☐
7.	Slowed activity	☐	☐	☐	☐
8.	Loss of energy/tiredness	☐	☐	☐	☐
9.	Poor appetite	☐	☐	☐	☐
10.	Weight loss	☐	☐	☐	☐
11.	Increased appetite	☐	☐	☐	☐
12.	Weight gain	☐	☐	☐	☐
13.	Initial insomnia	☐	☐	☐	☐
14.	Middle insomnia (broken sleep)	☐	☐	☐	☐
15.	Early morning waking	☐	☐	☐	☐
16.	Excessive sleep	☐	☐	☐	☐
17.	Diminished libido	☐	☐	☐	☐
18.	Agitated activity	☐	☐	☐	☐

	MANIC SYMPTOMS	**WE**	**LE**	**WE (PN)**	**WE (NON-PN)**
19.	Elevated mood	☐	☐	☐	☐
20.	Irritable mood	☐	☐	☐	☐
21.	Thoughts racing	☐	☐	☐	☐
22.	Pressured speech	☐	☐	☐	☐
23.	Distractibility	☐	☐	☐	☐
24.	Excessive activity	☐	☐	☐	☐
25.	Increased self esteem	☐	☐	☐	☐
26.	Reckless activity	☐	☐	☐	☐
27.	Reduced need for sleep	☐	☐	☐	☐
28.	Increased sociability	☐	☐	☐	☐

PSYCHOTIC SYMPTOMS		LE	WE (PN)	WE (NON-PN)
29.	Third person auditory hallucinations	☐	☐	☐
30.	Running commentary voices	☐	☐	☐
31.	Abusive/accusatory/persecutory voices	☐	☐	☐
32.	Other (non affective) auditory hallucinations	☐	☐	☐
33.*	Non-affective visual hallucinations	☐	☐	☐
34.	Non-affective hallucination in any other modality	☐	☐	☐
35.	Thought echo	☐	☐	☐
36.	Thought insertion	☐	☐	☐
37.	Thought broadcast	☐	☐	☐
38.	Thought withdrawal	☐	☐	☐
39.	Delusions of passivity	☐	☐	☐
40.	Delusions of influence	☐	☐	☐
41.	Primary delusional perception	☐	☐	☐
42.	Persecutory delusions	☐	☐	☐
43.	Bizarre delusions	☐	☐	☐
44.	Other primary delusions	☐	☐	☐
45.	Bizarre behaviour	☐	☐	☐
46.	Catatonia	☐	☐	☐
47.	Speech difficult to understand	☐	☐	☐
48.	Incoherent	☐	☐	☐
49.	Positive formal thought disorder	☐	☐	☐
50.	Negative formal thought disorder	☐	☐	☐
51.	Restricted affect	☐	☐	☐
52.	Blunted affect	☐	☐	☐
53.	Inappropriate affect	☐	☐	☐
54.*	Perplexity	☐	☐	☐

PSYCHOTIC AFFECTIVE SYMPTOMS		WE	LE	WE (PN)	WE (NON-PN)
55.	Grandiose delusions	☐	☐	☐	☐
56.	Delusions of guilt	☐	☐	☐	☐
57.	Delusions of poverty	☐	☐	☐	☐
58.	Nihilistic delusions	☐	☐	☐	☐
59.*	Mood congruent third person auditory hallucinations	☐	☐	☐	☐
60.*	Mood congruent second person auditory hallucinations	☐	☐	☐	☐
61.*	Mood congruent visual hallucinations	☐	☐	☐	☐
62.*	Mood congruent hallucinations in any other modality	☐	☐	☐	☐
63.*	Other secondary delusions	☐	☐	☐	☐

ADDITIONAL CRITERIA – OPCRIT Version 4.0

Details and History

1	Source of rating	(1-6)	
2	Time frame	(1-4)	
3	Gender	(0, 1)	
4	Age of onset		
5	Mode of onset	(1-5)	
6	Marital status	(0, 1)	
7	Unemployed	(0, 1)	
8	Duration of illness in weeks		
9	Poor premorbid work adjustment	(0, 1)	
10	Poor premorbid social adjustment	(0, 1)	
11	Premorbid personality disorder	(0, 1)	
12	Alcohol/drug abuse within 1 year of onset	(0, 1)	
13	Family history of schizophrenia	(0, 1)	
14	Family history of other psychiatric disorders	(0, 1)	
15	Coarse brain disease prior to onset	(0, 1)	
16	Definite psychosocial stressor prior to onset	(0, 1)	

Substance Abuse or Dependence

78	Lifetime diagnosis of alcohol abuse/dependence	(0, 1)	
79	Lifetime diagnosis of cannabis abuse/dependence	(0, 1)	
80	Lifetime diagnosis of other abuse/dependence	(0, 1)	
81	Alcohol abuse/dependence with psychopathology	(0, 1)	
82	Cannabis abuse/dependence with psychopathology	(0, 1)	
83	Other abuse/dependence with psychopathology	(0, 1)	

General Appraisal

84	Information not credible	(0, 1)	
85	Lack of insight	(0, 1)	
86	Rapport difficult	(0, 1)	
87	Impairment/incapacity during disorder	(0,1,2,3)	
88	Deterioration from premorbid level of function	(0, 1)	
89	Psychotic symptoms respond to neuroleptics	(0, 1)	
90	Course of Disorder	(0-5)	

Appendix G

List of variables analysed in the sample enriched for schizoaffective disorder

- BADDS Mania
- BADDS Depression
- BADDS Psychosis
- BADDS Incongruence
- GAS Depression
- GAS Mania
- GAS Psychosis
- GAS Worst Ever
- GAS Past Week
- No. Manic Episodes
- No. Dep. Episodes
- AOO Impairment
- Age of first mania
- Age of first depression
- Age of first psychosis
- ERS1
- ERS2
- ERS4
- ERS5
- ERS7
- ERS8
- ERS9
- Course of Disorder

Appendix H

Inter-rater reliability analyses performed on the SABP sample

Variable	ICC	p-value
BADDS Mania	0.797	p<0.001
BADDS Depression	0.687	0.001
BADDS Psychosis	0.989	p<0.001
BADDS Incongruence	0.914	p<0.001
GAS Depression	0.980	p<0.001
GAS Mania	0.991	0.005
GAS Psychosis	0.899	p<0.001
GAS Worst Ever	0.982	p<0.001
GAS Past Week	0.912	p<0.001
No. Manic Episodes	0.962	p<0.001
No. Dep. Episodes	0.988	p<0.001
AOO Impairment	0.997	p<0.001
Age of first mania	0.999	p<0.001
Age of first depression	0.991	p<0.001
Age of first psychosis	1.000	-
ERS1	0.768	p<0.001
ERS2	0.971	p<0.001
ERS4	0.739	0.011
ERS5	0.509	0.016
ERS7	0.857	p<0.001
ERS8	0.934	p<0.001
ERS9	1.000	-
Course of Disorder	0.845	p<0.001

Appendix I

Rating sheet used to record ratings made for cases in the large harmonised dataset

STUDY ID _____ **INITIALS** _____ **DOB** _____

RATER _____ **DATE** _____

AGE AT INT. _____ **DATE AT INT.** _____

GENDER _____ **[ETHNICITY** _____**]**

[STUDY _____] []= Fields not for consensus rating meetings

DSM-IV	ICD-10	RDC
Main:	**Main:**	**Main:**
2.	**2.**	**2.**
3.	**3.**	**3.**
4.	**4.**	**4.**
5.	**5.**	**5.**

PN CYCLOID	NON-PN CYCLOID

FH AFF _____ **FH OTHER** _____ **FH PN** _____

BADDS SCORES:

M _____

D _____

P _____

I _____

GAS SCORES:

LIFETIME WORST (IN DEPRESSIVE EPISODE) ____

LIFETIME WORST (IN MANIC EPISODE) ____

LIFETIME WORST (IN PSYCHOTIC EPISODE) ____

LIFETIME WORST EVER ____

PAST WEEK ____

SECTION 2 (LE) ____ **MOOD CONGRUENCE (LE)** ____

NEAR SECTION 2 (LE) _____

PREDOMINANT MAN AFFECT (LE) ____ **DYSPHORIC MAN (LE)** ____

NO. EPISODES:

MANIA _____ **DEP** _____ **NON-AFFECTIVE PSYCHOSIS** _____

LONGEST DURATION (EPISODE):

MANIA **DEP** **NON-AFFECTIVE PSYCHOSIS**

AGE OF ONSET:

SYMPTOM ____ IMPAIRMENT ____ CONTACT ____ ADMISSION ____

	MANIA	DEP	PSYCHOSIS	PN
SYMPTOM				
IMPAIRMENT				
TREATMENT				
ADMISSION				
MOST REC. ADMISSION				

NO. ADMISSIONS _____

LENGTH OF LONGEST ADMISSION _____

PROPORTION OF TIME ADMITTED _____**%**

PROPORTION OF TIME WELL SINCE ONSET _____% (Objective)

FIRST EPISODE PAST-PARTUM? Y / N / UK PUERPERAL EPISODE ____

RAPID CYCLING ____ (NB: Rate 9 if less than 7 years since onset and/or fewer than 3 episodes)

SUICIDAL IDEATION (LE) ____

MOOD SWITCH (D TO M) _____ **MOOD SWITCH (M TO D)** _____

MAXIMUM NUMBER OF SWITCHES IN ONE EPISODE _____

LITHIUM RESPONSE ____ ANTI-DEPRESSANT RESPONSE (inc ECT) ____

SWITCH OF POLARITY FOLLOWING ANTI-DEPRESSANTS ____

	PSYCHIATRIC SEQUELAE	ONSET (WKS AFTER DELIVERY)
FULL-TERM DELIVERY #1		
FULL-TERM DELIVERY #2		
FULL-TERM DELIVERY #3		
FULL-TERM DELIVERY #4		
FULL-TERM DELIVERY #5		
FULL-TERM DELIVERY #6		

POLARITY OF FIRST AFFECTIVE EPISODE _____

PSYCHOTIC SYMPTOMS PRESENT BEFORE ANY MOOD DISTURBANCE _____

EXTENDED RATING SCALES:

Scale 1 _____ (predominance mania)
Scale 2 _____ (affective vs. psychotic features)
Scale 3 _____ (fluctuations in mood)
Scale 4 _____ (instability)
Scale 5 _____ (periodicity)
Scale 6 _____ (predominance mixed)
Scale 7 _____ (dysphoric mania)
Scale 8 _____ (affective disorder vs. SZP)
Scale 9 _____ (Chronic defect state)
Scale 10 _____ (Catatonic Symptoms) (Max.=4)
Scale 10L _____ (Catatonic – LE)
Scale 11 _____ (Disorganised Behaviour) (Max.=2)
Scale 11L _____ (Disorganised Behaviour – LE)

ID: _____ Initials: _____

Modified OPCRIT:

Polarity of worst puerperal episode

1 Depression
2 Mania
3 Mixed
4 Not applicable. Rate all males here.
5 Psychosis only

DEPRESSIVE SYMPTOMS:	Worst Episode (WE)	LE – In context of Dep mood	LE – Context Independent	WE PN	WE NON-PN
1. Dysphoria					
2. Loss of pleasure					
3. Diurnal variation					
4. Suicidal ideation					
5. Excessive self-reproach					
6. Poor concentration					
7. Slowed activity					
8. Loss of energy/tiredness					
9. Poor appetite					
10. Weight loss					
11. Increased appetite					
12. Weight gain					
13. Initial insomnia					
14. Middle insomnia					
15. Early morning waking					
16. Excessive sleep					
17. Diminished libido					
18. Agitated activity					

MANIC SYMPTOMS:	Worst Episode (WE)	LE – In context of M mood	LE – Context Independent	WE PN	WE NON-PN
19. Elevated mood					
20. Irritable mood					
21. Thoughts racing					
22. Pressured speech					
23. Distractibility					
24. Excessive activity					
25. Increased self-esteem					
26. Reckless activity					
27. Reduced need for sleep					
28. Increased sociability					
28a.* Increased sexual activity (0-2)					

PSYCHOTIC SYMPTOMS:	LE – In mood episode	LE – Not in mood episode	LE	WE PN	WE NON-PN
29. Third person AHs					
30. Running commentary voices					
31. Abusive/accusatory/persecutory voices					
32. Other (non-affective) AHs					
33.* Non-affective VHs					
34. Non-affective hall in any other modality					
35. Thought echo					
36. Thought insertion					
37. Thought broadcast					
38. Thought withdrawal					
39. Delusions of passivity					
40. Delusions of influence					
41. Primary delusional perception					
42. Persecutory delusions					
43. Bizarre delusions					
44. Other primary delusions					
45. Bizarre behaviour			#		
46. Catatonia			#		
47. Speech difficult to understand			#		
48. Incoherent			#		
49. Positive formal thought disorder			#		
50. Negative formal thought disorder			#		
51. Restricted affect			#		
52. Blunted affect			#		
53. Inappropriate affect			#		
54.* Perplexity			#		
54a.* Aggressive behaviour (0-4)					

PSYCHOTIC AFFECTIVE SYMPTOMS:	Worst Episode (WE)	LE – In context of M/D mood	LE – Context Independent	WE PN	WE NON-PN
55. Grandiose delusions					
56. Delusions of guilt					
57. Delusions of poverty					
58. Nihilistic delusions					
59*. Mood congruent third person AHs			N/A		
59a. D congruent third person AHs*			*N/A*		
59b. M congruent third person AHs*			*N/A*		
60,* Mood congruent sec person AHs			N/A		
60a. D congruent second person AHs*			*N/A*		
60b. M congruent second person AHs*			*N/A*		
61.* Mood congruent VHs			N/A		
61a. D congruent VHs*			*N/A*		
61b. M congruent VHs*			*N/A*		
62. Mood cong Hs in any other modality			N/A		
62a. D cong Hs in any other modality*			*N/A*		
62b. M cong Hs in any other modality*			*N/A*		
63.* Other 2ndry dels (not necess. cong)			N/A		
63a Other dels secondary to D*			*N/A*		
63b Other dels secondary to M*					

DETAILS & HISTORY: [NB 9=Unsure, 8=Not Applicable except stated otherwise]	
1. Source of rating [1-6]	1
2. Time frame [1-4]	2
3. Sex [0,1]	3
4. Age of onset [Unknown =99]	4
5. Mode of onset [1-5] rate to one decimal place if necessary	5
6. Single [0,1]	6
7. Unemployed at onset [0,1]	7
8. Duration of illness in weeks [blank if unknown]	8
9. Poor work adjustment [0,1]	9
10. Poor pre-morbid social adjustment [0,1]	10
11. Premorbid personality disorder [0,1]	11
12. Alcohol/ drug abuse within one year of onset of psychotic symptoms [0,1]	12
13. Family history of schizophrenia [0,1]	13
14. Family history of other psychiatric disorder [0,1]	14
15. Coarse brain disease prior to onset [0,1]	15
16. Definite psychosocial stressor prior to onset [0,1]	16

SUBSTANCE ABUSE OR DEPENDENCE:	
78: Lifetime diagnosis of alcohol abuse/dependence [0,1]	78
79. Lifetime diagnosis of cannabis abuse/dependence [0,1]	79
80. Lifetime diagnosis of other abuse/dependence [0,1]	80
81. Alcohol abuse/dependence with psychopathology [0,1]	81
82. Cannabis abuse with psychopathology [0,1]	82
83. Other abuse/dependence with psychopathology [0,1]	83

GENERAL APPRAISAL:	
84. Information not credible [0,1]	84
85. Lack of insight [0,1]	85
86. Rapport difficult [0,1]	86
87. Impairment/incapacity during disorder [0-3]	87
88. Deterioration from premorbid level of functioning [0,1]	88
89. Psychotic symptoms respond to neuroleptics [0,1]	89
90. Course of disorder [1-5] rate to one decimal place if necessary	90

EXTRA ITEMS – COURSE OF DISORDER AND MODE OF ONSET:	
91.* Acute episode onset [0-4]	91
92.* Characteristic pattern to course of illness	92
93.* Mode of onset – first M [1-5] rate to one decimal place if necessary	93
94.* Mode of onset – first D [1-5] rate to one decimal place if necessary	94
95.* Mode of onset – first P [1-5] rate to one decimal place if necessary	95
96.* Mode of onset – typical M [1-5] rate to one decimal place if necessary	96
97.* Mode of onset – typical D [1-5] rate to one decimal place if necessary	97
98.* Mode of onset – typical P [1-5] rate to one decimal place if necessary	98

Appendix J

Rating guidelines used to rate items of psychopathology in the large harmonised dataset, the VCFS sample and the sample enriched for schizoaffective disorder

Section 2 Features (LE)

0 Not present
1 Present
9 Unsure/unknown

Mood Congruence (LE)

0 No Section 2 features
1 Virtually all content congruent with affective state
2 More congruent than not
3 Congruent and incongruent equally
4 More incongruent than congruent
5 Virtually all content incongruent
9 Unsure/unknown

Near Section 2 Features

Lifetime ever presence of near psychotic features. Refers to schizotypal features, e.g., second sight, feeling presences or some symptoms that come close to being psychotic but do not meet the threshold for clinical significance:

0 Not present
1 Present
2 Not applicable (as psychotic features present)
9 Unknown

(NB: A rating of '1' here can be used to highlight experiences which are unusual but not definitely schizotypal or psychotic - this may be due to lack of information. Such experiences should be rated as 'uncertain (1)' on the P dimension of BADDS).

Pred Manic Affect (LE)

1 Elation
2 Irritability
8 Not applicable
9 Unknown

(NB: The default rating for this item should be 'elation'. Requires clear evidence of irritability to rate '2')

Dysphoric Mania (LE)

0 No
1 Yes (*NB: Rating of 1 should be used for patients who have experienced at least one episode of mania in which the predominant mood state was dysphoria - ie. an unpleasant state characterized by unease or mental discomfort (including low mood).*
8 Not applicable
9 Unsure

Number of episodes:

NB: For the following items, please remember to enter 0 if there have been no such episodes. If you are unsure please enter 999.

Mania Number of episodes of mania **
Depression Number of episodes of depression **
Other psychotic Number of episodes of non-affective psychotic illness **

*(** NB: add .1 for +, e.g., 6+ = 6.1)*

Longest Duration: *For the following items, please enter 999 if you are unsure of duration.*

Mania	Longest episode of mania or hypomania in weeks **
Depression	Longest episode of depression in weeks **
Oth psychot	Longest episode of non-affective psychosis in weeks **

*(** NB: use first decimal place for days, e.g.,0.3 = 3 days; and use second decimal place for hours, e.g., 0.03 = 3 hours – if >9hours round up to one day)*

Age at onset: *NB: Where only an age range is known for illness onset put the lowest in the range as first symptom, and the highest in the range as first impairment.*
NB: for the following items, please enter 999 if you are unsure.
NB: use judgement when rating age at onset of schizoaffective cases. We are trying to rate the age at onset of the illness that we are interested in.

Symptom	age (years) of first symptom of affective illness. *NB: a) do not rate anxiety symptoms, unless there is evidence of accompanying mood disturbance. b) if age at first symptom is unknown, but known to be younger than first impairment – then leave age at first symptom blank.*
Impairment	age (years) of first impairment due to affective illness. *NB: symptoms occurring within the context of a mood episode that produce clinically significant impairment. First episode of hypomania should be included here.*
Contact	age (years) of first contact with psychiatric services for affective disturbance. *NB: contact must be with secondary specialist mental health services.*
Admission	age (years) of first admission to psychiatric hospital (include admission to a day hospital or intensive home treatment)

Number of admissions Number of psychiatric admissions (incl. Day Hospital & intensive home treatment)
NB: admissions are counted separately even if only 1 day between them.
NB: remember to enter 0 if there have been no admissions. Enter 999 if you are unsure.

Length of longest admission Duration in weeks of longest in-patient admission.

Proportion of time at first admitted Enter as percentage of duration of illness (i.e., from age impairment to current age). (incl. Day Hospital & intensive home treatment)
NB: remember to enter 0 if there have been no admissions. Enter 999 if you are unsure.

Approx. time well Since onset (objective) Enter percentage.
Enter 999 if unsure.

Puerperal Episode

0	No occurrence despite having had at least one child (include "blues" here)

1 Mania within 6 weeks of delivery *(include mania which begins exactly 6 weeks after delivery). Include hypomania here.*

2 Depression, but not mania within 6 weeks of delivery *(include depression which begins exactly 6 weeks after delivery)*

3 Onset of affective disturbance during pregnancy *(NB: onset of an episode is taken from the first impairment)*

4 Psychiatric disorder with onset within 6 weeks of delivery (*include clear psychiatric disturbance which does not meet full criteria for an episode)*

5 Mania within 3 months of delivery

6 Psychotic illness soon after delivery

7 Depression following childbirth (usually within 6 months, but rate unspecified PND here).

8 Never given birth. Rate all males here.

9 Unknown/unclear

NB: The cut-off for classing an episode as post-natal is 6 months after delivery.

NB: In the case of a woman who has an episode of mania/ hypomania following delivery and then an episode of depression – rate the manic/hypomanic episode as post-natal and the depression as non-postnatal even if the depression is within 6 months of delivery.

NB: The onset of a puerperal episode is taken as the time of 'change' from the prior mental state, this can be the onset of symptoms or the onset of impairment.

NB: Mania that begins >3 months and up to 6 months after delivery should be rated here as '9'. Please make a note in the comments box.

Rapid Cycling

0 Rapid cycling is not present or suspected *despite a period of observation of illness that includes at least 7 years from onset and at least 3 episodes of mood disorder*

1 Occurrence during illness of 4 or more episodes (mania or depression) in a 12 month period

2 Rapid cycling predominates course of illness and has been present for at least 5 years during the total course of the illness

9 Insufficient info to make a rating of 0, 1 or 2. This rating is used if there has been no rapid cycling but there has been less than 7 years from the onset of illness and/or fewer than 3 episodes of mood disorder

NB: Rapid cycling can be rated as present if mood episodes do not include mania.

Suicidal Ideation (LE) Rate most severe lifetime-ever:

0 Absent

1 Tedium vitae

2 Suicidal ideation

3 Suicide attempt unlikely to result in death

4 Suicide attempt likely to result in death

5 Multiple suicide attempts likely to result in death

9 Unknown

NB: Suicidal ideation/attempt does NOT have to be in the context of depression to be rated here.

Mood switch: (euthymia then) depression to mania

0 - Not known to occur despite good clinical information.
1 - Has occurred on at least one occasion.
2 - Has occurred commonly (i.e., in at least 50% of episodes of illness).
9 - Unknown or insufficient clinical information to make decision.
NB: this item does not rate any switches or cycling after the initial switch in a phase of illness.
NB: do include switches seemingly due to medication.
NB: a switch is defined as two periods of abnormal mood (one fulfilling criteria for (hypo)mania and one fulfilling criteria for major depression) with an intervening period of no more than one month.

Mood switch: (euthymia then) mania to depression

0 - Not known to occur despite good clinical information.
1 - Has occurred on at least one occasion.
2 - Has occurred commonly (i.e., in at least 50% of episodes of illness).
9 - Unknown or insufficient clinical information to make decision.
NB: this item does not rate any switches or cycling after the initial switch in a phase of illness.
NB: do include switches seemingly due to medication.
NB: a switch is defined as two periods of abnormal mood (one fulfilling criteria for (hypo)mania and one fulfilling criteria for major depression) with an

Lithium Response

0 No evidence of response
1 Subjective good response
2 Objective evidence for beneficial response, ie, clear reduction in number and/or severity of episodes following introduction of lithium prophylaxis. (Can only be rated if at least 3 episodes of illness have occurred before lithium prophylaxis and lithium response has been observed for at least 3 years)
3 Objective evidence for excellent response to lithium prophylaxis, ie, frequency of episodes reduced to <10% of frequency after lithium prophylaxis and/or 2 or more episodes of illness occurring within weeks of cessation of lithium. (Can only be rated if at least 3 episodes of illness have occurred before lithium prophylaxis and lithium response has been observed for at least 5 years)

8 Unsure of response
9 Never taken

NB: Rate 'unsure of response' for patients who have been on Lithium, but had it stopped after a brief period due to side effects.

Anti-Depressant Response (incl. ECT)

0 No evidence of response
1 Subjective good response
2 Objective evidence for beneficial response, ie, clear reduction in number or severity of symptoms, but not 3.
3 Objective evidence for excellent response, ie, always return to usual self and usual level of function following anti-depressant treatment.
8 Unsure of response
9 Never taken

NB: Rate patients who go high after anti-D treatment as '3 – excellent response' and rate the next item.

Switch of Polarity Following Anti-Depressants

0 None
1 Some manic features
2 Hypomanic Episode
3 Manic Episode
4 Unsure (despite taking anti-depressants)
8 Not applicable

NB: The switch must occur within 6 months of commencing anti-D treatment.

Appendix K

Inter-rater reliability for the Mood Disorders Research Team

Results provided by Dr Lisa Jones

1. Operational Criteria Symptom Checklist (OPCRIT)

SUMMARY

BP Field Team

Variable Numbers correspond to OPCRIT item number, see Appendix E	**Mean Kappa (Range)** **[95% CI]**
1 Dysphoria **WE**	0.84 (0.70-1.00) [0.64-1.00]
1 Dysphoria **LE**	0.94 (0.77-1.00) [0.76-1.00]
2 Loss Pleas **WE**	0.92 (0.88-1.00) [0.82-1.00]
2 Loss Pleas **LE**	0.98 (0.90-1.00) [0.90-1.00]
3 DVM **WE**	0.97 (0.86-1.00) [0.85-1.00]
3 DVM **LE**	0.91 (0.80-1.00) [0.74-1.00]
4 Suicidal **WE**	1.00 (1.00-1.00) [1.00-1.00]
4 Suicidal **LE**	0.98 (0.90-1.00) [0.90-1.00]
5 Self Reproach **WE**	0.92 (0.69-1.00) [0.68-1.00]
5 Self Reproach **LE**	0.92 (0.69-1.00) [0.68-1.00]
6 Poor Conc **WE**	0.88 (0.75-1.00) [0.75-1.00]
6 Poor Conc **LE**	0.94 (0.74-1.00) [0.73-1.00]
7 Slowed **WE**	0.91 (0.70-1.00) [0.68-1.00]
7 Slowed **LE**	0.95 (0.80-1.00) [0.79-1.00]
8 Loss Ener **WE**	1.00 (1.00-1.00) [1.00-1.00]
8 Loss Ener **LE**	0.97 (0.86-1.00) [0.85-1.00]
9 Poor App **WE**	0.98 (0.91-1.00) [0.91-1.00]
9 Poor App **LE**	0.90 (0.83-1.00) [0.79-1.00]

10 Loss Weig WE	0.94 (0.74-1.00) [0.73-1.00]
10 Loss Weig LE	0.93 (0.79-1.00) [0.77-1.00]
11 Inc App WE	1.00 (1.00-1.00) [1.00-1.00]
11 Inc App LE	0.93 (0.84-1.00) [0.79-1.00]
12 Inc Weig WE	1.00 (1.00-1.00) [1.00-1.00]
12 Inc Weig LE	1.00 (1.00-1.00) [1.00-1.00]
13 Init Insom WE	0.93 (0.80-1.00) [0.78-1.00]
13 Init Insom LE	0.86 (0.68-1.00) [0.65-1.00]
14 Mid Ins WE	0.96 (0.85-1.00) [0.84-1.00]
14 Mid Ins LE	0.85 (0.70-0.92) [0.69-1.00]
15 EMW WE	0.92 (0.89-0.93) [0.89-0.94]
15 EMW LE	0.90 (0.86-0.92) [0.86-0.95]
16 XS Sleep WE	0.97 (0.89-1.00) [0.89-1.00]
16 XS Sleep LE	0.87 (0.69-1.00) [0.66-1.00]
17 Dec Libido WE	0.92 (0.87-1.00) [0.83-1.00]
17 Dec Libido LE	0.90 (0.78-1.00) [0.75-1.00]
18 Agitation WE	0.96 (0.91-1.00) [0.88-1.00]
18 Agitation LE	0.93 (0.89-1.00) [0.85-1.00]
19 Elevation WE	0.80 (0.56-1.00) [0.50-1.00]
19 Elevation LE	0.86 (0.45-1.00) [0.42-1.00]
20 Irritable WE	0.87 (0.69-1.00) [0.66-1.00]
20 Irritable LE	0.97 (0.88-1.00) [0.87-1.00]
21 FOI WE	0.93 (0.85-1.00) [0.79-1.00]
21 FOI LE	0.94 (0.77-1.00) [0.76-1.00]
22 POS WE	0.86 (0.45-1.00) [0.42-1.00]
22 POS LE	1.00 (1.00-1.00) [1.00-1.00]
23 Distract WE	1.00 (1.00-1.00) [1.00-1.00]
23 Distract LE	1.00 (1.00-1.00) [1.00-1.00]
24 XS Activ WE	0.91 (0.64-1.00) [0.62-1.00]
24 XS Activ	0.82 (0.64-1.00)

LE	[0.49-1.00]
25 Inc SE **WE**	0.87 (0.49-1.00) [0.47-1.00]
25 Inc SE **LE**	0.84 (0.49-1.00) [0.45-1.00]
26 Reckless **WE**	0.78 (0.71-0.82) [0.70-0.85]
26 Reckless **LE**	0.81 (0.73-0.89) [0.70-0.91]
27 Red Sleep **WE**	0.74 (0.32-1.00) [0.22-1.00]
27 Red Sleep **LE**	1.00 (1.00-1.00) [1.00-1.00]
28 Inc Soc **WE**	0.73 (0.47-1.00) [0.39-1.00]
28 Inc Soc **LE**	0.64 (0.35-1.00) [0.21-1.00]
29 AH3 **LE**	0.82 (0.47-1.00) [0.44-1.00]
30 AH Commenting **LE**	1.00 (1.00-1.00) [1.00-1.00]
31 AH Abusive **LE**	1.00 (1.00-1.00) [1.00-1.00]
32 Other AH **LE**	0.77 (0.48-1.00) [0.42-1.00]
33 VH **LE**	0.59 (0.08-1.00) [0.00-1.00]
34 Other H **LE**	1.00 (1.00-1.00) [1.00-1.00]
35 Th Echo **LE**	1.00 (1.00-1.00) [1.00-1.00]
36 TH Insert **LE**	1.00 (1.00-1.00) [1.00-1.00]
37 Th Broad **LE**	1.00 (1.00-1.00) [1.00-1.00]
38 Th Withd **LE**	1.00 (1.00-1.00) [1.00-1.00]
39 Del Passivity **LE**	1.00 (1.00-1.00) [1.00-1.00]
40 Del Influence **LE**	0.95 (0.90-1.00) [0.86-1.00]
41 Primary Del Perception **LE**	1.00 (1.00-1.00) [1.00-1.00]
42 Pers Del **LE**	0.82 (0.68-1.00) [0.60-1.00]
43 Biz Del **LE**	0.98 (0.90-1.00) [0.90-1.00]
44 Oth Pri Dels **LE**	1.00 (1.00-1.00) [1.00-1.00]
45 Biz Beh **LE**	1.00 (1.00-1.00) [1.00-1.00]
46 Catatonia **LE**	0.91 (0.64-1.00) [0.62-1.00]
47 Speech Diff to Understand **LE**	0.97 (0.86-1.00) [0.85-1.00]
48 Incoherent **LE**	1.00 (1.00-1.00) [1.00-1.00]
49 PFTD **LE**	1.00 (1.00-1.00) [1.00-1.00]

50 NFTD **LE**	1.00 (1.00-1.00) [1.00-1.00]
51 Restrict Affect **LE**	1.00 (1.00-1.00) [1.00-1.00]
52 Blunted Aff **LE**	1.00 (1.00-1.00) [1.00-1.00]
53 Inapp Aff **LE**	1.00 (1.00-1.00) [1.00-1.00]
54 Perplexity **LE**	1.00 (1.00-1.00) [1.00-1.00]
55 Grand Del **WE**	0.83 (0.62-1.00) [0.57-1.00]
55 Grand Del **LE**	0.87 (0.78-1.00) [0.71-1.00]
56 Del Guilt **WE**	0.80 (0.49-1.00) [0.45-1.00]
56 Del Guilt **LE**	0.91 (0.62-1.00) [0.60-1.00]
57 Del Pov **WE**	1.00 (1.00-1.00) [1.00-1.00]
57 Del Pov **LE**	1.00 (1.00-1.00) [1.00-1.00]
58 Nihil Del **WE**	0.97 (0.86-1.00) [0.85-1.00]
58 Nihil Del **LE**	0.97 (0.86-1.00) [0.85-1.00]
59 MC AH3 **WE**	1.00 (1.00-1.00) [1.00-1.00]
59 MC AH3 **LE**	0.61 (0.37-1.00) [0.16-1.00]
60 MC AH2 **WE**	0.88 (0.72-1.00) [0.64-1.00]
60 MC AH2 **LE**	0.80 (0.61-1.00) [0.52-1.00]
61 MC VH **WE**	0.86 (0.45-1.00 [0.42-1.00]
61 MC VH **LE**	0.86 (0.45-1.00) [0.42-1.00]
62 MC Oth H **WE**	1.00 (1.00-1.00) [1.00-1.00]
62 MC Oth H **LE**	1.00 (1.00-1.00) [1.00-1.00]
63 Oth Sec D **WE**	0.87 (0.49-1.00) [0.47-1.00]
63 Oth Sec D **LE**	0.91 (0.74-1.00) [0.71-1.00]

Inter-Rater Reliability of Key Phenotypic Variables (20 cases v consensus)

SUMMARY

Variable	**Mean Kappa (Range) [95% CI]**
Puerperal Episode	0.97 (0.90-1.00) [0.91-1.00]
Section 2 Symptoms	0.97 (0.86-1.00) [0.89-1.00]
Suicidality	0.94 (0.81-1.00) [0.84-1.00]
ICD10 Diagnosis	0.94 (0.81-1.00) [0.82-1.00]
Co-occurrence (aff & psych) – Item 1	0.90 (0.85-0.92) [0.80-1.00]
Menstrual	0.90 (0.82-0.93) [0.84-0.96]
Co-occurrence (aff & psych) – Item 3	0.88 (0.63-1.00) [0.35-1.00]
Dysphoric Mania	0.87 (0.45-1.00) [0.58-1.00]
RDC Diagnosis	0.86 (0.74-0.91) [0.77-0.95]
Near Section 2 Symptoms	0.85 (0.75-0.90) [0.78-0.93]
Predominant Mania	0.84 (0.74-1.00) [0.70-0.97]
DSMIV Diagnosis	0.84 (0.66-1.00) [0.69-0.99]
Rapid Cycling	0.81 (0.71-1.00) [0.66-0.95]
Switch of Polarity following Anti-Ds	0.78 (0.71-0.84) [0.62-0.95]
Lithium Response	0.76 (0.65-0.87) [0.65-0.87]
Anti-D Response	0.76 (0.57-0.94) [0.56-0.96]
Congruence	0.76 (0.49-0.94) [0.52-1.00]
Co-occurrence (aff & psych) – Item 2	0.67 (0.33-0.88) [0.01-1.00]
	Mean ICC (Range) [95% CI]
Age of 1st Psychosis	1.00 (1.00-1.00) [1.00-1.00]
Age of 1st Symptom	0.99 (0.98-1.00) [0.98-1.00]
BADS – D	0.99 (0.98-0.99) [0.98-0.99]
Age of 1st Mania	0.98 (0.95-1.00) [0.96-1.00]
No. Episodes of Mania	0.98 (0.93-0.99) [0.94-1.00]
Length Longest Episode of Depression	0.98 (0.92-0.99) [0.94-1.00]
Number of Admissions	0.97 (0.94-1.00) [0.90-1.00]
Age of 1st Impairment	0.97 (0.92-0.99) [0.93-1.00]
BADS – M	0.96 (0.91-0.99) [0.90-1.00]
Length Longest Episode of Mania	0.96 (0.91-0.99) [0.92-1.00]
Age of 1st Contact	0.96 (0.87-0.99) [0.90-1.00]
GAS – Worst Mania	0.94 (0.87-0.98) [0.89-0.99]
Age of 1st Depression	0.93 (0.86-0.99) [0.85-1.00]
Number of Episodes of Depression	0.93 (0.83-0.99) [0.85-1.00]
Age of 1st Admission	0.93 (0.70-1.00) [0.77-1.00]
GAS – Worst Depression	0.92 (0.84-0.98) [0.84-1.00]
BADS – P	0.91 (0.77-0.99) [0.80-1.00]
BADS – I	0.89 (0.78-0.99) [0.77-1.00]
GAS – Past Week	0.87 (0.57-0.98) [0.66-1.00]

Appendix L

Summarised examples of cases that would score "0", "1" and "2" on the modified OPCRIT item 84: Information not credible

OPCRIT 84: Scored 2
There is not enough detail to make many positive ratings. The participant also had problems with her memory. No case-note information was present despite admissions to psychiatric hospital having occurred.

Summarised information from the participant's interview-vignette. Case-notes were not available.

Mrs B was a 62 year old lady with a long history of mental health problems. She was unclear about many of the details of her illness as she describes problems with her memory. Mrs B presented as a pleasant but anxious lady.

Her first admission to psychiatric hospital was in her early 20s. She doesn't remember why but she describes feeling very scared at the time.

She describes having experienced a "nervous breakdown" after the birth of her daughter. Her husband, who was present during the interview, describes this as a very difficult time during which she took to her bed for several weeks. She was eventually admitted to hospital for a period of 2-3 months.

She believes she has experienced episodes of depression in the past, although it was not possible to elucidate any specific symptoms during the interview.

She does not believe she has ever had a manic episode.

She did not recall any psychotic symptoms, although her husband believes that she was deluded during her first admission to hospital.

It was not possible to obtain any further detail on specific episodes of illness so the interview prematurely.

OPCRIT 84: Scored 1
This was rated "1" because: there is no information available on the participant's hospital admission in 1978; further clarification/description of some of the symptoms referred to would be needed in order to make positive ratings, e.g. "thoughts being distorted"; examples would be needed to rate the symptoms of thought interference mentioned.

Summarised information from case-notes available and interview-vignette

He was first seen in 1974 when he presented with symptoms of depression and was hearing voices telling him to do things. These voices had been present over the previous 10 years. He associated his unhappiness with the shape of his nose, saying that, "everyone takes the mickey out of it". He also had middle insomnia.

His first admission was in 1978 – no information is available for this admission.

In 1978 he believed he was grasped by evil forces and that he had demons in his head. He also felt that his mind was being controlled by evil forces. He was apprehensive and agitated.

1979 – "Depression"

March 1993 – Worst episode.
He said he felt "aggravation in the brain". He complained of inefficient thinking which he put down to his "thoughts being distorted". He had poor concentration, low mood and a loss of enjoyment. He made several suicide attempts. He had social withdrawal, self-depreciation and irritability. He gave descriptions of thought insertion, thought broadcast and had delusions that his thoughts were being read. He also had delusions of religion and felt that alien forces were penetrating his body.

Month prior to interview: Depressive symptoms reduced, moderately depressed with moderate loss of interests, moderate feelings of hopelessness and some irritability. He complained that, "the devil has got hold of my brain and is persecuting it". He felt electric shocks in his feet and voices in his head. He feels like he deserves to be punished.

OPCRIT 84: Scored 0
A detailed account of illness was present in the interview-vignette which was corroborated by the case-note information obtained.

NAME: L
SEX: Male
HOSPITAL NUMBER:
INTERVIEW DATE: 29.7.97

INFORMATION FROM CASENOTES

30.12.61 – 17.1.62
Admitted depressed, onset October, anergia, poor concentration, feelings of hopelessness, apathetic and retarded, diagnosed endogenous depression treated with IM tryptizol.

27.2.62
Seen on DV, hysterical fugue, left house earlier in the day and was later found under a hedge, says he woke up and it was night with no recollection of what had happened.

20.2.64
Admitted depressed, treated with ECT. He was dysphoric with DMV, EMW, loss of appetite and thoughts of committing suicide by driving into the sea.

5.12.66 – 24.1.67
Admitted depressed, took OD of barbiturates when on leave, treated with ECT.

23.2.68
"having a bad run of luck on the farm. I felt that I could have done better for him had I been a veterinary surgeon rather than a medical practitioner".

30.68- 11.1.69
admitted depressed

15.12.70 – 8.1.71
Admitted depressed
14.1.71 – 25.2.71
Admitted depressed

6.12.74 – 9.1.75
Admitted depressed given ECT – noted that pronounced seasonal pattern and unresponsive to tricyclics and MAOI's.

19.1.76 – 27.2.76
Admitted depressed.

Nov 1977
Seen Op with recurrence of depressive symptoms

1978
Started on prophylactic antidepressants in September to avoid winter relapse.

26.4.79 – 23.11.79
Admitted depressed, suicidal – left home with a rope to hang himself, DVM am, anergia, EMW, wt loss, treated with ECT.

2.4.80 – 25.4.80
Admitted depressed.

4.4.81 – 12.4.81
Admitted following OD, diagnosis personality disorder.

17.7.81 – 25.7.81
Admitted following possible OD, no evidence of depressive symptoms while on the ward, diagnosis attention seeking behaviour.

5.6.90
OP, symptoms described "that sound very much like hypomania", wakes early at 5 am, feels full of energy and enthusiasm, "when I'm up no one can stop me", cheerful and enthusiastic, Description from wife – high, 110%, hyperactive, sleeping only four hours, often happens when recovering from a depressive episode, hard to keep up with him, finds this state much better than his depression.
Hypomania – but not sufficiently high to warrant treatment with major tranquillisers.

1.7.91
OP, Hypomanic but not sectionable, elated, only sleeping three hours, possibly overspending.

8.8.91
Diagnosis – difficult personality on which is superimposed mood swings – depression in winter months and hypomania in the summer. Heavy alcohol intake noted.

16.4.93
GP letter – depression for many years, " I have also seen him euphoric and indeed in a high phase a few years ago he bought an additional farm at an inflated expense which has caused him a considerable debt burden"

20.4.93 – 8.10.93
Admitted, diagnosis – bipolar disorder – depressed phase.

1.11.94
OP, verbally aggressive to his wife, working too many hours a day, wife feels he is manic again, talkative at interview, lots of expansive plans, talking about spending money he has got, has been swindled out of £100,000, he is definitely euphoric but there is not enough evidence to call him manic, prescribed melleril.

INTERVIEW VIGNETTE

INTRODUCTION
66 year old married farmer seen at home following contact made via GP. Information considered reliable.

MSE AT INTERVIEW
Well, euthymic, no evidence of abnormal beliefs or perceptions.

BACKGROUND
Left school at 11 and has worked on the family farm since then. Tendency to get down at times throughout his life. Good relationships with others. Drinks 30 - 40 units a week and smokes 20 a day, no drugs.

PSYCHIATRIC HISTORY

Episodes of illness

Over the last 30 years had had at least one episode of severe depression each year (30 - 50) which have occurred in the months of November to January. Has been admitted on most of these occasions. On 5 - 10 occasions has had highs lasting for up to six weeks - thinks he has only ever had highs when on antidepressant medication.

Manic episode rated: 3 years ago

Description of manic episode

Duration of 3-4 weeks, elated mood, racing thoughts, overtalkativeness, overactivity - was working 22 hours a day, sharpened thinking, witty, exaggerated self esteem, over optimism, excessive spending, did not sleep for days on end, got into fights in bars - would over react if someone nudged him, was arrested, wife finds it impossible to live with him when he's high. Seen by psychiatrist on DV who adjusted medication and started him on lithium "to get me back on an even keel".

Depressive episode rated:. 10 years ago

Description of depressive episode

Unremitting depressed mood, duration of 6 months, tearful much of the time, total anhedonia, loss of hope of the future - "no light in the tunnel at all", DVM am, preoccupied with death, suicidal - severe suicide attempt admitted to hospital, loss of confidence, social withdrawal, loss of self esteem, dulled perceptions, poor concentration, inefficient thinking, loos of interests, subjective and objective retardation, loss of energy, overwhelmed by everyday tasks, loss of appt, increased sleep - didn't want to get up but stayed in bed all day.

Section 2 symptoms

Nil

Appendix M

Inter-rater reliability. ER's rating vs. consensus ratings made during reliability meetings

Variable	ICC / Kappa used	ICC	p-value
BADDSM	ICC	0.888	p<0.001
BADDSD	ICC	0.979	p<0.001
BADDSP	ICC	0.983	p<0.001
BADDSI	ICC	0.994	p<0.001
GASD	ICC	0.904	p<0.001
GASM	ICC	0.967	p<0.001
GASP	ICC	0.966	p<0.001
GASWE	ICC	0.967	p<0.001
GASPW	ICC	0.986	p<0.001
S2	Kappa	1.000	p<0.001
MC	ICC	0.700	p<0.001
Pred M Effect	Kappa	1.000	0.002
Dysphoric Mania	Kappa	1.000	0.003
N Eps M	ICC	0.948	p<0.001
N Eps D	ICC	0.955	p<0.001
N Eps NAP	ICC	0.629	0.006
Longest M	ICC	0.517	0.035
Longest D	ICC	1.000	p<0.001
Longest P	ICC	na	na
AOO S	ICC	0.999	p<0.001
AOO I	ICC	0.998	p<0.001
AOO C	ICC	1.000	-
AOO A	ICC	1.000	-
AOO M	ICC	0.999	p<0.001
AOO D	ICC	0.971	p<0.001
AOO P	ICC	1.000	-
No adms	ICC	0.997	p<0.001
Longest adm	ICC	0.996	p<0.001
% adm	ICC	0.999	p<0.001
% well	ICC	0.960	p<0.001
Puerperal Ep	ICC	1.000	-
Rapid Cycling	ICC	1.000	-
Suicidal ideation	ICC	0.990	p<0.001
ERS1	ICC	0.961	p<0.001
ERS2	ICC	0.993	p<0.001
ERS3	ICC	1.000	p<0.001
ERS4	ICC	0.843	p<0.001
ERS5	ICC	0.864	p<0.001
ERS6	ICC	1.000	-
ERS7	ICC	0.786	0.002
ERS8	ICC	0.846	p<0.001
ERS9	ICC	0.784	p<0.001
ERS10	ICC	na	na
ERS11	ICC	0.957	p<0.001
Mood Switch	Kappa	1.000	p<0.001
OPCRIT_1	Kappa	1.000	p<0.001
OPCRIT_2	Kappa	0.841	p<0.001
OPCRIT_3	Kappa	1.000	p<0.001
OPCRIT_4	Kappa	1.000	p<0.001
OPCRIT_5	Kappa	0.903	p<0.001
OPCRIT_6	Kappa	1.000	p<0.001
OPCRIT_7	Kappa	1.000	p<0.001
OPCRIT_8	Kappa	0.915	p<0.001
OPCRIT_9	Kappa	1.000	p<0.001
OPCRIT_10	Kappa	1.000	p<0.001
OPCRIT_11	Kappa	1.000	p<0.001
OPCRIT_12	Kappa	1.000	p<0.001
OPCRIT_13	Kappa	1.000	p<0.001
OPCRIT_14	Kappa	1.000	p<0.001
OPCRIT_15	Kappa	1.000	p<0.001
OPCRIT_16	Kappa	1.000	p<0.001
OPCRIT_17	Kappa	1.000	p<0.001
OPCRIT_18	Kappa	1.000	p<0.001
OPCRIT_19	Kappa	1.000	p<0.001
OPCRIT_20	Kappa	1.000	p<0.001
OPCRIT_21	Kappa	1.000	p<0.001
OPCRIT_22	Kappa	1.000	p<0.001
OPCRIT_23	Kappa	1.000	p<0.001
OPCRIT_24	Kappa	1.000	p<0.001
OPCRIT_25	Kappa	1.000	p<0.001
OPCRIT_26	Kappa	1.000	p<0.001
OPCRIT_27	Kappa	1.000	p<0.001
OPCRIT_28	Kappa	0.791	p<0.001
OPCRIT_28a	Kappa	1.000	p<0.001
OPCRIT_29	Kappa	na	na
OPCRIT_30	Kappa	1.000	p<0.001
OPCRIT_31	Kappa	0.880	p<0.001
OPCRIT_32	Kappa	1.000	p<0.001
OPCRIT_33	Kappa	1.000	p<0.001
OPCRIT_34	Kappa	na	na
OPCRIT_35	Kappa	1.000	p<0.001
OPCRIT_36	Kappa	na	na
OPCRIT_37	Kappa	na	na
OPCRIT_38	Kappa	1.000	p<0.001
OPCRIT_39	Kappa	0.455	0.021
OPCRIT_40	Kappa	1.000	p<0.001
OPCRIT_41	Kappa	na	na
OPCRIT_42	Kappa	0.750	0.002
OPCRIT_43	Kappa	1.000	p<0.001
OPCRIT_44	Kappa	1.000	p<0.001
OPCRIT_45	Kappa	1.000	p<0.001
OPCRIT_46	Kappa	na	na
OPCRIT_47	Kappa	1.000	p<0.001
OPCRIT_48	Kappa	na	na
OPCRIT_49	Kappa	na	na
OPCRIT_50	Kappa	na	na
OPCRIT_51	Kappa	na	na

OPCRIT_52	Kappa	na	na
OPCRIT_53	Kappa	0.692	0.001
OPCRIT_54	Kappa	1.000	p<0.001
OPCRIT_54a	ICC	1.000	p<0.001
OPCRIT_55	Kappa	1.000	p<0.001
OPCRIT_56	Kappa	1.000	p<0.001
OPCRIT_57	Kappa	na	na
OPCRIT_58	Kappa	na	na
OPCRIT_59	Kappa	1.000	p<0.001
OPCRIT_60	Kappa	1.000	p<0.001
OPCRIT_61	Kappa	1.000	p<0.001
OPCRIT_62	Kappa	0.791	p<0.001
OPCRIT_63	Kappa	1.000	p<0.001
OPCRIT2_4	ICC	1.000	-
OPCRIT2_5	ICC	0.927	0.004
OPCRIT2_6	Kappa	1.000	p<0.001
OPCRIT2_7	Kappa	0.692	p<0.001
OPCRIT2_8	ICC	0.947	p<0.001

OPCRIT2_9	Kappa	0.649	0.004
OPCRIT2_10	Kappa	na	na
OPCRIT2_11	Kappa	na	na
OPCRIT2_16	Kappa	1.000	0.002
OPCRIT2_78	Kappa	1.000	p<0.001
OPCRIT2_79	Kappa	na	na
OPCRIT2_80	Kappa	na	na
OPCRIT2_81	Kappa	0.692	0.001
OPCRIT2_82	Kappa	na	na
OPCRIT2_83	Kappa	na	na
OPCRIT2_84	Kappa	1.000	p<0.001
OPCRIT2_85	Kappa	0.821	0.001
OPCRIT2_86	Kappa	1.000	p<0.001
OPCRIT2_87	Kappa	0.894	p<0.001
OPCRIT2_88	Kappa	1.000	p<0.001
OPCRIT2_89	Kappa	1.000	p<0.001
OPCRIT2_90	ICC	0.923	p<0.001

- 100% agreement, no p-value produced
  - na = no variability within sample

Appendix N

Inter-rater reliability. ER's rating vs. consensus ratings made during reliability meetings (N=20)

Variable	ICC / Kappa used	ICC	p-value
BADDSM	ICC	1.00	P<0.001
BADDSD	ICC	1.00	P<0.001
BADDSP	ICC	1.00	-
BADDSI	ICC	0.975	P<0.001
GASD	ICC	1.00	-
GASM	ICC	1.00	-
GASP	ICC	1.00	-
GASWE	ICC	1.00	-
GASPW	ICC	1.00	-
S2	Kappa	1.00	P<0.001
MC	Kappa	1.00	P<0.001
Pred M Effect	Kappa	1.00	P<0.001
Dysphoric Mania	Kappa	1.00	P<0.001
N Eps M	ICC	1.00	-
N Eps D	ICC	1.00	-
N Eps NAP	ICC	1.00	-
Longest M	ICC	1.00	-
Longest D	ICC	1.00	-
Longest P	ICC	1.00	-
AOO S	ICC	1.00	-
AOO I	ICC	1.00	-
AOO C	ICC	1.00	-
AOO A	ICC	1.00	-
AOO M	ICC	1.00	-
AOO D	ICC	1.00	-
AOO P	ICC	1.00	-
No adms	ICC	1.00	-
Longest adm	ICC	1.00	-
% adm	ICC	1.00	-
% well	ICC	1.00	-
Puerperal Ep	ICC	1.00	-
Rapid Cycling	ICC	1.00	-
Suicidal ideation	ICC	1.00	-
ERS1	ICC	1.00	-
ERS2	ICC	1.00	-
ERS3	ICC	0.990	P<0.001
ERS4	ICC	1.00	-
ERS5	ICC	1.00	-
ERS6	ICC	1.00	-
ERS7	ICC	1.00	-
ERS8	ICC	0.989	P<0.001
ERS9	ICC	1.00	-
ERS10	Kappa	1.00	P<0.001
ERS10L	Kappa	1.00	P<0.001
ERS11	Kappa	1.00	P<0.001
ERS11L	Kappa	1.00	P<0.001
Mood Switch	Kappa	1.00	P<0.001

OPCRIT_1	Kappa	1.00	P<0.001
OPCRIT_2	Kappa	0.911	P<0.001
OPCRIT_3	Kappa	1.00	P<0.001
OPCRIT_4	Kappa	1.00	P<0.001
OPCRIT_5	ICC	1.00	-
OPCRIT_6	Kappa	1.00	P<0.001
OPCRIT_7	Kappa	1.00	P<0.001
OPCRIT_8	Kappa	1.00	P<0.001
OPCRIT_9	Kappa	1.00	P<0.001
OPCRIT_10	Kappa	1.00	P<0.001
OPCRIT_11	Kappa	1.00	P<0.001
OPCRIT_12	Kappa	1.00	P<0.001
OPCRIT_13	Kappa	1.00	P<0.001
OPCRIT_14	Kappa	1.00	P<0.001
OPCRIT_15	Kappa	1.00	P<0.001
OPCRIT_16	Kappa	1.00	P<0.001
OPCRIT_17	Kappa	1.00	P<0.001
OPCRIT_18	Kappa	1.00	P<0.001
OPCRIT_19	Kappa	1.00	P<0.001
OPCRIT_20	Kappa	1.00	P<0.001
OPCRIT_21	Kappa	1.00	P<0.001
OPCRIT_22	Kappa	1.00	P<0.001
OPCRIT_23	Kappa	1.00	P<0.001
OPCRIT_24	Kappa	1.00	P<0.001
OPCRIT_25	Kappa	1.00	P<0.001
OPCRIT_26	Kappa	1.00	P<0.001
OPCRIT_27	Kappa	1.00	P<0.001
OPCRIT_28	Kappa	1.00	P<0.001
OPCRIT_28a	Kappa	1.00	P<0.001
OPCRIT_29	Kappa	1.00	P<0.001
OPCRIT_30	Kappa	1.00	P<0.001
OPCRIT_31	Kappa	1.00	P<0.001
OPCRIT_32	Kappa	1.00	P<0.001
OPCRIT_33	Kappa	1.00	P<0.001
OPCRIT_34	Kappa	1.00	P<0.001
OPCRIT_35	Kappa	1.00	P<0.001
OPCRIT_36	Kappa	na	na
OPCRIT_37	Kappa	1.00	P<0.001
OPCRIT_38	Kappa	1.00	P<0.001
OPCRIT_39	Kappa	1.00	P<0.001
OPCRIT_40	Kappa	1.00	P<0.001
OPCRIT_41	Kappa	1.00	P<0.001
OPCRIT_42	Kappa	0.906	P<0.001
OPCRIT_43	Kappa	1.00	P<0.001
OPCRIT_44	Kappa	1.00	P<0.001
OPCRIT_45	Kappa	1.00	P<0.001
OPCRIT_46	Kappa	1.00	P<0.001
OPCRIT_47	Kappa	1.00	P<0.001
OPCRIT_48	Kappa	1.00	P<0.001
OPCRIT_49	Kappa	1.00	P<0.001
OPCRIT_50	Kappa	0.902	P<0.001

OPCRIT_51	Kappa	1.00	P<0.001
OPCRIT_52	Kappa	na	na
OPCRIT_53	Kappa	1.00	P<0.001
OPCRIT_54	Kappa	1.00	P<0.001
OPCRIT_54a	Kappa	1.00	P<0.001
OPCRIT_55	Kappa	1.00	P<0.001
OPCRIT_56	Kappa	1.00	P<0.001
OPCRIT_57	Kappa	1.00	P<0.001
OPCRIT_58	Kappa	1.00	P<0.001
OPCRIT_59	Kappa	na	na
OPCRIT_60	Kappa	1.00	P<0.001
OPCRIT_61	Kappa	1.00	P<0.001
OPCRIT_62	Kappa	1.00	P<0.001
OPCRIT_63	Kappa	1.00	P<0.001
OPCRIT2_1	Kappa	1.00	P<0.001
OPCRIT2_2	Kappa	1.00	P<0.001
OPCRIT2_3	Kappa	1.00	P<0.001
OPCRIT2_4	ICC	1.00	-
OPCRIT2_5	Kappa	1.00	P<0.001
OPCRIT2_6	Kappa	1.00	P<0.001
OPCRIT2_7	Kappa	1.00	P<0.001
OPCRIT2_8	ICC	1.00	-

OPCRIT2_9	Kappa	1.00	P<0.001
OPCRIT2_10	Kappa	1.00	P<0.001
OPCRIT2_11	Kappa	1.00	P<0.001
OPCRIT2_12	Kappa	1.00	P<0.001
OPCRIT2_13	Kappa	1.00	P<0.001
OPCRIT2_14	Kappa	1.00	P<0.001
OPCRIT2_15	Kappa	1.00	P<0.001
OPCRIT2_16	Kappa	1.00	P<0.001
OPCRIT2_78	Kappa	1.00	P<0.001
OPCRIT2_79	Kappa	1.00	P<0.001
OPCRIT2_80	Kappa	1.00	P<0.001
OPCRIT2_81	Kappa	1.00	P<0.001
OPCRIT2_82	Kappa	1.00	P<0.001
OPCRIT2_83	Kappa	1.00	P<0.001
OPCRIT2_84	Kappa	1.00	P<0.001
OPCRIT2_85	Kappa	1.00	P<0.001
OPCRIT2_86	Kappa	1.00	P<0.001
OPCRIT2_87	Kappa	1.00	P<0.001
OPCRIT2_88	Kappa	1.00	P<0.001
OPCRIT2_89	Kappa	1.00	P<0.001
OPCRIT2_90	ICC	0.975	P<0.001

- "-" = 100% agreement, no p-value produced
- "na" = insufficient variability for analyses to be performed correctly

Appendix O

Rater-drift reliability analyses performed on the same cases rated at different time-points (N=20)

Variable	ICC / Kappa used	ICC	p-value
BADDSM	ICC	0.983	P<0.001
BADDSD	ICC	0.970	P<0.001
BADDSP	ICC	0.974	P<0.001
BADDSI	ICC	0.975	P<0.001
GASD	ICC	0.921	P<0.001
GASM	ICC	0.827	P<0.001
GASP	ICC	0.870	P<0.001
GASWE	ICC	0.903	P<0.001
GASPW	ICC	0.912	P<0.001
S2	Kappa	1.00	P<0.001
MC	Kappa	0.853	P<0.001
Pred M Effect	Kappa	1.00	P<0.001
Dysphoric Mania	Kappa	1.00	P<0.001
N Eps M	ICC	0.990	P<0.001
N Eps D	ICC	0.904	P<0.001
N Eps NAP	ICC	0.981	P<0.001
Longest M	ICC	0.843	P<0.001
Longest D	ICC	0.734	P<0.001
Longest P	ICC	0.999	P<0.001
AOO S	ICC	1.00	P<0.001
AOO I	ICC	0.998	P<0.001
AOO C	ICC	0.995	P<0.001
AOO A	ICC	0.999	P<0.001
AOO M	ICC	0.997	P<0.001
AOO D	ICC	0.931	P<0.001
AOO P	ICC	0.995	P<0.001
No adms	ICC	0.992	P<0.001
Longest adm	ICC	0.992	P<0.001
% adm	ICC	0.827	P<0.001
% well	ICC	0.995	P<0.001
Puerperal Ep	ICC	1.00	P<0.001
Rapid Cycling	ICC	1.00	P<0.001
Suicidal ideation	ICC	0.838	P<0.001
ERS1	ICC	0.962	P<0.001
ERS2	ICC	0.978	P<0.001
ERS3	ICC	na	na
ERS4	ICC	1.00	P<0.001
ERS5	ICC	0.983	P<0.001
ERS6	ICC	na	Na
ERS7	ICC	0.787	P<0.001
ERS8	ICC	0.981	P<0.001
ERS9	ICC	0.936	P<0.001
ERS10	Kappa	1.00	P<0.001
ERS10L	Kappa	1.00	P<0.001
ERS11	Kappa	1.00	P<0.001
ERS11L	Kappa	1.00	P<0.001
Mood Switch	Kappa	0.821	0.001
OPCRIT_1	Kappa	0.821	0.001
OPCRIT_2	Kappa	0.866	P<0.001
OPCRIT_3	Kappa	1.00	P<0.001
OPCRIT_4	Kappa	1.00	P<0.001
OPCRIT_5	ICC	1.00	P<0.001
OPCRIT_6	Kappa	1.00	P<0.001
OPCRIT_7	Kappa	1.00	P<0.001
OPCRIT_8	Kappa	1.00	P<0.001
OPCRIT_9	Kappa	0.785	P<0.001
OPCRIT_10	Kappa	na	Na
OPCRIT_11	Kappa	1.00	P<0.001
OPCRIT_12	Kappa	1.00	P<0.001
OPCRIT_15	Kappa	0.779	P<0.001
OPCRIT_16	Kappa	na	na
OPCRIT_17	Kappa	1.00	P<0.001
OPCRIT_18	Kappa	1.00	P<0.001
OPCRIT_19	Kappa	0.767	0.001
OPCRIT_20	Kappa	1.00	P<0.001
OPCRIT_21	Kappa	1.00	P<0.001
OPCRIT_22	Kappa	1.00	P<0.001
OPCRIT_23	Kappa	1.00	P<0.001
OPCRIT_24	Kappa	0.976	P<0.001
OPCRIT_25	Kappa	0.767	P<0.001
OPCRIT_26	Kappa	0.823	P<0.001
OPCRIT_27	Kappa	1.00	P<0.001
OPCRIT_28	Kappa	1.00	P<0.001
OPCRIT_28a	Kappa	na	Na
OPCRIT_29	Kappa	1.00	P<0.001
OPCRIT_30	Kappa	1.00	P<0.001
OPCRIT_31	Kappa	na	Na
OPCRIT_32	Kappa	0.807	P<0.001
OPCRIT_33	Kappa	1.00	P<0.001
OPCRIT_34	Kappa	1.00	P<0.001
OPCRIT_35	Kappa	Na	Na
OPCRIT_36	Kappa	Na	Na
OPCRIT_37	Kappa	na	Na
OPCRIT_38	Kappa	1.00	P<0.001
OPCRIT_39	Kappa	na	Na
OPCRIT_40	Kappa	1.00	P<0.001
OPCRIT_41	Kappa	na	Na
OPCRIT_42	Kappa	0.885	P<0.001
OPCRIT_43	Kappa	Na	Na
OPCRIT_44	Kappa	Na	Na
OPCRIT_45	Kappa	0.904	P<0.001
OPCRIT_46	Kappa	Na	Na
OPCRIT_47	Kappa	Na	Na
OPCRIT_48	Kappa	Na	Na
OPCRIT_49	Kappa	Na	Na

OPCRIT_50	Kappa	Na	Na
OPCRIT_51	Kappa	0.738	0.001
OPCRIT_52	Kappa	na	Na
OPCRIT_53	Kappa	0.700	0.005
OPCRIT_54	Kappa	1.00	P<0.001
OPCRIT_54a	Kappa	1.00	-
OPCRIT_55	Kappa	1.00	P<0.001
OPCRIT_56	Kappa	1.00	P<0.001
OPCRIT_57	Kappa	na	Na
OPCRIT_58	Kappa	na	Na
OPCRIT_59	Kappa	na	Na
OPCRIT_60	Kappa	1.00	P<0.001
OPCRIT_61	Kappa	na	Na
OPCRIT_62	Kappa	na	Na
OPCRIT_63	Kappa	0.640	0.009
OPCRIT2_5	Kappa	1.00	-
OPCRIT2_6	Kappa	1.00	P<0.001
OPCRIT2_8	ICC	0.981	P<0.001
OPCRIT2_10	Kappa	0.821	0.001

OPCRIT2_11	Kappa	na	Na
OPCRIT2_12	Kappa	1.00	P<0.001
OPCRIT2_13	Kappa	1.00	P<0.001
OPCRIT2_14	Kappa	1.00	P<0.001
OPCRIT2_15	Kappa	1.00	P<0.001
OPCRIT2_16	Kappa	1.00	P<0.001
OPCRIT2_78	Kappa	1.00	P<0.001
OPCRIT2_79	Kappa	1.00	P<0.001
OPCRIT2_80	Kappa	1.00	P<0.001
OPCRIT2_81	Kappa	1.00	P<0.001
OPCRIT2_82	Kappa	1.00	P<0.001
OPCRIT2_83	Kappa	1.00	P<0.001
OPCRIT2_84	Kappa	na	Na
OPCRIT2_85	Kappa	1.00	P<0.001
OPCRIT2_86	Kappa	0.852	P<0.001
OPCRIT2_87	Kappa	1.00	P<0.001
OPCRIT2_88	Kappa	0.843	0.002
OPCRIT2_89	Kappa	1.00	0.008
OPCRIT2_90	ICC	0.914	P<0.001

"-" = 100% agreement, no p-value produced
"na" = insufficient variability for analyses to be performed correctly

Appendix P

MIXOR Input Data

7	1	1	0	0	1
7	2	1	1	0	1
7	3	1	0	0	1
7	4	1	1	-99	1
15	2	1	1	0	1
15	4	1	1	-99	1
15	5	1	1	0	1
15	8	1	1	-99	1
16	1	1	1	0	1
16	2	1	1	0	1
16	3	1	1	0	1
16	4	1	1	-99	1
16	6	1	0	-99	1
16	7	1	0	0	1
16	9	1	0	0	1
17	1	1	1	1	1
17	2	1	0	1	1
17	4	1	1	0	1
17	7	1	1	0	1
28	1	1	0	0	1
28	6	1	0	0	1
28	7	1	0	0	1
37	18	1	0	0	1
37	19	1	0	-99	1
50	1	1	0	-99	1
50	3	1	1	0	1
50	10	1	1	0	1
50	11	1	0	0	1
50	12	1	0	0	1
51	6	1	1	-99	1
51	8	1	0	0	1
52	1	1	1	0	1
52	3	1	0	-99	1
52	5	1	1	0	1
52	7	1	1	0	1
53	4	1	0	0	1
53	5	1	1	0	1
53	8	1	1	0	1
55	1	1	0	0	1
55	4	1	0	0	1
57	1	1	1	0	1
57	3	1	0	1	1
57	4	1	0	0	1
57	5	1	0	1	1
59	4	1	0	0	1
59	5	1	0	-99	1
62	3	1	0	-99	1
65	5	1	1	0	1
65	7	1	0	-99	1
65	8	1	0	0	1
68	1	1	0	-99	1
68	3	1	0	0	1
68	4	1	0	0	1
69	1	1	1	0	1

Notes

Data saved in .txt format

Column 1 – Family ID
Column 2 – Individual ID
Column 3 – Sample-of-origin (covariate)
Column 4 – Gender (covariate)
Column 5 – Variable-of-interest (in this example, cannabis abuse)
Column 6 - Intercept

Appendix Q

MIXOR Output

MIXOR Output - d:\rrm\man.out

```
MIXOR - The program for mixed-effects ordinal regression analysis
        (version 2)

MIXOR analysis on the large harmonised dataset
Variable of interest - Cannabis Abuse/Dependence (gender and

Response function: logistic

Random-effects distribution: normal

Covariate(s) and random-effect(s) mean subtracted from thresholds
==> positive coefficient = positive association between regressor
    and ordinal outcome


Numbers of observations
-----------------------

Level 1 observations =    632
Level 2 observations =    328


The number of level 1 observations per level 2 unit are:

   3   2   5   4   3   1   4   1   3   3   2   4   1   2   2   1   1   2   1
   2   2   2   3   2   2   2   2   1   2   2   2   3   3   3   2   2   5   1
   3   2   2   1   3   1   1   1   1   6   4   2   6   1   2   1   2   4   2
   2   1   2   2   3   3   4   1   1   2   2   2   3   1   1   1   1   1   1
   1   1   1   3   1   1   2   2   3   3   2   1   1   2   1   2   2   2   1
   2   1   1   2   2   1   1   1   1   1   1   2   2   3   2   3   2   2   1
   2   2   2   2   1   1   2   2   2   2   2   2   2   2   2   1   2   2   2
   1   1   2   2   1   2   2   3   1   1   1   2   1   2   2   2   2   1   1
   1   1   3   3   1   2   2   1   1   2   2   1   2   1   1   2   1   2   2
   2   1   1   2   2   1   1   1   2   3   1   2   2   2   2   2   2   2   2
   2   2   1   2   1   2   1   2   2   1   1   2   1   2   2   3   2   4   2
   2   2   1   1   1   2   1   1   2   2   1   2   1   2   2   2   2   2   2
   2   2   3   2   1   2   2   2   2   3   2   2   2   2   4   2   2   2   2
   2   3   1   2   2   2   2   2   3   2   2   1   2   3   5   1   1   1   2
   1   1   3   5   1   3   1   2   2   2   2   3   2   2   2   2   2   2   2
   2   2   2   2   4   2   1   2   2   2   3   1   2   3   2   2   2   2   2
   1   2   1   1   2   1   3   2   1   5   4   2   2   2   1   2   2   2   2
   2   1   1   2   3


Descriptive statistics for all variables
----------------------------------------

Variable            Minimum          Maximum             Mean       Stand. Dev.

outcome             0.00000          1.00000          0.13449          0.34145
Intercep            1.00000          1.00000          1.00000          0.00000
sample              1.00000          2.00000          1.48101          0.50004
gender              0.00000          1.00000          0.47310          0.49967


Categories of the response variable outcome
-------------------------------------------
```

MIXOR Output - d:\rrm\man.out - continued

```
Category         Frequency        Proportion

    0.00             547.00           0.86551
    1.00              85.00           0.13449


Starting values
---------------

mean          -2.678
covariates     0.459   0.290
var. terms     0.574


==> The number of level 2 observations with non-varying responses
    =    301 (  91.77 percent )



------------------------------------------------------------
* Final Results - Maximum Marginal Likelihood Estimates *
------------------------------------------------------------

Total Iterations  =  13
Quad Pts per Dim  =  10
Log Likelihood    =    -202.344
Deviance (-2logL) =     404.688
Ridge             =       0.000

Variable          Estimate      Stand. Error                Z          p-value
--------      ------------      ------------      ------------      ------------
Intercep           0.99150           0.77373           1.28147     0.20003   (2)
sample            -2.93990           0.71160          -4.13136     0.00004   (2)
gender            -1.30624           0.46094          -2.83388     0.00460   (2)

Random effect variance term (standard deviation)
Intercep           2.66676           0.65510           4.07078     0.00002   (1)


note: (1) = 1-tailed p-value
      (2) = 2-tailed p-value


Calculation of the intracluster correlation
-------------------------------------------
residual variance = pi*pi / 3 (assumed)
cluster  variance = (2.667 * 2.667) =  7.112

intracluster correlation =  7.112 / ( 7.112 + (pi*pi/3)) = 0.684
```

Appendix R

Summary of Categories for Continuous data

BADDS Depression and Mania

0	0
1-10	1
11-18	2
19	3
20-29	4
30-39	5
40	6
41-46	7
47-59	8
60	9
61-64	10
65-70	11
72-75	12
76-79	13
80	14
81-87	15
88-100	16

BADDS Psychosis

0	0
2-9	1
10-20	2
21	3
22-29	4
30-39	5
40-49	6
50-59	7
60-69	8
70-75	9
76-85	10
86-90	11
91-98	12
99-100	13

BADDS Incongruence

0-5	0
6-15	1
16-24	2
25-33	3
34-40	4
41-49	5
50-59	6
60-65	7
66-70	8
71-79	9
80-89	10
90-97	11
98-100	12

GAS Scores (depression, mania, psychosis, worst ever)

0-9	1
10-14	2
15-20	3
21-25	4
26-30	5
31-35	6
36-40	7
41-45	8
46-50	9
51-55	10

GAS Scores (past week)

0-25	1
26-30	2
31-40	3
41-50	5
51-55	6
56-60	7
61-69	8
70-79	9
80-84	10
85+	11

Number of episodes

1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11-20	11
21-30	12
31+	13

Episode length (weeks)

<1	1
1-2	2
3-4	3
5-8	4
9-12	5
13-16	6
17-26	7
27-39	8
40-51	9
52	10
53-70	11
71-99	12
100+	13

Ages of onset

<17	1
17-19	2
20-22	3
23-25	4
26-29	5
30-34	6
35-39	7
40-49	8
50+	9

Number of admissions

0	0
1	1
2	2
3	3
4	4
5	5
6	6
7-10	7
11-20	8
21+	9

Longest admission

<1	1
1-2	2
3-4	3
5-8	4
9-12	5
13-16	6
17-26	7
27-35	8
36-51	9
52-103	10
104+	11

Proportion of time admitted

0	0
1-5	1
6-10	2
11-20	3
21-30	4
31-40	5
41-50	6
51-60	7
61-70	8
71-80	9
81-85	10
86-100	11

Proportion of time well since onset

0	0
1-5	1
6-10	2
11-20	3
21-30	4
31-40	5
41-50	6
51-60	7
61-70	8
71-80	9
81-85	10
86-89	11
90-95	12
96-99	13

Extended Rating Scale 1

0	0
1	1-10
2	11-15
3	16-25
4	26-39
5	40-47
6	48-52
7	53-60
8	61-70
9	71-75
10	76-80
11	81-89
12	90-99
13	100

Extended Rating Scale 2

-20	0
-19- -10	1
-9- -2	2
0-5	3
6-15	4
16-24	5
25-33	6
34-40	7
41-49	8
50-59	9
60-65	10
66-70	11
71-79	12
80-89	13
90-99	14
100-109	15
110-120	16

Extended Rating Scale 3

0	0
1-35	1
36-45	2
46-59	3
60-75	4
76-90	5
91-100	6

Extended Rating Scale 4

0	0
1-10	1
11-20	2
30-40	3
41-60	4
61-70	5
71-79	6
80	7
81-89	8
90	9
91-95	10
96-100	11

Extended Rating Scale 5

0	0
1-10	1
11-20	2
21-30	3
31-40	4
41-50	5
51-60	6
61-70	7
71-80	8
81-89	9
90	10
91-100	11

Extended Rating Scale 6

0	0
1-10	1
11-20	2
21-29	3
30-40	4
41-60	5
61-100	6

Extended Rating Scale 7

0	0
1-10	1
11-20	2
21-30	3
31-40	4
41-50	5
51-60	6
61-70	7
71-100	8

Extended Rating Scale 8

0	0
1-5	1
6-10	2
11-15	3
16-25	4
26-35	5
36-44	6
45-55	7
56-65	8
66-70	9
71-75	10
76-80	11
81-85	12
86-90	13
91-95	14
96-99	15
100	16

Extended Rating Scale 9

0	0
1-5	1
6-10	2
11-19	3
20-24	4
25-30	5
31-40	6
41-55	7
56-60	8
61-80	9
81-100	10

Appendix S

List of cases used included in the Wellcome Trust Case Control Consortium (WTCCC)

7-1
15-2
17-1
28-1
37-18
50-11
51-8
52-3
55-4
57-3
59-5
62-3
65-7
68-3
69-1
72-11
75-3
76-3
79-4
80-4
81-3
83-6
84-5
85-4
86-3
87-9
104-2
500-4
501-8
504-5
505-6
507-4
508-7
509-3
510-5
511-5
512-4
513-3
514-4
515-3
516-5
517-3
518-4
519-4
520-6
522-4
523-7
524-5
525-5
527-3
528-5
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Appendix T

Search terms included in literature search.

The Functional Psychoses: Major mood and psychotic disorders of adulthood

Keywords:

i. Schizophrenia
ii. Bipolar Disorder
iii. Functional psychosis OR Functional psychoses
iv. Affective psychoses OR Affective Psychosis

"i. OR ii. OR iii. OR iv" AND

v. Review
vi. Illness course
vii. Illness onset
viii. Age at onset
ix. Epidemiology
x. Aetiology
xi. Heritability

Classification and nosology of the functional psychoses: Kraepelin's Dichotomy

Keywords:

xii. Kraepelin
xiii. Kraepelin's Dichotomy
xiv. "psychiatry OR "i. OR ii. OR iii. OR iv."" AND "nosology OR classification"
xv. Schizophrenia AND Bipolar Disorder
xvi. Schizophrenia AND "Affective disturbance OR Mood OR mania OR manic symptoms OR depression OR depressive symptoms"
xvii. First rank symptoms
xviii. Bipolar Disorder AND "Psychosis OR psychotic symptoms OR hallucinations OR delusions OR first rank symptomms"
xix. Schizoaffective Disorder OR Schizoaffective Psychoses
xx. Schizoaffective Disorder AND "v. OR vi. OR vii. OR viii. OR ix. OR x."
xxi. Diagnostic hierarchy
xxii. xx. AND xiii.
xxiii. "Family study OR familiality OR pedigrees OR heridity" AND "i. OR ii. OR iii. OR iv. OR xviii"

"i. OR ii. OR iii. OR iv OR xix" AND xxiv-xxvii

xxiv. Molecular genetics
xxv. Linkage analysis OR genetic linkage
xxvi. Association analysis OR genetic association
xxvii. Gene OR Genes
xxviii. COMT OR Catechol-o-methyltransferase
xxix. DISC1 OR Disrupted in Schizophrenia 1
xxx. DYSBINDIN OR dystrobrevin-binding protein 1
xxxi. DAOA OR D-amino acid oxidase activator
xxxii. NRG1 OR Neuregulin 1

Refining the phenotype

"i. OR ii. OR iii. OR iv. OR xix" AND:

xxxiii. Phenotype
xxxiv. Familiality OR Familial
xxxv. Family Study
xxxvi. Heredity
xxxvii. Clinical features OR Clinical measures OR Symptoms OR Dimensions OR Factors

NB: Where relevant papers were identified, citation-searches were performed to identify related papers of interest.